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STEREOCHEMICALLY CONTROLLED SYNTHESIS OF INDOLIZIDINES

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Hydride reduction by stereoselective delivery to a bicyclic iminium ion under stereoelectronic control can be used effectively as the key step in a total synthesis of tashiromine, an indolizidine alkaloid.

The use of this synthetic strategy was attempted for the synthesis of a more complex indolizidine, swainsonine.

Department……..Student's signature…….……..
Field of study……..Advisor's signature…….……..
Academic year ……...Co-Advisor's signature……...……...

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List of Abbreviations

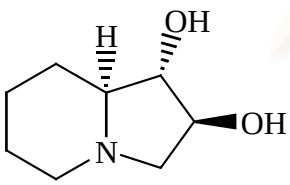
AIBN	2,2-Azobisisobutyronitrile	Ms	Methanesulfonyl
AA	Asymmetric	MS	Mass Spectrometry
Aminohydroxylation		Mw	Molecular weight
d	Doublet (NMR)	*m/z*	Mass per charge
DBU	1,8-Diazabicyclo[5.4.0]undec	NMO	*N*-methylmorpholine *N*-oxide
	-7-ene	NMR	Nuclear Magnetic Resonance
DMAP	4-Dimethylaminopyridine	ppm	Parts per million
DME	Dimethoxyethane	PPTS	Pyridinium *p*-toluenesulfonate
DMF	*N*,*N*-Dimethylformamide	s	Singlet
dd	Doublet of doublet	t	Triplet
dt	Doublet of triplet	TBAF	tetra-*n*-Butylammonium fluoride
EI	Electrochemocal ionization	TBS	*tert*-Butyldimethylsilyl
HRMS	High Resolution Mass	TFA	Trifluoroacetic acid
	Spectrometry	THF	Tetrahydrofuran
IR	Infrared	THP	Tetrahydropyranyl
J	Coupling constant	TMS	Trimethylsilyl
LDA	Lithium diisopropylamide	Wt	Weight
m	Multiplet	δ	Chemical shift
m.p.	Melting Point	ν	Wavenumber

CHAPTER I

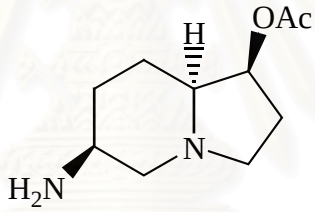
INTRODUCTION

The indolizidines make up one category of alkaloids.[1] They are bicyclic compounds with one nitrogen atom. These alkaloids are widely found in various natural sources, including frogs.[2] However, because of their low natural abundance, the relative and absolute stereochemistry of many of these alkaloids are still unknown.

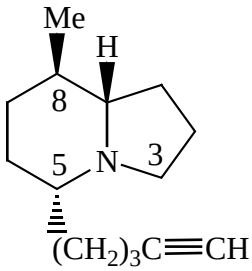
Two well-known indolizidines are slaframine and gephyrotoxin. Some polyhydroxylated indolizidines of current interest are lentiginosine, castanospermine and swainsonine.



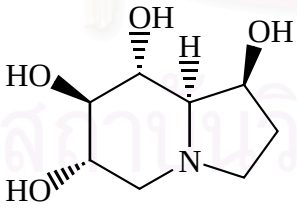
lentiginosine (**1**)



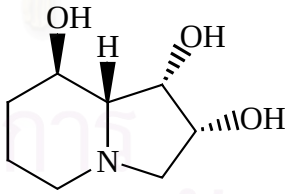
slaframine (**2**)



gephyrotoxin 205A (**3**)



castanospermine (**4**)



swainsonine (**5**)

Figure 1 Some Representative Indolizidines

Slaframine is a neurotoxic fungus metabolite that has potential use in the treatment of diseases involving cholinergic dysfunction. In the Gephyrotoxin family[3], the simple indolizidines contain a single substituent at C5 of the indolizidine skeleton

and the more complex members have substituents at either C3 and C5 or C5 and C8. These indolizidines inhibit muscular transmission. Castanospermine and swainsonine have already demonstrated specific inhibition of glycosidase, and hence, there are potential clinical anti-cancer and anti-HIV applications. Lentiginosine is a potent inhibitor of amyloglucosidase, an enzyme that is widely use for the conversion of starch into glucose. [4]

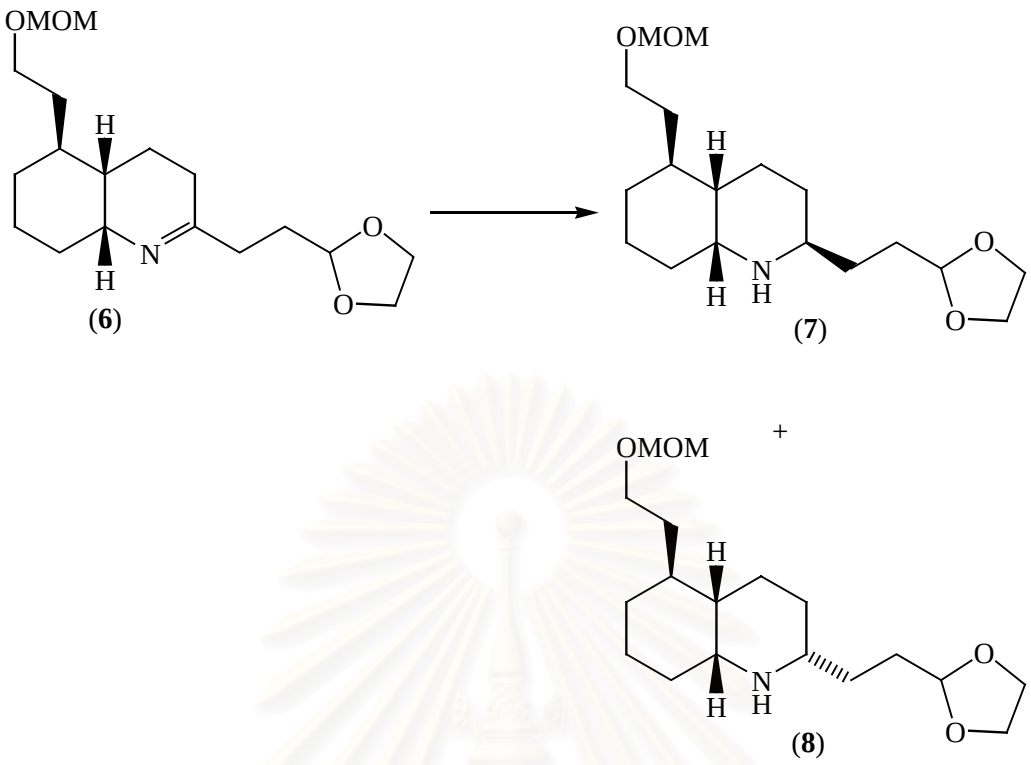
The structural diversity and the high potential of these alkaloids in a broad range of biological activities has resulted in a great deal of interest in the synthesis of these compounds.

There are the number of reported syntheses of indolizidine alkaloids but most of these utilize natural chiral starting materials. Therefore, it is useful to develop synthetic methods using non-natural starting materials to permit cost-effective and flexible methods.

Stereoelectronic control in alkaloid synthesis

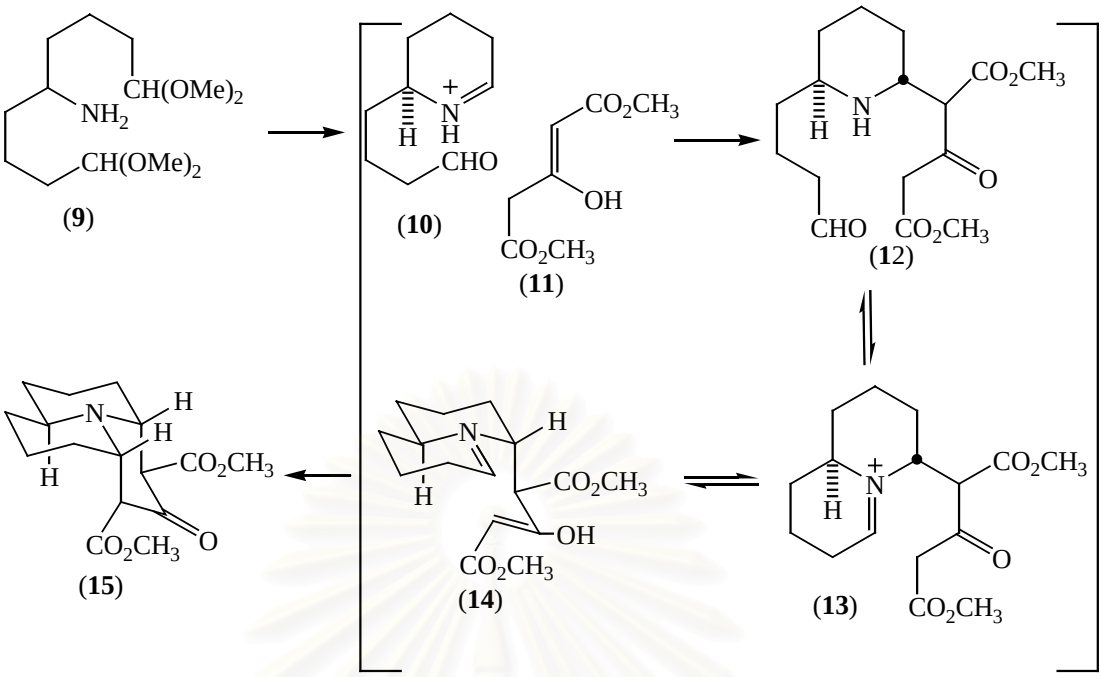
Several studies regarding stereoelectronic control of nucleophilic addition to cyclic iminium ions and its application to alkaloid synthesis have been reported.It is known that the stereoelectronic effect can be used to direct nucleophilic addition to the congested face of the imine. It can override steric effects and can, therefore, be of enormous synthetic utility.

For instance, reduction of the imine (**6**) using excess $LiAlH_4$ at -19^oC yielded the cis-decahydroquinoline (**7**) and (**8**) in a ratio of about 12:1 (**Scheme 1**).[5] The stereoelectronic preference is also on the more hindered face.



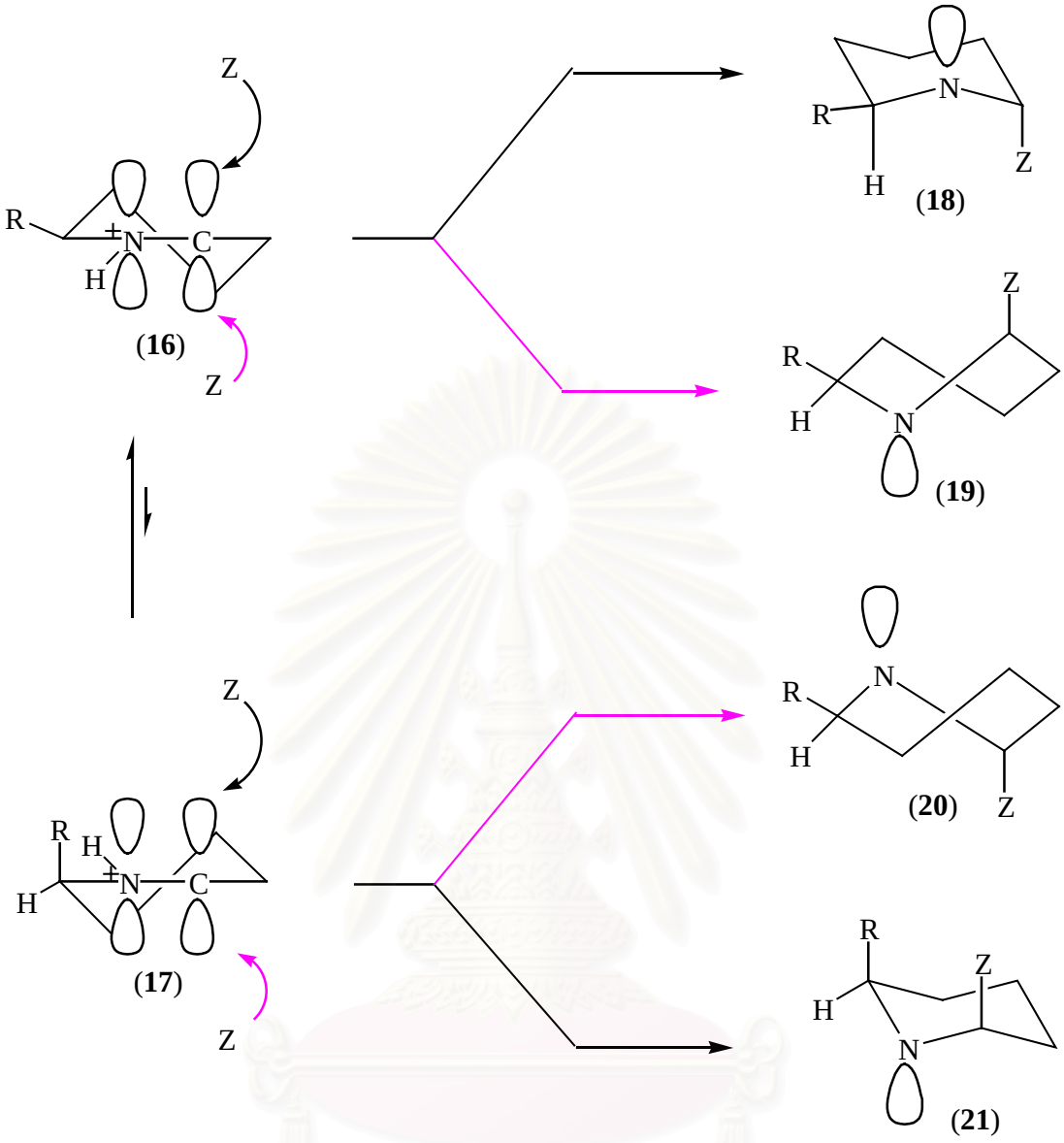
Scheme 1 Stereoelectronically Controlled Reduction of An Imine

In Steven's and Lee's classic synthesis of the ladybug defensive alkaloids (**Scheme 2**),[6] coccineline and precoccineline, intermediate (**10**) under acidic conditions reacted with acetone dicarboxylic ester (**11**). A single isomer (**15**) was obtained in good yield. The favorable arrangement of nucleophilic and electrophilic centers was established in the step of converting (**10**) to (**12**).



Scheme 2 Synthesis of The Ladybug Defensive Alkaloids

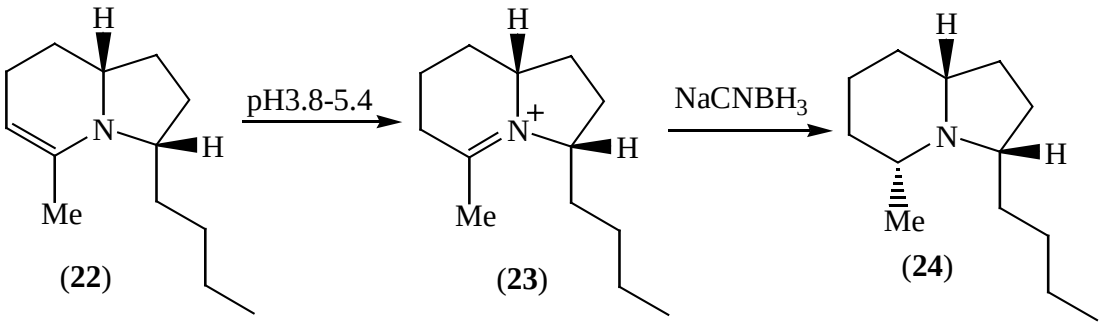
The reason is outlined in Scheme 3.[7] There are four possible transition states. Two of these require boat like conformations which are kinetically disfavored. The other two possibilities are chair like transition states which are thermodynamically favored, but (**21**) is less favored because of the 1,3-diaxial interaction between the R-group and the incoming nucleophile (**Z**). Hence, of the four possibilities which maintain maximum orbital overlap between the incoming nucleophile and the developing lone pair on nitrogen (**18**), has the lowest energy and leads to the observed product. This corresponds to the trans-diaxial arrangement of the incoming nucleophile and the developing N-lone pair.



Scheme 3 Stereoelectronic Preference of Axial Nucleophilic Addition

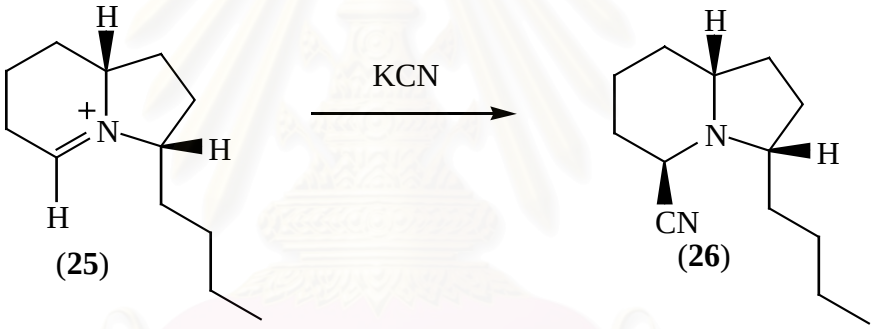
Many studies by Stevens have confirmed this stereoelectronic preference of axial nucleophilic addition to tetrahydropyridinium salts.

In an elegant total synthesis of (-)-Monomorine I,[8] direct reduction of endocyclic enamine (**22**) with sodium cyanoborohydride at pH 3.8-5.4 gave a single stereoisomer (**Scheme 4**).



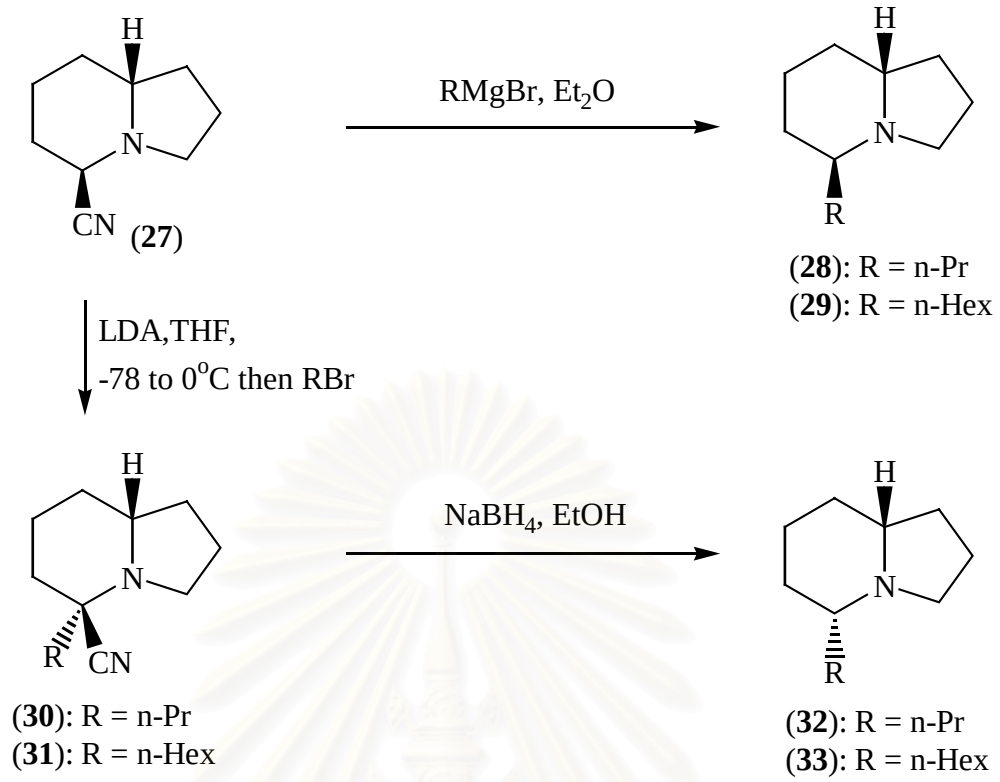
Scheme 4 Reduction of an Enamine in the Synthesis of (-)-Monomorine I

In addition, only one diastereomer was found in an attempt to make a cyanoamine *via* a tetrahydropyridinium salt (**25**),[9] showing that the effect is not limited to hydride nucleophiles (**Scheme 5**).



Scheme 5 Synthesis of a Cyanoamine *via* a Tetrahydropyridinium Salt

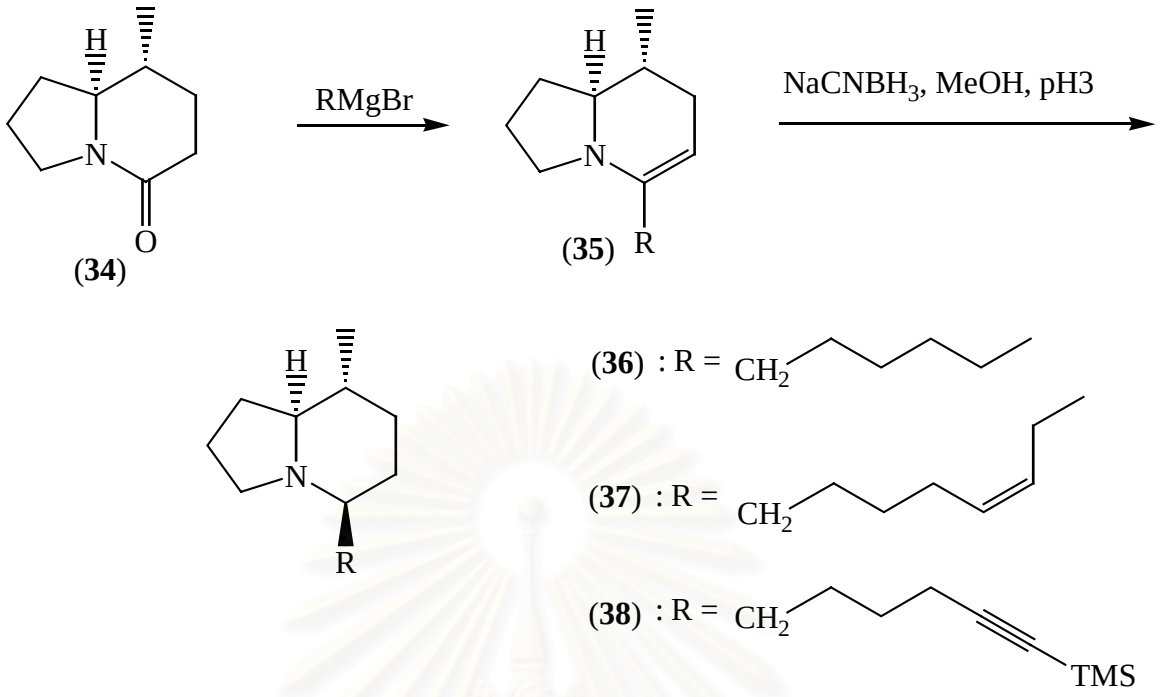
This synthetic strategy was later used to synthesize many of the gephyrotoxin alkaloids (**Scheme 6**).[10] For example, reduction of amino nitriles (**30**) and (**31**) with sodium borohydride in ethanol produced amines (**32**) and (**33**). Alternatively, reaction of cyano amine (**27**) with either propylmagnesium bromide or hexyl magnesium bromide afforded amines (**28**) and (**29**). All of these reactions proceed *via* axial attack on an iminium ion intermediate (**Scheme 6**).



Scheme 6 Stereoelectronic Control in Syntheses of Gephyrotoxin

The selectivity associated with both the hydride reduction of amino nitrile (**30**), (**31**) and Grignard addition to amino nitrile (**27**) is a result of stereoelectronic control as described above.

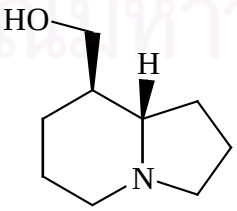
Related work was described by Shimizu and Satake.[11] They used the indolizidinone (**34**) as a synthetic intermediate in reactions with Grignard reagents, followed by reduction with $NaCNBH_3$ under acidic conditions (**Scheme 7**). Again, the stereochemistry was controlled by the stereoelectronic effect.



Scheme 7 Stereoelectronically Controlled Additions to an Indolizidinone

Tashiromine

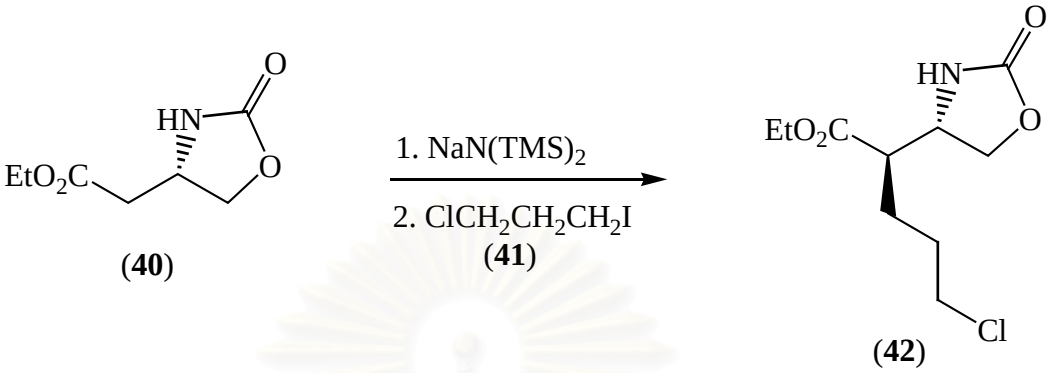
Tashiromine is an alkaloid of the indolizidine type (**Figure 2**). It was isolated from the stems of an Asian deciduous shrub, *Macckia tashiroi*.[12] The optical rotation remains uncertain due to the shortage of natural material and the absolute stereochemistry has yet to be determined. To our knowledge, there are only 6 reports on the total synthesis of tashiromine. Most of them started with chiral starting materials or used other strategies with complex systems.



(**39**)

Figure 2 Tashiromine

(+)-Tashiromine has been synthesized starting with the diastereoselective alkylation of (*S*)-4-carbethoxymethyl-2-oxazolidinone (**40**) with 1-chloro-3-iodopropane and $NaN(TMS)_2$ (**Scheme 8**).[13]



Scheme 8 Diastereoselective Alkylation

This highly diasteroselective alkylation appears to involve chelation of sodium between the enolate oxygen and the oxazolidinone nitrogen which directed the alkylation to the less hindered face to give the anti product (**42**) (**Figure 3**).[14]

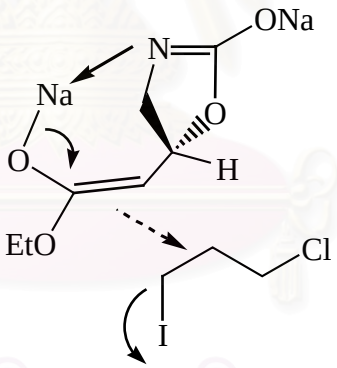
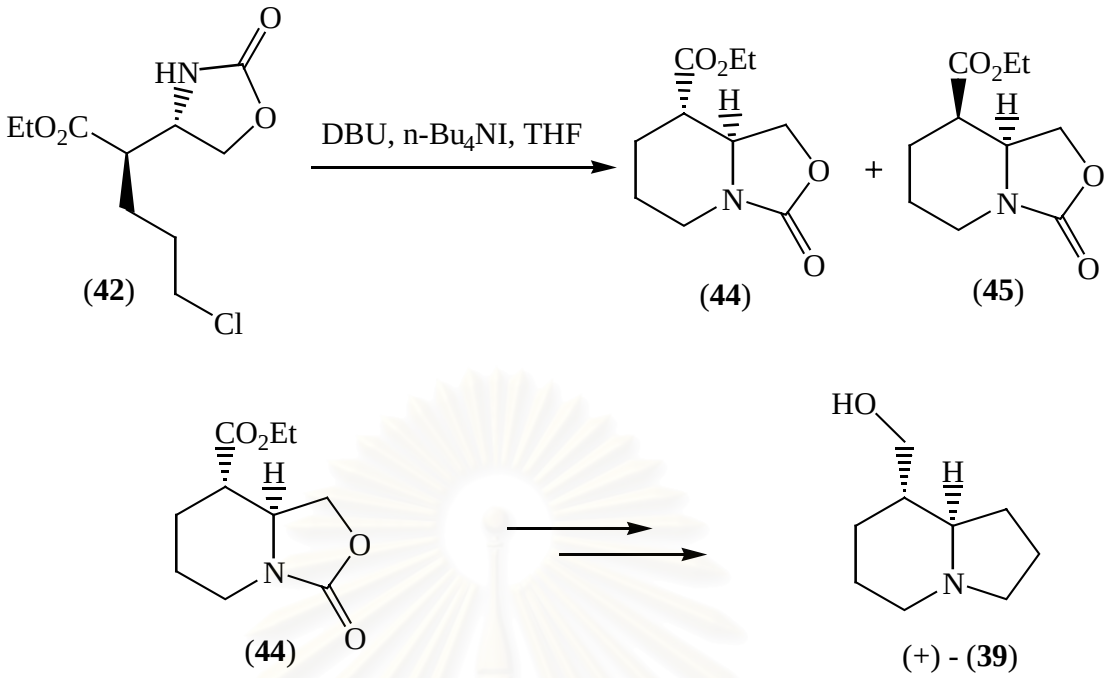


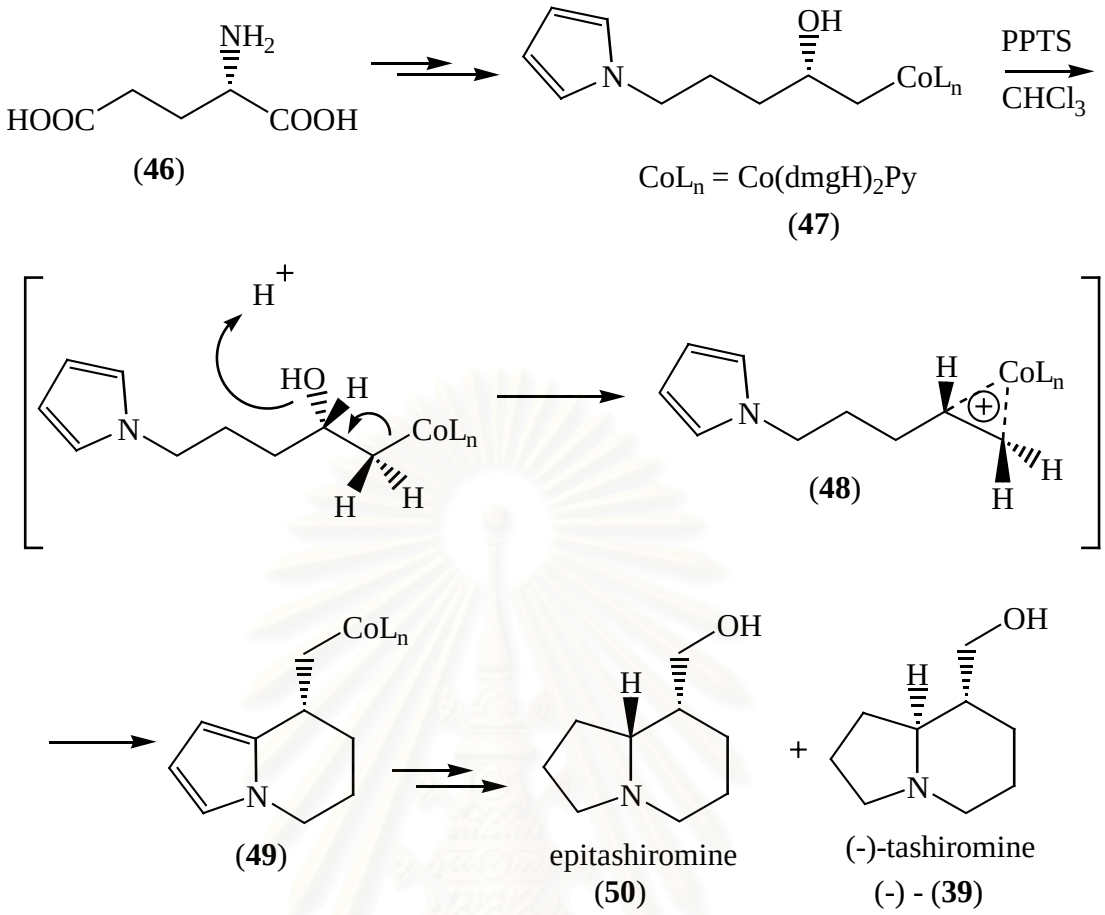
Figure 3 The Origin of the Diastereoselective Alkylation

Refluxing oxazolidinone (**42**) with DBU and a catalytic amount of n-Bu_4NI in THF gave the cyclic trans-carbamate (**44**) together with cis-product (**45**) in a ratio of 68:5 (**Scheme 9**). After separation of the mixture by column chromatography, the trans bicyclic carbamate (**44**) was converted to (+)-tashiromine.



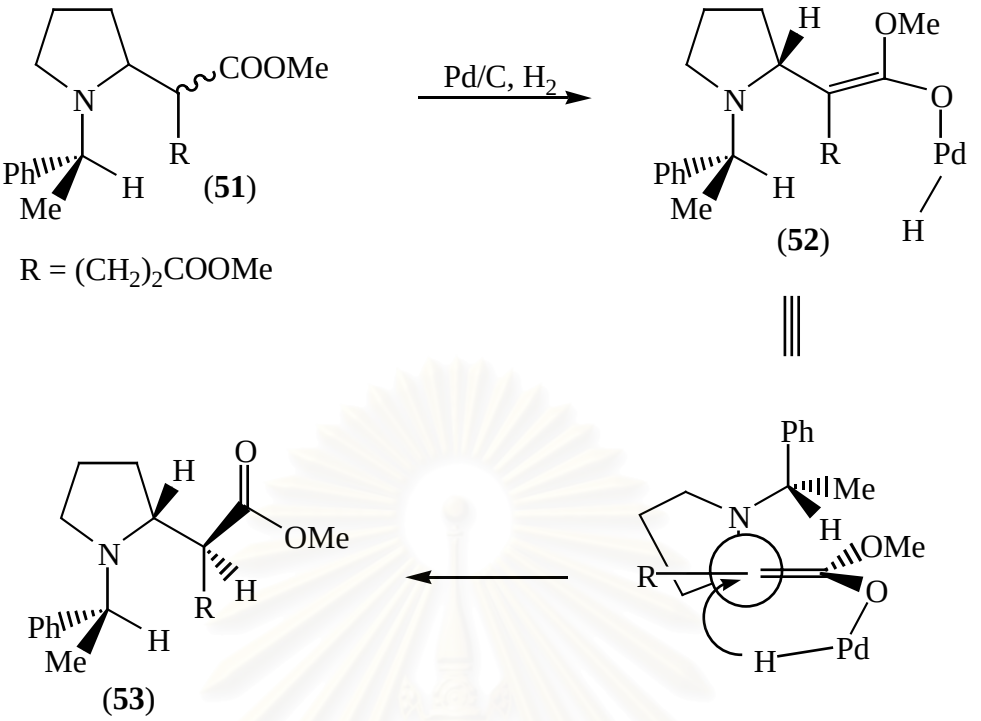
Scheme 9 The Synthesis of Tashiromine

Gage and Branchaud used L-glutamic acid (**46**) as the chiral starting material to prepare 5-*N*-pyrrolyl-2-hydroxypentyl cobaloxime (**47**) (**Scheme 10**). Intramolecular electrophilic attack onto the pyrrole ring promoted by a hyperconjugated cobaloxime π-cation proceeded *via* a relatively strain-free and low energy 6-exo cyclization. Oxygenative cleavage of the Co-C bond and reduction of the pyrrole ring gave a mixture of epi-tashiromine as the major product and (-)-tashiromine as the minor product in overall 13 steps.[15]



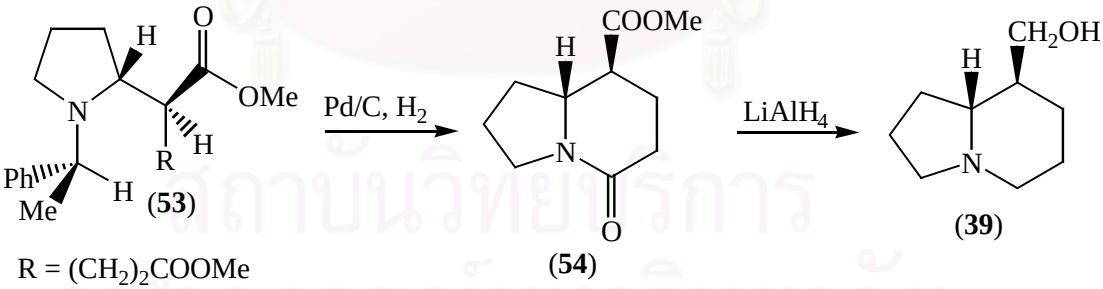
Scheme 10 A Synthesis of Tashiromine *via* a ¶-cation

Another asymmetric method used a chiral β-enamino diester to give the pyrrolidine which could be converted to tashiromine by routine chemistry (**Scheme 11**).[16] The β-enamino ester (**51**) was derived from a condensation reaction as a mixture of E/Z isomers in a ratio of 65:35. Without separation, this was hydrogenated to give only one main product. It was proposed that the first hydrogen adds from the less hindered face of the enamino ester double bond resulting in a palladium enolate. The more favored transition state structure forming is based on the conformation in which 1,3-allylic strain is minimized and the C-N bond becomes perpendicular to the π-system. Stereoselective hydrogen transfer leads to the trans-configuration of the two hydrogens.



Scheme 11 Stereoselective Hydrogen Transfer

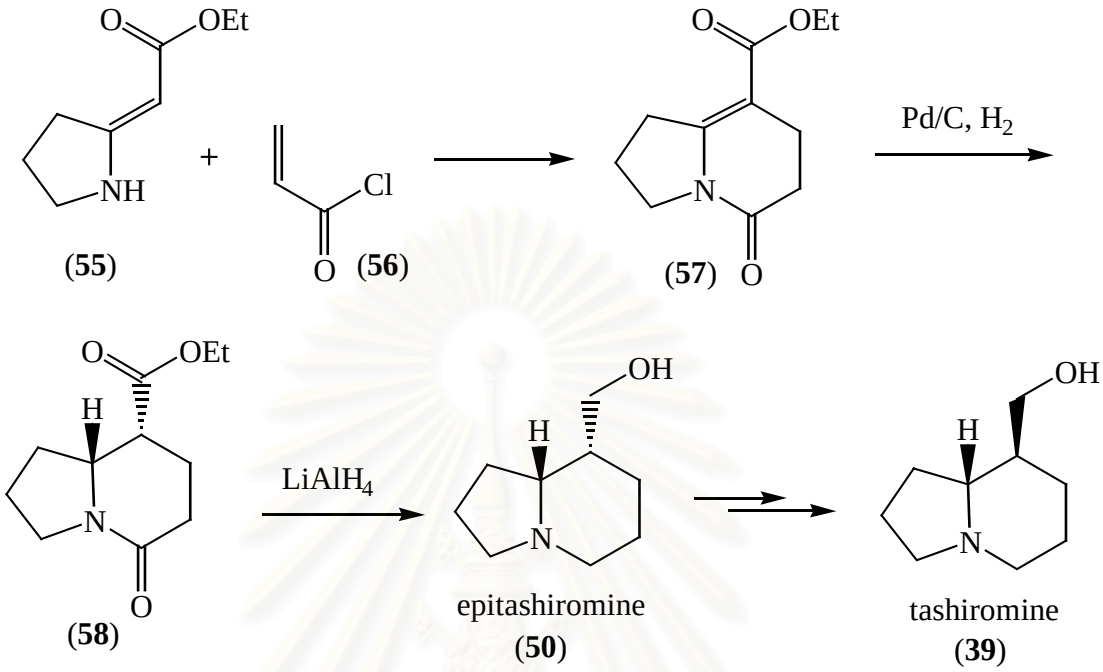
Hydrogenolysis of the benzylic amine (**53**) and the subsequent ring closing gave rise to the bicyclic lactam (**54**) (**Scheme 12**). This was reduced routinely to give tashiromine.



Scheme 12 Completion of a Tashiromine Synthesis

Stille, in his story of azaannulation,[17] showed that treatment of the enamine with acryloyl chloride (**56**) yielded the bicyclic enamine (**57**) (**Scheme 13**). This could be reduced in two steps to epitashiromine (**50**). The conversion of epitashiromine (**50**)

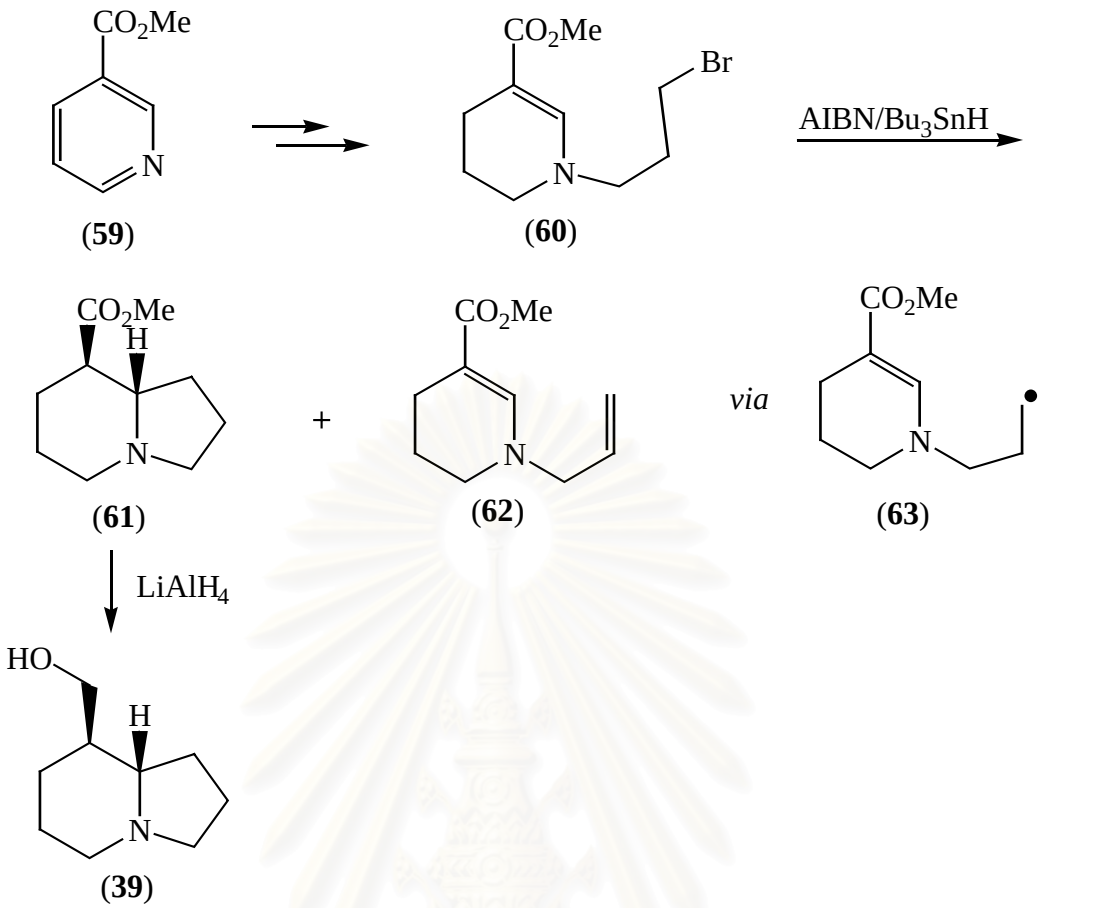
to tashiromine (**39**) can be achieved by base mediated equilibration of the corresponding aldehyde.



Scheme 13 The Synthesis of Tashiromine by the Azaannulation

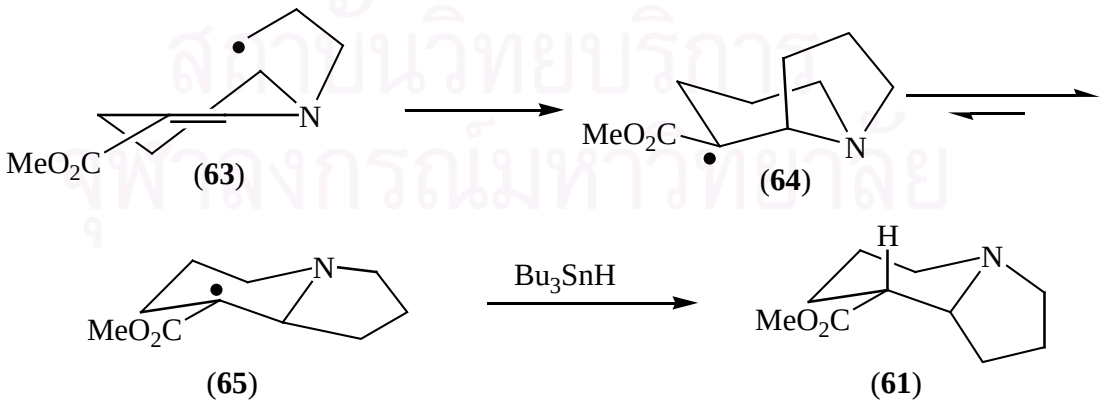
In a study of formation of indolizidine and quinolizidine ring systems by free radical cyclization, the synthesis of tashiromine was achieved, although at that time, tashiromine was not yet known as a natural product (**Scheme 14**). [18]

Treatment of the bromide (**60**) under typical free radical conditions gave the indolizidine (**61**) which could be reduced to tashiromine (**39**). The stereochemistry has been attributed to stereoelectrically controlled abstraction of a hydrogen from Bu_3SnH by the adduct radical.



Scheme 14 The Formation of Tashiromine by Free Radical Cyclization

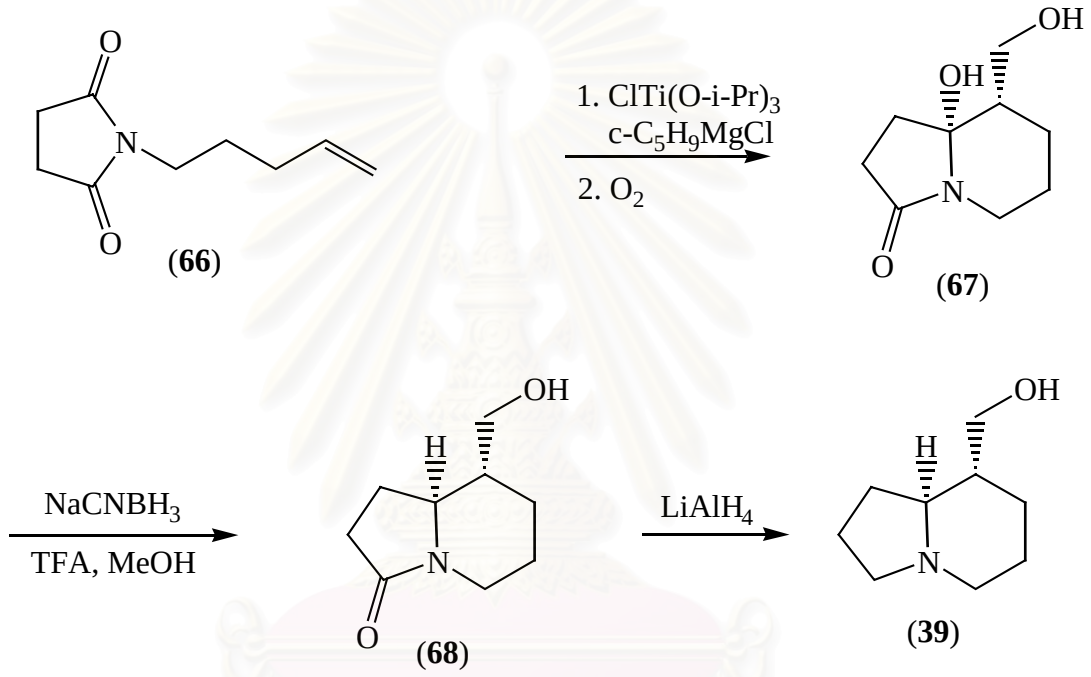
The initial radical addition is believed to give the axial adduct (**64**) which undergoes a rapid conformation change with inversion of nitrogen (**Scheme 15**). Axial abstraction of hydrogen then leads to the observed product (**61**).



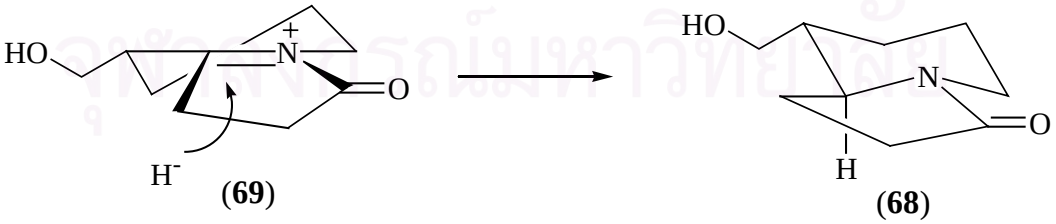
Scheme 15 Stereocontrol of the Free Radical Cyclization

Cha, et.al. used the titanium-mediated cyclization of an ω-vinyl imide for making an indolizidine-like bicyclic intermediate (**67**) (**Scheme 16**). Then, reduction with $NaCNBH_3$ and treatment of the lactam (**68**) with $LiAlH_4$ yielded tashiromine.[19]

Cyanoborohydride reduction in acidic methanol gave a high degree of trans-stereochemistry. This can be rationalized as the result of stereoelectronically controlled axial attack of hydride onto an intermediate acyliminium ion (**69**) (**Scheme 17**).

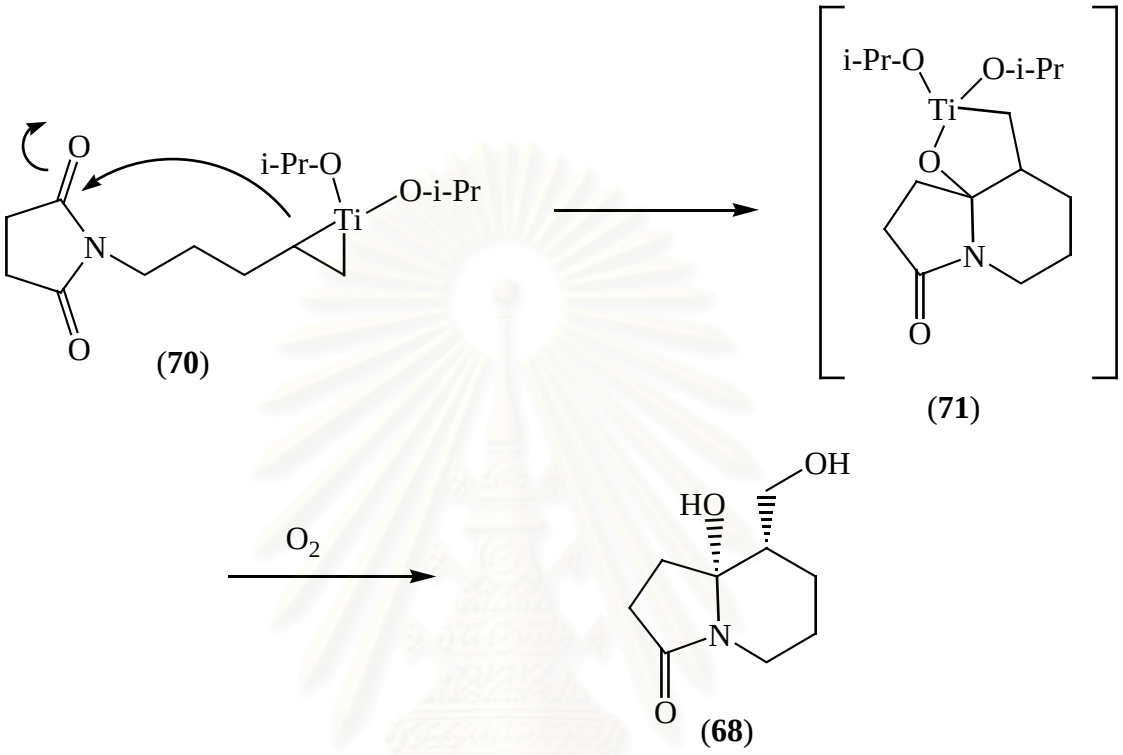


Scheme 16 The Synthesis of Tashiromine *via* the Kulinkovich Reaction



Scheme 17 Stereoelectronically Controlled Attack of Hydride on the Acyliminium Ion.

The key step is the Kulinkovich reaction involving ring closing of the unsaturated imide (**70**) (**Scheme 18**). The intermediate titanacyclopropane (**71**) is cyclized by attack on one imide carbonyl. Oxidation of the remaining C-Ti bond introduces the desired alcohol group.

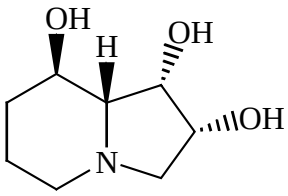


Scheme 18 The Kulinkovich Reaction of the Unsaturated Imide

Swainsonine

Swainsonine was first isolated in 1973 from the fungus *Rhizoctonia leguminicola*[20] and was later found in the plants *Swainsona canesces*[21] and *Astragalus letiginosus*[22] and also in the fungus *Metarhizium anisopiliae*.

It is one of the polyhydroxylated indolizidines. The structure of natural (-) - swainsonine, is shown in figure (**4**).[23]

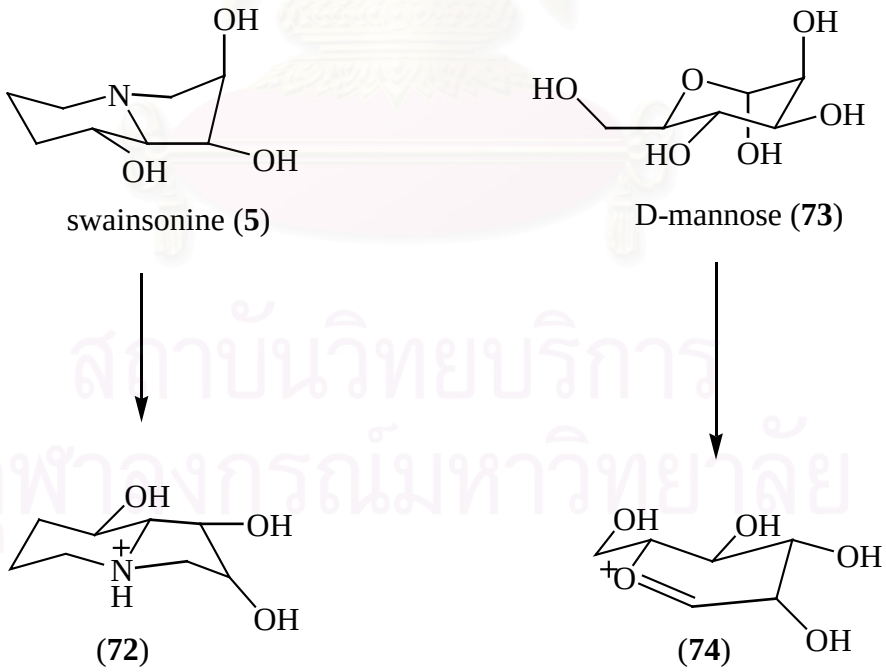


(**5**)

Figure 4 swainsonine

Swainsonine is an effective inhibitor of lysosomal α-mannosidase, which is involved in the cellular degradation of polysaccharides, and mannosidase II, which is an important enzyme in glycoprotein processing. In addition, Swainsonine is the first glycoprotein-processing inhibitor to be tested as an anticancer drug in clinical trials.[24]

Swainsonine is believed to be a substrate-site directed inhibitor of α-mannosidase because of the structural similarity between swainsonine (**5**) and α-D-mannose (**73**) (**Scheme 19**). Dorling and co-workers have speculated that the inhibitory action of swainsonine results from the similarity in spatial relationship between the protonated form of swainsonine (**72**) and the mannosyl cation (**74**) which is the proposed intermediate in hydrolysis of α–linked polysaccharides.[25]



Scheme 19 Comparison of Swainsonine and the Mannosyl Cation

Swainsonine has been of interest in both synthetic and medical studies for a long time; however, its high cost still hinders clinical trials. To date, there have been a

number of swainsonine syntheses. [26] All of these can be divided into two categories: one group employs chiral starting materials and the other group utilizes asymmetric synthesis with non-chiral starting materials.

1. Syntheses starting from chiral precursor

1.1 carbohydrate based approach

Because of its sugar-like structure, it is not surprised that most of the total syntheses of swainsonine used sugars or sugar derivatives as the chiral synthons (figure 5). Among these, hexoses such as D-mannose and D-glucose and pentoses such as D-lyxose and D-erythrose and also their derivatives have been popular and attractive starting materials.

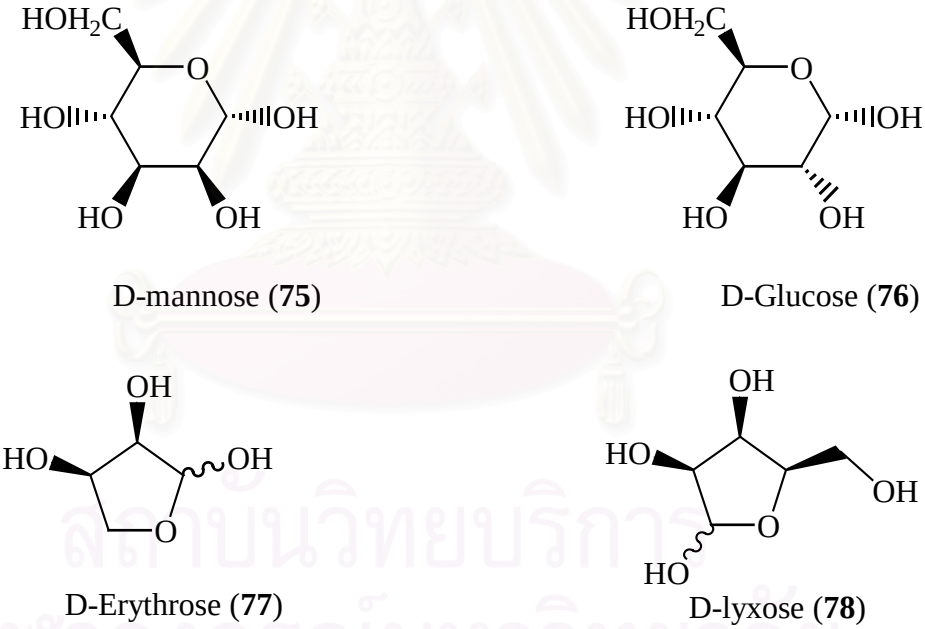
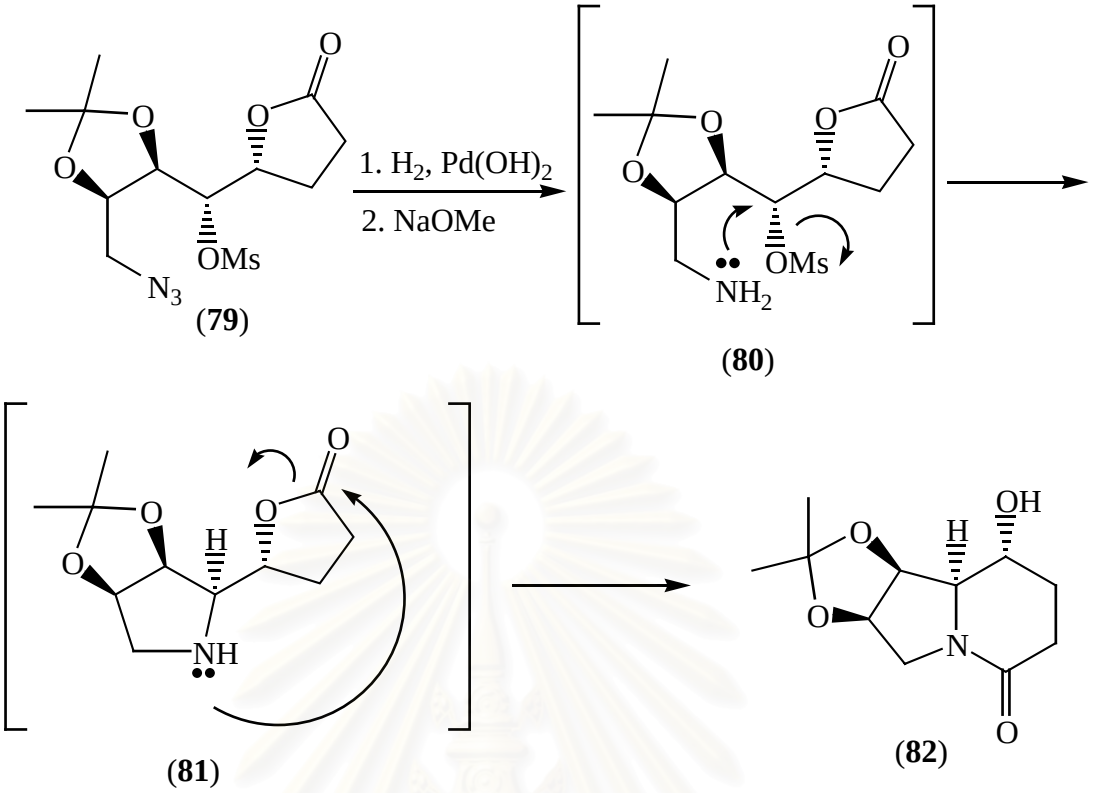


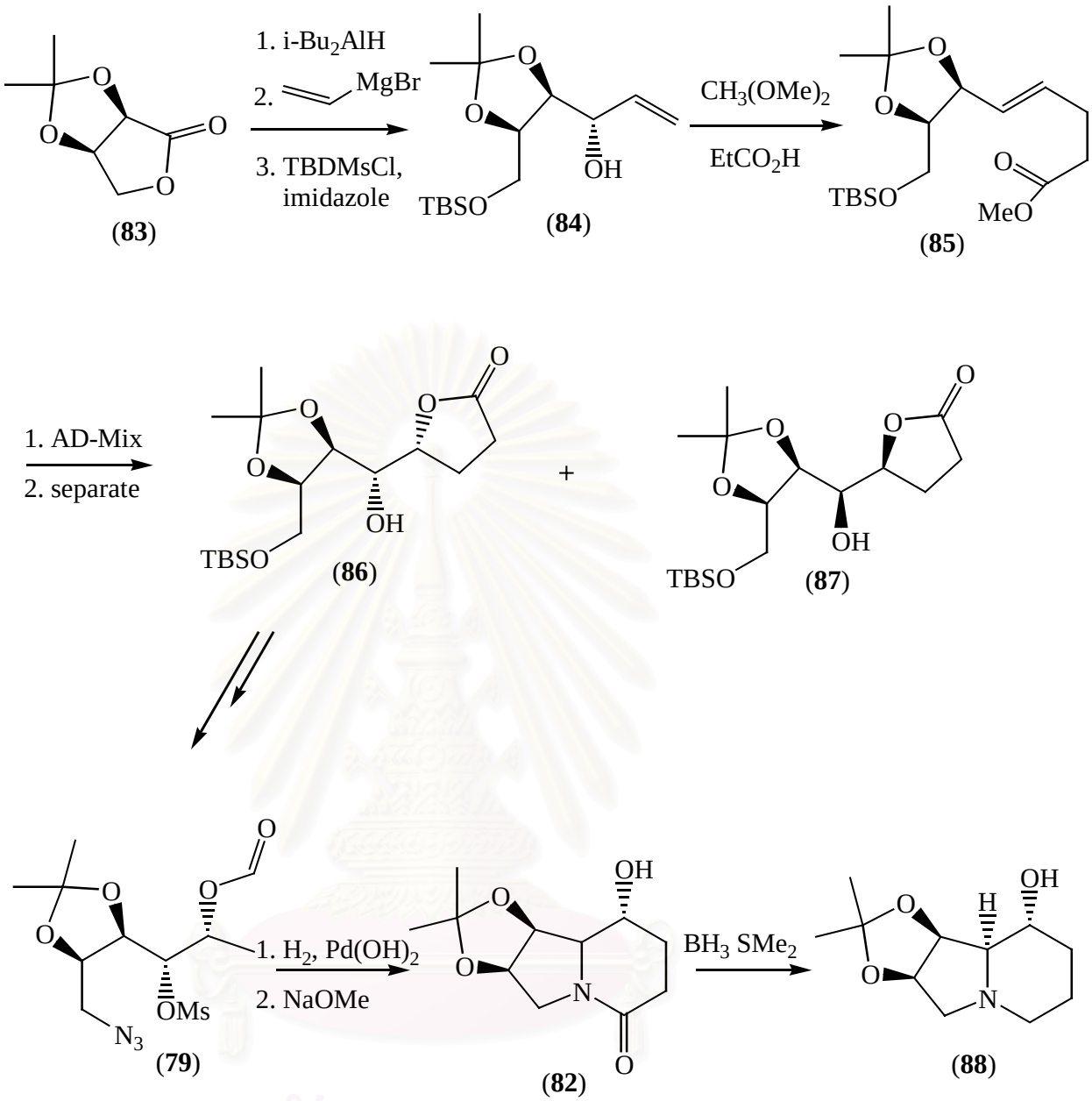
Figure 5 Carbohydrate Precursors

One good and efficient approach that can generate multigram quantities was reported by Pearson and Hembre.[27] The key step is the tandem reduction double cyclization of an azide bearing two remote electrophilic sites (**Scheme 20**).



Scheme 20 Tandem Reduction Double Cyclization of an Azide

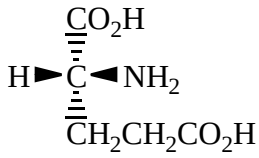
The synthesis started with a commercially available derivative of D-erythrose, 2-3-*O*-isopropylidene-D-erythronolactone (**83**) (**Scheme 21**). Conversion of (**84**) to the α,β- unsaturated ester (**85**) gave only the *E*-isomer when the allylic alcohol (**84**) was subjected to the Johnson orthoester Claisen rearrangement. Sharpless asymmetric dihydroxylation yielded a mixture of the lactones (**86**) and (**87**) in 70% and 9% yields. After purification, the protected alcohol was converted to the azide (**79**), then reduction to the amine (**80**) resulted in spontaneous double cyclization to produce the bicyclic lactam (**82**). Subsequently, this was converted to swainsonine.



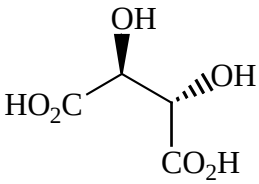
Scheme 21 Synthesis of Swainsonine by Pearson and Hembre

1.2 non-carbohydrate-based approach

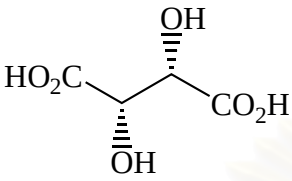
Beside carbohydrates, some syntheses employed chiral precusors such as R-glutamic acid, D-tartaric acid, D-malic acid and D-isoascorbic acid (**Figure 6**).



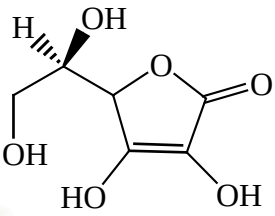
R-glutamic acid (**89**)



D-malic acid (**90**)



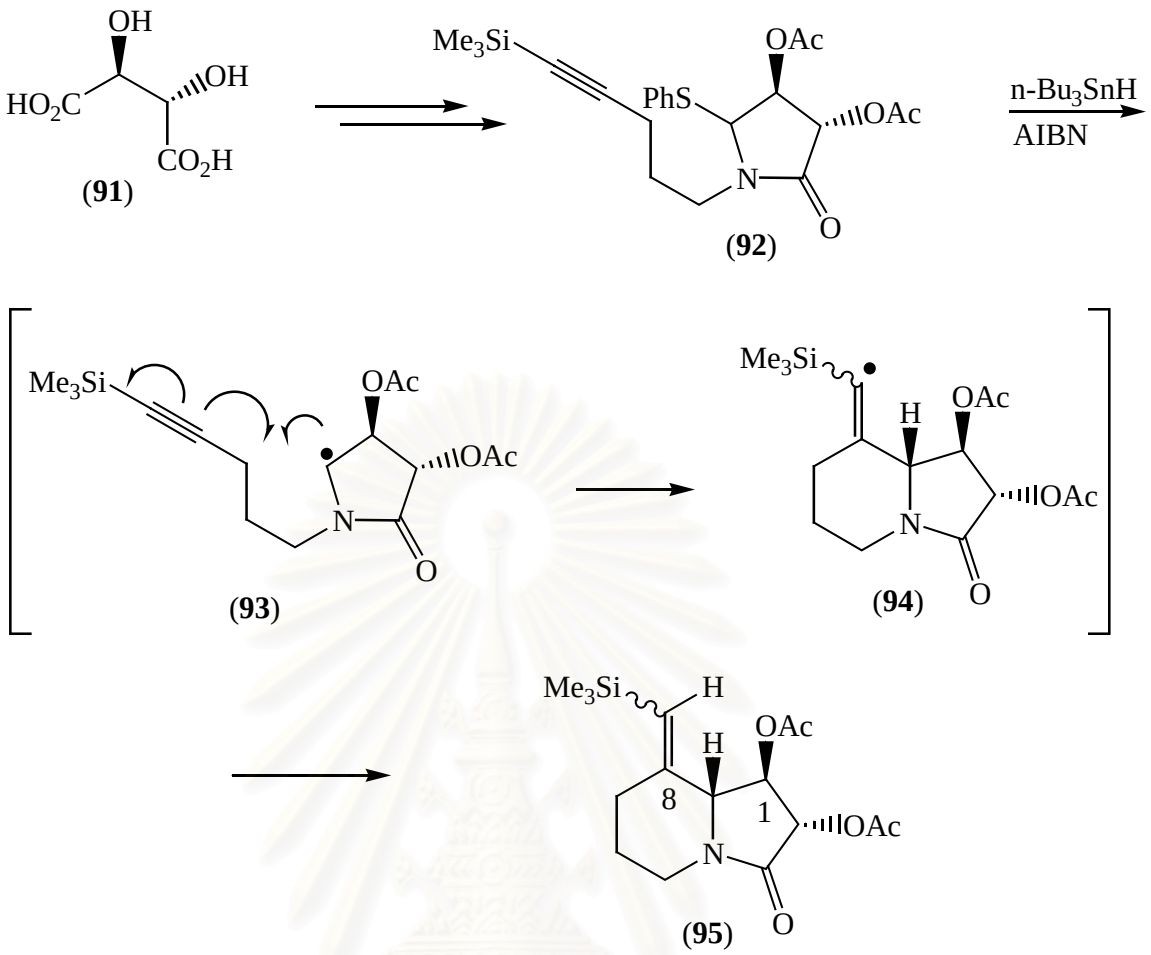
D-tartaric acid (**91**)



D-iso ascorbic acid (**92**)

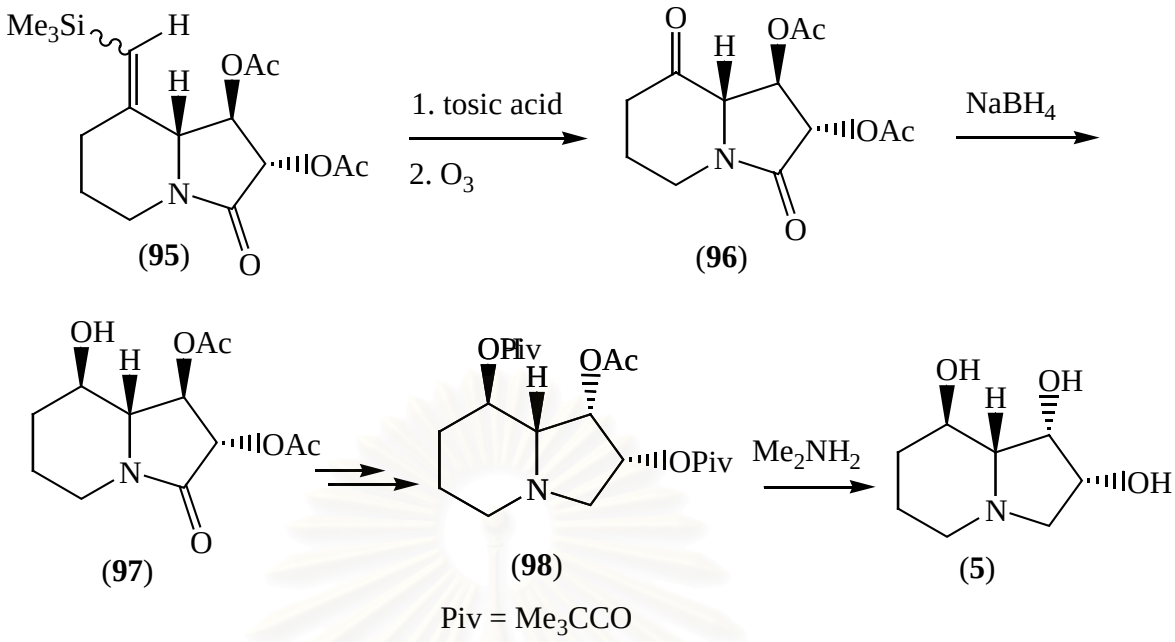
Figure 6 Non-carbohydrate Precursors

One example was reported by Hart and coworkers.[28] They used D-tartaric acid (**91**) as the chiral precursor and an α-acylamino radical cyclization as the key step (**Scheme 22**). Free radical precursor (**92**), which was prepared from D-tartaric acid (**91**), was cyclized *via* radical cyclization to give the indolizidine skeleton (**95**). The stereochemistry at C(8) position was established by cyclization opposite to the C(1) acetoxy group.



Scheme 22 An α-Acylamino Radical Cyclization

Desilylation and ozonolysis followed by stereocontrolled reduction of the ketone (**96**) with sodium borohydride resulted in hydride delivery to the unhindered face of cyclohexanone to give (**97**) (**Scheme 23**). This was followed by steps for the inversion of the C(1) stereochemistry and conversion of (**98**) to swainsonine.

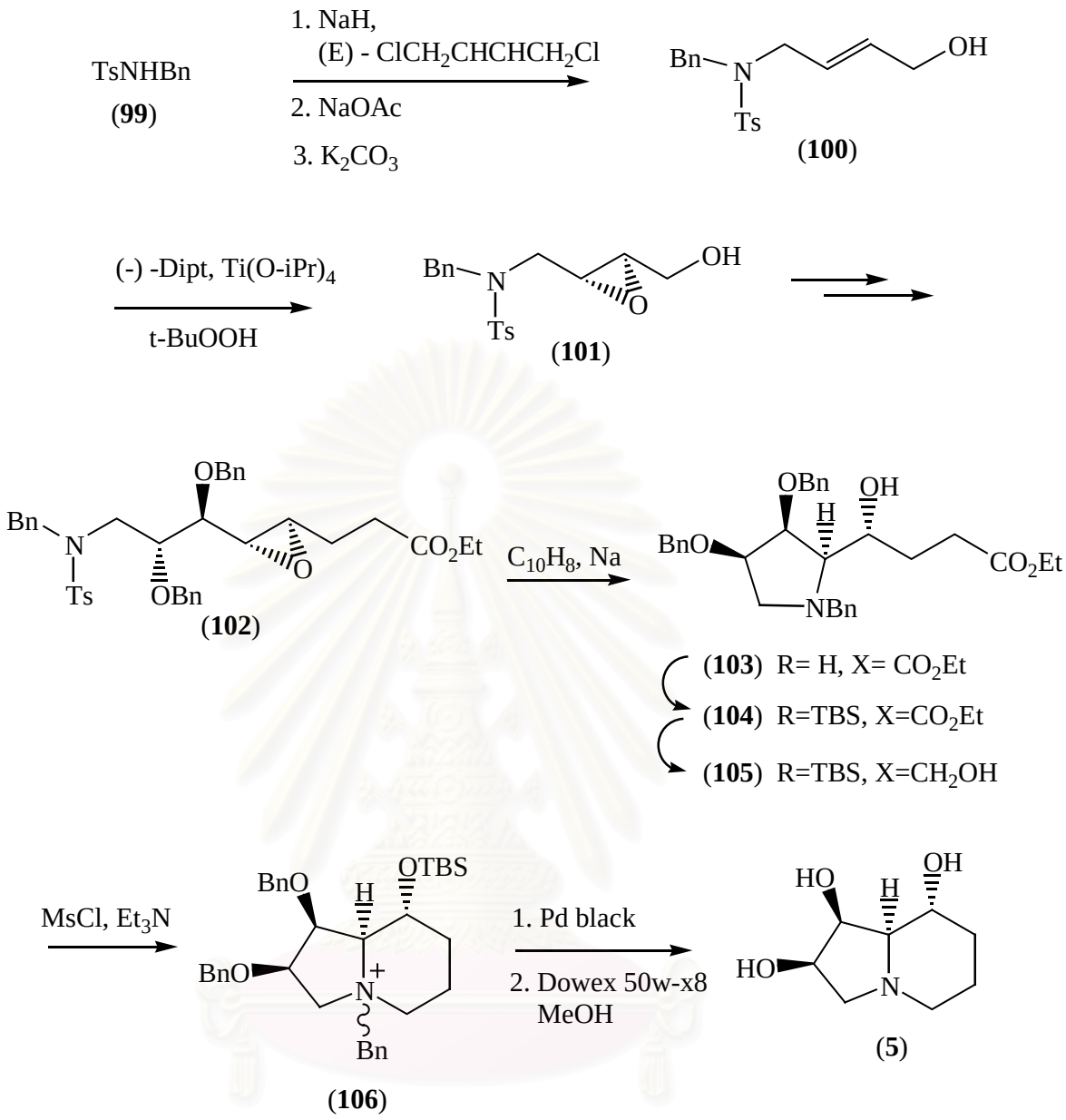


Scheme 23 Conversion of the Indolizidinone to Swainsonine

2. syntheses starting from achiral precursors

The first report of a non-chiral precursor route is the synthesis by Sharpless and co-workers.[29] The *p*-Toluenesulfonyl group was found to be suitable as an N-protecting group in order to render the nitrogen resistant to oxidation and prevent it from acting as an intramolecular nucleophile towards the epoxide function (**Scheme 24**).

The alkene (**100**) obtained from N-benzyl-*p*-toluenesulfonamide (**99**) underwent asymmetric Sharpless epoxidation to produce the epoxy alcohol (**101**) in 95%ee. This was converted to the epoxy ester (**102**). Detosylation resulted in epoxide opening and afforded the pyrolidine hydroxy ester (**103**). Mesylation of the pyrollidine (**105**) which was obtained from (**104**) lead to a mixture of *cis*- and *trans*-fused bicyclic quaternary ammonium salts due to the stereogenicity of N. Without purification, debenzylation of (**106**) gave a single amino diol which was desilylated to swainsonine. The overall yield was 6.6% in 21 steps.



Scheme 24 A Non-chiral Precursor Route in the Synthesis by Sharpless et. al.

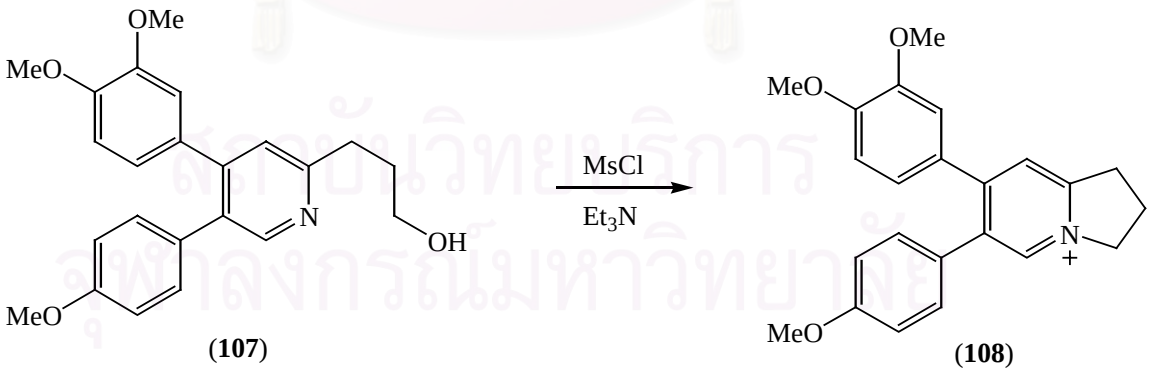
CHAPTER II

RESULTS AND DISCUSSION

We anticipated that the stereochemistry of indolizidines could be controlled by applying stereoelectronic factors to the transformations of bicyclic pyridinium salts. This could be applied to synthesize many stereoenriched indolizidines.

Aromatic heterocycles have emerged as useful intermediates for the synthesis of many organic compounds.[30] Pyridines have also been utilized as building blocks for the synthesis of many alkaloid natural products. They constitute a valuable pool of starting materials as many are commercially available or can be elaborated using heteroarene chemistry. In their quaternized form, they are susceptible to nucleophilic attack by various reagents including hydrides and carbanion.

The oxidative cyclization developed by Ciufolini et. al.[31] is an elegant and useful strategy for making cyclic intermediates (**Scheme 25**). Completion of the molecular framework of phenanthroizidine alkaloids was done by cyclization using Et_3N and MsCl in CH_2Cl_2 to give the pyridinium salt (**108**).

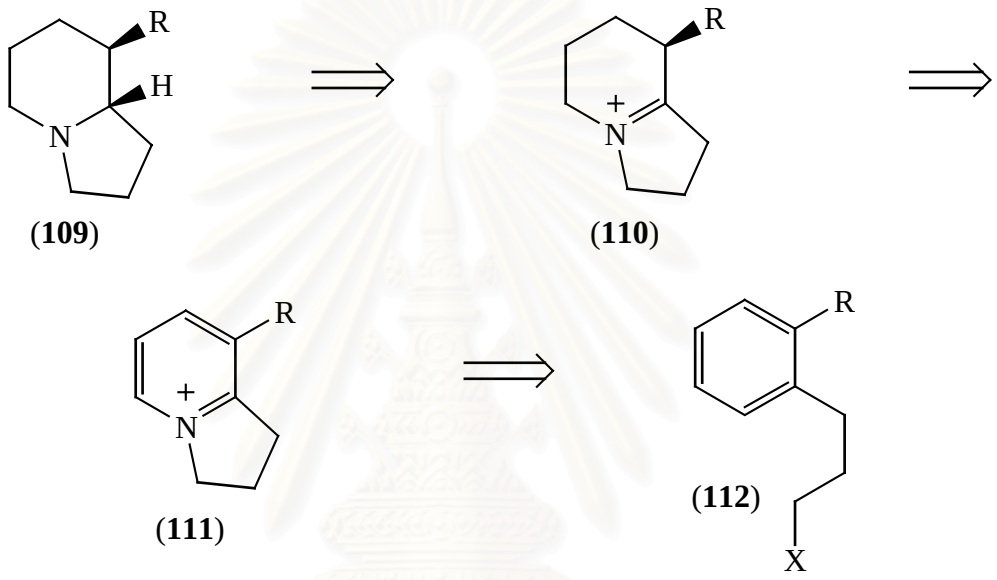


(**107**) (**108**)

Scheme 25 Cyclization Developed by Ciufolini et. al.

We planned to apply the stereoelectronic control principle to the synthesis of indolizidines starting with an achiral pyridine compound.

A bicyclic pyridinium salt with the indolizidine skeleton could be formed by cyclization of the substituted pyridine using Ciufolini's method (**Scheme 26**). Reduction of the pyridinium salt (**111**) via the cyclic iminium ion (**110**) would give the desired product. Stereochemistry could be controlled by stereoelectronic hydride delivery to this iminium ion.



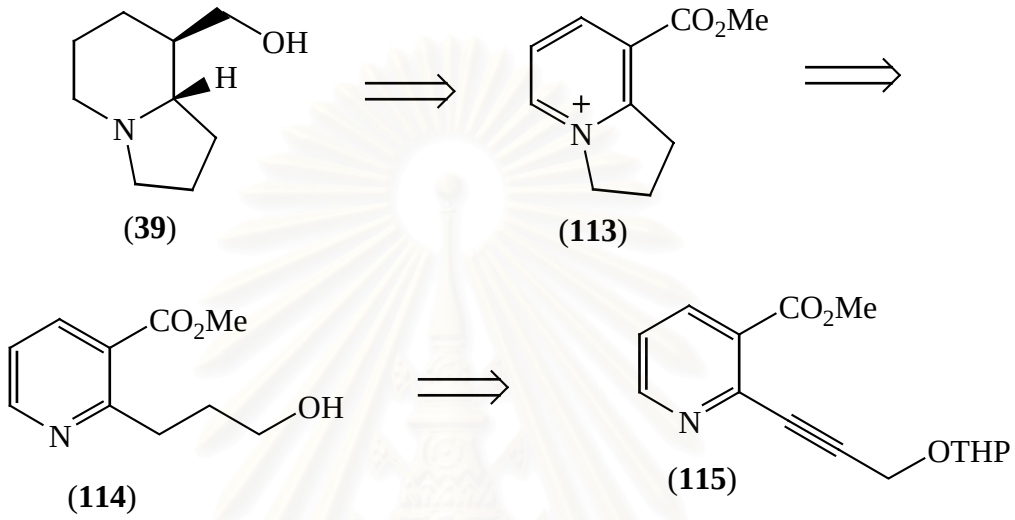
Scheme 26 Synthetic Plan for Indolizidine Skeleton

In order to demonstrate this stereocontrol strategy for the synthesis of chiral indolizidines, tashiromine and swainsonine were chosen as synthetic targets.

Tashiromine

Because of its simple molecular structure, tashiromine was the first molecule selected to verify the stereoelectronic control strategy for the indolizidine ring.

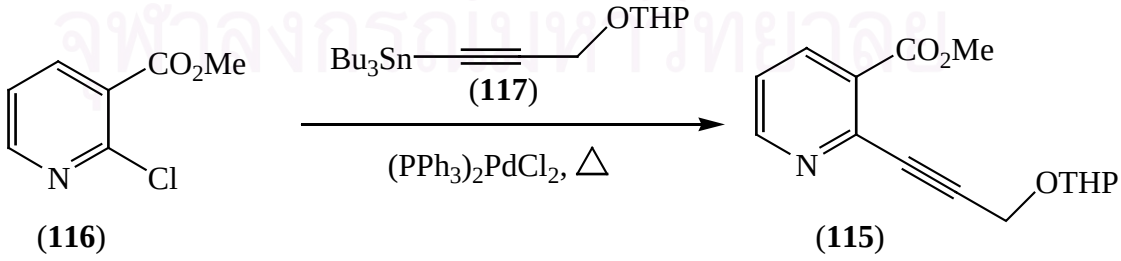
The alcohol side chain (**114**) of the required pyridine would be prepared by hydrogenation of the pyridinyl alkyne (**115**) (**Scheme 27**). Then, this would be cyclized to form the bicyclic pyridinium salt (**113**) necessary for the series of reductions to make tashiromine.



(**39**) (**113**) (**114**) (**115**)

Scheme 27 Retrosynthesis of Tashiromine

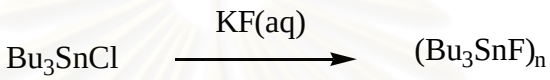
The coupling reaction between the pyridinyl chloride and the propargyl alcohol derivative was achieved by Stille coupling (**Scheme 28**).[32] Methyl-2-chloronicotinate (**116**) was coupled with the tri-*n*-butyl-tin derivative of the THP ether of propargyl algohol (**117**) in good yield.



(**116**) (**117**) (**115**)

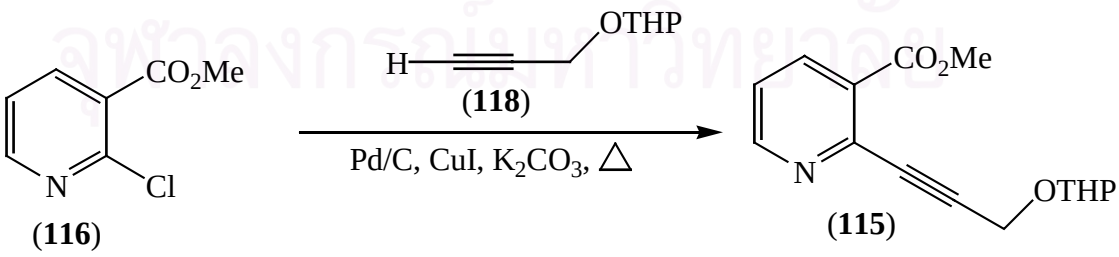
Scheme 28 The Stille Coupling Reaction

Although aryl chlorides are generally unreactive in palladium catalyzed reactions, in this case the chlorine is activated by its position relative to the ring nitrogen and the ester group. The acceleration of Pd-catalyzed coupling reaction by appropriately placed electron withdrawing groups has been demonstrated.[33] The Stille reaction produces a stoichiometric amount of tri-*n*-butyl tin halide. This can be removed by stirring the reaction mixture with aqueous potassium fluoride to generate the polymeric fluoro stannane which is insoluble in water and hydrocarbon solvents (**Scheme 29**). Despite this, there was still some tin contamination in the product after purification by column chromatography.



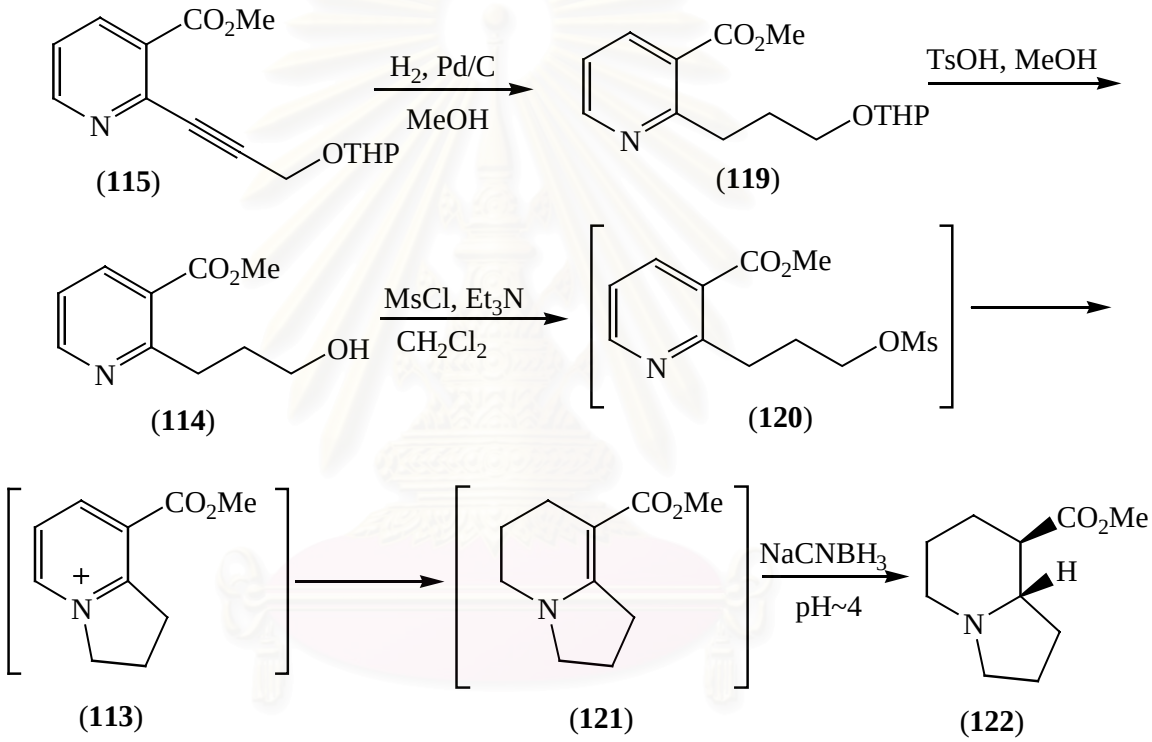
Scheme 29 Polymerization of Tin Waste with KF

An alternative method for the aryl-alkyne cross coupling is the Sonogashira reaction.[34] It was found that Cosford's heterogeneous conditions[35] were effective provided that absolute methanol, rather than aqueous methanol, was used as the solvent (**Scheme 30**). The terminal alkyne (**118**) was coupled with the methyl-2-chloronicotinate (**116**) using Pd on carbon as the source of palladium. The methods gave comparable yields (Stille, 86%; Sonogashira, 83%); however, the Sonogashira method has the advantage over the Stille method of avoiding the use of tin which is toxic and contaminates the product. In addition, it is more convenient to use the alkyne directly rather than a pre-forming stannane.



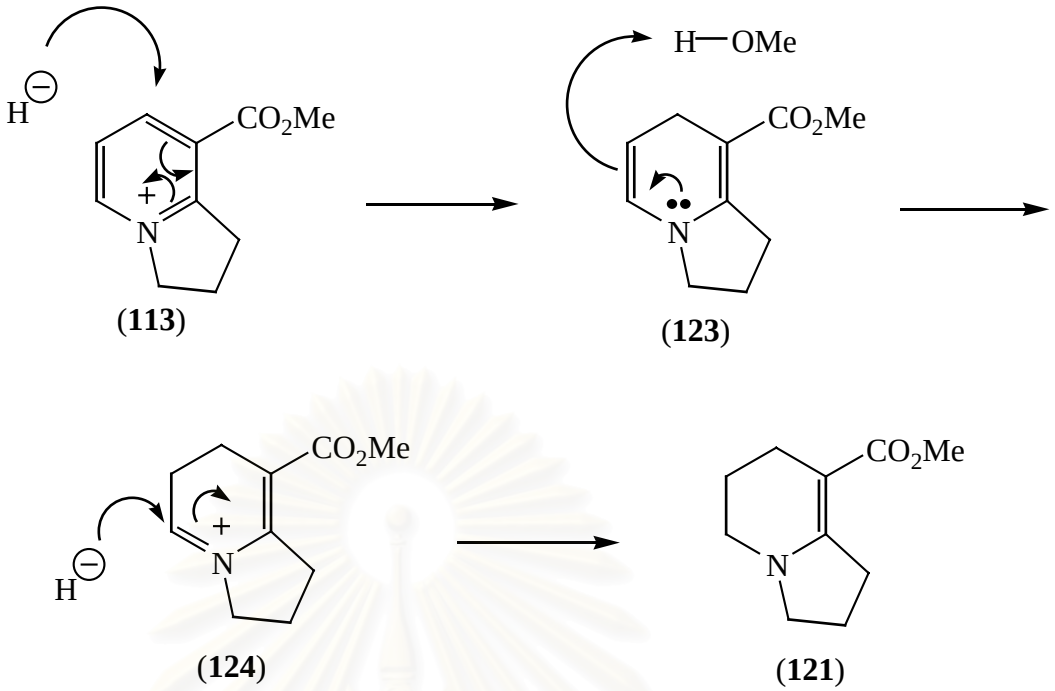
Scheme 30 The Sonogashira Coupling Reaction

Hydrogenation of the alkyne (**115**) over a palladium catalyst at atmospheric pressure following by deprotection of the THP ether under acidic conditions gave the propanol (**114**) (**Scheme 31**). The cyclization of the second ring was achieved with MsCl and Et_3N and yielded the bicyclic pyridinium salt (**113**). The salt (**113**) was not isolated. Instead, after evaporation of the volatiles, it was taken up in methanol and treated with $NaCNBH_3$. Reduction stopped at the vinylogous carbamate (**121**), but recommenced when the mixture was acidified to pH~4 by addition of methanol/HCl using bromocresol green as an indicator.[36]



Scheme 31 The Formal Synthesis of Tashiromine

Although generally, reduction of pyridines with sodium borohydride gives mixtures of 1,2- and 1,4- dihydropyridines,[37] the reduction of the pyridinium salt to the vinylogous carbamate (**121**) is a result of initial 1,4 addition (**Scheme 32**). This is the effect of the electron withdrawing ester group activating the 4-position of the pyridine. The second hydride is delivered to the 6-position after protonation of the intermediate enamine (**123**). The vinylogous carbamate (**121**) is less electron rich and is only protonated and reduced after addition of acid.



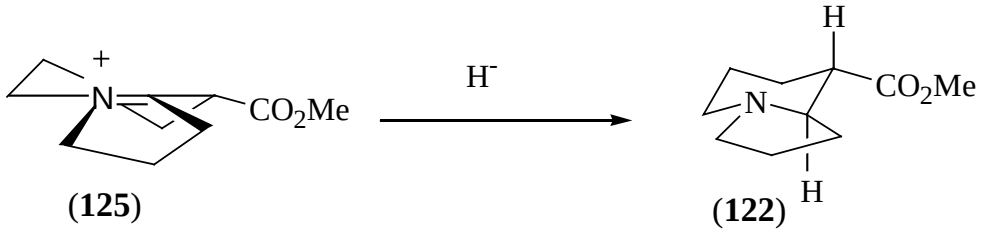
Scheme 32 Mechanism of the Reduction of the Pyridinium Salt by 1,4 – addition

This reaction completed the formal synthesis of tashiromine. A single diastereomer of the indolizidine ester was isolated in 65 % yield from the alcohol (**114**). The ^{1}H and ^{13}C NMR data were very close to the reported by Beckwith (**Table 1**).[18]

Table 1 Comparison with reported NMR data for the ester (**122**)

	Literature data	**The indolizidine ester** (**122**)
^{1}H-NMR	3.65 (s, 3H)	3.62 (s, 3H)
	3.1-3.3 (m, 5H)	3.05 (m, 2H)
	1.2-2.4 (m, 9H)	1.4-2.4 (m,12H)
^{13}C-NMR	172.3, 65.3, 54.1, 52.3, 51.7, 47.8, 29.2, 28.2, 24.7, 20.5	174.4, 64.8, 53.6, 51.9, 51.1, 47.5, 28.8, 27.8, 24.3, 20.1

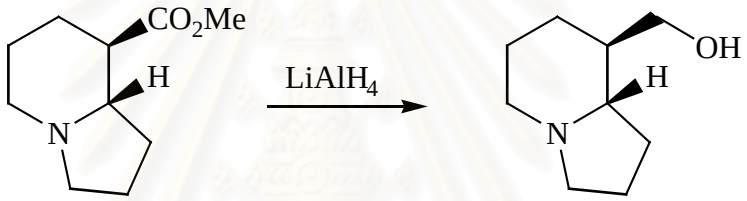
The stereochemistry was controlled by axial hydride delivery the iminium ion, as anticipated (**Scheme 33**).



(**125**) (**122**)

Scheme 33 Axial Hydride Delivery to Imine Ion

To complete tashiromine synthesis, the ester (**122**) was reduced with $LiAlH_4$ to give racemic tashiromine (**39**) (**Scheme 34**).



(**122**) (**39**)
tashiromine

Scheme 34 Reduction of the Methyl Ester

The spectroscopic data of ^{1}H and ^{13}C NMR closely matched those reported by Cha for tashiromine and were quite different to those reported for epi-tashiromine (**Table 2**).[19]

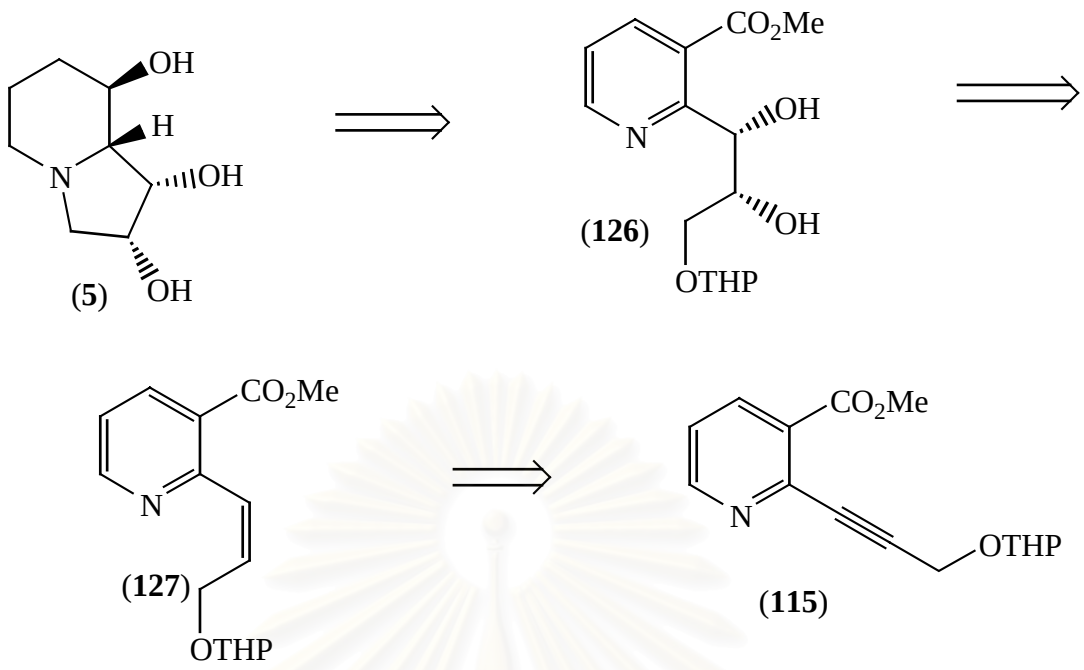
The data do not match perfectly, but it is known that trace impurities can result in distinct in the ^{1}H and ^{13}C chemical shift in hydroxylated alkaloids.[38]

Table 2 Comparison with reported NMR data for the indolizidine (**39**)

	Literature data : Tashiromine	**Literature data: Epi-tashiromine**	**The indolizidine (39)**
^{1}H-NMR	3.67 (dd,J=10.8,4.6Hz)	4.18 (dd,J=10.7, 4.0)	3.59 (dd,J=11,6Hz)
	3.44 (dd,J=10.8,6.3)	3.74 (br d, J=10.7)	3.47 (dd,J=11,5Hz)
	2.98-3.10 (m)	3.07-3.15 (m)	3.1-3.3 (m)
	2.03 (q,J=9.0Hz)	3.00-3.05 (m)	1.6-2.2 (m)
	1.36-1.97 (m)	2.24-2.32 (m)	1.1 (m)
	1.01 (qd,J=12.7,4.7Hz)	1.96-2.12 (m)	
		1.67-1.95 (m)	
		1.45-1.63 (m)	
^{13}C-NMR	20.2, 24.6, 27.2, 28.5, 44.0, 52.2, 53.7, 64.6, 66.0	20.8, 23.3, 25.8, 30.6, 35.3, 53.5, 54.5, 65.7, 66.8	19.9, 23.5, 26.5, 27.7, 42.5, 51.6, 52.8, 64.0, 66.4

Swainsonine

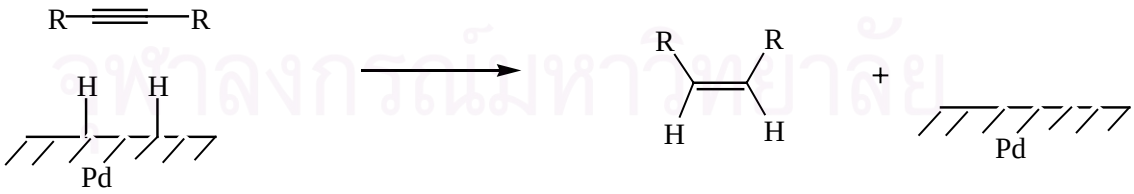
As the diol moiety of Swainsonine has cis stereochemistry, it was anticipated that this could be introduced by osmium catalyzed dihydroxylation[39] of the cis alkene (**126**) (**Scheme 35**). This allows the possibility of asymmetric dihydroxylation which can be effective for cis allylic alcohols.[40] A possible objection is that the osmium would be coordinated by the pyridine nitrogen and rendered inactive. However, it is known that pyridine itself can enhance dihydroxylation and dihydroxylation of vinyl quinolines has been reported. Cyclization after appropriate protection would yield the desired bicyclic pyridinium salt. A suitable starting material could then be the pyridyl alkyne (**115**) used in tashiromine synthesis.



Scheme 35 Retrosynthesis of Swainsonine

1. Direct Reduction

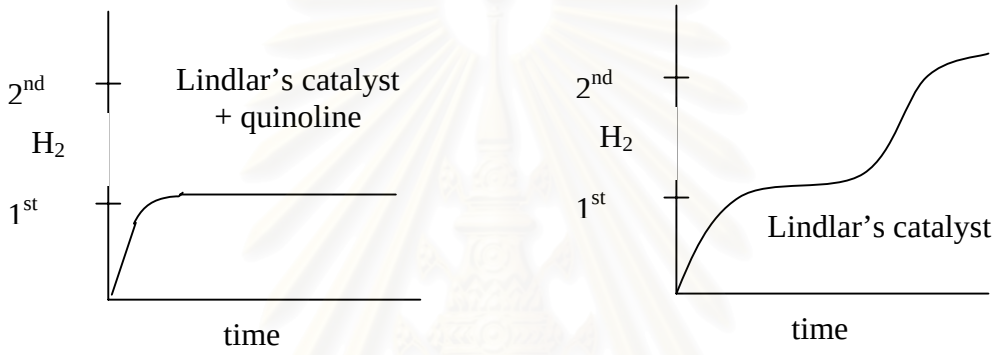
cis-Alkenes can be obtained by semihydrogenation of alkynes with several catalysts. The best known one is palladium on $CaCO_3$ poisoned with lead, known as Lindlar's catalyst.[41] Highly stereoselective cis-reduction is derived from attachment of two hydrogens to the same side of the alkyne coordinated to the catalyst surface (**Scheme 36**).



Scheme 36 Stereoselective cis-Reduction of Alkynes using Lindlar's Catalyst

In the reduction with Lindlar's catalyst, quinoline or pyridine is often added as an inhibitor or secondary poison to stop the reduction at the half way point. Without added quinoline, the reduction of an alkyne can proceed to the corresponding alkane (**Scheme 37**). Indeed, Lindlar's catalyst in the absence of a secondary poison has been used for the selective reduction of less hindered alkenes.[42]

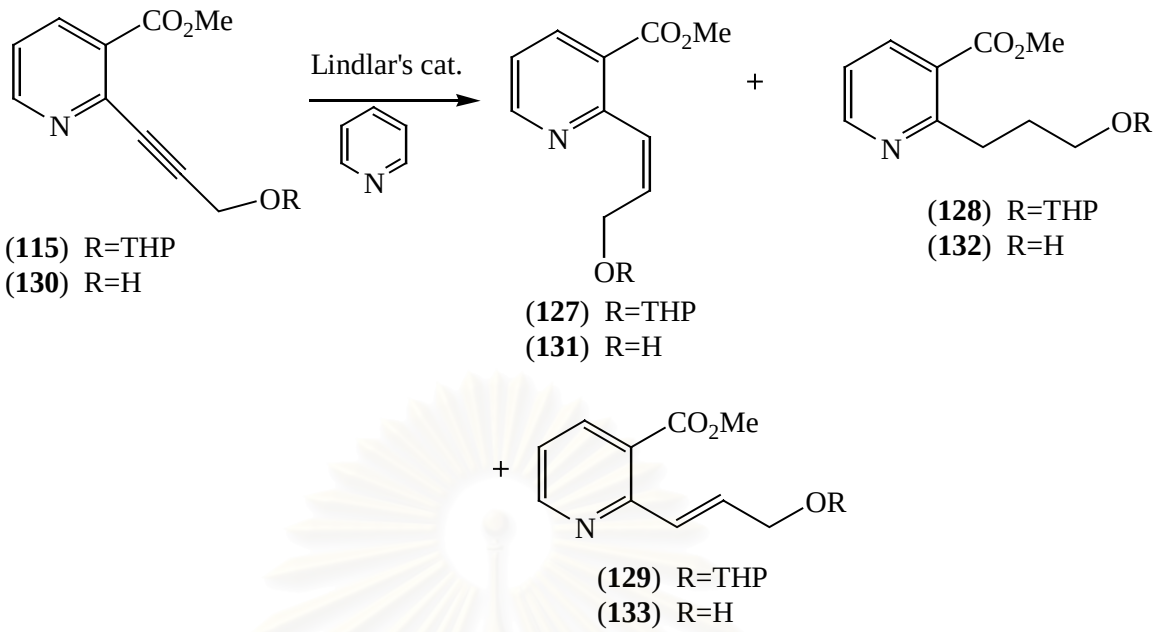
Quinoline or pyridine can coordinate with the catalyst surface more strongly than an alkene but not better than an alkyne. Quinoline leaves an alkyne coordinated with the catalyst surface, then replaces the alkene; consequently, semi-reduction can be successful.



Scheme 37 Controlling of Inhibitor to Catalytic Hydrogenation

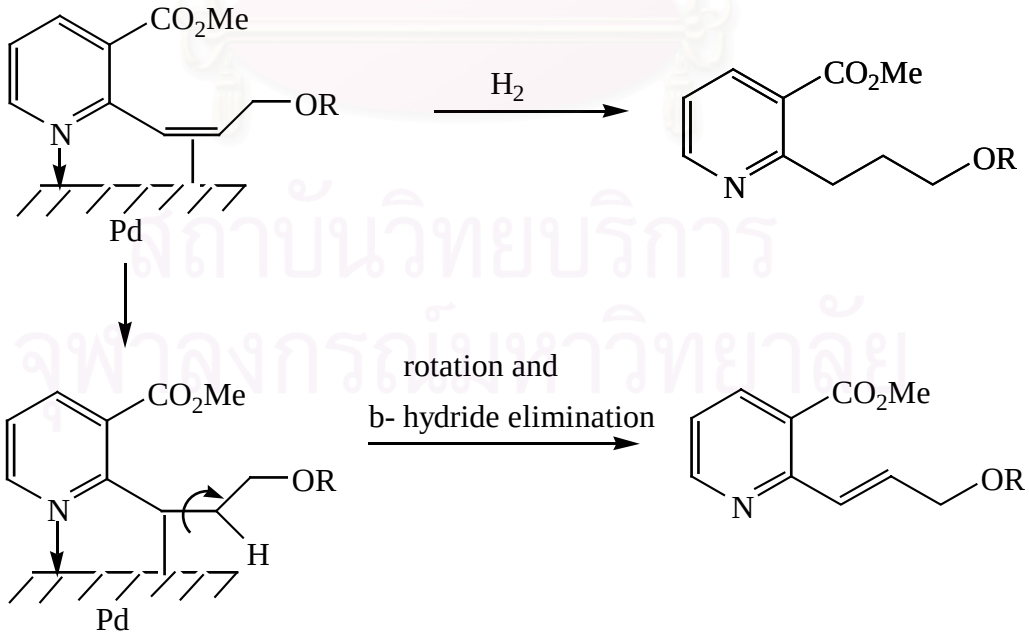
The alkyne (**115**) which has a THP protecting group and was a tashiromine intermediate, was reduced in the usual way with Lindlar's catalyst. Pyridine was used as an inhibitor to stop the reaction at the half way stage in order to get only cis- alkene without over reduction (**Scheme 38**). However, this reaction was not reliable. The yield of cis-alkene (**127**) varied and both the trans-alkene (**129**) and the saturated compound (**128**) were also isolated from this reaction. Reduction of the corresponding alcohol with Lindlar's catalyst gave a similar result.Yields of the three product were capricious. The best yield of cis-alkene (**127**) was 62 % but the result was not reproduced.

The stereochemistry of the reduction products was clearly determined by ^{1}H NMR. The coupling constant of the *cis*-isomer is 4Hz, while that of the *trans*-isomer is 10 Hz.



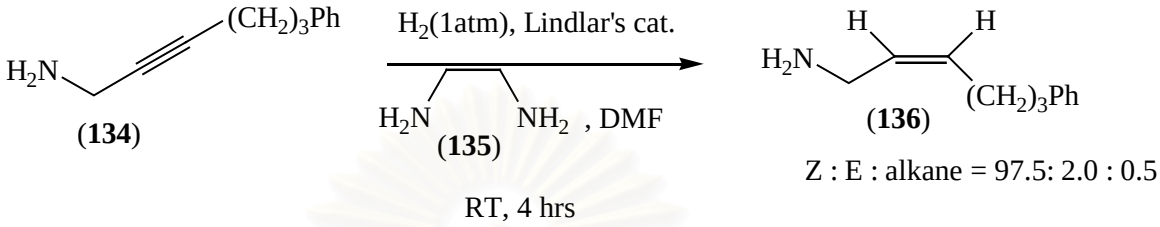
Scheme 38 Reduction of the Alkynes by Lindlar's Catalyst with Pyridine as Inhibitor

It can be proposed that the lone-pair of the nitrogen of the pyridine can bind to the catalyst surface, so that the substrate and the desired initial product function as bidentate ligands (**Scheme 39**). The consequent long residence time on the surface permits Pd catalysed isomerization and over-reduction.



Scheme 39 Over-Reduction and Isomerization of Catalytic Hydrogenation

During the course of this work, a report from the Merck research labs described the same problem in the case of a long chain aminoalkyne (**Scheme 40**). [43] The solution was the addition of a competitive bidentate ligand, ethylenediamine (**135**).



Scheme 40 Semi-Reduction of Aminoalkyne

However, in our hands, using ethylenediamine with the pyridinyl alkyne (**130**) resulted in no reaction. The diamine (**135**) completely coordinated with the catalyst, therefore inhibiting the reaction.

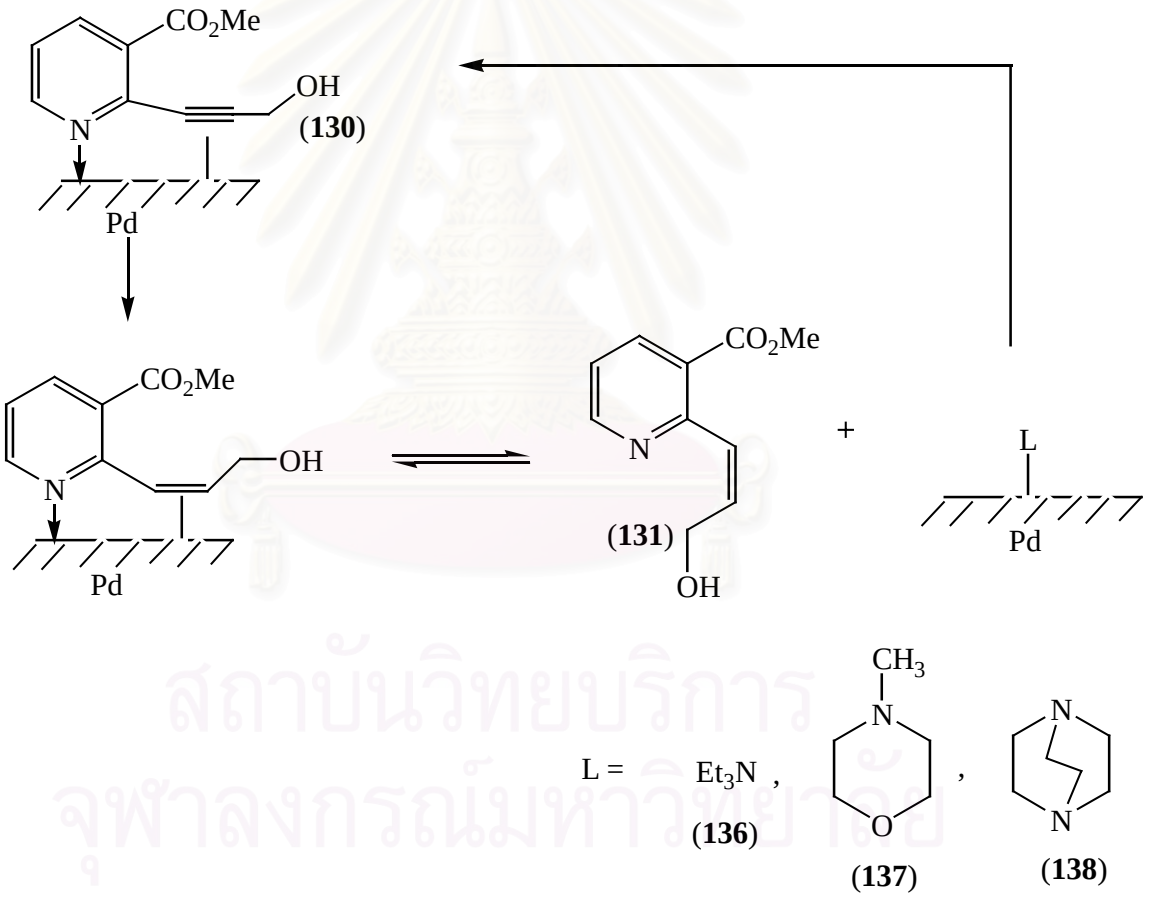
Clearly a diamine containing two sp^3 hybridized nitrogen atoms was too strong as a donor to allow binding of the substrate to the catalyst. While pyridine, containing one sp^2 hybridized nitrogen, was too weak to act as an inhibitor of the undesirable side reactions. Monodentate sp^3-donors were therefore selected as a compromise between these two positions.

Triethylamine (**136**), which is cheap and volatile, gave some improvement over pyridine. *N*-methyl Morpholine (**137**), a stronger monodentate sp^3-donor than triethylamine because of its lesser steric hindrance, gave a better E:Z ratio. Among these reagents, DABCO (**138**) is the best donor because of its rigid structure. The optimum results were obtained using this reagent.

Table 3 Ratio of cis to trans from the Lindlar reduction with monodentate sp^3-donors

Amine	Equivalents	Ratio of cis to trans
Triethylamine	1.2	1.6:1
N-methyl Morpholine	1.2	2.2:1
DABCO	1.2	7:1
DABCO	1.5	13:1

DABCO (**138**) is a worse ligand for the catalyst compared with the alkyne but is better than the alkene. Therefore, a high ratio of cis to trans was obtained. In these experiments, none of the saturated compound was obtained (**Scheme 41**).

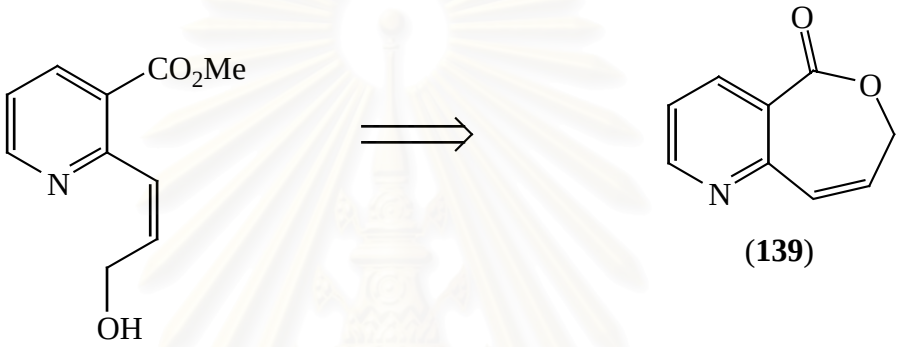


Scheme 41 Competitive Coordination of Inhibitors to the Alkene in Catalytic Hydrogenation

Before the solution to the problem associated with Lindlar's catalyst was found, alternative methods to synthesize the alkene were explored.

2. cis-Alkene *via* cyclic-Alkene

Ring opening of a lactone (**139**) in which the alkene could only be cis would give the desired allylic alcohol (**131**) (**Scheme 42**). Several methods can be considered for the formation of this compound.

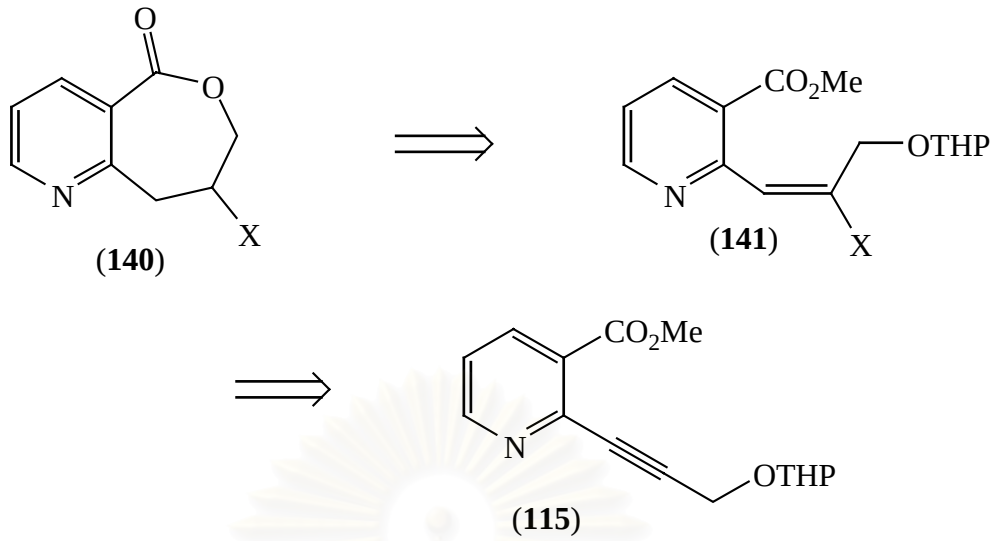


(**131**) (**139**)

Scheme 42 Retrosynthesis of the *cis*-Alkene

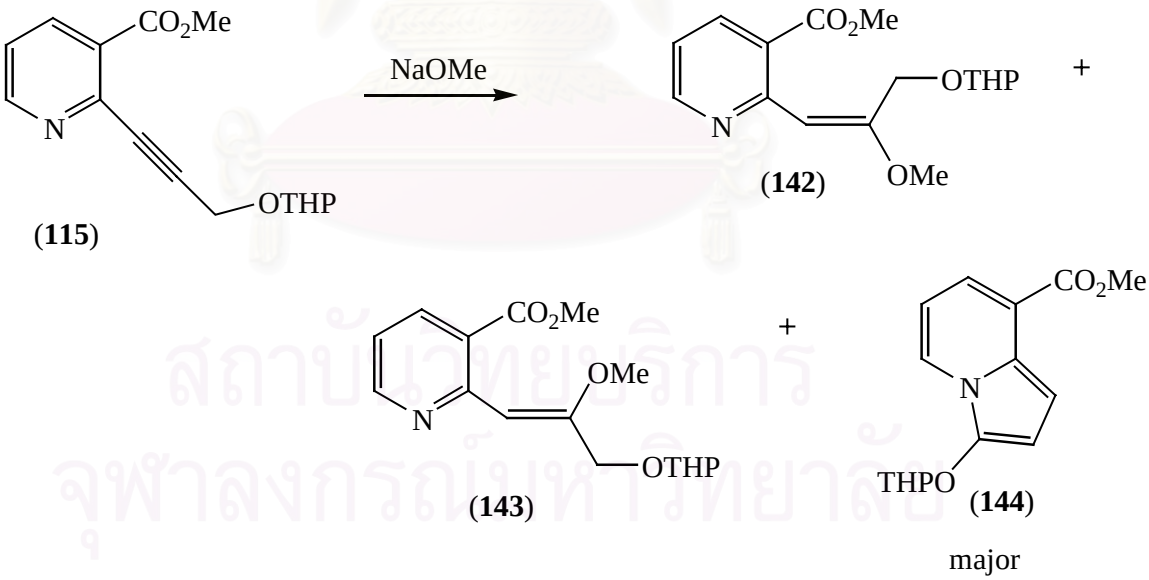
2.1 Michael addition

Elimination of a group, X, from a saturated lactone would give the desired unsaturated lactone (**Scheme 43**). As pyridyl alkynes are known Michael acceptors, [44] the reaction of alkyne (**115**) with various heteroatom nucleophiles was examined as a way to introduce the group X.



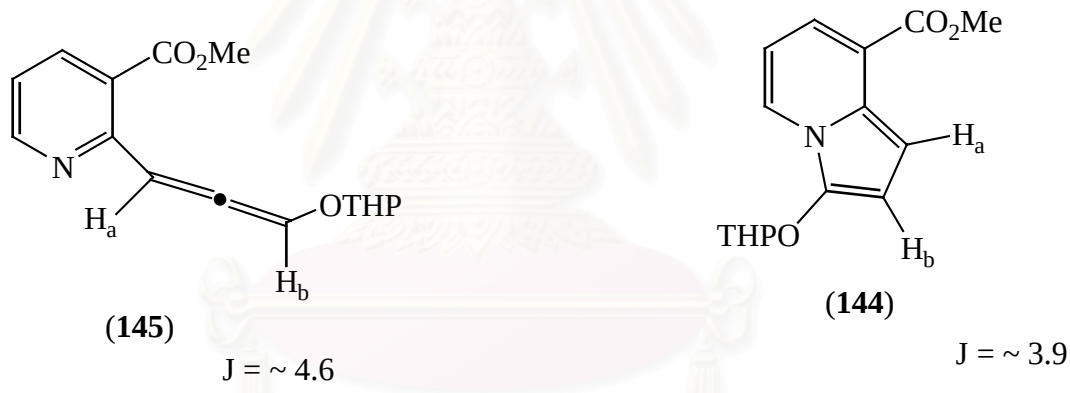
Scheme 43 Retrosynthesis of the Michael Route

Sodium methoxide was selected as the first nucleophile to try (**Scheme 44**). From the reaction two minor adducts (**142**) and (**143**) were isolated, but the major product (**144**) showed only aryl or vinyl protons other than the OMe and THP groups.



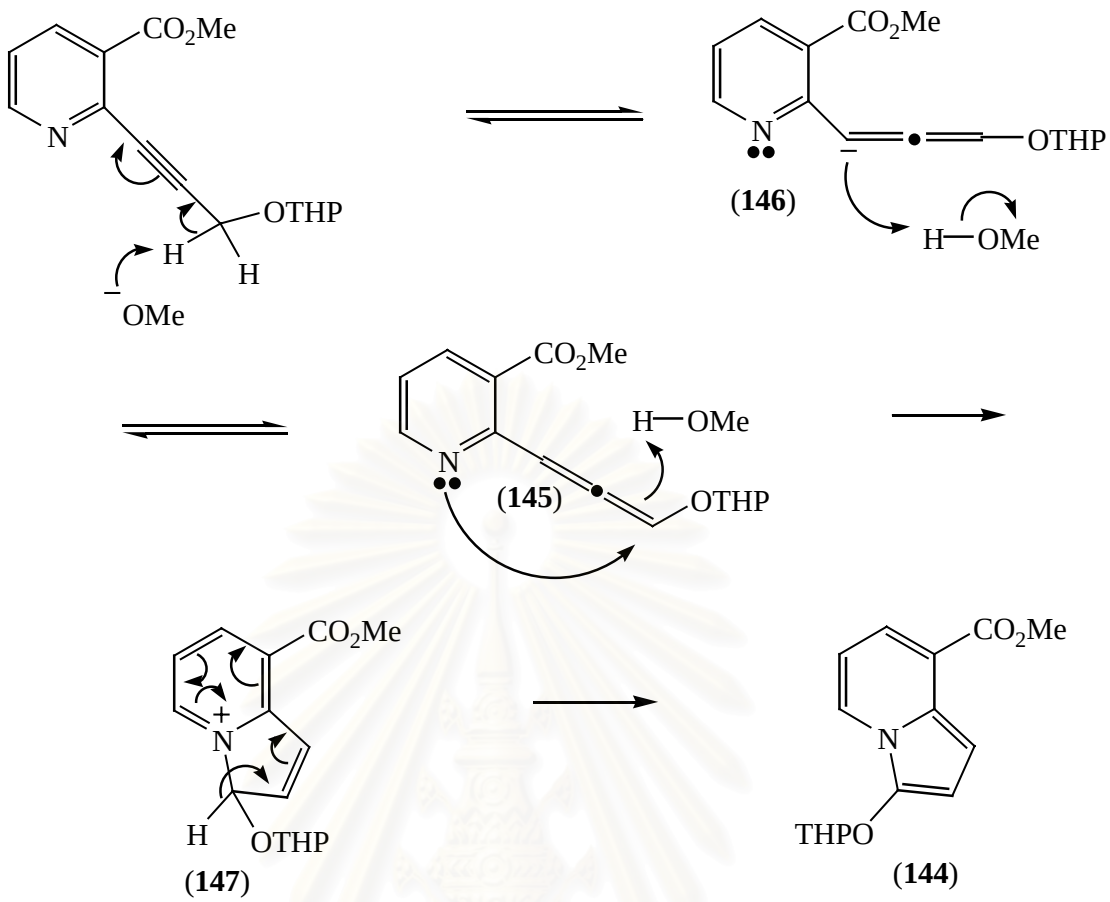
Scheme 44 The Reaction of the Alkyne with NaOMe

Initially we suspected that the product could be the allene (**145**) as isomerization of propargylic ethers is well known[45] and the ^{1}H NMR included two doublets with coupling constants of ~ 4Hz,[46] not unreasonable for a 1,3 disubstituted allene (**Scheme 45**). Acidic hydrolysis of such an allene would be expected to yield a useful cis aldehyde,[47] but it did not, giving only decomposition. In addition, inspection of the ^{13}C NMR spectrum revealed the absence of any signal in the region of the central carbon of the allene (**145**) (ca 200 ppm) and the IR spectrum did not show the expected absorbance at ~ 1950 cm^{-1} in the region characteristic of a cummulene. In addition, a 1,3-disubstituted allene bearing a THP group would be expected to exist as a mixture of diastereomers but this compound was clearly a single isomer. The structure were therefore reassigned to that of the indolizidine (**144**) which is consistant with all of the data, including the pair of 4Hz doublets in the ^{1}H NMR. These could be assigned to H_a and H_b.



Scheme 45 Coupling Constants of the Allene and the Indolizine

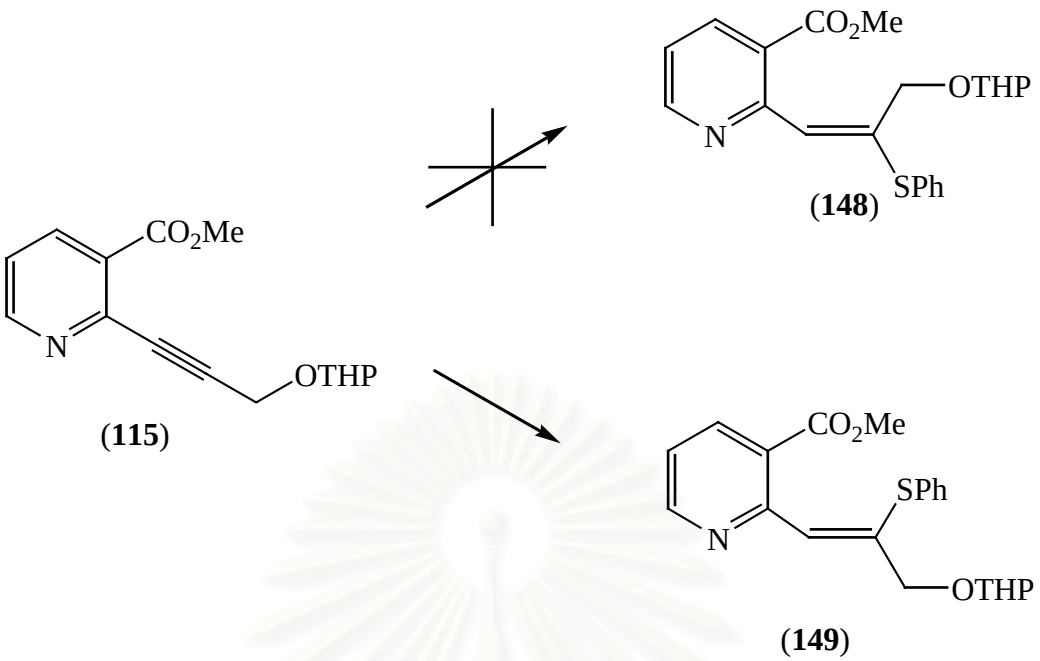
It can be proposed that the methoxide ion acts as base, catalyzing isomerization to give an allene intermediate (**Scheme 46**). Intramolecular cyclization then gives an indolizine product.



Scheme 46 Proposed Mechanism of Indolizine Formation

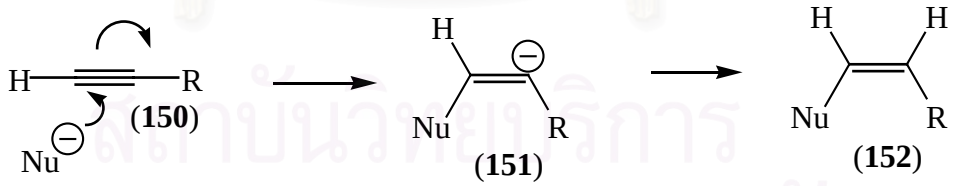
Thiophenol is a better nucleophile than methoxide and a weaker base (pKa value: ArSH 6-8, MeOH 15.2).[48] Therefore, it was anticipated that the Michael adduct would be favored and indolizidine formation avoided.

Michael addition of the thiophenol to the alkyne (**115**) gave the Michael adduct in high yield but the geometry of the Michael product, determined by NOESY, was opposite to that required (**Scheme 47**). The sulfide was located cis to the pyridine ring and therefore the product could not cyclize.



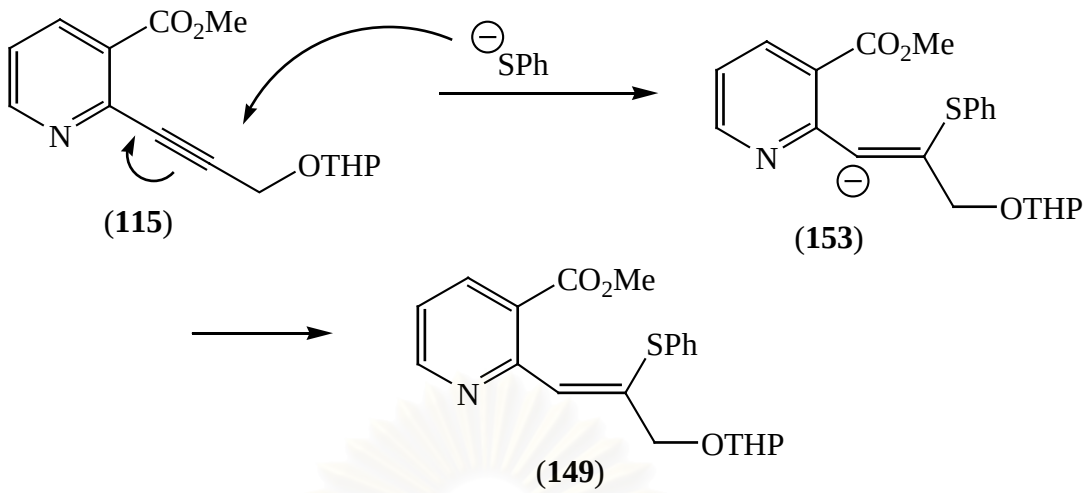
Scheme 47 The Michael Reaction of the Alkyne with Thiophenol

Addition of a nucleophile to a triple bond under kinetic control gives the product with substituents trans to each other (**Scheme 48**). The formation of the carbanion intermediate (**151**) is the rate determining step. The lone pair is trans to the incoming nucleophile which is stabilised by the favorable antiperiplanar interaction of the localised non-bonding electron-pair with the σ* orbital of the C-Nu bond.[49]



Scheme 48 Nucleophilic Addition to an Alkyne

Hence in the nucleophilic addition of the sulfide, the vinyl proton is trans to the sulfide according to the geometry of the carbanion intermediate (**Scheme 49**).



Scheme 49 Nucleophilic Addition of the Sulfide to the Pyridyl Alkyne

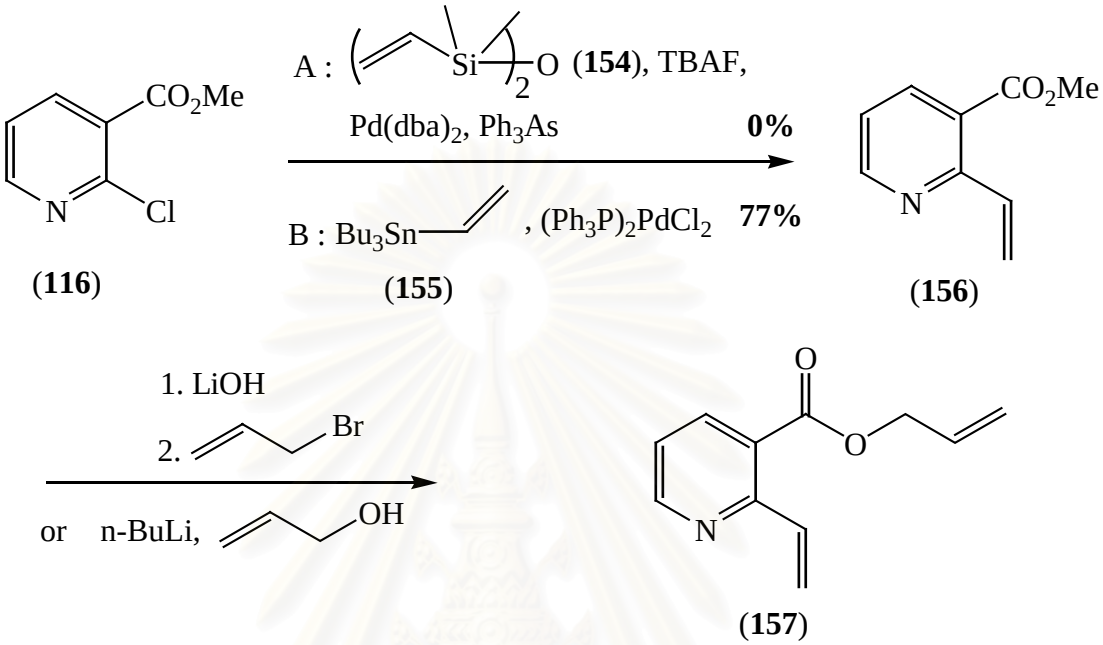
2.2 Alkene metathesis

Since the discovery by Grubbs and Schrock of stable yet active catalysts, ring closing metathesis have been widely used to form cyclic compounds.[50] There have been many reports of the use of alkene ring closing metathesis to form heterocyclic rings. We considered that this chemistry might be applicable to lactone formation. The substrate required would be the vinyl pyridine (**157**) (**Scheme 50**).

Cross coupling of the chloro pyridine (**116**) using Denmark's modification[51] of the Hiyama reaction failed, while the corresponding Stille coupling proceeded uneventfully (**Scheme 50**). In general, palladium catalyzed reactions of 2-halopyridines are faster than those of 3-halopyridines due to the electron withdrawing effect of the nitrogen. In the case of Denmark's coupling reaction, the reverse is true, but it remains unclear why this is so.[52]

The methyl ester (**156**) was converted to the allyl ester (**157**) by saponification with lithium hydroxide followed by evaporation of the volatiles to leave the carboxylate salt as a solid. Addition of allyl bromide gave the desired diene product. It is interesting to note that there was no serious competition from N-allylation.

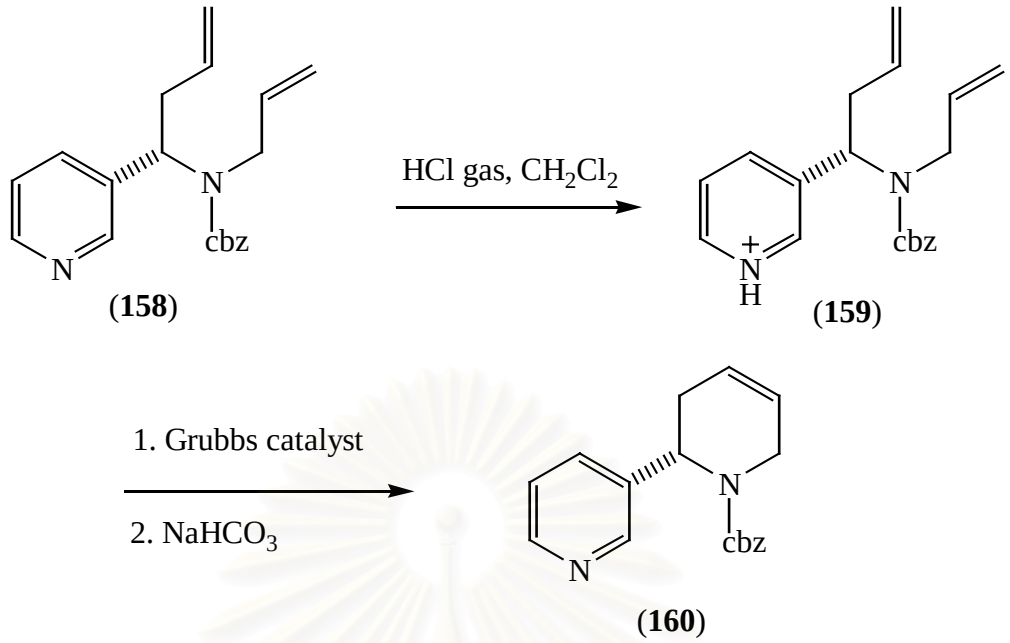
Transesterification with a lithium allyloxide catalyst[53] could also be used, however, because it is a reversible reaction, a large amount of allyl alcohol must be used. Therefore, the saponification-alkylation route was preferred.



Scheme 50 The Synthesis of the Metathesis Precursor

Attempts to effect ring closing metathesis using the Grubbs catalyst were unsuccessful. Only starting material could be recovered. Due to the air sensitivity of the Schrock catalyst, which requires glove box handling, it was not used.

One plausible explanation is that pyridine nitrogen interferes with the catalytic cycle by coordination with the ruthenium atom. In a synthesis of (*S*)-Anatabine,[54] blocking the nitrogen by protonation with acid result in a good yield of the desired metathesis product (**Scheme 51**). However, addition of acid to the pyridine substrate (**157**) during metathesis still gave only starting material.

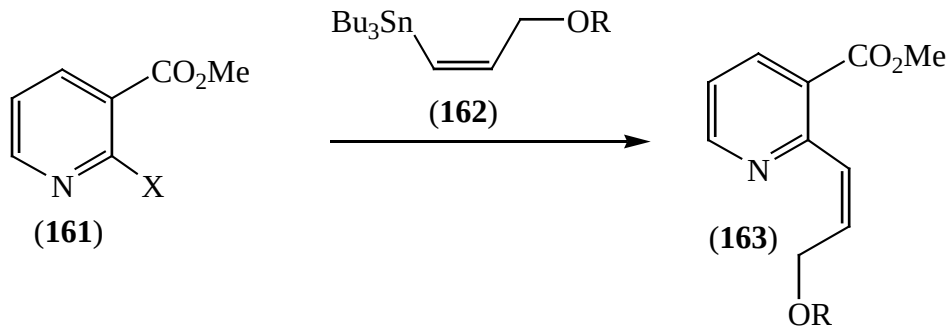


Scheme 51 Successful Alkene Metathesis by Nitrogen Protonation

Grubbs has reported the effect of alkene substituents on ring closing metathesis. [55] With electron withdrawing groups on the diene, the rate of ring closing metathesis with the ruthenium alkylidene becomes so slow that catalyst decomposition is faster than ring closing metathesis. Therefore, in the pyridinyl diene (**157**), the pyridine and the ester group which are electron withdrawing, retard the ring closing metathesis.

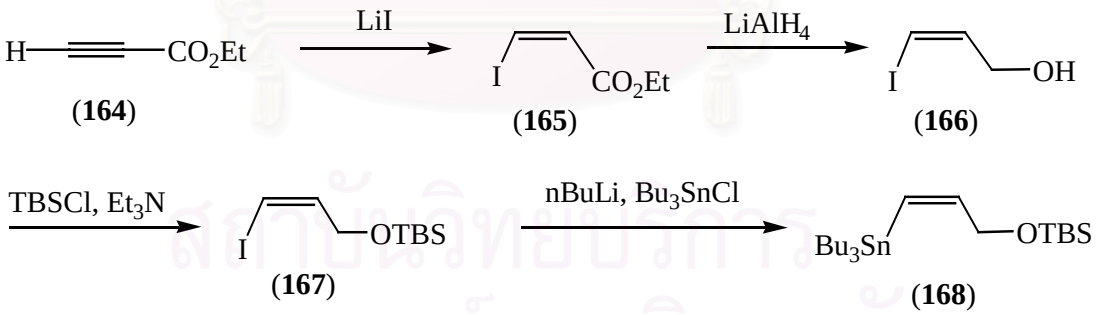
3. Direct cross coupling

An alternative method to obtain the desired cis alkene would be by directly coupling with a three carbon fragment (**Scheme 52**).

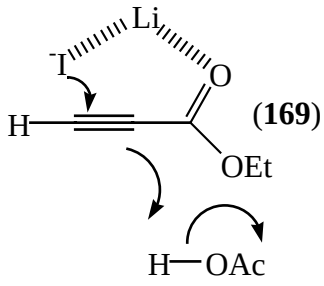


Scheme 52 Direct Coupling Reaction

The cis stannyl alkene was prepared from methyl propionate (**164**) (**Scheme 53**). Stereospecific hydrohalogenation with lithium iodide gave the cis-alkene (**165**).[56] This stereospecific control can be rationalized by two explanations. One is that coordination of the lithium ion with the carbonyl oxygen atom and the iodide ion, causes attack on the triple bond from the same side of the carbonyl (**Scheme 54**). Another explanation of this stereospecificity is the stabilization of the carbanion by the C-I σ* orbital to make the incoming nucleophile to be trans position to the cabanion as in Scheme 48. This ester (**165**) was followed by reduction, protection the hydroxy group, lithiation and transmetallation to give the cis-alkene fragment (**168**).[57]



Scheme 53 The Synthesis of the Substituted Vinyl Stannane

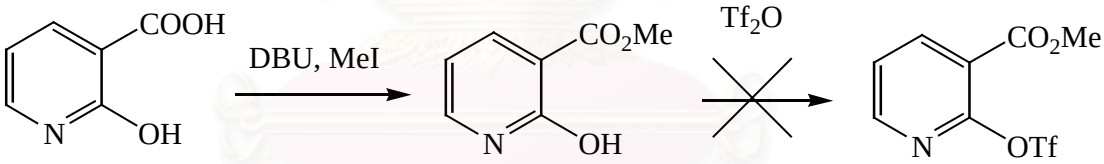


(**169**)

Scheme 54 Addition of the Hydrogen Iodide to the Propiolate

However attempted coupling of either (**168**) or the corresponding free alcohol gave at best only traces of the alkenes, Various techniques to improve yields in the Stille reaction have been used. A variety of catalysts, including the thermally stable Hermann's catalyst,[58] $Pd(dba)_2$,$(Ph_3P)_2PdCl_2$ and Pd/C, and a variety of solvents were tried but to no avail.

Changing from the chloro pyridine to the more reactive bromo compound[59] also gave no improvement. An alternative leaving group to a halide is triflate. However, attempts to make the pyridinyl trifate (**172**) failed (**Scheme 55**).



(**170**) (**171**) (**172**)

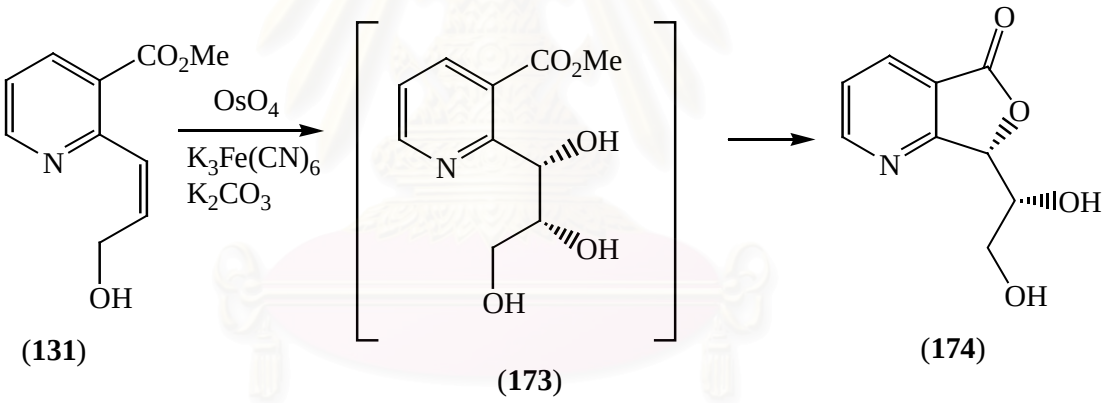
Scheme 55 The Synthesis of Pyridyl Triflate

The unsubstituted vinyl stannane (**155**) can be coupled effectively with the chloro pyridine while the more highly substituted stannane (**162**) cannot. The failure of this coupling reaction can be attributed to the greater steric hindrance of the alkene.

Dihydroxylation

The oxidation of alkenes using osmium tetroxide to give cis-diols is a well-known reaction. Because of its high cost and toxicity, the use of catalytic amounts of osmium has replaced the stoichiometic reaction by using cooxidants. The Upjohn[60] procedure uses NMO as cooxidant and the Tsuji[61] procedure uses $K_3Fe(CN)_6$ as cooxidant.

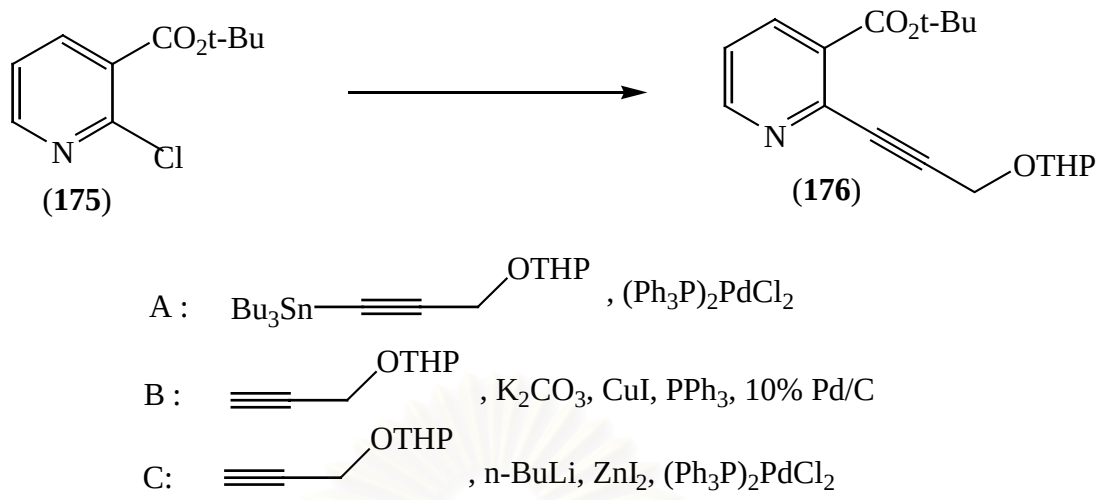
With the cis-allylic alcohol (**131**) in hand, dihydroxylation with Tsuji's procedure was attempted. However, the product that was obtained in low yield was not the triol (**173**), but the diol (**174**) formed by further lactonization of the alcohol (**Scheme 56**). Such a process is precedented.[62] The methoxide group is too labile so that lactonization is facile.



(**131**) (**173**) (**174**)

Scheme 56 Further Lactonization of the Alcohol

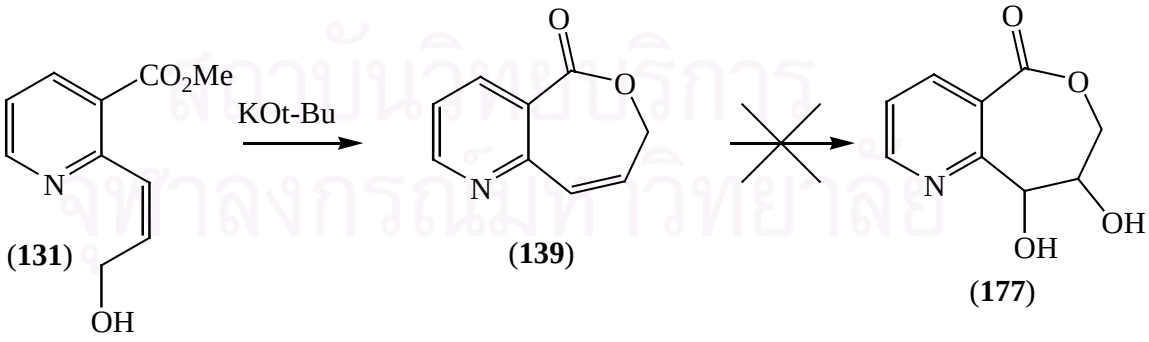
Changing the ester group to one with more steric hindrance in order to avoid lactonization was considered; however, t-butyl-2-chloronicotinate (**166**) failed to couple with the alkyne, due to the increased steric hindrance (**Scheme 57**).



Scheme 57 Coupling of the Alkyne with the More Hindered Chloro Pyridine

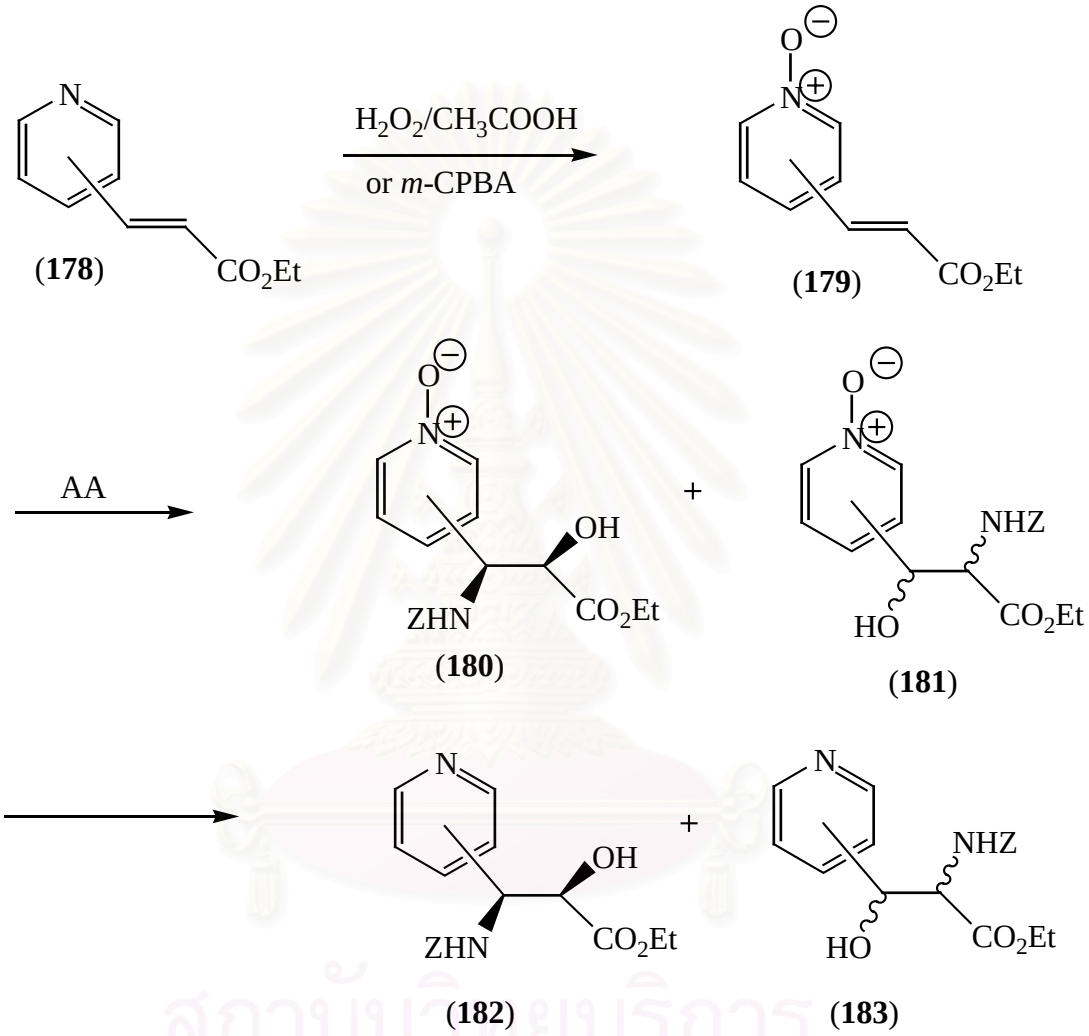
In any case, the yield of lactone obtained under Tsuji condition was very low. In contrast, the Upjohn procedure gave no product.

We suspected that chelation of osmium in the intermediate might block the catalytic pathway. This was tested by converting the alcohol (**131**) to lactone (**139**) by treatment with base (**Scheme 58**). Triethylamine, DBU and tetra methyl guanidine were tried, but in each case the starting material was not consumed. With potassium t-butoxide, the reaction proceeded to completion. The lactone, however, did not undergo dihydroxylation under either the Tsuji or Upjohn conditions.



Scheme 58 Attempted Dihydroxylation of the Lactone

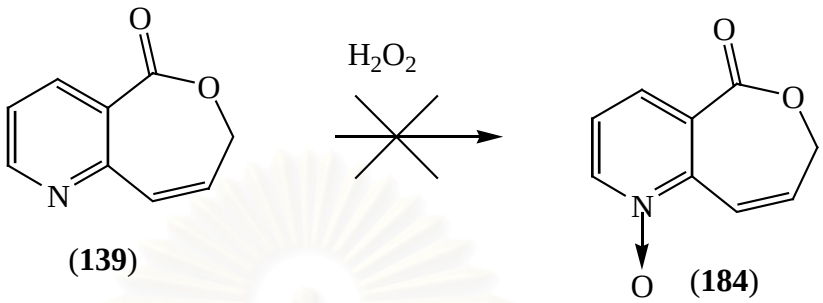
Reiser et. al. reported the asymmetric aminohydroxylation of heteroaromatic acrylates (**Scheme 59**).[63] The N-oxide derivative of the pyridine (**179**) underwent aminohydroxylation to give the regioisomers (**180**) and (**181**). In the pyridine N-oxide, the nitrogen lone pair is blocked and cannot interfere with the hydroxylation process.



Scheme 59 Aminohydroxylation Reaction

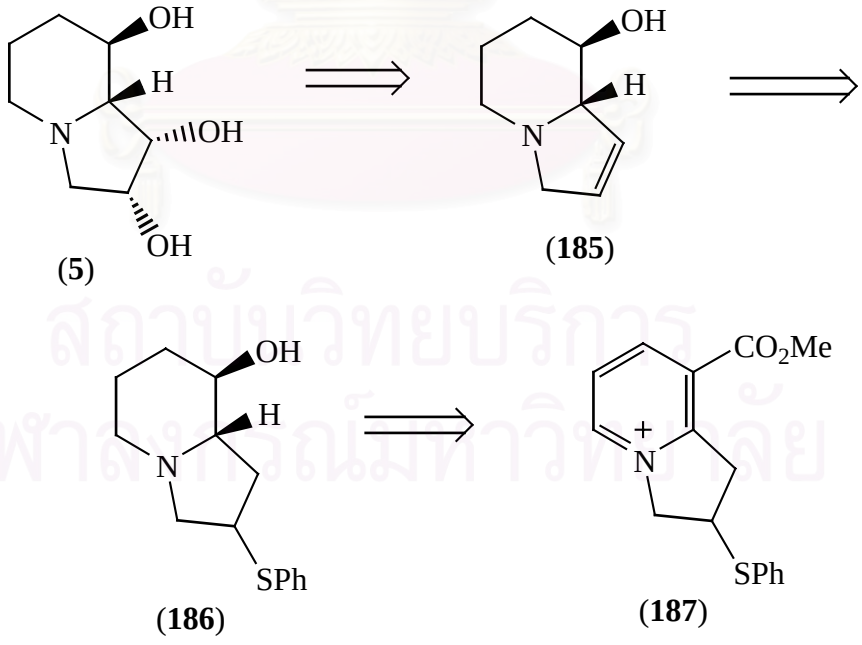
The two common methods to oxidise the pyridine nitrogen to N-oxide are the use of peracids[64] and hydrogen peroxide.[65] As epoxidation might be a competing process with peracids, the reaction with H_2O_2 was selected.

H_2O_2 was added to a solution of the pyridine in acetic acid. The *N*-oxide product was obtained in very low yield (**Scheme 60**). When dioxane was used as the solvent, starting material was recovered.



Scheme 60 The Attempted Synthesis of the *N*-Oxide

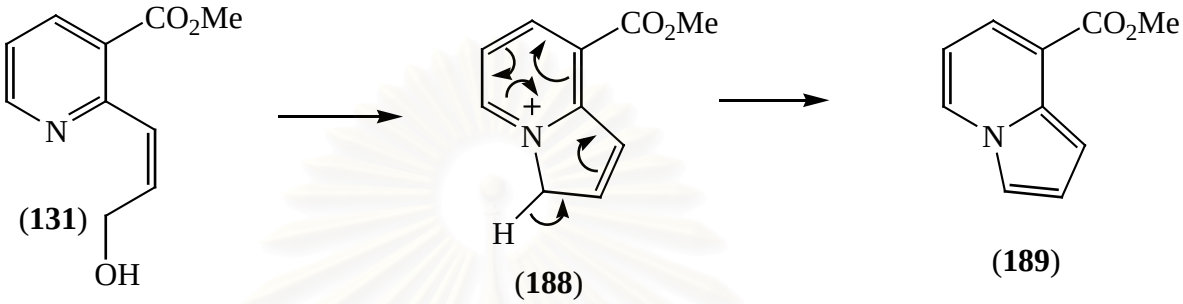
We turned our attention to reduction of the bicyclic pyridinium salt (**187**) before dihydroxylation (**Scheme 61**). We expected that after the series of reductions, the formation of a cyclic olefin (**185**) and then dihydroxylation would give the desired product.



Scheme 61 Retrosynthesis of the Sulfide Route

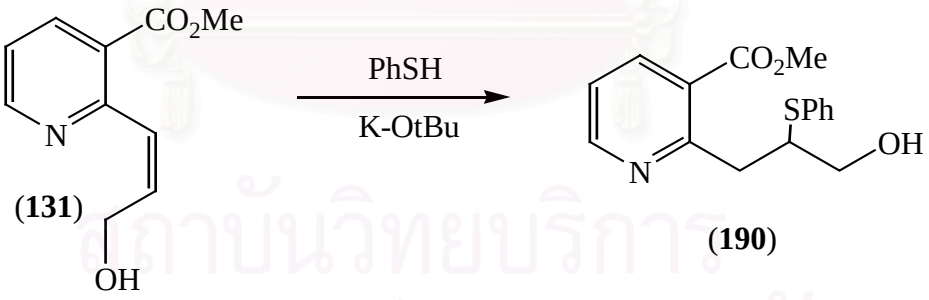
It was deemed necessary to make the alkene after the cyclization procedure as otherwise the pyridium salt (**188**) which would be formed from the allylic alcohol (**131**) could aromatize to give the indolizine (**189**) (**Scheme 62**).

It was planned to use a sulfur group to mask the alkene as subsequent elimination might be achieved by pyrolysis of the sulfoxide.



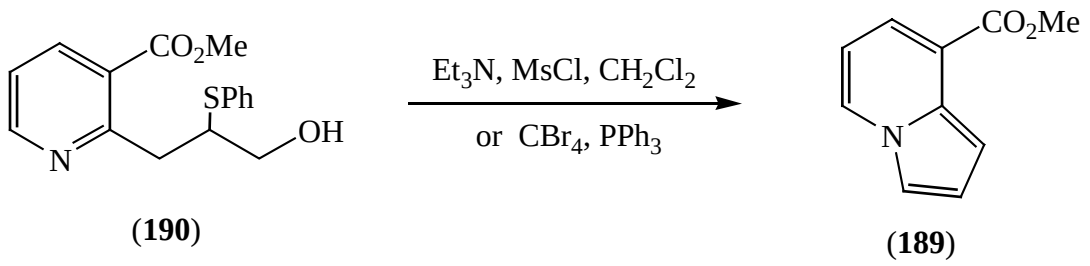
Scheme 62 Isomerization of the Pyridinium Salt to the Indolizine

Nucleophilic addition of thiophenol to the cis-double bond gave the substituted side chain (**190**) (**Scheme 63**). The product was obtained in very high yield and the rapidity of the reaction confirmed the very electron-poor nature of the alkene.



Scheme 63 Nucleophilic Addition of Thiophenol to the cis-Double Bond

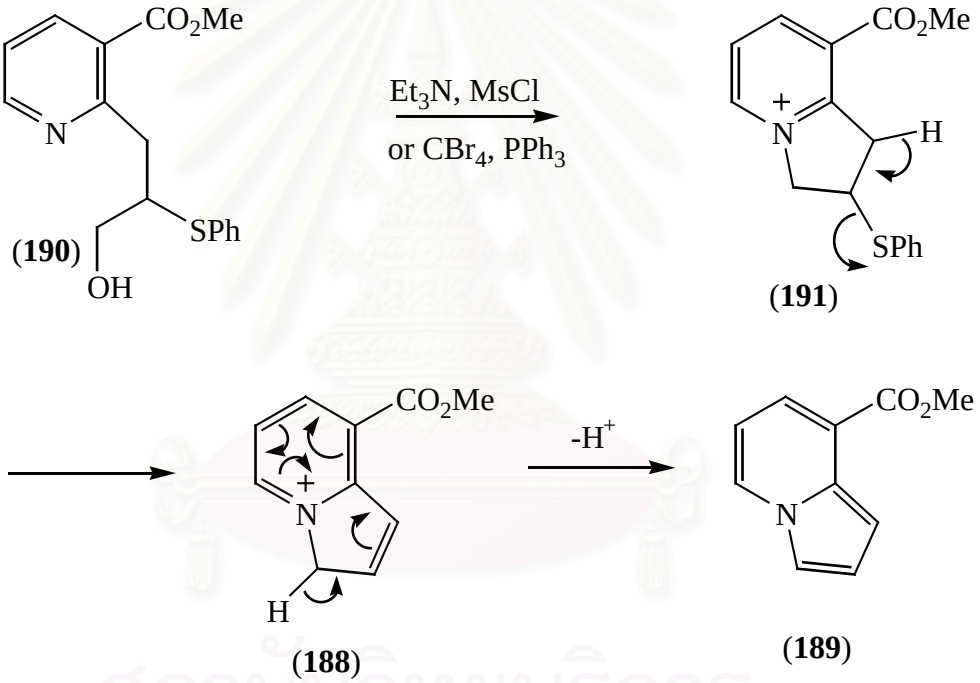
Attempts to make the bicyclic pyridinium salt using Ciufolini's method instead gave a product to which the indolizine structure (**189**) could be assigned (**Scheme 64**). Changing to neutral conditions, using CBr_4 and PPh_3, gave the same product.



(**190**) (**189**)

Scheme 64 The Undesired Product from Cyclization

It is likely that the expected pyridinium salt (**191**) is formed, but the high acidity of the α-proton of the pyridinium salt results in rapid elimination of thiophenol, followed by loss of a proton (**Scheme 65**).



(**190**) (**191**) (**188**) (**189**)

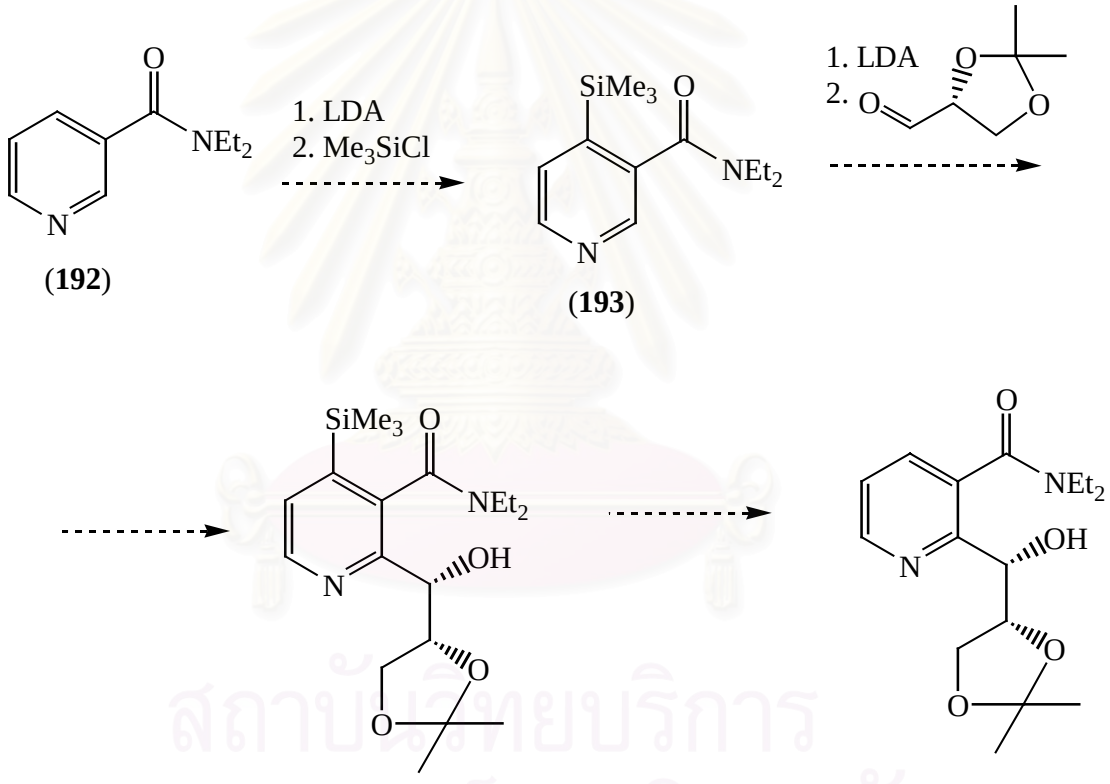
Scheme 65 Proposed Elimination Mechanism to the Indolizine

Changing the sulfide to another group to overcome the elimination problem might be possible but elimination is ultimately essential and might be difficult without sulfur.

Future work

An alternative method for making a monocyclic precursor for swainsonine could by the lithiation of an N, N-dialkylnicotinamide (**192**) (**Scheme 66**).[66]

It is known that lithiation in the 4-position is favored. This can be blocked by silylation. Lithiation should then proceed in the 2-position, allowing quenching with a highly functionized aldehyde such as the readily available acetonide of glyceraldehyde.[67]



(**192**) (**193**) (**194**) (**195**)

Scheme 66 Lithiation Chemistry to form a Monocyclic Precursor for Swainsonine

CHAPTER III

CONCLUSION

A successful synthesis of tashiromine with the desired relative stereochemistry demonstrates that the stereoelectronic effect can be used effectively to control stereochemistry. Tashiromine can be synthesized by the exclusive axial hydride delivery to one face of the iminium ion. This resulted in the more stable chair like transition state which leads to the product which has hydrogens in trans diaxial positions.

For swainsonine, the same strategy for synthesis was proposed. Attempts to make precursor for the bicyclic pyridinium intermediate were unsuccessful. However, these studies led to some interesting results concerning coupling reactions of halopyridines, control of Lindlar reduction, Michael additions and indolizine formation.

CHAPTER V

EXPERIMENTAL

Dioxane, THF and DME were purified by distillation from Na/benzophenone; dichloromethane was distilled from CaH_2; triethylamine was distilled from KOH; methanol was heated at reflux over, then distilled from Mg. NMR spectra were recorded on a Varian Gemini 2000 at 200 MHz (^{1}H) or 50 MHz (^{13}C) in $CDCl_3$ using Me_4Si or $CHCl_3$ as an internal reference. Coupling constants (*J*) are in Hz. IR spectra were recorded on a Perkin Elmer 1760X spectrometer. Mass spectra were recorded on a Finnigan Polaris and a Finnigan MAT in the EI mode.

Palladium catalysts[68] and tin reagents (**115**)[69] and (**84**)[56, 57] were prepared by literature data.

Tashiromine

Pyridyl alkyne (**115**)

(a) A mixture of methyl 2-chloronicotinate (**116**) (2.66 g, 15.4 mmole), stannane (**117**) (3 g, 6.99 mmole) and bis(triphenylphosphine) palladium dichloride (123 mg, 0.18 mmole) in dioxane (8 cm^3) was heated at reflux under nitrogen for 1 hour. The mixture was cooled to room temperature and treated with an excess of saturated aqueous potassium fluoride. The precipitated tributyltin flouride polymer was removed by filtration through celite, washing with ethyl acetate. The solvents were evaporated and the residue was purified by flash chromatography on silica gel (24 g) eluting with 15 and 25 % ethyl acetate/ hexane to give the pyridyl alkyne (**115**) (3.66 g, 86 %) as an oil. Found: C 65.4, H 6.2, N 5.0. $C_{15}H_{17}NO_4$ requires C 65.4, H 6.2, N 5.1%; ν /cm^{-1}: 2943, 2865, 2236, 1729; ^{1}H 8.71 (1H, dd, *J* 5,2, ArH), 8.23 (1H, dd, *J* 8,2, ArH), 7.33 (1H, dd, *J* 5,8, ArH), 5.05 (1H, m, OCHO), 4.62 (2H, s, CH_2O), 3.98 (3H, s, OMe), 3.90 (1H, m, CH), 3.60 (1H, m, CH), 1.5 - 1.9 (6H, m, $(CH_2)_3$); ^{13}C 165.2, 152.3, 142.0, 138.0, 131.9, 128.4, 122.4, 96.6, 90.6, 84.0, 54.4, 52.4, 30.1, 25.3, 18.9; m/z (EI) 174 (100%), 160 (26), 85 (53).

(b) A mixture of methyl 2-chloronicotinate (**116**) (2 g, 11.67 mmole), potassium carbonate (4.04 g, 29.18 mmole), copper (I) iodide (88 mg, 0.47 mmole) and palladium on carbon (10%, 618 mg) in DME (40 cm^3) were stirred for thirty minutes under nitrogen. A solution of the alkyne (**118**) (4.08 g, 29.18 mmole) in DME (10 cm^3) was then added. The mixture was heated at reflux overnight, then cooled, filtered through celite, washed with ethyl acetate, and concentrated. The residue was purified by flash chromatography on silica gel (90 g) eluting with 30% ethyl acetate/ hexane to give the alkyne (**115**) (2.71 g, 83%)

Pyridyl alkane (**119**)

The pyridyl alkyne (**115**) (710 mg, 2.58 mmole) was taken up in methanol (15 cm^3) and stirred under hydrogen (balloon) in the presence of a 10% Pd/C catalyst (71 mg) for 3 hours. The mixture was flushed with nitrogen and filtered through celite. Evaporation of the solvent gave the crude pyridine (**119**) as an oil (722 mg, 99 %) which was used without further purification. ν /cm^{-1}: 2943, 2865, 1724; ^{1}H 8.61 (1H, dd, *J* 5,2, ArH), 8.13 (1H, dd, *J* 7,2, ArH), 7.19 (1H, dd, *J* 7,5, ArH), 4.57 (1H, t, *J* 3, OCHO), 3.88 (3H, s, OMe), 3.80 (2H, m, OCH_2), 3.45 (3H, m, OCH_2CH), 3.23 (2H, m, CH_2), 2.05 (2H, m, CH_2), 1.45-2.00 (6H, m, $(CH_2)_3$); ^{13}C 165.2, 152.3, 142.0, 138.0, 131.9, 128.4, 122.4, 96.6, 90.6, 84.0, 54.4, 52.4, 30.1, 25.3, 18.9; m/z: 194 (29%), 178 (100), 164 (9), 151 (29).

Pyridyl propanol (**114**)

p-Tosic acid (500 mg, 2.9 mmole) was added to a solution of the pyridine (**119**) (544 mg, 1.95 mmole) in dry methanol (40 cm^3). After 40 minutes the mixture was neutralised with aqueous sodium carbonate and extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by flash chromatography on silica gel (16 g), eluting with 30 and 60 % ethyl acetate/ hexane to give the alcohol (**114**) as an oil (294 mg, 77 %). ν /cm^{-1}: 3377, 2943, 2865, 1724; ^{1}H 8.64 (1H, dd, *J* 5,2, ArH), 8.20 (1H, dd, *J* 8,2, ArH), 7.23 (1H, dd, *J* 5,8, ArH), 3.95 (3H, s, OMe), 3.66 (2H, t, *J* 6, OCH_2), 3.32 (2H, t, *J* 7, CH_2), 2.05 (2H, m, CH_2); ^{13}C 165.2, 152.3,

142.0, 138.0, 131.9, 128.4, 122.4, 96.6, 90.6, 84.0, 54.4, 52.4, 30.1, 25.3, 18.9; m/z (EI): 196 (26%, M^+), 178 (23), 164 (29), 151 (97), 136 (25), 93 (100); exact mass 195.089959, $C_{10}H_{13}NO_2$ requires 195.089543.

Indolizidine ester (**122**)

Mesyl chloride (195 μL, 1.28 mmole) was added dropwise to a solution of the alcohol (**114**) (250 mg, 1.28 mmole) and triethylamine (473 μL, 3.42 mmole) in dichloromethane (20 cm^3) at 0°C. The mixture was stirred for 30 minutes, then the volatiles were evaporated under reduced pressure and the residue was taken up in dry methanol (15 cm^3). Sodium cyanoborohydride (209 mg, 3.33 mmole) was added and the mixture was stirred for 3 hrs. Bromocresol green was added and over the next 3 hours the mixture was maintained at *ca* pH 4 by gradual addition of a solution of hydrogen chloride in methanol (2 M, generated by cautious addition of acetyl chloride to methanol). After 3 hrs, the solution remained permanently acidic and the solvents were then removed under reduced pressure. The residue was neutralised with aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (10 g) eluting with 2% methanol/ chloroform to give the indolizidine ester (**122**) as an oil (155 mg, 66%). ^{1}H: 3.62 (3H, s, OMe), 3.05 (2H, m, CH), 1.4-2.4 (12H, m, CH); ^{13}C: 172.3, 65.3, 54.1, 52.3, 51.7, 47.8, 29.2, 28.2, 24.7, 20.5; m/z (EI) 183 (20%, M^+), 182 (20), 152 (11), 124 (29), 96 (100).

(±)-Tashiromine (**39**)

Lithium aluminium hydride (115 mg, 3.03 mmole) was added to a solution of the indolizidine ester (**122**) (109 mg, 0.60 mmole) in anhydrous THF (5 cm^3) at 0°C. The reaction mixture was stirred at room temperature for one hr. Excess hydride was then cautiously quenched with a little water. The precipitated white solids were removed by filtration, washing thoroughly with ethyl acetate. Evaporation of the volatiles gave tashiromine (**39**) as an oil (88 mg, 96 %). ν /cm^{-1}: 3403, 2924, 2859, 2789; ^{1}H: 4.5 (1H, br s, OH), 3.59 (1H, dd, *J* 6,11, C<u>H</u>HOH), 3.47 (1H, dd, *J* 6,11, C<u>H</u>HOH), 3.25

(1H, m, CH), 1.5-2.6 (13H, m, CH); ^{13}C: 66.4, 64.0, 52.8, 51.6, 42.5, 27.7, 26.5, 23.5, 19.9; m/z (EI) 155 (37%, M^+), 154 (47), 138 (54), 124 (45), 96 (100), 84 (60); exact mass 155.131025, $C_9H_{17}NO$ requires 155.131014.

Swainsonine

Hydroxy alkyne (**130**)

A catalytic amount of tosic acid was added to a stirred solution of the alkyne (**115**) (500 mg, 1.8 mmol) in methanol (5 cm^3). The solution was stirred for 2 hours, neutralized with aqueous sodium hydrogen carbonate. Methanol was removed by evaporation and the residue was extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by flash chromatography on silica gel (10 g) eluting with 50% ethyl acetate-hexane to give the alcohol (**130**) as a solid (240 mg, 70%). Found : C 62.9, H 4.7, N 7.3, $C_{10}H_9NO_3$ requires C 62.8, H 4.7, N 7.3 %; ν /cm^{-1}: 3206, 2920, 2847, 2224, 1734; ^{1}H: 8.75 (1H, dd, *J* 2,5, ArH), 8.25 (1H, dd, *J* 2,8, ArH), 7.34 (1H, dd, *J* 5,8, ArH), 4.59 (2H, d, 6, CH_2O), 3.96 (3H, s, OMe); ^{13}C: 165.2, 152.5, 142.2, 138.2, 128.1, 122.5, 93.3, 83.7, 52.6, 51.4; m/z (EI) 192 (28%, $M+H^+$), 148 (100); m.p. 94.1-95.0 ^{o}C.

Cis-alcohol (**131**)

DABCO (81 mg, 0.79 mmole) and Lindlar's catalyst (4 mg, 4wt%) were added to a solution of the alkyne (**130**) (100 mg, 0.52 mmole) in DMF (2 cm^3) under N_2. The reaction flask was purged with H_2, then stirred under a hydrogen atmosphere for 4 hours and 30 minutes. The solution was filtered through celite and evaporated. DMF was removed by distillation under reduced pressure. The residue was purified by flash chromatography on silica gel (3 g) eluting with 10% and 30 % ethyl acetate-hexane to give the alcohol (**131**) as a solid (74 mg, 74%). Found: C 62.2, H 5.8, N 7.3, $C_{10}H_{11}NO_3$ requires C 62.2, H 5.7, N 7.3 %; ν /cm^{-1}: 3261, 1718; ^{1}H: 8.66 (1H, dd, *J* 2,5, ArH), 8.22 (1H, dd, *J* 2,8, ArH), 7.50 (1H, d, *J* 12, CH=), 7.26 (1H, d, *J* 5,8, ArH), 6.37 (1H, dt, *J* 12,7, CH=), 5.56 (1H, s, OH), 4.22 (2H, s, CH_2O), 3.90 (3H, s,

OMe); ^{13}C: 166.4, 155.1, 150.9, 139.2, 137.6, 129.6, 125.8, 121.6, 58.5, 52.6; m/z (EI) 194 (10%, $M+H^+$), 164 (100), 132 (82), 104 (85); m.p. 76.6-77.0 ^{o}C.

Indolizine (**144**)

A solution of the alkyne (**115**) (100 mg, 0.36 mmole) and sodium methoxide (5mg, 25 mol%) in methanol (4 cm^3) was heated at reflux overnight protected from moisture by a drying tube. It was neutralized with pH7 buffer and extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was purified by flash chromatography on silica gel (10 g) eluting with 20% ethyl acetate-hexane to give the indolizine as an oil (**144**) (25 mg, 20%). ν /cm^{-1}: 2942, 2849, 1718; ^{1}H: 7.96 (1H, d, *J* 7, ArH), 7.40 (1H, d, *J* 7, ArH), 6.90 (1H, d, *J* 4, ArH), 6.46 (1H, t, *J* 7, ArH), 6.34 (1H, d, *J* 4, ArH), 5.75 (1H, m, OCHO), 3.91 (3H, s, OMe), 3.90 (1H, m, OCH), 3.65 (1H, m, OCH), 2.10-1.20 (6H, m, CH_2); ^{13}C: 166.4, 137.2, 124.1, 122.1, 121.3, 120.5, 108.1, 100.2, 98.4, 96.8, 62.3, 53.4, 51.9, 30.2, 25.0, 18.6; m/z (EI) 276 (44%, $M+H^+$), 191 (100), 133 (16).

Alkenyl sulfide (**149**)

Thiophenol (37 μl, 0.36 mmole) was added to a solution of potassium tertiary butoxide (40.3 mg, 0.36 mmole) in methanol (1 cm^3). The solution was stirred for 1 hour, then it was added to a solution of the alkyne (**115**) (100 mg, 0.36 mmole) in methanol (1 cm^3) by cannula. The mixture was allowed to stir for about 15 hours, then it was neutralized with pH7 buffer and extracted with ethyl acetate. The combined organic layers were dried and evaporated. The residue was purified by flash chromatography on silica gel (4.5 g) eluting with 5% ethyl acetate-hexane to give the sulfide (**149**) as a yellow oil (118 mg, 86%).ν /cm^{-1} : 3051, 2948, 2863, 1724; ^{1}H 8.81 (1H, dd, *J* 5,2, ArH), 8.22 (1H, dd, *J* 8,2, ArH), 7.72 (1H, s, ArH), 7.53 (2H, m, ArH), 7.30 (3H, m ArH), 7.20 (1H,dd, *J* 8,5, ArH), 4.45 (1H, t, *J* 3, OCHO), 4.15 (2H, ddd, *J* 30,14,1, OCH_2), 3.92 (3H, s, OMe), 3.72 (1H, m, OCH), 3.44 (1H, m, OCH), 1.60 (6H, m, CH_2).

Methyl 2-viylnicotinate (**156**)

A solution of tri-n-butyl vinyl tin in dioxane (800mg, 2.5 mmole) was transferred to a flask containing the chloro pyridine (**116**) (289 mg, 1.68 mmole) in dioxane (10 cm^3) by cannula. Bis-triphenylphosphine dichloride (59 mg, 5 mol%) was added. The mixture was heated at reflux overnight under N_2, then cooled to room temperature. Aqueous potassium fluoride was added to the mixture. The reaction was further stirred for 30 minutes, then filtered through celite. The filtrate was extracted with ethyl acetate. The combined organic layer was dried and evaporated. The residue was purified by flash chromatography on silica gel (10 g) eluting with 2 % and 5% ethyl acetate-hexane to give the vinyl pyridine (**156**) as an oil (185 mg, 77%). ν /cm^{-1}: 2953, 1718, 1626; ^{1}H: 8.63(1H, dd, *J* 5,2, ArH), 8.09 (1H, dd, *J* 8,2, ArH), 7.58 (1H, dd, *J* 17,11, =CH), 7.18 (1H, dd, *J* 8,5, ArH), 6.45 (1H, dd, *J* 17,2, =CH), 5.52 (1H, dd, *J* 11,2, =CH), 3.84 (3H, s, OMe); ^{13}C: 166.7, 155.0, 152.0, 138.3, 133.6, 124.0, 121.8, 121.4, 52.3; m/z (EI) 163 (25%, M^+), 148 (100), 132 (17), 104 (28); exact mass 163.0629350, $C_9H_9NO_2$ requires 163.0633285.

Allyl 2-vinyl nicotinate (**157**)

Lithium hydroxide monohydrate (26 mg, 0.61 mmole) was added to a solution of the vinyl pyridine (**156**) (100 mg, 0.61 mmole) in THF (2 cm^3). Water was added (a few drops) to dissolve the salt. The mixture was stirred for 1 hour, then evaporated. Toluene was added to the residue and then removed under reduced pressure to remove the rest of water. DMF (2 cm^3) and allyl bromide (42 μl, 0.49 mmole) were added to the solid under N_2. The mixture was stirred overnight, washed with water and extracted with ethyl acetate. The combined organic layers were evaporated and the residue was taken up in hexane and washed with water. The hexane layer was dried and evaporated. The residue was purified by flash chromatography on silica gel (3 g) eluting with 3 % ethyl acetate-hexane to give the allyl ester (**157**) as an oil (88 mg, 95%). ν /cm^{-1}: 2951, 1724, 1650; ^{1}H: 8.71 (1H, dd, *J* 5,2, ArH), 8.19 (1H, dd, *J* 8,2, ArH), 7.62 (1H, dd, *J* 17,11, =CH), 7.25 (1H, dd, 8,5, ArH), 6.50 (1H, dd, 17,2, =CH), 6.02 (1H, ddt, *J* 17,10,6, =CH), 5.60 (1H, dd, *J* 2,11, =CH), 5.42 (1H, dq, *J* 17,1, =CH), 5.36 (1H, dq, *J* 17,1, =CH), 4.83 (2H, dt, *J* 6,1, =CH); ^{13}C: 165.9, 155.0,

152.0, 138.3, 133.7, 131.6, 124.1, 121.8, 121.5, 118.8, 66.0; m/z (EI) 190 (100%, M^+); exact mass 189.080040, $C_{11}H_{11}NO_2$ requires 189.07898.

Methyl 2-hydroxynicotinate (**171**)

DBU (118 μl, 0.79 mmol) was added to a solution of the hydroxy acid (**170**) (100 mg, 0.72 mmol) in acetonitrile (2 cm^3). This was stirred for 5 minutes. Methyl iodide (49 μl, 0.79 mmol) was added and the reaction mixture was stirred overnight. The mixture was acidified with aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried and evaporated to give the ester (**171**) as white crystals (83 mg, 81%). Found: C 55.0, H 4.6, N 9.2, $C_7H_7NO_3$ requires C 54.9, H 4.6, N 9.2 %;ν /cm^{-1}: 3430, 3067, 1734; ^{1}H: 14.25 (1H, s, OH), 8.50 (1H, dd, *J* 7,2, ArH), 7.68 (1H, dd, *J* 7,2, ArH), 6.55 (1H, t, 7, ArH), 3.66 (3H, s, OMe); ^{13}C: 165.2, 164.4, 145.5, 142.1, 118.2, 108.1, 38.3; m/z (EI) 154 (15%, $M+H^+$), 109(75), 80(100); m.p. 185.4-186.9 ^{o}C.

Lactone (**139**)

Potassium tertiary butoxide (cat.) was added to a solution of the cis-alkene (**131**) (307 mg, 1.59 mmole) in THF (4 cm^3) under N_2. The reaction was allowed to stir at room temperature for 4 hours. The mixture was neutralized with pH7 buffer and extracted with ethyl acetate. The combined organic layers were dried and evaporated. The residue was purified by flash chromatography on silica gel (15g) eluting with 30% and 50 % ethyl acetate-hexane to give the lactone (**139**) as a solid (199 mg, 77%). Found: C 67.1; H 4.3; N 8.8, $C_9H_7NO_2$ requires C 67.1, H 4.4, N 8.7 %; ν /cm^{-1}: 3097, 3047, 1708, 1580; ^{1}H: 8.78 (1H, dd, *J* 5,2, ArH), 8.32 (1H, dd, *J* 8,2, ArH), 7.36 (1H, dd, *J* 8,5, ArH), 7.10 (1H, d, *J* 11, $=CH_2$), 6.64 (1H, dt, *J* 7,11, $=CH_2$), 4.54 (2H, d, *J* 7, CH_2O); ^{13}C: 168.7, 152.8, 152.4, 140.5, 138.1, 131.3, 127.4, 122.6, 62.2; m/z (EI) 162 (100%, $M+H^+$), 144 (93), 105 (60); m.p. 57.7-58.4 ^{o}C.

Methyl 2- (3'-hydroxy-2'-phenylthio-1'-propyl) nicotinate (**190**)

Thiophenol (309 μl, 3 mmole) was added to a solution of the alkene (**131**) (580 mg, 3 mmole) in methanol (5 cm^3). A catalytic amount of potassium tertiary butoxide was added. The solution was stirred under N_2 at room temperature for 2 hours. Then, the mixture was neutralized by pH7 buffer and extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was purified by flash chromatography on silica gel (15g) eluting with 40 % ethyl acetate-hexane to give the hydroxy sufide (**190**) as a solid (741 mg, 82%). Found: C 63.5, H 5.3, N 5.1, $C_{16}H_{17}NO_3S$ requires C 63.4, H 5.7, N 4.6 %; ν/cm^{-1}: 3199, 2947, 1729; ^{1}H: 8.64 (1H, dd, *J* 5,2, ArH), 8.18 (1H, dd, *J* 8,2, ArH), 7.43 (2H, m, ArH), 7.25 (4H, m, ArH), 3.84 (3H, s, OMe), 3.63 (5H, m, CH_2O); ^{13}C: 166.8, 159.5, 151.5, 138.7, 134.2, 132.0, 128.8, 127.0, 126.4, 121.5, 63.6, 52.5, 50.7, 37.9; m/z (EI) 304 (16%, $M+H^+$), 286 (63), 252 (100) ; m.p. 77.1-77.4 ^oC.

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