CHAPTER I

INTRODUCTION

Pyrrolizidine Necine Bases

The pyrrolizidine alkaloids are a major group of alkaloids, isolated from a range of plants. They have been isolated in both the free and esterified forms. The free form is known as the necine base and has the 1-azabicyclo[3.3.0]octane ring system (**Figure 1**). The necic acids are mono or dibasic and carry a number of hydroxyl groups. They are beyond the scope of this review.
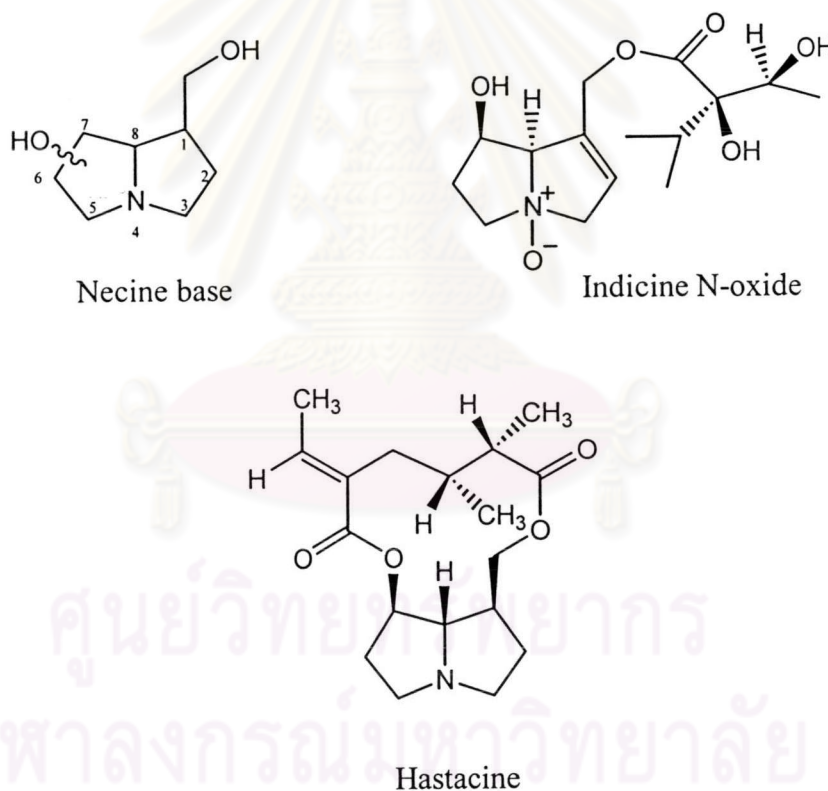

Necine base

Indicine N-oxide

Hastacine

Figure 1 General structure and pyrrolizidine examples

There have been many routes developed for the synthesis of pyrrolizidines.[1-13] As the field has been thoroughly and regularly reviewed, only a small sample is presented here.

Some pyrrolizidine alkaloids have shown effective anti-cancer activity and one, indicine-N-oxide, has been in clinical trials. Unfortunately, all pyrrolizidines, especially those with same unsaturation, are hepatotoxic. The pyrrolizidine rings are oxidized to pyrroles *in vivo*. Ionization under physiological conditions of hydroxy and carboxy functions that are α-to the pyrrole generates potent electrophiles **(Scheme 1)**.[14]

Dihydropyrrolizine
(Didehydropyrrolizidine)
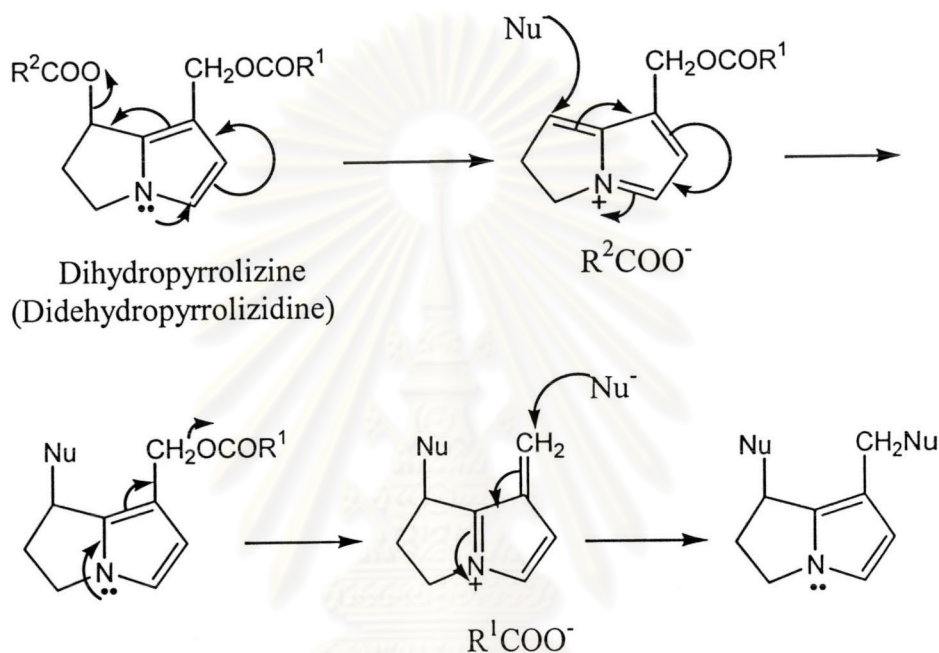
Scheme 1 *In vivo* pyrrolizidine biotransformations

Pyrrolizidine alkaloids may be grouped according to the position and degree of hydroxylation. The simplest have only a single hydroxymethyl group at C-1. A large number of pyrrolizidine diols are known. The most common have the additional hydroxyl group at C-7. A small number of pyrrolizidine diols and triols possess a hydroxyl group at C-1. Recently a family of pyrrolizidines with a second hydroxyl at C-6 have been isolated. In these molecules, the amphorogynines, C-1' is at the carboxylic acid oxidation state (see **Figure 7**). There is an abundance of more highly hydroxylated pyrrolizidines. Casuarine (see **Figure 8**) is a recently isolated example of one of these alkaloids. Subgroups with a hydroxy methyl group at C-3 are the alexines and australines.

1. Monohydroxylated Pyrrolizidines
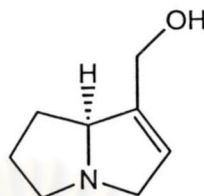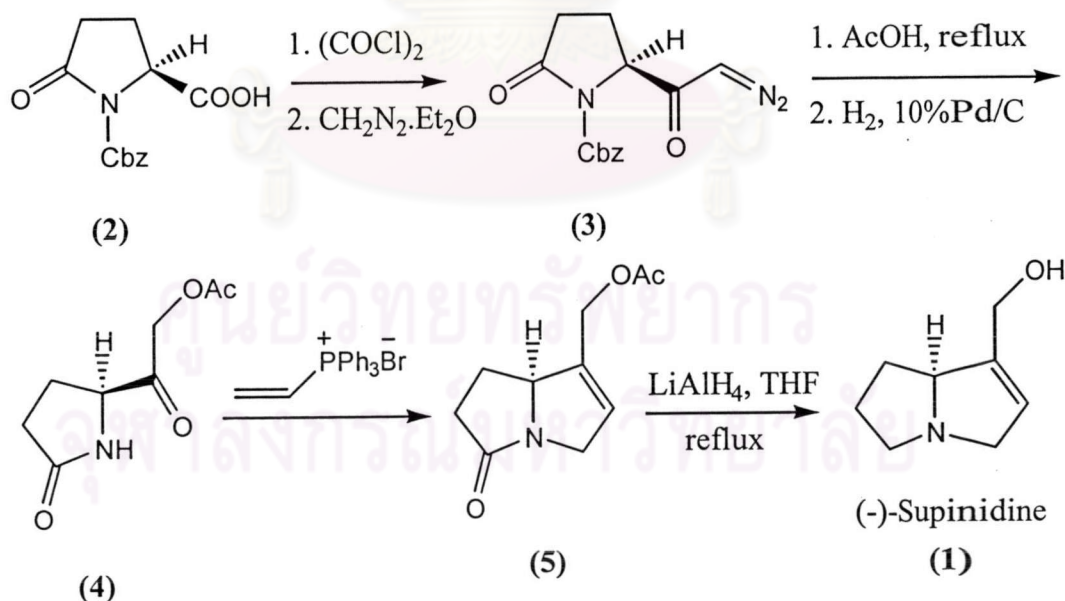
Unsaturated monohydroxylated pyrrolizidines

Figure 2   (-)-Supinidine **(1)**

Hewson's group has synthesized (-)-supinidine **(1)** using an intramolecular Wittig reaction as the cyclization step.[15] (S)-N-Benzyloxycarbonyl pyroglutamic acid **(2)** was converted to diazoketone **(3)** which, on heating with acetic acid, followed by removal of Cbz group provided pyrrolidine-2-one **(4)**. This compound **(4)** was cyclized with the vinylphosphonium salt to provide the pyrrolizidine **(5)**. After that, **(5)** was reduced to supindine **(1)** with LiAlH$_4$ (Scheme 2).

Scheme 2   Synthesis of (-)-Supinidine

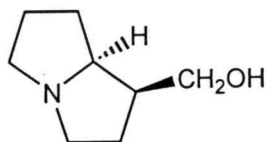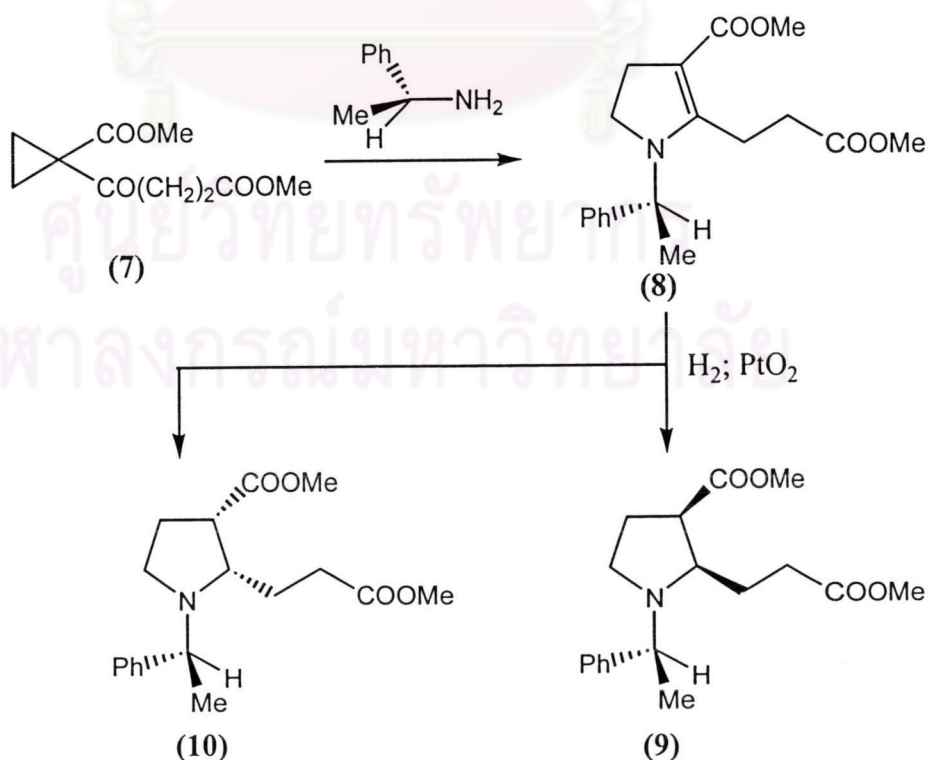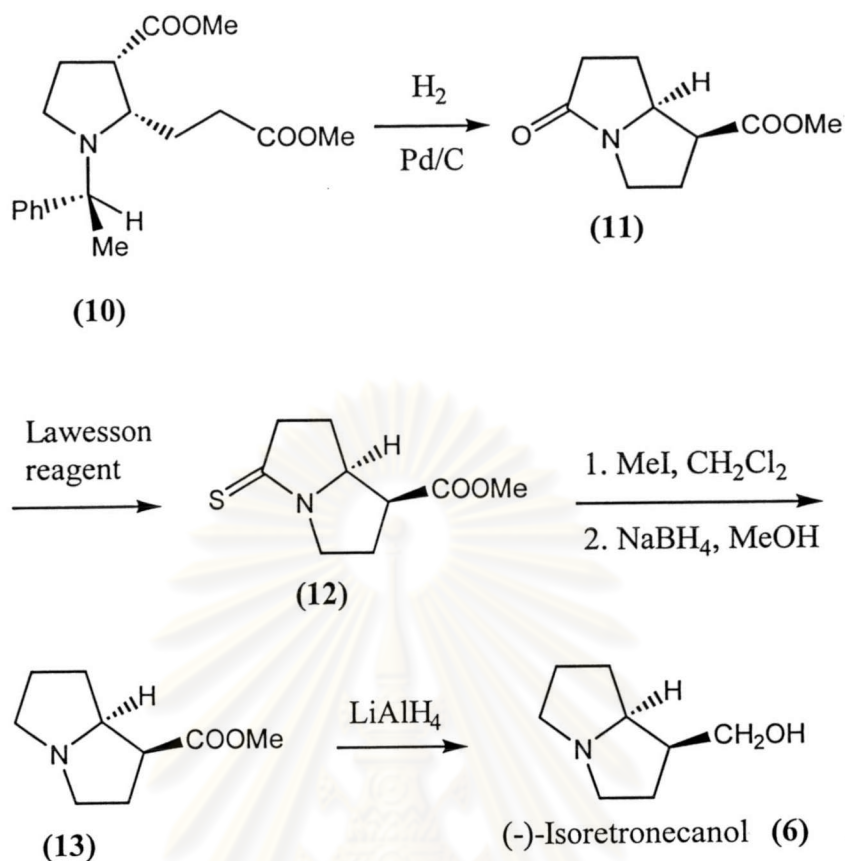## 1.2 Saturated monohydroxylated pyrrolizidines

Figure 3   (-)-Isoretronecanol **(6)**

Lhommet's group[16] has completed a stereoselective synthesis of (-)-isoretronecanol starting from cyclopropane **(7)**. The first step is the homoconjugate addition of (S)-α–methylbenzylamine to cyclopropane **(7)**. The ring opening product underwent cyclization *in situ* to give β-enamino ester **(8)**. Catalytic hydrogenation gave the diastereoisomeric cis isomers **(10)** and **(9)** with a diastereoisomeric excess of 90%. They were separated by chromatography. The isomer **(10)** was hydrogenated to remove the chiral auxiliary to afford bicyclic lactams **(11)**. Selective reduction of the carbonyl lactam was achieved *via* formation of the thiolactam **(12)**. Finally, the intermediate (-)-chysine **(13)** was converted to enantiomerically pure (-)-isoretronecanol **(6)** by reduction with LiAlH₄ **(Scheme 3)**.

(10) → H₂ / Pd/C → **(11)**

(11) → Lawesson reagent → **(12)** → 1. MeI, CH₂Cl₂ / 2. NaBH₄, MeOH →

(13) → LiAlH₄ → (-)-Isoretronecanol **(6)**

Scheme 3   Synthesis of (+)-Isoretronecanol

2. 7-Hydroxylated Pyrrolizidines

(-)-Hastanecine **(14)** was isolated from *Cacalia hastata*, family Compoitae (tribe Senecioneae) and *Cacalia robusta* (**Figure 4**).
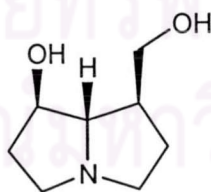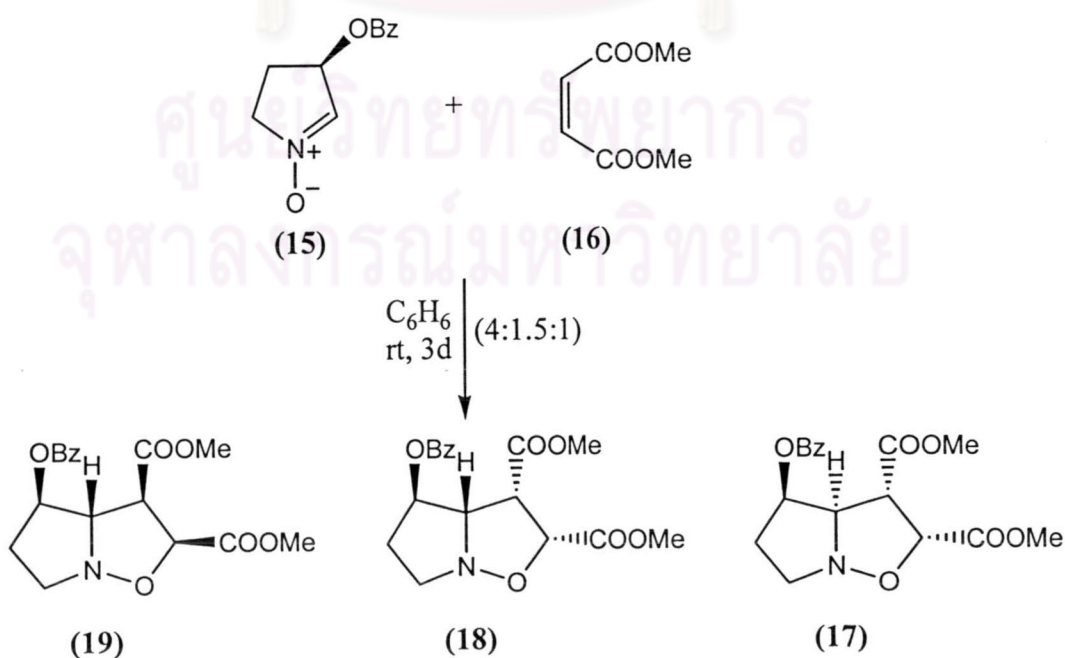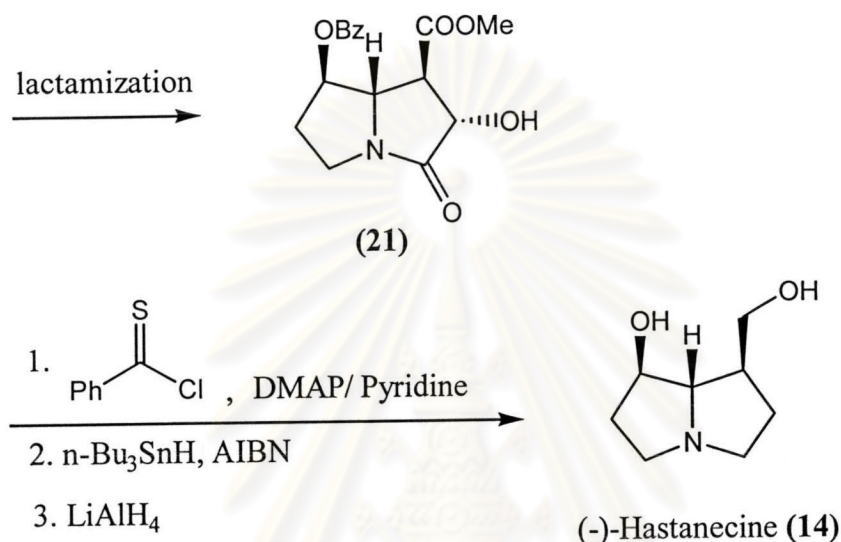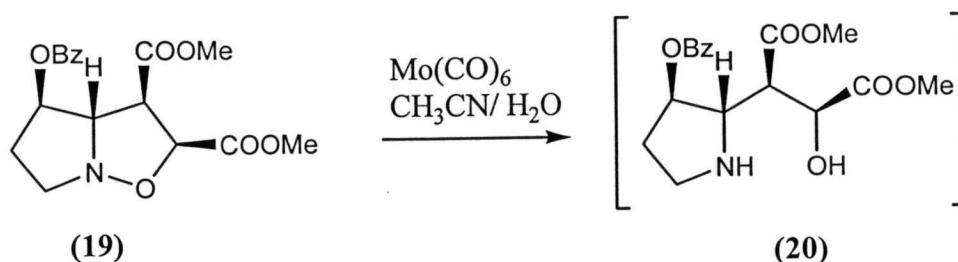

Figure 4   (-)-Hastanecine **(14)**

Goti's group has synthesized (-)-hastanecine **(14)** *via* cycloaddition of a nitrone, which was conveniently synthesized from L-malic acid[17]. The cycloaddition of the nitrone **(15)** to dimethyl maleate **(16)** gave three diastereoisomers **(19)**, **(18)** and **(17)** in 4:1.5:1 ratio. Both **(19)** and **(18)** resulted

from addition of the dipolarophile to the less hindered face of the nitrone. The major product (19) was derived from an *exo*-transition state and has the correct *trans-trans* relative stereochemistry required for the synthesis of (-)-hastanecine. The diastereomeric mixture was separated by chromatography, affording pure (19). Cycloadduct (19) was easily converted to lactam (21) by isoxazolidine ring opening with Mo(CO)$_6$. Reductive cleavage of the isoxazolidine ring with molybdenum hexacarbonyl gave intermediate 1,3-aminoalcohol (20) which underwent lactamization to give lactam (21). The lactam (21) contained all stereocenters and functionality needed for (-)-hastanecine, but it was over-functionalized for (-)-hastanecine synthesis. As the result, completion of the synthesis was by radical deoxygenation and reduction of the amide and the ester.

Goti used the same strategy as Denmark *et al.*[18] for converting the same intermediate lactam (21) to (-)-hastanecine. Activation of the alcohol with phenyloxy chlorothionocarbonate, followed by reduction with AIBN and tributyltin hydride afforded the deoxygenated product. The final stages of the synthesis involved reduction of the lactam to a pyrrolizidine, reduction of the ester to a primary alcohol, and removal of the benzoate protecting group. These three transformations could all be completed with LiAlH$_4$ in one step to give (-)-hastanecine (14) (Scheme 4).

(19)   Mo(CO)$_6$ / CH$_3$CN/ H$_2$O   **(20)**

lactamization

(21)

1. [Ph-C(=S)-Cl], DMAP/ Pyridine

2. n-Bu$_3$SnH, AIBN

3. LiAlH$_4$

(-)-Hastanecine **(14)**

Scheme 4   Synthesis of (-)-Hastanecine **(14)**

3. 1-Hydroxylated Pyrrolizidines

Curassanecine **(22)** is a saturated amino alcohol pyrrolizidine alkaloid, isolated from *Heliotropium curassavicum*. This molecule is the first alkaloid in the series with a quaternary carbon atom at C-1 that bears a tertiary alcohol functional group **(Figure 5)**.
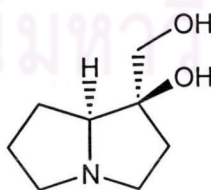
Figure 5   Curassanecine **(22)**

A short total synthesis of (+/-)-curassanecine[19] was achieved by the condensation of methyl oxalate with the enolate of N-acetylpyrrolidine **(23)** to give α-ketoester **(24)**. Photolysis yielded the diastereoisomeric hydroxy esters in a

1:1 ratio. After separation of the two diastereoisomers, the synthesis was completed by reduction of the ester and the amide groups in one step (**Scheme 5**).
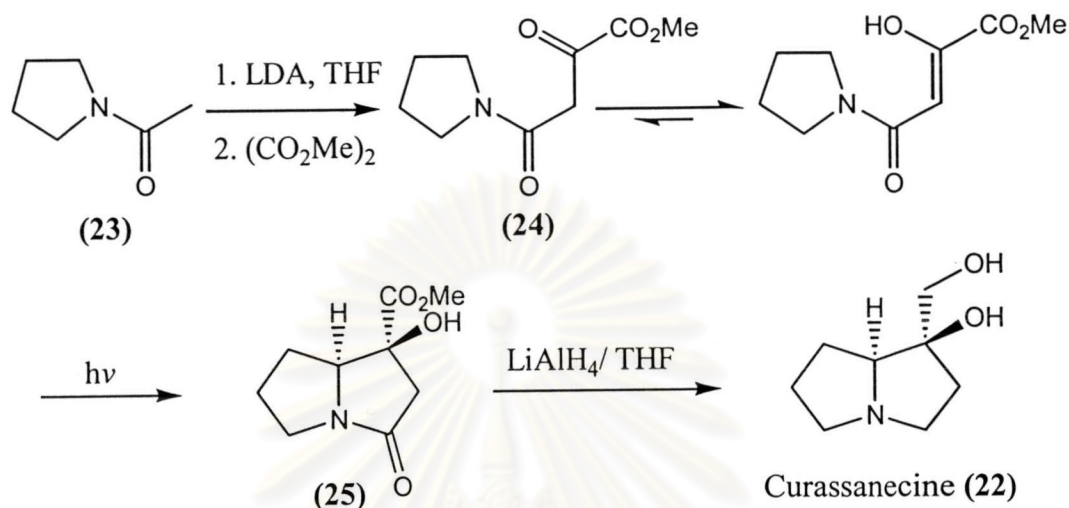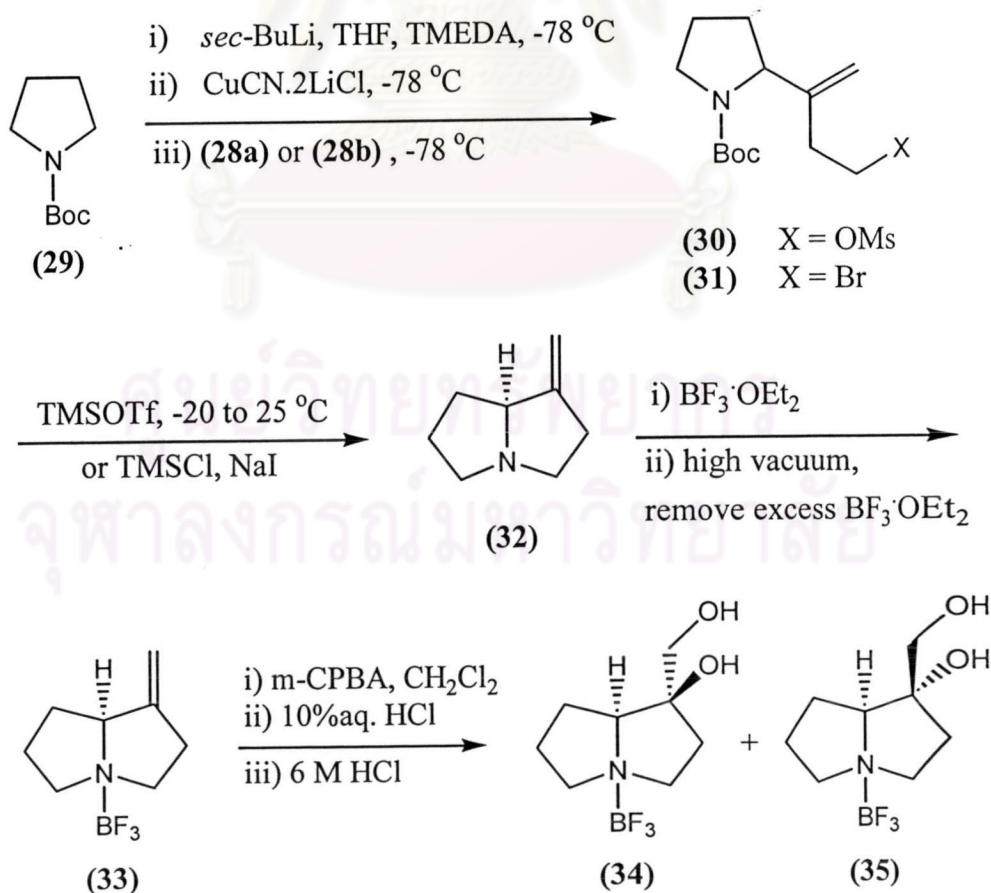

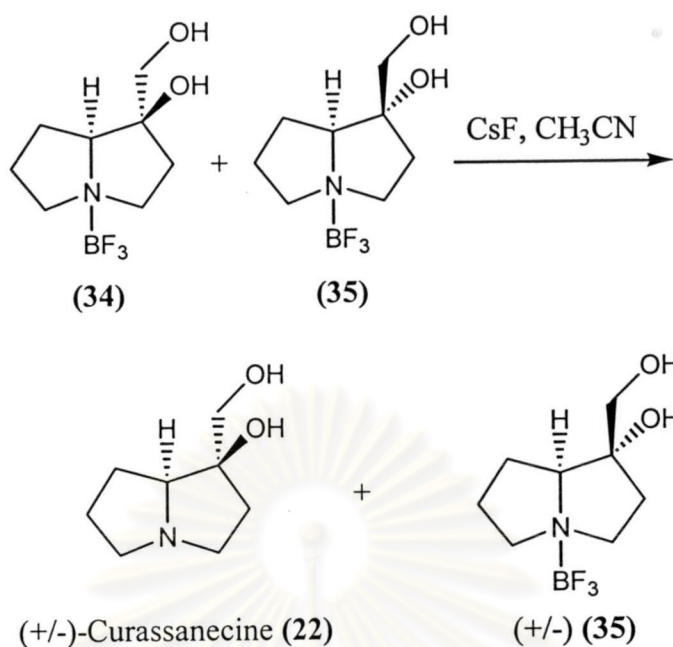**Scheme 5** Synthesis of (+/-) Curassanecine

Dieter and Watson[20] synthesized (+/-) curassanecine to examine the utility of α-(*N*-carbamoyl)alkylcuprate chemistry in alkaloid synthesis and to explore issues of stereocontrol resulting from this strategy. Hydroxy vinyl iodide (**27**), was readily prepared by addition of *in situ* generated HI to alkynyl alcohol (**26**), and converted to either the mesylate (**28a**) or bromide (**28b**) (**Scheme 6**).
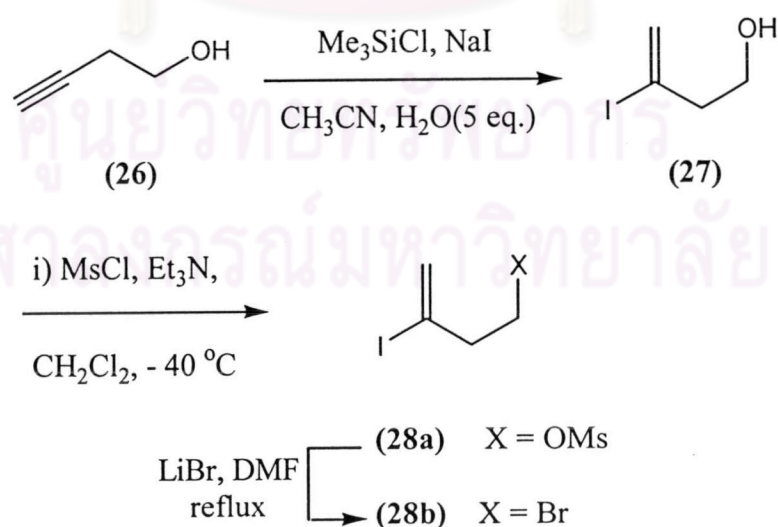
Scheme 6 Synthesis of vinyl iodide

The pyrrolidinyl cuprate from (29) afforded excellent yields of vinylation products on reaction with (28a) or (28b). Utilization of alkylcyanocuprate reagent (i.e. RCuCNLi) efficiently conserves the α-(*N*-carbamoyl)alkyl ligand. N-Boc deprotection and cyclization of (28a) or (28b) yielded the pyrrolizidine (32). Effort the epoxidize (32) with either m-chloroperbenzoic acid, oxone or peroxytrifluoroacetic acid were unsuccessful as were attempts to effect dihydroxylation. Treatment of (32) with $BF_3 \cdot OEt_2$ quantitatively afforded (33) which upon reaction with m-chloroperbenzoic acid gave a complex mixture after treatment with 10% aq. HCl. Coordination to boron acts to protect the tertiary nitrogen. This last result is surprising given the success of Hanselmann and Benn (vide infra, **Scheme 8**). A mixture of diastereoisomeric epoxides and diols are converted to the BF_3-complexes of (+/-)-Curassanecine (34) and its diastereomer (35) upon treatment with 6 M HCl. Treatment of the diastereoisomeric mixture with CsF in acetonitrile gave (+/-)-curassanecine (22) and recovered (+/-) (35) (Scheme 7).

Scheme 7 Synthesis of (+/-) curassanecine

Hadinecine (36) is in the same class as curassanecine, having a tertiary alcohol group (Figure 6).
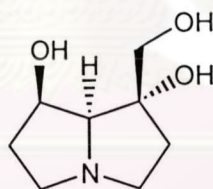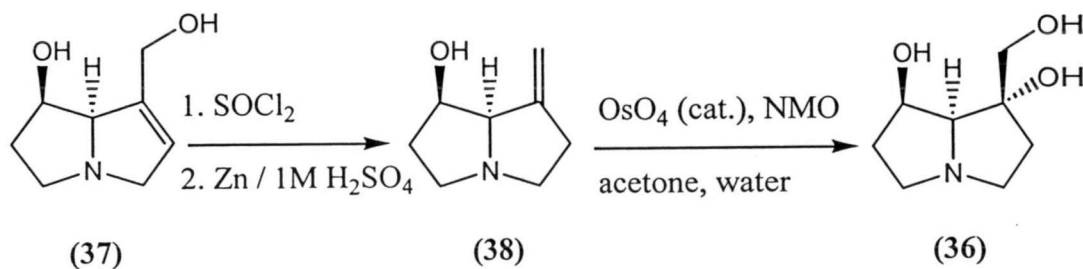

Figure 6 Hadinecine (36)

Benn and Hanselman[21] employed dihydroxylation to introduce the 1,2-diol moiety. Notably, dihydroxylation of (38), prepared from the natural product (+)- retronecine (37), is stereoselective due to the shape of the pyrrolizidine nucleus (Scheme 8).

Scheme 8 Synthesis of Hadinecine from Retronecine

4. 6-Hydroxylated Pyrrolizidines

The amphorogynines A-D[22] **(Figure 7)** are unique amongst pyrrolizidine alkaloids, in having an additional hydroxyl only at C-6. They have been isolated from the leaves of *Amphorogyne spicata* Stauffer & Hürlimann (Santalaceae). To our knowledge there have been no further reports of these alkaloids.
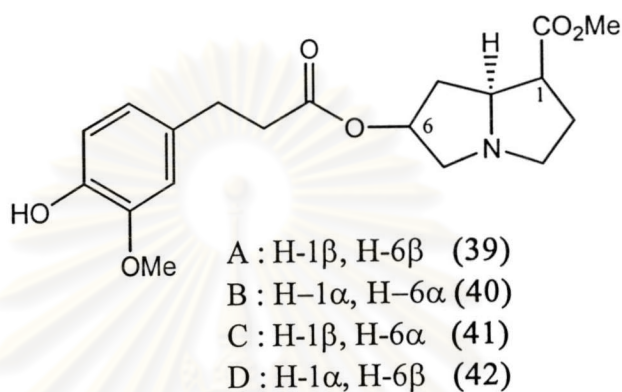

A : H-1β, H-6β   (39)
B : H–1α, H–6α (40)
C : H-1β, H-6α   (41)
D : H-1α, H-6β   (42)

Figure 7   Amphorogynines A-D

They are of interest in terms of their biological properties because, if the right hand ring is oxidized to a pyrrole *in vivo*, the remaing carboxy substitutent is in the β-position and, therefore, not easily ionized. It may be predicted that the amphorogynines would be distinctly less hepatotoxic than most pyrrolizidines.

5. Polyhydroxylated Pyrrolizidines

(+)-Casuarine **(43)**, a pentahydroxyl pyrrolizidine alkaloid, was isolated from the bark of *Casuarina equisetfolia* L. (Casurinaceae). Polyhydroxylated pyrrolizidines and indolizidine alkaloids are potential anti-cancer and anti-viral agents. Casuarine **(43)** is an effective inhibitor of glycosidase I (72% inhibition at 5 µg/ml) compared with castanosperinine **(44)** (84% inhibition at 5 µg/ml) **(Figure 8)**.
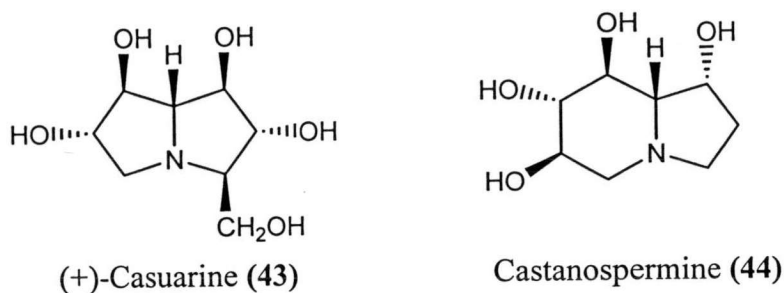
Figure 8   (+)-Casuarine and Castanospermine

Denmark's group has used the tandem [4+2]/[3+2] nitroalkene cycloaddition for the efficient synthesis of several pyrrolizidine and indolizidine alkaloids[23].

(+)-Casuarine was synthesized from the oxygenated dipolarophile (45) and benzoyloxy vinyl ether (Z)-(46) which carried a diphenylcyclopentyl chiral auxiliary.[24] Tin (IV) chloride was determined to be the optimum Lewis acid catalyst. The nitronate (47) was produced as a mixture of diastereoisomers and both diastereoisomers possessed the desired C-4/C-5 *trans* relationship. Nitronate (47) was immediately treated with the β-silyl enone (48) to afford nitroso acetals (49) (Scheme 9).
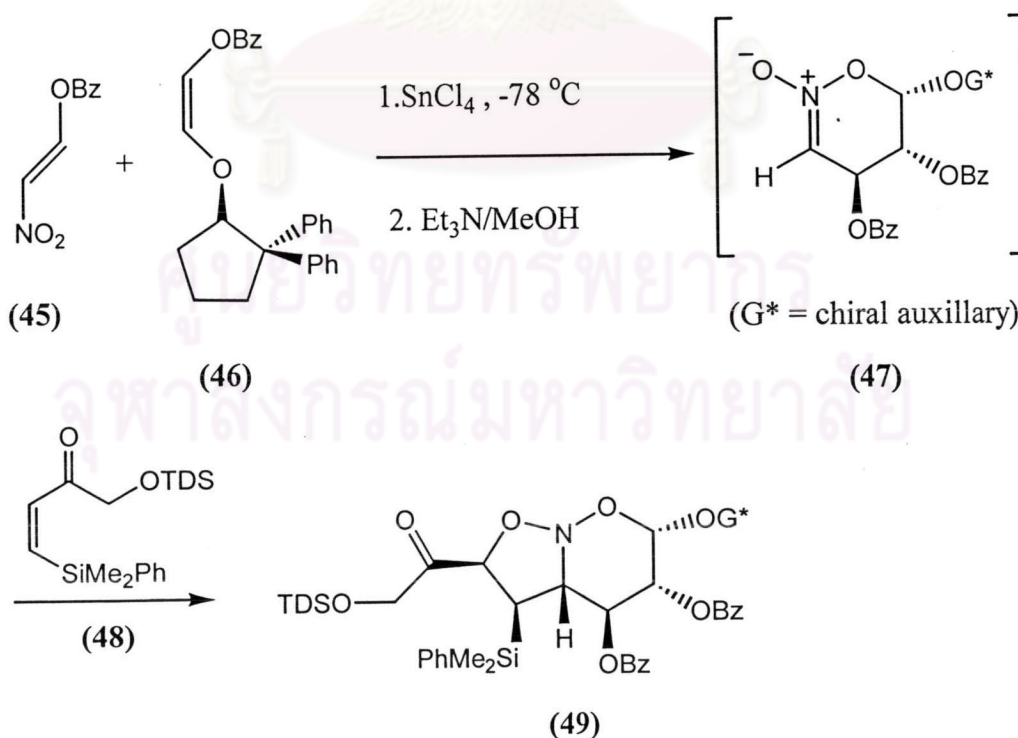
Scheme 9   Synthesis of (+)-Casuarine

The process established all but one of the stereocenters of casuarine. The *trans* relative stereochemistry between the two benzoates is due to a favoured *exo* transition state in the Diels-Alder reaction. This reaction also established the absolute stereochemistry which was under the central of the chiral auxilary, G*. Modelling studies indicated that one of the phenyl groups blocks one of the faces of the enol ether in the *s-trans* conformation **(Figure 9)**.
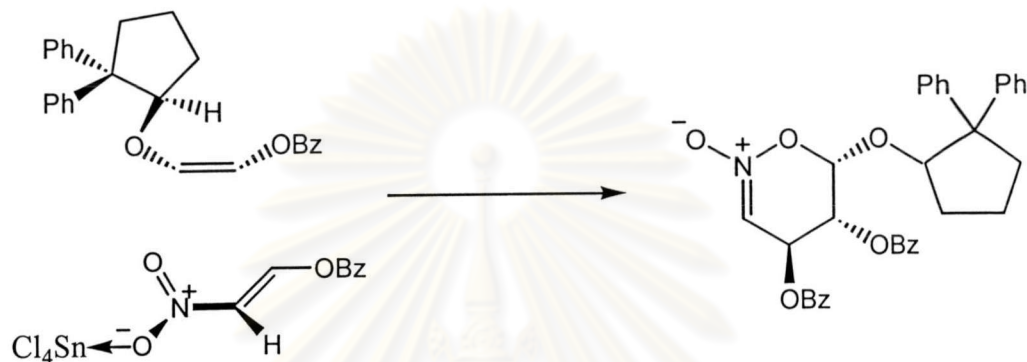

**Figure 9**   Diels-Alder reaction of a vinyl nitro compound

The second cycloaddition, the 1,3-dipolar cycloaddition, established three stereocentres. The most important effect here was considered to be shielding of one face of the nitronate by the adjacent benzoate substituent, requiring the alkene to approach from the opposite face **(Figure 10)**.

Figure 10   1,3-Dipolar cycloaddition of the nitronate

The synthesis was completed by stereoselective reduction of the ketone and conversion of the resulting alcohol into a mesylate. Hydrogenation at pressures of 160 psi or more yielded the pyrrolizidine **(51)**. The exact sequence of events in the hydrogenation is unclear but it involves cleavage of the two N-O bonds, expulsion of the chiral auxiliary to liberate an aldehyde, reductive-

alkylation of the new amine by the new aldehyde and intramolecular nucleophilic displacement of the mesylate by the amine. An alkaline workup also cleaved the two benzoate groups. Finally, the remaining protecting group was removed and the carbon-silicon bond was oxidized under carefully controlled conditions in a single step to yield casuarine (43) (Scheme 10).
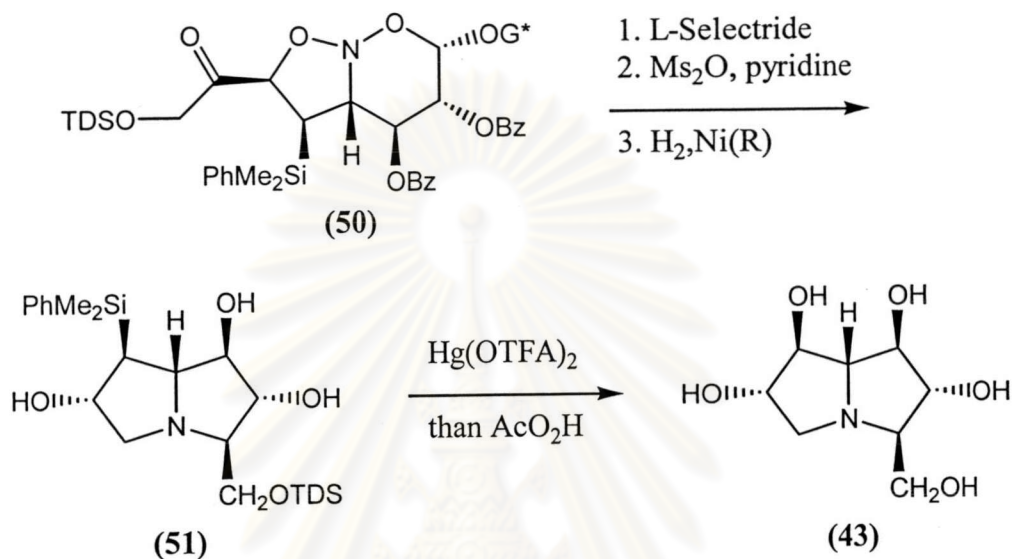
Scheme 10 Completion of the Synthesis of (+)-Casuarine

In conclusion, The pyrrolizidine have continued to attracted the attention of synthetic organic chemists because of the challenge of preparing such molecules in stereochemically defined form strategies continue to be developed in order to tackle the most complex examples which are the ones with the most potent biological activity. In addition, the isolation of new pyrrolizidine natural products, such as the amphorogynine, presents new targets. Therefore, the objective of this study is to examine new methodology for the synthesis of amphorogynine, using organometallic method.