SYNTHESIS OF SPIROCYCLOHEXENE-PYRROLIDONE ALKALOIDS

By
MISS Sunisa MOONGMAI

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

การสังเคราะห์สไปโรไซโคลเฮกซีน-ไพโรริโดน อัลคอลอยด์

โดย
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Title	Synthesis of Spirocyclohexene-pyrrolidone alkaloids
By	MISS Sunisa MOONGMAI
Field of Study	(CHEMISTRY)
Advisor	Assistant Professor Punlop Kuntiyong, Ph.D.

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630720010 : Major (CHEMISTRY)
Keyword : N-acyliminium ion spirocyclization, FR901483, D-ring homolog of cephalotaxine, aryl analog of lepadiformine C

MISS SUNISA MOONGMAI : SYNTHESIS OF SPIROCYCLOHEXENE-PYRROLIDONE ALKALOIDS THESIS ADVISOR : ASSISTANT PROFESSOR PUNLOP KUNTIYONG, Ph.D.

In this thesis, synthetic studies of biologically active spirocyclic alkaloids are discussed. The selected targets contain common structural feature, namely spiro[cyclohexane-pyrrolidine]. The selected targets are immunosuppressive FR901483, homolog of cytotoxic cephalotaxine, and aryl analog of lepadiformine C, a potential cardiovascular drug. The common structural feature can be synthesized in diastereoselective fashion using chiral pool starting material L-asparagine which was converted to *N*-alkylsuccinimide. Grignard addition to the succinimide with *in situ* generated pentenylmagnesium bromide gave the corresponding g-pentenyl-g-hydroxylactam. This intermediate underwent acid-promoted spirocyclization to give spiro[cyclohexane-pyrrolidone] in highly diastereoselective fashion. The cyclized product could be used as synthetic precursor for construction of the polycyclic core of the target molecules with formation of additional ring between the cyclohexene and the *N*-alkyl group.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my thesis adviser, Asst. Prof. Dr. Punlop Kuntiyong for his invaluable help, useful guidance and constant encouragement throughout my years in graduate school. I appreciate him for his advices and teaching, not only the research methodologies but also many other methodologies in life.

Next, I would like to thank the Graduate Research Assistant Scholarship from the Faculty of Science, Silpakorn University: Academic Years 2021 and 2022 for providing me a scholarship.To committee members, Asst. Prof. Dr. Panupan limpachayaporn, Assoc. Prof. Rungnapha Saeeng , I would like to thank them for time and support.

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

MISS Sunisa MOONGMAI

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF SCHEME

Page

CHAPTER 1

INTRODUCTION

Background and Signification of the Research Problem

Alkaloids are organic compounds that contain nitrogen within their molecules in the form of amines, amide and imine. Nitrogen atoms in alkaloids are obtained from amino acids. Alkaloids generally have basic properties but more or less depends on the amount of nitrogen. However, some alkaloids are neutral or weak acid. Substances in the alkaloid group have medicinal effects. In nature, alkaloids are found in higher plants in different parts of plants, less in lower plants, animals and microorganism. Alkaloids can be classified according to their chemical structure as non-heterocyclic alkaloids and heterocyclic alkaloids. Heterocyclic alkaloids can be divided into subgroups which include pyrrole, pyridine, piperidine, pyrrolozidine, tropane, quinoline, isoquinoline, aporphine, indole, imidazole, purine and steroids[1].

Our research group studies substrate-controlled asymmetric synthesis of indolizidine alkaloids with the 1-azabicyclo[4.3.0]nonane system and quinolizidine alkaloids with 1-azabicyclo[4.4.0]decane system. Our approach uses L-aspartic acid or L-asparagine and L-glutamic acid or L-glutamine as chiral pool starting material for synthesis of indolizidine and quinolizidine, respectively. The amino acid would be converted to chiral 3-dibenzylaminosuccinimide and 3-dibenzylaminoglutarimide which represent the pyrrolidine and piperidine ring in alkaloids, respectively. *N*-Arylethyl-succinimide or *N*-arylethyl-glutarimide underwent regioselective hydride reduction of the less hindered carbonyl to give the corresponding hydroxylactam. Treatment of this intermediate with acid mediator leads to *N*-acyliminium ion cyclization to form arene-fused quinolizidine and indolizidine. *N*-alkenylsuccinimide and *N*-alkenylglutarimide can also undergo the analogous reaction sequence to give non-aromatic indolizidine and quinolizidine, respectively [2]. At present the scope of products that we have synthesized with this method are dibenzylamino-indoloquinolizidinone **A**, dibenzylamino-benzoquinolizidinone **B**, dibenzylamino indoloindolizidinone **C** and benzoindolizidinone **D**. Moreover, *N*-acyliminium ion cyclization of *N*-butenyl-succinimide and *N*-butenyl-glutarimide derivatives, both terminal alkene (R = H) and internal alkene (R = alkyl), give simple indolizidinone **E** and quinolizinone **F** as shown in Figure 1.

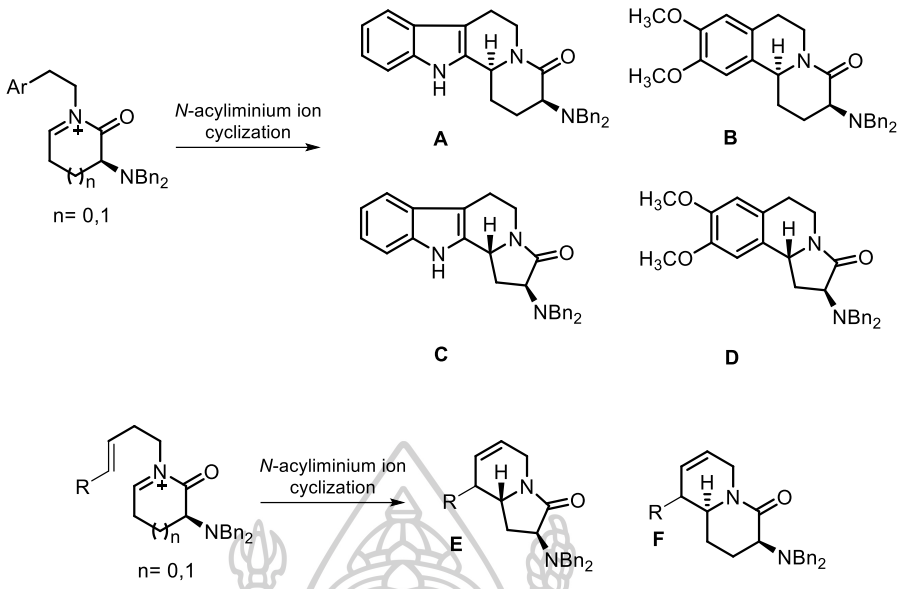


Figure 1 Reaction of *N*-acyliminium ion cyclization

The natural products and their analogs that we have synthesized using this methodology are shown in Figure 2. These include schulzeines B and C, crispine A methyl analog, tetrabenazine core, Erythrina alkaloid core and Rhynchophylline core.

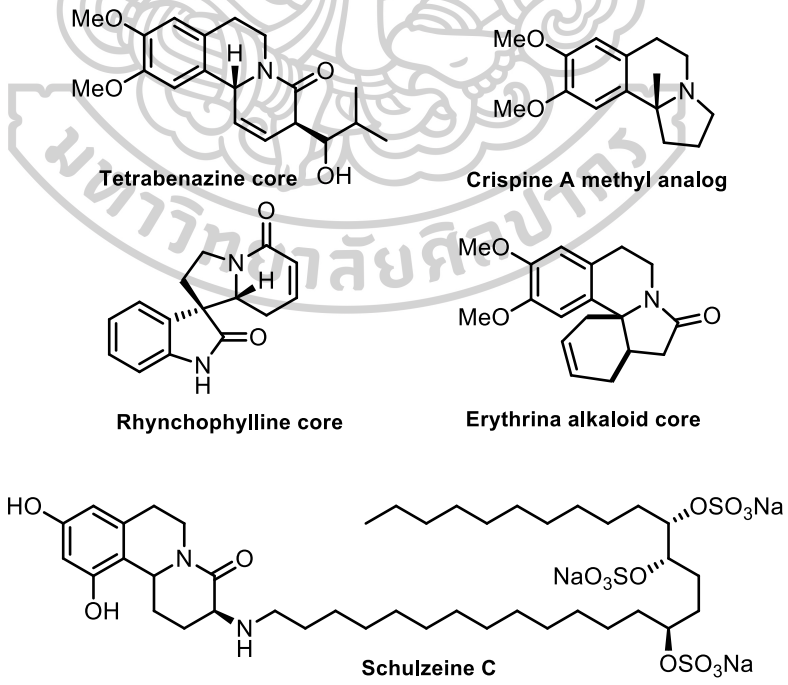


Figure 2 Examples of natural products in the group of indolizidine alkaloids and quinolizidine alkaloids which have been synthesized by our group

To expand the scope of our methodology, we explore *N*-acyliminium ion cyclization to form spirocyclic system. We hypothesize that if the *N*-alkyl group of hydroxylactam cannot participate as a nucleophile in *N*-acyliminium ion cyclization, an alkenyl group on the γ-carbon of the γ-hydroxylactam can cyclize to form a spirocyclic ring. For example, the pentenyl group on the γ-carbon can lead to spirocyclohexene-pyrrolidone. The dibenzylamino group will control stereochemistry of the spirocyclization so that the addition occurs on the opposite side of the NBn_2 group as shown in Figure 3.

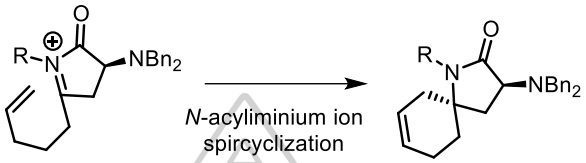


Figure 3 Synthesis of spirocyclohexene-pyrrolidone

Around 47,000 compounds recently identified containing spirocycle in various structures that were active against some 200 drug targets and there is potential to expand the spirocyclic chemicals for drug discovery. In the present, there are available some 14 marketed spirocyclic containing medicines, ranging from the treatment of anxiety disorders (Buspirone) to schizophrenia, antipsychotics (Fluopireline). Natural product inspired synthesis of spirooxindoles has led to the emergence of applications as anticancer, antiviral, cardiovascular, anti-hypertensive and neuroprotective agents [3].

In this thesis, we will discuss *N*-acyliminium ion (6-*exo*-*trig*) spirocyclization of γ-pentenyl-γ-hydroxylactam to give spirocyclohexene-pyrrolidone that can be applied in synthesis studies of various types of spirocyclic alkaloids. The example of spirocyclic alkaloids shown in Figure 4 include lepadiformine, FR901483, TAN1251C and cephalotaxine homolog.

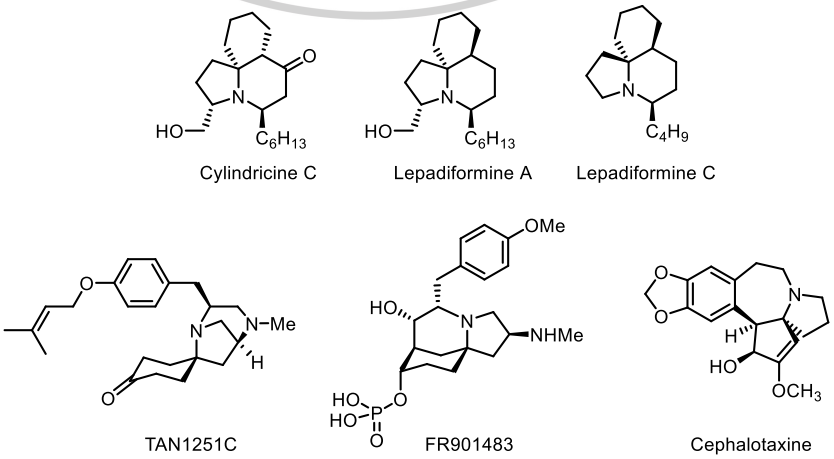


Figure 4 Examples of spirocyclic alkaloids

Objectives of Research

1. To develop the procedure of *N*-acyliminium ion spirocyclization for the synthesis of spirocyclohexene-pyrrolidone.
2. To develop a synthetic methodology of immunosuppressive FR901483
3. To develop a synthetic methodology of Cephalotaxine or D-ring homolog of cephalotaxine
4. To develop a synthetic methodology of aryl analog of Lepadiformine C

CHAPTER 2

LITERATURE REVIEW

FR901483

FR901483 is an immunosuppressive alkaloid isolated from fermentation broth of *Cladobotrym sp*. No.11231 [4] by Fujisawa and coworker in 1996. The molecular formula of FR901483 has been determined as $C_{20}H_{31}N_2O_6P$. FR901483 exerts a potent immunosuppressive activity in vitro and significantly prolongs graft survival time in the rat skin allograft model. This compound has an intriguing tricyclic structure possessing a phosphate ester in its molecule (Figure 5). The ester residue may play an important role in exerting immunosuppressive activity because the dephosphoryl compound is devoid of activity. Other biological activities are antimetabolite by adenylosuccinate synthetase and adenylosuccinate lyase inhibition.

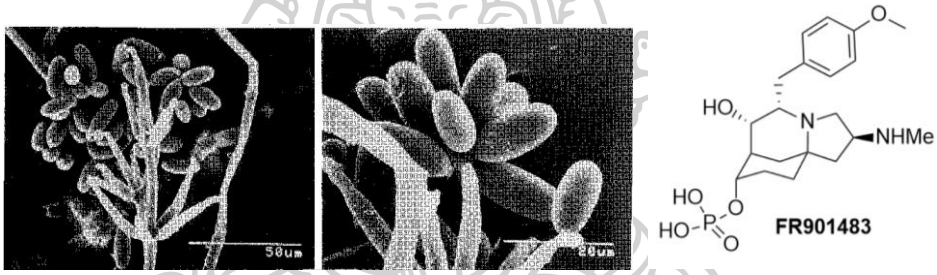
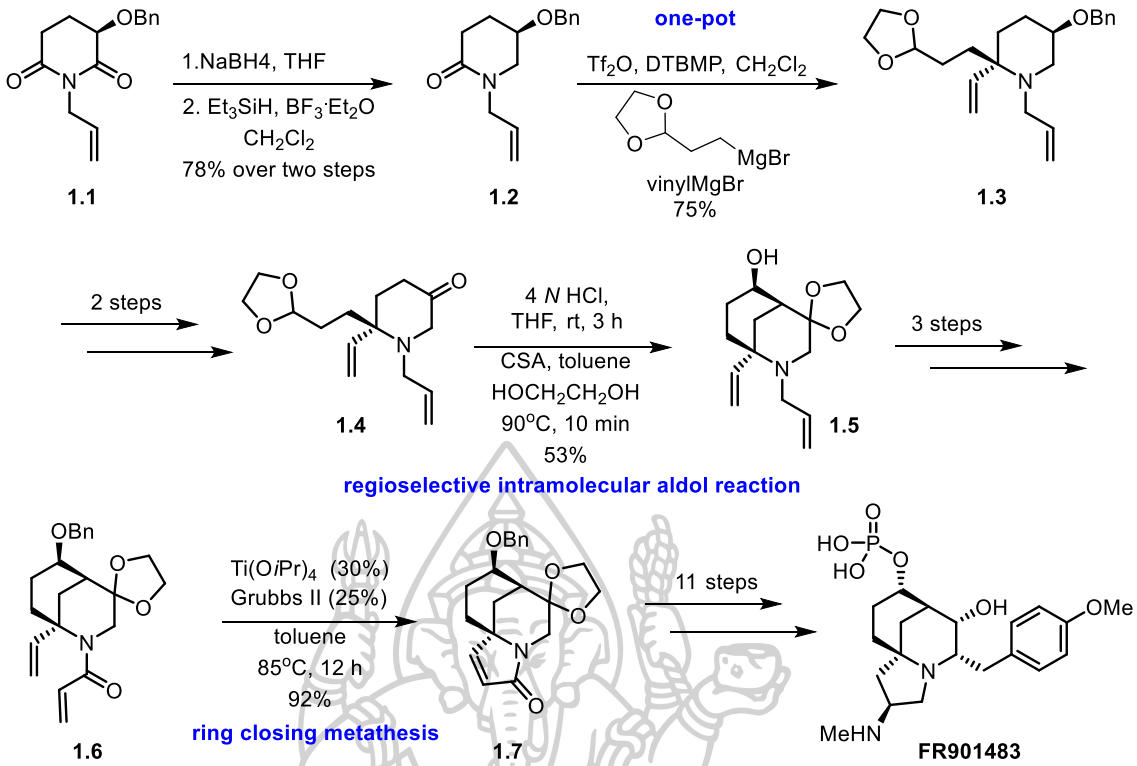


Figure 5 *Cladobotrym sp*. No.11231[4] and structure of FR901483

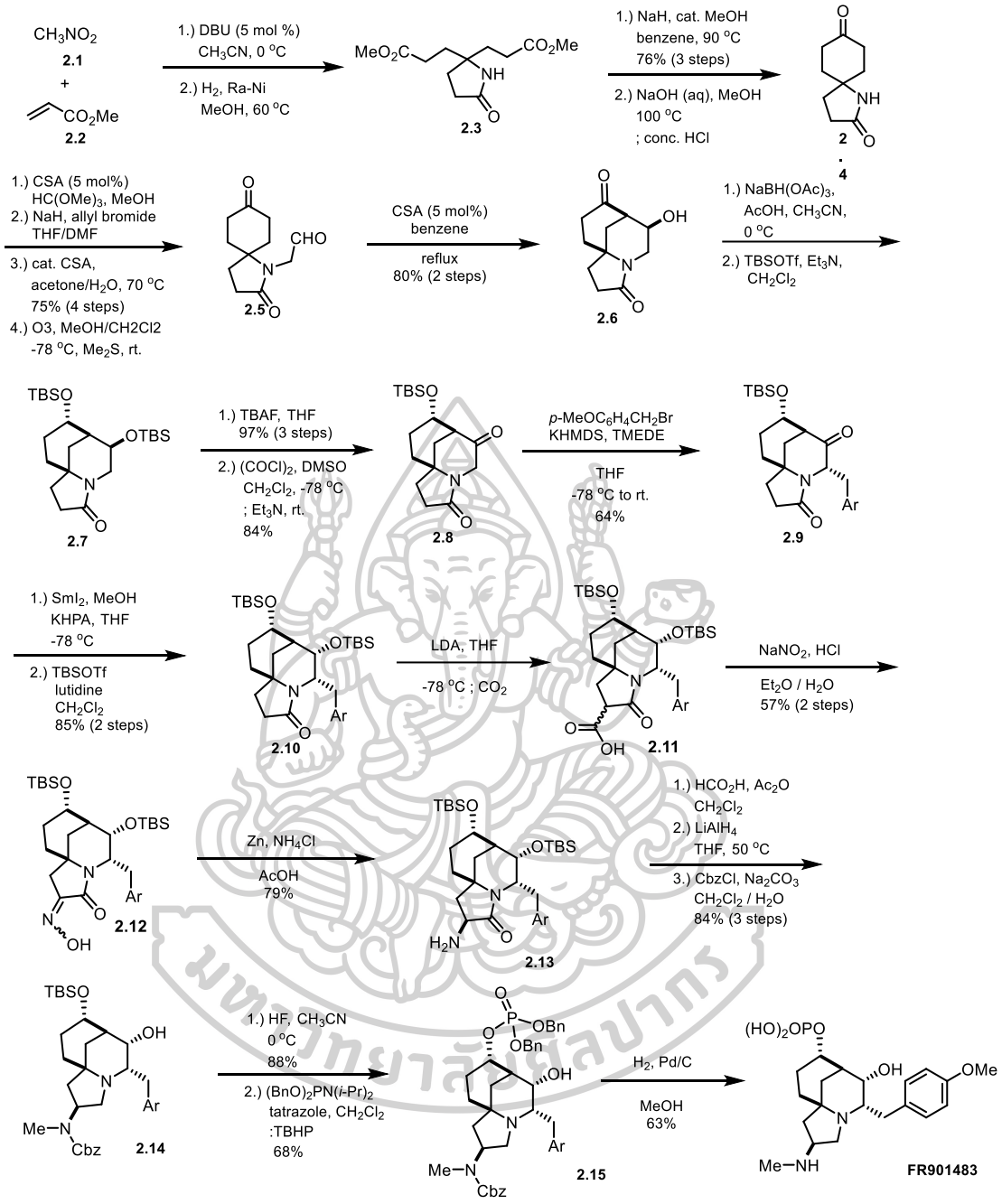
Previous syntheses of FR901483

In 2012, a formal enantioselective total synthesis of FR901483 was reported by Huang and coworkers. The synthesis started from (*3R*)-benzyloxyglutarimide **1.1** with featuring one-pot amide reductive bisalkylation to construct the chiral aza-quaternary center and regio- and diastereoselective intramolecular aldol reaction to build the bridged ring and ring closing metathesis to form the 3-pyrrolin-2-one ring. The synthesis of FR901483 was completed in 18 steps with an overall yield of 4.1% [5] (scheme 1).



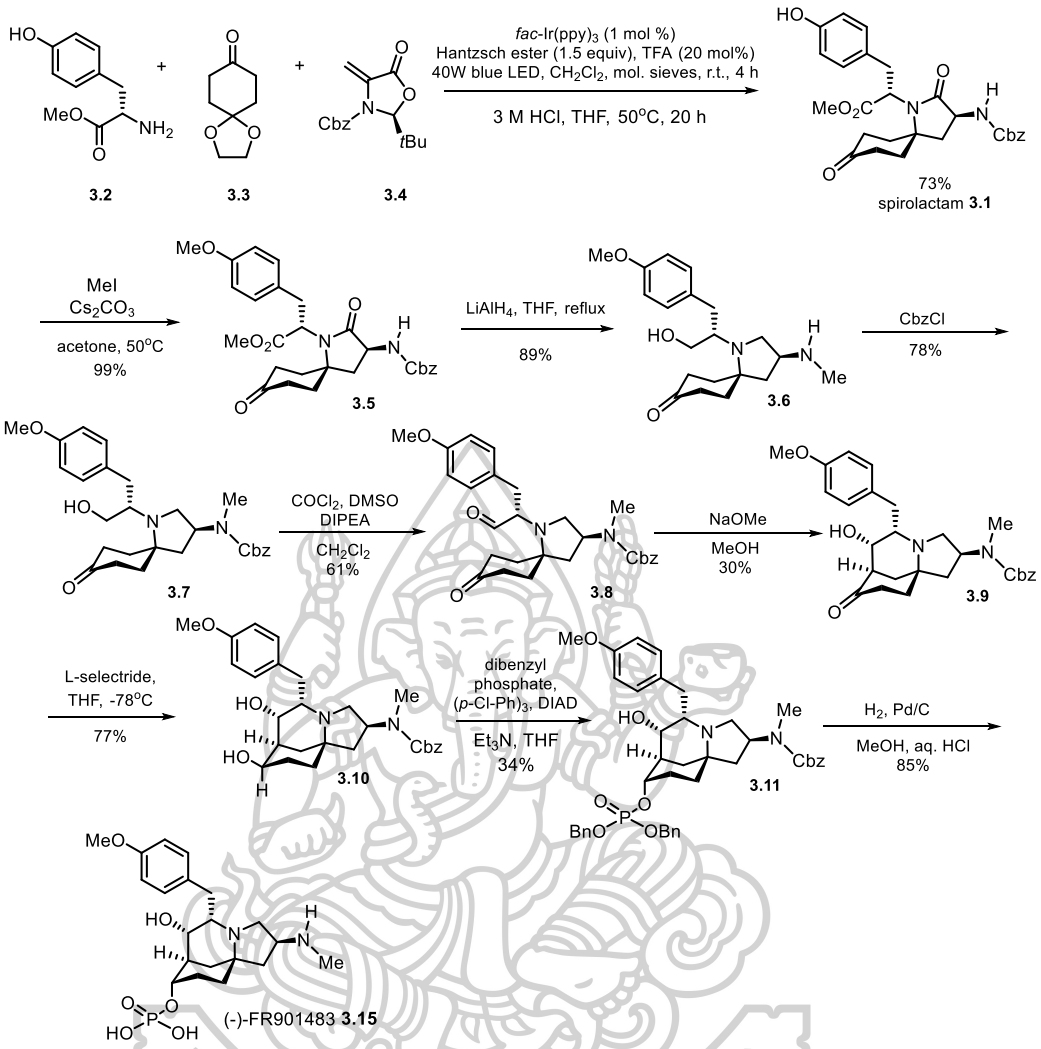
Scheme 1 Synthesis of FR901483 by Huang and coworker

In 2004, a stereocontrolled total synthesis of FR901483 was reported by Fukuyama and coworkers. The synthesis started from nitromethane and ethyl acrylate with Michael reaction, Diekmann condensation, intramolecular aldol reaction and one-electron reduction as key reactions [6] (scheme 2).

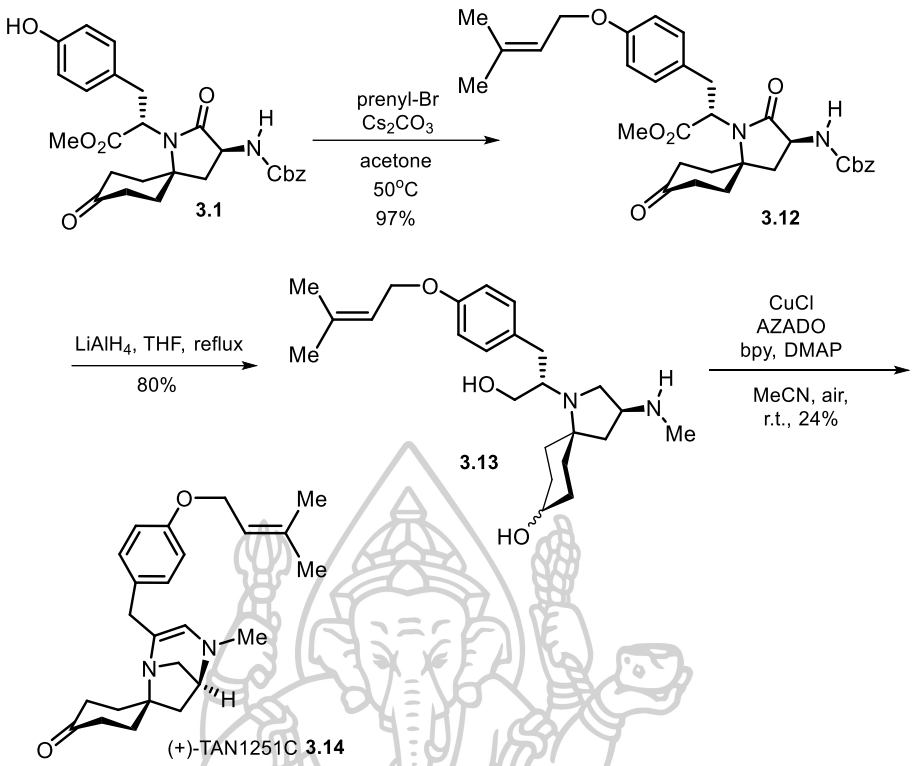


Scheme 2 Synthesis of FR901483 by Fukuyama and coworker

In 2020, rapid syntheses of (-)-FR90483 and (+)-TAN1251C enabled by complexity-generating photocatalytic olefin hydroaminoalkylationwas [7] reported by Matthew and coworker. Both molecules were synthesized through the same intermediate spirolactam **3.1**. The synthesis started from L-tyrisune methyl ester **3.2**, 1,4-cyclohexenedione monoethylene **3.3** and dehydroalanine derivative **3.4** featuring photocatalytic olefin hydroaminoalkylation as the key reaction to give the key intermediate spirolactam **3.1**(scheme 3 and scheme 4).



Scheme 3 Synthesis of FR901483 by Matthew and coworker



Scheme 4 Synthesis of TAN1251C by Matthew and coworker

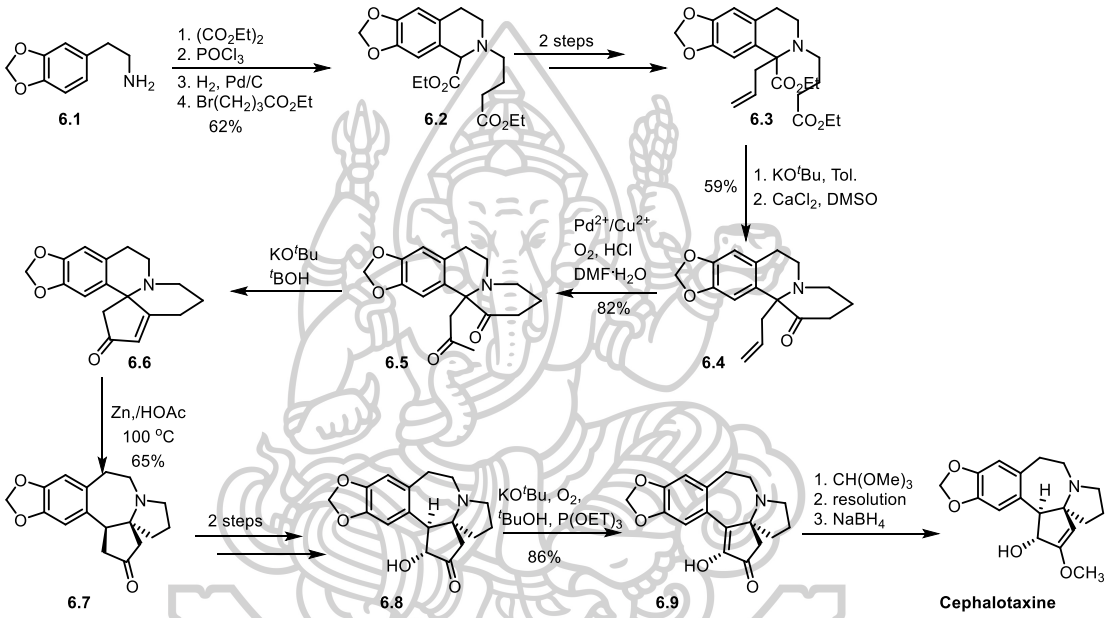
Cephalotaxine

Cephalotaxine is the major alkaloids isolated from Cephalotaxus drupacea species in 1963 by Paudler and coworker. The subsequent discovery of promising antitumor activity among new Cephalotaxus derivatives reported by Chinese, Japanese, and American teams led to interests in its total synthesis studies. Cephalotaxine possesses a unique benzazepine-bearing pentacyclic ABCDE-ring skeleton with spirocyclic junction between D and E rings as shown in Figure 6. Naturally occurring esters of cephalotaxine have been found to be highly effective for the treatment of acute human leukemia and are currently undergoing advanced clinical trials. The unique structure and the therapeutic potential of this group alkaloids have stimulated much synthetic research that has produced several elegant total syntheses of cephalotaxine and numerous studies on the construction of the pentacyclic ring. [8, 9]

Figure 6 *Cephalotaxus harringtonia*[10] and structure of cephalotaxine

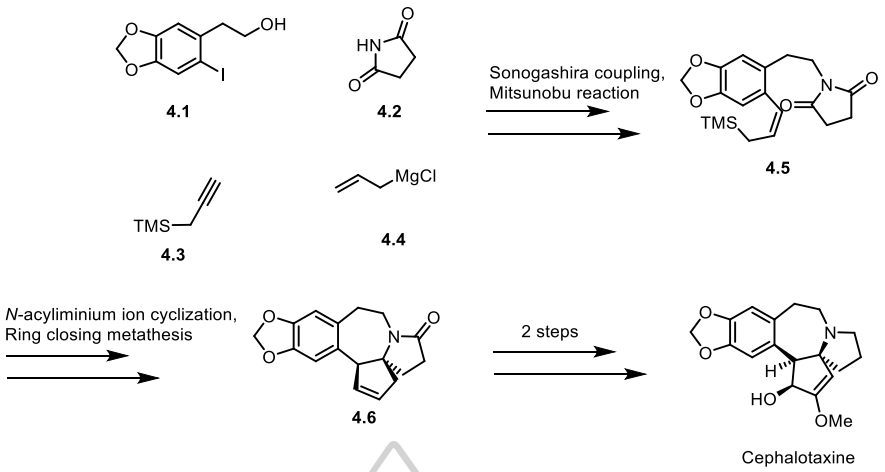
Previous syntheses of cephalotaxine

In 2003, an efficient total synthesis of cephalotaxine [11] was reported by Li and coworkers. The synthesis started from β-(3,4-methylenedioxy)phenethylamine **6.1** that was converted to tetrahydroisoquinoline **6.2** via Bischler-Napieralski reaction and arylquinolizidine-diketone **6.5**. Intramolecular aldol condensation gave tetracyclic precursor **6.6** that underwent the key transformation, transannular reductive rearrangements to establish the pentacyclic ring skeleton of cephalotaxine (scheme 5).



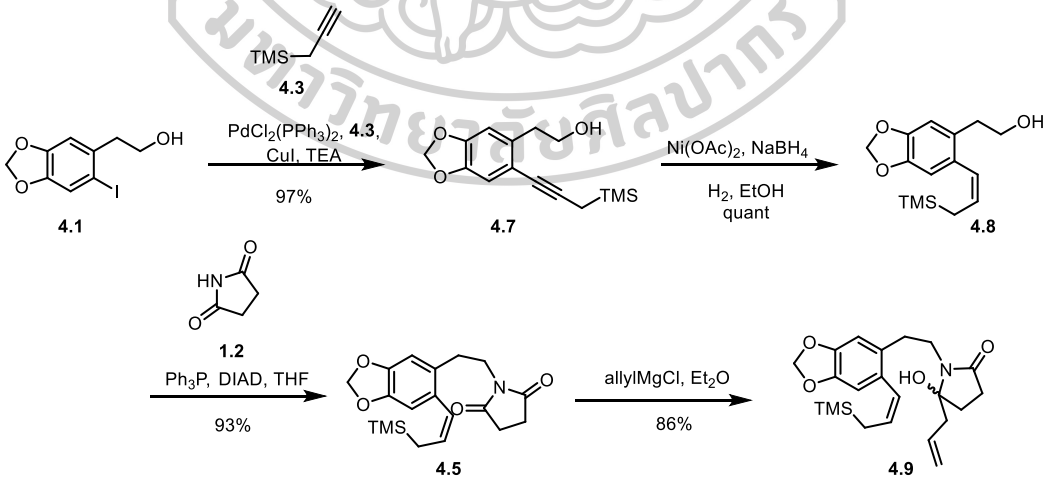
Scheme 5 Synthesis of cephalotaxine reported by Li and coworkers

In 2015, a stereoselective *N*-iminium ion cyclization was applied in an efficient synthesis of cephalotaxine reported by Hao and coworkers. The synthesis started from phenylethanol **4.1**, propargyl trimethylsilane **4.3**, succinimide **4.2** and allylmagnesium chloride **4.4** with important reactions such as Sonogashira coupling, Mitsunobu reaction to form *N*-(TMSallylaryl)ethylsuccinimide **4.5** as an important precursor. Grignard addition of the succinimide and subsequent *N*-acyliminium ion cyclization followed by ring closing metathesis constructed the pentacyclic core of cephalotaxine (scheme 6).[12]

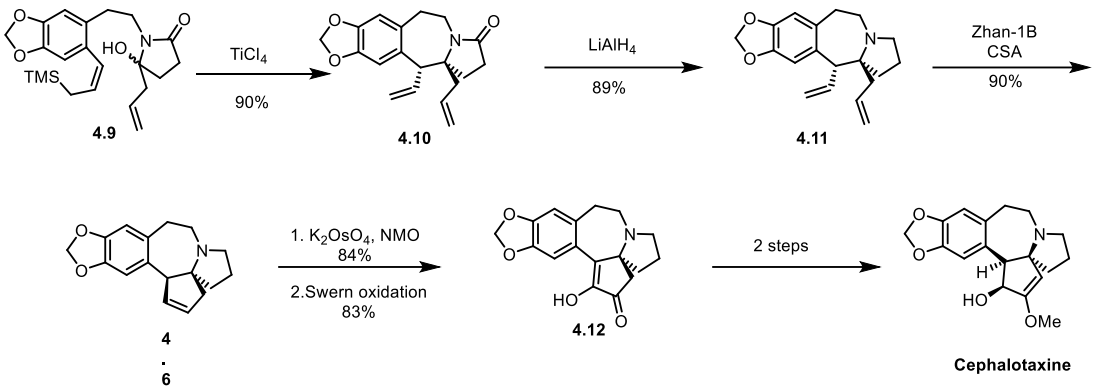


Scheme 6 Synthesis of cephalotaxine by Hong and coworkers

The synthesis started from phenylethanol **4.1** which was converted to alkyne **4.7** via Sonogashira coupling with propargyl trimethylsilane **4.3** using $PdCl_2(PPh)_3$. Partial hydrogenation of the alkyne **4.7** gave allylsilane **4.8** using Lindlar catalyst. Mitsunobu reaction of primary alcohol **4.8** with succinimide **4.2** gave *N*-(TMSallylaryl)ethylsuccinimide **4.5** using PPh_3 and DIAD. Grignard reaction of succinimide **4.5** using allylmagnesium chloride and subsequent *N*-acyliminium ion cyclization using $TiCl_4$ led to tricyclic diene **4.10**. Lactam reduction using $LiAlH_4$ and and ring closing metathesis with Zhan-1B catalyst constructed the pentacyclic core **4.6**. Dihydroxylation and Swern oxidation then gave demethylcephalotaxinone **4.12** From this intermediate the total synthesis of cephalotaxine was completed in 2 steps (schemes 7and 8).



Scheme 7 Synthesis of hydroxylactam 4.9



Scheme 8 Synthesis of cephalotaxine

Lepadiformine

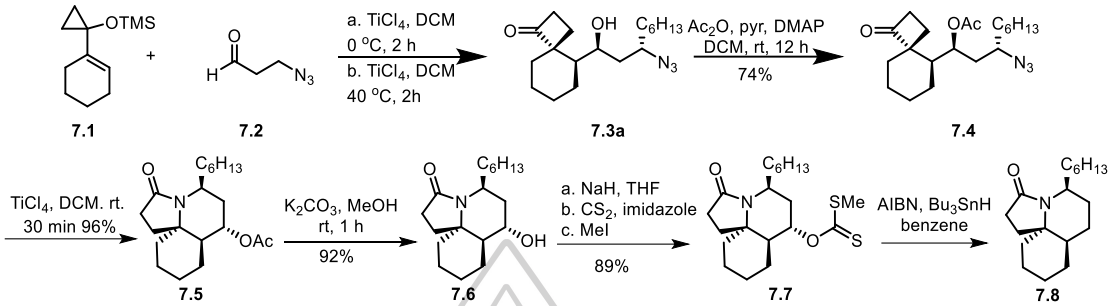
Lepadiformine C is the tricyclic marine alkaloid isolated from the tunicate *Clavelina moluccensis* along with lepadiformine A and B by Sauviet and coworkers in Djibouti water. It was reported that lepadiformine A-C showed strong cardiovascular effects *in vitro* and *in vivo* and blocked the cardiac inward rectifying K^+ channel. In addition, these alkaloids exhibit cytotoxicity against several tumor cell lines as well as antiarrhythmic and antihypertensive properties. They have a tricyclic framework characterized by *trans*-1-azadecalin A/B ring and the AC spiro-cyclic ring system as shown in Figure 7.[13]

Figure 7 Clavelina moluccensis [14, 15] and structure of lepadiformine C

Previous syntheses of lepadiformines

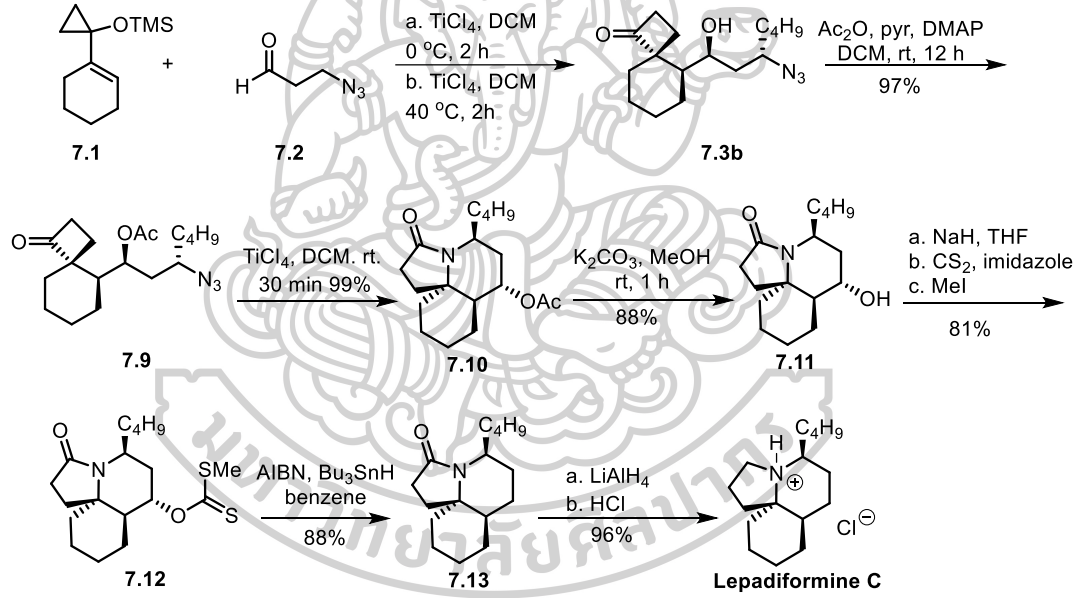
In 2010, a Tandem Prins/Schmidt reaction approach to marine alkaloids was employed in formal and total syntheses of lepadiformine A and C [16] reported by Jeffrey and coworkers. They developed a route to the tricyclic core of lepadiformine families using several variations of a tandem Prins/Schmidt sequence. The synthesis

started from cyclopropane **7.1** and achieved a formal synthesis of lepadiformine A in 12 steps with 8% overall yield and the first total synthesis of lepadiformine C in 9 steps with 10% overall yield (scheme 9 and 10).



7.1 7.2 7.3a 7.4 7.5 7.6 7.7 7.8

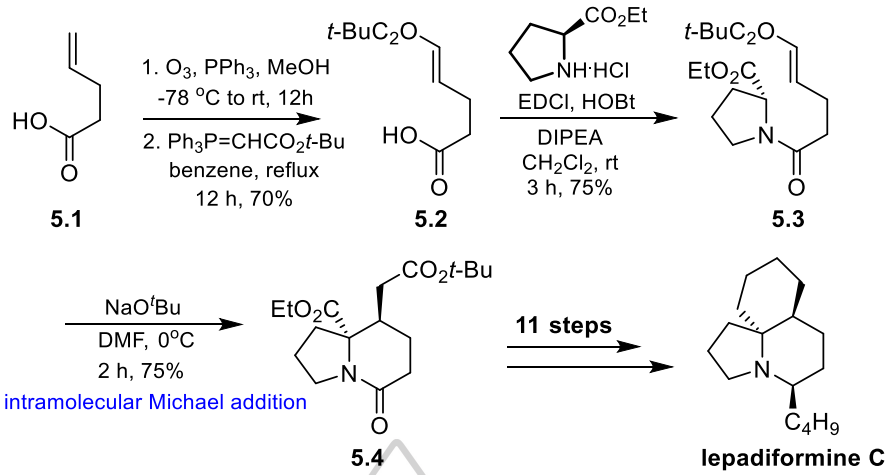
Scheme 9 Formal synthesis of lepadiformine A



7.1 7.2 7.3b 7.9 7.10 7.11 7.12 7.13 Lepadiformine C

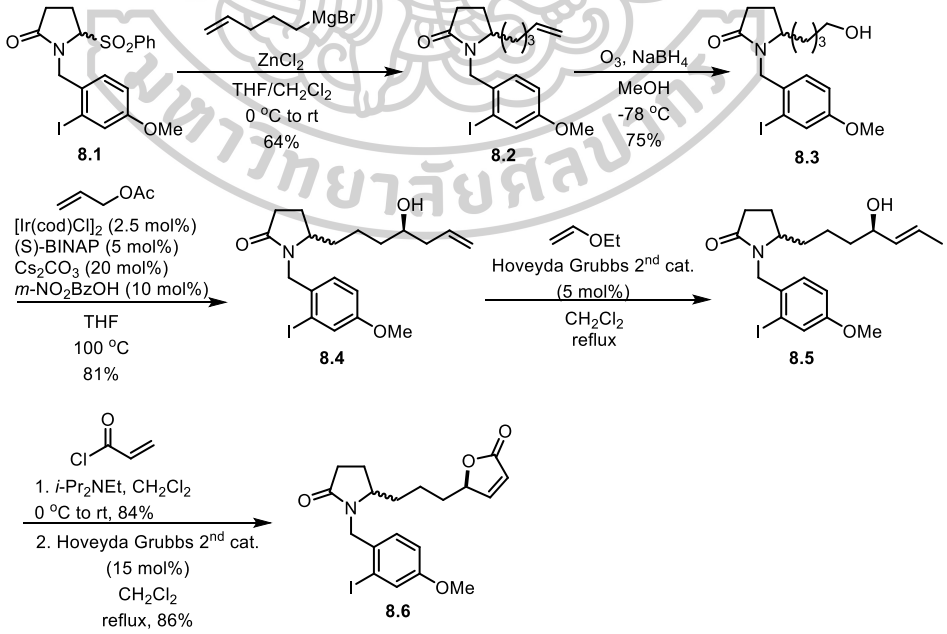
Scheme 10 Total synthesis of lepadiformine C

In 2017, asymmetric total synthesis of lepadiformine C [17] using ‘memory of chirality’ concept in intramolecular ester enolate Michael addition of proline-derived precursor to form chiral indolizidinone core was reported by Kim and coworkers. The synthesis started from γ,δ-unsaturated acid **5.1** and was completed in 15 steps (scheme 11).



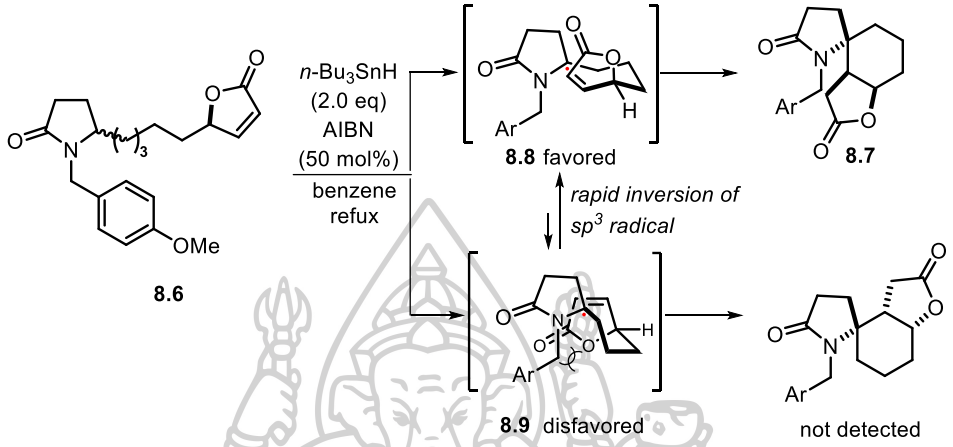
Scheme 11 Asymmetric total synthesis of lepadiformine C using memory of chirality in intramolecular ester enolate Michael addition by Kim and coworkers

In 2020, a total synthesis of (-)-lepadiformine A via radical translocation-cyclization was reported by Tokuyama and coworkers. They accomplished a total synthesis of (±)-lepadiformine that involved a radical translocation-cyclization strategy for the construction of the 1-azaspiro[4,5]-decane ring system. The synthesis started from sulfone **8.1** which was converted to alcohol **8.3** via Grignard reaction and ozonolysis. The Krische's catalytic asymmetric allylation, acryloylation and ring closing metathesis of alcohol **8.3** gave butanolide **8.6**. (scheme 12).[18]



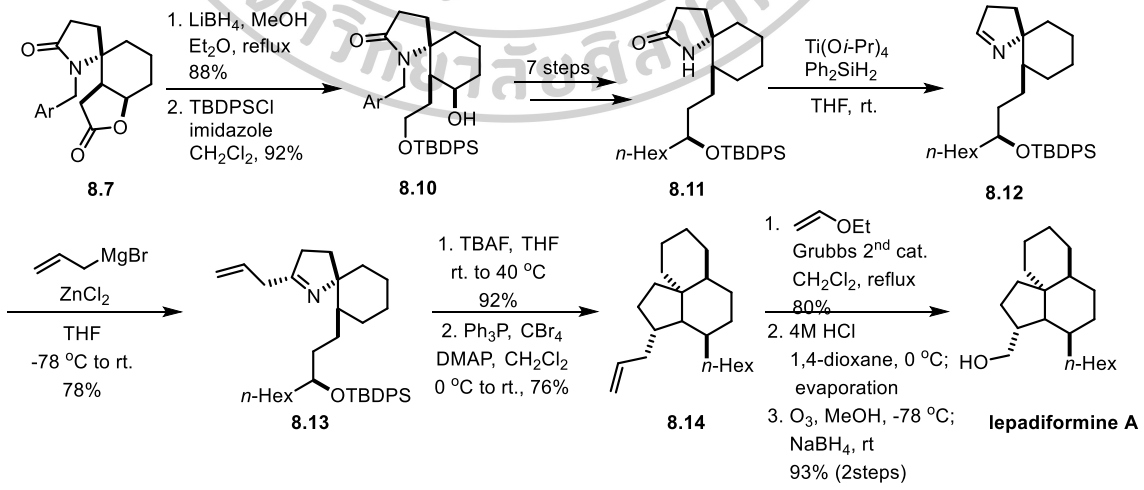
Scheme 12 Synthesis of spirocyclic precursor 8.6

They then examined the key radical translocation-cyclization reaction as they expected, treatment of **8.6** with AIBN and *n*-Bu_3SnH afforded spirocyclic product **8.7**. The perfect diastereoselectivity indicated that, under rapid inversion of C-10 sp^3 radical center, the *6-exo-trig* radical cyclization proceeded via intermediate **8.8** (scheme 13).



Scheme 13 Key radical translocation-cyclization reaction

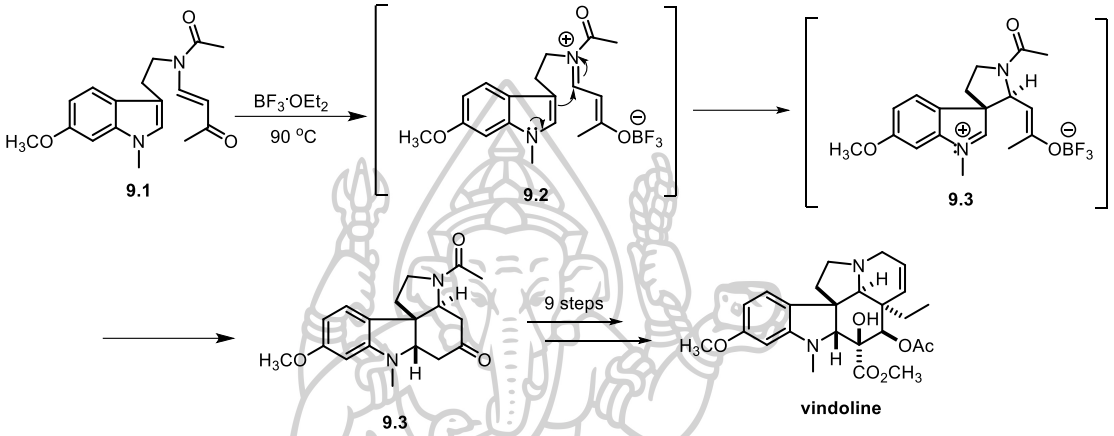
Finally, after reduction of lactone **8.7** to corresponding diol, the secondary hydroxy group was removed after selective protection of the primary alcohol to give TBDPS-protected compound **8.10** and further 13 steps of functional group manipulation completed the total synthesis of lepadiformine A (scheme 14).



Scheme 14 Total synthesis of (-)-lepadiformine A

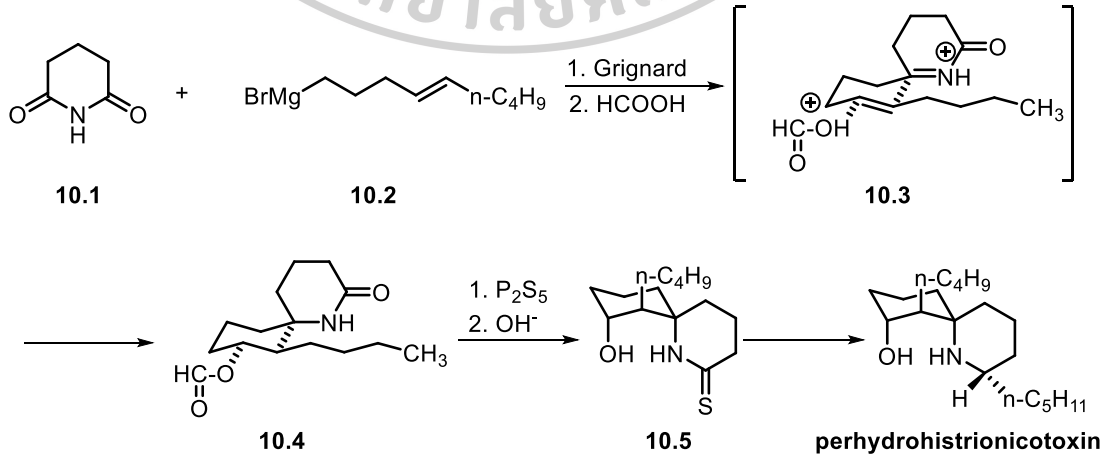
N-Acyliminium ion spirocyclization

N-acyliminium ion spirocyclization is useful in some syntheses that we have discussed before. Additional selected syntheses of the natural and non-natural analogues of alkaloids via *N*-acyliminium ion spirocyclization will be discussed here.[2, 19] A total synthesis of (±)-Vindoline was reported by Vedejs and coworkers. The synthesis applied *N*-acyliminium ion spirocyclization of vinylogous indole-enamide **9.1** which was initiated with $BF_3{\cdot}OEt_2$ to give the tetracyclic core **9.3** of vindoline in 56% yield (scheme 15).[20]



Scheme 15 Synthesis of vindoline by Vedejs

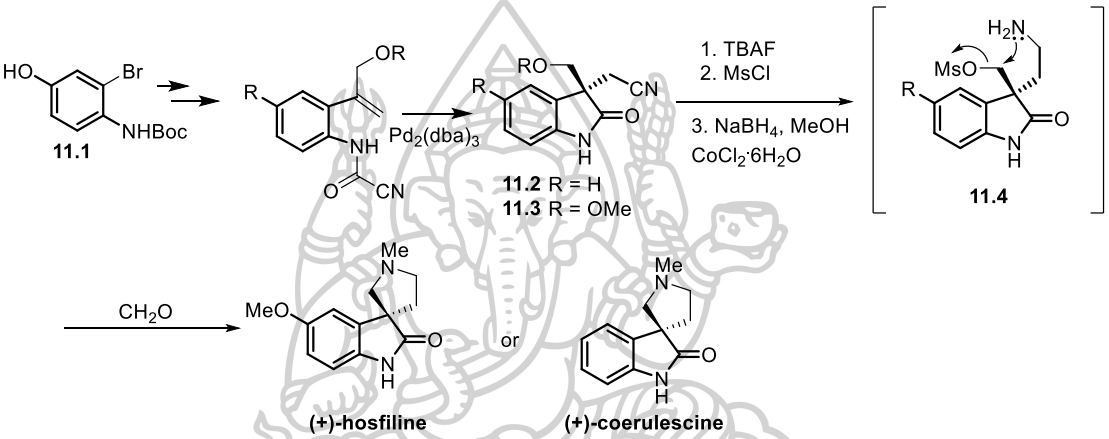
A short and stereoselective synthesis of perhydrohistrionicotoxin [21] was reported by Speckamp and coworkers. The synthesis started from glutarimide **10.1** using Grignard reagent and subsequent acid catalyzed *N*-acyliminium ion spirocyclization to give ester **10.4**. The cationic intermediate in the cyclization step was terminated as a formate ester which was removed in 2 steps to furnish perhydrohistrionicotoxin in 70% yield (scheme 16).



Scheme 16 Synthesis of perhydrohistrionicotoxin by Speckamp

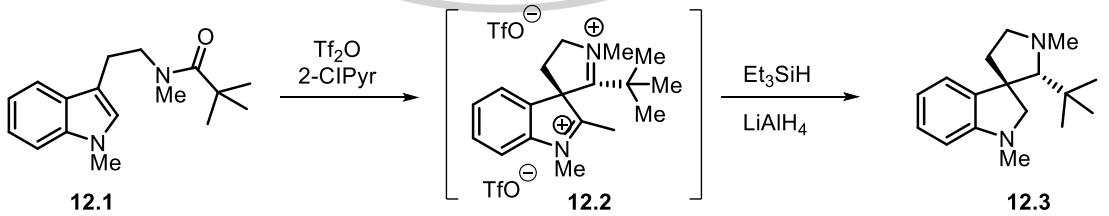
Other examples of syntheses of spirocyclic alkaloids

In 2009, Douglas and Reddy was reported synthesis (+)-horsfiline, (-)-coerulescine, and (-)-Esermthole via Pd-catalyzed intramolecular cyanoamidation. The synthesis started form *N*-boc-protected 2-bromoanilines **11.1** which was converted to oxindole **11.2** and **11.3** via Pd-catalyzed Suzuki coupling and cyanoamidation. Mesylates **11.2** and **11.3** were converted to (-)-horsfiline in 54% and 49% yield (scheme 17).[22]



Scheme 17 Synthesis of (+)-horsfiline and (+)-coerulescine

In 2013, Mohammad and coworkers reported a synthesis of spirocyclic indolines by interruption of the Bischer-Napieralski reaction. The synthesis started from tryptamines **12.1** which was converted to spirocyclic indoline in 91% (scheme 18).[23]



Scheme 18 Synthesis of spirocyclic indolines

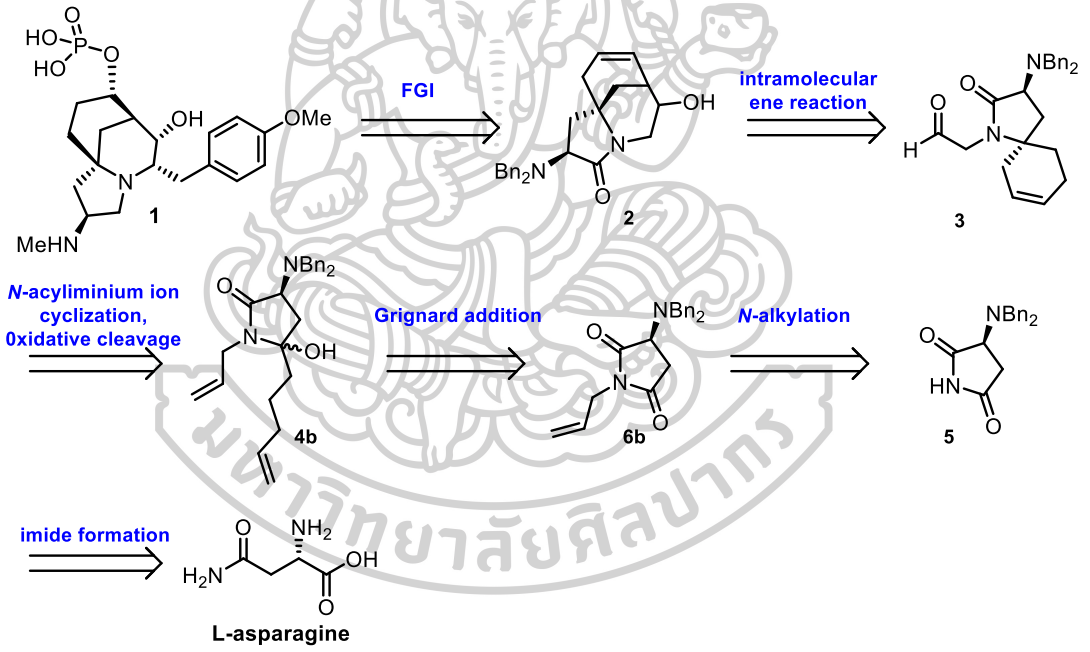
CHAPTER 3

SYNTHETIC STUDY

Part A: Synthetic studies of FR901483 route 1

Retrosynthetic analysis

The synthesis of FR901483 was envisioned that it would be derived from caged tricyclic lactam **2** via functional group interconversion. The cage tricyclic lactam **2** could be derived from spirocyclohexene-pyrrolidone **3** via intramolecular ene reaction. The spirocyclohexene-pyrrolidone **3** would be synthesized from *N*-acyliminium ion spirocyclization and oxidative cleavage of γ-pentenyl-γ-hydroxylactam **4b**. The γ-pentenyl-γ-hydroxylactam **4b** could be derived from *N*-allyl succinimide **6b** via Grignard addition. The *N*-allyl succinimide **6b** would be synthesized from *N*-alkylation and imide formation of L-asparagine (scheme 19).

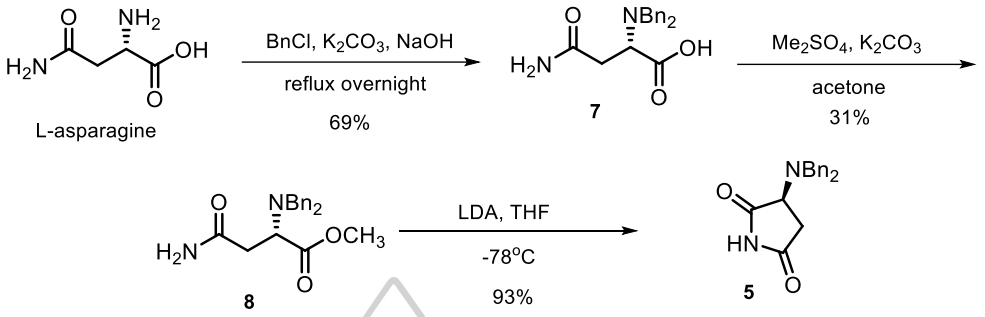


Scheme 19 Retrosynthetic analysis of FR901483 route 1

Synthetic study of FR901483 route 1

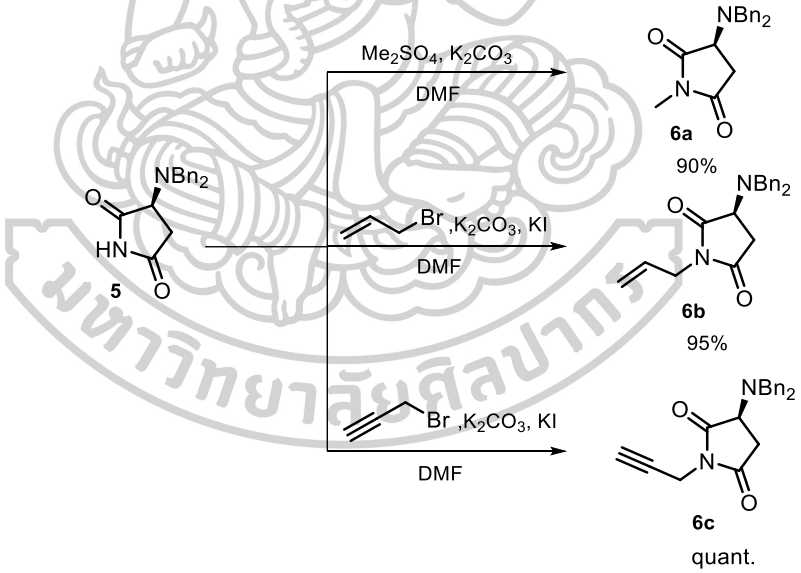
The synthetic study of FR901483 started from benzylation of commercially available L-asparagine in basic condition using benzyl chloride, NaOH and K_2CO_3 in MeOH and H_2O to give *N*,*N*-dibenzyl-L-asparagine **7** in 69% yield. The methylation of benzylated asparagine **7** in the presence of Me_2SO_4 and K_2CO_3 in acetone provided

methyl ester **8** in 29% yield. This was transformed to chiral succinimide **5** with *n*-BuLi in THF in 89% yield (scheme 20).



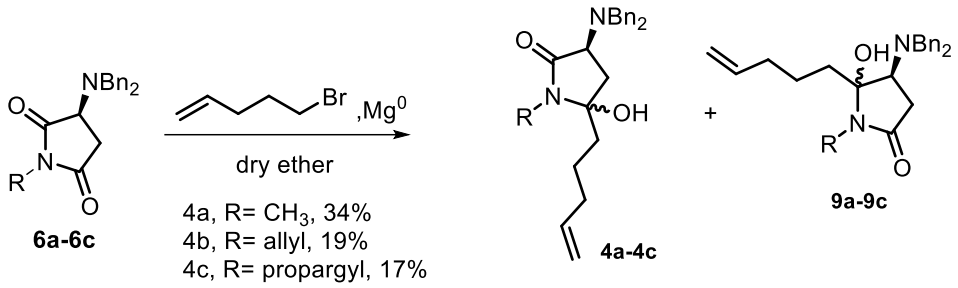
Scheme 20 Synthesis of chiral succinimide **5**

After obtaining precursor **5**, the *N*-alkylation of succinimide **5** with dimethyl sulfate (Me_2SO_4), allyl bromide and propargyl bromide afforded desired product *N*-methyl succinimide **6a**, *N*-allyl succinimide **6b** and *N*-propargyl succinimide **6c** in 90%, 95% and quantitative yield, respectively (scheme 21).



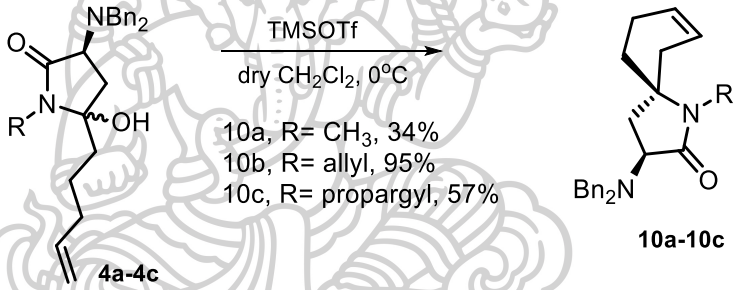
Scheme 21 Synthesis of *N*-methyl succinimide **6a**, *N*-allyl succinimide **6b** and *N*-propargyl succinimide **6C**

After that, The Grignard addition of *N*-methyl succinmide **6a**, *N*-allyl succinimide **6b** and *N*-propargyl succinimide **6c** using 5-bromo-1-pentene and Mg^0 in diethyl ether gave γ-pentenyl-γ-hydroxylactam **4a**-**4c** which is the major product and **9a**-**9c** is the minor product (scheme 22).



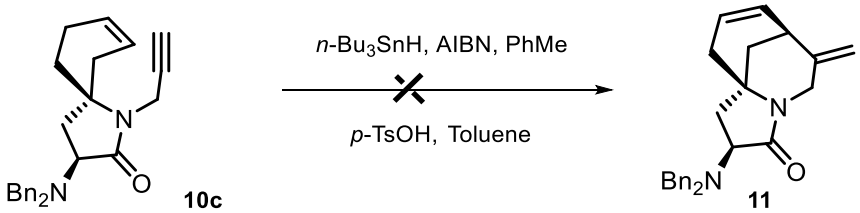
Scheme 22 Synthesis of γ-pentenyl-γ-hydroxylactam 4

The *N*-acyliminium ion spirocyclization of γ-pentenyl-γ-hydroxylactam **4a**-**4c** using trimethylsilyl trifluoromethanesulfonate (TMSOTf) gave cyclization to the γ position to give *N*-alkyl-spirocyclohexene-pyrrolidone **10a**-**10c** in moderate to good yields (scheme 23).



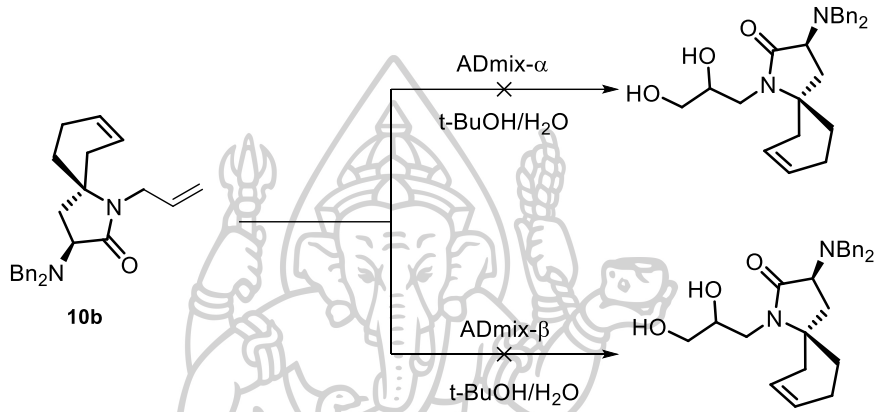
Scheme 23 Synthesis of *N*-alkyl-spirocyclohexene-pyrrolidone 10

After the *N*-alkyl-spirocyclohexene-pyrrolidones were obtained, we explored the reactions that could form the piperidine ring in the caged tricyclic system of FR901483. First, the radical cyclization of *N*-propargyl-spirocyclohexene-pyrrolidones **10c** using tributyltin hydride (*n*-Bu_3SnH) and AIBN was explored However, the complex crude product mixture was obtained and we could not prove the formation of the desired product (scheme 24).



Scheme 24 Synthesis of cage tricyclic lactam 11

Next, an intramolecular ene reaction between the cyclohexene moiety and an aldehyde would be investigated. In this regard, we wished to convert the allyl group of *N*-allyl-spirocyclohexene-pyrrolidone **10b** to aldehyde. We expected that a selective dihydroxylation of the allyl group over the cyclohexene would be possible using Sharpless Asymmetric Dihydroxylation. However, either Admix-α or Admix-β, did not yield the desired product. We suspected that the spirocyclohexene-pyrrolidone could not fit into the quinine or quinidine ligands in the Admix-α and Admix-β in the SAD reaction (scheme 25). We concluded that a new approach in which the *N*-alkyl group can be selectively converted to an aldehyde has to be developed.

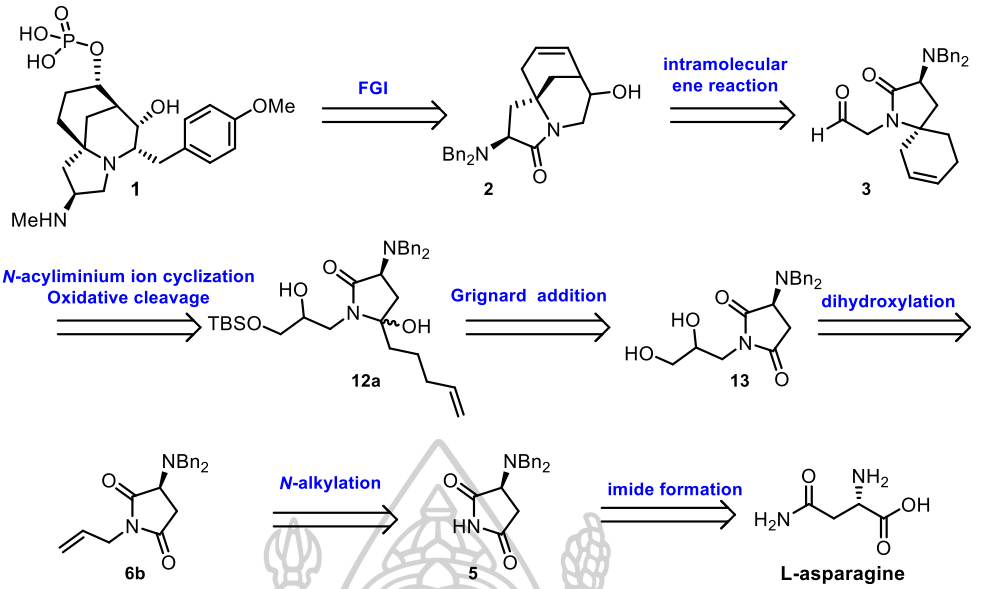


Scheme 25 Sharpless Asymmetric Dihydroxylation

Synthetic studies of FR901483 route 2

Retrosynthetic analysis

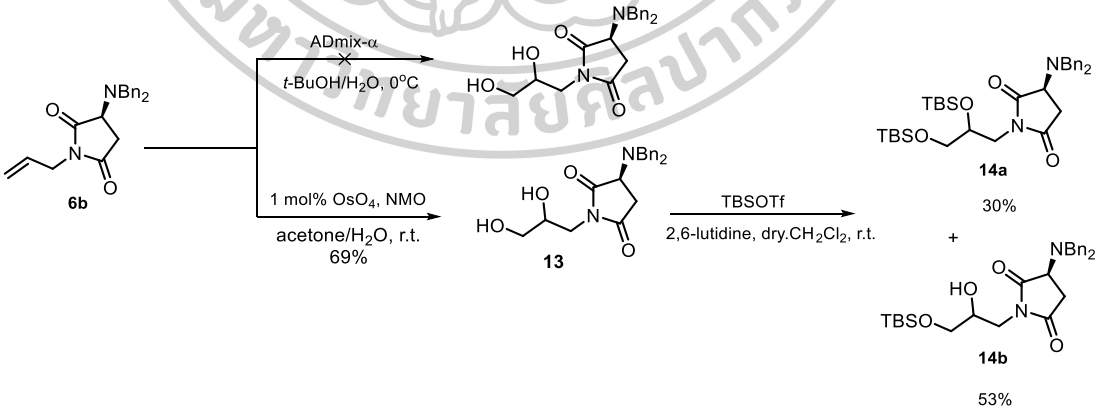
The second FR901483 synthesis study modified the reaction sequence by performing dihydroxylation of *N*-allyl succinimide before Grignard addition and spirocyclization. The synthesis of FR901483 was envisioned that it would be derived from caged tricyclic lactam **2** via functional group interconversion. The cage tricyclic lactam **2** could be derived from spirocyclohexene-pyrrolidone **3** via intramolecular ene reaction. The spirocyclohexene-pyrrolidone **3** would be synthesized from *N*-acyliminium ion spirocyclization of the γ-pentenyl-γ-hydroxylactam **12** and oxidative cleavage of the *N*-propanediol moiety. The γ-pentenyl-γ-hydroxylactam **12a** could be derived from protected *N*-(2,3-dihydroxylpropyl)-succinimide **13** via Grignard addition. The 2,3-dihydroxylpropyl)-succinimide **13** would be synthesized from dihydroxylation of *N*-allylsuccinimide **6b** (scheme 26).



Scheme 26 Retrosynthetic analysis of FR901483 route 2

Synthetic study of FR901483 route 2

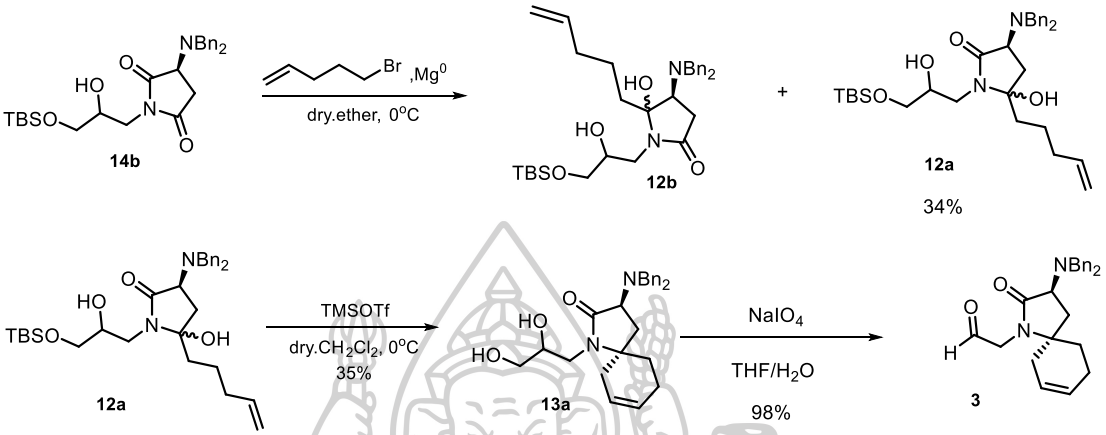
We attempted another asymmetric dihydroxylation of *N*-allyl succinimide **6b** using Admix-α at the allyl group. Disappointingly, the reaction did not proceed to give the desired diol. However, dihydroxylation with catalytic osmium tetroxide (OsO_4) and NMO converted the *N*-allyl group to *N*-(propanediol) succinimide **13** in 69% yield. The protection of dihydroxy succinimide **13** in good yield. This compound was converted to TBS-ethers **14a** and **14b** using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in 30% and 53% yield, respectively (scheme 27).



Scheme 27 Synthesis of TBS-ether compound **14a** and **14b**

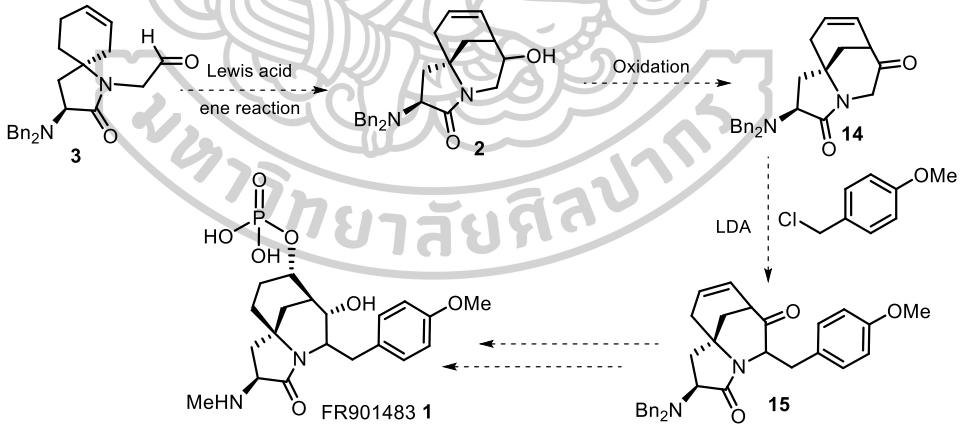
After that, Grignard addition of bisTBS-ether **14b** gave γ-pentenyl-γ-hydroxylactam **12** using 5-bromo-1-pentene and Magnesium in ether. The *N*-acyliminium ion spirocyclization of γ-pentenyl-γ-hydroxylactam **12a** with

trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided dihydroxy-spirocyclohexene-pyrrolidone **13a** in 35% yield. The TBS-silyl protecting group was concomitantly hydrolyzed in acidic condition of the spirocyclization step to give the diol. The oxidative cleavage of *N*-propanediol **13a** using sodium periodate ($NaIO_4$) provided *N*-ethanalylspirocyclohexene-pyrrolidone **3** in 98% yield (scheme 28).



Scheme 28 Synthesis of *N*-ethanalylspirocyclohexene-pyrrolidone **3**

After aldehyde **3** has been successfully synthesized, we expected that aldehyde **3** could be used to synthesize FR901483 by intramolecular ene reaction using Lewis acid to form cage tricyclic core **2**, followed by oxidation and C-alkylation with PMBCl after which functional group interconversion would lead to FR901483 (scheme 29).



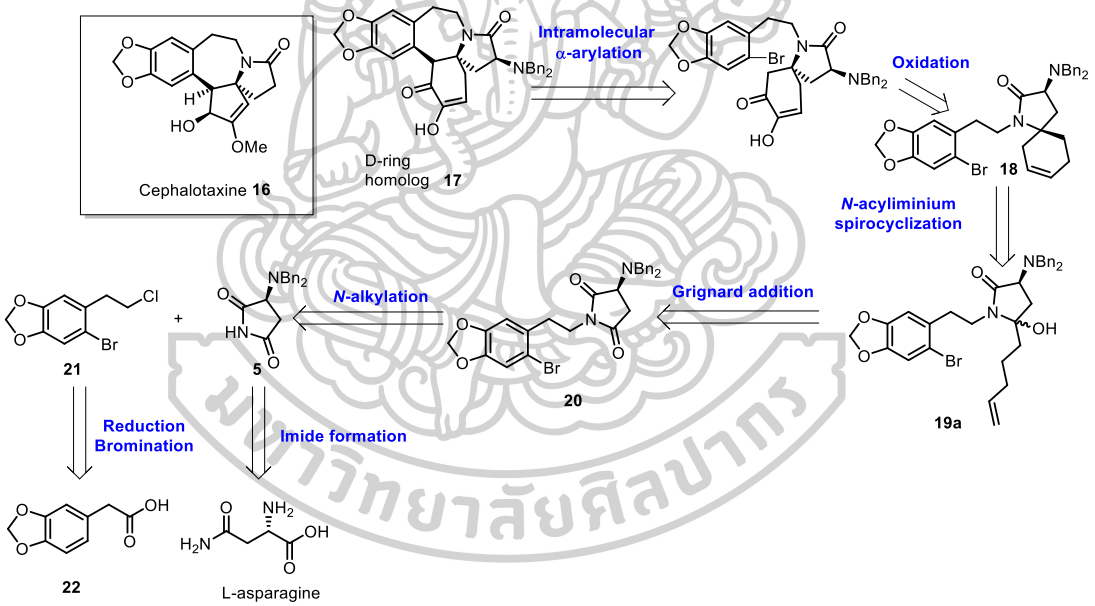
Scheme 29 Future work plan for FR901483 synthesis

Part B: Synthetic studies of D-ring homolog of Cephalotaxine

We envision that our synthetic approach for spirocyclohexene-pyrrolidone can be applied to synthesis of non-natural analogs of natural spirocyclic alkaloids for biological activity screening. In this regard, we investigate synthesis route for D-ring homolog of Cephalotaxine.

Retrosynthetic analysis

The synthesis of D-ring homolog **17** of cephalotaxine could be obtained from intramolecular α-arylation of spirocyclohexenone-pyrrolidone which is the oxidation product of spirocyclohexene-pyrrolidone **18**. This would be derived from *N*-acyliminium ion spirocyclization of γ-pentenyl-γ-hydroxylactam **19a**, which is synthesized from Grignard addition of *N*-bromohomopiperonylsuccinimide **20**. The homopiperonylsuccinimide **20** would be synthesized from succinimide **5** and 6-bromohomopiperonyl chloride **21** (scheme 30).

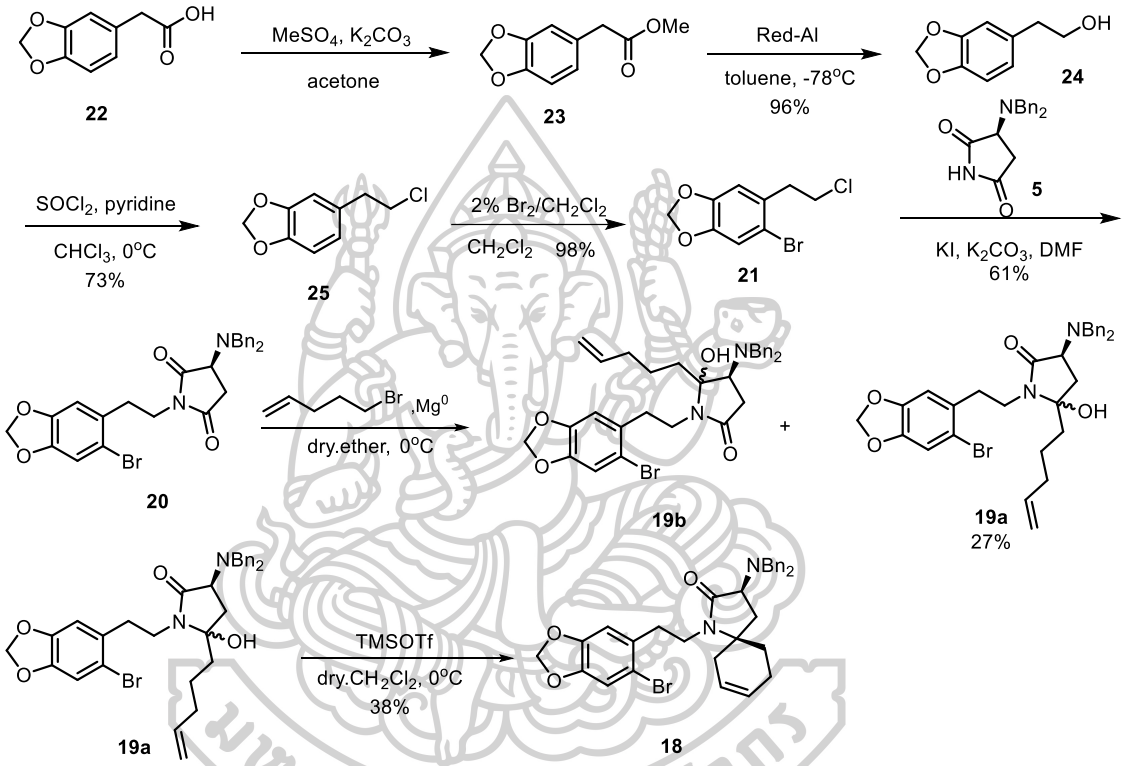


Scheme 30 Retrosynthetic analysis of D-ring homolog **17** of cephalotaxine

Synthetic study of D-ring homolog 17 of cephalotaxine

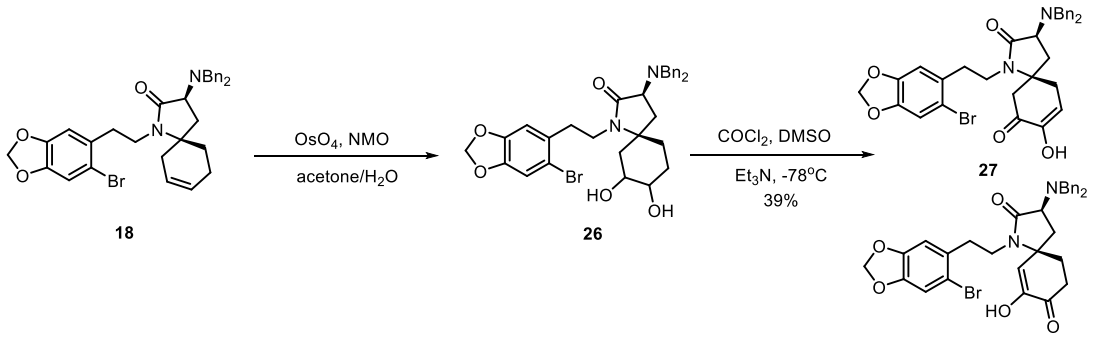
The synthetic study of D-ring homolog **17** of cephalotaxine started from methylation of commercially available homopiperonylic acid **22** in basic condition using dimethyl sulfate (Me_2SO_4) and K_2CO_3 in acetone to give methyl ester **23** in quantitative yield. Reduction of methyl ester **23** with Red-Al in toluene provided homopiperonyl alcohol **24** in 96% yield. The chlorination of homopiperonyl alcohol **24** was achieved to give homopiperonyl chloride **25** using $SOCl_2$ and pyridine in $CHCl_3$ in 73% yield. Bromination of homopipronyl chloride **25** in the presence of 2% Br_2 in

CH_2Cl_2 provided. 6-bromohomopiperonyl chloride compound **21** in 98% yield. The *N*-alkylation chiral succinimide **5** with 6-bromohomopiperonyl chloride using KI and K_2CO_3 in DMF gave *N*-bromohomopiperonylsuccinimideimide **20** in 61% yield. The Grignard addition of succinimide **20** using 5-bromo-1-pentene, Mg in diethyl ether led to γ-pentenyl-γ-hydroxylactam **19a** in 27% yield and **19b** in smaller amount. *N*-acyliminium ion spirocyclization of γ-pentenyl-γ-hydroxylactam **19a** was mediated by TMSOTf to give *N*-bromoarylethyl spirocyclohexene-pyrrolidone **18** in 38% yield (scheme 31).



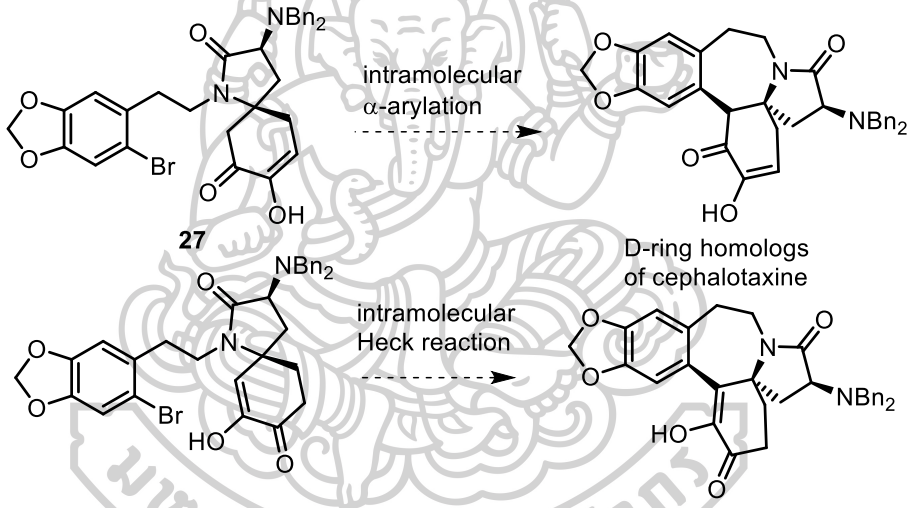
Scheme 31 Synthesis of spirocyclohexene-pyrrolidone **18**

After obtaining precursor **18**, dihydroxylation of the cyclohexene moiety in succinimide **18** with osmium tetroxide (OsO_4) and NMO afforded the desired product spirocyclohexanediol **26** and Swern oxidation of dihydroxy spirocyclohexene-pyrrolidone 26 was converted to hydroxycyclohexenone **27** as mixture of regioisomers in 39% yield (scheme 32).



Scheme 32 Synthesis of spirocyclohexenone **27**

After obtaining spirocyclohexenone **27**, We are currently investigating the formation of the aryl-cyclohexeone connection to form the azepine B ring of cephalotaxine either by intramolecular α-arylation or Heck reaction (scheme 33).



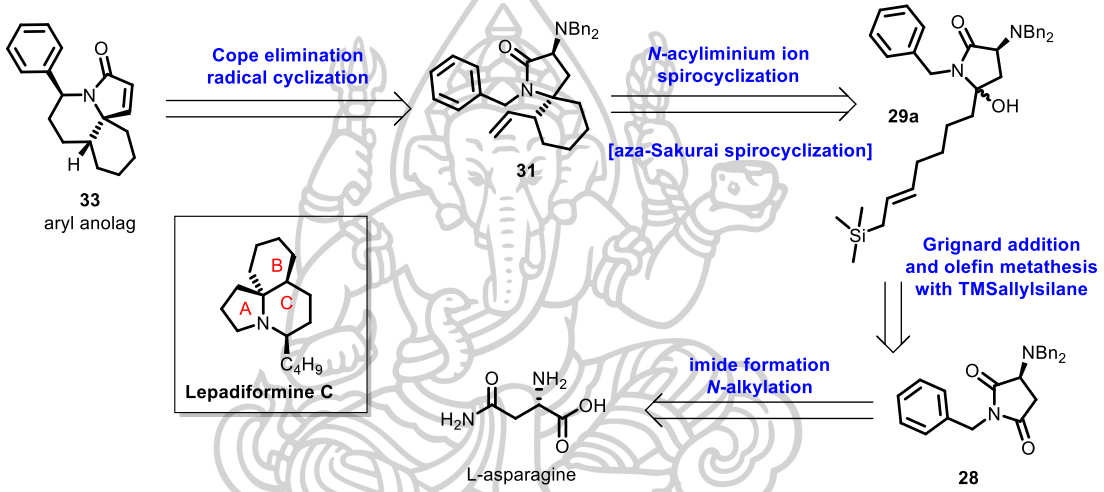
Scheme 33 Future work plan of D-ring homolog **17** of cephalotaxine

Part C: Synthetic studies of aryl analog of lepadiformine C

Lepadiformines has a piperidine ring fused with spirocyclohexane-pyrrolidine system. To apply our spirocyclization approach to lepadiformine synthesis, we need a substituent on the cyclohexane moiety on the carbon adjacent to the spirocyclic carbon. In this regard, a vinyl group is desirable since it can potentially be manipulated to form the piperidine ring with the *N*-alkyl group either by radical cyclization or ring closing metathesis. To prove this concept, we explore a synthetic study of an aryl analog of lepadiformine C.

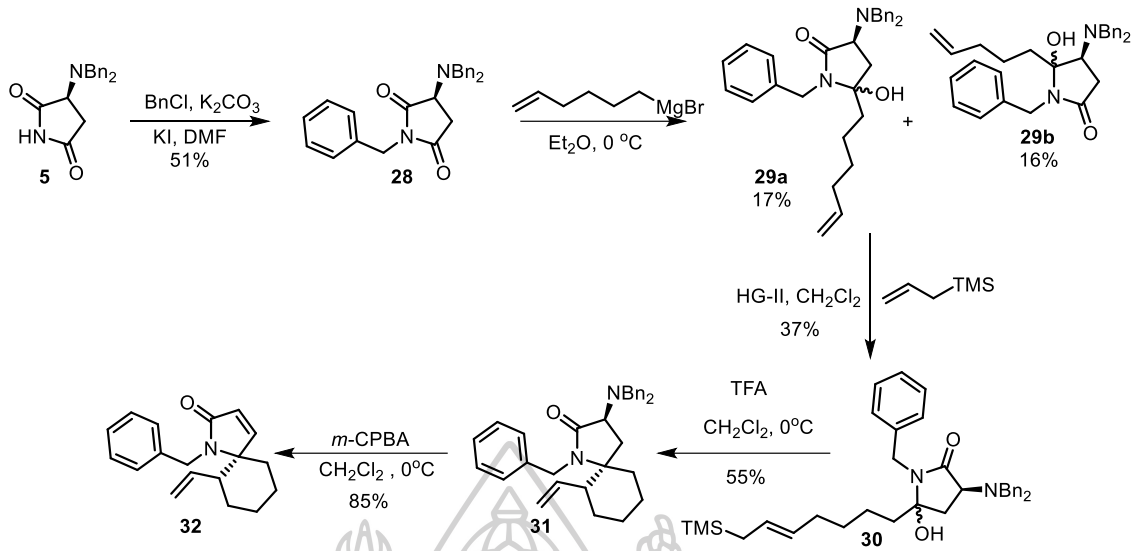
Retrosynthetic analysis

The synthesis of aryl analog **33** of lepardiformine C could be conceived from Cope elimination of the dibenzylamino group and radical cyclization to form the C-C bond between the benzylic position on the nitrogen atom of pyrrolidone ring and terminal carbon of the vinyl group on the cyclohexane ring of (3*S*,5*R*,6*S*)-1-benzyl-3-(dibenzylamino)-6-vinyl-1-azaspiro[4.5]decan-2-one **31**. The vinyl spirocyclohexane could be derived from *N*-acyliminium ion spirocyclization or aza-Sakurai spirocyclization of γ-7-trimethylsilyl-5-heptenyl-γ-hydroxylactam **29a**, which could be synthesized from Grignard addition of *N*-benzylsuccinimide **28** followed by olefin metathesis with TMS-allylsilane. The *N*-benzylsuccinimide **28** could be synthesized from L-asparagine using our procedure discussed earlier (scheme 34).



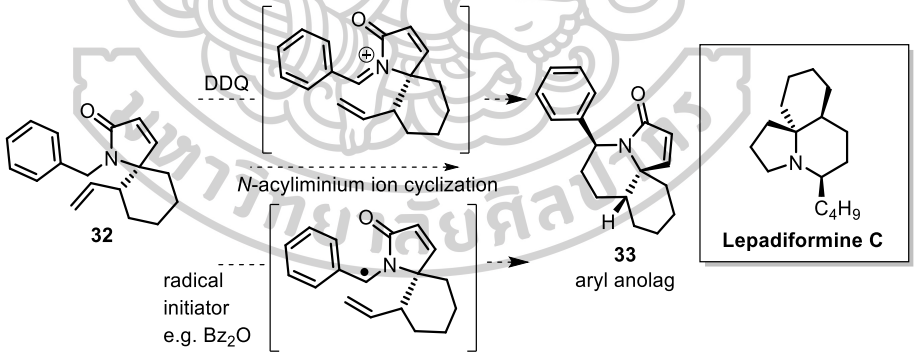
Scheme 34 Retrosynthetic analysis of aryl analog **33** of lepadiformine C

The synthetic study of aryl analog of lepadiformine C **33** started from *N*-alkylation of 3-dibenzylaminosuccinimide **5** in basic condition using BnCl and K_2CO_3 and KI in DMF to give *N*-benzylsuccinimide **28** in 55% yield. The Grignard addition of *N*-benzylsuccinimide **28** using 6-bromo-1-hexene and Mg in diethyl ether provided γ-hexenyl-γ-hydroxylactam **29a** in 17% yield and **29b** in 16% yield. g-hexenyl-g-hydroxylactam **29a** was converted to *N*-benzyl-7-(trimethylsilyl)hept-5-en-1-yl)-pyrrolidone **30** via olefin metathesis using allyl trimehylsilane and Hoveyda-Grubbs catalyst^{TM} 2nd generation in 37% yield. The *N*-acyliminium ion spirocyclization of compound **30** in aza-Sakurai fashion mediated by TFA in CH_2Cl_2 delivered (3*S*,5*R*,6*S*)-1-benzyl-3-(dibenzylamino)-6-vinyl-1-azaspiro[4.5]decan-2-one **31** in 55% yield. This spirocyclized **31** was converted to (5*R*,6*S*)-1-benzyl-6-vinyl-1-azaspiro[4.5]dec-3-en-2-one **32** via Cope elimination using *m*-CPBA in 85% yield (scheme 35).



Scheme 35 Synthesis of (5R,6S)-1-benzyl-6-vinyl-1-azaspiro[4.5]dec-3-en-2-one **32**

After obtaining (5*R*,6*S*)-1-benzyl-6-vinyl-1-azaspiro[4.5]dec-3-en-2-one **32**, We are currently investigating reactions that can form C-C bond between the benzylic position and the vinyl terminal carbon. This can conceivably be done via cationic (*N*-acyliminium ion) or radical reaction to form the aryl analog of lepadiformine C (scheme 36).



Scheme 36 Future work plan of aryl analog of lepadiformine C

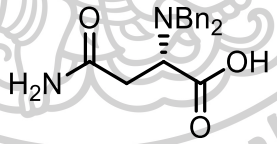
CHAPTER 4

EXPERIMENTAL PROCEDURE

General

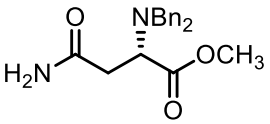
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and diethyl ether was distilled from sodium and benzophenone under argon.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

Synthesis of dibenzyl-L-asparagine (7)



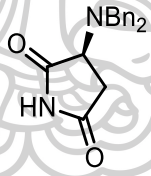
To a solution of L-asparagine (5.00 g, 33.3 mmol) in MeOH and H_2O (1:1, 100 mL) was asses NaOH (3.33 g, 83.3 mmol), K_2CO_3 (11.5 g, 83.8 mmol) and BnCl (15.46, 133 mmol). The mixture was heated to reflux at 95^{o}C overnight and acidified with 1 M HCl. Then the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (siliga gel, 2:1 hexane/EtOAc) to give dibenzyl-*L*-asparagine (7) (7.0491 g, 63%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.13 (m, 10H), 6.00 (brs, 1H), 5.37 (brs, 2H), 5.30 (s, 2H), 4.08 (d, *J* = 13.4 Hz, 2H), 4.03-3.87 (m, 3H), 3.00 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.72 (dd, *J* = 16.3, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 172.3, 135.4 (2C), 129.6 (4C), 128.9 (4C), 128.3 (2C), 59.8, 54.8 (2C), 33.4; $[\alpha]_{25}^{D}$ -48.8 (c 1.7, $CHCl_3$); ν_{max} (film) 3192, 3064, 2924, 2852, 1669, 1495, 1456, 1365, 1285, 1182 cm^{-1} ; ESI-HRMS calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$ 335.1366, found 335.1368.

Synthesis of *N*,*N*-dibenzyl methyl ester (8)



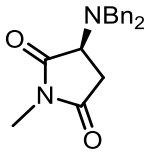
To a solution of dibenzyl-L-asparagine (**7**) (4.4751 g, 14.3 mmol) in acetone (80 mL) was added K_2CO_3 (2.97 g, 21.5 mmol) and Me_2SO_4 (2.75 mL, 28.7 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered to remove K_2CO_3 and to the solution was added dropwise sat. eq. 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, 4:1 hexane/EtOAc) to give *N*,*N*-dibenzyl methyl ester (**8**) (1.26 g, 31%) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.08; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (m, 10H), 6.16 (brs, 1H), 5.49 (brs, 1H), 3.93- 3.82 (m, 3H), 3.80 (s, 3H), 3.57 (d, *J* = 13.6 Hz, 2H), 2.68 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.61 (dd, *J* = 15.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.4, 139.0 (2C), 129.0 (4C), 128.5 (4C), 127.3 (2C), 58.3, 54.9 (2C), 51.6, 35.6; $[\alpha]_{25}^{D}$ -103.8 (c 1.6, $CHCl_3$); ν_{max} (film) 3349, 3355, 3196, 2951, 2844, 1730, 1672, 1495, 1453, 1366, 1173 cm^{-1} ; ESI-HRMS calculated for $C_{19}H_{22}N_2NaO_3$ $[M+Na]^+$ 349.1523, found 349.1520.

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



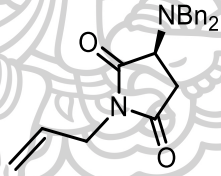
To a solution of *N*,*N*-dibenzyl methyl ester (**8**) (1.26 g, 3.86 mmol) in dry THF (20 mL) under argon atmosphere at -78ºC was added LDA (4.83 mL of 2.0 M solution, 7.72 mmol) and the mixture was stirred for 3 hours at -78ºC. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give chiral succinimide (**5**) (0.92 g, 81%) as a white crystal. R_f (2:1 hexane/EtOAc) 0.60; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.15 (m, 10H) ; 5.40-4.40 (brs, 1H) ; 3.95 (dd, *J*=8.9, 5.9 Hz, 1H) ; 3.83 (d, *J*= 13.3 Hz, 2H) ; 3.60 (d, *J*=13.5 Hz, 2H) ; 2.80 (dd, *J*=18.7, 9.1 Hz, 1H) ; 2.60 (dd, *J*=18.7, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 178.6, 176.3, 176.2, 138.3 (2C), 128.9 (4C), 128.6 (4C), 127.6 (2C), 58.8, 54.7 (2C), 33.1; $[\alpha]_{25}^{D}$ -25.4 (c 1.6, $CHCl_3$); ν_{max} (film) 3234, 2923, 2849, 1782, 1705, 1494, 1454, 1338, 1191, 1165 cm^{-1} ; ESI-HRMS calculated for $C_{18}H_{18}N_2O_2$ $[M+H]^+$ 317.1260, found 317.1260.

Synthesis of *N*-methyl succinimide (6a)



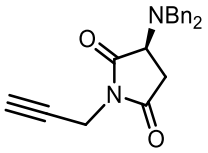
To a solution of chiral succinimide (**5**) (249.8 mg, 0.85 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added K_2CO_3 (141.0 mg, 1.02 mmol), KI (17.0 mg, 0.10 mmol) and Me_2SO_4 (0.10 mL, 1.02 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give *N*-methyl succinimide (**6a**) (235.9 mg, 90%) as a yellow crystal. R_f (4:1 hexane/EtOAc) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.20 (m, 10) ; 3.95 (dd, *J*= 8.7, 5.4 Hz, 1H) ; 3.80 (d, *J*= 13.4 Hz, 2H) ; 3.60 (d, *J*= 13.4 Hz, 2H) ; 2.95 (s, 3H) ; 2.75 (dd, *J*= 18.6, 9.0 Hz, 1H) ; 2.63 (dd, *J*= 18.3, 5.4 Hz, 1H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.2, 138.3 (2C), 128.9 (4C), 128.5 (4C), 127.4 (2C), 57.5, 54.6 (2C), 31.8, 24.3 $[\alpha]_{25}^{D}$ -5.5 (*c* 1.3, $CHCl_3$); ν_{max} (film) 3082, 3029, 2941, 2847, 1170, 1702, 1360, 1195, 1130, 698 cm^{-1}; ESI-HRMS calculated for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1598, found 309.1603.

Synthesis of *N*-allyl succinimide (6b)



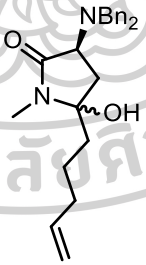
To a solution of chiral succinimide (**5**) (203.7 mg, 0.69 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (114.4 mg, 0.83 mmol), KI (14.0 mg, 0.0083 mmol) and allyl bromide (0.07 mL, 0.81 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give *N*-allyl succinimide (**6b**) (220.4 mg, 95%) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.68; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.15 (m, 10H) ; 5.75 (ddt, *J*= 16.2, 9.9, 6.0 Hz, 1H), 4.85 (d, *J*= 7.1 Hz, 2H) ; 3.92 (dd, *J*= 9, 5.6 Hz, 1H) ; 3.82 (d, *J*= 13.6 Hz, 2H) ; 3.63 (d, *J*= 13.3 Hz, 2H) ; 2.75 (dd, *J*= 18.8, 5.6 Hz, 1H) ; 2.61 (dd, *J*= 18.5, 5.4 Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 174.6, 138.2 (2C), 130.7, 129.6 (4C), 129.1 (4C), 127.4 (2C), 118.5, 57.4, 54.6 (2C), 40.6, 32.1; $[\alpha]_{25}^{D}$ -8.3 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3086, 3028, 2928, 2853, 1777, 1699, 1391, 1330, 1194, 741, 697 cm^{-1} ; ESI-HRMS calculated for $C_{21}H_{23}N_2O_2$ $[M+H]^+$ 335.1754, found 335.1759.

Synthesis of *N*-propargyl succinimide (6c)



To a solution of chiral succinimide (**5**) (222.8 mg, 0.76 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (126.0 mg, 0.91 mmol), KI (15.1 mg, 0.009 mmol) and propargyl bromide (0.14 mL, 0.91 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give *N*-propargyl succinimide (**6c**) (283.2 mg, quantitative yield) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.56 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.15 (m, 10H) ; 4.19 (d, *J*= 2.4 Hz, 2H) ; 3.90 (dd, *J*= 9.0, 5.4 Hz, 1H) ; 3.80 (d, *J*= 13.5 Hz, 2H) ; 3.61 (d, *J*= 13.5 Hz, 2H) ; 2.72 (dd, *J*= 18.8, 9.0 Hz, 1H) ; 2.57 (dd, *J*= 18.8, 5.4 Hz, 1H) ; 2.16 (t, *J*= 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 173.8, 138.1 (2C), 128.8 (4C), 128.5 (4C), 127.6 (2C), 77.0, 71.5, 57.5, 54.7, 32.4, 27.4 $[\alpha]_{25}^{D}$ -3.2 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3280, 3029, 2939, 2847, 1174, 1702, 1398, 1360, 1195, 1130, 699 cm^{-1} ; ESI-HRMS calculated for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ 333.1598, found 333.1603.

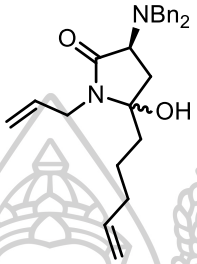
Synthesis of γ-pentenyl-γ-hydroxylactam (4a)



To a solution of magnesium (239.8 mg, 9.99 mmol) in diethyl ether (10 mL) under argon atmosphere at room temperature was added 5-bromo-1-pentene (0.40 mL, 3.34 mmol) and was added *N*-methyl succinimide (**6a**) (343.3 mg, 1.11 mmol) at 0^{o}C and the mixture was stirred for 3 hours. The mixture was filtered to remove magnesium and to the spolution was added dropwise sat. aq. NH_4Cl (10 mL). Then mixture was extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4:1 hexane:EtOAc) to give γ-pentenyl-γ-hydroxylactam (**4a**) (120.2 mg, 34%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.14 (m, 10H), 5.74 (dddd, *J*= 17.1, 10.4, 6.9 Hz, 1H), 5.10-4.89 (m, 2H), 3.89 (d, *J*= 13.8 Hz, 2H), 3.70 (d, *J*= 13.8 Hz, 2H), 3.61-3.44 (m, 1H), 2.69 (s, 3H), 2.11-1.84 (m, 3H), 1.70

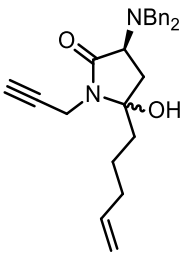
(td, J= 10.1, 5.4 Hz, 1H), 1.61-1.42 (m, 1H), 1.31-1.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 139.4 (2C), 137.8, 128.8 (4C), 128.6 (4C), 127.0 (2C), 115.3, 88.8, 59.3, 54.8 (2C), 37.1, 36.9, 33.3, 23.6, 22.8; $[\alpha]_{25}^{D}$ -17.3 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3392, 2935, 1664, 1477, 1230, 1036, 699 cm^{-1} ; ESI-HRMS calculated for $C_{24}H_{31}N_2O_2$ $[M+H]^+$ 379.2380, found 379.2386.

Synthesis of γ-pentenyl-γ-hydroxylactam (4b)



To a solution of magnesium (192.9 mg, 8.04 mmol) in diethyl ether (10 mL) under argon atmosphere at room temperature was added 5-bromo-1-pentene (0.32 mL, 2.68 mmol) and was added *N*-allyl succinimide (**6b**) (328.2 mg, 0.89 mmol) at 0ºC and the mixture was stirred for 3 hours. The mixture was filtered to remove magnesium and to the solution was added dropwise sat. aq. NH_4Cl (10 mL). Then mixture was extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4:1 hexane:EtOAc) to give γ-pentenyl-γ-hydroxylactam (**4b**) (84.2 mg, 19%) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 5.90-5.55 (m, 2H), 5.30-4.85 (m, 4H), 3.91 (d, *J*= 14.1 Hz, 2H), 3.73 (d, *J*= 14.1 2H), 3.60-3.45 (m, 1H), 2.40-2.25 (m, 1H), 2.05-1.90 (m, 3H), 1.80-1.70 (m, 1H), 1.55-1.35 (m, 1H), 1.30-1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 139.4 (2C), 137.8, 128.8 (4C), 128.6 (4C), 127.0 (2C), 115.3, 88.8, 59.3, 54.8 (2C), 37.1, 36.9, 33.3, 23.6, 22.8; $[\alpha]_{25}^{D}$ -17.3 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3392, 2924, 1667, 1452, 1267, 1075, 697 cm^{-1}

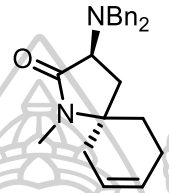
Synthesis of γ-pentenyl-γ-hydroxylactam (4c)



To a solution of magnesium (145.4 mg, 5.99 mmol) in diethyl ether (10 mL) under argon atmosphere at room temperature was added 5-bromo-1-pentene (0.25 mL, 2.14 mmol) and was added *N*-propargyl succinimide (**6c**) (284.2 mg, 0.86 mmol) at 0ºC and the mixture was stirred for 3 hours. The mixture was filtered to remove magnesium

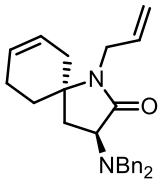
and to the solution was added dropwise sat. aq. NH_4Cl (10 mL). Then mixture was extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4:1 hexane:EtOAc) to give γ-pentenyl-γ-hydroxylactam (**4a**) (59.0 mg, 17%) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H) ; 5.85-5.60 (m, 1H) ; 5.10-4.80 (m, 2H) ; 4.30-4.15 (m, 1H) ; 4.05-3.80 (m, 2H) ; 3.80-3.65 (m, 2H) ; 3.65-3.50 (m, 1H) ; 2.70-2.25 (m, 2H) ; 2.20-2.10 (m, 1H) ; 2.10-1.50 (m, 6H)

Synthesis of *N*-methyl spirocyclohexene-pyrrolidone (10a)



To a solution of γ-pentenyl-γ-hydroxylactam **4a** (40.7 mg, 0.11 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0°C was added TMSOTf (0.05 mL, 0.27 mmol) and the mixture was stirred for 3 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 *N*-methyl spirocyclohexene-pyrrolidone (**10a**) (19.0 mg, 34%) as yellow oils. R_f (4:1 hexane/EtOAc) 0.54; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J*= 6.4 Hz, 2H), 7.39-7.08 (m, 6H), 5.66 (d, *J*= 10.2 Hz, 1H), 5.52 (dt, *J*= 10.2, 1.8 Hz), 4.05 (d, *J*= 13.5 Hz, 2H), 3.89-3.70 (m, 3H), 2.75 (s, 3H), 2.28-2.14 (m, 4H), 2.00-1.82 (m, 1H), 1.74-1.54 (m, 1H), 1.43 (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 140.0 (2C), 128.6, 128.4 (4C), 128.2 (4C), 126.9 (2C), 125.2, 59.7, 54.8 (2C), 32.9, 32.2, 32.1, 29.7, 23.3, 22.1; $[\alpha]_{25}^{D}$ +6.8 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3084, 3029, 2939, 2847, 1774, 1702, 1398, 1360, 1195, 1130 cm^{-1} ; ESI-HRMS calculated for $C_{24}H_{29}N_2O$ $[M+H]^+$ 361.2274, found 361.2281.

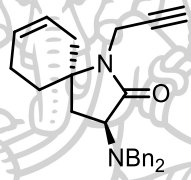
Synthesis of *N*-allyl spirocyclohexene-pyrrolidone (10b)



To a solution of γ-pentenyl-γ-hydroxylactam (**4b**) (70.7 mg, 0.15 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0°C was added TMSOTf (0.07 mL, 0.36 mmol) and the mixture was stirred for 3 hours at 0°C to room temperature. To this

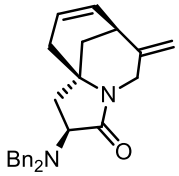
mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative column chromatography (silica gel, hexane/EtOAc) to give *N*-allyl spirocyclohexene-pyrrolidone (**10b**) (17.8 mg, 32%) as yellow oils. R_f (4:1 hexane/EtOAc) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J*= 7.1 Hz, 4H), 7.40-7.15 (m, 6H), 5.82 (dddd, *J*= 17.1, 10.2, 7.2, 6.8 Hz, 1H), 5.77 (d, *J*=10.1 Hz, 1H), 5.60 (dt, *J*= 10.1, 2.0 Hz, 1H), 5.17 (d, *J*= 17.1 Hz, 1H), 4.10-3.93 (m, 3H), 3.98-3.59 (m, 4H), 2.30-2.10 (m, 3H), 1.91-1.79 (m, 1H), 1.78-1.58 (m, 3H), 1.50 (d, J= 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 139.9 (2C),134.8, 129.4, 128.5 (4C), 128.3 (4C), 126.9 (2C), 124.8, 116.4, 59.0, 58.1, 54.5, 50.8, 41.9, 33.9, 33.6, 33.3, 23.2; $[\alpha]_{25}^{D}$ -6.4 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3084, 3029, 2939, 2847, 1689, 1362, 1195, 1130, 698 cm^{-1} ; ESI-HRMS calculated for $C_{26}H_{31}N_2O$ $[M+H]^+$ 387.2431, found 387.2436.

Synthesis of *N*-propargyl spirocyclohexene-pyrrolidone 10c



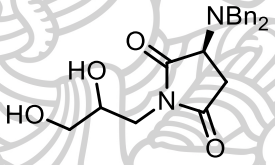
To a solution of γ-pentenyl-γ-hydroxylactam (**4c**) (199.9 mg, 0.50 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0°C was added TMSOTf (0.23 mL, 1.24 mmol) and the mixture was stirred for 3 hours at 0°C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the 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, hexane/EtOAc) to give *N*-propargyl spirocyclohexene-pyrrolidone (**10c**) (108.9 mg, 57%) as yellow oils. R_f (4:1 hexane/EtOAc) 0.44; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 5.75-5.60 (m, 1H), 5.60-5.49 (m, 1H), 4.05-3.91 (m, 3H), 3.85-3.63 (m, 4H), 2.44 (d, *J*=18.5 Hz, 1H), 2.30-2.18 (m, 4H), 2.15 (t, *J*= 2.4 Hz, 1H), 1.80-1.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 139.8 (2C), 128.8 (4C), 128.4(4C), 126.9 (2C), 126.4, 124.7, 80.0, 70.7, 59.1, 58.0, 54.6, 53.4, 33.8, 33.5, 32.8, 27.8, 23.1; $[\alpha]_{25}^{D}$ -31.7 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3270, 3042, 3020, 2938, 2847, 1688, 1360, 1195, 1131, 698 cm^{-1} ; ESI-HRMS calculated for $C_{26}H_{29}N_2O$ $[M+H]^+$ 385.2274, found 385.2275.

Synthesis of tricyclic core (11)



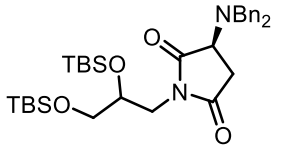
To a solution of *n*-Bu_3SnH (0.05 mL, 0.001 mmol) and AIBN (0.01 mL, 0.002 mmol) in toluene (1 mL) under argon atmosphere at room temperature was added *N*-propargyl spirocyclohexene-pyrrolidone **10c** (25.6 mg, 0.066 mmol) and the mixture was heated to reflux at 90°C 1 hour. The solution was concentrated under reduced pressure and added CH_2Cl_2 and *p*-TsOH the mixture stirred 30 minutes at room temperature. The mixture was added 5% NaOH and stirred 30 minutes. The extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give tricyclic core (**11**) as a colorless oil.

Synthesis of (3*S*)-3-(dibenzylamino)-1-(2,3-dihydroxypropyl)pyrrolidine-2,5-dione (13)

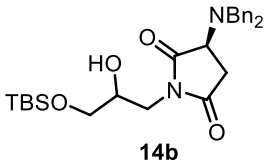


To a solution of *N*-allyl succinimide (**6a**) (313.4 mg, 0.94 mmol) in acetone: H_2O (7:3 mL) at room temperature was added 4-methylmorpholine N-oxide (NMO) (0.10 mL, 0.93 mmol) and was added Osmium tetroxide (OsO_4) (0.05 mL, 0.086 mmol) the mixture was stirred for 3 hours. To the mixture was added sat. aq. $Na_2S_2O_3$ and stirred 1 hours. To this mixture was extracted with EtOAc (3 × 10 mL) and extracted with brine (1 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative column chromatography (silica gel, 1:2 hexane/EtOAc) to give (3*S*)-3-(dibenzylamino)-1-(2,3-dihydroxypropyl)pyrrolidine-2,5-dione (**13**) (216.5 mg, 69%) as yellow oils. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H); 4.00-3.90 (m, 1H) ; 3.79 (d, *J*= 13.6 Hz, 2H) ; 3.70-3.30 (m, 4H) ; 2.80-2.65 (m ,1H) ; 2.65-2.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 176.3, 138.2 (2C), 128.8 (4C), 128.4(4C), 127.5 (2C), 69.5, 64.0, 57.5, 54.7, 43.1, 41.0, 31.9

Synthesis of (3*S*)-1-(2,3-bis((*tert*-butyldimethylsilyl)oxy)propyl)-3-(dibenzylamino)pyrrolidine-2,5-dionedione (14a) and (3*S*)-1-(3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxypropyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (14b)



14a



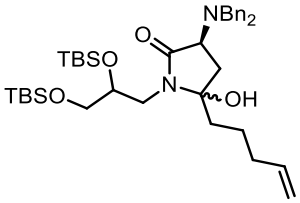
14b

To a solution of (3*S*)-3-(dibenzylamino)-1-(2,3-dihydroxypropyl)pyrrolidine-2,5-dione (**13**) (228.0 mg, 0.62 mmol) in CH_2Cl_2 (6 mL) under argon atmosphere at room temperature was added 2,6-lutidine (0.16mL, 1.36 mmol) and was added TBSOTf (0.32 mL, 1.36 mmol) the mixture was stirred for 30 minutes. To the mixture was added sat. aq. $NaHCO_3$. To this 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 column chromatography (silica gel, 10:1 hexane/EtOAc) to give **(**3*S*)-1-(2,3-bis((*tert*-butyldimethylsilyl)oxy)propyl)-3-(dibenzylamino)pyrrolidine-2,5-dionedione (**14a**) (111.2 mg, 30%) and (3*S*)-1-(3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxypropyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (**14b**) (159.2 mg, 53%) as colorless oils.

(3*S*)-1-(2,3-bis((*tert*-butyldimethylsilyl)oxy)propyl)-3(dibenzylamino)pyrrolidine-2,5-dionedione (**14a**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 4.00-3.90 (m, 2H), 3.82 (d, *J*= 13.8 Hz, 2H), 3.60 (d, *J*= 12.0 Hz, 4H), 3.52-3.35 (m, 2H), 2.70 (dd, *J*= 18.1, 8.9 Hz, 1H), 2.65-2.50 (m, 1H), 0.90 (s, 9H), 0.81 (s, 9H), 0.02 (s, 6H), -0.01 (s, 6H)

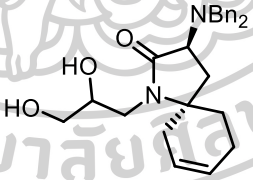
(3*S*)-1-(3-((*tert*-butyldimethylsilyl)oxy)-2-hydroxypropyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (14b); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.15 (m, 10H), 3.97 (dd, *J*= 8.7, 4.9 Hz, 1H), 3.90-3.75 (m, 2H), 3.75-3.60 (m, 1H), 3.60-3.45 (m, 2H), 2.79 (dd, *J*= 18.5, 9.2 Hz, 2H), 2.70-2.50 (m, 2H) ; 0.91 (s, 9H), 0.075 (s, 6H)

Synthesis of (3*S*)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-3-(dibenzylamino)-5-hydroxy-5-(pent-4-en-1-yl)pyrrolidin-2-one (12a)



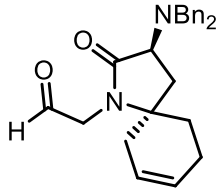
To a solution of magnesium (40.0 mg, 1.69 mmol) in diethyl ether (5 mL) under argon atmosphere at room temperature was added 5-bromo-1-pentene (0.03 mL, 0.188 mmol) and was added (3*S*)-1-(2,3-bis((*tert*-butyldimethylsilyl)oxy)propyl)-3-(dibenzylamino)pyrrolidine-2,5-dionedione (**14a**) (37.5 mg, 0.063 mmol) at 0^{o}C and the mixture was stirred for 3 hours. The mixture was filtered to remove magnesium and to the solution was added dropwise sat. aq. NH_4Cl (mL). Then mixture was extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 6:1 hexane:EtOAc) to give (3*S*)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-3-(dibenzylamino)-5-hydroxy-5-(pent-4-en-1-yl)pyrrolidin-2-one (**12a**) (14.1 mg, 34%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 5.90-5.60 (m, 1H), 5.10-4.80 (m, 2H), 4.10-3.20 (m, 7H), 2.75-2.55 (m, 1H), 2.55-2.40 (m, 1H), 2.20-1.10 (m, 6H), 0.89 (s, 9H), 0.85 (s, 9H), 0.4 (s, 6H), 0.1 (s, 6H)

Synthesis of *N*-(2,3-dihydroxy-propyl)spirocyclohexene-dibenzylamin-opyrrolidone (13a)



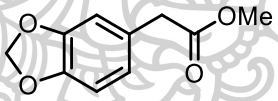
To a solution of (3*S*)-1-(2,3-bis((tert-butyldimethylsilyl)oxy)propyl)-3-(dibenzylamino)-5-hydroxy-5-(pent-4-en-1-yl)pyrrolidin-2-one (**12a**) (14.1 mg, 0.002 mmol) in dry CH_2Cl_2 (1 mL) under argon atmosphere at 0^{o}C was added TMSOTf (0.01 mL, 0.0053 mmol) and the mixture was stirred for 3 hours at 0^{o}C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (3 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative column chromatography (silica gel, 1:2 hexane/EtOAc) to give *N*-(2,3-dihydroxy-propyl)spirocyclohexene-dibenzylaminopyrrolidone (**13a**) (3.1 mg, 35%) as yellow oils. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 5.70-5.60 (m, 1H), 5.60-5.45 (m, 2H), 4.10-3.40 (m, 7H), 2.80-1.30 (m, 12H)

Synthesis of 2-((3*S*)-3-(dibenzylamino)-2-oxo-1-azaspiro[4.5]dec-7-en-1-yl)acetaldehyde (3)



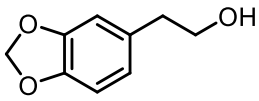
To a solution of dihydroxy spirocyclohexene-oyrrolidone (**13a**) (49.0 mg, 0.012 mmol) in THF : H_2O (3:3 mL) room temperature was added $NaIO_4$ (50.0 mg, 0.024 mmol) and the mixture was stirred for 1 hour. To this mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give (44.0 mg, 98%) as yellow oils. R_f (1:2 hexane/EtOAc) 0.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, J= 6.3 Hz, 1H), 7.50-7.10 (m, 10H), 5.55-5.45 (m, 1H), 5.70-5.60 (m, 1H), 4.35 (s, 2H), 4.20-4.10 (m, 1H), 4.10-4.00 (m, 1H), 4.00-3.90 (m, 2H), 3.90-3.80 (m, 2H), 2.30-2.15 (m, 1H), 2.05-1.95 (m, 2H), 1.90-1.70 (m, 2H), 1.70-1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 176.5, 138.15 (2C), 128.5 (4C), 124.2, 58.0, 54.7, 47.8, 32.2, 29.7, 23.0; (*c* 1.6, $CHCl_3$); ν_{max} (film) 2923, 1703, 1409, 1265, 1073, 733, 697 cm^{-1}

Synthesis of homo piperonyl methyl ester (23)



To a solution of homo piperonylic acid (**22**) (1.088 g, 6.04 mmol) in acetone (50 mL) was added K_2CO_3 (1.2522 g, 9.06 mmol) and Me_2SO_4 (1.15 mL, 12.1 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. eq. 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 product was obtained without purification to give homo piperonyl methyl ester (**23**) (2.5032, quantitative yield) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.83

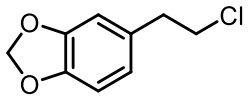
Synthesis of homo piperonyl alcohol (24)



To a solution of homo piperonyl methyl ester (**23**) (3.59 g, 18.5 mmol) in toluene (20 mL) under argon atmosphere at -78^{o}C was added Red-Al (8.50 mL, 27.7 mmol) and the mixture was stirred at -78^{o}C 2 hours. The mixture was added dropwise

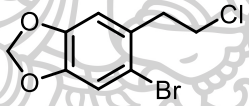
sat. eq. $NaHCO_3$ (30 mL). Then the mixture was extracted with EtOAc (3 × 50 mL) dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The product was obtained without purification to give homo piperonyl alcohol (**24**) (2.9135 g, 96%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ δ 6.73-6.60 (m, 3H), 5.92 (s, 2H), 3.79 (t, *J*= 6.5 Hz, 2H), 2.77 (t, *J*= 6.5 Hz, 2H), 1.92 (brs, 1H)

Synthesis of homo piperonyl chloride (25)



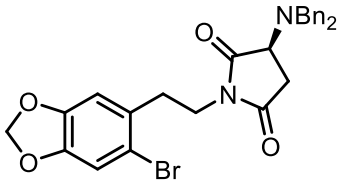
To a solution of homo piperonyl alcohol (**24**) (2.9135 g, 17.8 mmol) in $CHCl_3$ (20 mL) under argon atmosphere at 0^{o}C was added pyridine (1.50 mL, 17.8 mmol) and was added $SOCl_2$ (1.70 mL, 21.3 mmol) the mixture was stirred at 0^{o}C overnight and acidified with 5 M HCl. Then the mixture was extracted with CH_2Cl_2 (3 × 20 mL), extracted with H_2O (3 × 20 mL) and extracted with 10% Na_2CO_3 (100 mL) dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The crude product was purified by preparative column chromatography (silica gel, 4:1 hexane/EtOAc) to give homo piperonyl chloride (**25**) (2.3937 g, 73%) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73-6.60 (m, 3H), 5.92 (s, 2H), 3.79 (t, *J*= 7.4 Hz, 2H), 2.77 (t, *J*= 7.4 Hz, 2H)

Synthesis of 2-bromo-homo piperonyl chloride (21)



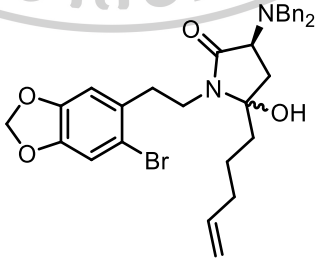
To a solution of homo piperonyl chloride (0.9605 g, 5.25 mmol) in CH_2Cl_2 (20 mL) at room temperature was added 2% Br_2/CH_2Cl_2 (20 mL). The mixture was stirred at room temperature at overnight. To this mixture was concentrated under reduced pressure. The product was obtained without purification to give 2-bromo homo piperonyl chloride (**21**) (1.3416 g, 98%) as a colorless oil. R_f (4:1, hexane/EtOAc) 0.80; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.76 (s, 1H), 5.95 (s, 2H), 3.65 (t, *J*= 7.4 Hz, 2H), 2.95 (t, *J*= 7.4 Hz, 2H).

Synthesis of *N*-bromoarylethyl-3-dibenzylamino succinimide (20)



To a solution of chiral succinimide (**5**) (450.0 mg, 1.53 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added K_2CO_3 (422.9 mg, 3.06 mmol), KI (30.5 mg, 0.0.18 mmol) and 2-bromo homo piperonyl chloride (**21**) (484.0 mg, 1.84 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4:1 hexane:EtOAc) to give *N*-bromoarylethyl-3-dibenzylamino succinimide (**20**) (272.1 mg, 61%) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.20 (m, 10H), 6.88 (s, 1H), 6.71 (s, 1H), 3.91-3.80 (m, 2H), 3.82 (s, 3H), 3.81-3.74 (m, 1H), 3.73 (s, 3H), 3.70 (d, *J*= 13.5 Hz, 1H), 3.52 (d, *J*= 13.5 Hz, 2H), 3.10-2.85 (m, 2H), 2.71 (dd, *J*= 18.6, 9.6 Hz, 1H), 2.60 (dd, *J*= 18.6, 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 175.1, 147.4 (2C), 138.4 (2C), 130.1, 128.5 (4C), 128.2 (4C), 127.5 (2C), 114.9, 112.8, 110.4, 101.8, 57.5, 54.5 (2C), 38.1, 33.7, 31.9; $[\alpha]_{25}^{D}$ +40.9 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3061, 3028, 2922, 1700, 1477, 1396, 1231, 1035, 736, 698 cm^{-1} ; ESI-HRMS calculated for $C_{22}H_{24}N_2NaO_2$ $[M+H]^+$ 371.1730, found 371.1725.

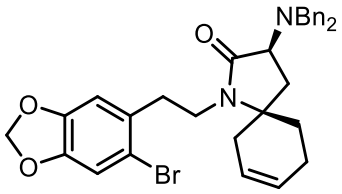
Synthesis of γ-pentenyl-γ-hydroxylactam 19a



To a solution of magnesium (51.2 mg, 2.11 mmol) in diethyl ether (5 mL) under argon atmosphere at room temperature was added 5-bromo-1-pentene (0.08 mL, 0.70 mmol) and was added *N*-bromoarylethyl-3-dibenzylamino succinimide (**20**) (121.9 mg, 0.23 mmol) at 0^{o}C and the mixture was stirred for 3 hours. The mixture was filtered to remove magnesium and to the spolution was added dropwise sat. aq. NH_4Cl (mL). Then mixture was extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was carried on to next step

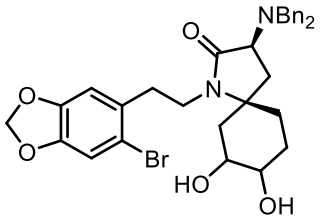
without purification give γ-pentenyl-γ-hydroxylactam (**19a**) (35.9 mg, 27%) as a colorless oil.

Synthesis of *N*-bromoarylethylspirocyclohexene-pyrrolidone (18).



To a solution of g-pentenyl-g-hydroxylactam (**19a**) (37.3 mg, 0.066 mmol) in dry CH_2Cl_2 (2 mL) under argon atmosphere at 0°C was added TMSOTf (0.03 mL, 0.17 mmol) and the mixture was stirred for 3 hours at 0°C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (3 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-bromoarylethylspirocyclohexene-pyrrolidone (**18**) 2.9 mg, 38%) as yellow oils. R_f (4:1 hexane/EtOAc) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J*= 7.1 Hz, 4H), 7.40-7.20 (m, 6H), 6.96 (s, 1H), 6.84 (s, 1H), 5.96 (s, 1H), 5.84 (s, 1H), 5.75-5.60 (m, 1H), 5.58-5.44 (m, 1H), 4.01 (d, *J*= 13.9 Hz, 2H), 3.82-3.61 (m, 3H), 3.43 (dd, *J*= 7.0, 4.7 Hz, 1H), 3.20-3.05 (m, 1H), 3.04-2.92 (m, 2H), 2.30-2.10 (m, 4H), 2.08-1.90 (m, 1H), 1.75-1.58 (m, 2H), 1.35 (d, *J*= 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 145.5, 138.3 (2C), 130, 126.6 (4C), 125.5 (4C), 125.2 (2C), 124.8, 123.1, 112.8, 110.9, 109.2, 100.0, 57.2, 56.4, 52.9 (2C), 38.2, 34.0, 32.2, 31.7, 31.3, 21.6; $[\alpha]_{25}^{D}$ +15.0 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3060, 3027, 2925, 2844, 1680, 1476, 1229, 1128, 1036, 734, 698 cm^{-1} ; ESI-HRMS calculated for $C_{32}H_{34}BrN_2O_3$ $[M+H]^+$ 573.1747, found 573.1752.

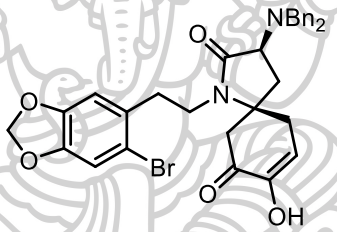
Synthesis of (3*S*,5*R*)-1-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)-3-(dibenzylamino)-7,8-dihydroxy-1-azaspiro[4.5]decan-2-one (26)



To a solution of *N*-bromoarylethylspirocyclohexene-pyrrolidone (**18**) (239.4 mg, 0.42 mmol) in acetone: H_2O (7:3 mL) at room temperature was added 4-methylmorpholine N-oxide (NMO) (0.05 mL, 0.46 mmol) and was added Osmium tetroxide (OsO_4) (0.02 mL, 0.0042 mmol) the mixture was stirred for 3 hours. To the

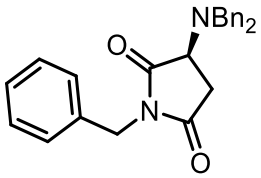
mixture was added sat. aq. $Na_2S_2O_3$ and stirred 1 hour. To this mixture was extracted with EtOAc (3 × 10 mL) and extracted with brine (1 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative column chromatography (silica gel, 2:1 hexane/EtOAc) to give (3*S*,5*R*)-1-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)-3-(dibenzylamino)-7,8-dihydroxy-1-azaspiro[4.5]decan-2-one (**26**) (56.4 mg) as yellow oils. R_f (1:1 hexane/EtOAc) 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J*= 7.1 Hz, 4H), 7.40-7.20 (m, 6H), 6.95 (s, 1H), 6.83 (s, 1H), 5.90 (d, *J*= 13.4 Hz, 2H), 4.00-3.85 (m, 3H), 3.65 (d, *J*= 13.5 Hz, 4H), 3.50-3.30 (m, 1H), 3.20-3.05 (m, 1H), 2.96-2.91 (m, 2H), 2.30-2.10 (m, 2H), 1.95-1.70 (m, 3H), 1.65-1.50 (m, 1H) 1.35-1.15 (m, 2H), 1.15-1.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 150.0 (2C), 145.9, 138.1, 126.8 (4C), 126.7 (4C), 125.4 (2C), 113.0, 111.0, 109.3, 100.4, 68.0, 65.8, 59.2, 56.9, 52.9, 38.3, 34.6, 34.2, 32.0, 28.0, 23.6; $[\alpha]_{25}^{D}$ +7.96

Synthesis of (3*S*,5*R*)-1-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)-3-(dibenzylamino)-8-hydroxy-1-azaspiro[4.5]dec-8-ene-2,7-dione (27)



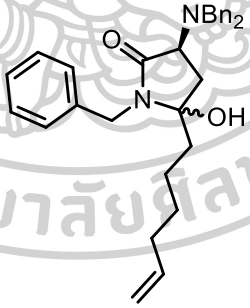
To a solution of COCl2 (0.03 mL, 0.35 mmol) in CH_2Cl_2 (5 mL) at -78ºC was added DMSO (0.05 mL, 0.70 mmol) the mixture stirred 30 min and was added diol (**26**) in CH_2Cl_2 (31.0 mg, 0.051 mmol) the mixture stirred 1 hour. The mixture was added Et_3N (0.15 mL, 1.08 mmol) and stirred 45 minutes at room temperature. The mixture was added H2O and extracted with CH2Cl2 ((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 (3*S*,5*R*)-1-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)-3-(dibenzylamino)-8-hydroxy-1-azaspiro[4.5]dec-8-ene-2,7-dione (**27**) (11.9, 39%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.15 (m, 10H), 6.98 (s, 1H), 6.85 (s, 1H), 5.90 (d, *J*= 15.0 Hz, 2H), 5.75-5.60 (m, 1H), 4.00-3.95 (m, 2H), 3.80-3.55 (m, 4H), 3.50-3.40 (m, 1H), 3.30-3.15 (m, 1H), 3.10-2.90 (m, 3H), 2.75-2.60 (m, 1H), 2.35-1.70 (m, 4H), 1.35-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 174.4, 147.5, 146.9, 139.3 (2C), 131.0 (2C), 128.7 (4C), 128.6 (4C), 127.1 (2C), 121.7, 114.5, 114.4, 113.7, 112.7, 101.8, 61.4, 60.4, 58.4, 57.6, 54.6, 53.4, 45.9, 40.9, 40.6, 36.3, 36.2, 35.8, 35.2, 35.1,35.6, 29.7; $[\alpha]_{25}^{D}$ +15.13

Synthesis of *N*-benzyl imide (28)



To a solution of chiral succinimide (**5**) (319.3 mg, 1.86 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added K_2CO_3 (179.7 mg, 1.30 mmol), KI (21.6 mg, 0.13 mmol) and BnCl (0.15 mL, 1.30 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (5 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give *N*-benzyl imide (**28**) (367.1 mg, 51%) as a yellow crystal. R_f (4:1 hexane/EtOAc) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7..45-7.15 (m, 15H), 4.50 (d, *J*= 4.3 Hz, 2H), 3.90 (dd, *J*= 9.0, 5.3 Hz, 1H), 3.75 (d, *J*= 16.5 Hz, 2H), 3.55 (d, *J*= 13.5 Hz, 2H), 2.80 (dd, *J*=18.7, 9.1 Hz, 1H) ; 2.65 (dd, *J*=18.7, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 173.6, 159.5, 137.0 (2C), 134.5, 127.6 (3C), 127.0 (3C), 126.4, 126.2 (2C), 56.2, 53.4 (2C), 40.9, 31.0, 28.4. (*c* 1.6, $CHCl_3$); ν_{max} (film) 3030, 2927, 1697, 1939, 1151, 695 cm^{-1}.

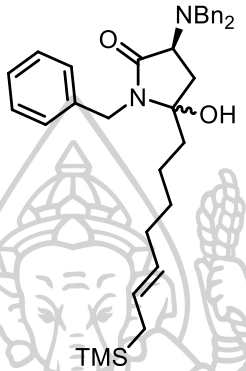
Synthesis of γ-hex-5-en-1-yl-γ-hydroxylactams (29a)



To a solution of magnesium (261.4 mg, 10.9 mmol) in diethyl ether (10 mL) under argon atmosphere at room temperature was added 6-bromo-1-hexene (0.49 mL, 3.64 mmol) and was added *N*-benzyl succinimide (**28**) (414.6 mg, 1.21 mmol) at 0^{o}C and the mixture was stirred for 3 hours. The mixture was filtered to remove magnesium and to the spolution was added dropwise sat. aq. NH_4Cl (mL). Then mixture was extracted with CH_2Cl_2 (3 × 10 mL) dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4:1 hexane/EtOAc) to give g-pentenyl-g-hydroxylactam (**29a**) (75.9 mg, 19%) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7..45-7.15 (m, 15H), 5.70-5.50 (ddt, *J*= 15.9, 10.1, 7.1 Hz, 1H), 4.85 (m, 2H), 4.20 (d, *J*= 6.2 Hz, 2H), 3.90 (d, *J*= 13.8 Hz, 2H), 3.75 (d, *J*= 13.8 Hz, 2H),

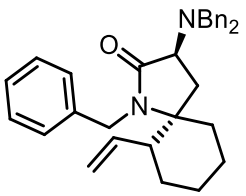
3.55 (dd, *J*=8.9, 5.9 Hz, 1H), 2.65 (t, *J*= 8.5, 1H), 2.30 (dd, *J*=18.7, 5.7 Hz, 1H), 1.95-1.85 (m, 1H), 1.85-1.70 (m, 2H), 1.75-1.50 (m, 1H), 1.45-1.30 (m, 1H), 1.20-0.90 (m, 1H), 0.90-0.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 139.8 (2C), 139.5, 138.6, 129.3 (4C), 128.5 (4C), 127.3 (2C), 114.7, 90.0, 59.1, 54.9, 42.3, 38.9, 37.3, 33.4, 28.5, 24.8, 23.1 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3334, 2927, 1659, 1453, 1353, 1028, 698 cm^{-1}.

Synthesis of *N*-benzyl-7-(trimethylsilyl)hept-5-en-1-yl)-pyrrolidone (30)



To a solution of g-pentenyl-g-hydroxylactam (**29a**) (73.5 mg, 0.163 mmol) in dry CH_2Cl_2 (3mL) under argon atmosphere at room temperature was added allyl trimethylsilane (0.17 mL, 0.81 mmol) and Hoveyda-Grubbs catalyst^{TM} 2 nd generation (1.1 mg, 1.63 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 thin layer chromatography (silica gel, 6:1 hexane/EtOAc) to give *N*-benzyl-7-(trimethylsilyl)hept-5-en-1-yl)-pyrrolidone (**30**) (24.5 mg, 37%) as a yellow oil. R_f (6:1 hexane/EtOAc) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.15 (m, 15H), 5.45-5.20 (m, 1H), 5.20-4.95 (m, 1H) 4.60-4.30 (m, 2H), 3.95 (d, J= 13.8 Hz, 2H), 3.75 (d, *J*= 13.8 Hz, 2H), 3.70-3.60 (m, 1H), 2.50-2.30 (m, 1H), 2.00-1.90 (m, 1H), 1.90-1.75 (m, 1H), 1.75-1.60 9m, 2H), 1.50-1.35 (m, 2H), 1.35-1.25 (m, 1H), 1.25-1.00 (m, 2H), 1.00-0.80 (m, 2H), -2.2 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 139.8 (2C), 138.8, 128.4 (4C), 127.7 (4C), 127.0 (2C), 126.4, 90.3, 59.4, 54.9, 42.5, 38.9, 32.6, 28.5, 23.3, 22.8, 18.7, -1.59 (3C) (*c* 1.6, $CHCl_3$); ν_{max} (film) 3357, 2949, 1664, 1452, 1249, 1151, 854, 743, 699 cm^{-1}.

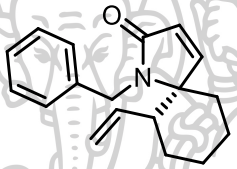
Synthesis of (3*S*,5*R*,6*S*)-1-benzyl-3-(dibenzylamino)-6-vinyl-1-azaspiro[4.5]decan-2-one (31)



To a solution of *N*-benzyl-7-(trimethylsilyl)hept-5-en-1-yl)-pyrrolidone (**30**) (20.2 mg, 0.036 mmol) in dry CH_2Cl_2 (2 mL) under argon atmosphere at 0^{o}C was added

TFA (0.02 mL, 0.15 mmol) and the mixture was stirred for 3 hours at 0°C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (3 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (silica gel, 4:1 hexane/EtOAc) to give (3*S*,5*R*,6*S*)-1-benzyl-3-(dibenzylamino)-6-vinyl-1-azaspiro[4.5]decan-2-one (**31**) (9.3 mg, 55%) as colorless oils. R_f (4:1 hexane/EtOAc) 0.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J*= 7.1 Hz, 4H), 7.35-7.15 (m, 11H), 5.30 (ddd, *J*= 17.4, 10.2, 7.5 Hz, 1H), 4.90-4.70 (m, 3H), 4.15 (d, *J*= 15.6 Hz, 1H), 3.95 (d, *J*= 13.8 Hz, 2H), 3.75-3.60 (m, 3H), 2.50-2.2.35 (m, 1H), 2.35-2.00 (m, 1H), 1.90-1.70 (m, 1H), 1.70-1.40 (m, 5H), 1.40-1.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 139.9, 136.1, 128.8 (4C), 128.5 (2C), 128.2 (2C), 127.3 (2C), 126.9 (2C), 118.0, 70.2, 58.8, 54.6 (2C), 48.0, 42.5, 37.8, 32.8, 26.9, 19.8; $[\alpha]_{25}^{D}$ -4.30

Synthesis of (5*R*,6*S*)-1-benzyl-6-vinyl-1-azaspiro[4.5]dec-3-en-2-one (32)

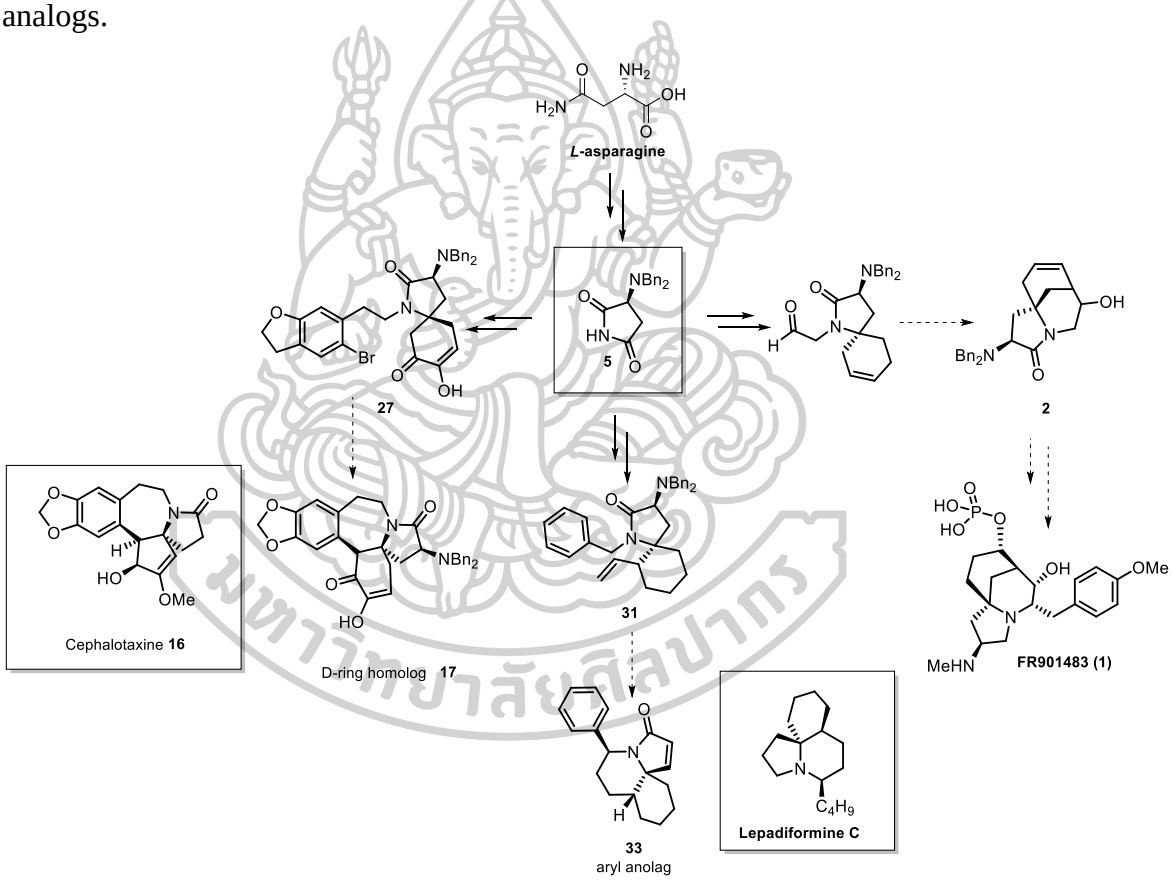


To a solution of *N*-benzyl spirocyclohexene-pyrrolidone (**31**) (9.3 mg, 0.02 mmol) in dry CH_2Cl_2 (2 mL) under argon atmosphere at 0°C was added m-CPBA (4.0 mg, 0.025 mmol) and the mixture was stirred for 3 hours at 0°C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (3 mL) and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (silica gel, 2:1 hexane/EtOAc) to give **(**5*R*,6*S*)-1-benzyl-6-vinyl-1-azaspiro[4.5]dec-3-en-2-one (**32**) (4.5 mg, 85%) as colorless oils. R_f (2:1 hexane/EtOAc) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 7.00 (d, *J*= 6.0 Hz, 1H), 6.15 (d, *J*= 6.0 Hz, 1H), 5.30 (ddd, *J*= 17.4, 10.2, 7.5 Hz, 1H), 5.00-4.80 (m, 1H), 4.70-4.45 (m, 3H), 2.80-2.65 (m, 1H), 2.10-1.90 (m, 1H), 1.90-1.70 (m, 4H), 1.80-1.65 (m, 1H), 1.60-1.35 (2H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 148.9, 138.6, 135.4, 127.7 (2C), 127.6 (2C), 127.1, 124.9, 116.6, 47.7, 41.7, 31.4, 29.0, 20. (*c* 1.6, $CHCl_3$); ν_{max} (film) 2926, 1676, 1396, 1198, 916, 813, 709, cm^{-1}.

CHAPTER 5

CONCLUSION

In summary, the synthetic studies of immunosuppressant FR901483, D-ring homolog of cephalotaxine and aryl analog of lepadiformine C have been discussed. This research shows that the chiral succinimide **5** synthesized from L-asparagine can be useful in synthetic approach of natural products containing pyrrolidine ring. The key step of the synthesis, *N*-acyliminium ion spirocyclization succeeded in constructing spirocyclohexene-pyrrolidone. The remaining steps involve construction of an additional ring between the cyclohexene moiety and the *N*-alkyl group and necessary functional group conversions of specific targets to complete the natural products and analogs.



Scheme 37 Conclusion of finding from this research

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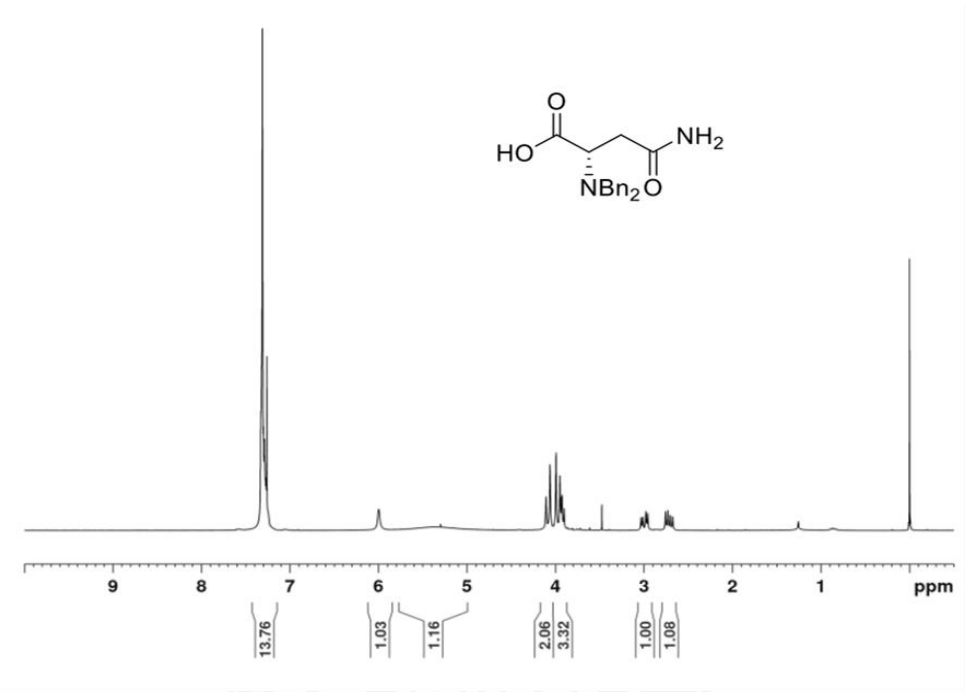
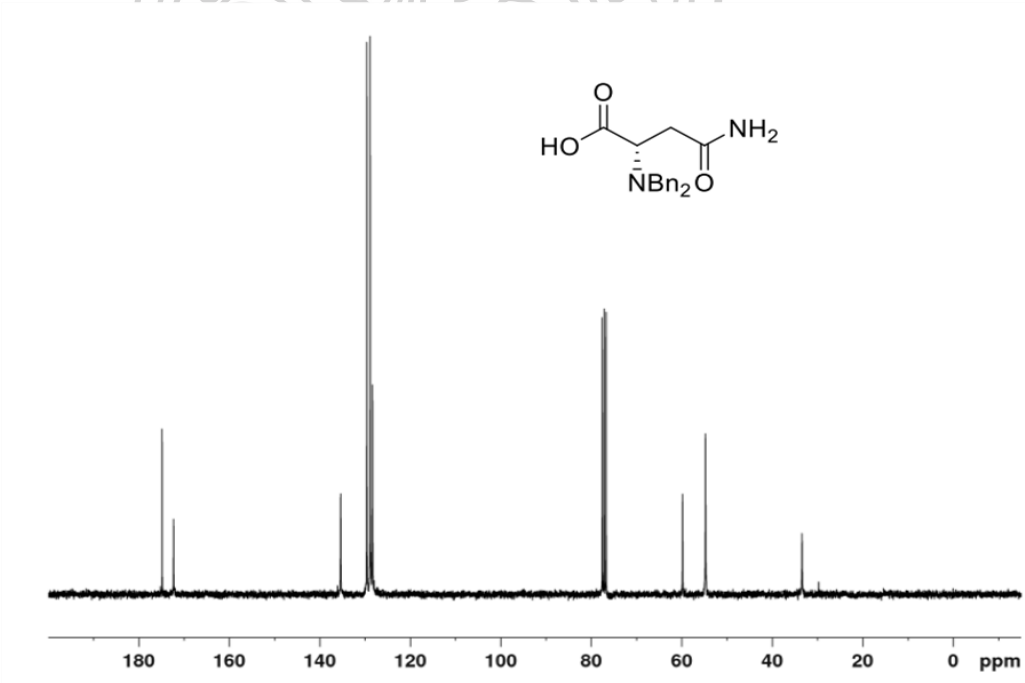
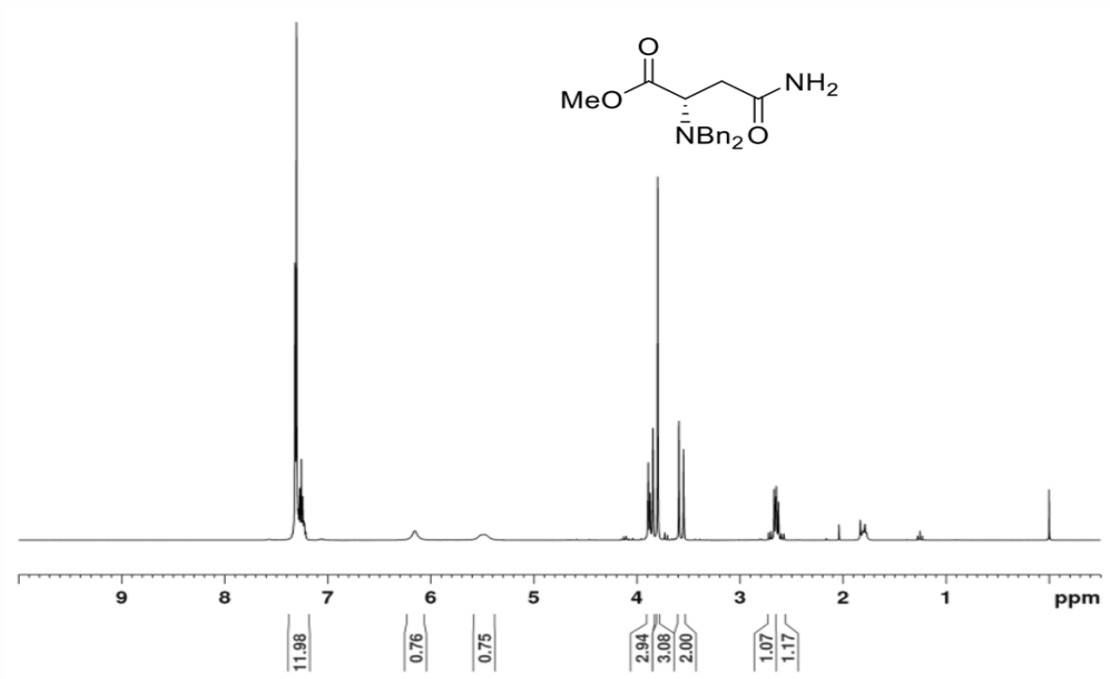
APPENDIX



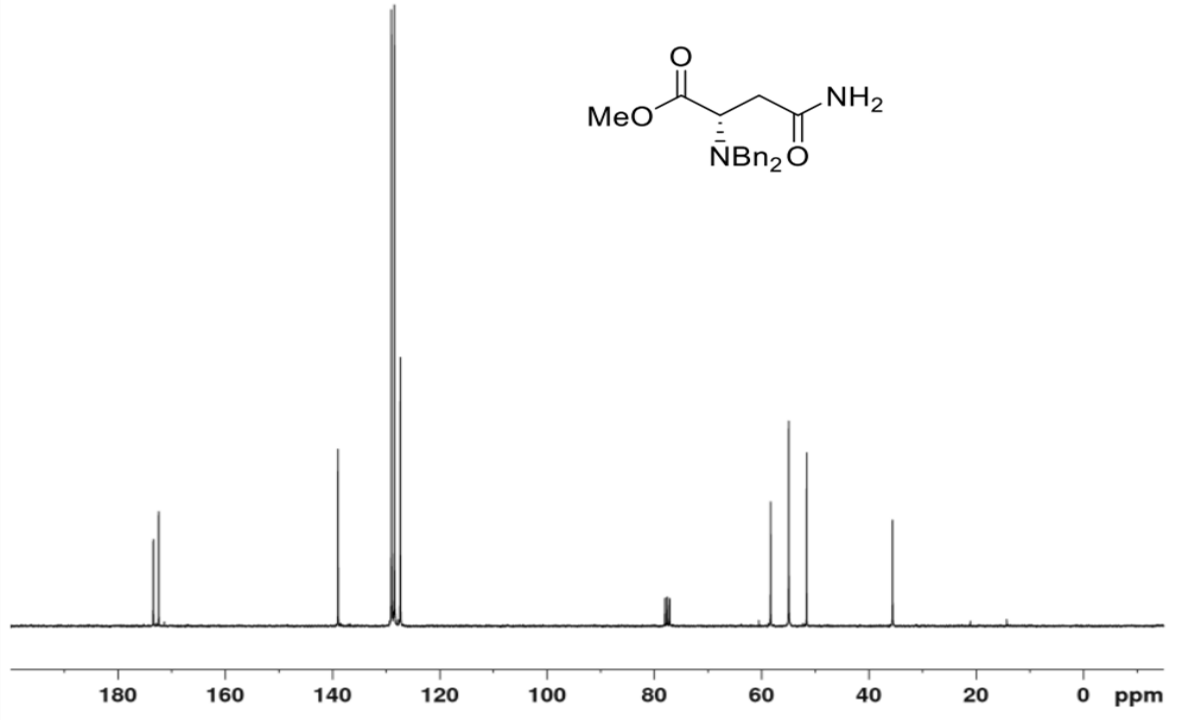
^{1}H NMR of compound 7



^{13}C NMR compound 7



^{1}H NMR of compound 8



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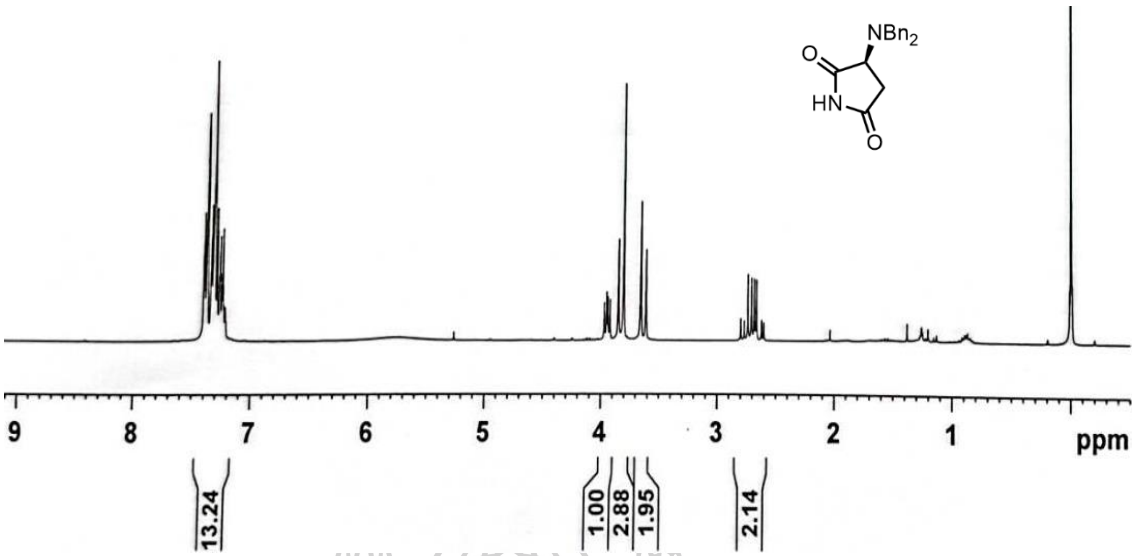
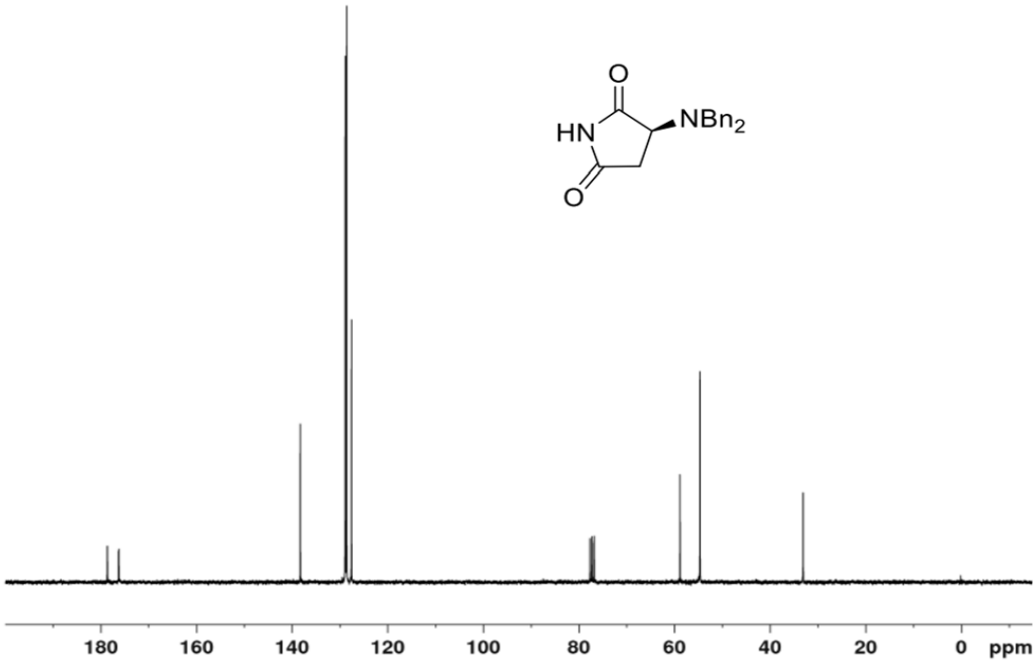
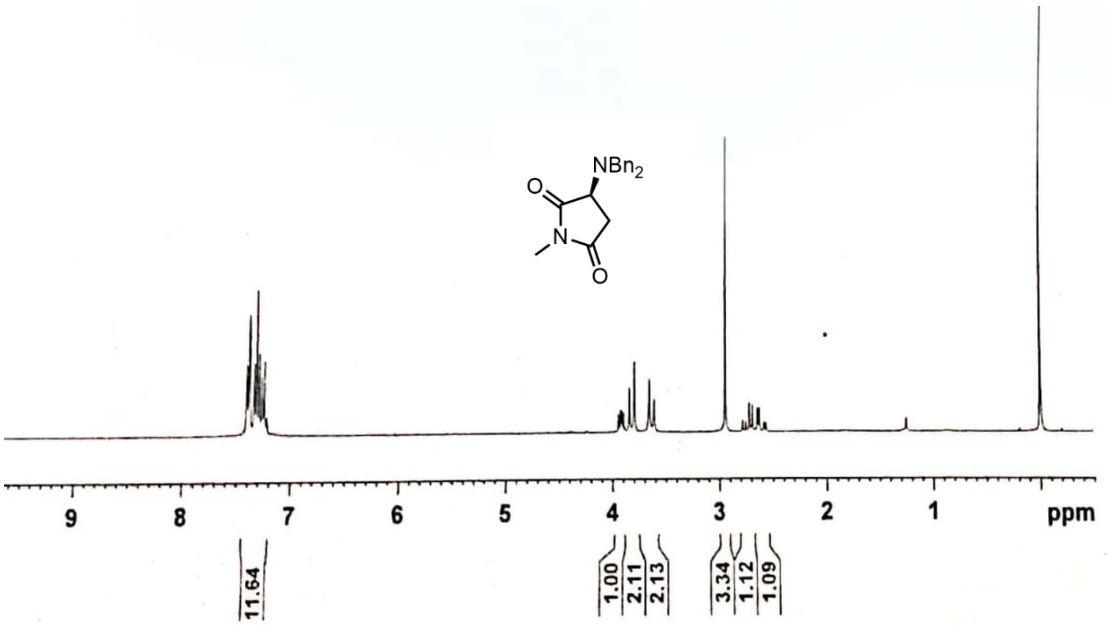


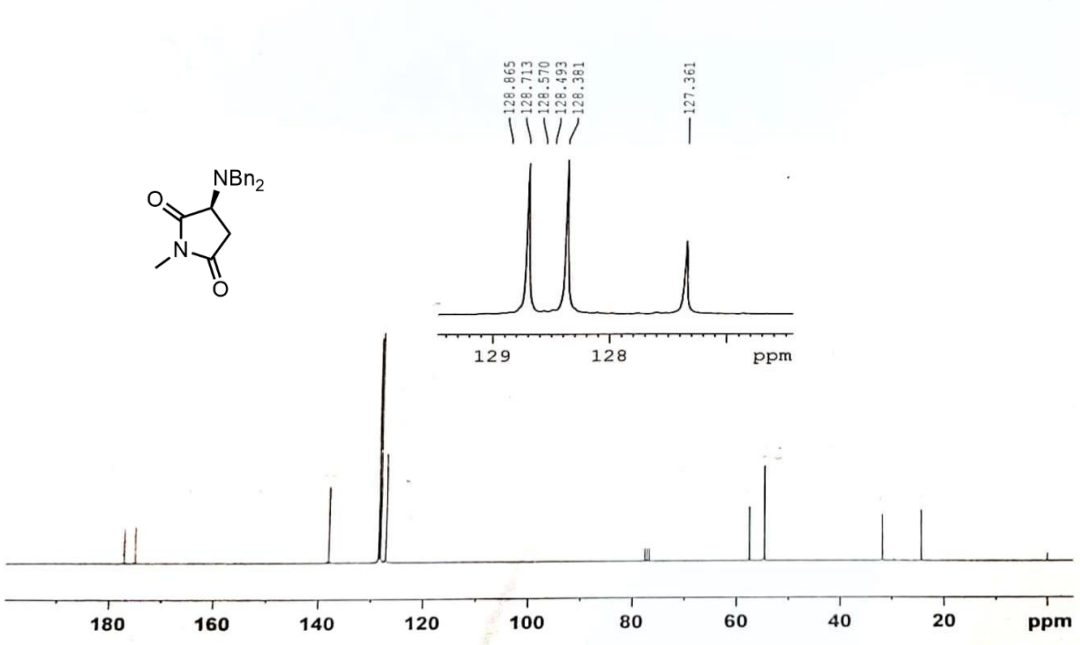
^{1}H NMR of compound 5



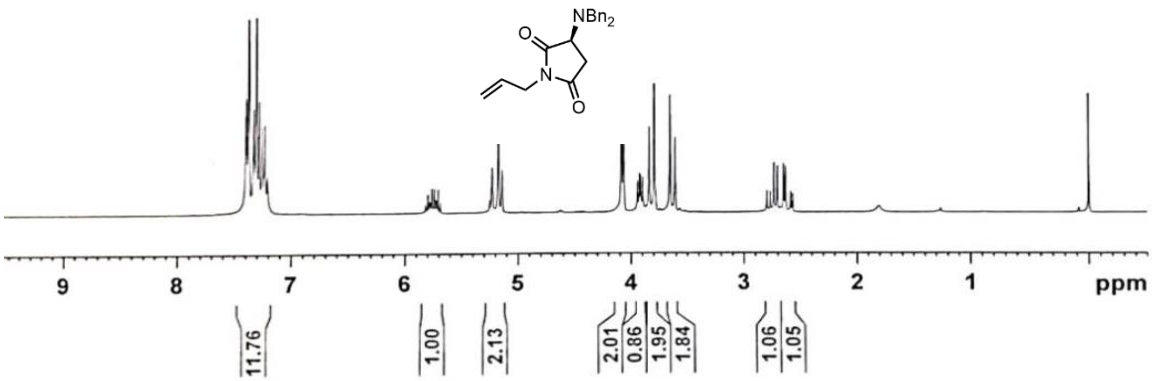
^{13}C NMR compound 5



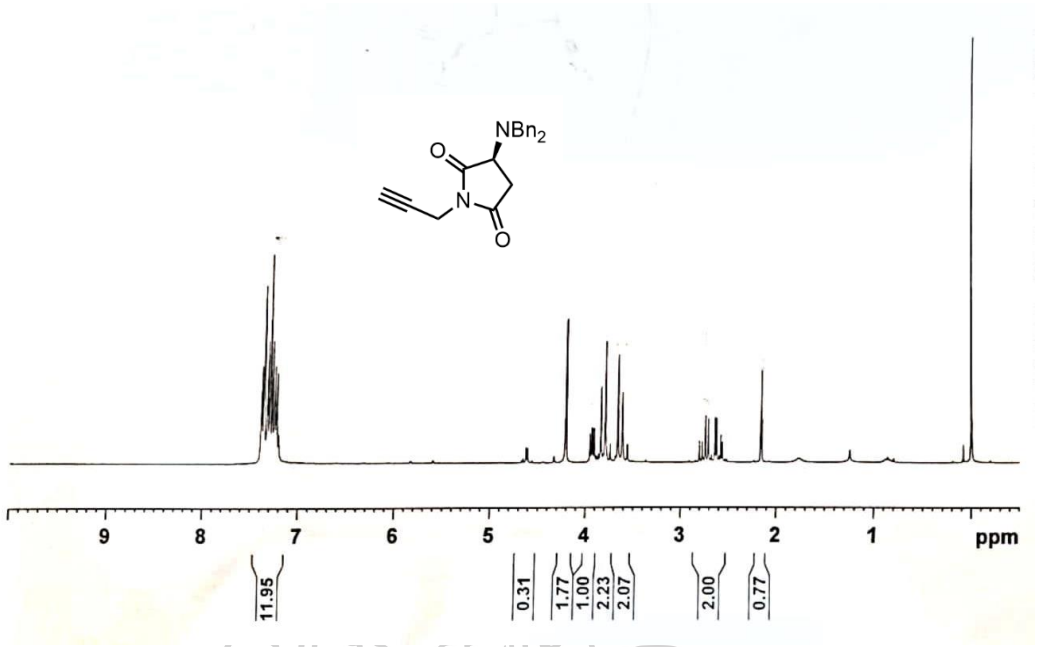
^{1}H NMR of compound 6a



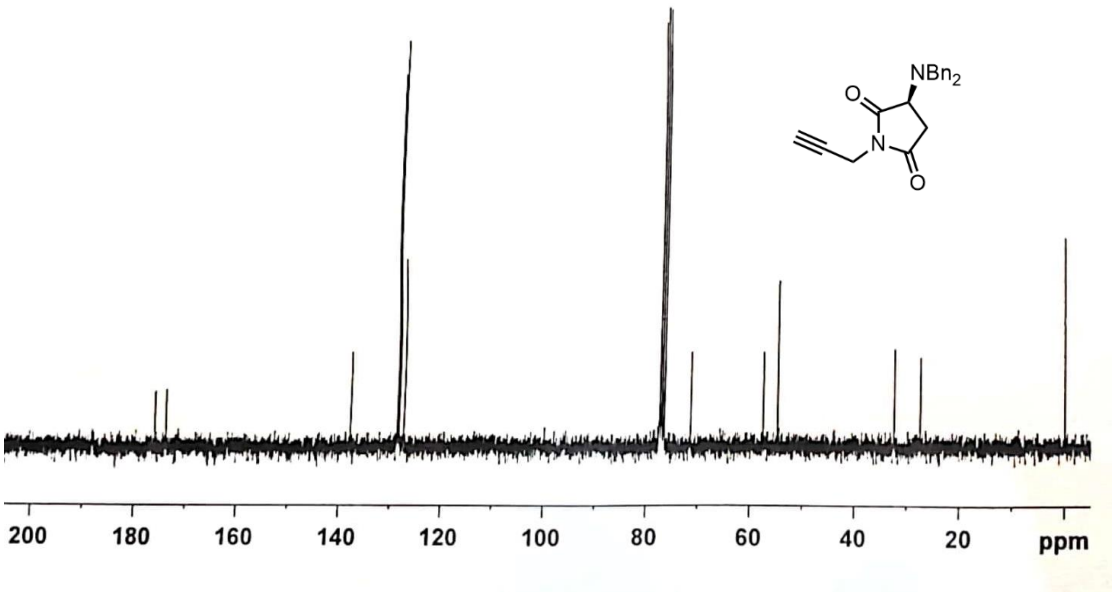
^{13}C NMR compound 6a



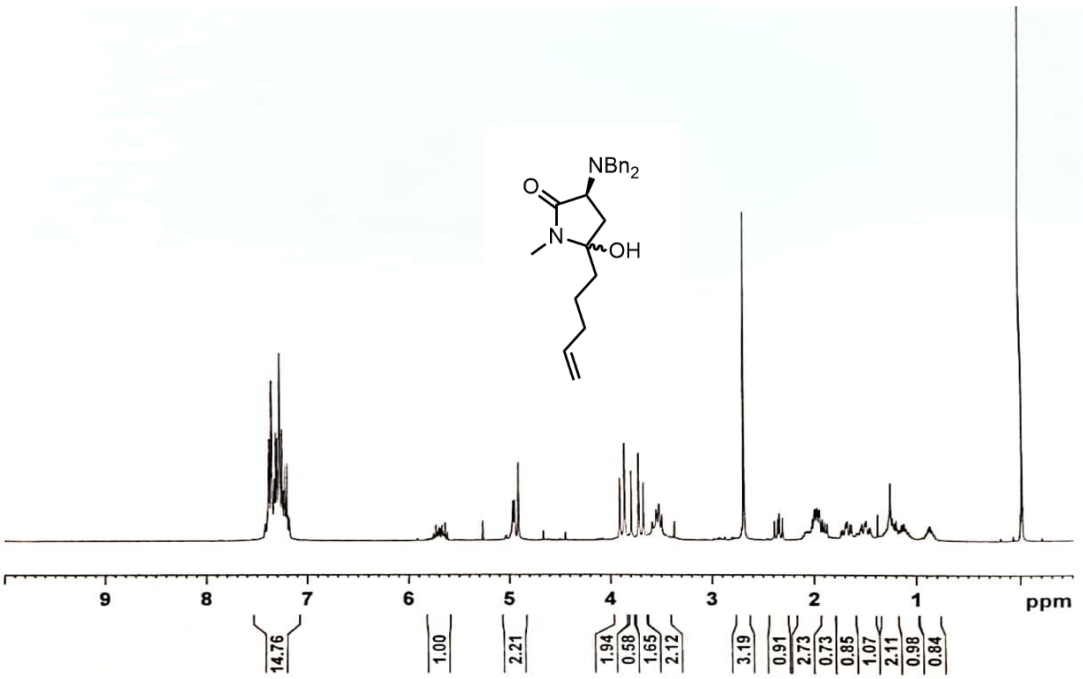
^{1}H NMR of compound 6b



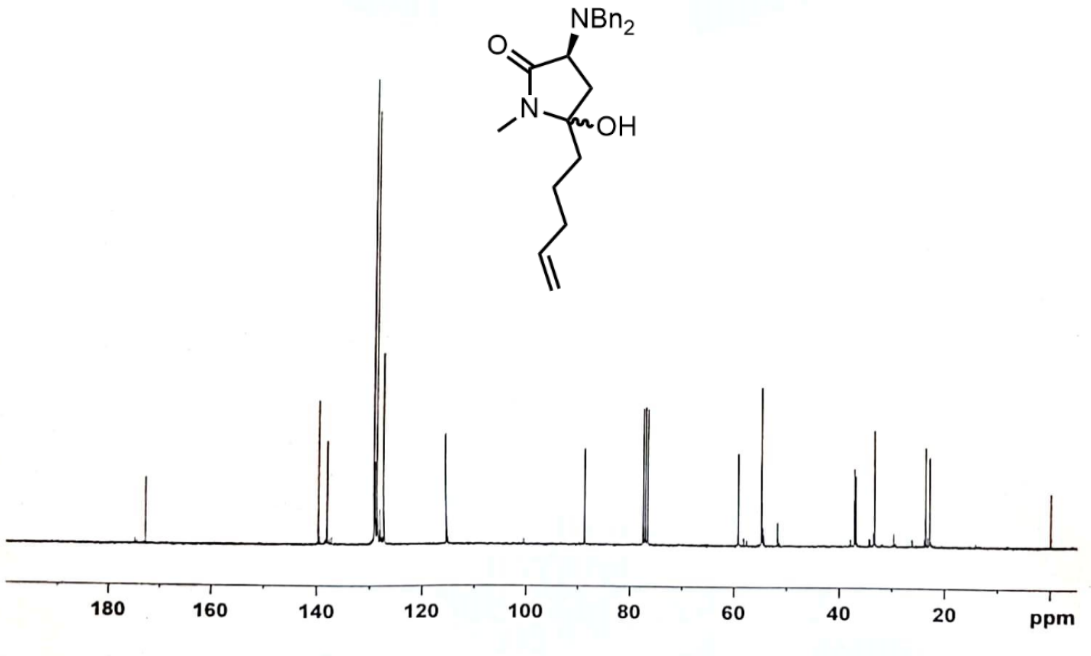
^{1}H NMR of compound 6c



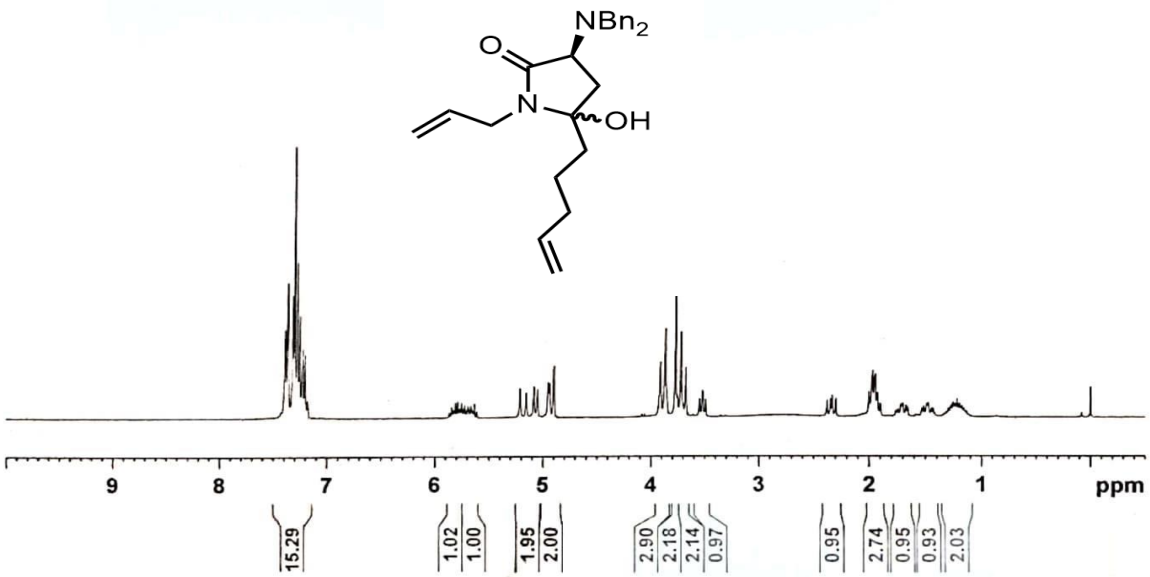
^{13}C NMR compound 6c



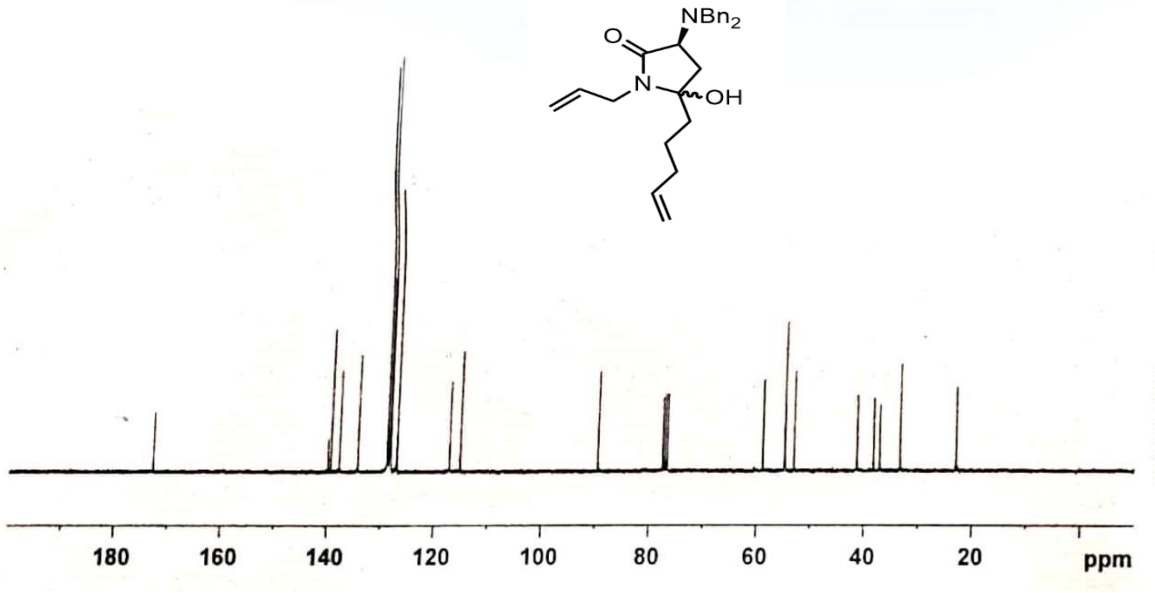
[1]H NMR of compound 4a



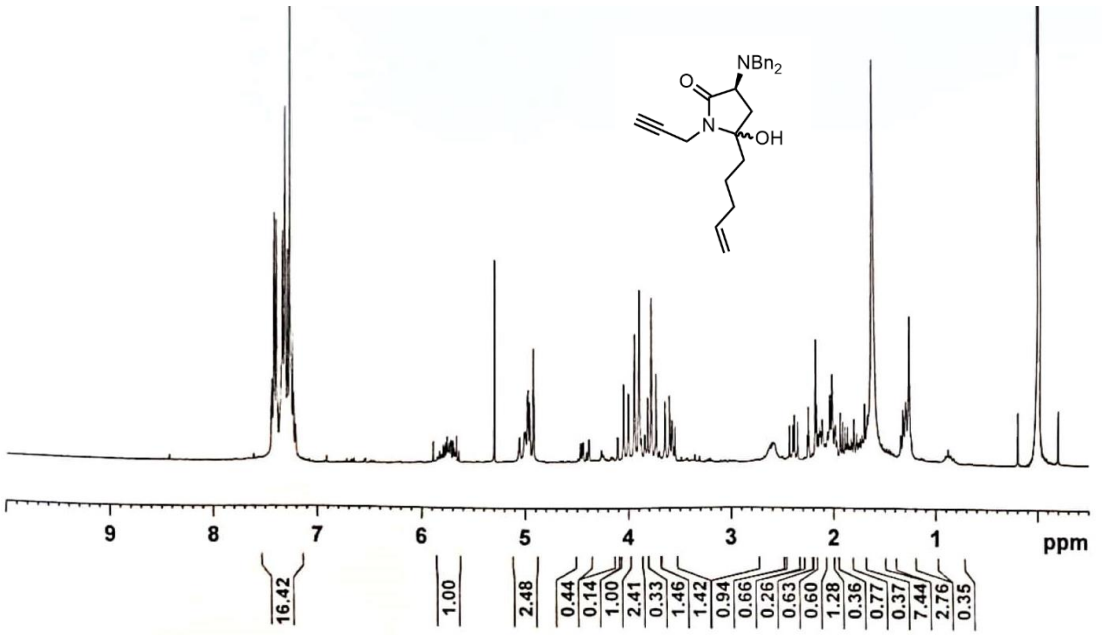
[13]C NMR compound 4a



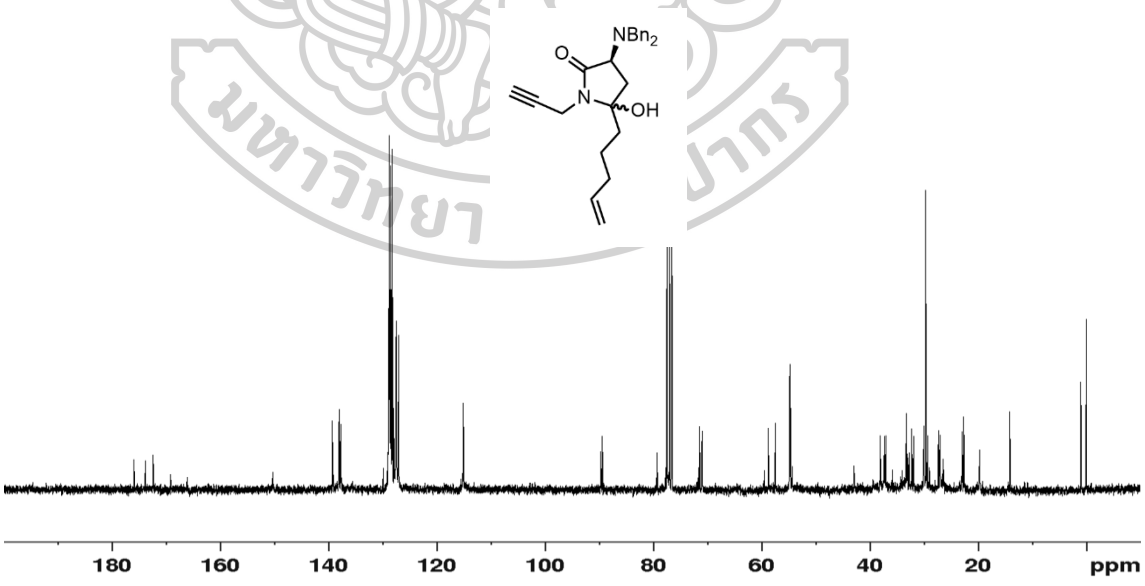
^{1}H NMR of compound 4b



^{13}C NMR compound 4b



[1]H NMR of compound 4c



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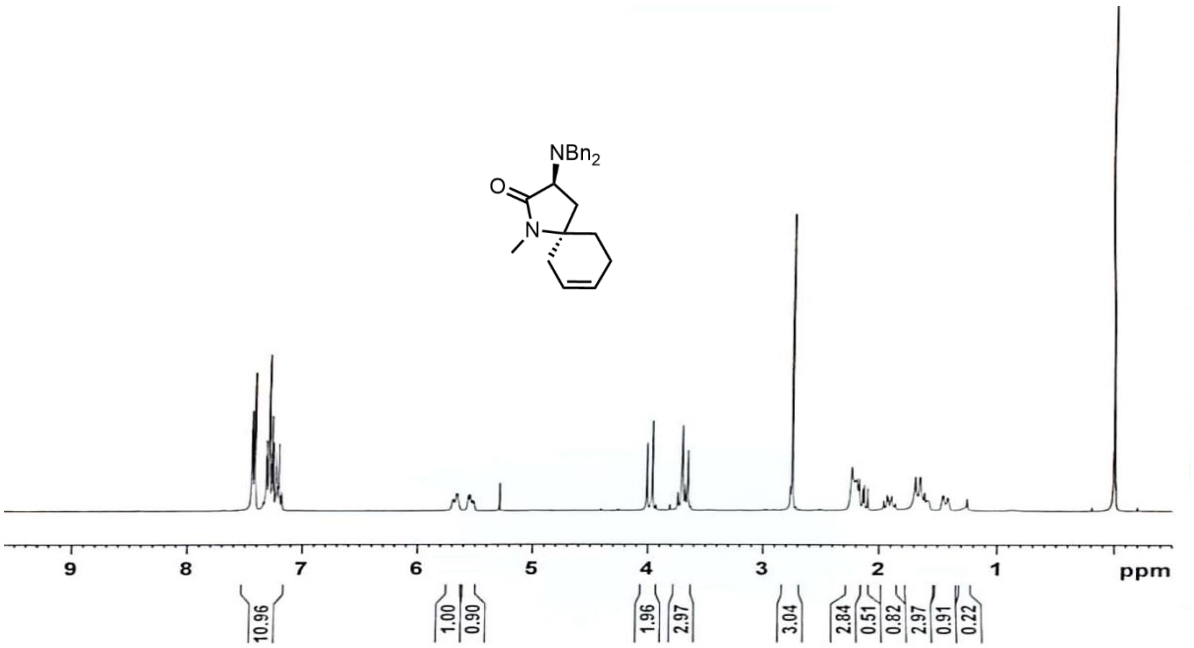
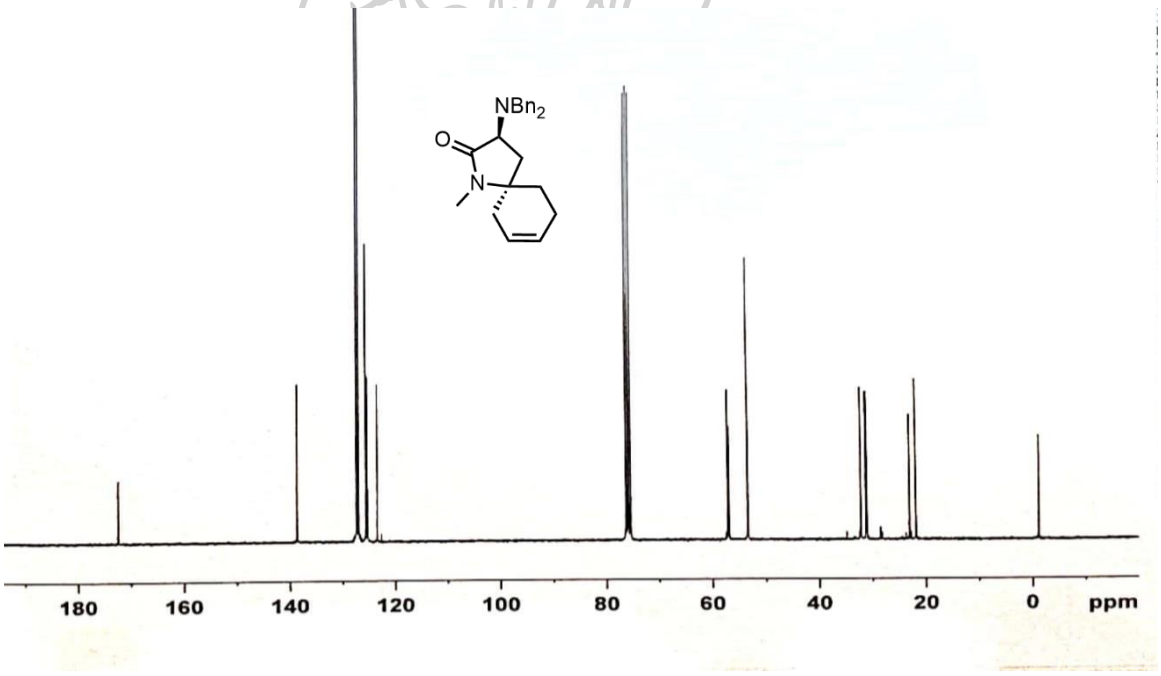
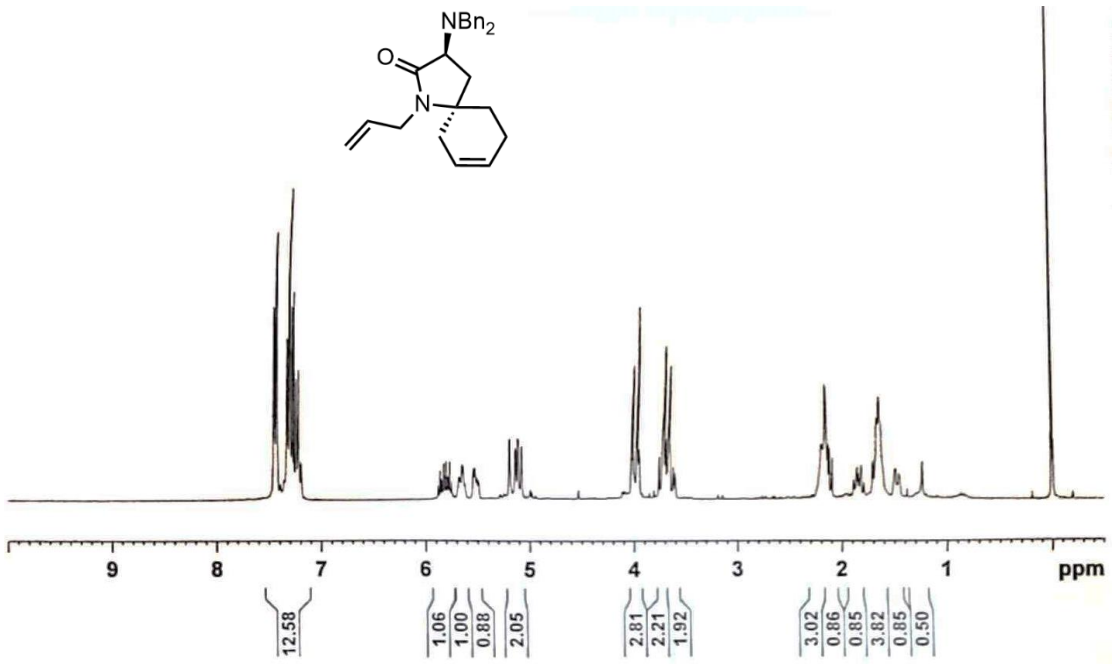


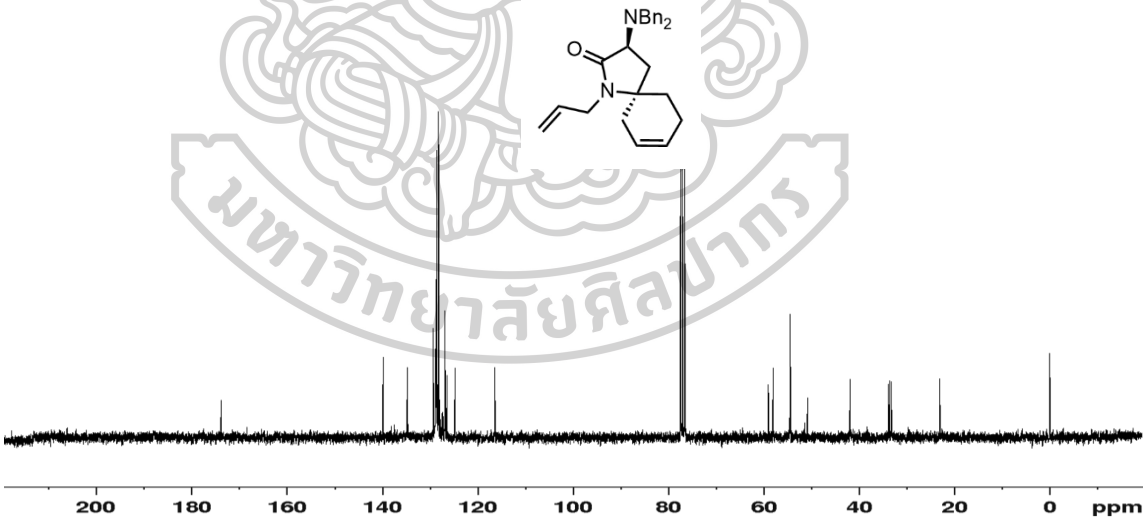
^{1}H NMR of compound 10a



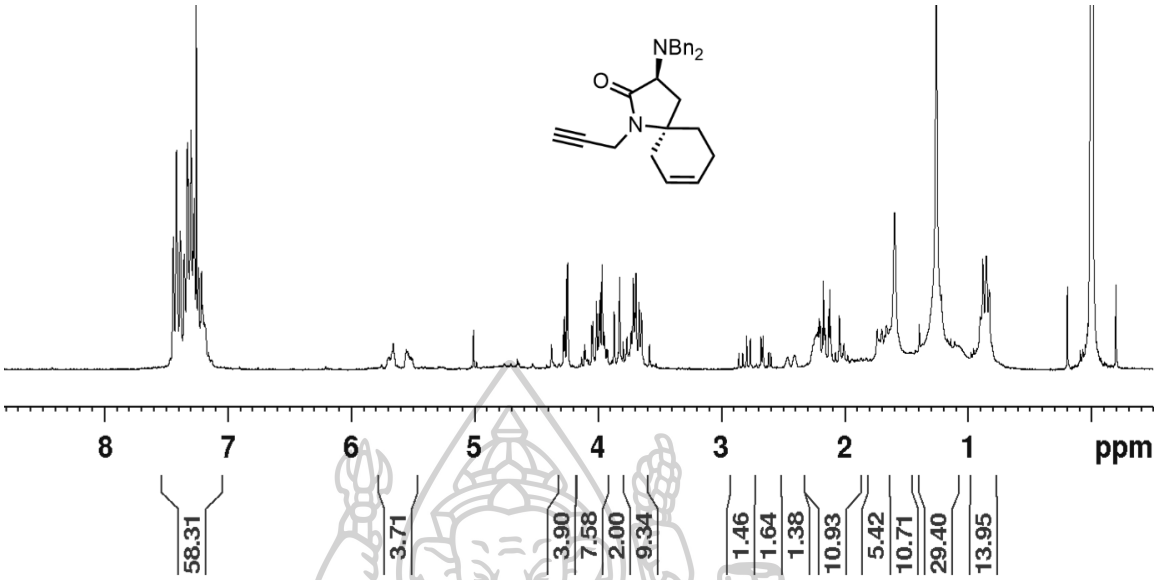
^{13}C NMR compound 10a



^{1}H NMR of compound 10b



^{13}C NMR compound 10b



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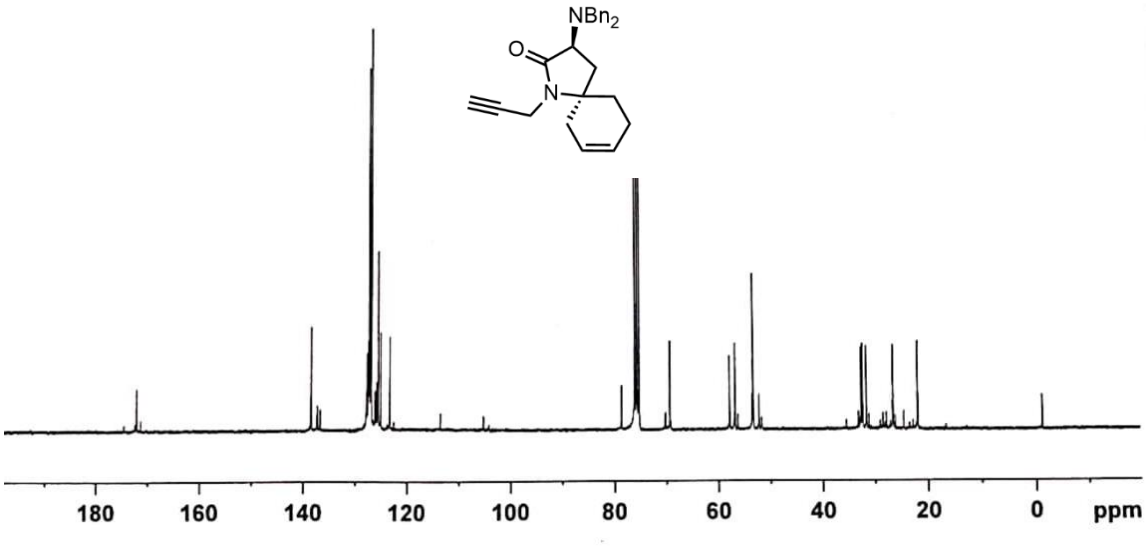

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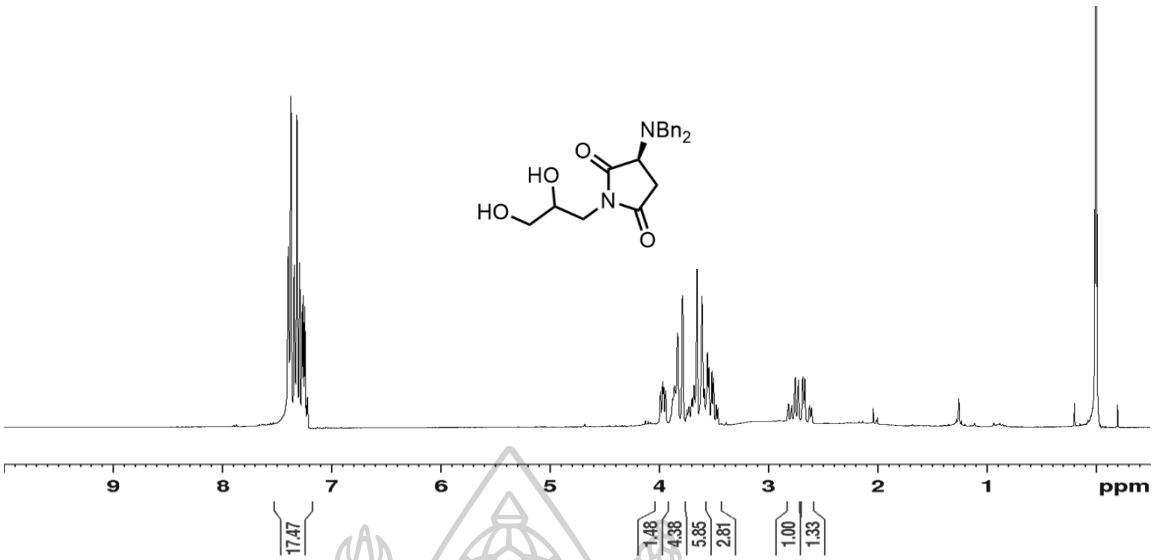
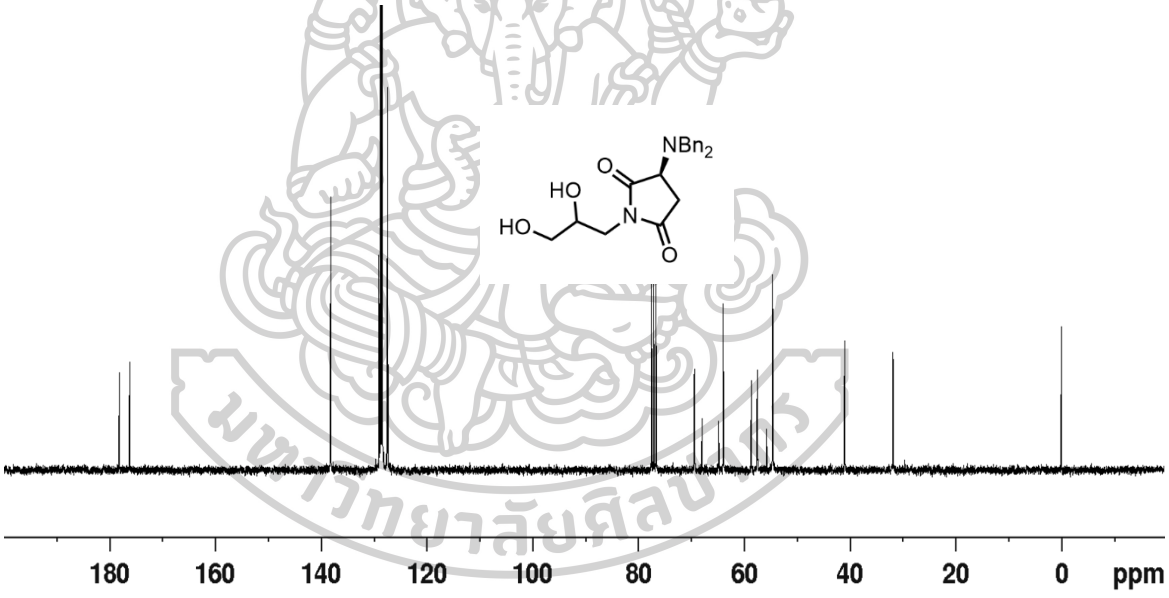
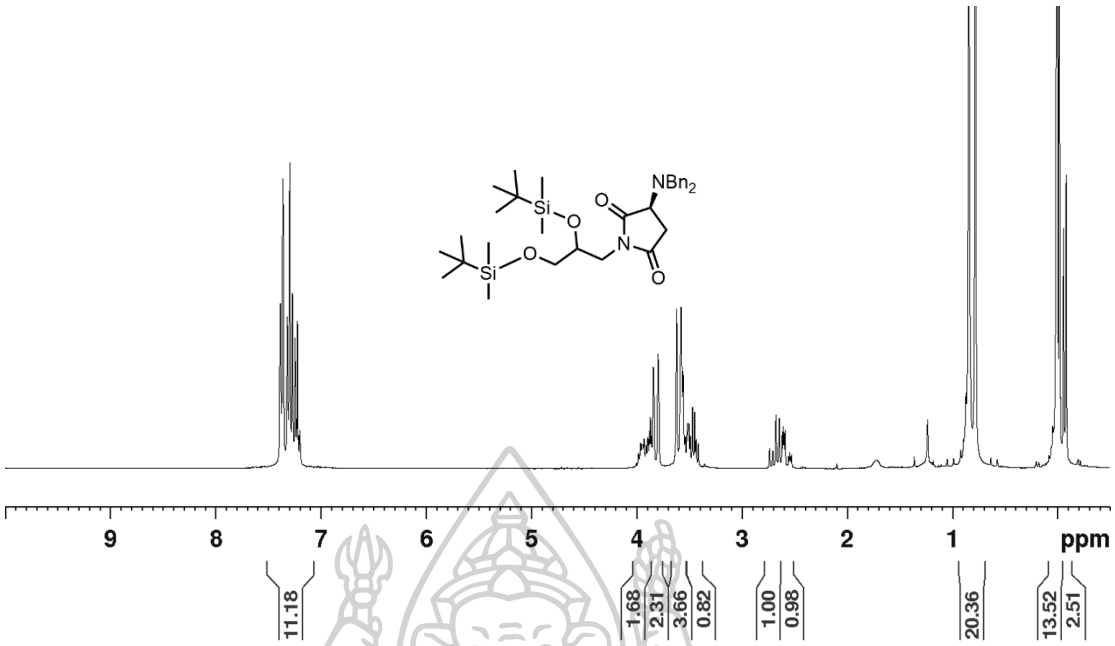


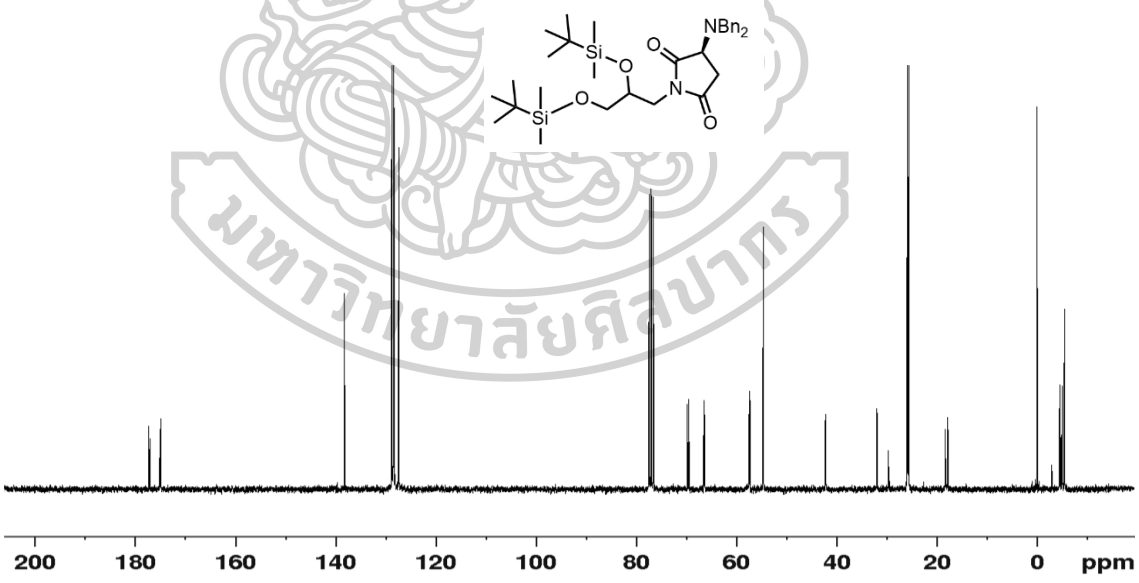
^{1}H NMR of compound 13



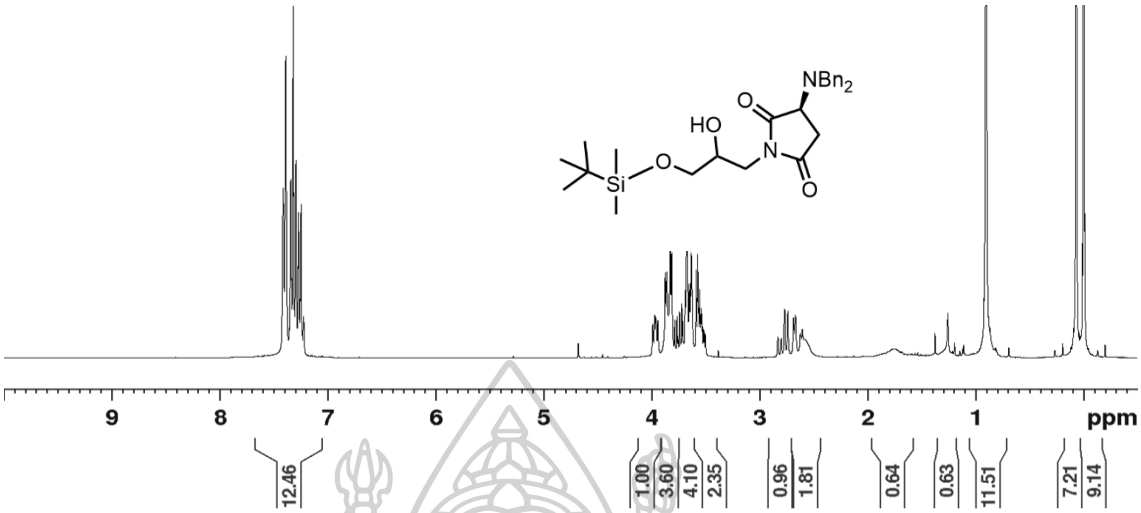
^{13}C NMR compound 13



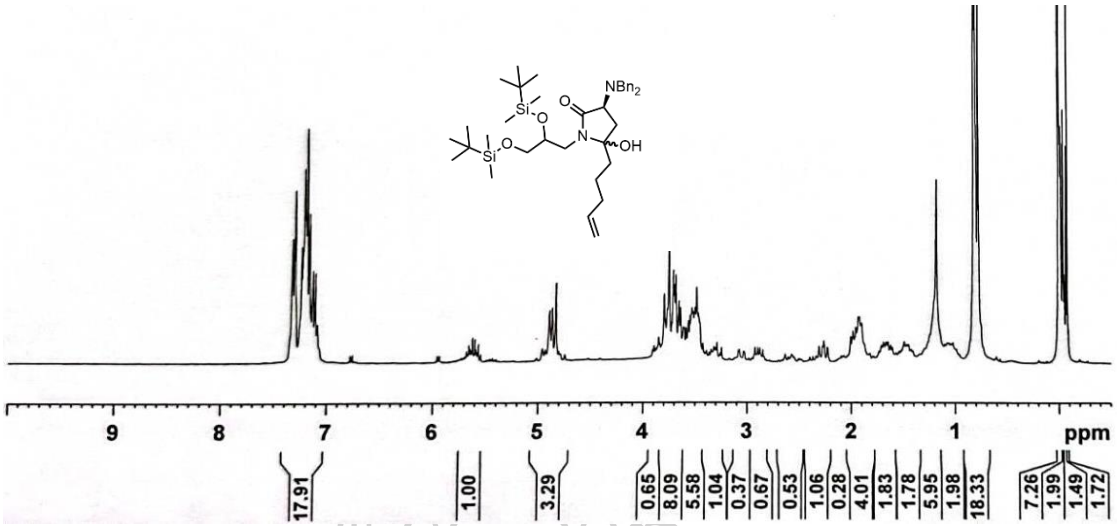
^{1}H NMR of compound 14a



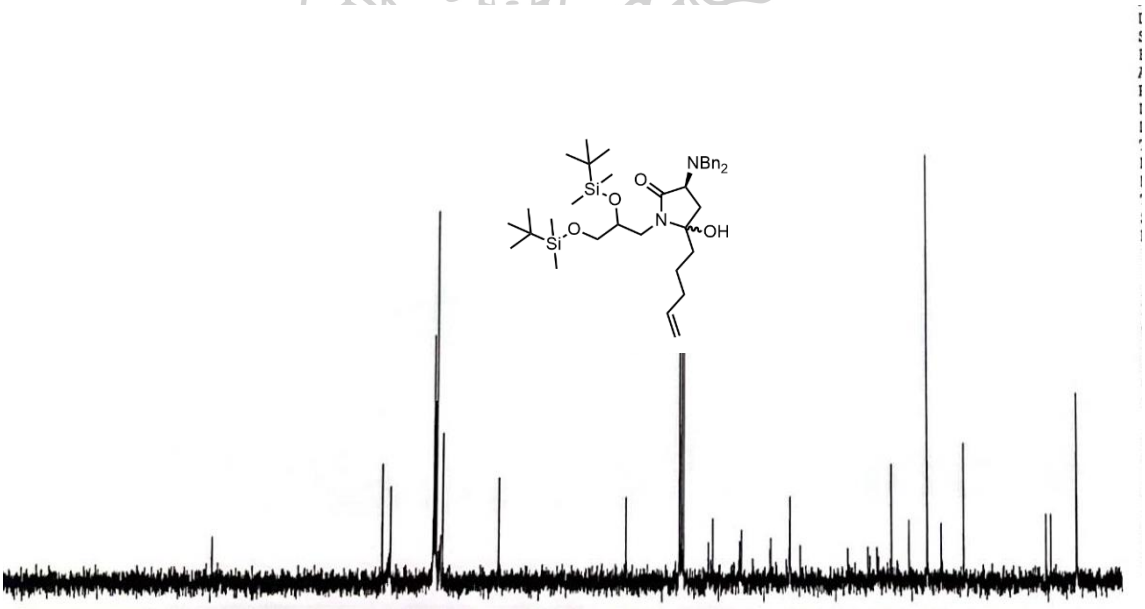
^{13}C NMR compound 14a



^{1}H NMR of compound 14b



^{1}H NMR of compound 12a



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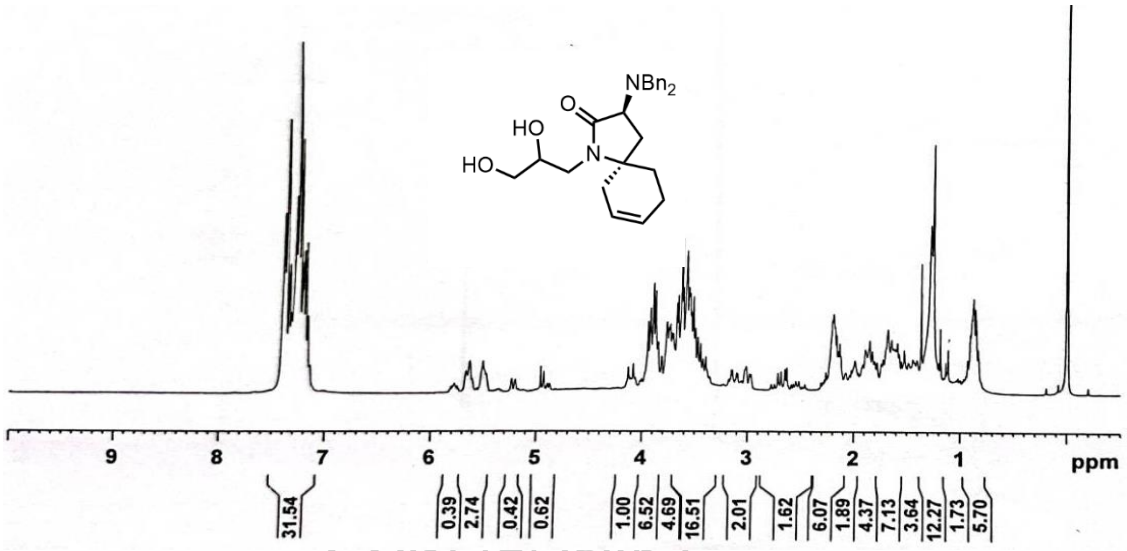
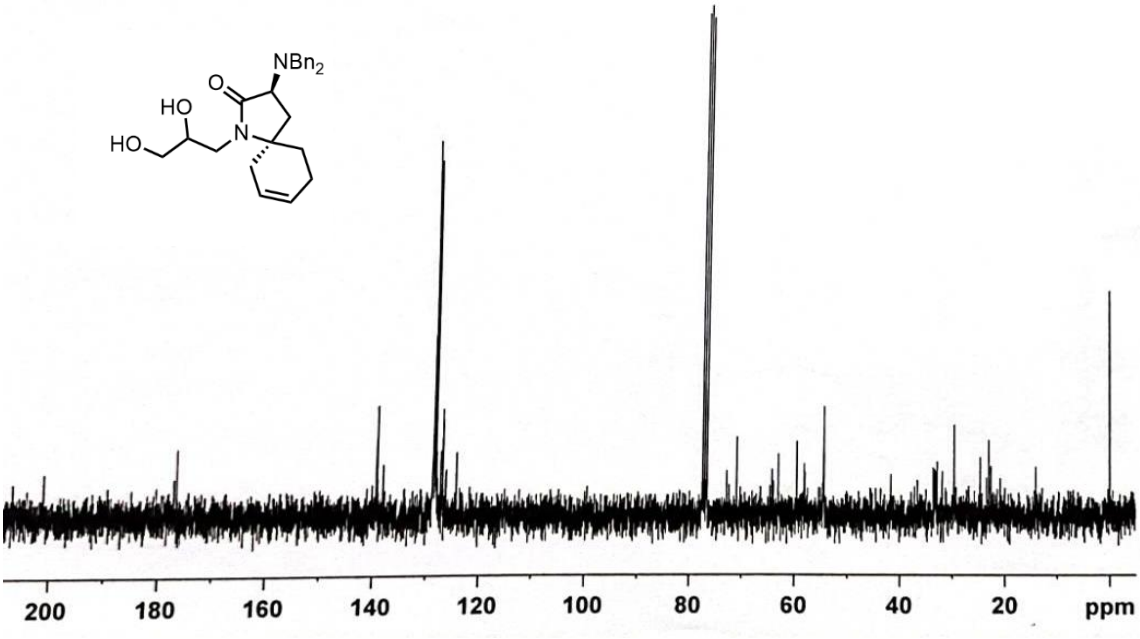
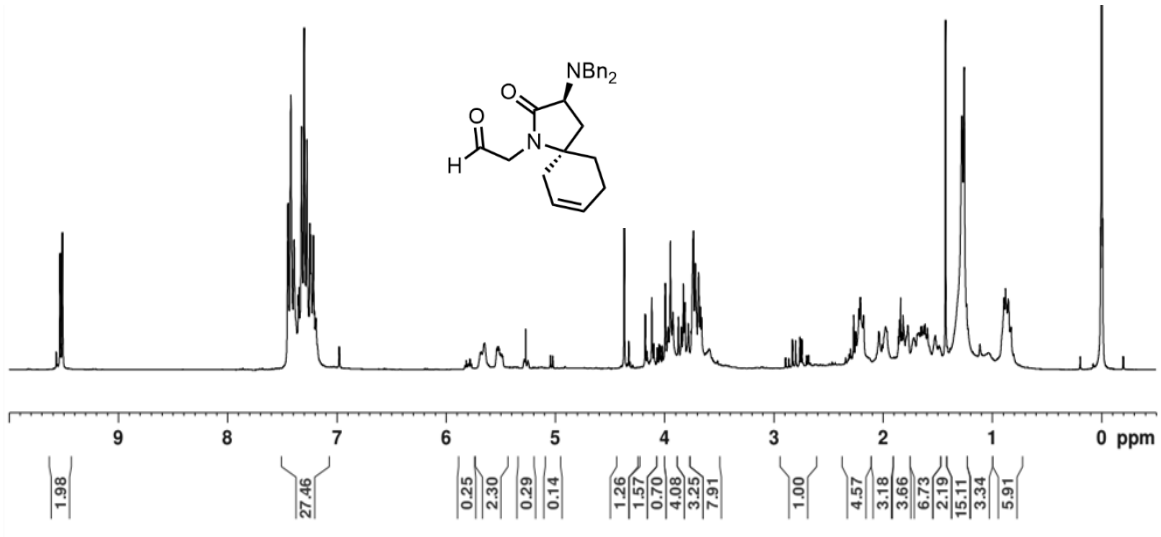


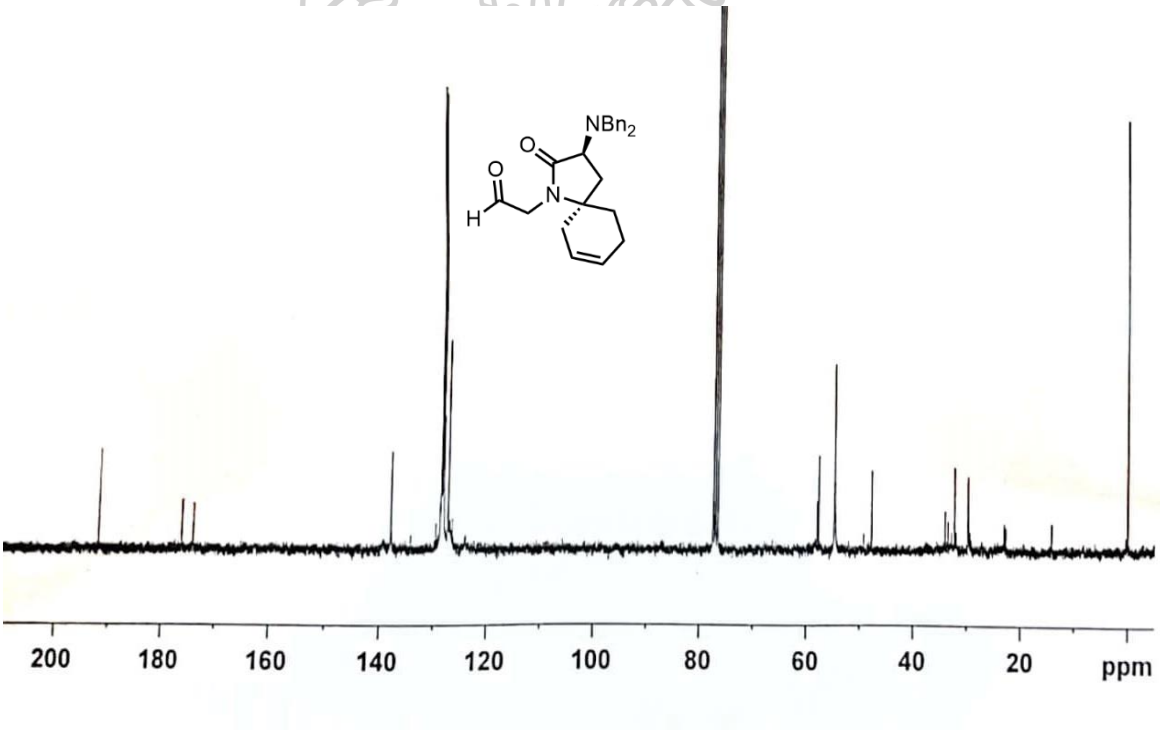
^{1}H NMR of compound 13a



^{13}C NMR compound 13a



^{1}H NMR of compound 3



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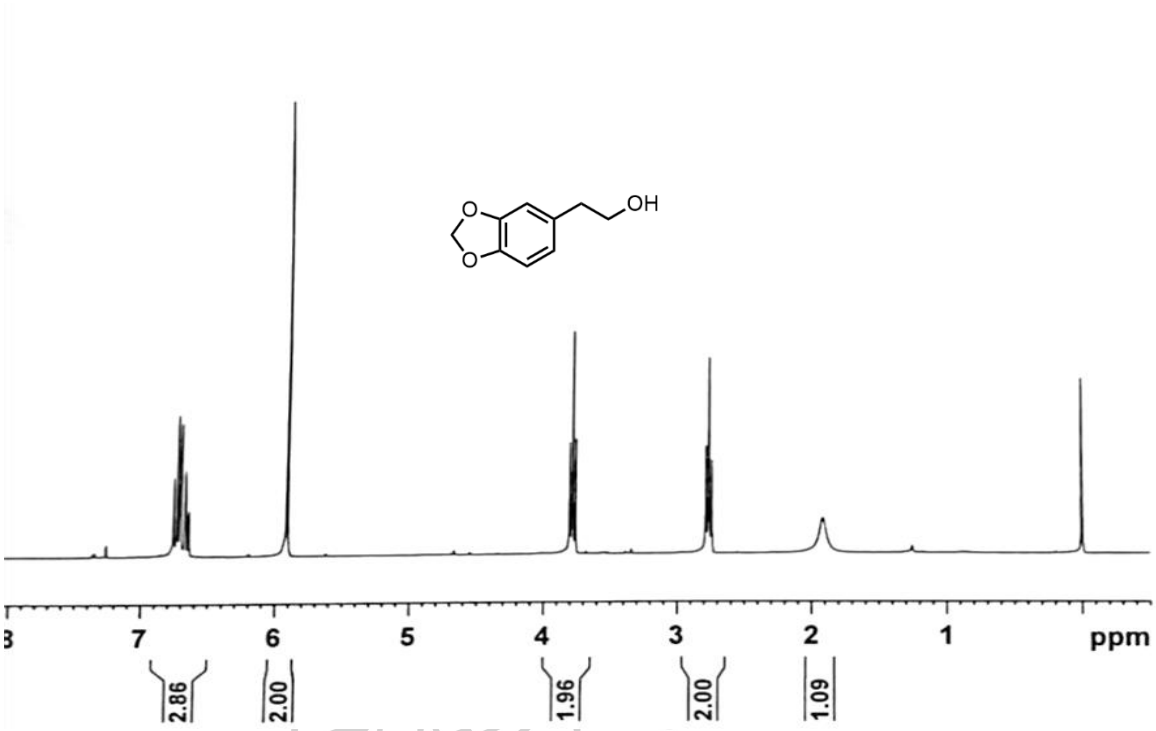
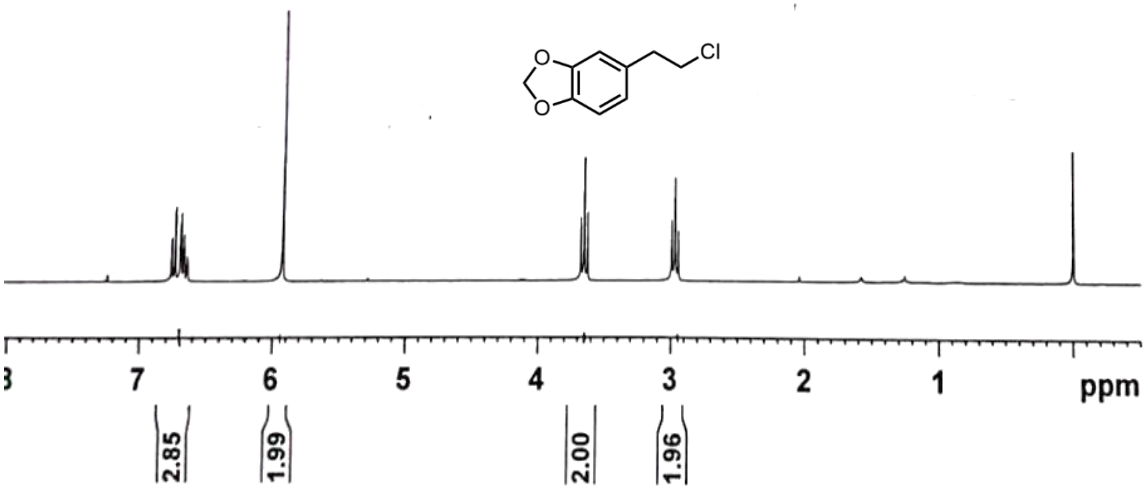
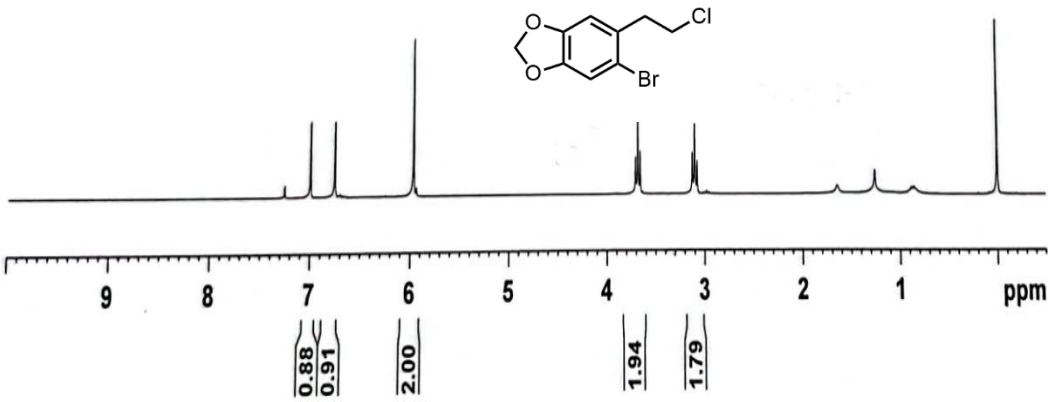


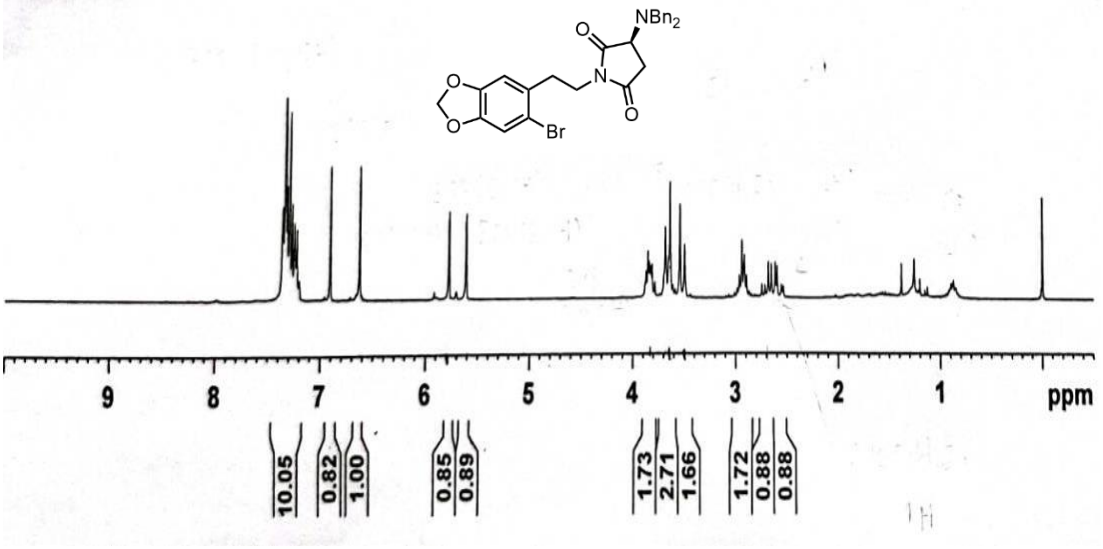
^{1}H NMR of compound 24



^{1}H NMR of compound 25



^{1}H NMR of compound 21



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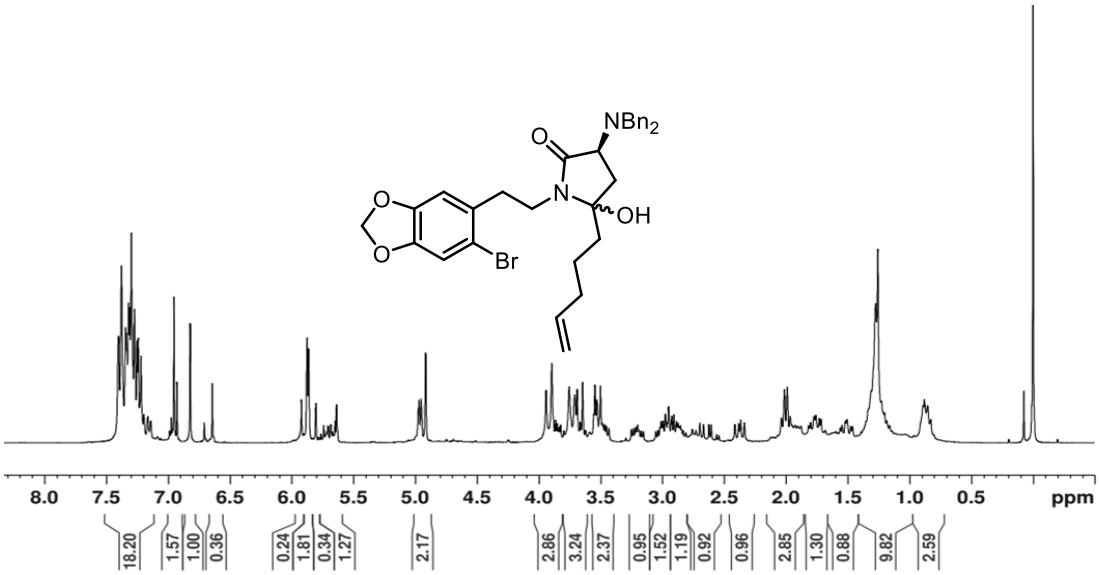
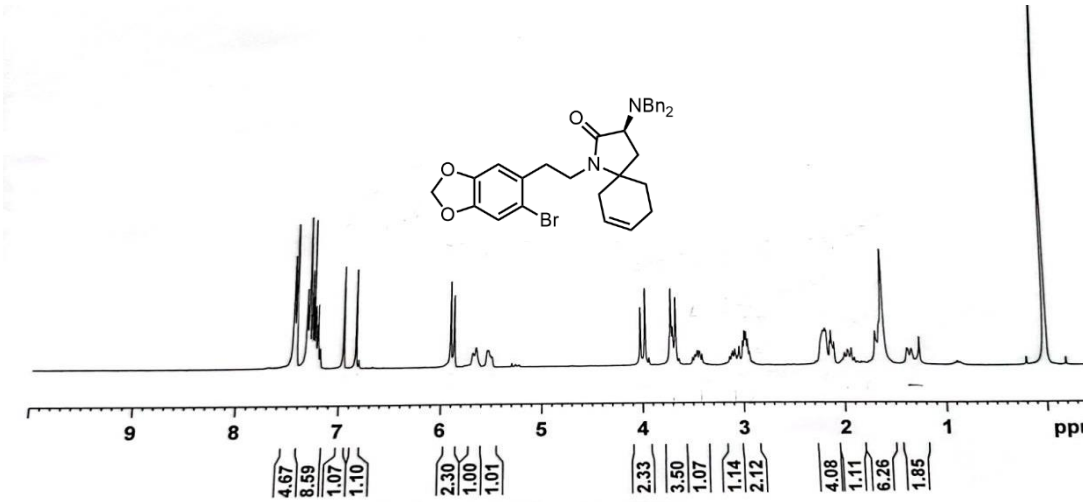
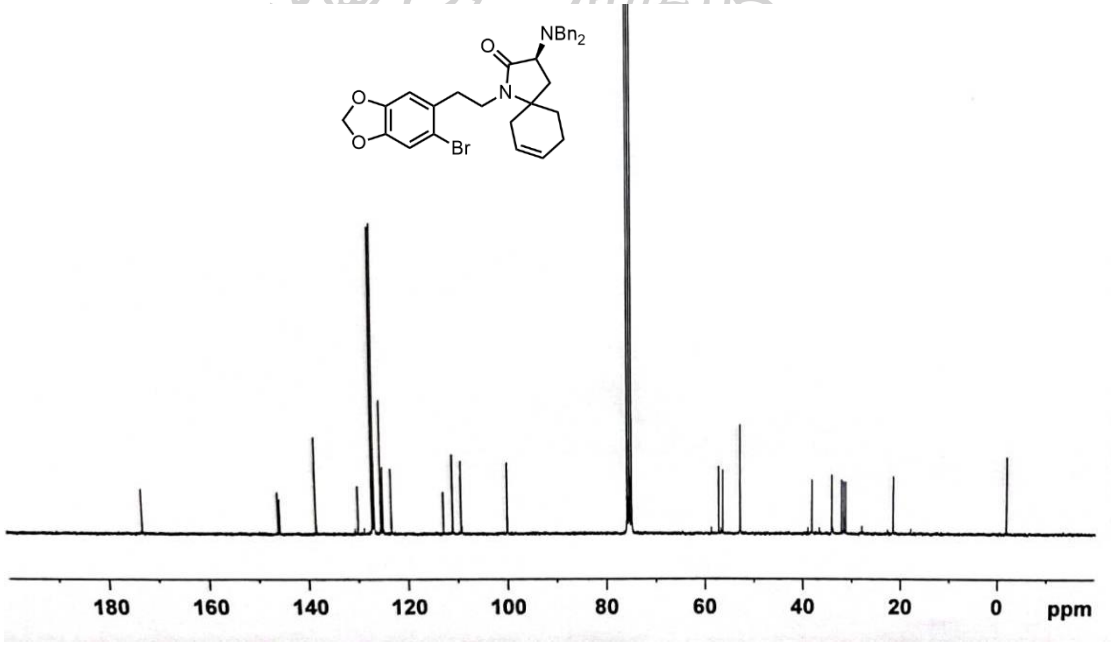


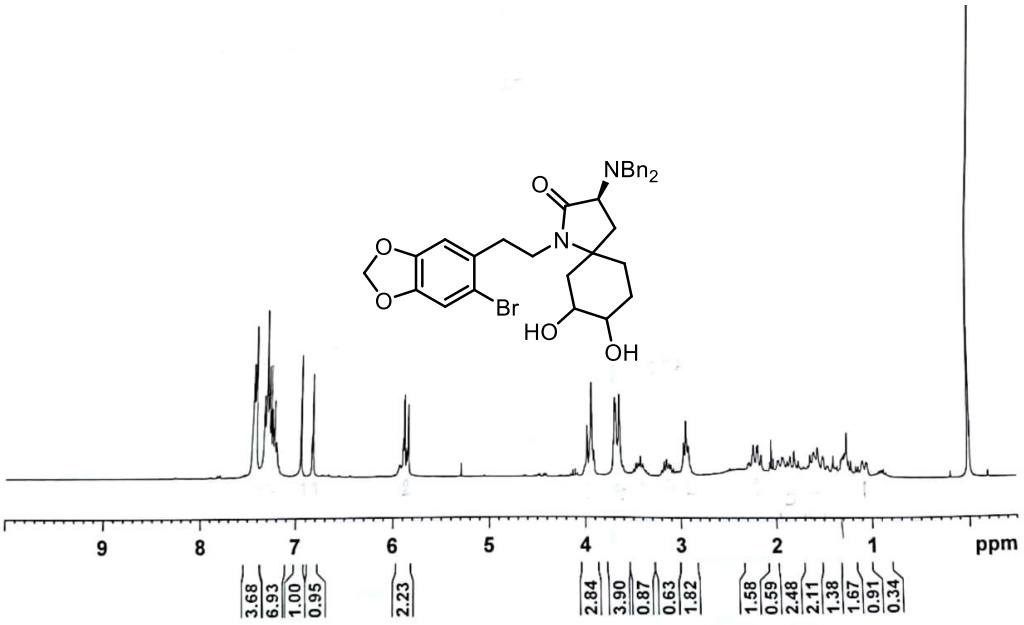
^{1}H NMR of compound 19a



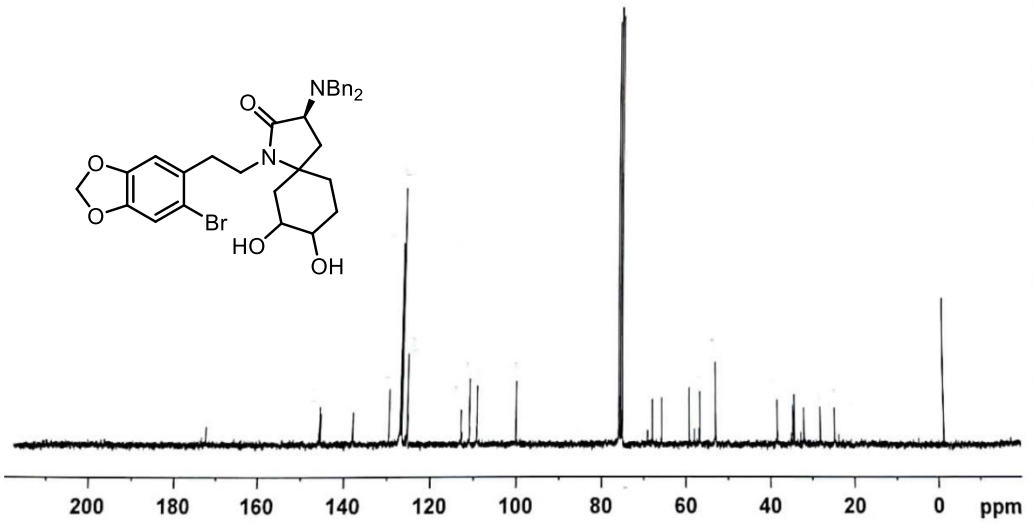
^{1}H NMR of compound 18



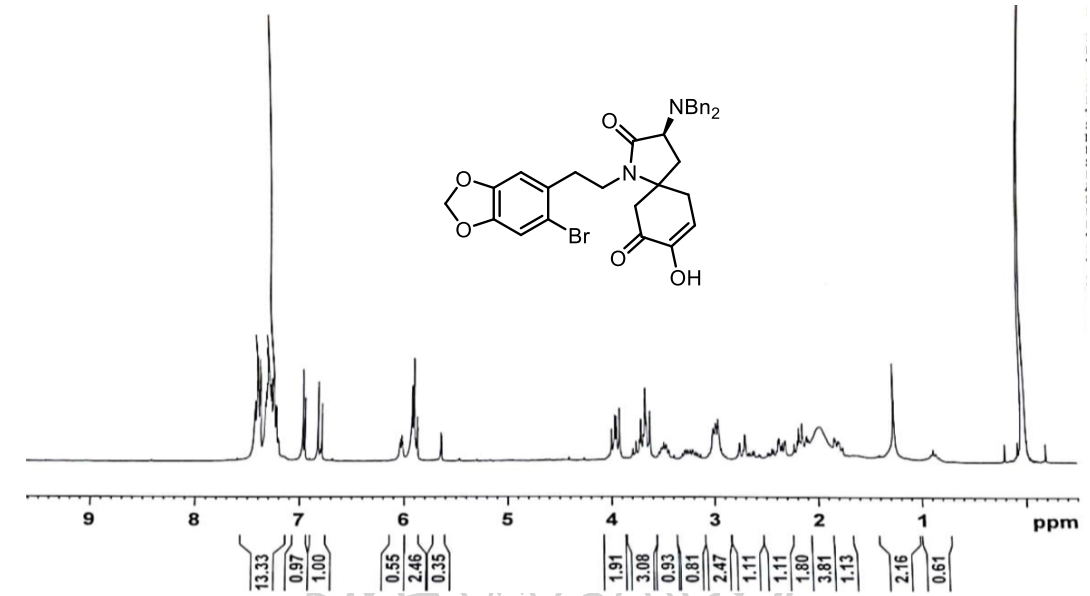
^{13}C NMR of compound 18



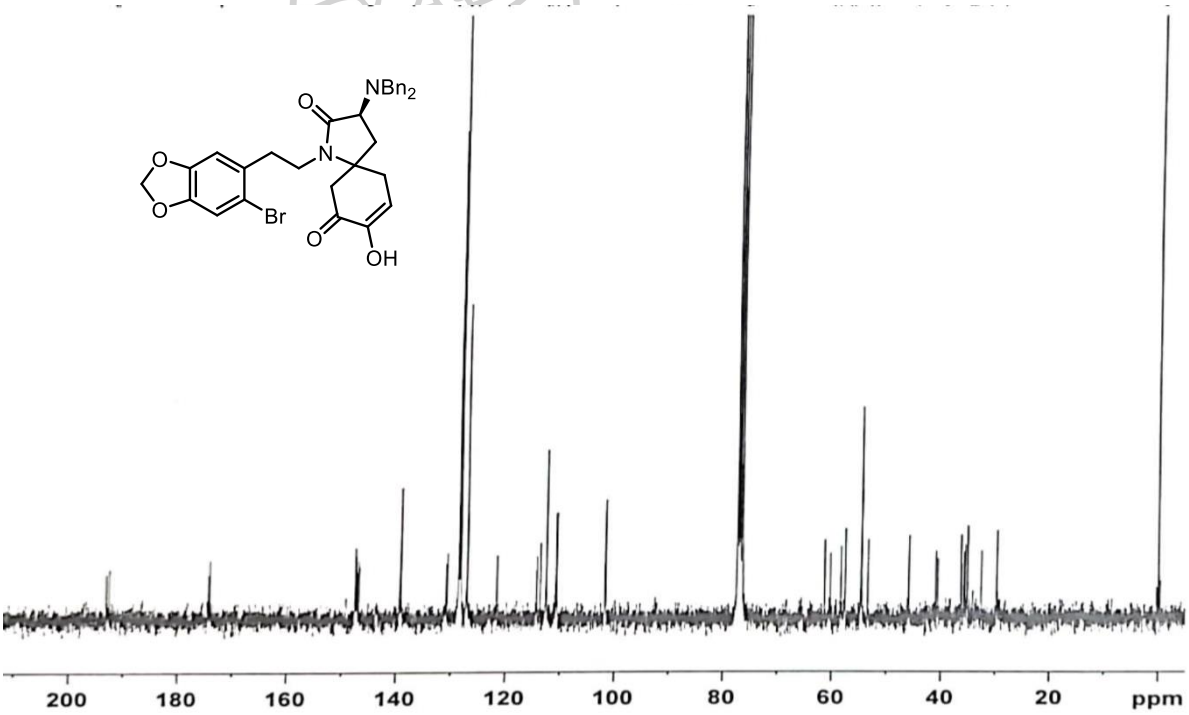
^{1}H NMR of compound 26



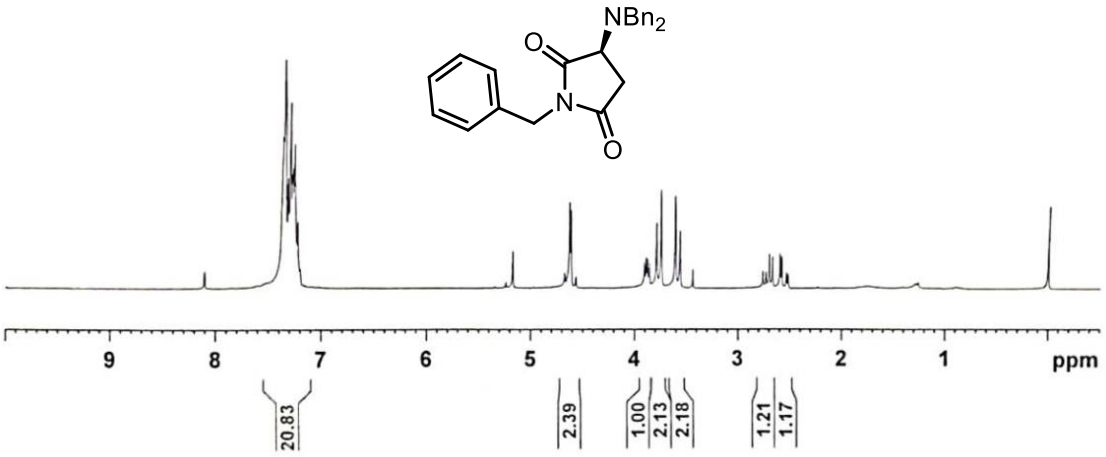
^{13}C NMR of compound 26



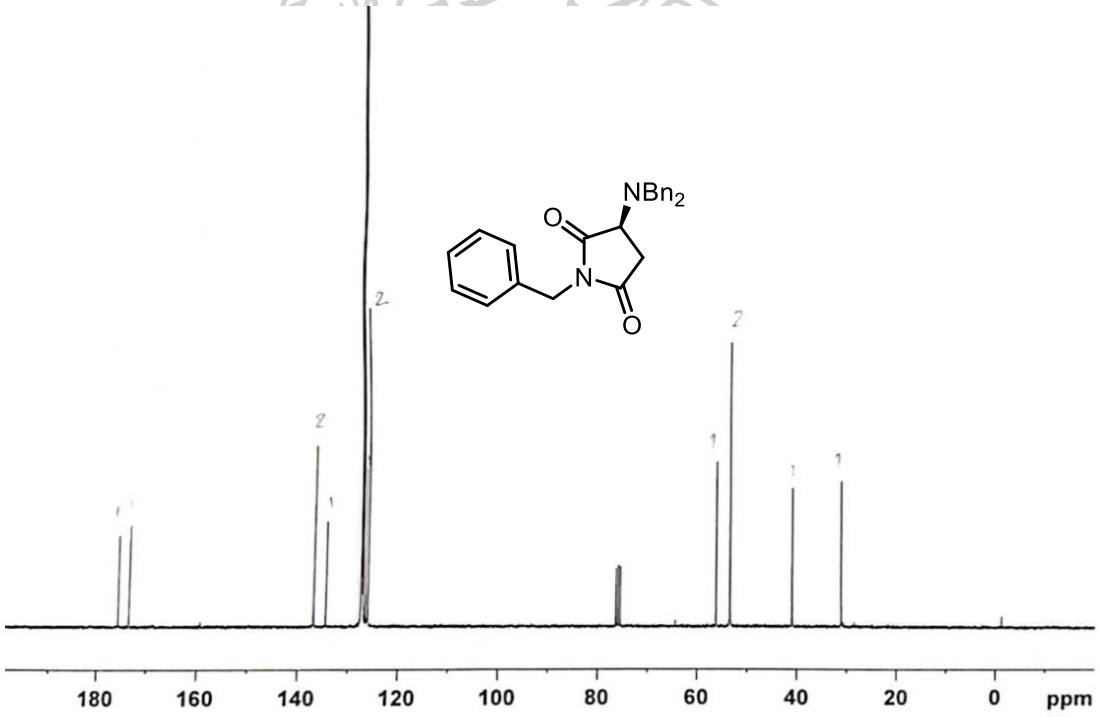
^{1}H NMR of compound 27



^{13}C NMR of compound 27

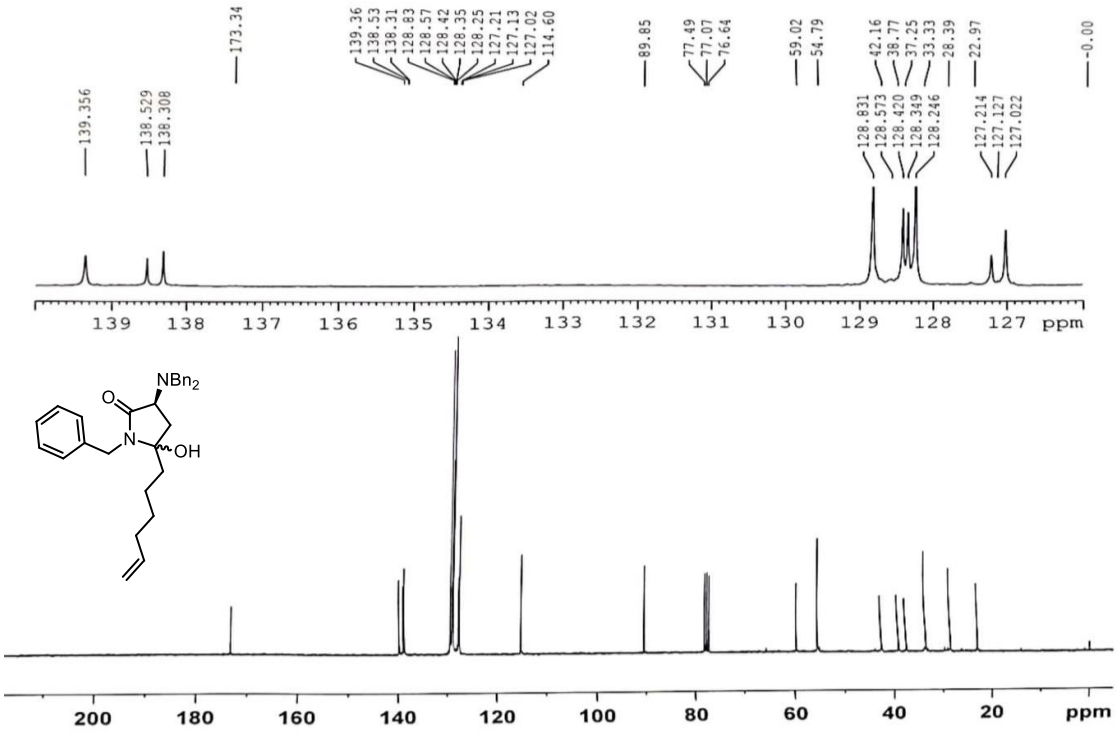


^{1}H NMR of compound 28

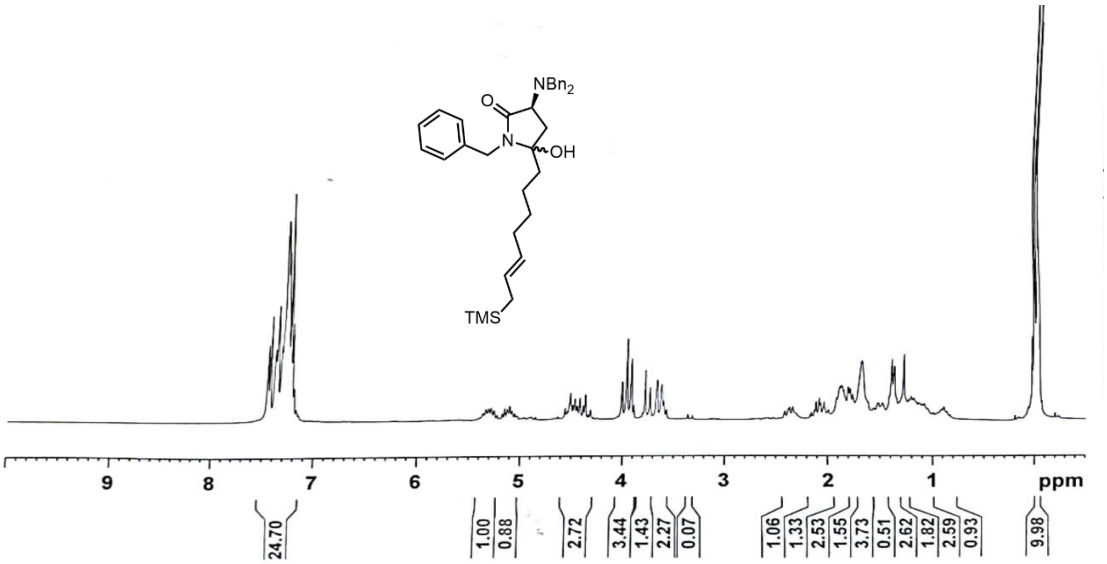


^{13}C NMR of compound 28

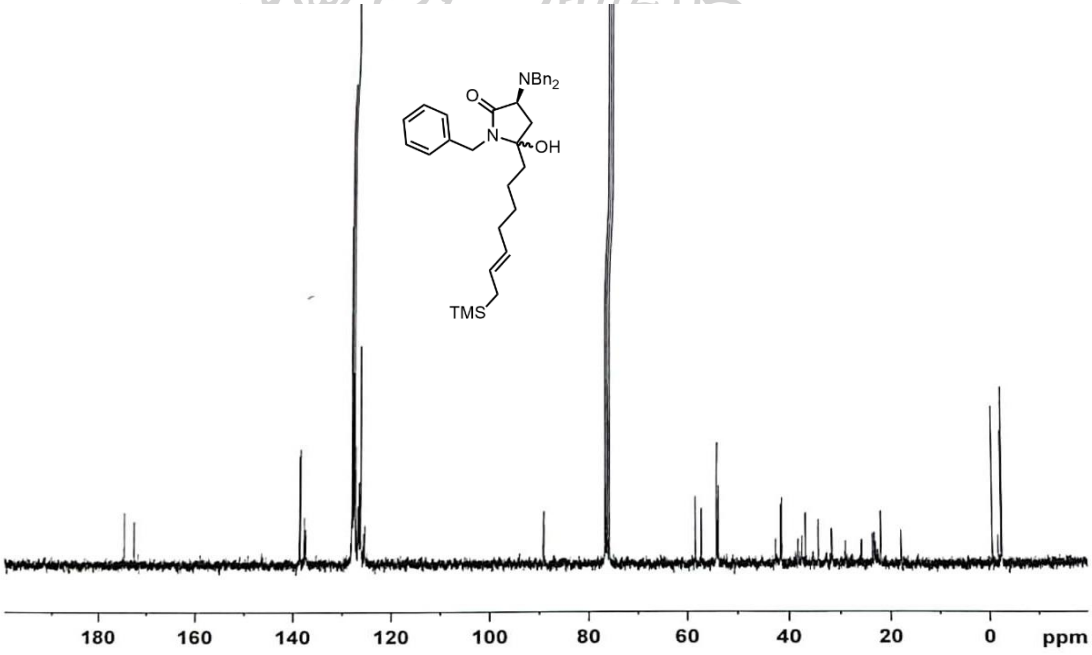
^{1}H NMR of compound 29a



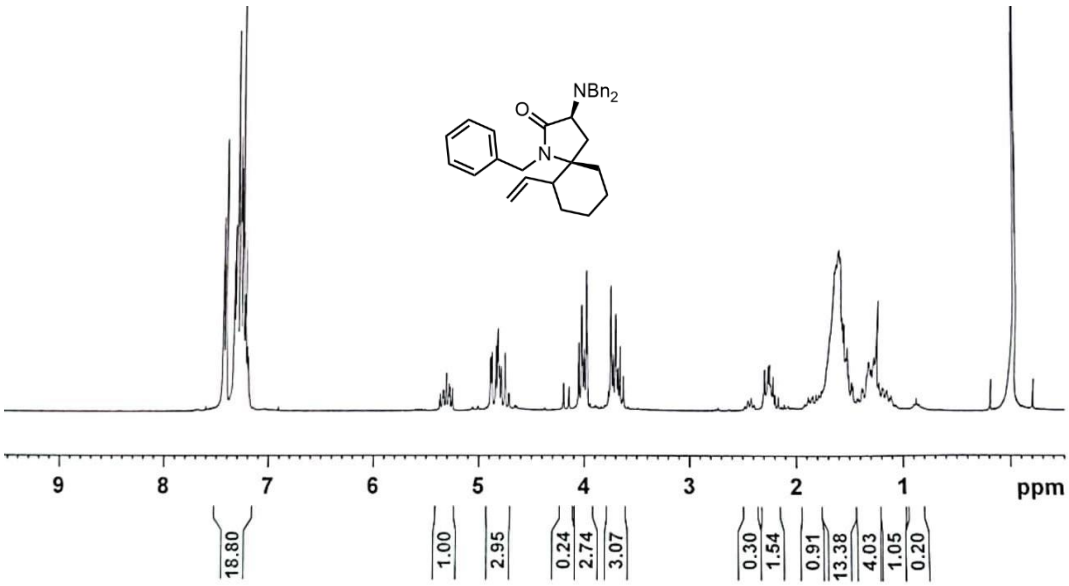
^{13}C NMR of compound 29a



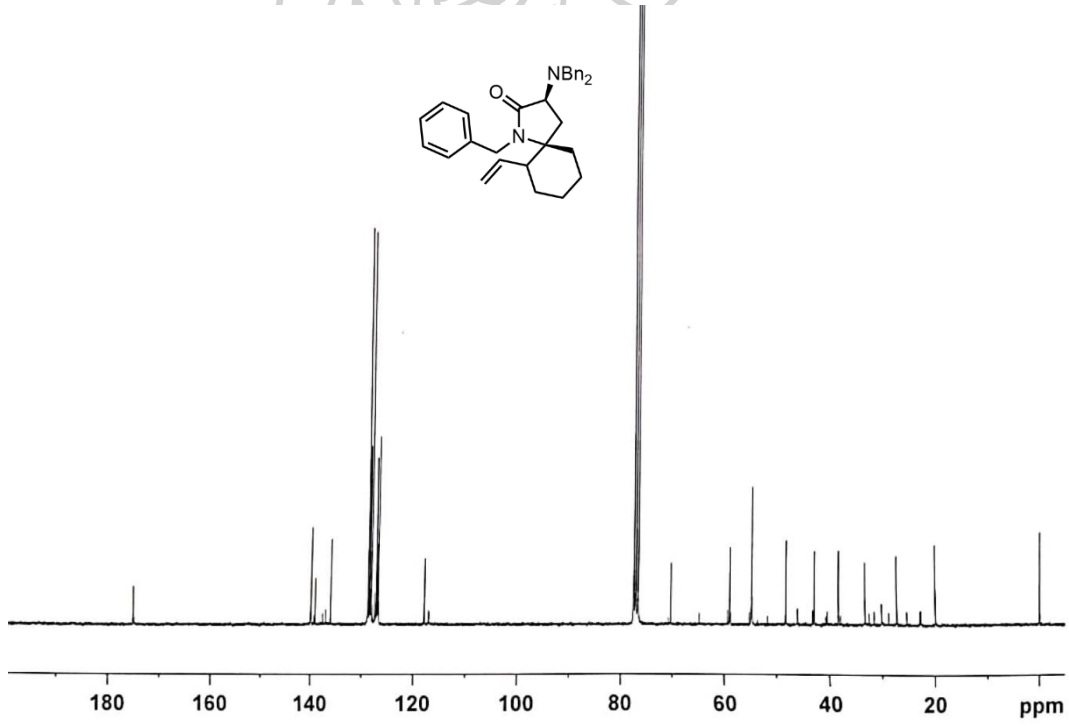
^{1}H NMR of compound 30



^{13}C NMR of compound 30



^{1}H NMR of compound 31



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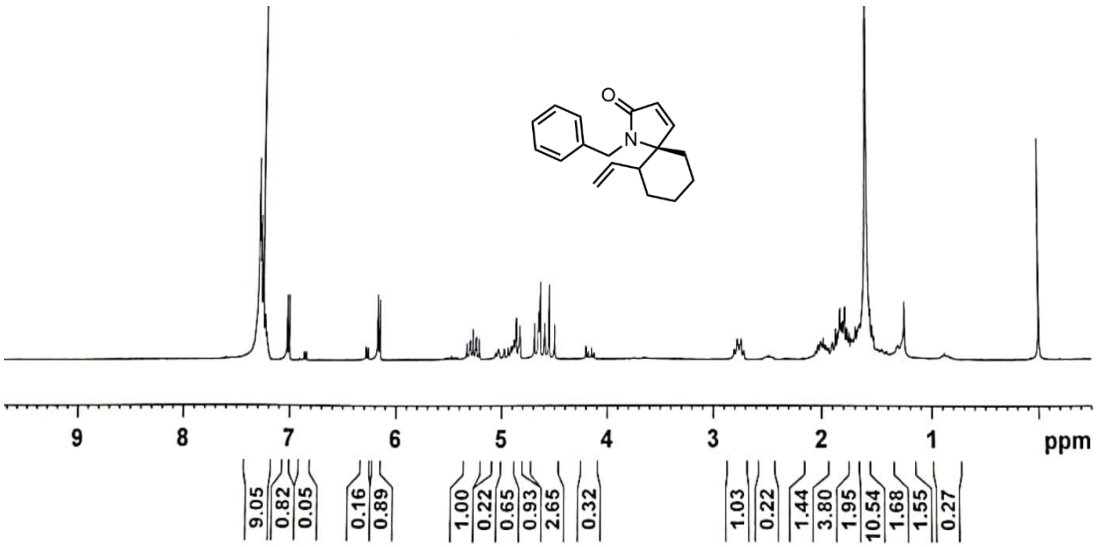
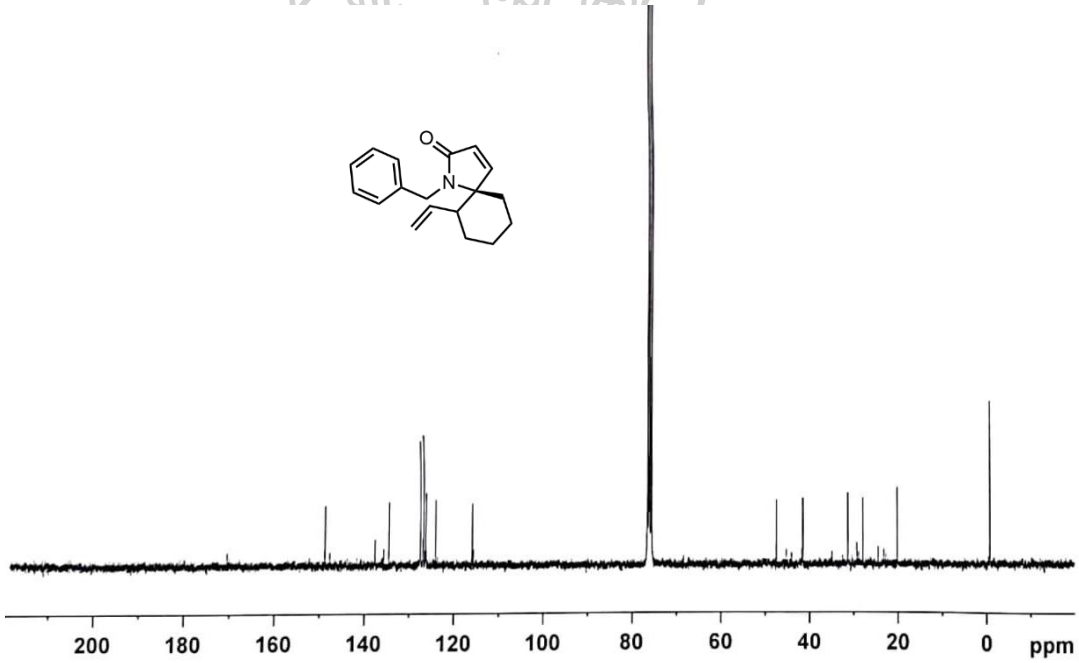


^{1}H NMR of compound 32



^{13}C NMR of compound 32

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