SYNTHESIS OF PLICAMINE

By
MR. Ittiphat KLAYPARN

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

การสังเคราะห์พลิคามีน

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Title	Synthesis of Plicamine
By	MR. Ittiphat KLAYPARN
Field of Study	(CHEMISTRY)
Advisor	Assistant Professor Punlop Kuntiyong, Ph.D.

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

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MR. Ittiphat KLAYPARN : Synthesis of Plicamine Thesis advisor : Assistant Professor Punlop Kuntiyong, Ph.D.

The *Amaryllidaceae* alkaloids have become targets for synthetic chemists, due to their wide variety of bioactivities and potential for utilization in medicinal chemistry. In addition, the structural complexity of these alkaloids makes them interesting and challenging to synthesize and most of them are classified as isoquinoline alkaloids, whose structures are often different. The study showed that it was formed biogenetically by intramolecular oxidative coupling of norbelladines. At present, there is an isolation of *Amaryllidaceae* alkaloids from more than 100 plants and through spectroscopic structure determination.

At present, our research group is studying the synthesis of natural products in the indolizidine, quinolizidine, and other related alkaloids, including isoquinoline alkaloids, using chiral succinimide and chiral glutarimide as key intermediates in the synthesis, both of which are synthesized from L-amino acid.

In this research, we will discuss synthetic studies of plicamine, which are not classified as indolizidine or quinolizidine alkaloids but could be synthesized using chiral dibenzylamino-succinimide as a key intermediate as well.

Plicamine is an Amaryllidaceae alkaloid isolated by Manfred's research group in 1999 from *Galanthus plicatus* subsp. *byzantinus*, a plant native to northwestern Turkey. Moreover, plicamine possesses *in vitro* anti-inflammatory activity by the inhibition of lipopolysaccharide (LPS)-induced nitric oxide (NO) production.

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MR. Ittiphat KLAYPARN

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CHAPTER 1

INTRODUCTION

Background and Signification of the Research Problem

The *Amaryllidaceae* alkaloids have become targets for synthetic chemists, due to their wide variety of bioactivities and potential for utilization in medicinal chemistry. In addition, the structural complexity of these alkaloids makes them interesting and challenging to synthesize. Most *Amaryllidaceae* alkaloids are classified as isoquinoline alkaloids. Some representative members of this group such as lycorine, plicamine, crinine, tazettine and galanthamine are shown in Figure 1. Biosynthetic study showed that they were formed biogenetically by intramolecular oxidative coupling of norbelladines. At present, *Amaryllidaceae* alkaloids have been isolated from more than 100 plants and their structures were confirmed through spectroscopic structure determination [1].

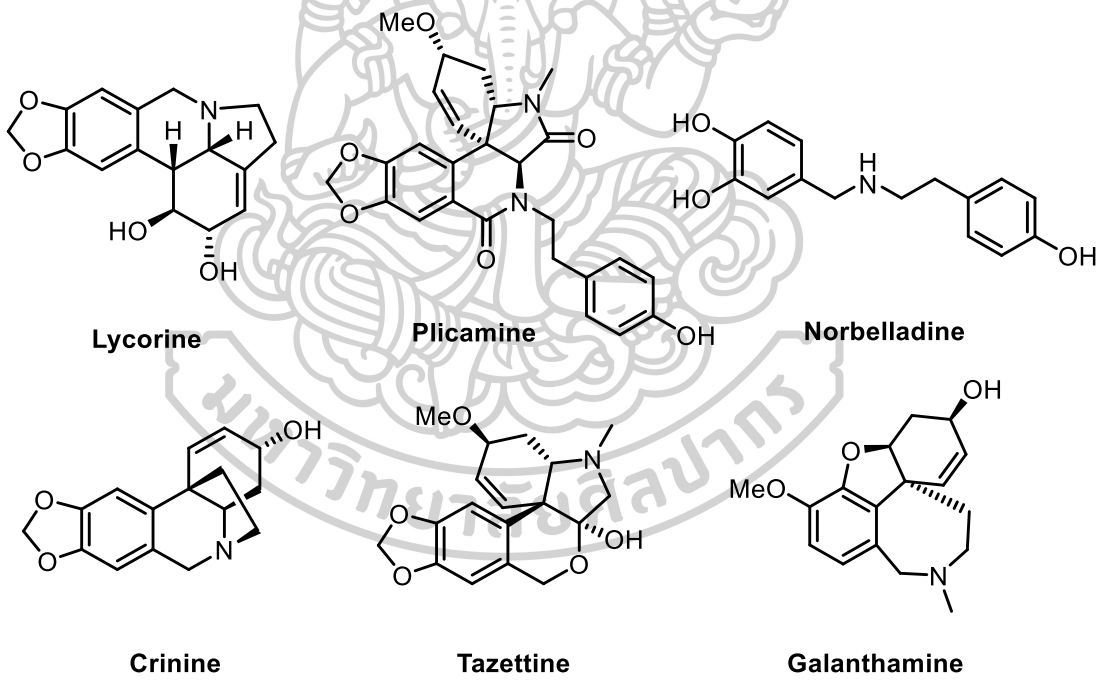


Figure 1 Examples of the *Amaryllidaceae* alkaloid family

Due to their biological activities and variety of structural complexity, synthetic chemists have been interested in synthesis of biologically active alkaloids and their analogues. At present, our research group has conducted asymmetric synthetic studies of indolizidine, quinolizidine alkaloid natural products. Our synthesis plans use chiral succinimide and glutarimide as key intermediates for construction of pyrrolidine and piperidine found in the target molecules. The key cyclic imides are synthesized from L-amino acid.

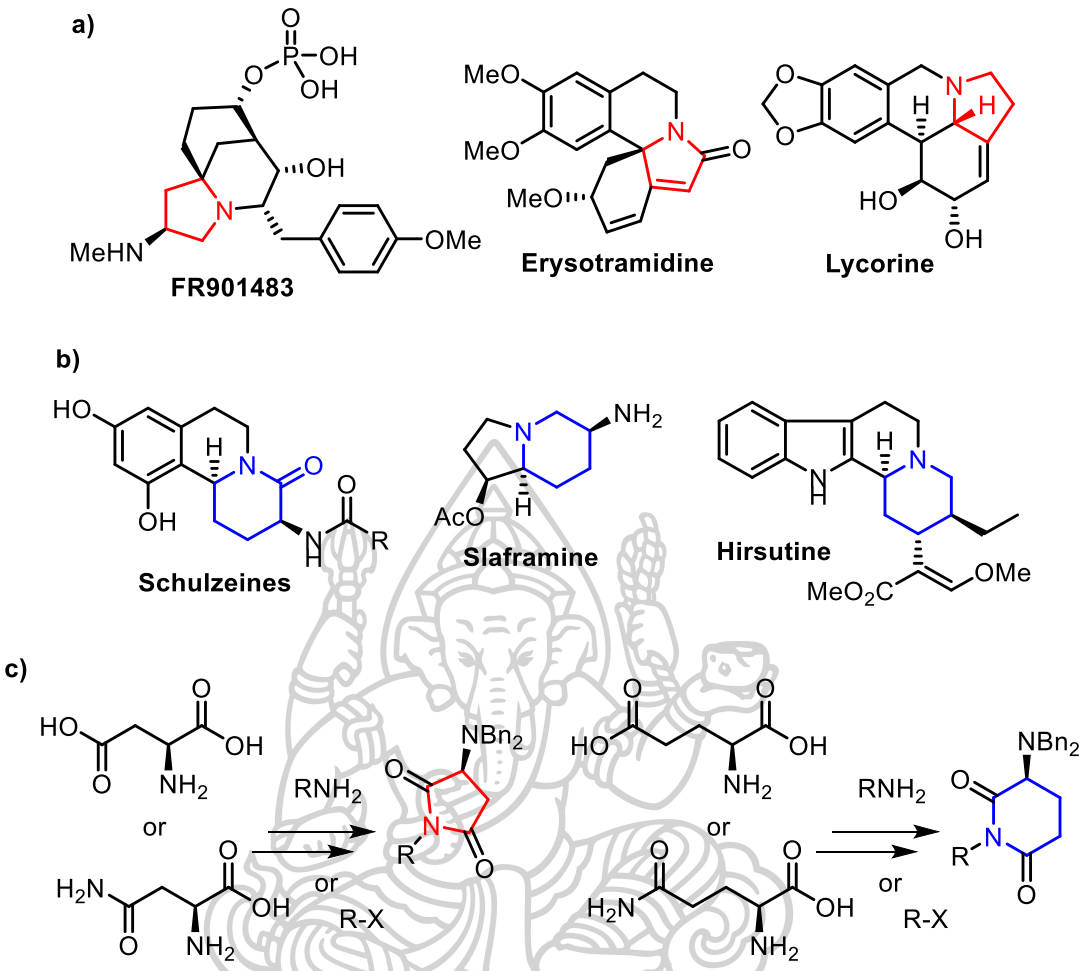
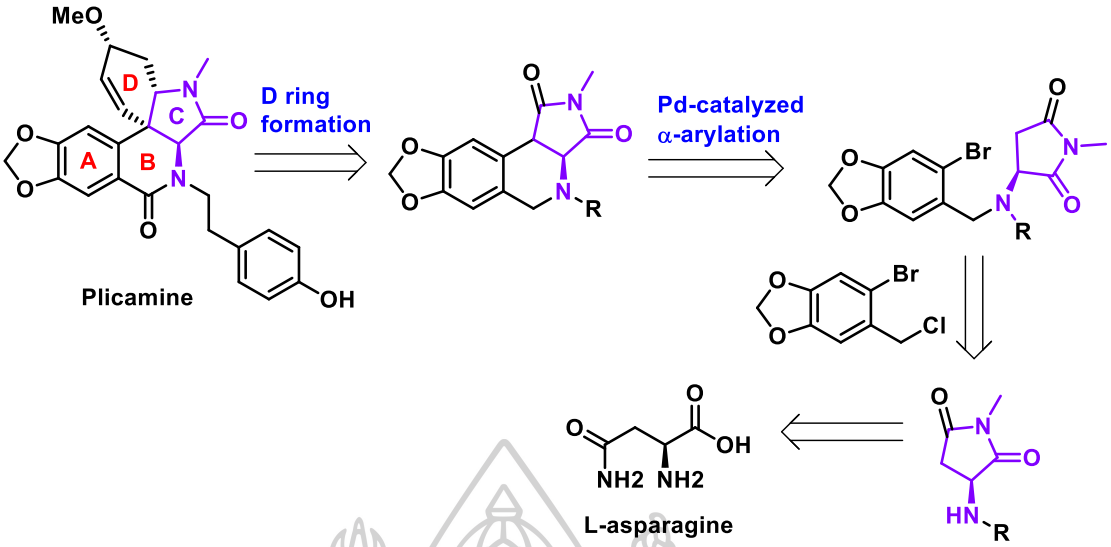


Figure 2 Indolizidine (**a**) and quinolizidine alkaloids (**b**) that can potentially be synthesized from chiral succinimide and glutarimide intermediates which can be prepared from L-amino acids (**c**)

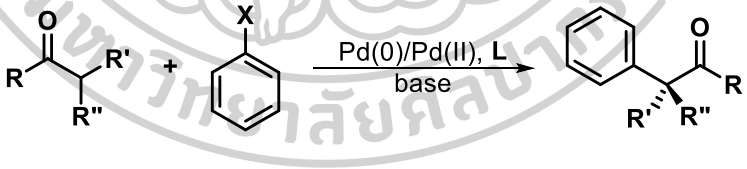
In this research, we will discuss synthetic studies of plicamine, which is not classified as indolizidine or quinolizidine alkaloid. Its structure consists of dioxolane-fused isoquinolinone (AB rings) and tetrahydrooxindole (CD rings). However, we envision that it could be synthesized using chiral dibenzylamino-succinimide as the key intermediate representing the C ring of plicamine and its synthesis can be incorporate well in our main asymmetric synthesis scheme of alkaloids. The key reaction of the syntheses is palladium-catalyzed α-arylation to form the B ring. The key chiral succinimide intermediate would be synthesized using L-asparagine as the chiral starting material.



Scheme 1 Our synthesis plan for plicamine

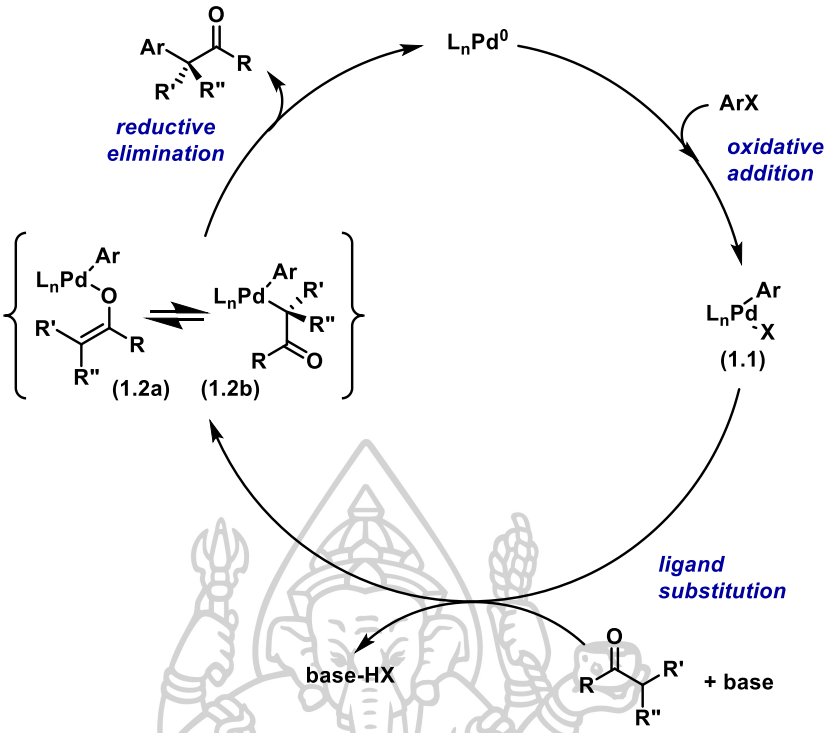
One of the most common reactions for the formation of a C-C bond between an aromatic carbon and the carbon alpha of a carbonyl group is the palladium-catalyzed α-arylation [2, 3], which has become a useful and general synthetic method for both inter- and intramolecular arylation.

In this reaction, palladium is able to catalyze a cross-coupling process that results in nucleophilic aromatic substitution of aryl halides by enolates, which are generated from a carbonyl group. Enolates may be generated *in situ* in the presence of a base or pre-formed enolates may be used without a need for a base during the cross-coupling reaction (Scheme 2).



Scheme 2 Palladium-catalyzed α-arylation reaction

The palladium-catalyzed α-arylation reaction mechanism [2] was proposed as shown in Scheme 3. Oxidative addition of an aryl halide to a Pd(0) complex would form an arylpalladium(II)halide complex **1.1**. Substitution of the coordinated halide by an enolate nucleophile and reductive elimination from the resulting palladium enolate complex **1.2a** or **1.2b** would form the α-aryl ketone, ester, or amide and regenerate the Pd(0) complex that started the cycle.



Scheme 3 Proposed palladium-catalyzed α-arylation mechanism

Objectives of Research

To study a synthetic methodology of plicamine, an *Amaryllidaceae* alkaloid based on substrate-controlled asymmetric synthesis using L-asparagine as chiral starting material. The synthesis of key tricyclic core of plicamine will employ palladium-catalyzed α-arylation. The key reaction can potentially lead to 2 isomeric products; a) cyclization to form the ABC core of plicamine and b) spirocyclization to form spiro[isoindoline-pyrrolidine-dione] which is a potential aldolase or aldose reductase inhibitor.

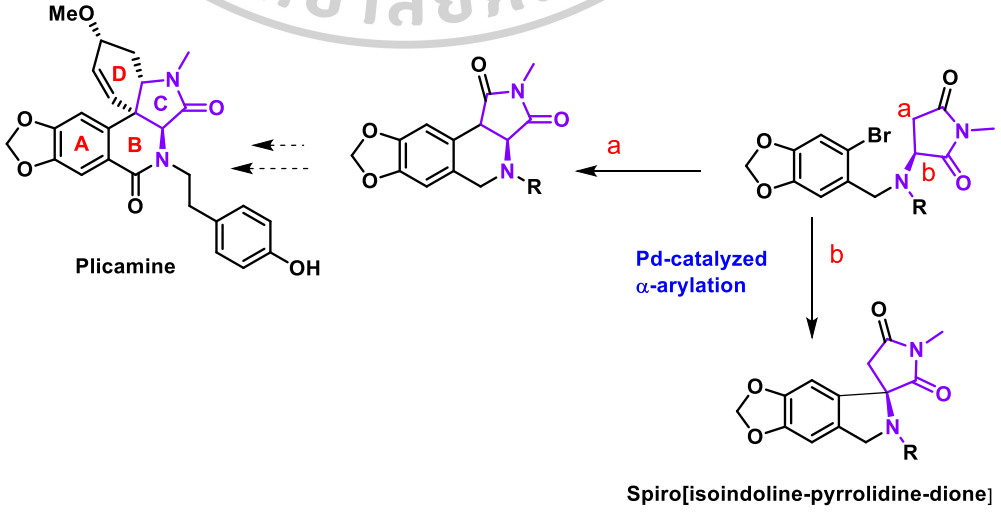


Figure 3 Objectives of Research

CHAPTER 2

LITERATURE REVIEW

Plicamine

Plicamine is an Amaryllidaceae alkaloid isolated by Manfred's research group [4] in 1999 from *Galanthus plicatus* subsp. *byzantinus*, a plant native to northwestern Turkey. Moreover, plicamine possesses *in vitro* anti-inflammatory activity by the inhibition of lipopolysaccharide (LPS)-induced nitric oxide (NO) production.

Figure 4 Flowers of the *Galanthus plicatus* [5]

The structures and the stereochemistry of plicamine were determined by detailed NMR experiments. It consists of a pentacyclic core structure formed by dihydroisoquinolinone (AB ring) connected to tetrahydro-oxindole (CD ring) containing a 6,6-spirocyclic core at the B and D rings. There are four stereogenic centers as shown in Figure 5.

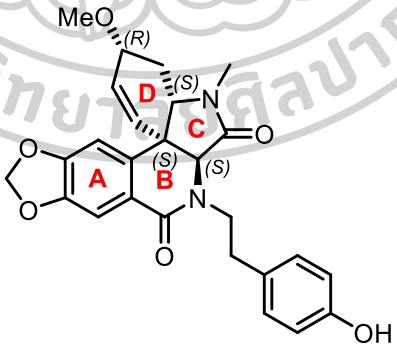
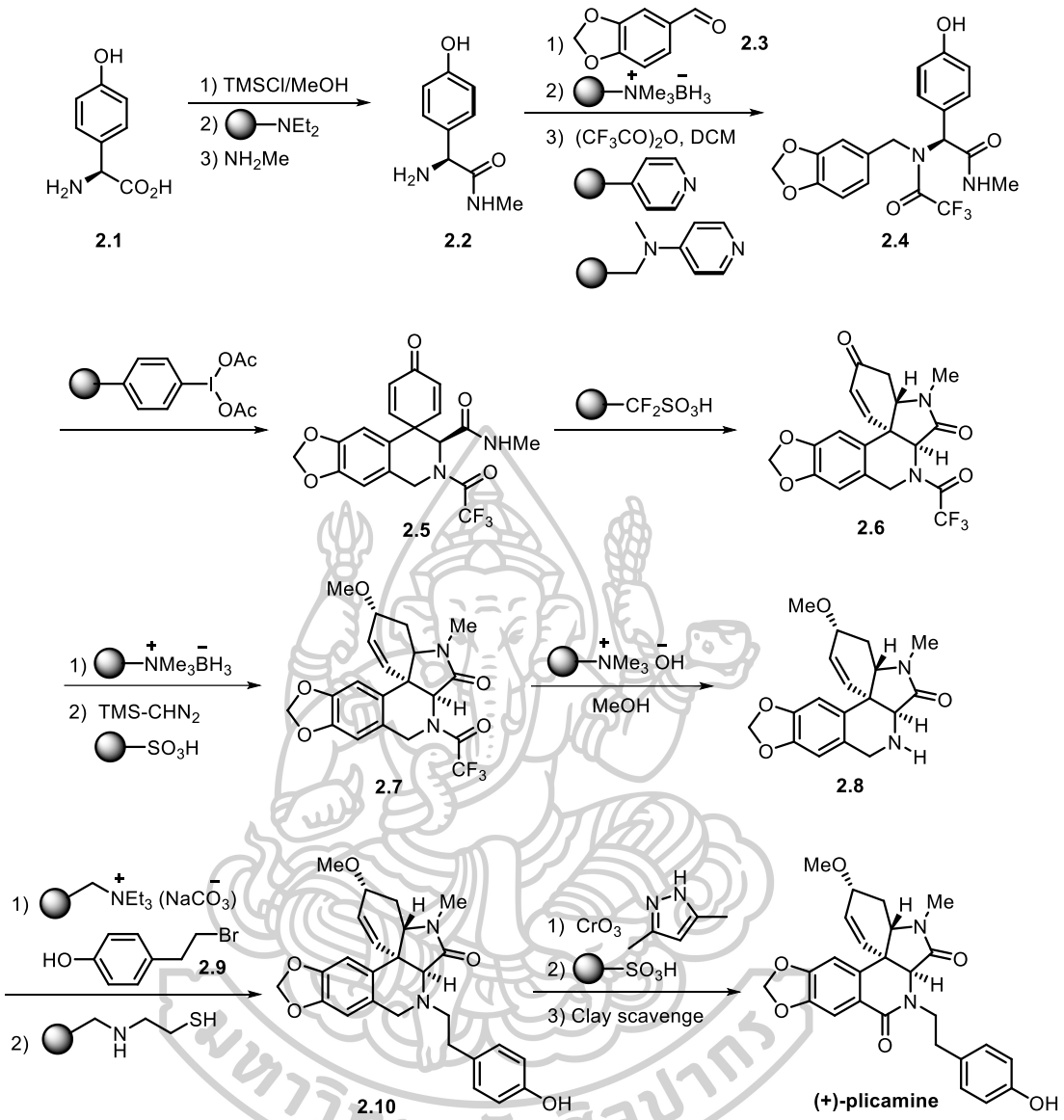


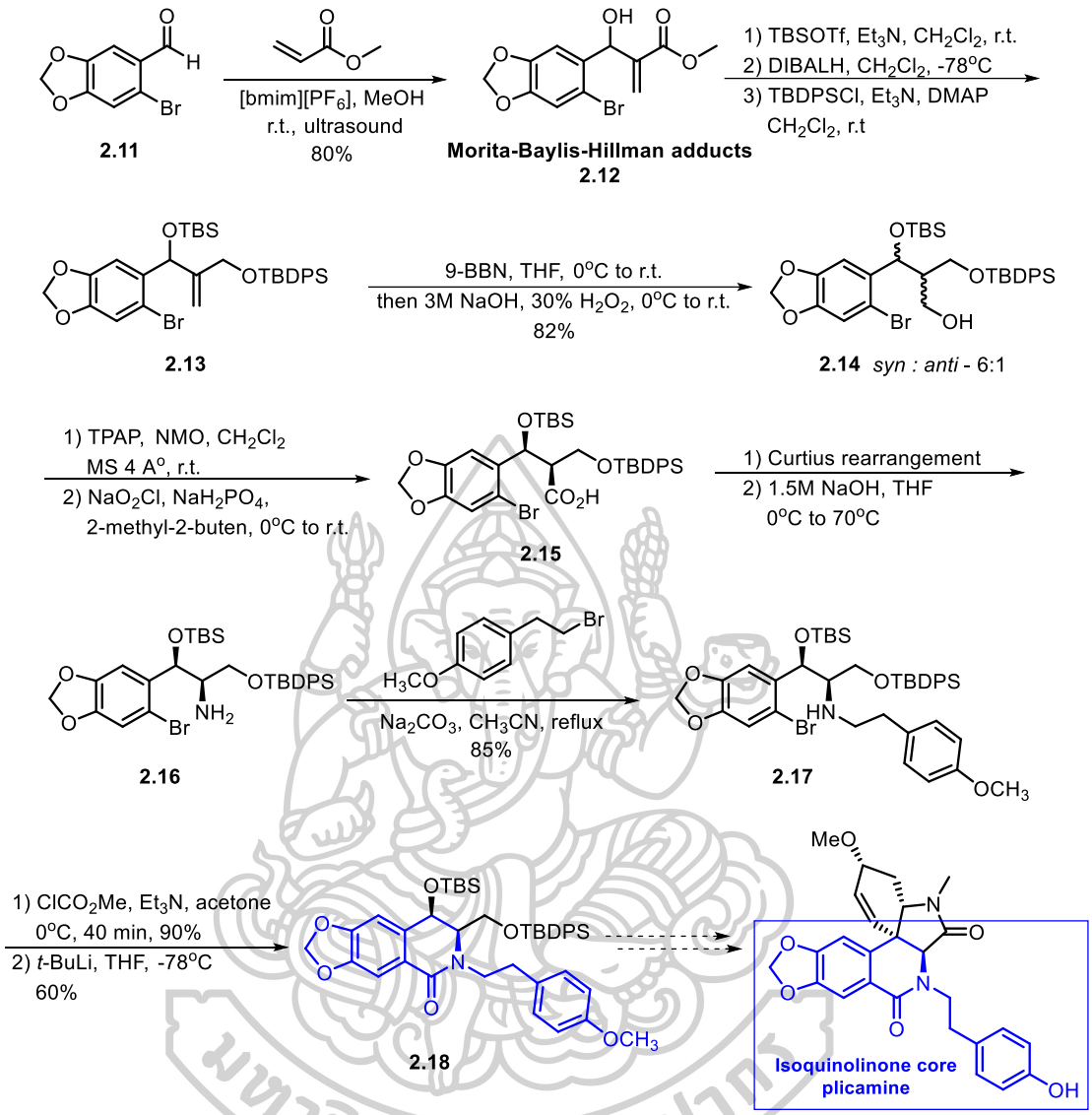
Figure 5 Structure of plicamine

In 2002, Ley and co-workers [6] reported a total synthesis of (+)-plicamine, an *Amaryllidaceae* alkaloid using solid-supported reagents and scavenger. Starting with the simple amino acid, L-4-hydrohyphenylglycine **2.1** as a suitable starting material, it could be synthesized via intermolecular oxidative coupling, conjugate addition, selective reduction, and alkylation reactions that delivered (+)-plicamine as the product (Scheme 4).



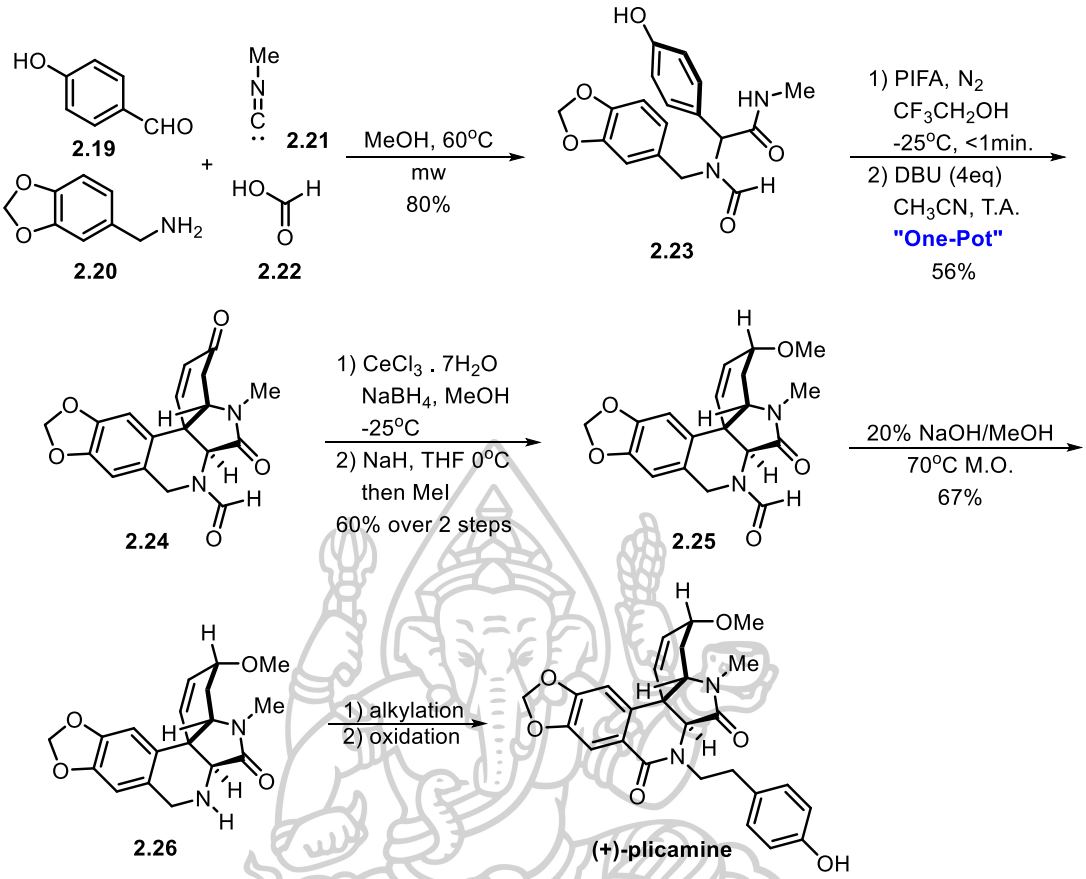
Scheme 4 Synthesis of (+)-plicamine by Ley and co-workers

In 2007, Coelho and co-workers reported the total synthesis of the functionalized dihydroisoquinolin-5(6*H*)-one core [7], which is the bottom part of the plicamine skeleton using Morita-Baylis-Hillman adducts **2.12** as substrate. The synthesis started with Morita-Baylis-Hillman reaction between 6-bromopiperonal **2.11** and methyl acrylate to give Morita-Baylis-Hillman adducts **2.12**. The adduct **2.12** was converted to acid **2.15** in 6 steps and the Curtius rearrangement of acid **2.15** provided amine **2.16**. Finally, isoquinolinone **2.18** synthesis was accomplished in 3 steps from amine **2.16**, where the structure of **2.18** exhibits all substituents that are found on the bottom part of the structure of plicamine (Scheme 5).



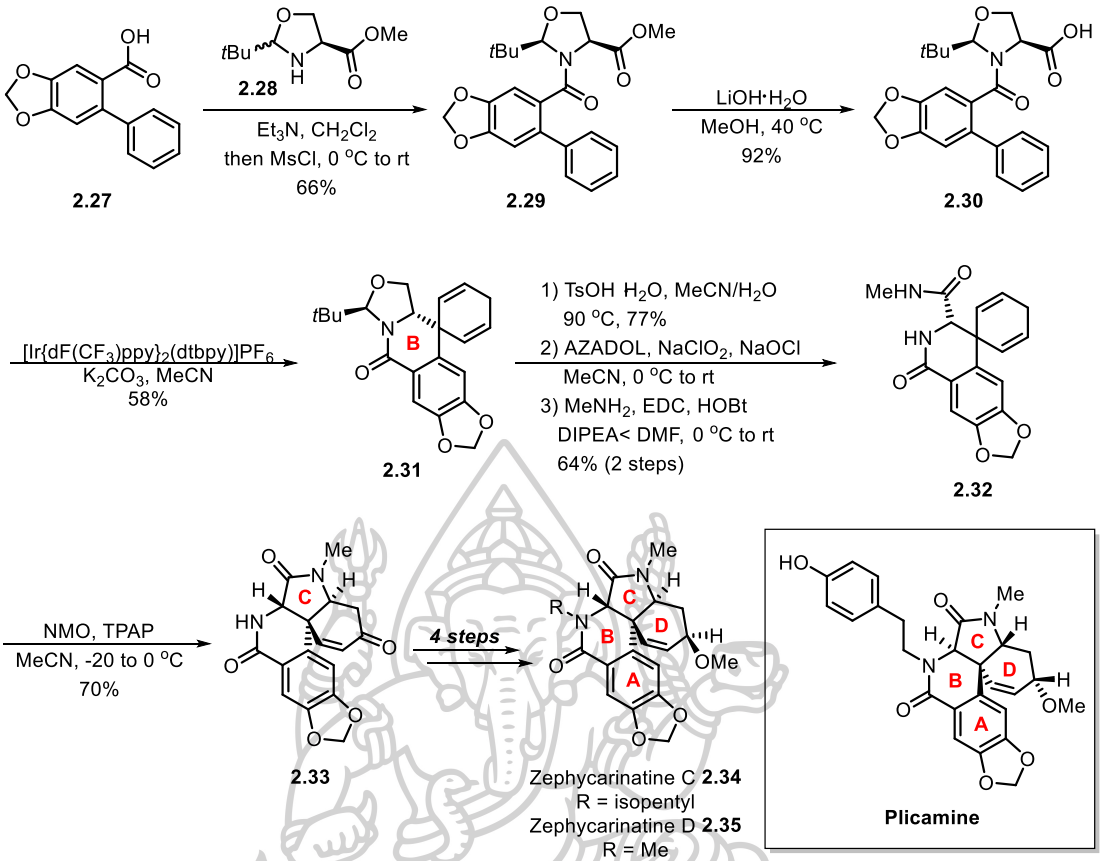
Scheme 5 Synthesis of dihydroisoquinolin-5(6H)-one core by Coelho and co-workers

Miranda and Mijangos reported a formal synthesis of (±)-plicamine [8]. An Ugi four-component reaction (Ugi-4CR) between *p*-hydroxybenzaldehyde **2.19**, piperonyl amine **2.20**, an isocyanide **2.21**, and a carboxylic acid **2.22** would provide the α-substituted bisamide **2.23**. After that, indoloisoquinolones **2.24** was obtained by a one-pot oxidative dearomative phenol coupling/Michael addition and converted to (±)-plicamine in 5 steps (Scheme 6).



Scheme 6 Synthesis of (±)-plicamine by Miranda and Mijangos

The latest work was reported in 2020, Ohno and co-workers reported a total synthesis of zephycarinatines C and D [9], which were the plicamine-type alkaloids. The synthesis started from the coupling reaction between the known oxazolidine **2.28** derived from L-serine and the biphenyl-2-8-carboxylic acid derivative **2.27** to give ester **2.29** as a single diastereomer. Then, treatment of the ester **2.29** with LiOH·H_2O afforded the key carboxylic acid **2.30**. The stereoselective construction of the B-ring was obtained by photocatalytic reductive radical *ipso*-cyclization. The TPAP oxidation of 1,4-diene **2.31** followed by intramolecular 1,4-addition allowed the construction of C-ring. Finally, zephycarinatines C **2.34** and D **2.35** were synthesized in 4 additional steps (Scheme 7).



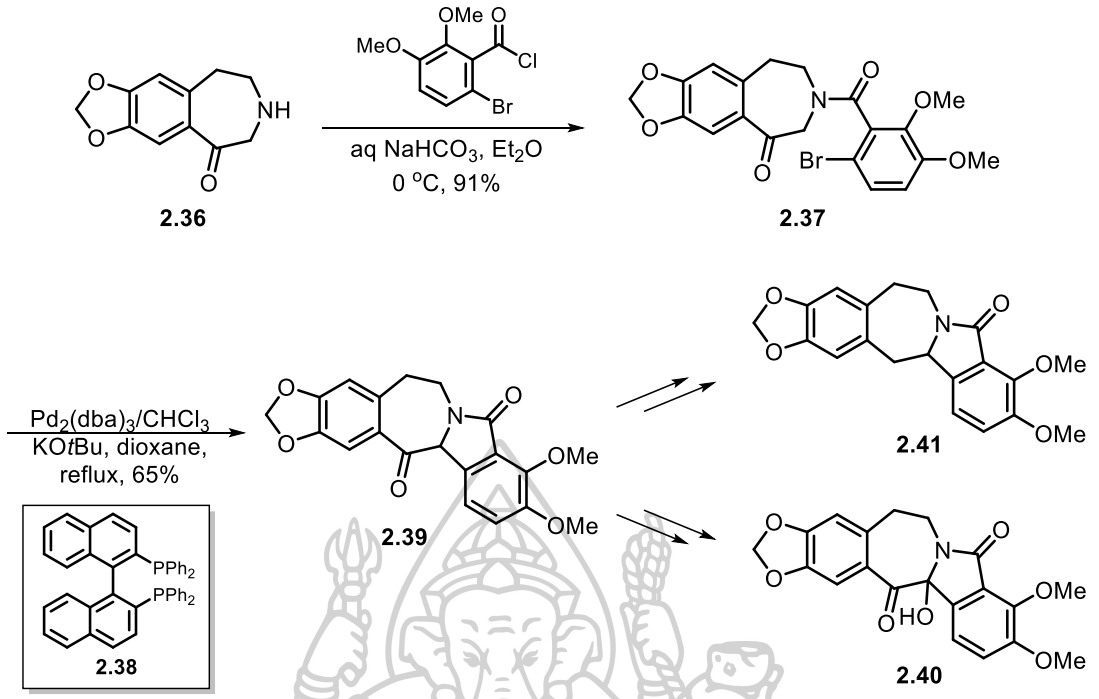
Scheme 7 Synthesis of zephycarinatines C and D by Ohno and co-workers

Palladium-catalyzed α-arylation

Palladium-catalyzed α-arylation is useful for the synthesis of natural products and active pharmaceutical ingredients (APIs). In this research, we used palladium-catalyzed α-arylation to construct the B-ring of plicamine as the key step. Examples of inter- and intramolecular palladium-catalyzed α-arylation in synthesis are shown in the following schemes.

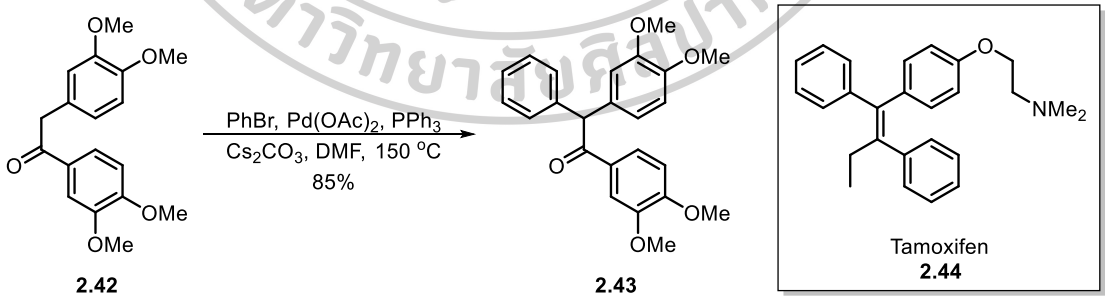
I) Palladium-catalyzed α-arylation of Ketones

Honda and Sakamaki reported the synthesis of isoindolobenzazepine alkaloids, chilenine **2.40** and lennoxamine **2.41** [10]. The synthesis started with Schotten–Baumann acylation reaction to produce amide **2.37**, which underwent intramolecular α-arylation when treated with a catalyst system consisting of $Pd_2(dba)_3{\cdot}CHCl_3$ and (±)-BINAP **2.38**. The cyclized product, 13-deoxychilenine **2.39** was obtained in 65% yield. Then, it was converted to (±)-chilenine **2.40** and (±)-lennoxamine **2.41** in a few steps (Scheme 8).



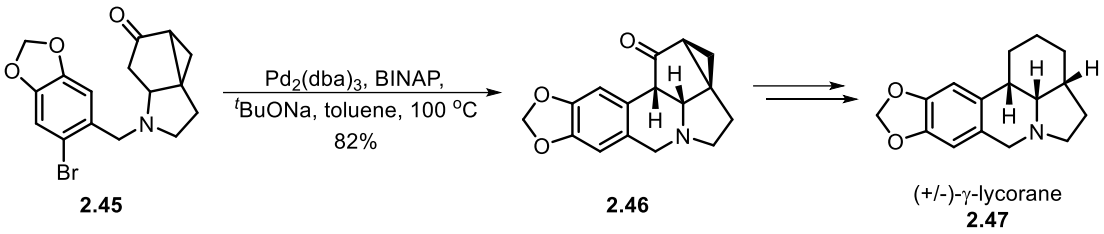
Scheme 8 Synthesis of chilenine and lennoxamine by Honda and Sakamaki

Monodentate phosphine ligands such as PPh_3 and P(*t*-Bu)$_3$ have also been used in α-arylation for the synthesis of natural products. Dominguez and co-workers reported a high-yielding procedure for the preparation of (±)-1,2,2-triarylethanones **2.43** [11], skeletal analogues of tamoxifen **2.44**, from deoxybenzoins **2.42** was treated with bromobenzene catalyzed by $Pd(OAc)_2$ and PPh_3 as a ligand. The α-arylation product was formed without any side reactions, such as dehalogenation of the aryl bromide (Scheme 9).



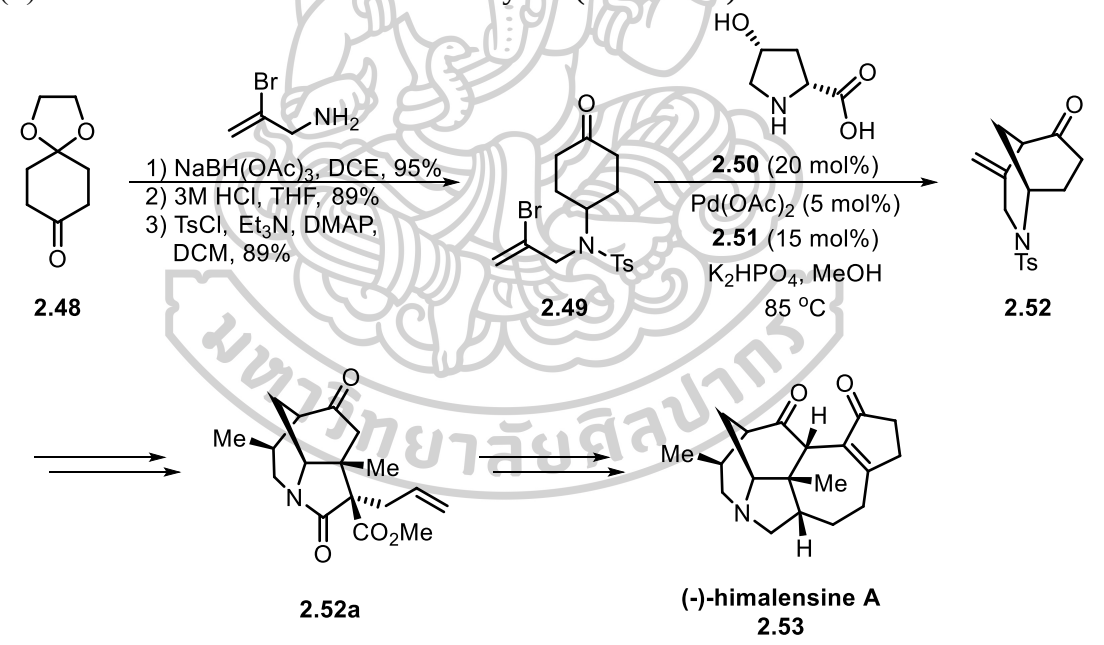
Scheme 9 Synthesis of 1,2,2-triarylethanones by Dominguez and co-workers

In 2014, Liu reported a synthesis of γ-lycorane [12] using palladium-catalyzed intramolecular α-arylation of the ketone in tricyclic *N*-bromoarylmethyl-indolinone **2.45** catalyzed by $Pd_2(dba)_3$/BINAP with ^{t}BuONa as a base to give the complete skeleton **2.46** of lycorine-type alkaloid **2.47** in good yield (Scheme 10).



Scheme 10 Synthesis of lycorine-type alkaloids by Liu and co-workers

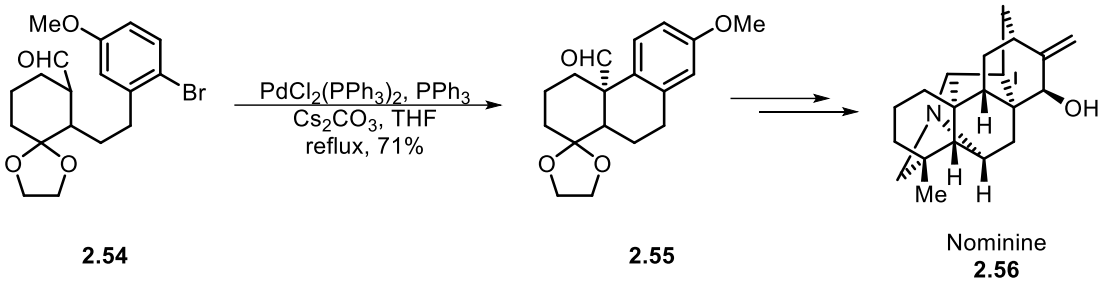
Moreover, analogous palladium-catalyzed C-C bond formation can also be performed between ketone and vinyl halide, as reported by Dixon and co-workers [13]. They reported the total synthesis of (−)-himalensine A via enantioselective desymmetrizing α-vinylation using a dual palladium/4-hydroxyproline catalyst system. The synthesis started with reductive amination of cyclohexanone **2.48** with 2-bromoprop-2-en-1-amine followed by ketal hydrolysis and amine tosylation to afford compound **2.49**. The condensation with 4-hydroxyproline **2.50** as the chiral amine organocatalyst and *p*-trifluoromethyl-substituted triaryl phosphine **2.51** as the ligand led to the desired cyclized product **2.52** in excellent yield. Then, it was converted to (−)-himalensine A **2.53** in 10% overall yield (Scheme 11).



Scheme 11 Synthesis of (−)-himalensine A by Dixon and co-workers

II) Palladium-catalyzed α-arylation of Aldehydes

The synthesis of (±)-nominine **2.56** was reported by Muratake and Natsume [14]. This synthesis involved the α-arylation of aldehyde **2.54** in the presence of the classical $PdCl_2(Ph_3P)$ catalyst, giving a 71% yield of the product. Then, the α-arylated aldehyde **2.55** was subsequently transformed into the target molecule **2.56** (Scheme 12).

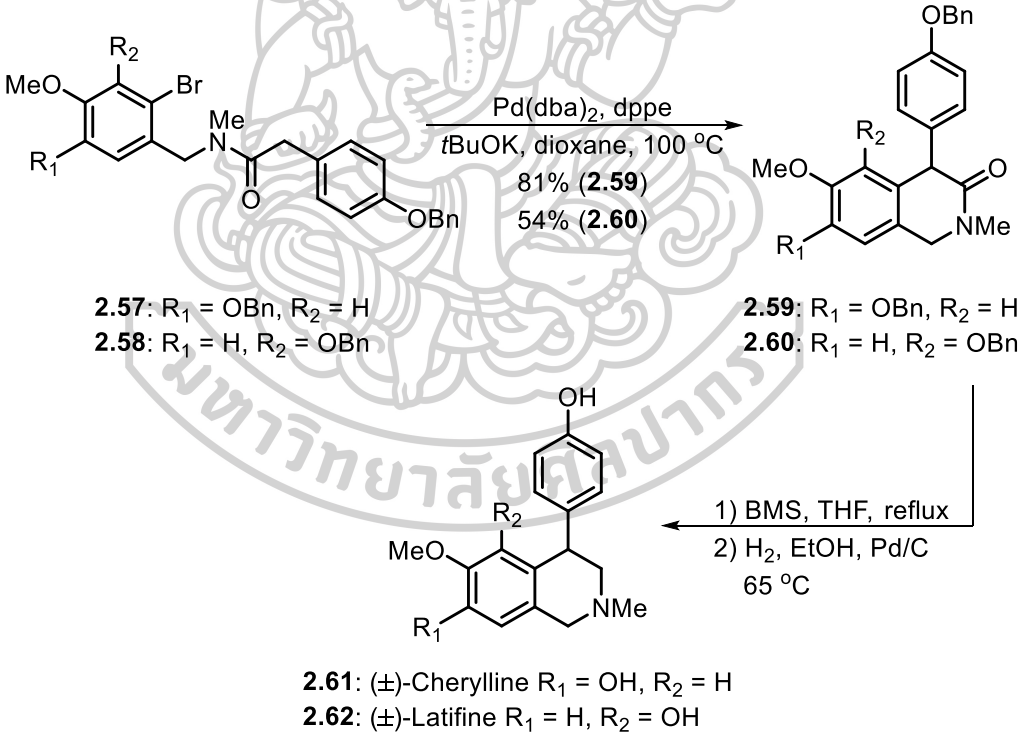


2.54 **2.55** Nominine **2.56**

Scheme 12 Synthesis of (±)-nominine by Muratake and Natsume

III) Palladium-catalyzed α-arylation of Amides

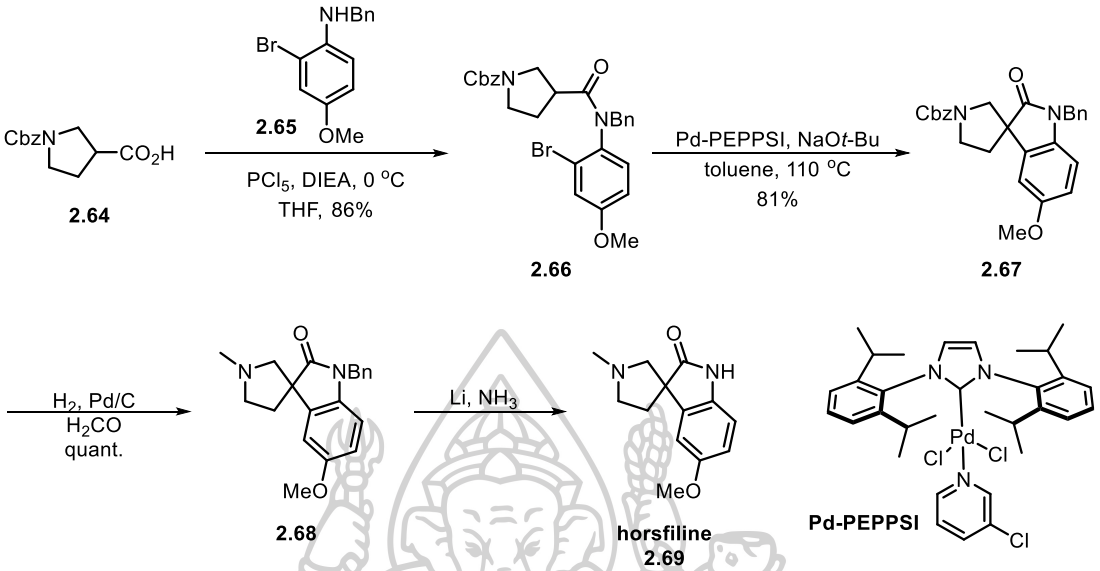
In 2001, Honda and co-workers reported short syntheses of cherylline and latifine, two natural products containing 4-aryl-THIQ (tetrahydroisoquinolines) cores [15] by palladium-catalyzed intramolecular coupling of amide enolate and aryl halides. The synthesis started with substrates **2.57** and **2.58** which were treated with $Pd(dba)_2$/dppe and KO*t*Bu to generate tetrahydroisoquinolines **2.59** and **2.60**, respectively. Then, α-aryl amides were converted to (±)-cherylline **2.61** and (±)-latifine **2.62** by borane reduction and subsequent deprotection (Scheme 13).



Scheme 13 Synthesis of cherylline and latifine by Honda and co-workers

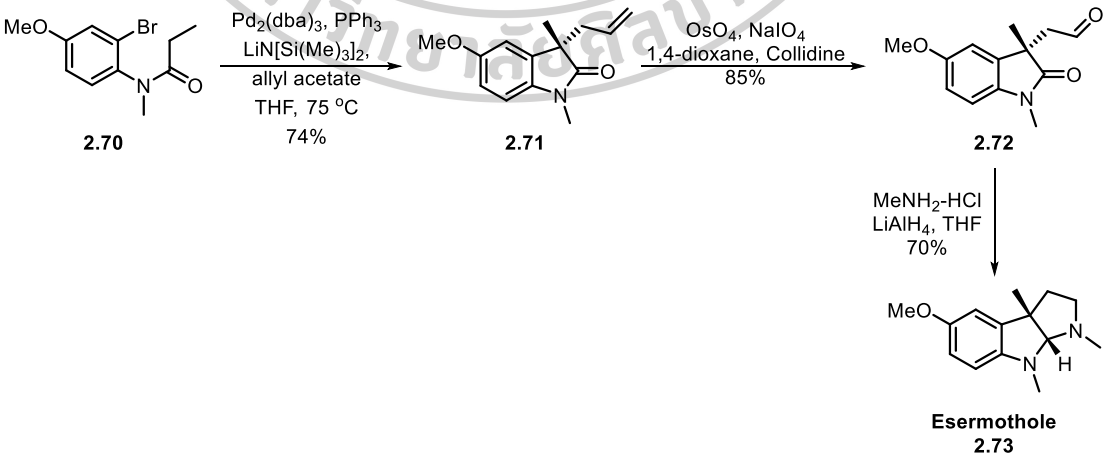
In 2010, Deppermann and co-workers reported the synthesis of the spirooxindole natural product horsfiline with intramolecular α-arylation of amide **2.63** as a key step [16]. The reaction between Cbz-protected homoproline **2.64** and the appropriate *o*-halogenated aniline **2.65** formed amide **2.66**, which was subjected to α-arylation reaction conditions catalyzed by [Pd]-PEPPSI to give spirooxindole **2.67**

with no dehalogenated byproduct. Finally, horsfiline **2.69** was obtained in 2 steps from spirooxindole **2.67** (Scheme 14).



Scheme 14 A Short synthesis of horsfiline by Deppermann and co-workers

The other example of palladium-catalyzed α-arylation was reported in 2011. Zhang and co-worker developed a synthetic route for the preparation of oxindoles bearing an all-carbon quaternary center through sequential arylation/allylation, as well as the synthesis of esermethole, a hexahydropyrrolo[2,3-*b*]indole alkaloids [17]. The amide **2.70** was treated with the $Pd_2(dba)_3/PPh_3$ complex in the presence of lithium bistrimethylsilylamide as a base in THF to afford oxindoles **2.71** in a 74% yield. Then, (±)-esermethole **2.73** was obtained over two steps via oxidative cleavage of the double bond and reductive aminocyclization (Scheme 15).



Scheme 15 α-Arylation/allylation sequence and synthesis of esermothole by Zhang

Azaspirocyclic Compounds

Spirocyclic compounds isolated from plant and animal origins have important applications in medicinal chemistry. Spiropyrrolidines and oxindole moieties are present in a wide range of active pharmaceuticals and biologically important natural alkaloids. Examples of biologically active alkaloids with this feature are spiro[succinimide-isoindolinone]s (**a**), which are aldolase inhibitors [18], spiro[γ-hydroxylactam-isoindolinone] (**b**), a potent inhibitor of human protein farnesyltransferase (FTase) in cancer treatment [19] and horsfiline (**c**) and coerulescine [20] (**d**) which are oxindole alkaloids with analgesic property found in plant *Horsifieldia superba* and cipargamin (**e**), an antimalarial drug [21] as shown in Figure 6.

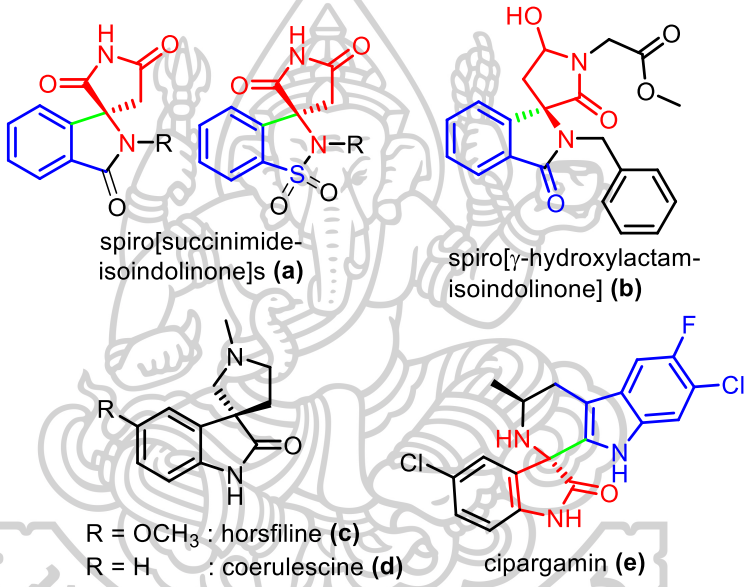
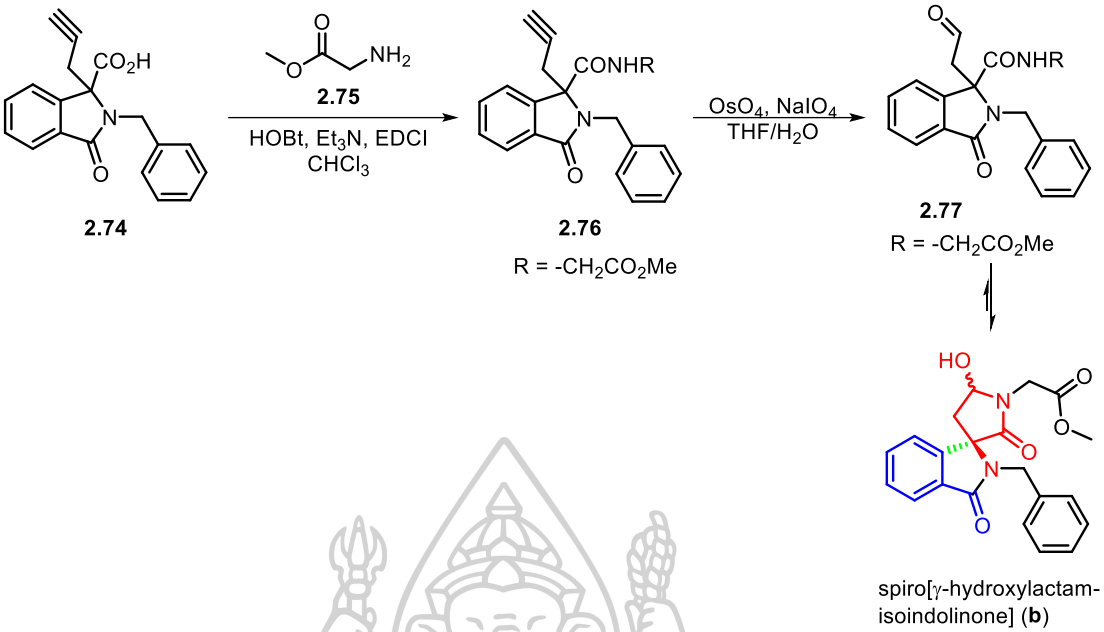


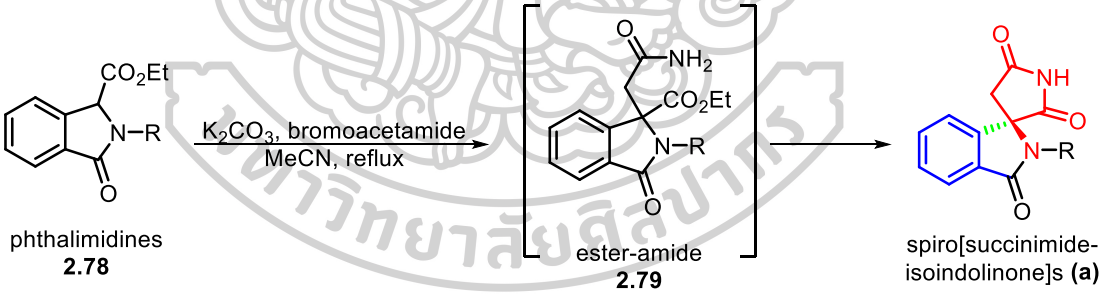
Figure 6 Examples of biologically active spiropyrrolidone alkaloids

In 2019, Othman and co-workers reported the synthesis of a new family of potent farnesyltransferase (FTase) inhibitors [18]. The propargyl-substituted isoindolinone carboxylic acid **2.74** was treated with primary amine **2.75** under peptide coupling condition to give amides **2.76**. Then, oxidative cleavage of the triple bond, followed by immediate purification using a silica gel chromatography column gave (±)-spiro[γ-hydroxylactam-isoindolinone] **(b)** while the corresponding aldehydes (±)-**2.77** was not isolated (Scheme 16).



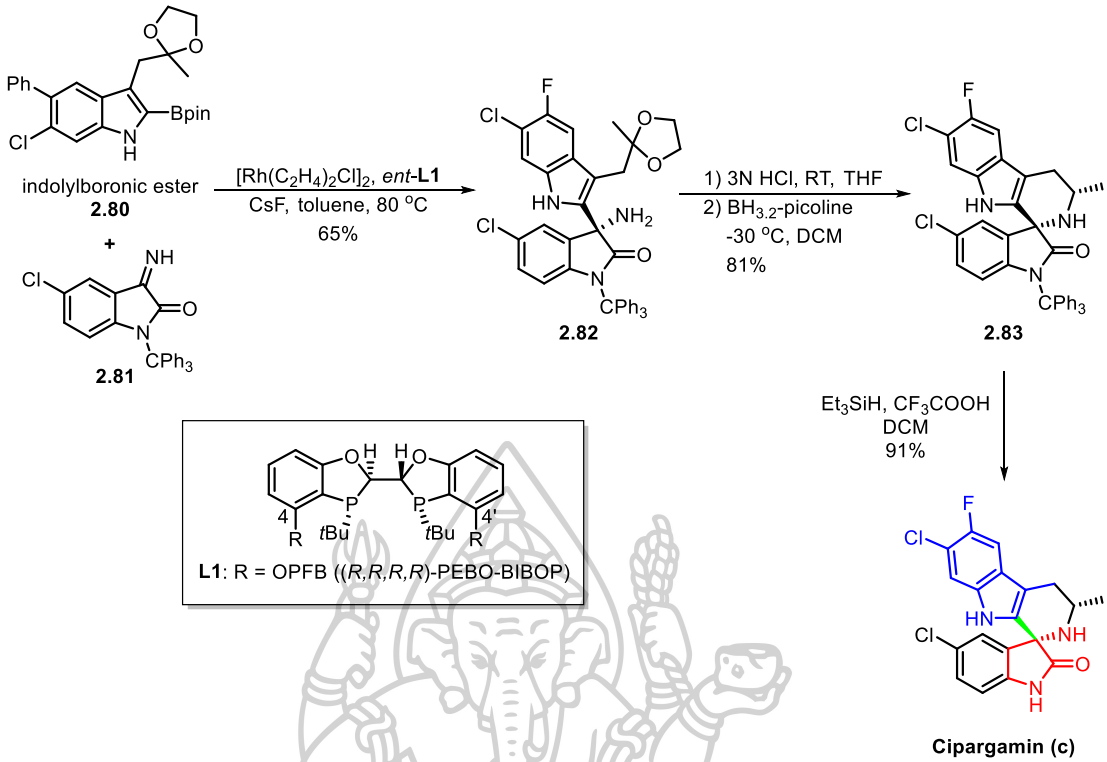
Scheme 16 Synthesis of spiro[γ-hydroxylactam-isoindolinone] **(b)** by Othman et al.

Moreover, they also reported the synthesis of aldose reductase inhibitors. The spiro[succinimide-isoindolinone]s **(a)** were prepared using the tandem angular *C*-alkylation/peptide coupling. Accordingly, phthalimidine **2.78** was treated with K_2CO_3 and *N*-substituted α-bromoacetamides to afford spiro[succinimide-isoindolinone]s (±)-**(a)** in one step (Scheme 17).



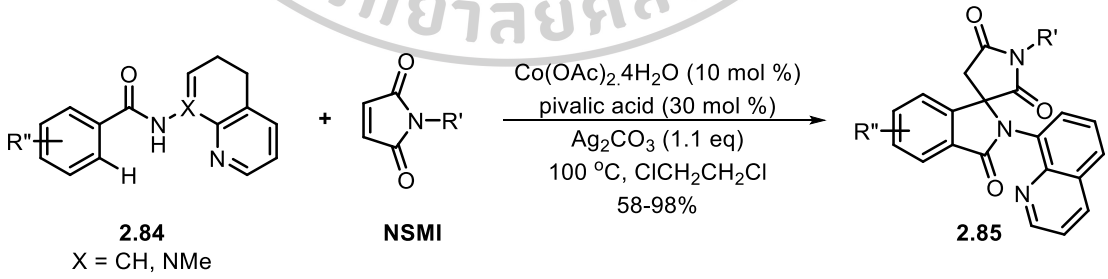
Scheme 17 Synthesis of aldose reductase inhibitors **(a)** by Othman et al.

In the same year, Tang and co-workers reported an efficient synthesis of cipargamin **(c)** [22]. It is a PfATP4 inhibitor for the treatment of malaria. The synthesis started with rhodium-catalyzed addition of indolylboronic ester **2.80** to *N*-H ketimine **2.81** in the presence of the Rh/*ent*-**L1** catalyst with CsF as the base in toluene provided chiral amine **2.82**. Then, acidic treatment followed by reduction with Shibasaki's conditions (BH_3.2-picoline) afforded spirocyclic **2.83**. Finally, trityl removal with Et_3SiH/TFA furnished cipargamin **(c)** (Scheme 18).

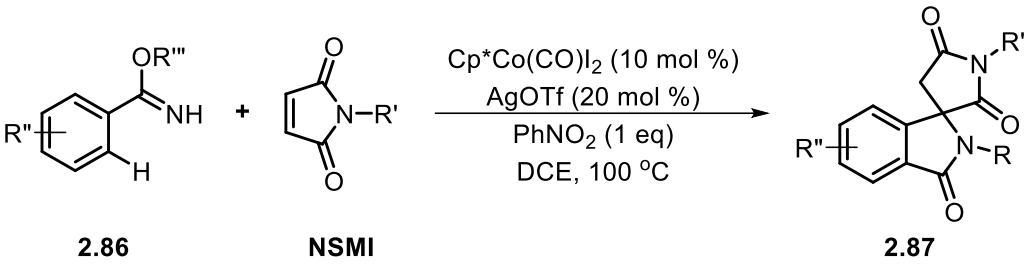


Scheme 18 Synthesis of cipargamin **(c)** by Tang and co-workers

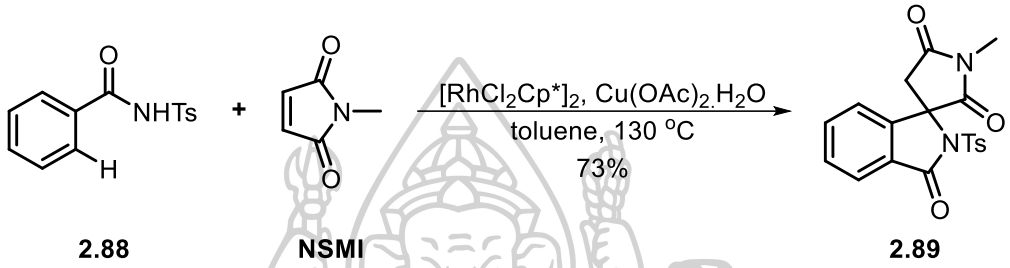
In the examples that have been discussed above are oxindole-based approach in which alkylation of oxindole carboxyl-oxindole [23, 24] led to quaternary center of the spirocyclic system and the succinimide ring would be formed in the latter step (Schemes 16-17). Additional previous syntheses of spiro[isoindoline-1,3'-pyrrolidine-2',5'-dione] are shown in schemes 19-21. This alternative *N*-alkylsuccinimide-based approach utilizes hetero-Michael addition of benzamide derivative to *N*-alkylsuccinimide (NSMI) followed by C-H activation and spirocyclization to form the oxindole ring in the target molecule.[25-30]



Scheme 19 Synthesis of isoindolone spirosuccinimides [25]



Scheme 20 Cobalt-catalyzed oxidant-free spirocycle synthesis [28]



Scheme 21 Rhodium catalyzed C–H olefination of N-benzoylsulfonamides [30]

Aldose Reductase

Aldose reductase (AR) is involved in the pathogenesis of diabetes, which is one of the major threats to global public health (Figure 7a. Structure of aldose reductase retrieved from the PDB database with ID: 1XGD).

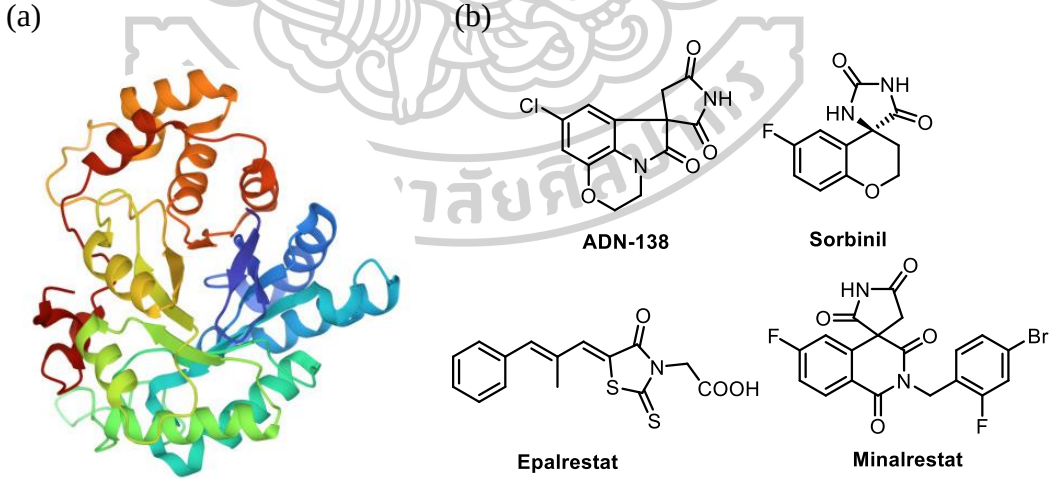


Figure 7 (a) Structure of aldose reductase retrieved from the PDB database with ID: 1XGD (b) Examples of aldose reductase inhibitors (ARIs)

Aldose reductase inhibitors (ARIs) are used for the treatment of diabetic complications, including neuropathy and retinopathy. In Figure 7b, some examples of ARIs are shown, such as sorbinil, which plays a therapeutic role in treating diabetes and diabetic complications, decreases AR activity, and inhibits the polyol pathway. It was found to be found comparatively safer than other ARIs for human use [31]. Epalrestat is a highly effective and safe agent for the treatment of diabetic neuropathy [32], and Minalrestat is a potent and orally active ARIs. Minalrestat has been used in the research of diabetes [33].

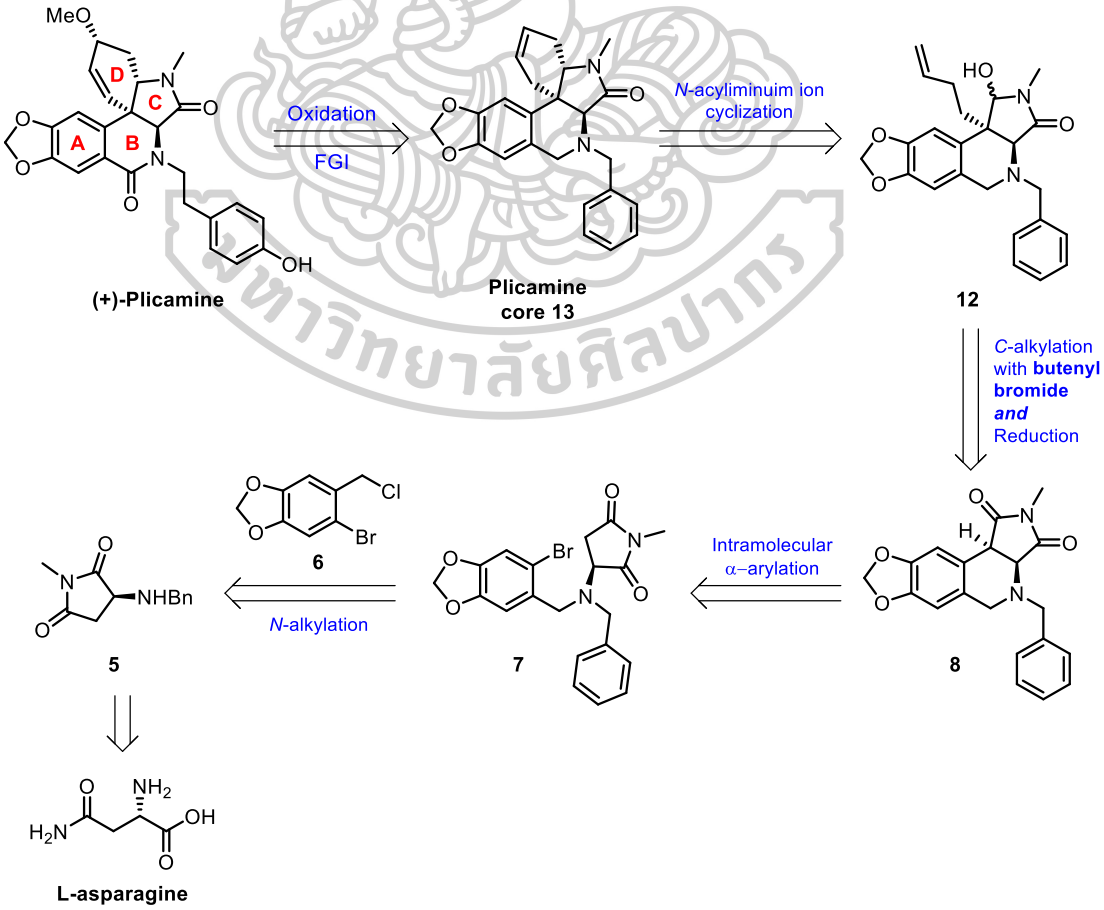
CHAPTER 3

SYNTHETIC STUDY

The synthetic studies of plicamine were divided into 3 routes. First, the synthetic methodology (route I) was envisioned that the D-ring of plicamine would be derived via *N*-acyliminium ion cyclization. Another two routes (routes II and III) would be derived via ring-closing metathesis.

Retrosynthetic analysis I

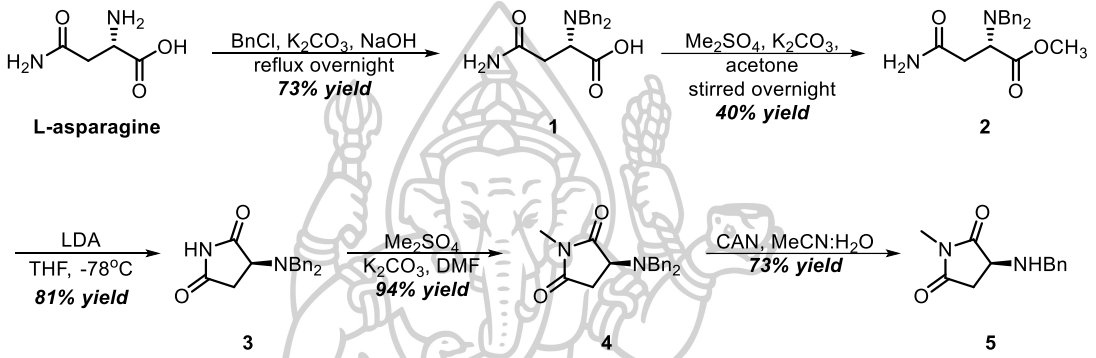
The initial retrosynthetic analysis envisioned that plicamine would be derived from hydroxylactam **12** as an advanced intermediate where the D-ring of plicamine would be synthesized via *N*-acyliminium ion cyclization and the B-ring would be derived from the A and C rings via an intramolecular α-arylation reaction. The hydroxylactam **12** could be synthesized from the corresponding butenylated tetracyclic succinimide via reduction. The butenyl group would be added at the B and C ring junctions by *C*-alkylation of tetracyclic succinimide **8**, which would be derived by an intramolecular α-arylation reaction of *N*-(bromoaryl)methylamino-succinimide **7,** whereas compound **7** could be synthesized via *N*-alkylation of benzylamino-succinimide **5** and 2-bromoarylmethyl chloride **6** (Scheme 22).



Scheme 22 Retrosynthetic analysis I of plicamine

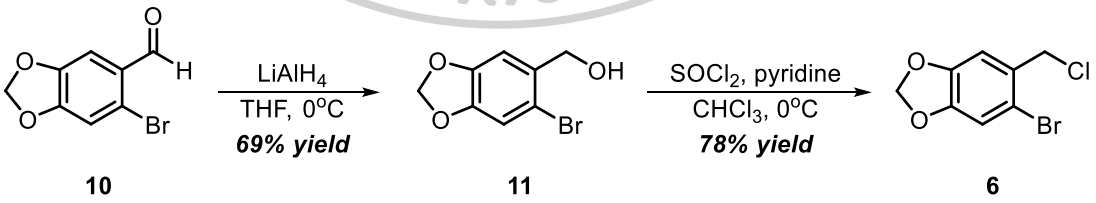
Synthetic study I of plicamine

The synthetic study of plicamine started from the benzylation of L-asparagine in basic condition using benzyl chloride, K_2CO_3, and NaOH in MeOH and H_2O to give *N*,*N*-dibenzyl asparagine **1**. The methylation of compound **1** in the presence of Me_2SO_4 and K_2CO_3 in acetone provided methyl ester asparagine **2**. Then, the conversion of methyl ester **2** via imide formation using LDA in THF afforded succinimide **3** in excellent yield. This was converted to *N*-methyl succinimide **4** with Me_2SO_4 and K_2CO_3 in DMF. Finally, the monodebenzylation of *N*-methyl-3-dibenzylaminosuccinimide **4** using CAN (ceric (IV) ammonium nitrate) in a 5:1 ratio of MeCN and H_2O afforded the desired product **5** (Scheme 23).



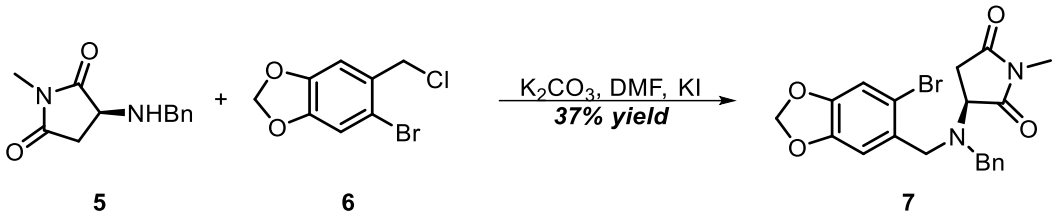
Scheme 23 Synthesis of monobenzylamino succinimide **5**

According to the retrosynthetic analysis, a *N*-(bromoaryl)methylamino-succinimide **7** would be derived from the *N*-alkylation of benzylaminosuccinimide **5** and 2-bromoarylmethyl chloride **6**. The synthesis of 2-bromoarylmethyl chloride **6** started from the reduction of 6-bromopiperonal **10** by using $LiAlH_4$ as a reducing agent in THF to give 6-bromopiperonol **11**. After that, chlorination of compound **11** with $SOCl_2$ and pyridine in $CHCl_3$ provides 2-bromoarylmethyl chloride **6** (Scheme 24).



Scheme 24 Synthesis of 2-bromoarylmethyl chloride **6**

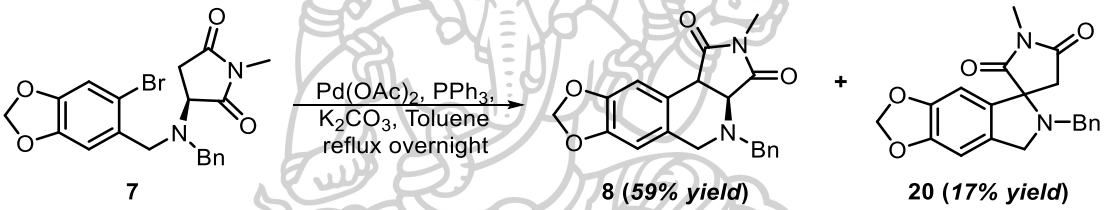
After obtaining precursor **5** and **6**, the *N*-alkylation between benzylamino succinimide **5** and 2-bromoarylmethyl chloride **6** using K_2CO_3 and KI as a catalyst in DMF gave *N*-(bromoaryl)methylamino-succinimide **7** (Scheme 25).



5 **6** **7**

Scheme 25 Synthesis of *N*-(bromoaryl)methylamino-succinimide **7**

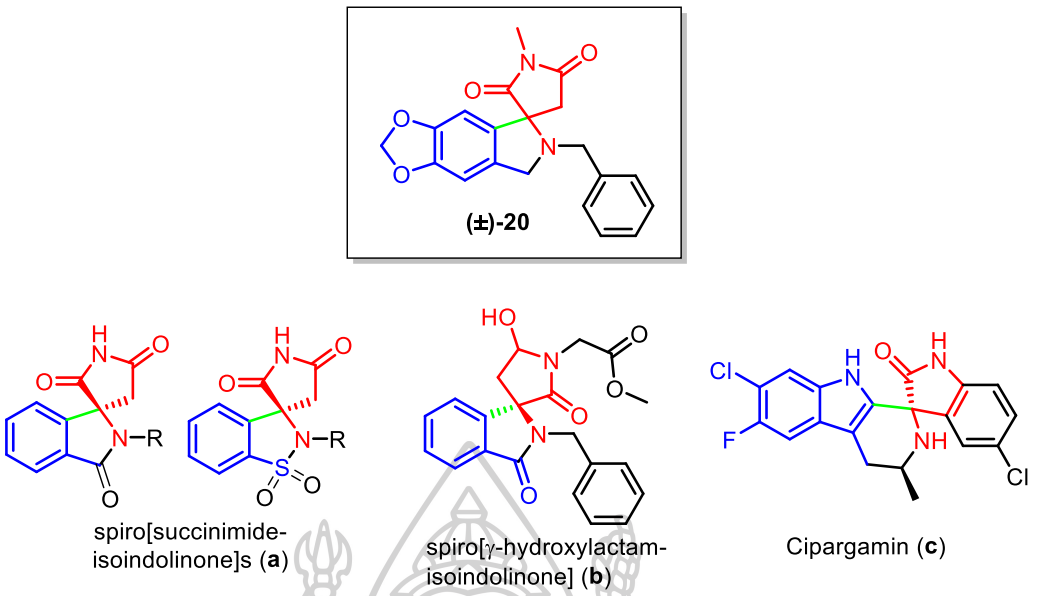
Then, the intramolecular α-arylation of *N*-(bromoaryl) methylamino-succinimide **7** catalyzed by $Pd(OAc)_2$ in the presence of PPh_3 ligand and K_2CO_3 in toluene afforded the desired tetracyclic succinimide-isoquinoline **8** and racemic spiro[isoindoline-succinimide] **20** which are regioisomer (Scheme 26). However, after purification by column chromatography, the NMR spectroscopy data of the product **8** showed that it contained unidentified impurities while spirocycic product **20** was obtained cleanly [ESI-HRMS 351.1339 calculated for $C_{20}H_{19}N_2O_4^+$ $[M+H]^+$ found 351.1575 for **8** and 351.1344 for **20**].



7 **8** (*59% yield*) **20** (*17% yield*)

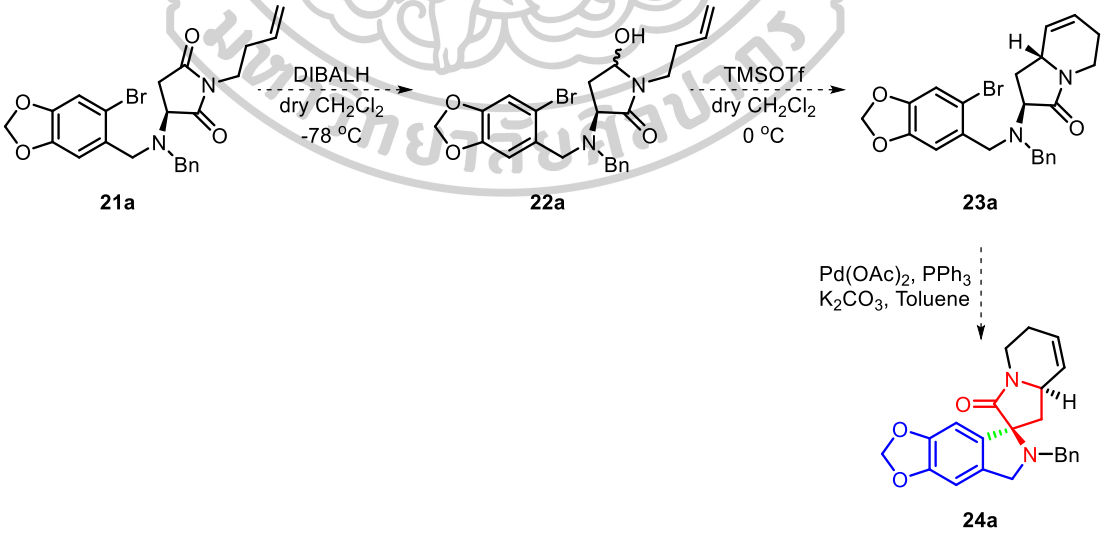
Scheme 26 Synthesis of desired tetracyclic **8** and spiro-cyclic **20**

Interestingly, the Pd-catalyzed intramolecular α-arylation gave racemic spiro[isoindoline-succinimide] **20** classifieds as spiropyrrolidone which is an important structural motif present in a wide range of active pharmaceuticals and biologically important natural alkaloids. Examples of biologically active alkaloids with this feature are **(a)** spiro[succinimide-isoindolinone]s which are aldolase inhibitors, **(b)** spiro[γ-hydroxylactam-isoindolinone], a potent inhibitor of human protein farnesyltransferase (FTase) in cancer treatment and **(c)** cipargamin, an antimalarial drug (Scheme 27).

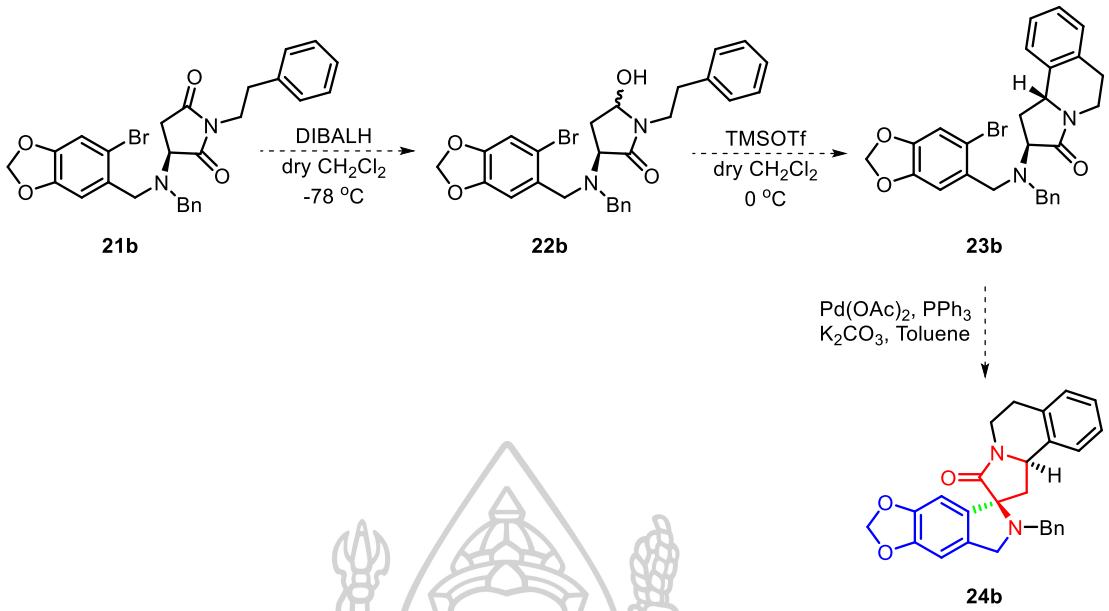


Scheme 27 Examples of biologically active spiropyrrolidone alkaloids

However, this result led to a new asymmetric synthetic approach to the spiropyrrolidone compound. We envision that *N*-butenyl imide **21a** and *N*-homobenzyl imide **21b** would be converted to hydroxylactams **22a** and **22b**, respectively, via DIBALH reduction. Then, *N*-acyliminium ion cyclization of both **22a** and **22b** can be used to synthesize the bicyclic **23a** and **23b** as a single diastereomer. Finally, we expect that stereocenters of spiropyrrolidone **24a** and **24b** would be controlled by precursors **23a** and **23b** via Pd-catalyzed intramolecular α-arylation (Scheme 28 and 29).

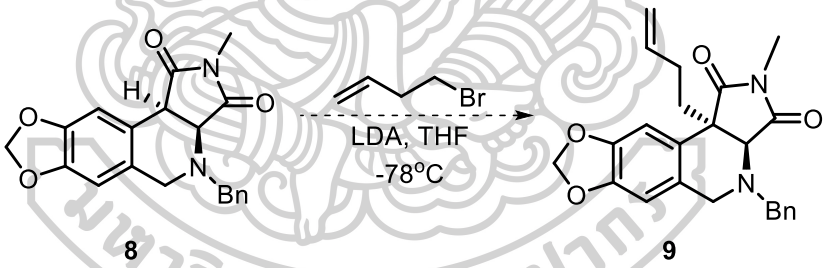


Scheme 28 Asymmetric synthesis plan for spiropyrrolidone **24a**



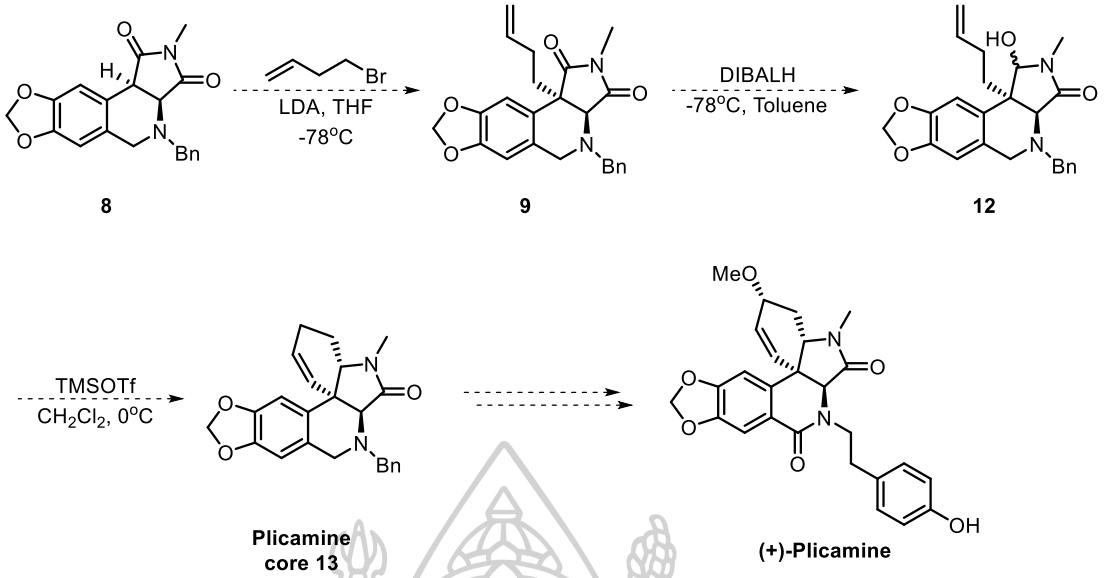
Scheme 29 Asymmetric synthesis plan for spiropyrrolidone **24b**

For the desired tetracyclic **8**, the next step is alkylation at the B-C ring junction with 4-bromo-1-butene in basic condition. However, initial attempt to install the butenyl group using LDA as a base in THF was unsuccessful (Scheme 30).



Scheme 30 The attempt of *C*-alkylation of desired tetracyclic **8**

To complete the synthesis of plicamine, an optimal condition to install the butenyl group at the B/C ring junction of the intramolecular α-arylation product **8** to give the key intermediate **9** must be established. Then, it would be converted to plicamine ABCD core **13** with DIBALH reduction and *N*-acyliminium ion cyclization. Finally, the remaining step would involve functional group interconversion to complete the synthesis of plicamine (Scheme 31).

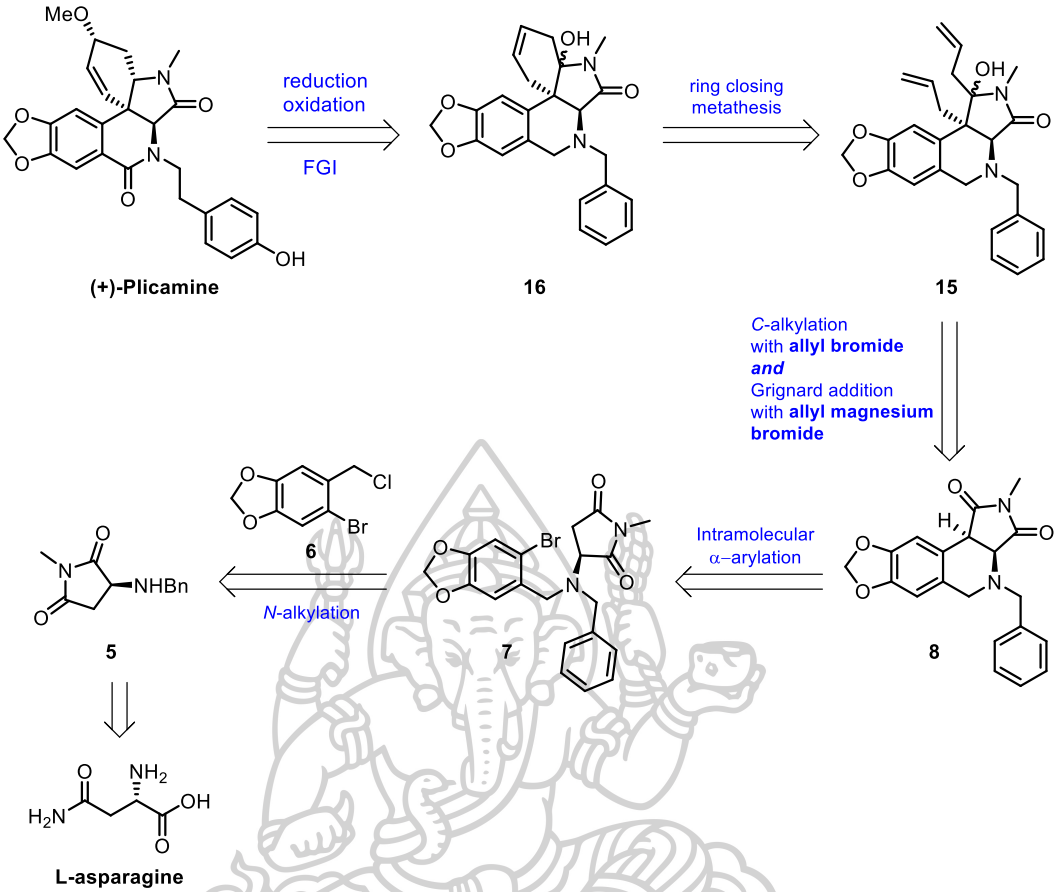


Scheme 31 Synthesis plan for plicamine (I)

We suspect that butenyl bromide may not be a sufficient electrophile. Therefore, a more reactive electrophile would be preferable especially the reaction will establish an all-carbon quaternary center. In this regard, an allyl halide would be used instead of butenyl bromide. However, the allyl group at the same position would not permit the construction of the D ring via *N*-acyliminium ion cyclization as planned. Therefore, a new synthetic route must be conceived.

Retrosynthetic analysis II

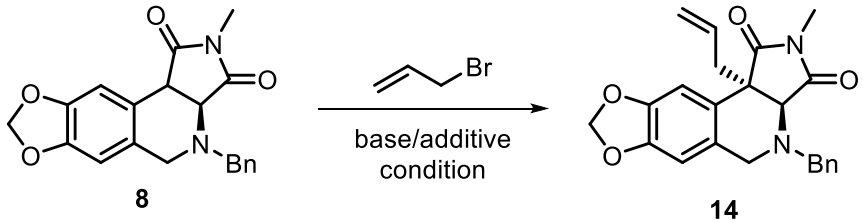
The second synthetic route of plicamine (Scheme 32) was envisioned in which the advanced ABCD core intermediate **16** would be synthesized from diene **15** via ring-closing metathesis. Diene **15** could be derived from tetracyclic **8** via *C*-alkylation with allyl bromide and Grignard addition with allyl magnesium bromide, respectively. The tetracyclic **8** would be prepared from the previous route, which has been explained.



Scheme 32 Retrosynthetic analysis II of plicamine

Synthetic study II of plicamine

As previously described, tetracyclic ABC core **8** was synthesized from L-asparagine in 7 steps featuring intramolecular α-arylation of succinimide as the key step. In this second route it would be converted to allylated-tetracyclic core **14** by *C*-alkylation with allyl bromide. The results of *C*-alkylation of tetracyclic **8** by various bases and conditions are shown in Scheme 33 and Table 3.1. Although tetracyclic ABC core **8** failed to react with allyl bromide in the presence of NaHMDS/HMPA and 3 eq. of LDA (entries 1-2), allylated-tetracyclic core **14** was obtained with 1.1 eq. of LDA (entry 3) in a low yield. ESI-HRMS 391.1652 calculated for $C_{23}H_{23}N_2O_4^+$ found 391.1929.

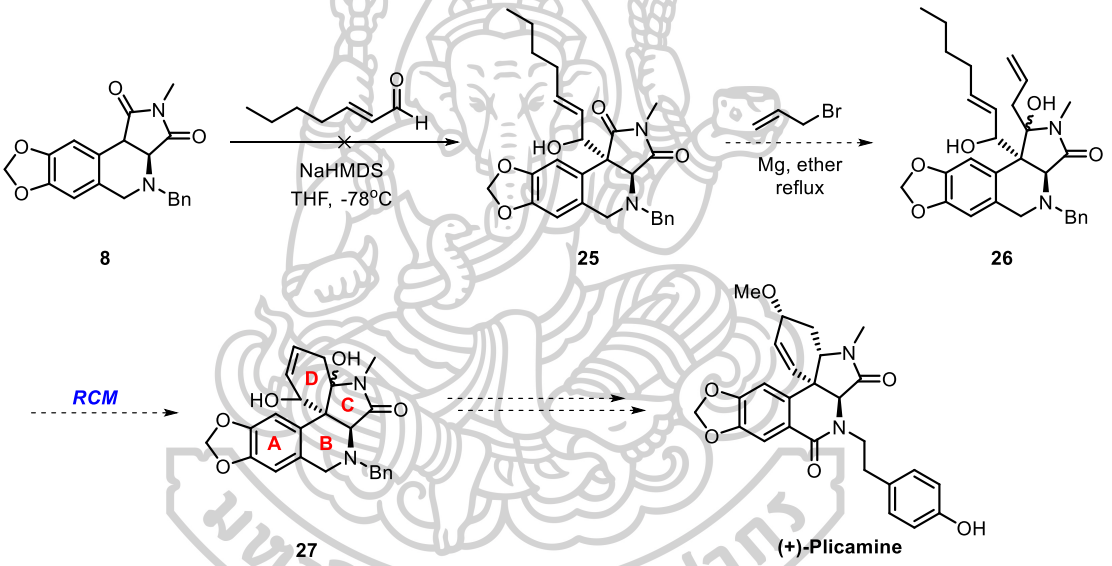


Scheme 33 C-allylation of tetracyclic **8**

Entry	Base/additive	Solvent	Temperature (°C)	Yield of 14 (%)
1	NaHMDS/HMPA	THF	-78	0
2	LDA (3 eq.)	THF	-78	0
3	LDA (1.1 eq.)	THF	-78	5

Table 3.1 *C*-allylation of tetracyclic core **8**

Due to a low yield of *C*-allylation, a different approach was attempted, namely, an aldol reaction with a vinylic aldehyde. In this regard, tetracyclic core **8** was used treated with trans-2-heptenal in basic condition. We envisioned that aldol-adduct **25** would be derived. It can be used to construct a D-ring of plicamine via ring-closing metathesis. Unfortunately, the aldol reaction between tetracyclic **8** and trans-2-heptenal in the presence of NaHMDS in THF did not yield the desired product **25** (Scheme 34).

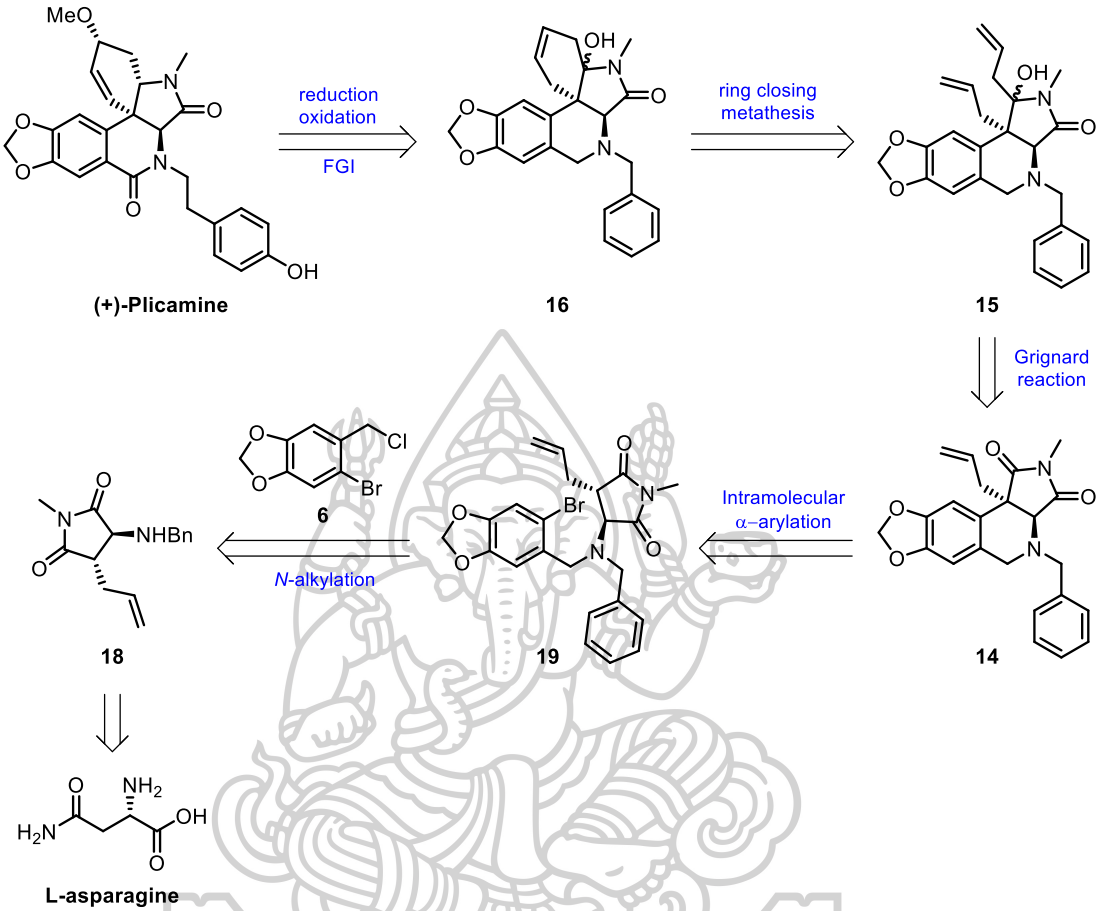


Scheme 34 The attempt of aldol reaction between tetracyclic core **8** and trans-2-heptenal

Retrosynthetic analysis III

The third strategy for plicamine synthesis was envisioned based on the poor results of *C*-allylation in the previous route. We hypothesized that the low yield of *C*-alkylation or aldol reaction of the tetracyclic core **8** was due to the intrinsic difficulty of forming an all-carbon center via an intermolecular reaction. Therefore, in the third approach to the target molecule, the ABCD core **16** would be obtained from ring closing metathesis of diene **15** which in turn would be derived from Grignard addition of allylmagnesium bromide to the allylated ABC core **14**. We planned to form the all-carbon quaternary center at the B/C ring junction in **14** via the key intramolecular α-arylation of *N*-(bromoaryl)-methylamino-allylated-succinimide **19**. This precursor would be synthesized from *N*-alkylation of 2-bromoarylmethyl chloride **6** and

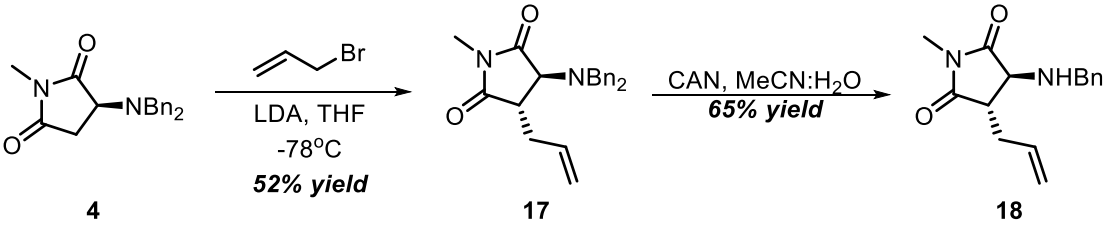
allylated-benzylamino succinimide **18**, which was derived from the *C*-allylation of *N*-methyl-3-dibenzylaminosuccinimide **4** with allyl bromide (Scheme 35).



Scheme 35 Retrosynthetic analysis III of plicamine

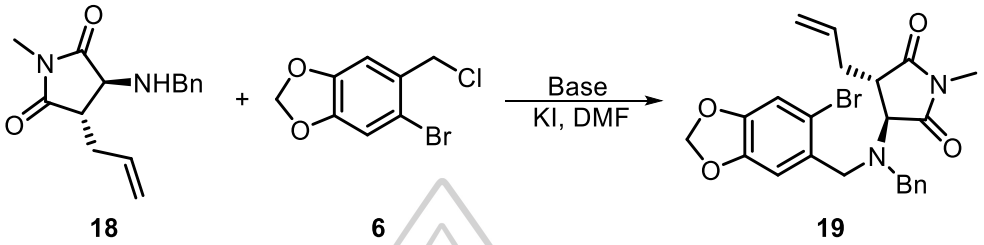
Synthetic study III of plicamine

The synthetic study III of plicamine began with the *C*-allylation of *N*-methyl-3-dibenzylaminosuccinimide **4**, which was derived from L-asparagine (Scheme 23), with allyl bromide, LDA in THF to give allylated-succinimide **17** in 52% yield. Monodebenzylation with CAN in MeCN and H_2O gave allylated-benzylamino succinimide **18** in good yiled (Scheme 36).



Scheme 36 Synthesis of allylated-monobenzylamino succinimide **18**

The synthesis of *N*-(bromoaryl)-methylamino-allylated-succinimide was achieved by *N*-alkylation of allylated-benzylamino succinimide **18** and 2-bromoarylmethyl chloride **6** in the presence of Na_2CO_3 and KI in catalytic amount to give *N*-(bromoaryl)-methylamino-allylated-succinimide **19** in 31% yield. Selection of base affected the yield of the reaction K_2CO_3 gave lower yield than Na_2CO_3 (Scheme 37 and Table 3.2).

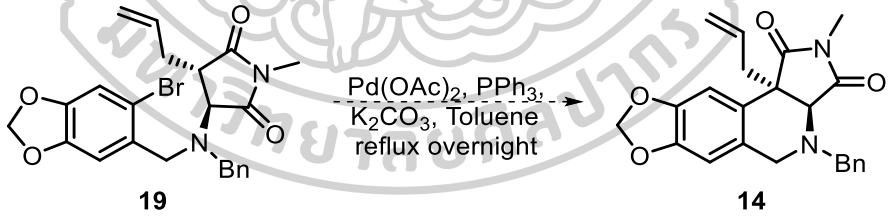


Scheme 37 Synthesis of *N*-(bromoaryl)-methylamino-allylated-succinimide **19**

Entry	Base	Yield of 19 (%)
1	K_2CO_3	22
2	Na_2CO_3	31

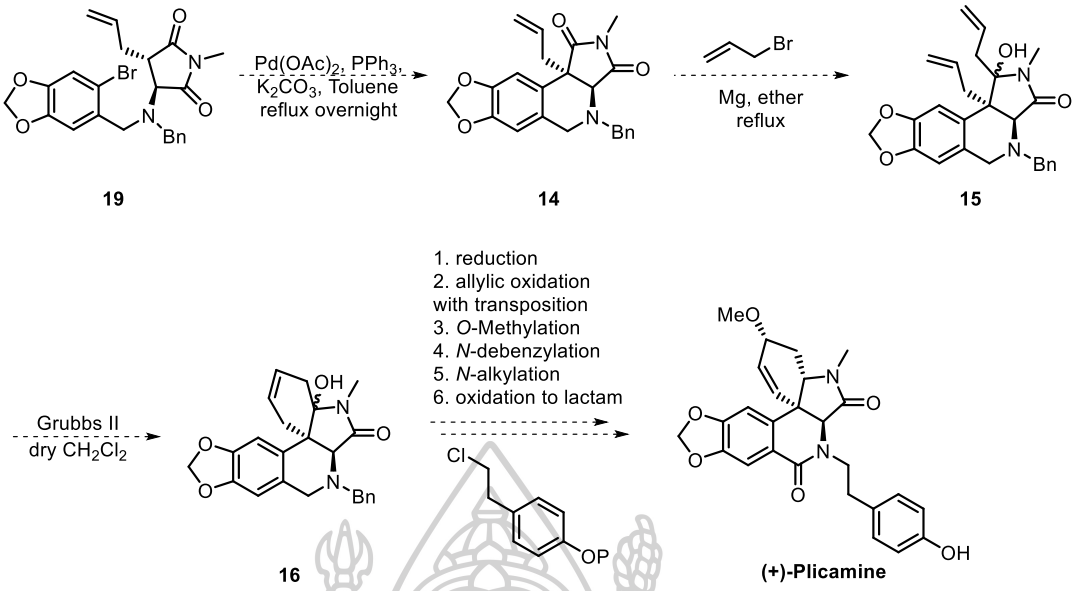
Table 3.2 *N*-alkylation of allylated-benzylamino succinimide **18**

Unfortunately, the attempt of intramolecular α-arylation of *N*-(bromoaryl)-methylamino-allylated-succinimide **19** catalyzed by $Pd(OAc)_2$ in the presence of PPh_3 ligand and K_2CO_3 in toluene did not give the desired tetracyclic ABC core **14** in a complex mixture of unidentifiable products (Scheme 38).



Scheme 38 The attempt of intramolecular α-arylation

The plan for completion of a synthesis of plicamine is shown in Scheme 39. We envision that optimization of the intramolecular α-arylation step to give allylated-tetracyclic ABC core **14** will be the key to the successful synthesis. Then, the D-ring of plicamine would be constructed via Grignard addition with allylmagnesium bromide and ring-closing metathesis to afford pentacyclic ABCD core **16**, which was an advanced intermediate to complete the synthesis of plicamine.



Scheme 39 The plan for completion of a synthesis of plicamine

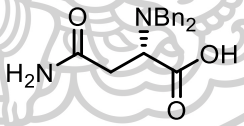
CHAPTER 4

EXPERIMENTAL PROCEDURE

General

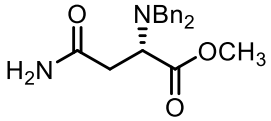
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Toluene and dichloromethane were distilled from calcium hydride under argon. Tetrahydrofuran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

Synthesis of *N,N*-dibenzyl asparagine (1)



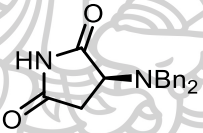
To a solution of L-asparagine (5.66 g, 42.5 mmol) in MeOH and H_2O (1:1, 100 mL) was added NaOH (4.25 g, 106.3 mmol), K_2CO_3 (14.70 g, 106.3 mmol) and BnCl (19.6 mL, 170.0 mmol). The mixture was heated to reflux at 95 ^{o}C overnight and acidified with 5M HCl. Then the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give *N,N*-dibenzyl asparagine **1** (9.63 g, 73%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 10H), 4.30-4.10 (m, 1H), 4.10-3.80 (m, 4H), 2.90 (dd, J = 16.3, 6.4 Hz, 1H), 2.65 (dd, J = 16.3, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 172.3, 135.4, 129.6, 128.9, 128.3, 59.8, 54.8, 33.4; $[a]_D^{25}$-48.8 (c 1.7, $CHCl_3$); ν_{max} (film) 3192, 3064, 2924, 2852, 1669, 1495, 1456, 1365, 1285, 1182 cm^{-1}

Synthesis of methyl ester asparagine (2)



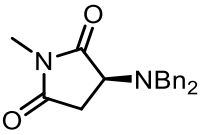
To a solution of *N*,*N*-dibenzyl asparagine **1** (7.22 g, 23.1 mmol) in acetone (80 mL) was added K_2CO_3 (4.80 g, 34.7 mmol) and Me_2SO_4 (3.30 mL, 34.7 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered to remove K_2CO_3 and to the solution was added dropwise sat. aq. NH_4Cl (40 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 methyl ester asparagine **2** (2.99 g, 40%) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.08; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 10H), 6.30 (br s, 1H), 5.85 (br s, 1H), 3.90-3.80 (m, 1H), 3.85 (d, *J* = 13.6 Hz, 2H), 3.80 (s, 3H), 3.55 (d, *J* = 13.6 Hz, 2H), 2.65 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.53 (dd, *J* = 15.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.4, 139.0, 129.0, 128.5, 127.3, 58.3, 54.9, 51.6, 35.6; $[a]_D^{25}$ -103.8 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3349, 3355, 3196, 2951, 2844, 1730, 1672, 1495, 1453, 1366, 1173 cm^{-1}

Synthesis of succinimide (3)



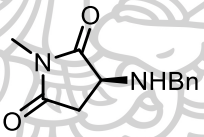
To a solution of methyl ester asparagine **2** (2.77 g, 8.49 mmol) in dry THF (10 mL) under argon atmosphere at -78 ºC was added LDA (12.7 mL of 2 M solution, 25.47 mmol) and the mixture was stirred for 3 hours at -78 ºC. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give succinimide **3** (2.02 g, 81%) as a white crystal. R_f (2:1 hexane/EtOAc) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.40–7.23 (m, 10H), 3.98 (dd, J = 8.9, 5.8 Hz, 1H), 3.85 (d, J = 13.5 Hz, 2H), 3.66 (d, J = 13.5 Hz, 2H), 2.80 (dd, J = 18.6, 9.1 Hz, 1H), 2.67 (dd, J = 18.6, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 176.2, 138.2, 128.8, 128.5, 127.9, 58.9, 54.7, 31.8; $[a]_D^{25}$ -25.4 (*c* 1.6, $CHCl_3$); ν_{max} (film) 3234, 2923, 2849, 1782, 1705, 1494, 1454, 1338, 1191, 1165 cm^{-1}

Synthesis of *N*-methyl-3-dibenzylaminosuccinimide (4)



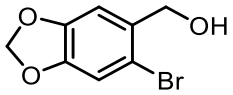
To a solution of succinimide **3** (412.3 mg, 1.40 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (232.6 mg, 1.68 mmol) and Me_2SO_4 (0.16 mL, 1.68 mmol) and the mixture was stirred for overnight. To this the mixture was filtered to remove K_2CO_3 and to the solution 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 (5×20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained without purification to give *N*-methyl succinimide **4** (407.1 mg, 94%) as a pale-yellow crystal. R_f (4:1 hexane/EtOAc) 0.63; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 10H), 3.93 (dd, J = 8.9, 5.5 Hz, 1H), 3.82 (d, J = 13.4 Hz, 2H), 3.65 (d, J = 13.4 Hz, 2H), 2.96 (s, 3H), 2.75 (dd, J = 18.4, 9.1 Hz, 1H), 2.61 (dd, J = 18.6, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 175.2, 138.2, 128.4, 128.2, 127.4, 57.6, 54.7, 31.9, 24.4; $[a]_D^{25}$ -5.5 (*c* 1.3, $CHCl_3$); ν_{max} (film) 3082, 3029, 2939, 2847, 1770, 1688, 1360, 1195, 1130, 698 cm^{-1}

Synthesis of monobenzylamino succinimide (5)



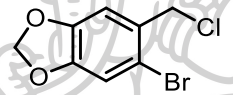
To a solution of *N*-methyl-3-dibenzylaminosuccinimide **4** (176.0 mg, 0.57 mmol) in MeCN and H_2O (5:1, 18 mL) was added CAN (ceric (IV) ammonium nitrate) (1.26 g, 2.29 mmol) and the mixture was stirred for overnight. To this the mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and stirred for 10 minutes. Then the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give monobenzylamino succinimide **5** (90.7 mg, 73%) as a brown oil. R_f (4:1 hexane/EtOAc) 0.13; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 3.87 (d, *J* = 3.9 Hz, 2H), 3.77 (dd, *J* = 8.3, 4.8 Hz, 1H), 2.99 (s, 3H), 2.87 (dd, *J* = 17.9, 8.1 Hz, 1H), 2.52 (dd, *J* = 17.7, 4.9 Hz, 1H), 2.05 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 175.4, 138.7, 128.6, 128.5, 127.9, 55.5, 51.8, 36.3, 24.8; $[a]_D^{25}$ -5.5 (*c* 1.3, $CHCl_3$); ν_{max} (film) 3317, 1697, 1605, 1412, 1282 cm^{-1}

Synthesis of 6-bromopiperonol (11)



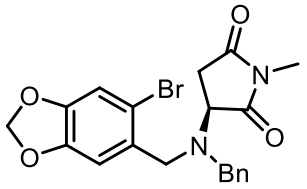
To a solution of 6-bromopiperonal **10** (3.03 g, 13.2 mmol) in dry THF (10 mL) under argon atmosphere at 0 ^{o}C was added $LiAlH_4$ (730.0 mg, 19.8 mmol) and the mixture was stirred for 30 minutes at 0 ^{o}C. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL). Then the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give 6-bromopiperonol **19** (247.3 mg, 69%) as a brown crystal. R_f (2:1 hexane/EtOAc) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.95 (s,1H), 6.06 (s, 2H), 4.65 (s, 2H), 2.12 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 147.4, 133.1, 133.1, 112.6, 109.1, 101.8, 64.9

Synthesis of 2-bromoarylmethyl chloride (6)



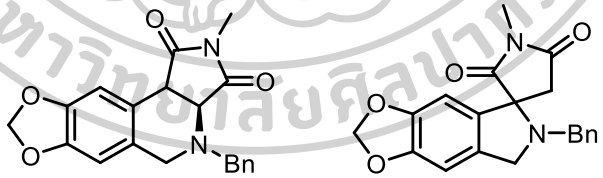
To a solution of 6-bromopiperonol **19** (1.97 g, 8.53 mmol) in $CHCl_3$ under argon atmosphere was added pyridine (0.65 mL, 8.02 mmol) and the mixture was stirred at 0 ^{o}C. Then, it was added $SOCl_2$ (0.74 mL, 10.2 mmol) and stirred for overnight. The reaction was quenched with adding 5 M HCl (10 mL). The mixture was washed with water (2×20 mL) and 10% Na_2CO_3 (100 mL). Then the organic layer was extracted with water (2×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained without purification to give 2-bromoarylmethyl chloride **6** (1.95 g, 78%) as a brown oil. R_f (4:1 hexane/EtOAc) 0.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.92 (s, 1H), 6.04 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.4, 129.5, 114.9, 112.9, 110.2, 102.1, 46.5; ν_{max} (film) 3455, 3010, 2905, 2076, 1738, 1621, 1231, 1114, 1035 cm^{-1}

Synthesis of *N*-(bromoaryl)methylamino-succinimide (7)



To a solution of monobenzylamino succinimide **5** (35.2 mg, 0.16 mmol) in DMF (3 mL) under argon atmosphere at room temperature was added K_2CO_3 (44.2 mg, 0.32 mmol), KI (3.2 mg, 0.02 mmol) and 2-bromoarylmethyl chloride **6** (40.3 mg, 0.16 mmol) and the mixture was stirred for overnight. To this the mixture was filtered to remove K_2CO_3 and to the solution was added water (10 mL) and the mixture was extracted with CH_2Cl_2 (3×5 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 crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give *N*-(bromoaryl)methylamino-succinimide **7** (28.4 mg, 37%) as an orange oil. R_f (4:1 hexane/EtOAc) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.11 (m, 5H), 7.11 (s, 1H), 6.95 (s, 1H), 6.05 (s, 2H), 3.94 (dd, *J* = 8.6, 5.6 Hz, 1H), 3.80 (d, *J* = 13.8 Hz, 2H), 3.67 (d, *J* = 14.1 Hz, 2H), 2.98 (s, 3H), 2.74 (dd, *J* = 18.5, 8.7 Hz, 1H), 2.69 (dd, *J* = 18.5, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.2, 147.7, 137.9, 130.4, 128.9, 128.6, 127.6, 114.5, 112.8, 110.5, 101.9, 64.8, 58.1, 54.9, 53.9, 31.7, 24.6; $[\alpha]_D^{25}$ -26.5 (*c* 1.3, CH_2Cl_2); ν_{max} (film) 2923, 2853, 1695, 1474, 1379, 1230, 1112 cm^{-1}

Synthesis of tetracyclic succinimide-isoquinoline (8) and (±)-spiro[isoindoline-succinimide] (20)



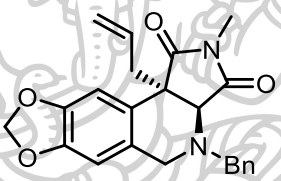
8 **20**

To a solution of *N*-(bromoaryl)methylamino-succinimide **7** (26.8 mg, 0.06 mmol) in dry toluene (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (15.6 mg, 0.11 mmol), PPh_3 (2.9 mg, 0.01 mmol) and $Pd(OAc)_2$ (1.3 mg, 0.006 mmol) and the mixture was heated to reflux at 120 ^{o}C overnight. To this the mixture was filtered to remove $Pd(OAc)_2$ and to the solution was extracted with EtOAc (3×5 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give tetracyclic succinimide-isoquinoline **8** (11.6 mg, 59%) and (±)-spiro[isoindoline-succinimide] **20** (3.4 mg, 17%) as a yellow oil.

tetracyclic succinimide-isoquinoline (8); R_f (4:1 hexane/EtOAc) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.45 (s, 1H), 6.00-5.90 (m, 2H), 4.20-3.42 (m, 5H), 3.15-2.95 (m, 1H), 2.91 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.4, 147.1, 146.6, 137.8, 130.3, 128.9, 128.5, 128.1, 127.9, 127.5, 110.0, 109.7, 101.1, 57.9, 54.6, 51.5, 31.1, 24.4, 21.6; ESI-HRMS calculated for $C_{20}H_{19}N_2O_4^+$ $[M+H]^+$ 351.1339, found 351.1575.

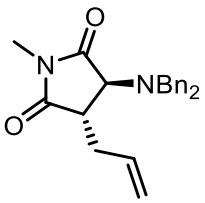
(±)-spiro[isoindoline-succinimide] (20); R_f (4:1 hexane/EtOAc) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 6.68 (s, 1H), 6.49 (s, 1H), 5.97 (d, *J* = 1.2 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 12.2 Hz, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.84 (d, *J* = 12.9 Hz, 1H), 3.07 (s, 1H), 3.04 (s, 3H), 3.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 175.0, 148.6, 147.6, 137.9, 133.4, 133.3, 128.6, 127.6, 103.8, 101.5, 101.4, 73.8, 57.3, 53.2, 41.1, 29.7, 24.7; ν_{max} (film) 3356, 2924, 2854, 1710, 1462, 1378, 1259, 1157, 1018 cm^{-1}; ESI-HRMS calculated for $C_{20}H_{19}N_2O_4^+$ $[M+H]^+$ 351.1339, found 351.1344.

Synthesis of allylated-tetracyclic (14)



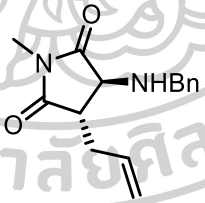
To a solution of tetracyclic succinimide-isoquinoline **8** (17.1 mg, 0.05 mmol) in dry THF (2 mL) under argon atmosphere at -78 ºC was added LDA (0.06 mL of 2 M solution, 0.12 mmol) and the mixture was stirred for 15 minutes. Then, it was added allyl bromide (0.02 mL, 0.15 mmol) and stirred at -78 ºC for 5 hours. To this mixture was added dropwise sat. aq. NH_4Cl (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 thin-layer chromatography (silica gel, 6:1 hexane/EtOAc) to give allylated-tetracyclic **14** (0.9 mg, 5%) as a white crystal. R_f (4:1 hexane/EtOAc) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-712 (m, 5H), 7.03 (s, 1H), 6.70 (s, 1H), 5.98 (s, 2H), 5.39-5.20 (m, 1H), 4.80 (d, *J* = 12.7 Hz, 1H), 4.45 (d, *J* = 16.9 Hz, 1H), 3.83-3.48 (m, 5H), 2.88 (s, 3H), 2.36-2.25 (m, 1H), 2.07-1.93 (m, 1H); ESI-HRMS calculated for $C_{23}H_{23}N_2O_4^+$ $[M+H]^+$ 391.1652, found 391.1929.

Synthesis of allylated-succinimide (17)



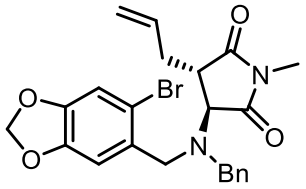
To a solution of *N*-methyl succinimide **4** (338.6 mg, 1.10 mmol) in dry THF (10 mL) under argon atmosphere at -78 ^{o}C was added LDA (0.60 mL of 2 M solution, 1.21 mmol) and the mixture was stirred for 15 minutes. Then, it was added allyl bromide (0.14 mL, 1.65 mmol) and stirred at -78 ^{o}C for 5 hours. To this mixture was added dropwise sat. aq. NH_4Cl (5 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give allylated-succinimide **17** (200.1 mg, 52%) as a yellow oil. R_f (4:1 hexane/EtOAc) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 10H), 5.39 (dddd, *J* = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 4.81 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.48 (dd, *J* = 17.1, 1.3 Hz, 1H), 3.90 (d, *J* = 13.4 Hz, 2H), 3.74 (d, *J* = 13.4 Hz, 2H), 3.65 (d, *J* = 5.3 Hz, 1H), 2.96 (s, 3H), 2.76 (dd, *J* = 10.9, 5.6 Hz, 1H), 2.50 (ddd, *J* = 5.3 Hz, 1H), 2.25 (ddd, *J* = 5.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 176.9, 138.6, 132.4, 129.0, 128.4, 127.5, 119.4, 60.8, 55.2, 44.3, 32.2, 24.3; $[\alpha]_D^{25}$ -100.0 (*c* 9.0, CH_2Cl_2); ν_{max} (film) 3460, 3063, 3029, 2921, 2850, 1774, 1698, 1431, 1377, 1275cm^{-1}

Synthesis of allylated-monobenzylamino succinimide (18)



To a solution of allylated-succinimide **17** (194.1 mg, 0.56 mmol) in MeCN and H_2O (5:1, 12 mL) was added CAN (ceric (IV) ammonium nitrate) (1.22 g, 2.23 mmol) and the mixture was stirred for 3 hours. To this the mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and stirred for 10 minutes. Then the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give allylated-monobenzylamino succinimide **18** (93.7 mg, 65%) as an orange oil. R_f (2:1 hexane/EtOAc) 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.23 (m, 5H), 5.66 (dddd, *J* = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 5.11-4.98 (m, 2H), 3.92 (s, 2H), 3.53 (d, *J* = 5.3 Hz, 1H), 2.96 (s, 3H), 2.73 (dd, *J* = 10.9, 5.6 Hz, 1H), 2.50 (m, 2H), 2.29 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 176.1, 137.9, 132.0, 127.4, 127.1, 126.3, 118.1, 58.6, 50.7, 46.1, 32.2, 23.6; $[\alpha]_D^{25}$ -94.0 (*c* 13.4, CH_2Cl_2); ν_{max} (film) 3320, 3012, 2920, 1776, 1695, 1435, 1381, 1281 cm^{-1}

Synthesis of *N*-(bromoaryl)methylamino-allylated-succinimide (19)

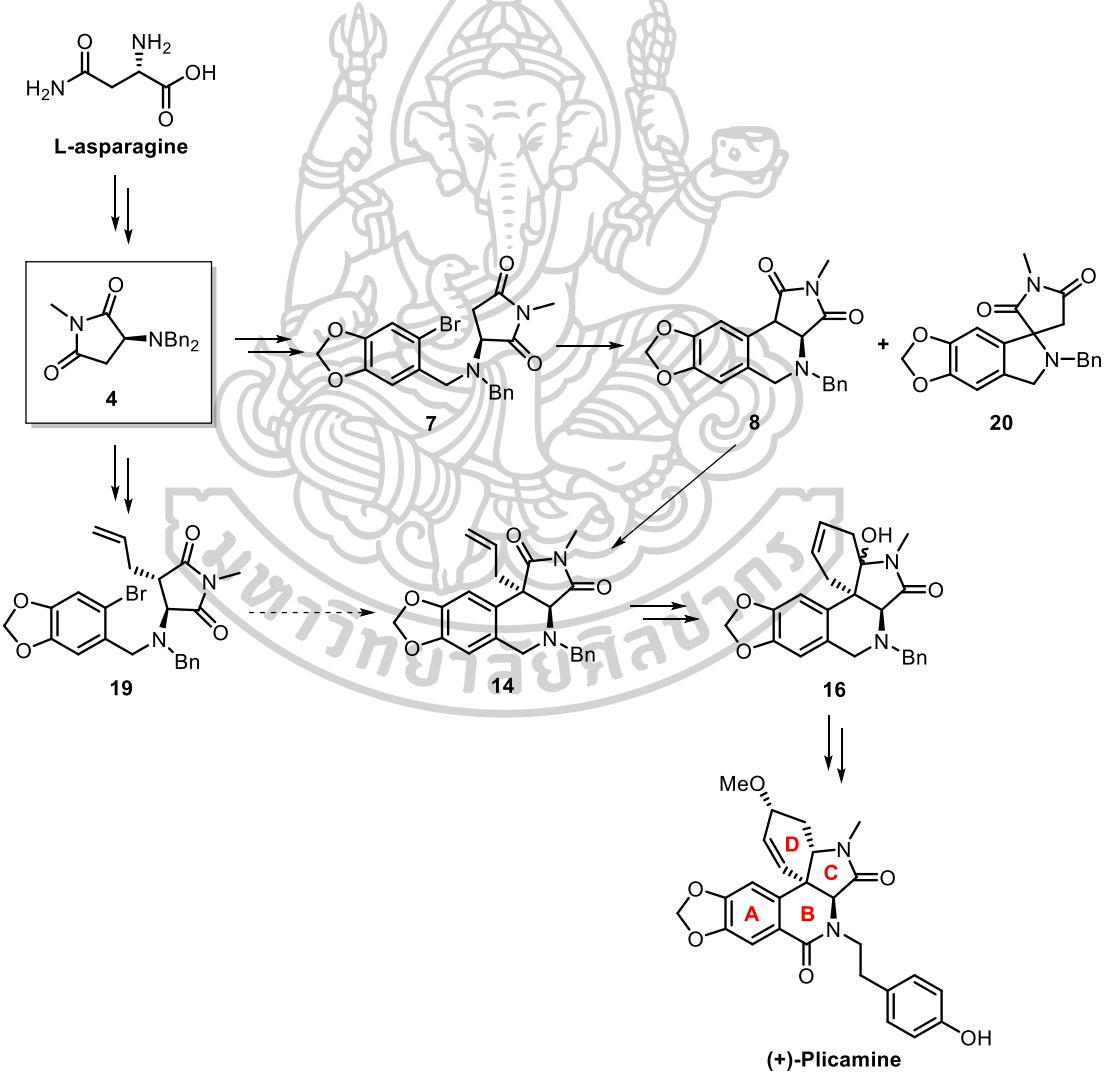


To a solution of allylated-monobenzylamino succinimide **18** (46.6 mg, 0.18 mmol) in DMF (4 mL) under argon atmosphere at room temperature was added Na_2CO_3 (38.3 mg, 0.36 mmol), KI (3.6 mg, 0.02 mmol) and 2-bromoarylmethyl chloride **6** (49.6 mg, 0.19 mmol) and the mixture was stirred for overnight. To this the mixture was filtered to remove Na_2CO_3 and to the solution 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 (5×20 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*-(bromoaryl)methylamino-allylated-succinimide **19** (26.5 mg, 31%) as an orange oil. R_f (4:1 hexane/EtOAc) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.20 (m, 5H), 7.06 (s, 1H), 6.98 (s, 1H), 5.98 (s, 2H), 5.39 (dddd, *J* = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 4.86 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 17.0 Hz, 1H), 3.97 (d, *J* = 14.2 Hz, 2H), 3.77 (d, *J* = 13.5 Hz, 2H), 3.66 (d, *J* = 5.5 Hz, 1H), 2.98 (s, 3H), 2.86 (q, *J* = 5.4 Hz, 1H), 2.60-2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 176.7, 147.8, 147.6, 132.5, 129.3, 128.5, 127.7, 119.4, 114.9, 112.8, 110.8, 101.8, 61.2, 55.6, 54.6, 43.8, 32.5, 24.5; ν_{max} (film) 2961, 1698, 1475, 1377, 1231, 1110 cm^{-1}

CHAPTER 5

CONCLUSION

In summary, our synthetic studies of plicamine evolved into 3 routes. The *N*-methyl succinimide **4** synthesized from L-asparagine was vital in the synthetic approaches in all routes. The intramolecular α-arylation reaction was successful in constructing the B-ring of plicamine and spiro[isoindoline-1,3'-pyrrolidin-2'-5'-di-one] **20**. The remaining steps involve optimization of this intramolecular arylation and *C*-allylation step. Completion of the D-ring of plicamine would be performed via *N*-acyliminium ion cyclization in synthetic methodology route I or another two routes (routes II and III) would be derived via ring-closing metathesis and functional group interconversions to complete the synthesis of plicamine.



Scheme 40 Conclusion of finding from this research

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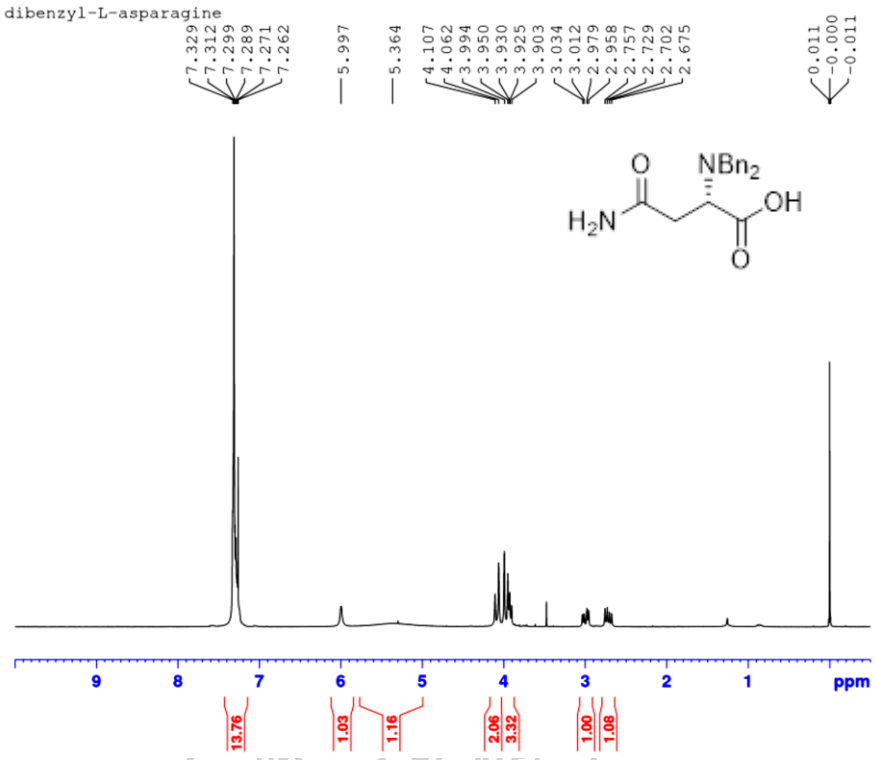
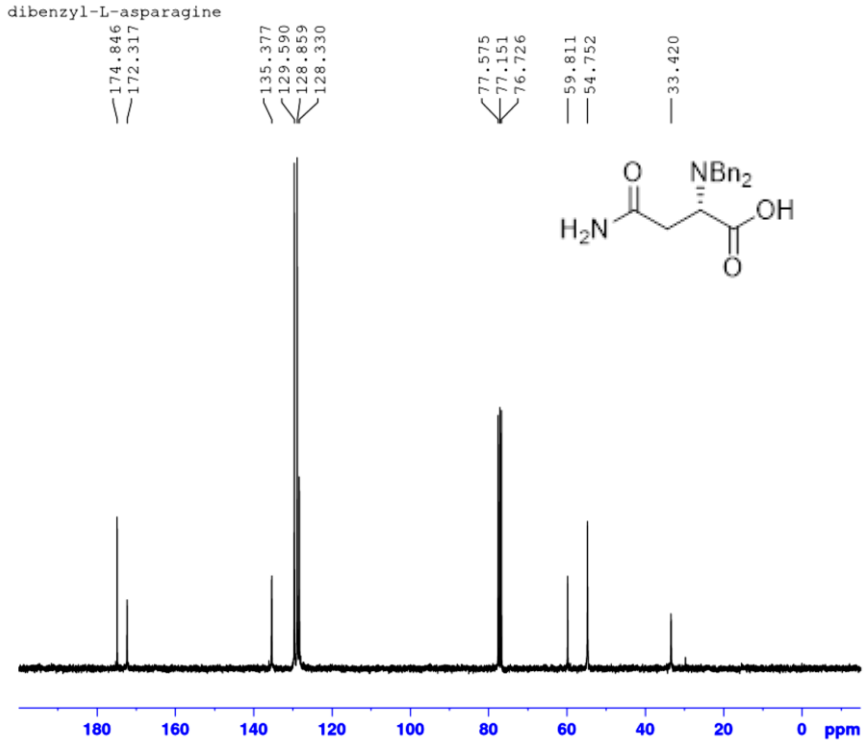
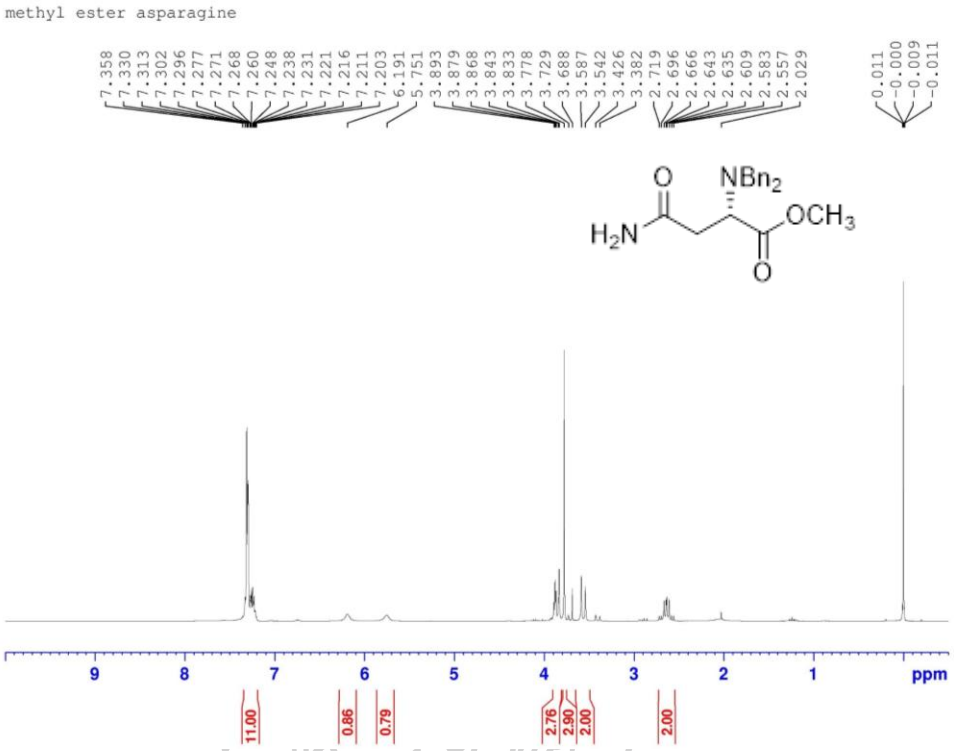
APPENDIX



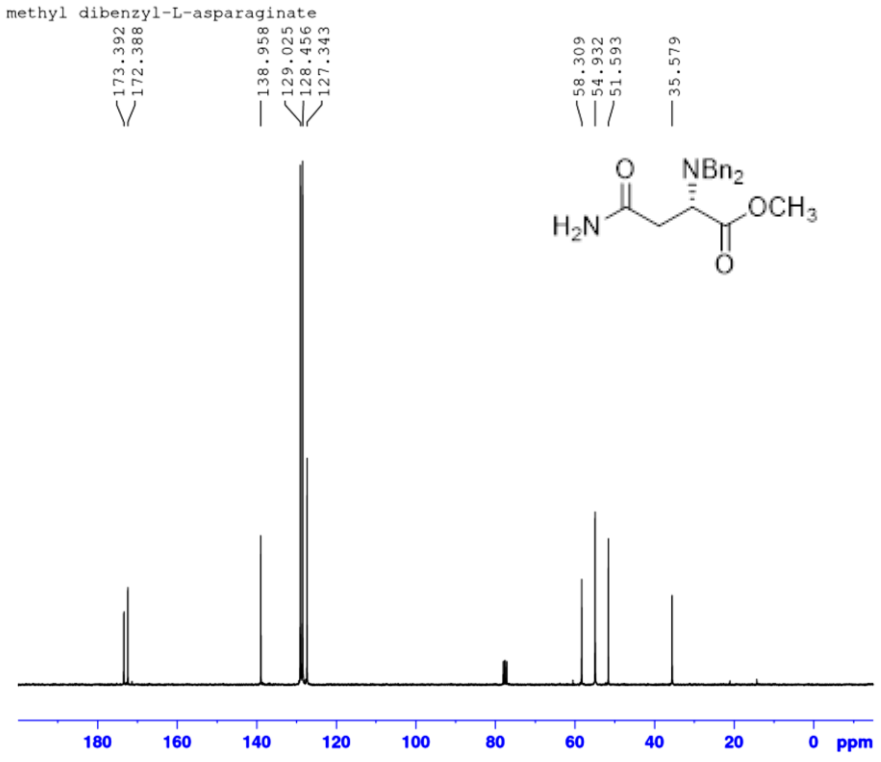
^{1}H NMR of *N*,*N*-dibenzyl asparagine **(1)**



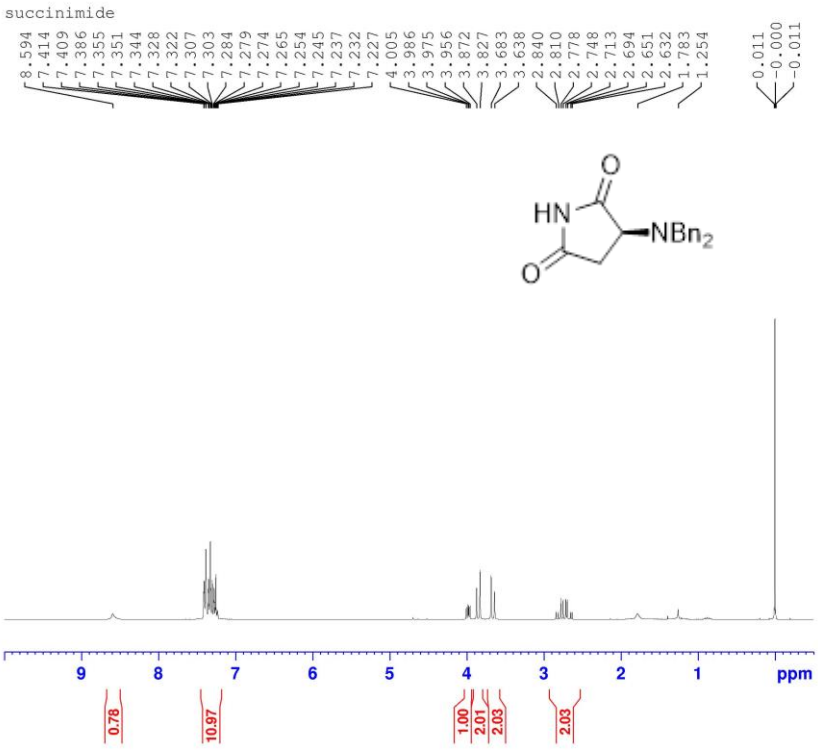
^{13}C NMR of *N*,*N*-dibenzyl asparagine **(1)**



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



^{13}C NMR of methyl ester asparagine **(2)**



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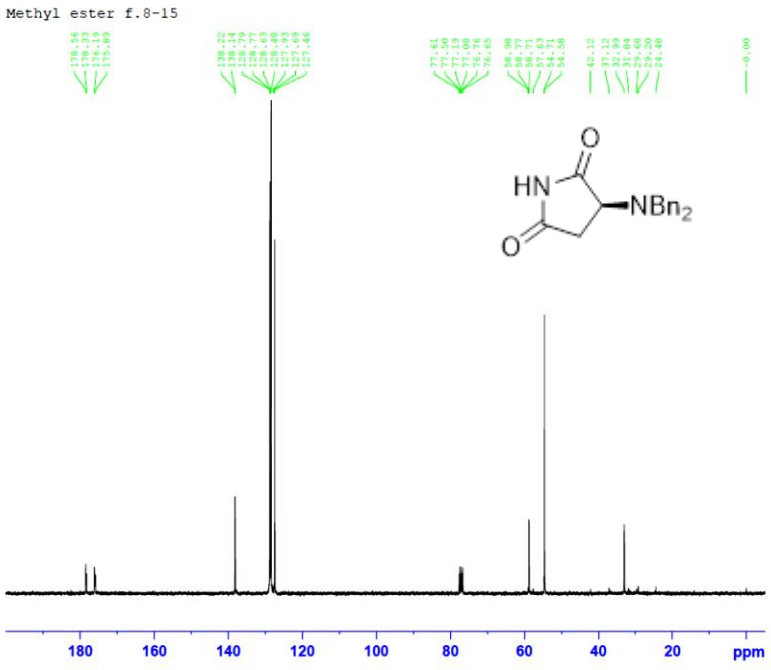

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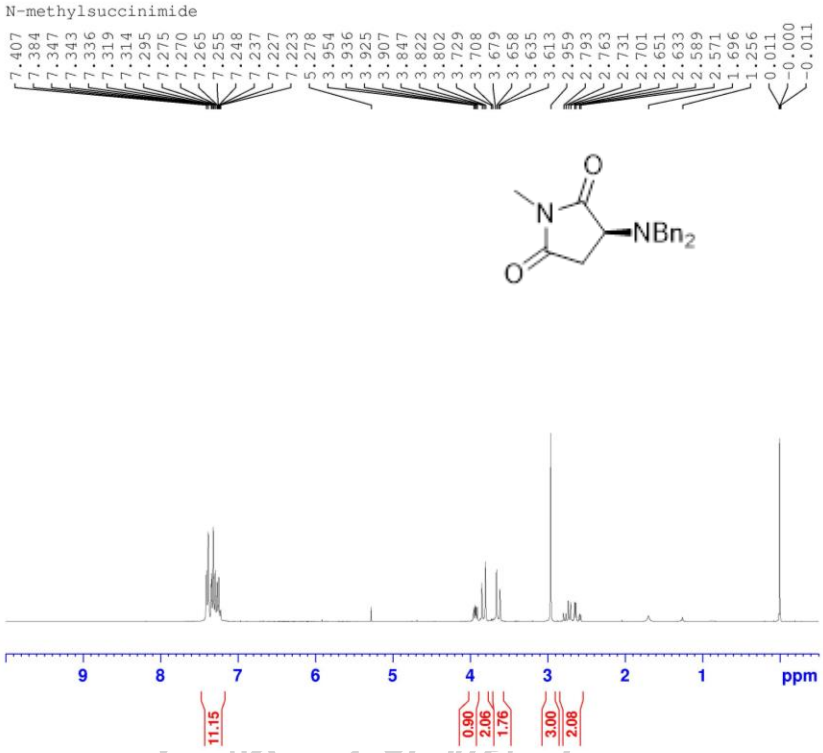

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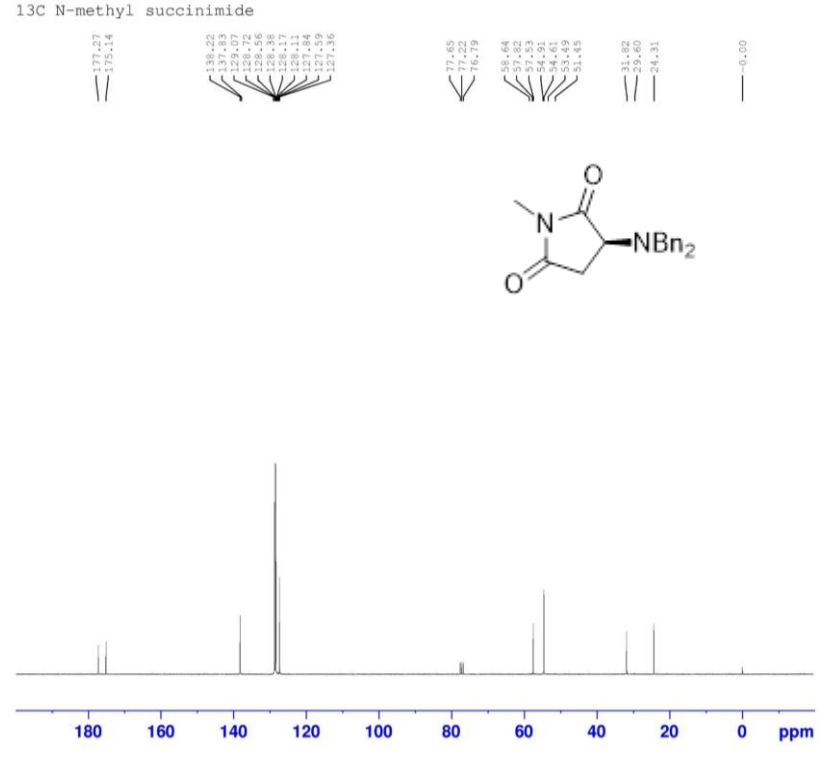

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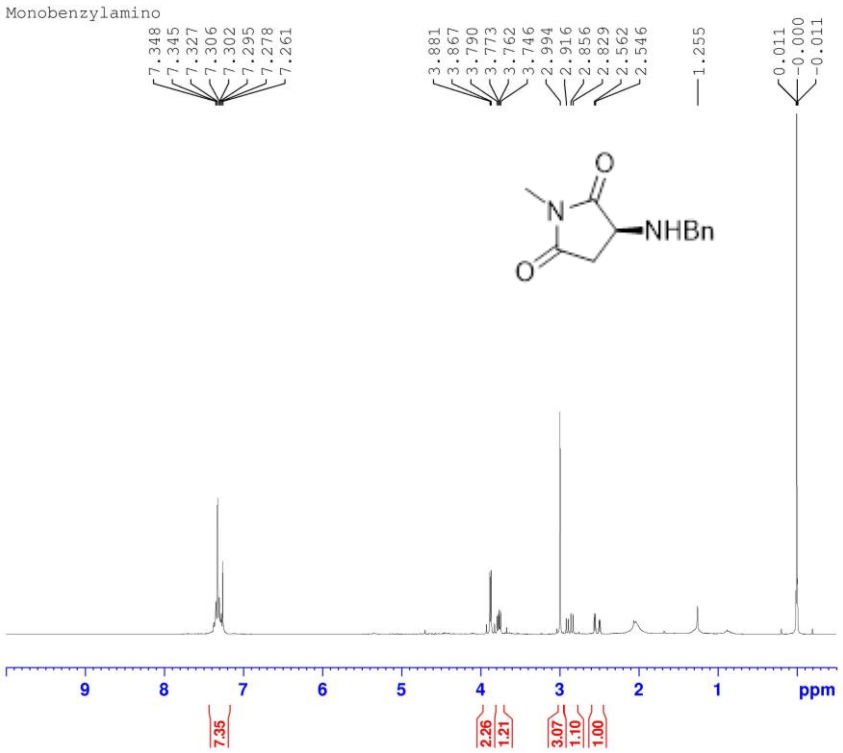

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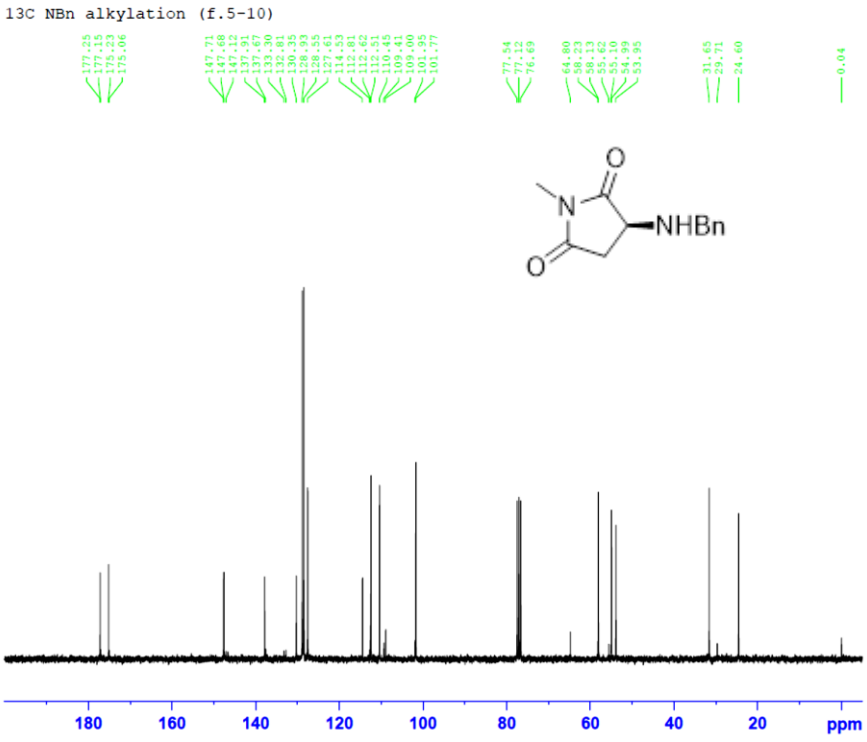

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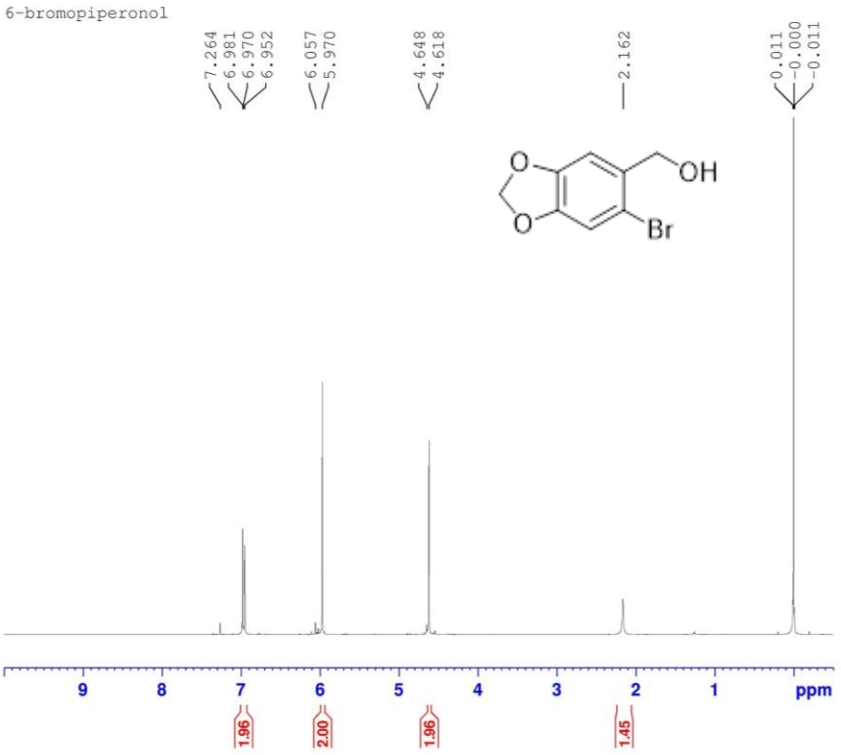
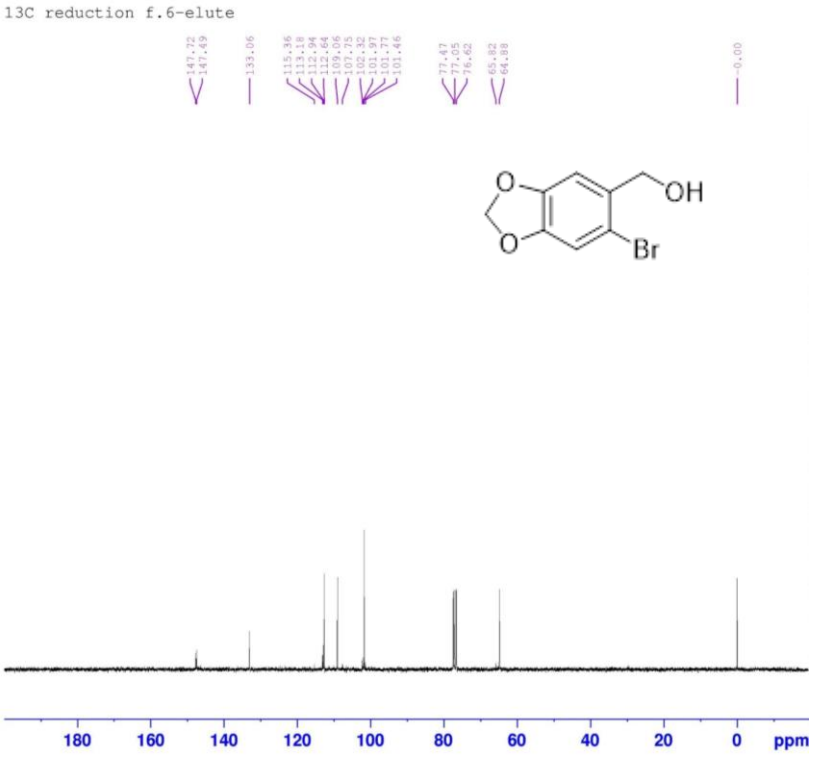
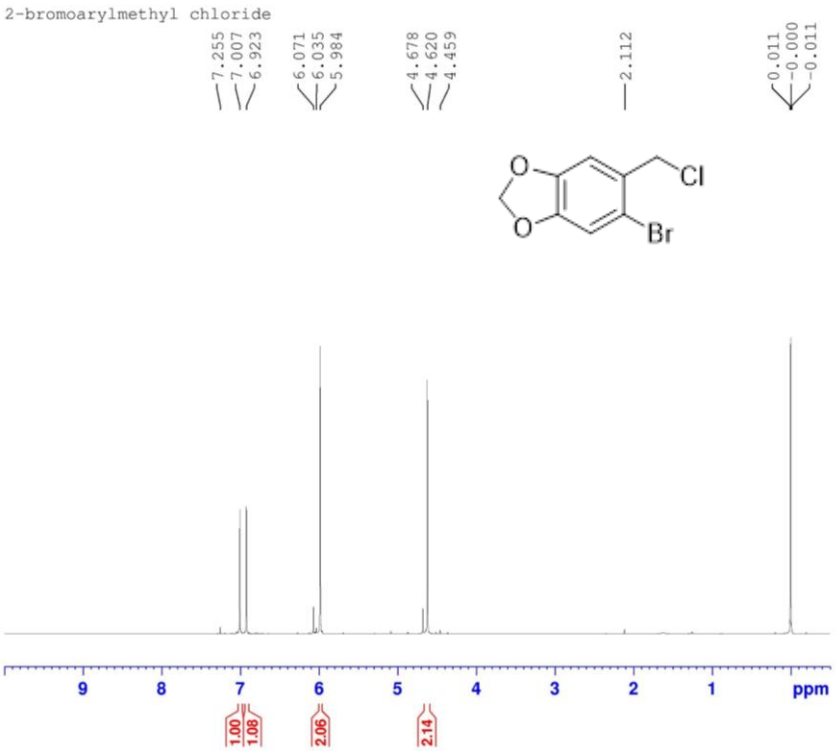


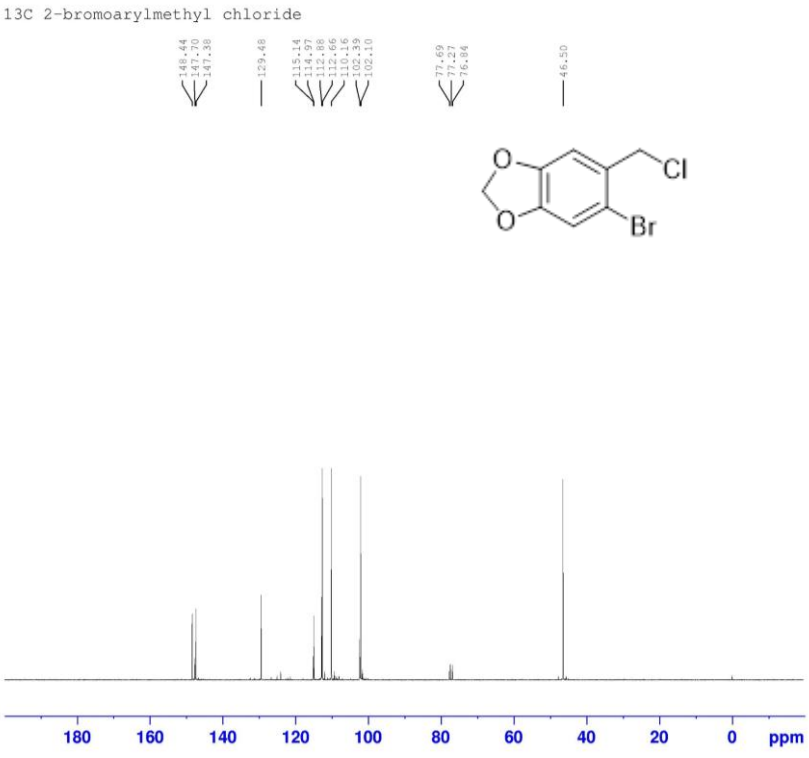
^{1}H NMR of 6-bromopiperonol **(11)**



^{13}C NMR of 6-bromopiperonol **(11)**



^{1}H NMR of 2-bromoarylmethyl chloride **(6)**



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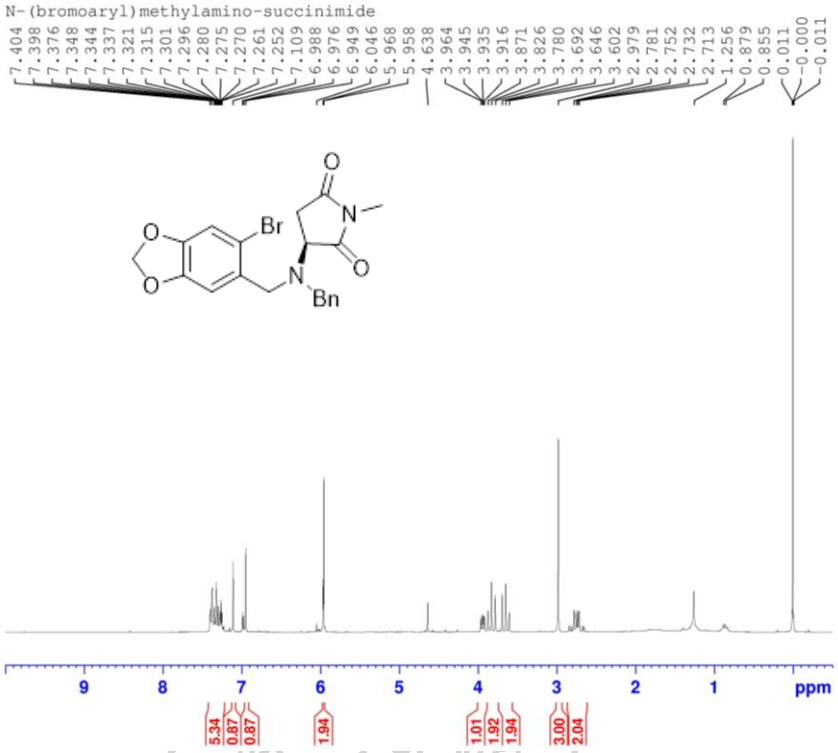
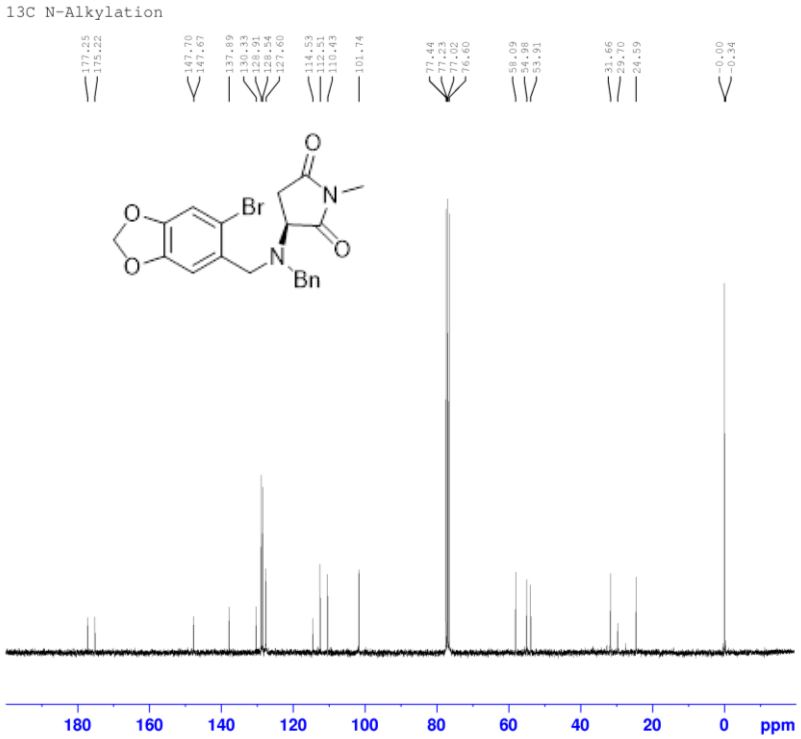
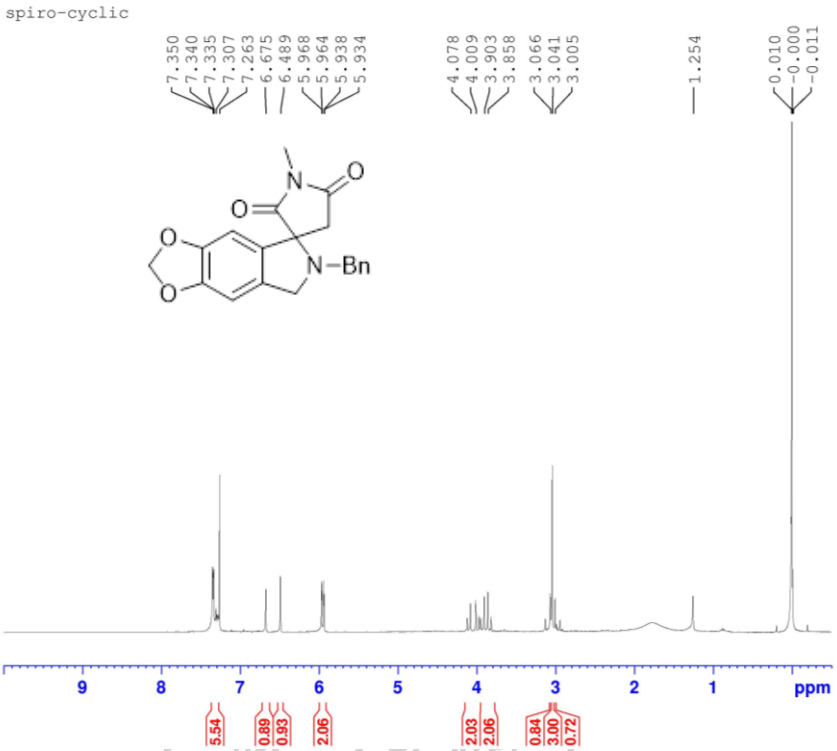


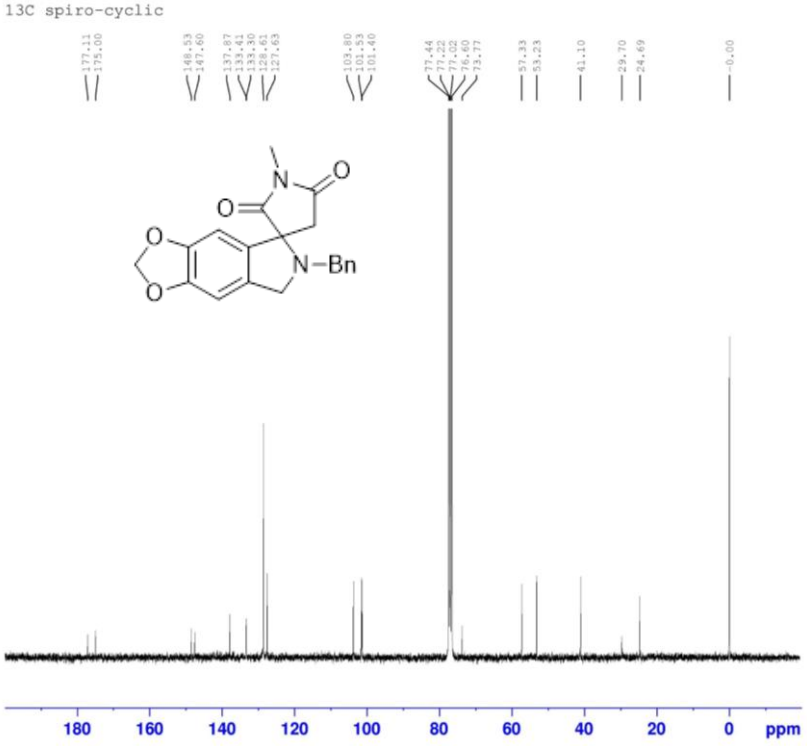
^{1}H NMR of *N*-(bromoaryl)methylamino-succinimide **(7)**



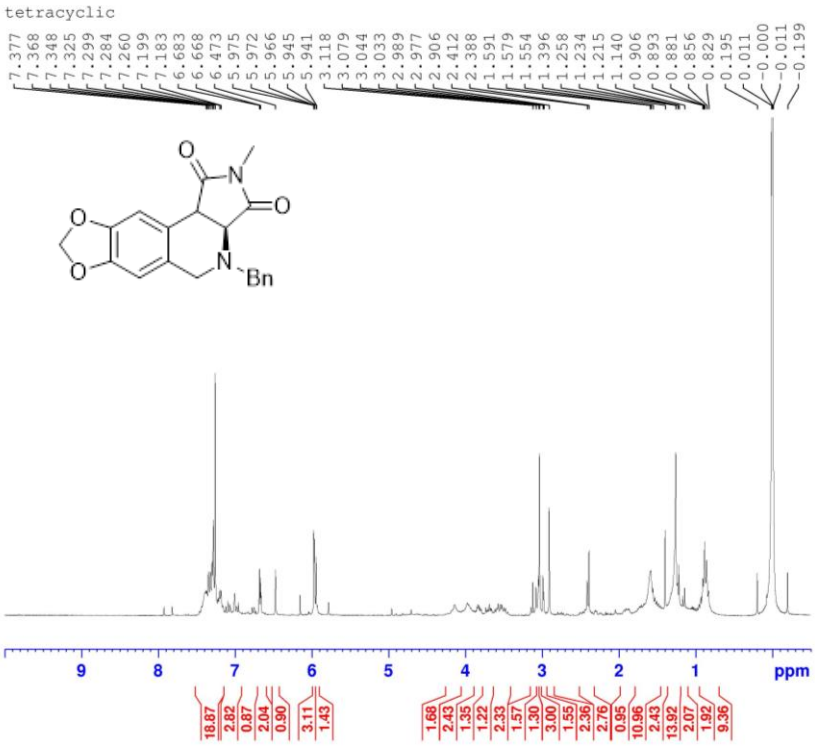
^{13}C NMR of *N*-(bromoaryl)methylamino-succinimide **(7)**



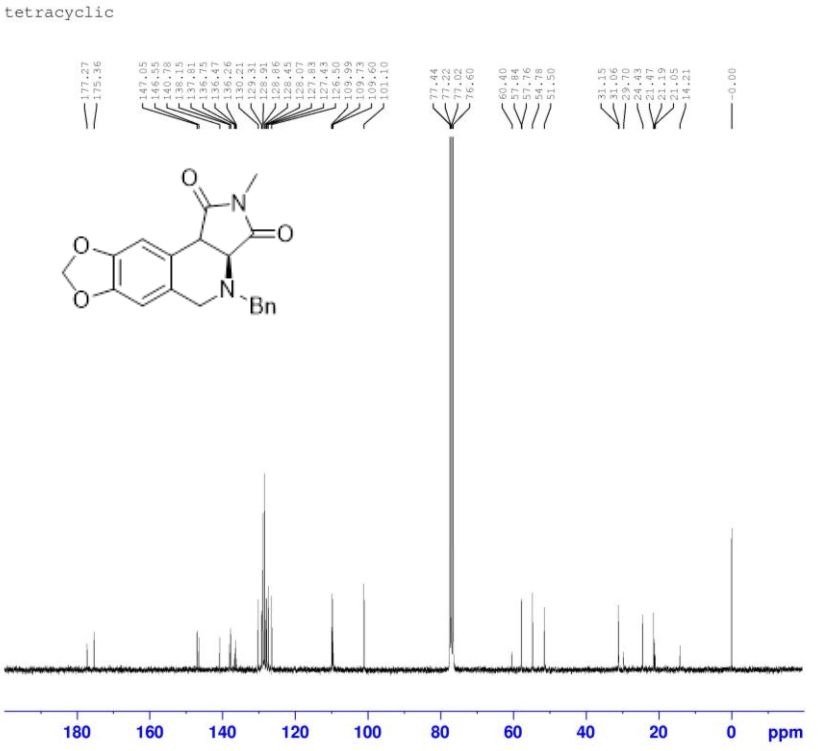
^{1}H NMR of spiro[isoindoline-succinimide] **(20)**



^{13}C NMR of spiro[isoindoline-succinimide] **(20)**



^{1}H NMR of tetracyclic succinimide-isoquinoline **(8)**



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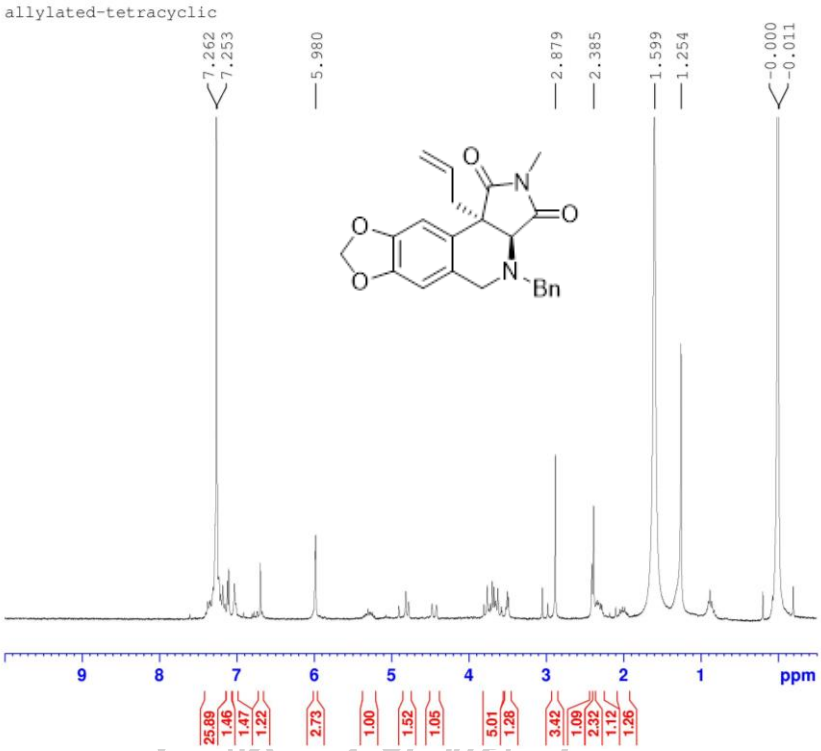
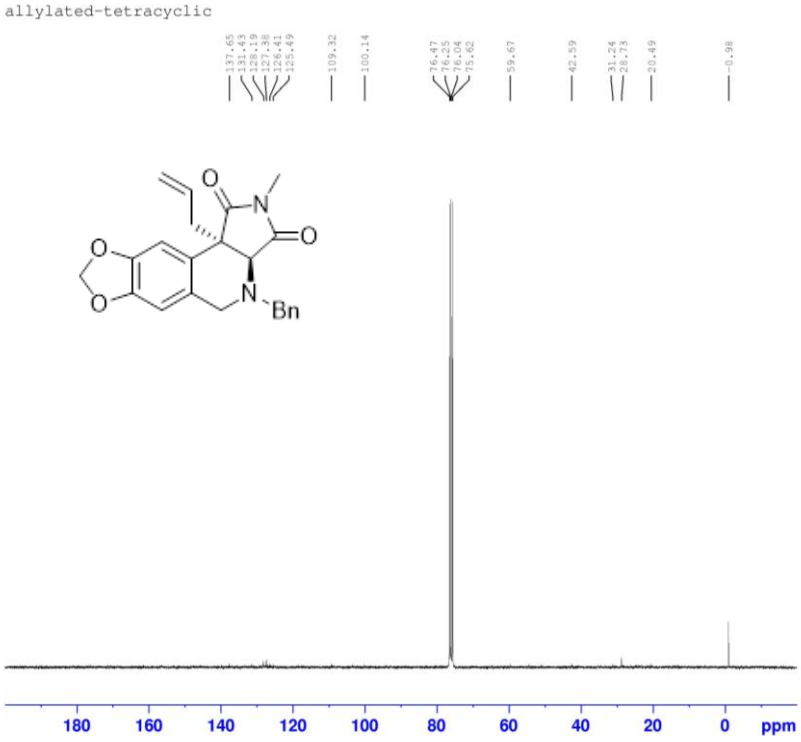
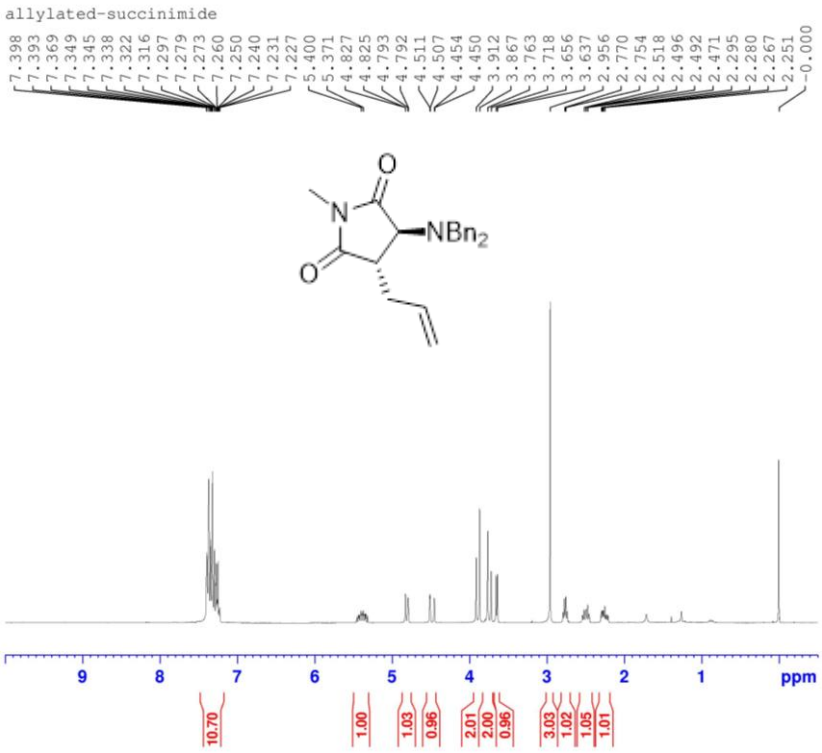


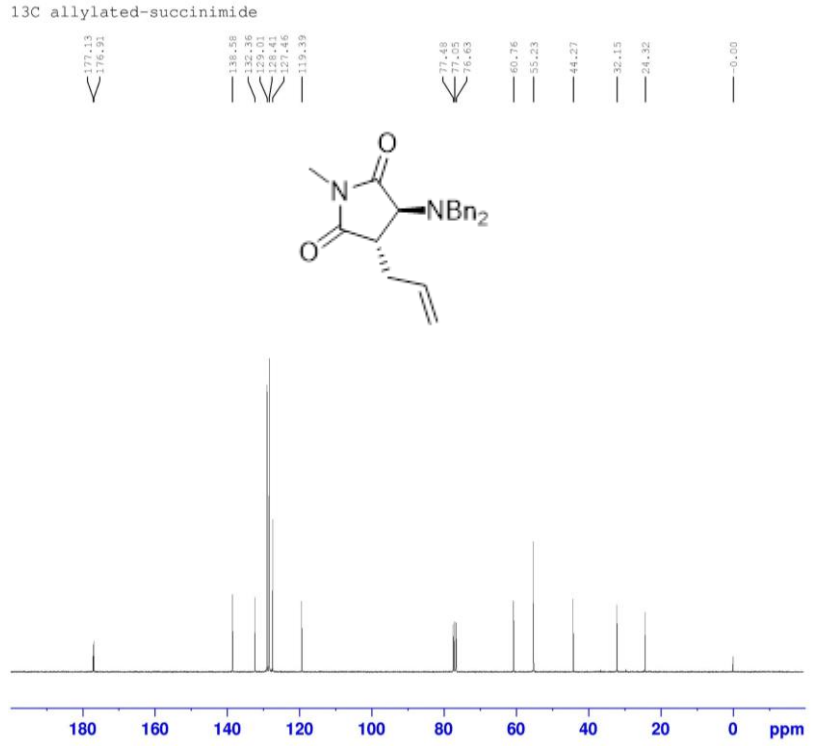
^{1}H NMR of allylated-tetracyclic **(14)**



^{13}C NMR of allylated-tetracyclic **(14)**



^{1}H NMR of allylated-succinimid**e (17)**



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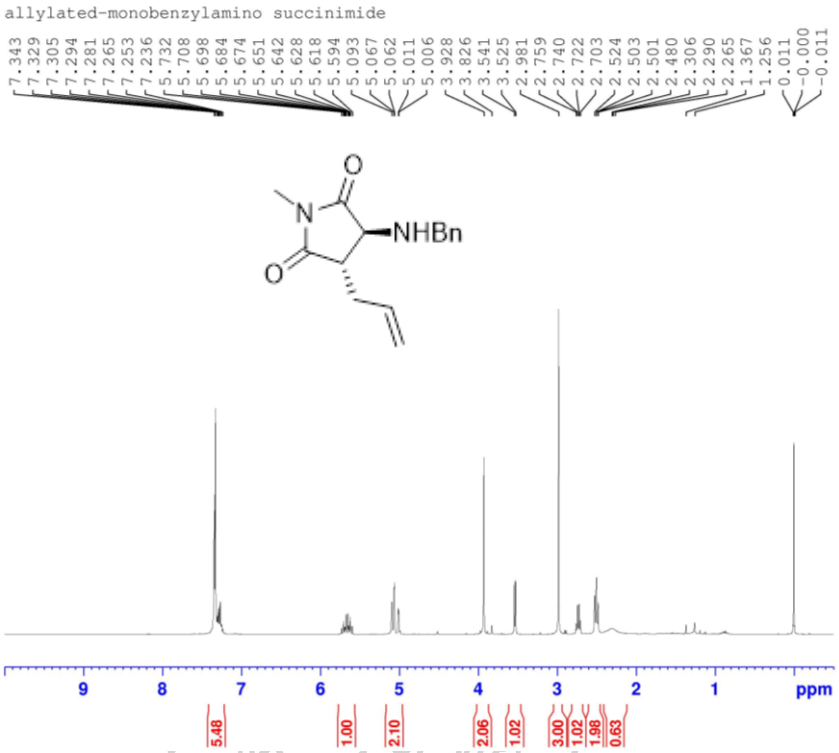
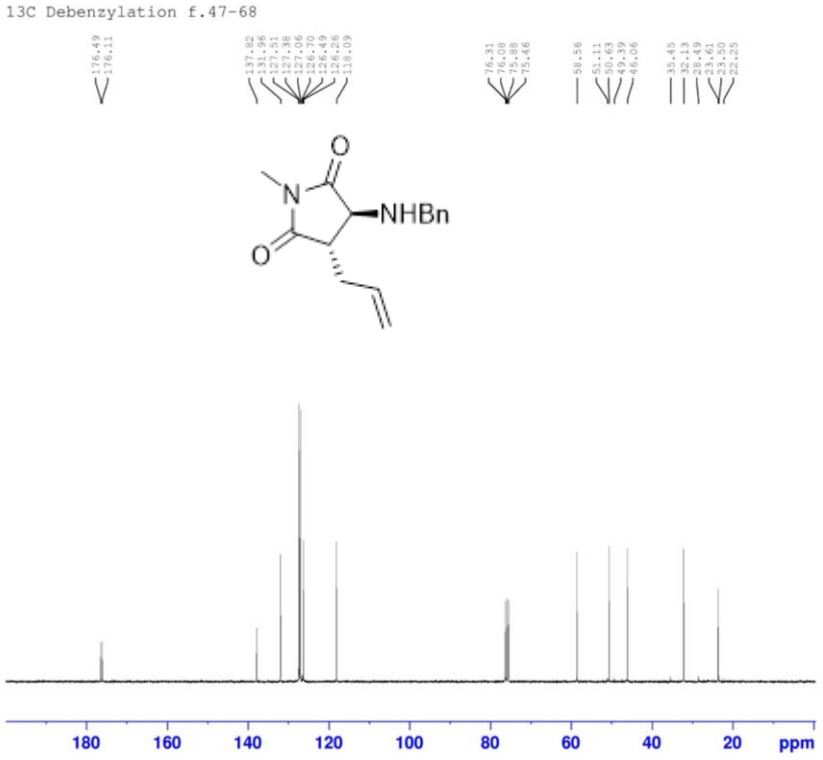
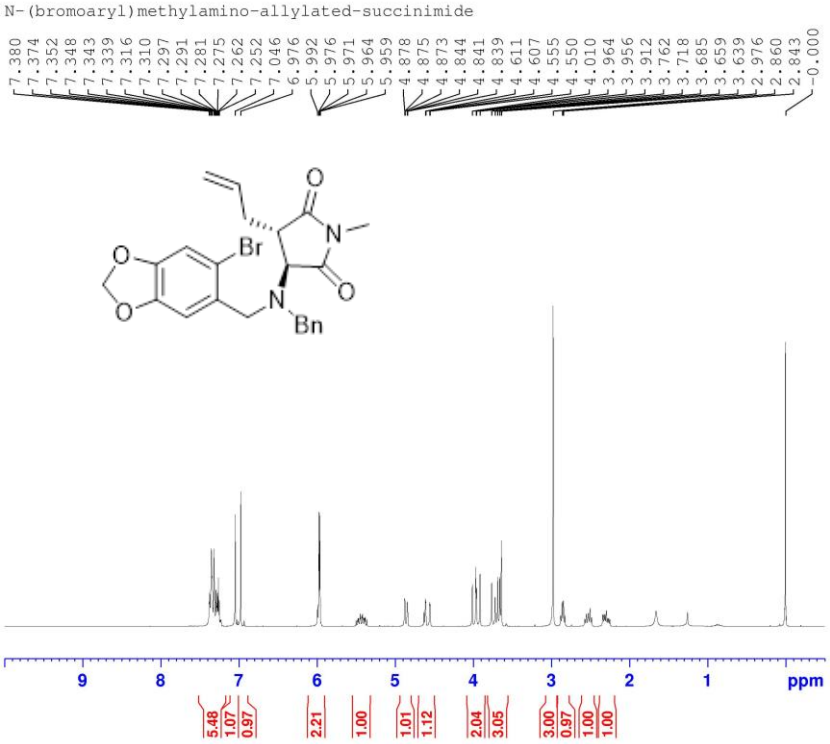


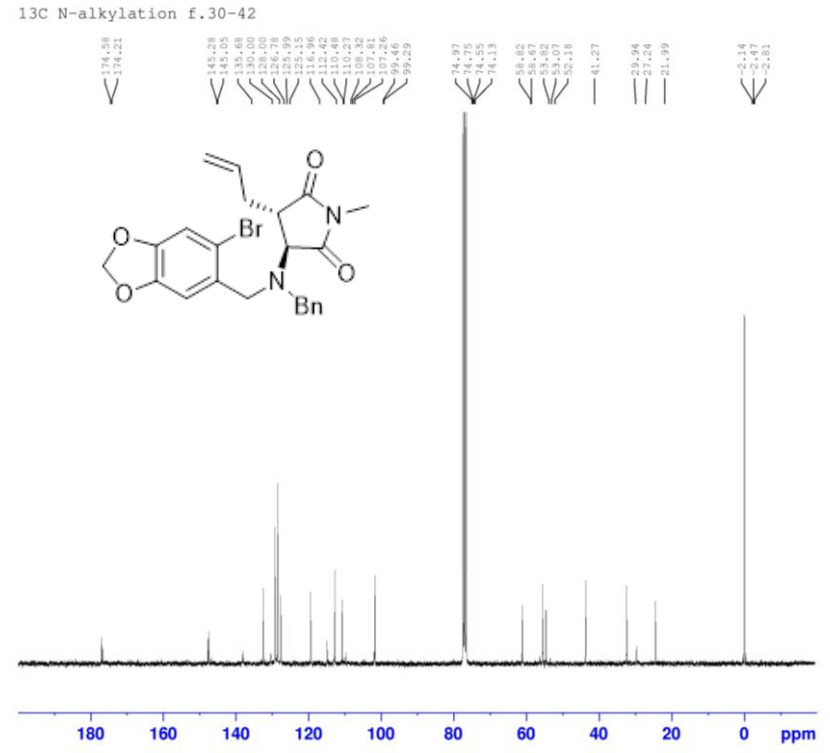
^{1}H NMR of allylated-monobenzylamino succinimide **(18)**



^{13}C NMR of allylated-monobenzylamino succinimide **(18)**



^{1}H NMR of *N*-(bromoaryl)methylamino-allylated-succinimide **(19)**



^{13}C NMR of *N*-(bromoaryl)methylamino-allylated-succinimide **(19)**

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OM-P-043

Synthesis of spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] via palladium-catalyzed intramolecular α-arylation

Ittiphat Klayparn, Punlop Kuntiyong*
Department of Chemistry, Faculty of Science, Silpakorn University, Sanamchandra Palace, Nakhon Pathom, 73000, Thailand
**E-mail: kuntiyong_p@su.ac.th*

Abstract:

In this work, we discuss synthesis of spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] classified as spiropyrrolidone which is an important structural motif present in a wide range of active pharmaceuticals and biologically important natural alkaloids. We are particularly interested in spirocyclic alkaloids containing 3-aminopyrrolidone moiety which can be derived from L-asparagine. Our synthesis uses L-asparagine as the chiral starting material which was converted to the key intermediate *N*-methyl-3-benzylaminosuccinimide in four steps with high yield. *N*-Alkylation with (2-bromoaryl)methyl chloride gave *N*-(bromoaryl) methylamino-succinimide which was the precursor for pivotal palladium-catalyzed intramolecular α-arylation. The key reaction produced the mixture of racemic spiro[isoindoline-succinimide] and tetracyclic succinimide-isoquinoline, which are regioisomers.

1. Introduction

Spirocyclic alkaloids isolated from plant and animal origins have important applications in medicinal chemistry. Spiropyrrolidines and oxindole moieties are present in a wide range of active pharmaceuticals and biologically important natural alkaloids. Examples of biologically active alkaloids with this feature are spiro[succinimide-isoindolinone]s (**a**), which are aldolase inhibitors,[1] spiro[γ-hydroxylactam-isoindolinone] (**b**), a potent inhibitor of human protein farnesyltransferase (FTase) in cancer treatment[2] and horsfiline (**c**) and coerulescine[3] (**d**) which are oxindole alkaloids with analgesic property found in plant *Horsfieldia superba* and cipargamin (**e**), an antimalarial drug[4] (Figure 1).

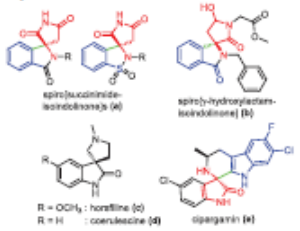
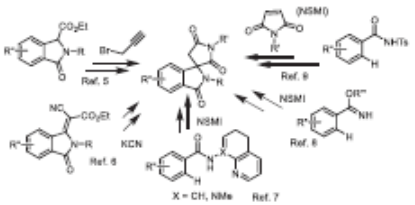


Figure 1. Examples of biologically active spiropyrrolidone alkaloids.

Previous syntheses of spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] are shown in Scheme 1. There are two major strategies, namely oxindole-based and *N*-alkylsuccinimide-based approaches. Alkylation of oxindole and conjugate addition of carboethoxymethelenyloxindole led to quaternary center of the spirocyclic system and the succinimide ring would be formed in the latter step.[5,6] Whereas hetero-Michael addition of benzamide derivative to *N*-alkylsuccinimide (NSMI) followed by C-H activation and spirocyclization would form the oxindole ring in the target molecule.[7-9]

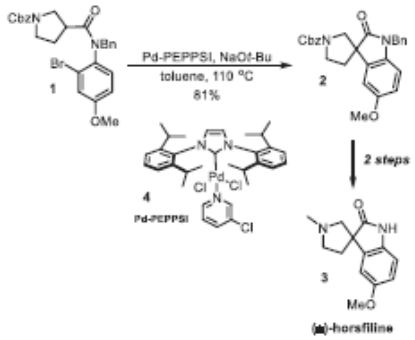


Scheme 1. Previous syntheses of spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione].

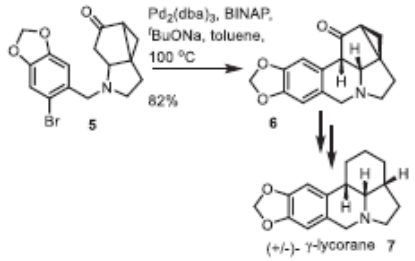
One of the most common reactions for the formation of a C-C bond between an aromatic carbon and the alpha carbon of a carbonyl group is the palladium-catalyzed α-arylation. Both intermolecular and intramolecular version of this reaction have become a useful and general synthetic method for natural products.[10] In 2010, Deppermann and co-workers reported the application of intramolecular α-arylation of *N*-bromoaryl amide **1** catalyzed by Pd-PEPPSI (**4**) with NHC ligand and ^{t}BuONa as base to give the spirocyclic product **2** in a synthesis of the spirooxindole horsfiline (**3**) (Scheme 2).[11]

In 2014, Liu reported a synthesis of γ-lycorane using palladium catalyzed intramolecular α-arylation of the ketone in tricyclic *N*-bromoarylmethyl-indolinone **5** catalyzed by

$Pd_2(dba)_3$/BINAP with ^tBuONa as a base to give the complete skeleton **6** of lycorine-type alkaloid **7** in good yield (Scheme 3).[12]



Scheme 2. Short synthesis of horsfiline by Deppermann and co-workers.



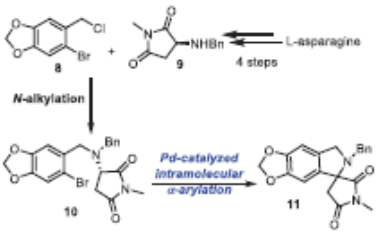
Scheme 3. Synthesis of γ-lycorane by Liu using palladium-catalyzed α-arylation.

In this work, we discuss the synthesis of spiro[succinimide-isoindolinone] using palladium catalyzed intramolecular α-arylation of succinimide derived from L-asparagine (Scheme 4).

2. Materials and Methods

2.1 Materials

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



Scheme 4. Synthesis of spiro[succinimide-isoindolinone] using palladium-catalyzed α-arylation.

2.2 Spectroscopic measurement

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

2.3 Synthesis of compounds

2.3.1 Synthesis of *N*-methyl-3-benzylamino-succinimide 9

To a solution of *N*-methyl-3-dibenzylamino-succinimide **13** (176 mg, 0.57 mmol) in MeCN and H_2O (5:1, 18 mL) was added CAN (ceric(IV) ammonium nitrate) (1.26 g, 2.29 mmol) and the mixture was stirred overnight at room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and stirred for 10 minutes. Subsequently it was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexanes/EtOAc) to give *N*-methyl-3-benzylamino-succinimide **9** (91 mg, 73%) as a

brown oil.: R_f (4:1 hexane/EtOAc) 0.13; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 3.87 (d, J = 3.9 Hz, 2H), 3.77 (dd, J = 8.3, 4.8 Hz, 1H), 2.99 (s, 3H), 2.87 (dd, J = 17.9, 8.1 Hz, 1H), 2.52 (dd, J = 17.7, 4.9 Hz, 1H), 2.05 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 175.4, 138.7, 128.6, 128.5, 127.9, 55.5, 51.8, 36.3, 24.8; $[\alpha]_D^{25}$ -5.5 (c 1.3, $CHCl_3$); IR (film) ν_{max} 3317, 1697, 1605, 1412, 1282 cm^{-1}

2.3.2 Synthesis of (2-bromoaryl)methyl chloride 8

To a solution of 6-bromopiperonol **14** (1.97 g, 8.53 mmol) in $CHCl_3$ under argon atmosphere was added pyridine (0.65 mL, 8.02 mmol) and the mixture was stirred at 0 °C. To the solution was added $SOCl_2$ (0.74 mL, 10.2 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with 5 M HCl (10 mL). The mixture was washed with water (2×20 mL) and 10% Na_2CO_3 (100 mL). The phases were separated, and the organic layer was washed with water (2×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product (2-bromoaryl)methyl chloride **8** was obtained without purification as a brown oil (1.95 g, 78%).: R_f (4:1 hexanes/EtOAc) 0.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.92 (s, 1H), 6.04 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.4, 129.5, 114.9, 112.9, 110.2, 102.1, 46.5; IR (film) ν_{max} 3455, 3010, 2905, 2076, 1738, 1621, 1231, 1114, 1035 cm^{-1}

2.3.3 Synthesis of *N*-(bromoaryl) methylamino-succinimide 10

To a solution of *N*-methyl-3-benzylaminosuccinimide **9** (35 mg, 0.16 mmol) in DMF (3 mL) under argon atmosphere at room temperature was added K_2CO_3 (44 mg, 0.32 mmol), KI (3 mg, 0.02 mmol) and (2-bromoaryl)methyl chloride **8** (40 mg, 0.16 mmol) and the mixture was stirred overnight at room temperature. The mixture was filtered to remove K_2CO_3 and to the solution were added water (10 mL) and CH_2Cl_2 (5 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 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 crude product was purified by flash chromatography (silica gel, 4:1 hexanes/EtOAc) to give *N*-(bromoaryl) methylamino-succinimide **10** (28 mg, 37%) as an orange oil.: R_f (4:1 hexane/EtOAc) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.11 (m, 5H), 7.11 (s, 1H), 6.95 (s, 1H), 6.05 (s, 2H), 3.94 (dd, J = 8.6, 5.6 Hz, 1H), 3.80 (d, J = 13.8 Hz, 2H), 3.67 (d, J = 14.1 Hz, 2H), 2.98 (s, 3H), 2.74 (dd, J = 18.5, 8.7 Hz, 1H), 2.69 (dd, J = 18.5, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.2, 147.7, 137.9, 130.4, 128.9, 128.6, 127.6, 114.5, 112.8, 110.5, 101.9, 64.8, 58.1, 54.9, 53.9, 31.7, 24.6; $[\alpha]_D^{25}$ -26.5 (c 1.3, CH_2Cl_2); IR (film) ν_{max} 2923, 2853, 1695, 1474, 1379, 1230, 1112 cm^{-1}; ESI-HRMS calculated for $C_{20}H_{20}BrN_2O_4^+$ $[M+H]^+$ 431.0601, found 431.0604.

2.3.4 Synthesis of (±)-spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] (11) and tetracyclic succinimide-isoquinoline (15)

To a solution of *N*-(bromoaryl)methylamino-succinimide **3** (27 mg, 0.06 mmol) in dry toluene (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (16 mg, 0.11 mmol), PPh_3 (3 mg, 0.01 mmol) and $Pd(OAc)_2$ (1.3 mg, 0.006 mmol) and the mixture was heated at reflux at 120 °C overnight. This the mixture was filtered to remove $Pd(OAc)_2$ and to the solution was extracted with EtOAc (3×5 mL) and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexanes/EtOAc) to give (±)-spiro[isoindoline-1,3'-pyrrolidine-2',5'-dione] **11** (11.6 mg, 59%) and tetracyclic succinimide-isoquinoline **15** (3.4 mg, 17%) as a yellow oil.

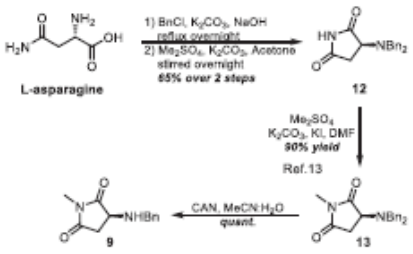
Compound (±)-**11**; R_f (4:1 hexane/EtOAc) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 6.68 (s, 1H), 6.49 (s, 1H), 5.97 (d, J = 1.2 Hz, 1H), 5.94 (d, J = 1.4 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 3.98 (d, J = 12.2 Hz, 1H), 3.93 (d, J = 12.9 Hz, 1H), 3.84 (d, J = 12.9 Hz, 1H), 3.07 (s, 1H), 3.04 (s, 3H), 3.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 175.0, 148.6, 147.6, 137.9, 133.4, 133.3, 128.6, 127.6, 103.8, 101.5, 101.4, 73.8, 57.3, 53.2, 41.1, 29.7, 24.7; IR (film) ν_{max} 3356, 2924, 2854, 1710, 1462, 1378, 1259, 1157, 1018 cm^{-1}; ESI-HRMS calculated for $C_{20}H_{19}N_2O_4^+$ $[M+H]^+$ 351.1339, found 351.1344.

Compound **15**; R_f (4:1 hexanes/EtOAc) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.45 (s, 1H), 6.00-5.90 (m, 2H), 4.20-3.42 (m, 5H), 3.15-2.95 (m, 1H), 2.91 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.4, 147.1, 146.6, 137.8, 130.3, 128.9, 128.5, 128.1, 127.9, 127.5, 110.0, 109.7, 101.1, 57.9, 54.6, 51.5, 31.1, 24.4, 21.6; IR

(film) ν_{max} 3358, 2924, 2854, 1712, 1463, 1380, 1259, 1157, 1020 cm^{-1};ESI-HRMS calculated for $C_{20}H_{19}N_2O_4^+$ $[M+H]^+$ 351.1339, found 351.1575.

3. Results & Discussion

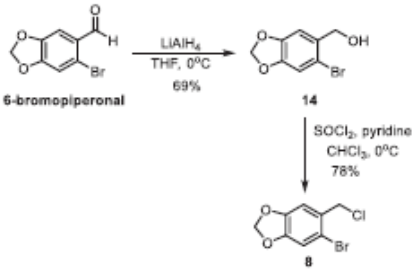
The synthesis started from the benzylation of L-asparagine in basic condition using benzyl chloride, K_2CO_3, and NaOH in MeOH and H_2O to give *N,N*-dibenzyl asparagine. The methylation of ester in the presence of Me_2SO_4 and K_2CO_3 in acetone provided methyl ester intermediate followed by imide formation to give succinimide **12**. This was converted to *N*-methyl-3-dibenzylamino-succinimide **13** with Me_2SO_4 and K_2CO_3 in DMF as previously described.[13] Finally, the monodebenzylation of *N*-methyl-3-dibenzyl-aminosuccinimide **13** using CAN in a 5:1 ratio of MeCN and H_2O afforded the desired precursor **9** (Scheme 5).



Scheme 5. Synthesis of *N*-methyl-3-benzylamino-succinimide **9**.

N-(Bromoaryl)methylamino-succinimide **10** would be derived from the *N*-alkylation of *N*-methyl-3-benzylaminosuccinimide **9** and (2-bromoaryl)methyl chloride **8**. The synthesis of (2-bromoaryl)methyl chloride **8** started from the reduction of 6-bromopiperonal by using $LiAlH_4$ as the reducing agent in THF to give 6-bromopiperonol **14**. After that, chlorination with $SOCl_2$ and pyridine in $CHCl_3$ provides (2-bromoaryl)methyl chloride **8** in excellent yield (Scheme 6).

After obtaining the precursors, *N*-alkylation between *N*-methyl-3-benzylaminosuccinimide **9** and (2-bromoaryl)methyl chloride **8** using K_2CO_3 and KI as a catalyst in DMF gave *N*-(bromoaryl)methylamino-succinimide **10** in 37% yield with some recovered starting materials (Scheme 7).

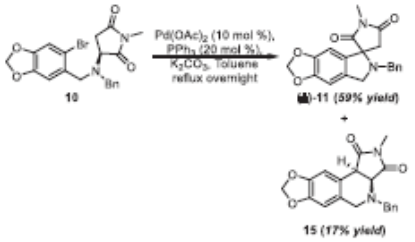


Scheme 6. Synthesis of (2-bromoaryl)methyl chloride **8**.

Scheme 7. Synthesis of *N*-(bromoaryl)methylamino-succinimide **10**.

Then, the palladium-catalyzed intramolecular α-arylation of *N*-(bromoaryl)methylamino-succinimide **10** catalyzed by $Pd(OAc)_2$ in the presence of PPh_3 ligand and K_2CO_3 in toluene afforded the desired (±)-spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] **11** and tetracyclic succinimide-isoquinoline **15** which are regioisomers (Scheme 8). The spirocycic product **11** was obtained cleanly after chromatographic separation, however, the regioisomeric product **15** contained unidentified impurities after repeated attempts at purification (ESI-HRMS 351.1339 calculated for $C_{20}H_{19}N_2O_4^+$ $[M+H]^+$ found 351.1344 for **11** and 351.1575 for **15**).

The racemization of compound **11** was confirmed by high-performance liquid chromatography with diode-array detection (HPLC-DAD). Separation was performed using a CHIRALPAK IC (10 mm × 250 mm × 5 µm) and a flow rate was 2 mL/min with the following gradient. Water (Solvent A) and acetonitrile (Solvent B) were used as a mobile phase. From the result, two peaks were observed at retention times of 63.379 and 64.385 min in a 1:1 ratio, concluding that the synthesized compound **11** was racemic.



Scheme 8. Palladium-catalyzed intramolecular α-arylation of *N*-(bromoaryl)- methylamino-succinimide **10**.

4. Conclusion

In conclusion, we have synthesized a (±)-spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] **11** form L-asparagine in 6 steps (LLS, 8 total steps). Palladium-catalyzed intramolecular α-arylation of *N*-(bromoaryl) methylamino-succinimide **10** resulted in the formation of (±)-spiro[isoindoline-1,3′-pyrrolidine-2′,5′-dione] **11** and tetracyclic succinimide-isoquinoline **15**. We are currently investigating the application of intramolecular α-arylation of aminosuccinimide or aminolactam to form spirocyclic pyrrolidone in biologically active molecules.

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