



**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**SYNTHESIS OF PIPERIDINE NATURAL
PRODUCTS BY ALLENIC CYCLISATION**

LIM CHIA JUAN

**SCHOOL OF PHYSICAL AND MATHEMATICAL
SCIENCES**

**DIVISION OF CHEMISTRY AND
BIOLOGICAL CHEMISTRY**

2013

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A thesis submitted to the Nanyang Technological University
In partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2013

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A.1 Selected NMR Spectra

A.2 Chiral HPLC Data

ABSTRACT

The various strategies for the synthesis of Nuphar alkaloids that have been reported to date are reviewed.

Earlier applications of silver catalysed cyclisation of allenic hydroxylamines are discussed. The synthesis of four Nuphar alkaloids using allenic hydroxylamine cyclisation is discussed. The allenic alcohol precursor is obtained in optically active form using an enzymatic resolution procedure, optimised by DOE methods. The cyclisation reaction is found to be highly dependant on the specific silver salt employed and also on the presence of moisture. The side chains required for the unnamed Nuphar indolizidine and Nupharamine are introduced by cross metathesis. The side chain for (-)-deoxynupharidine and Castoramine are introduced by cross metathesis, followed by a subsequent stereoselective alkylation.

The previous synthesis of Cernuine is discussed. Preliminary studies for the formation of 1,3-diamines *via* N-N tethered allenic cyclisation or Michael addition are discussed. A potential precursor for the preparation of the 1,3-diamine moiety in the total synthesis of Cernuine using Denmark's carbonylation and Feringa's methylation is described.

PUBLICATIONS

Bates, R. W., **Lim, C. J.** Synthesis of Two Nuphar Alkaloids by Allenic Cyclisation, *Synlett*, **2010**, 866

POSTER PRESENTATION

Chia Juan Lim, Roderick W. Bates* Synthesis of Nuphar Alkaloids. 22nd International Symposium: Synthesis in Organic Chemistry, University of Cambridge, UK. Poster Presentation 11-14th July 2011

Chia Juan Lim, Roderick W. Bates* Asymmetric Synthesis of Nuphar Alkaloids. 13th Belgian Organic Synthesis Symposium (BOSS XIII), Leuven, Belgium. Poster Presentation 15-20th July 2012

ABBREVIATION

Å	angstrom unit
Ac	acetyl
Acac	acetylacetonate
ADDP	1,1'-(azodicarbonyl)dipiperidine
AIBN	Azobisisobutyronitrile
App	apparent
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino-1,1'- binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOM	Benzyloxymethyl
br	Broad
b.p.	boiling point
Bz	benzoyl
Calcd.	calculated
CBS	Corey-Bakshi-Shibata reagent
Cbz	benzyloxycarbonyl
COSY	correlated spectroscopy
conc.	concentrated
CSA	camphorsulfonic acid
Cy	Cyclohexyl

d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DOE	Design of Experiments
DPPP	1,3-bis(diphenylphosphino)propane
dr	diastereoisomeric ratio
EDA	ethylenediamine
EDCI	<i>N</i> -Ethyl- <i>N'</i> - (3-dimethylaminopropyl)carbodiimide
e.e.	enantiomeric excess
eq.	equivalent
Et	ethyl
GC	Gas chromatography
HMPA	Hexamethylphosphoramide
hr	hour
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry

<i>i</i>	iso
IBX	2-iodoxybenzoic acid
IR	Infra-red spectroscopy
<i>J</i>	Coupling constant
LDA	Lithium diisopropylamide
LiHMDS	Lithium Hexamethyldisilazane
Lit.	Literature
m	Multiplet
mCPBA	3-Chloroperoxybenzoic acid
Me	methyl
m.p.	melting point
MS	mass spectrometry
Ms	mesyl
MTBE	Methyl <i>tert</i> -butyl ether
NaHMDS	Sodium Hexamethyldisilazane
NMR	Nuclear magnetic resonance
<i>n</i> -Bu	butyl
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Pr	propyl
N.D.	Not Determined
Nosyl	2-nitrobenzenesulfony
Nu	Nucleophile(s)
<i>p</i>	para
PG	Protecting group(s)

Ph	phenyl
Phth	phthaloyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
Py.	pyridine
q	quartet
quant.	quantitative
R	undefined alkyl or aryl group
r.t.	room temperature
RCM	ring closing metathesis
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride
S	singlet
sat.	saturated
T	triplet
TBDMS/TBS	<i>tert</i> -butyldimethylsilyl
<i>tert</i>	tertiary
TBAF	Tetrabutylammonium fluoride
Tf	Trifyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	Tetrahydropyran
TIPS	triisopropylsilyl

TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMG	tetramethylguanidine
TMS	trimethylsilyl
Ts	Tosyl

CHAPTER 1: REVIEW

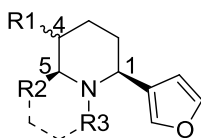
Nuphar Alkaloids, Interesting Targets of Synthesis

Nuphar Alkaloids: Interesting Targets of Synthesis

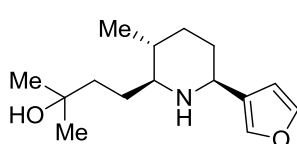
Introduction

Nuphar alkaloids constitute a group of alkaloids that have been isolated from plants of the genus *Nuphar*, such as *Nuphar Japonica*, *Nuphar Japonicum*, *Nuphar Luteum*, *Nuphar Pumilium* and many more. Plants of genus *nuphar* are commonly known as water lilies. Surprisingly, a few of the Nuphar alkaloids can be extracted from the dried scent glands of the Canadian beaver (*Castor Fiber*).¹ It has been speculated that the nuphar alkaloids were generated as metabolism products of alkaloids from nuphar species consumed by the beavers through their diet but no experimental demonstration has been done so far.² In recent studies, several of the nuphar alkaloids showed biological activities such as immunosuppressive activity, in which inhibition of anti-sheep erythrocyte plaque forming cell formation was observed in mouse splenocytes.^{3a} Several nuphar alkaloids showed insecticidal activity against larvae and adult *Drosophila melanogaster*.^{3b} Nuphar alkaloids, especially the dimeric sesquiterpene thioalkaloids extracted from *Nuphar Pumilium*, showed apoptosis-inducing activity on human leukemia cells (U973)⁴ and anti-metastatic activity on lung tumors in mice.⁵ Nuphar alkaloids have been a popular synthetic target mainly due to their unique and interesting structure as well as the stereochemical challenge. Several reviews on nuphar alkaloids have been published so far focusing mainly on isolation, elucidation of structure and also with brief discussion of a few early syntheses.¹ In this review, the synthesis of the nuphar alkaloids will be comprehensively discussed. The general structure of the nuphar alkaloids has a core piperidine ring with a 3-furyl substituent at the C1 position, with a methyl group at the C4 position and different substituents at the C5 position. The nitrogen on the piperidine ring can exist as a secondary amine, an *N*-oxide or a tertiary amine. The substituent at C5 can be either part of another piperidine

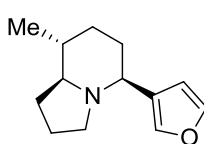
or pyrrolidine ring or be an alkyl chain. There are several nuphar alkaloids that exist as dimers, in which the two monomers are connected by a thiophene derivative such as (-)-neothiobinupharidine.



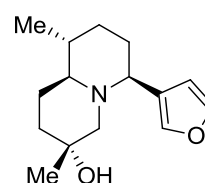
Scheme 1-1 General Structure of Nuphar Alkaloids



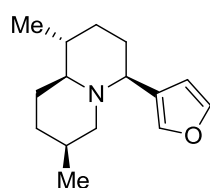
(-)-Nupharamine
1.1



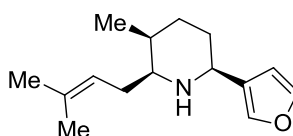
(-)-(5*S*,8*R*,9*S*)-5-(3-Furyl)-
8-methyloctahydroindolizidine
1.2



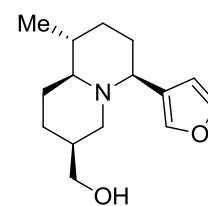
(-)-Nupharolutine
1.3



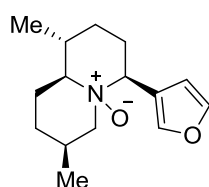
(-)-Deoxynupharidine
1.4



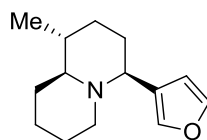
(-)-Nuphenine
1.5



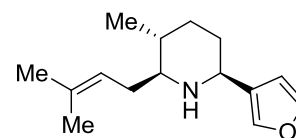
(-)-Castoramine
1.6



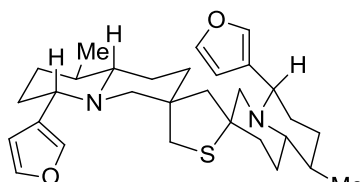
(-)-Nupharidine
1.7



(-)-Demethyldeoxynupharidine
1.8



(-)-Anhydronupharamine
1.9



(-)-Neothiobinupharidine
1.10

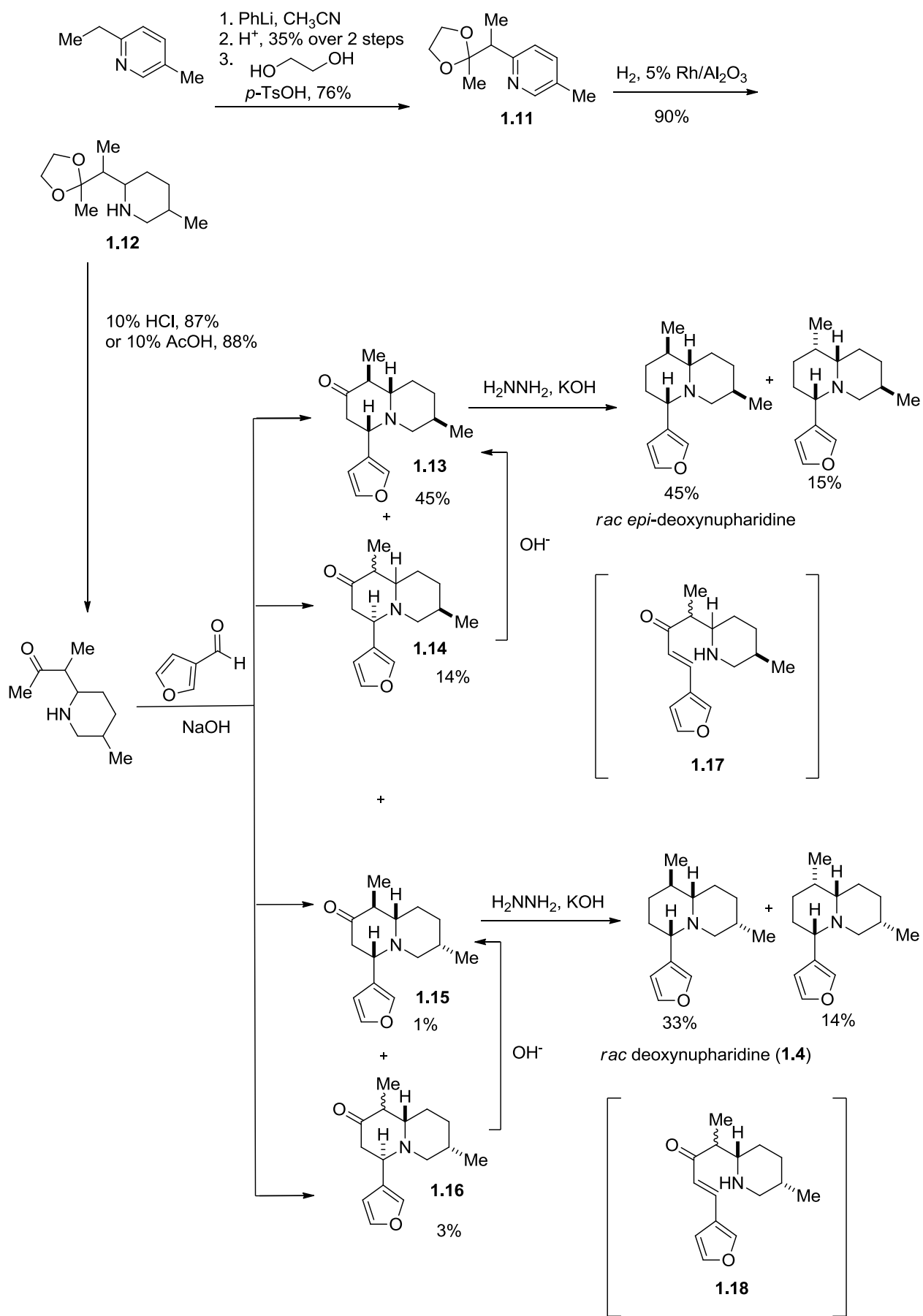
Scheme 1-2 Examples of the nuphar alkaloids as targets of synthesis

Various Strategies for the Synthesis of Nuphar Alkaloids

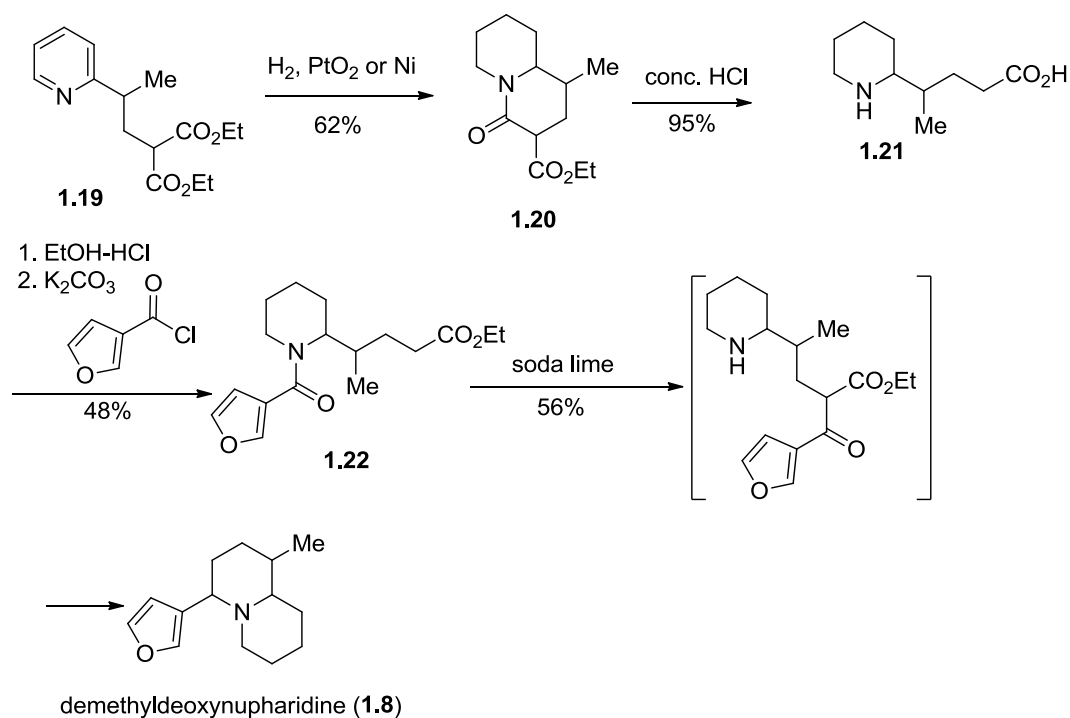
1. Pyridine reduction

Reduction of pyridines is perhaps one of the most straight forward ways to obtain piperidines. However, direct reduction of pyridines often does not give access to piperidines in a stereoselective or asymmetric manner, meaning that a separation of stereoisomers is required. While pyridines may be reduced by several methods including catalytic hydrogenation, Birch reduction and hydride addition, the first of these methods is most commonly used.

Arata and co-workers started their synthesis with 2-ethyl-5-methylpyridine, which was functionalized to pyridine **1.11** and reduced to give piperidine **1.12**, presumably as a mixture of all possible stereoisomers (Scheme 1.3). Piperidine **1.12** underwent deprotection, followed by either tandem aldol-Michael or condensation then Mannich reaction with furfuraldehyde to form a mixture of diastereoisomers. The stereogenic centre at the α -position to the nitrogen on piperidine **1.14** and **1.16** could be equilibrated to the desired epimer **1.13** and **1.15** respectively *via* a retro-Michael reaction which is shown through intermediates **1.17** and **1.18**, but the methyl group could not. Finally, piperidines **1.13** and **1.15** underwent Wolff-Kishner reduction to give racemic deoxynupharidine (**1.4**) and its epimers.⁶ Non selective hydrogenation of the pyridine and poor stereoelectronic control of the cyclisation *via* tandem aldol-Michael or condensation then Mannich reaction led to the formation of diastereomers and an inefficient synthesis of the desired natural product, deoxynupharidine (**1.4**).

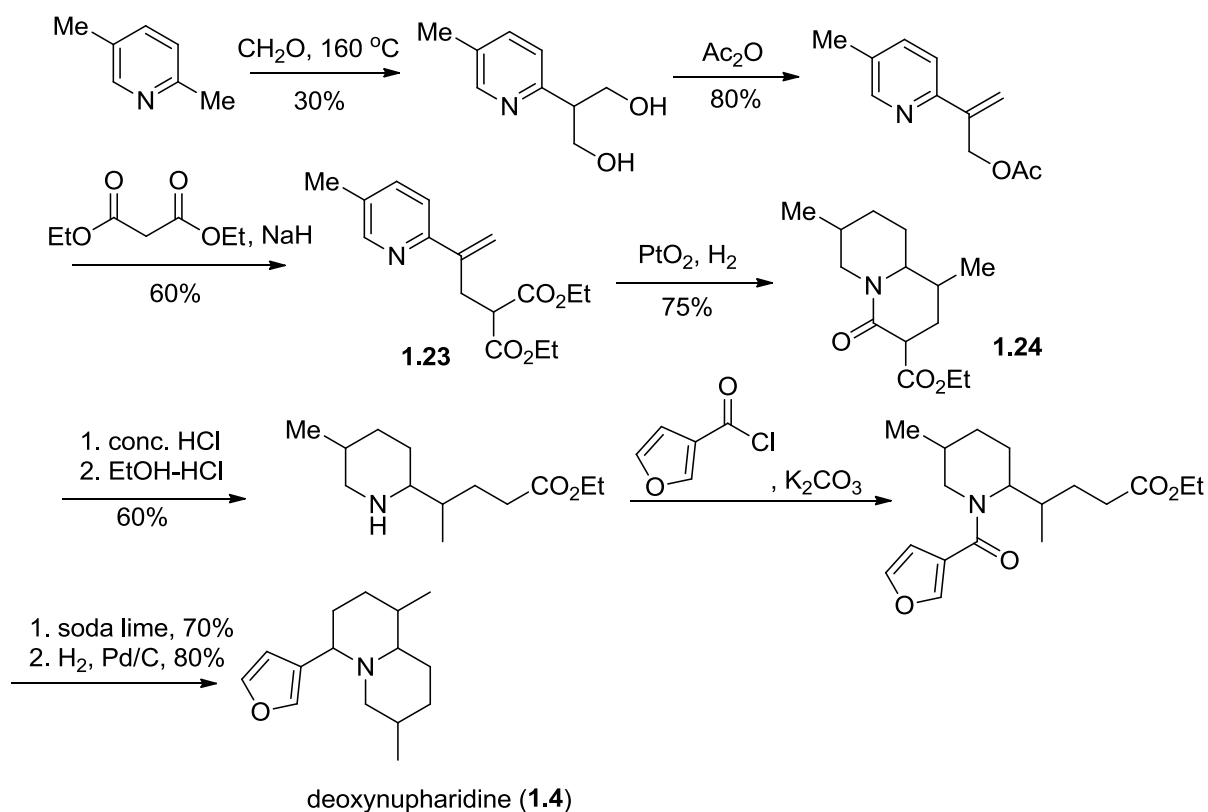


Scheme 1-3



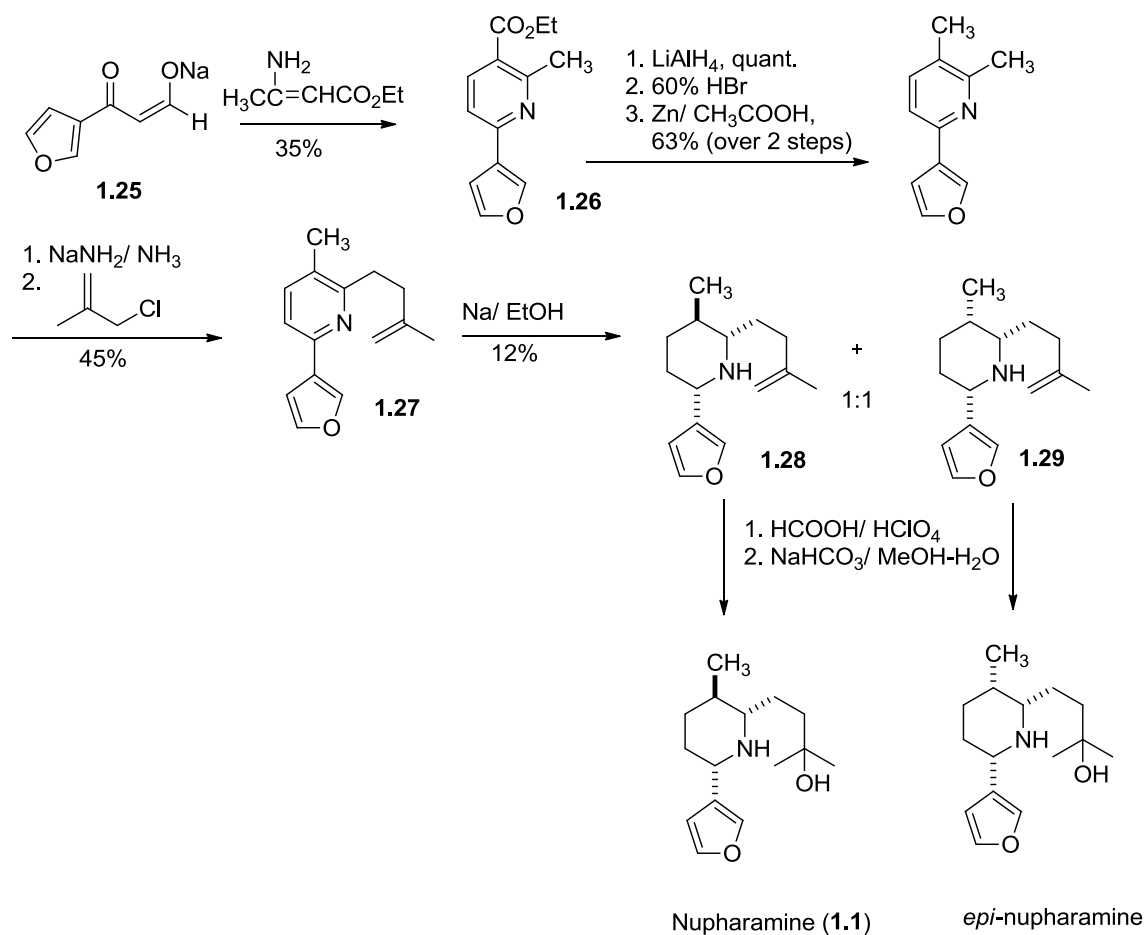
Scheme 1-4

Kaneko and co-workers also synthesised demethyldeoxynupharidine starting with alkylated pyridine **1.19** which was reduced by hydrogenation over PtO_2 or a Ni catalyst to obtain the bicyclic lactam **1.20** presumably as a mixture of diastereomers (Scheme 1.4). Hydrolysis and decarboxylation then gave carboxylic acid **1.21**. Upon esterification and acylation, ester **1.22** was synthesised.⁷ In the presence of soda lime, the carbon α to the ester was deprotonated and underwent *trans* acylation. Subsequently, cyclisation occurred to form a lactam that underwent *in situ* dealkoxy carbonylation and reduction to form demethyldeoxynupharidine (**1.8**) as a diastereomeric mixture.⁸ Kaneko and co-workers had synthesized the racemic diastereomers mixture of demethyeoxynupharidine by short synthetic route of 6 steps with an overall yield of 8%. No issues of stereochemistry were discussed in the report, but it is likely that mixtures were obtained. The identification of the final product was based on the IR spectroscopy comparison of deoxynupharidine (**1.4**).



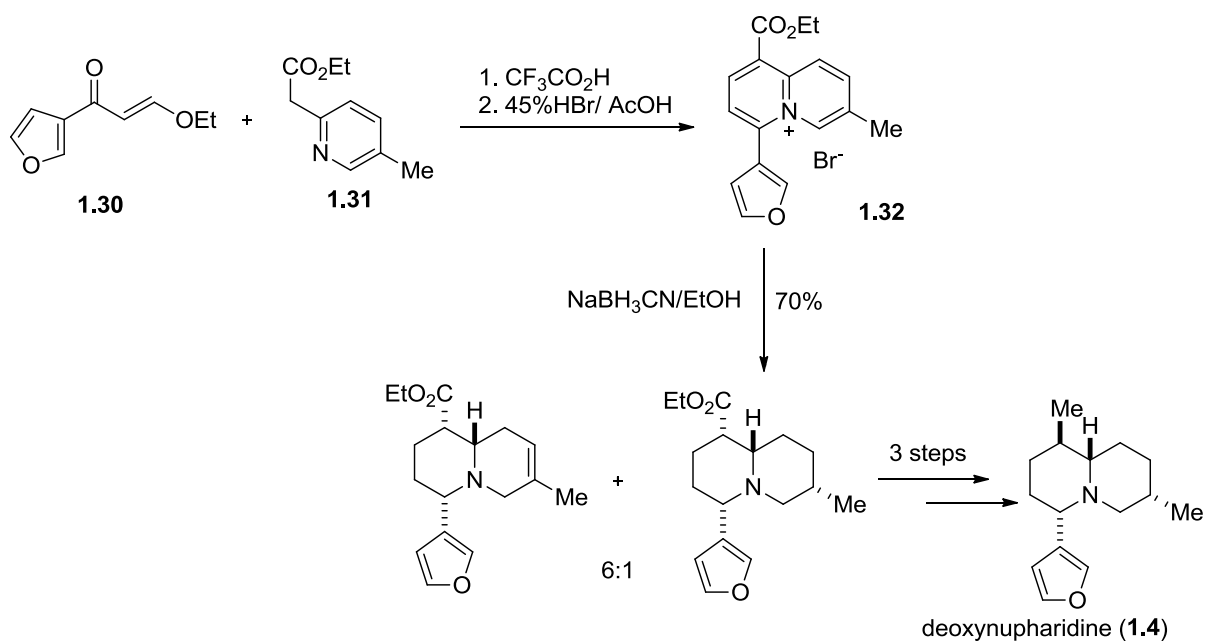
Scheme 1-5

Kaneko and co-workers employed a similar strategy, reduction of pyridine and *trans* acylation, to obtain the piperidine in a synthesis of deoxynupharidine **1.4** (Scheme 1.5). 2,5-Dimethylpyridine was converted in 3 steps to malonate **1.23** which was reduced, undergoing cyclisation to form a diastereomeric mixtures of bicyclic lactams **1.24**. Further reactions gave a diastereoisomeric mixture of deoxynupharidine (**1.4**) in a method similar to the synthesis of demethyldeoxynupharidine (**1.8**).⁹ The final product was characterised by IR spectroscopy: the spectra of the synthetic deoxynupharidine was superimposed upon the spectra of the natural products.



Scheme 1-6

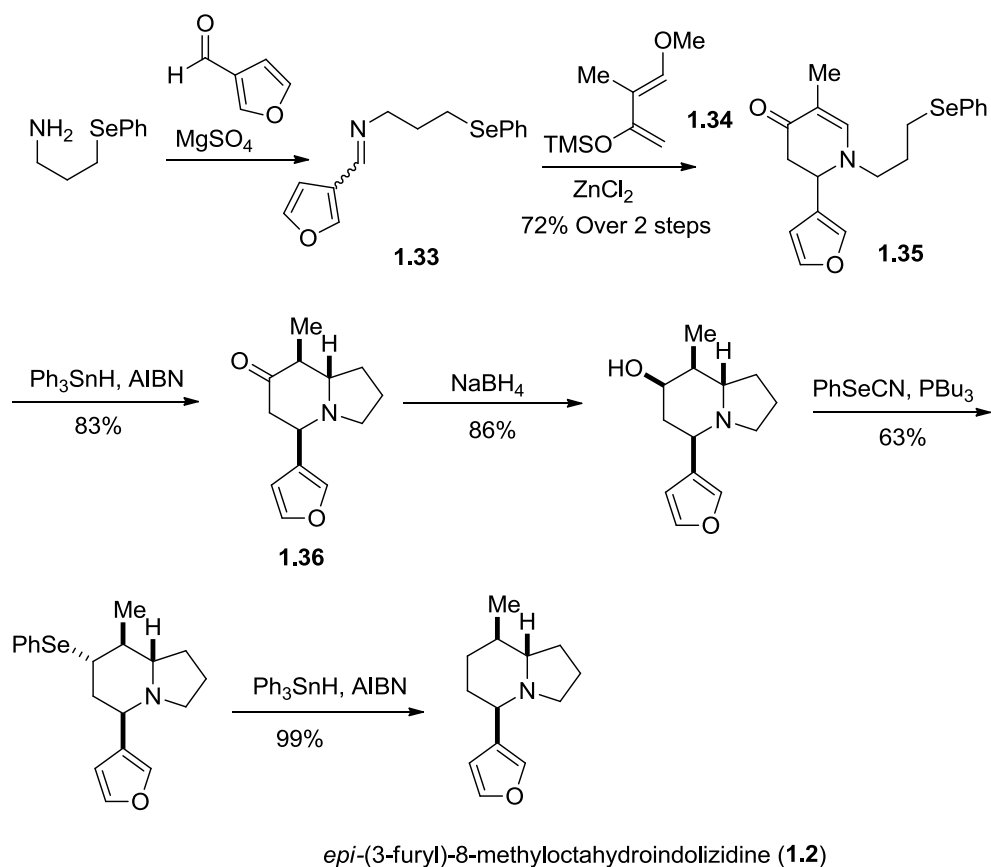
Pyridine **1.26** was synthesised by Wrobél and co-workers by reacting furyl derivative **1.25** with 3-aminocrotonate in a Hantzsch condensation. Pyridine **1.26** underwent several functional group interconversions to provide alkene **1.27**. Piperidines **1.28** and **1.29** were formed by Birch reduction, in low yields and then converted into nupharamine (**1.1**) and its epimer in racemic form by alkene hydration.¹⁰ The whole synthesis is relatively short, the Birch reduction is both low yielding and gives a mixture of stereoisomers (Scheme 1-6).



Scheme 1-7

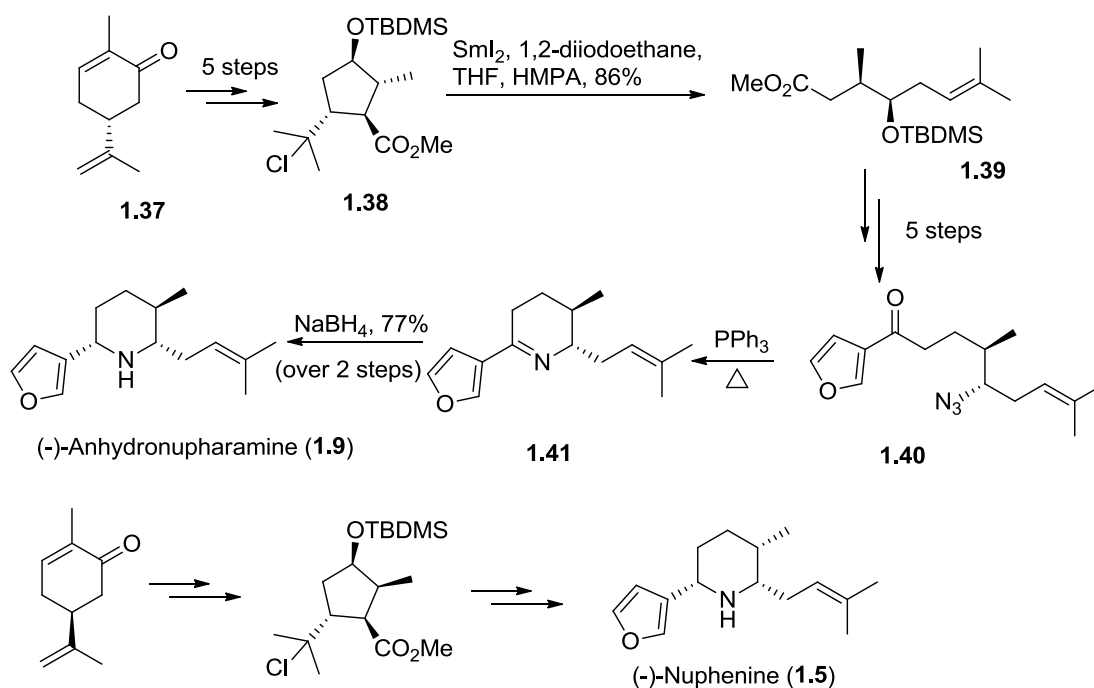
Wrobél and co-workers also completed another synthesis of the nuphar alkaloid, deoxynupharidine **1.4**, by reducing quinolizinium salt **1.32** which was formed from enol ether **1.30** and pyridine ester **1.31**. The reduction gave a mixture of two products. It was claimed that the major product could be suitable for the synthesis of nupharolutine **1.3** and isocastoramine although this was not demonstrated. The minor product was subsequently transformed to racemic deoxynupharidine (**1.4**).¹¹ This synthesis could not be considered as efficient despite the short synthetic route being employed as the desired target molecule, deoxynupharidine (**1.4**), was derived from the minor product of the quinolizinium salt reduction (Scheme 1-7).

2. Radical reactions



Scheme 1-8

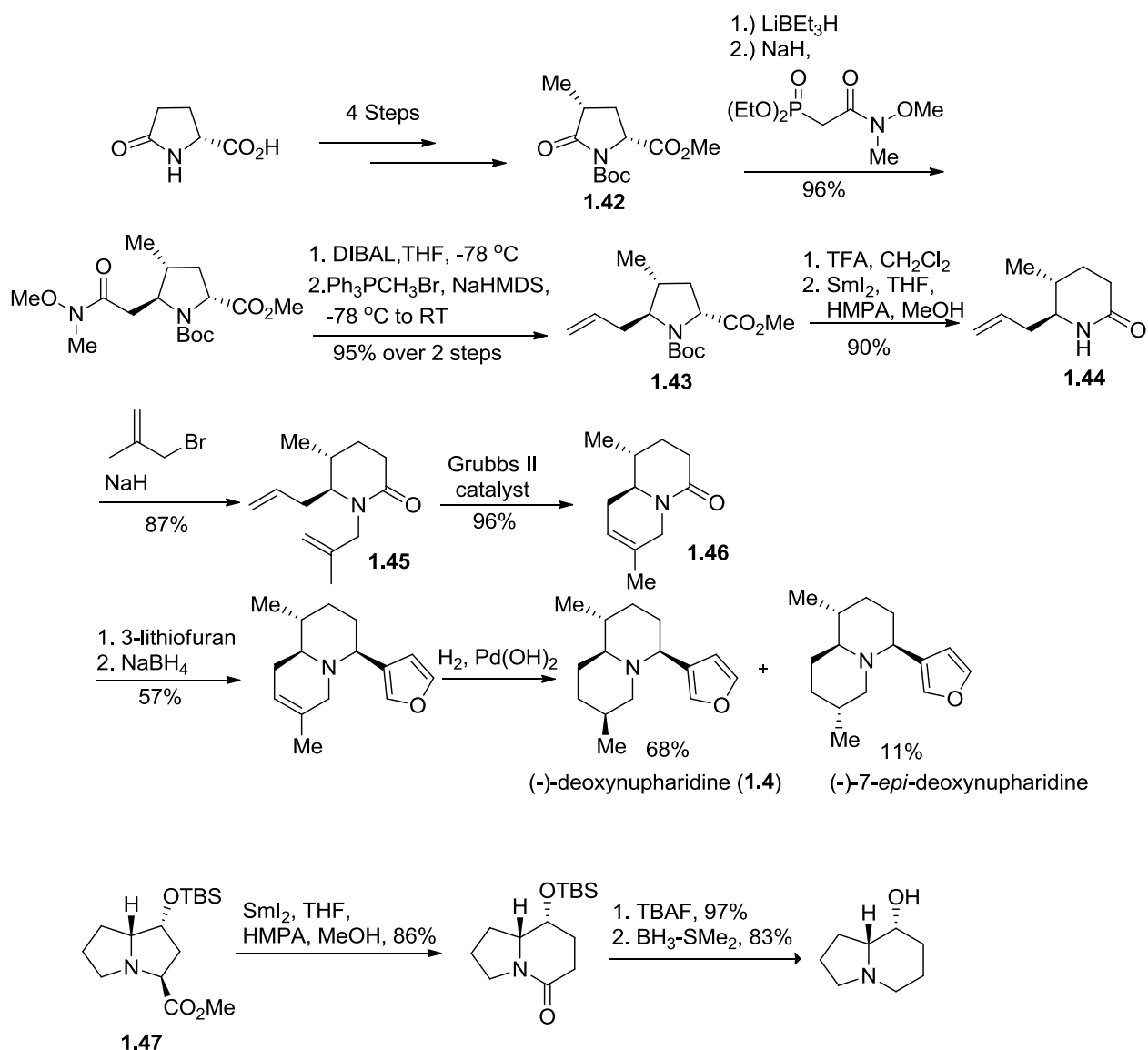
The racemic synthesis of (3-furyl)-8-methyloctahydroindolizidine epimer was achieved by Clive and Bergstra (Scheme 1-8). Piperidinone **1.35**, which was formed from the Michael-Mannich reaction of imine **1.33** and Danishefsky diene **1.34**, underwent radical ring cyclisation, in the presence of triphenyltin hydride with AIBN as an initiator, to form indolizidinone **1.36**. This subsequently led to the efficient synthesis of the racemic alkaloid **1.2** by a short synthetic route (6 steps) with a good overall yield of 33%.¹² The principle drawback, by current standards, is the lack of atom efficiency and the use of toxic organic tin reagents in the two radical steps.



Scheme 1-9

Honda and co-workers have developed a synthetic route which could lead to the synthesis of (-)-anhydronupharamine (**1.9**), (-)-nupharamine (**1.1**), (-)-nuphenine (**1.5**) and (+)-3-*epi*-nupharamine (Scheme 1-9). The synthesis started with commercially available (-)-carvone **1.37** which was converted to the highly functionalized cyclopentane **1.38**. Cyclopentane **1.38**, which is also a γ -halo ester, underwent regioselective SmI₂ mediated fragmentation to provide the acyclic alkene ester **1.39**. After several steps, azide **1.40** was obtained and an intramolecular aza-Wittig reaction occurred in the presence of triphenyl phosphine to afford imine **1.41**. The imine was reduced under stereoelectronic control to provide (-)-anhydronupharamine (**1.9**), which upon hydration, gave nupharamine (**1.1**). A similar synthetic strategy applied to (+)-carvone which led to the synthesis of (-)-nuphenine (**1.5**) and subsequently (+)-3-*epi*-nupharamine.¹³ Honda and co-workers had shown an excellent design of the synthetic route that allows access to those members of the nuphar alkaloids family

with trisubstituted alkene moiety *via* a common synthetic route with enantiomers of the starting material and functionalization of synthetic intermediate.

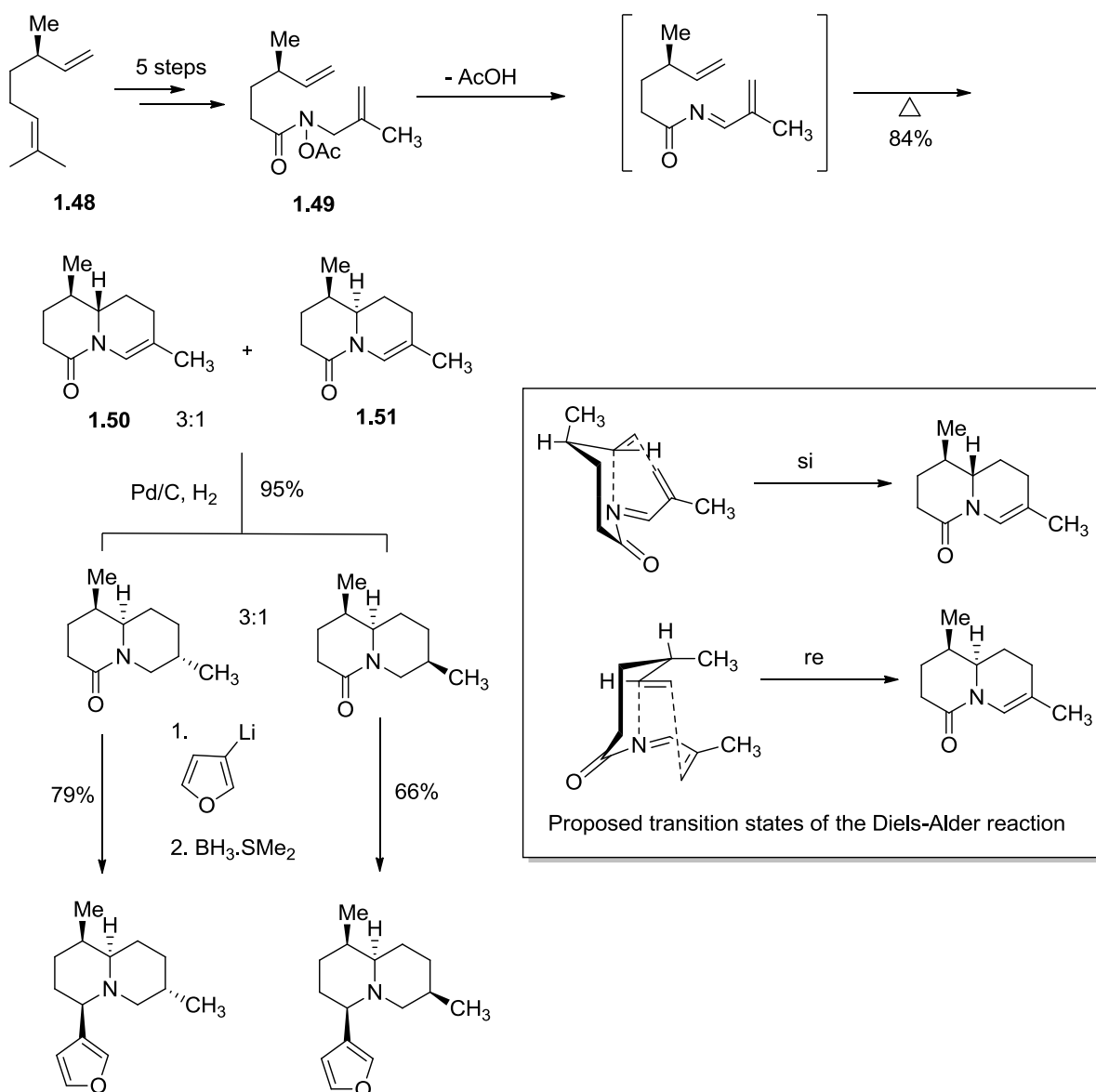


Scheme 1-10

Honda and co-workers also accomplished the synthesis of another nuphar alkaloid, (-)-deoxynupharidine (**1.4**) (Scheme 1-10). The synthesis started with ester **1.42**, which was derived from readily available (*R*)-pyroglutamic acid.¹⁴ Ester **1.42** underwent several transformations to form alkene **1.43** as the key intermediate. After N-

deprotection, alkene **1.43** was subjected to SmI₂ mediated tandem reductive carbon-nitrogen bond cleavage and recyclisation to form lactam **1.44**. Lactam **1.44** was *N*-alkylated to form diene **1.45** which underwent ring closing metathesis to form bicyclic lactam **1.46**. Introduction of the furan ring, followed by reductive amination and subsequently facial selective hydrogenation, gave (-)-deoxynupharidine **1.4** and its epimer.^{15a,b} A similar strategy was applied to the synthesis of (+)-(8*R*, 8*aR*)-perhydro-8-indolizidinol from ester **1.47**,^{13b} demonstrating the versatility of the C-N bond cleavage-recyclisation method. Honda and co-workers synthesised the target alkaloids starting from a chiral pool compound and installed the other chiral centres of the target molecules efficiently *via* stereoelectronic control.

3. Cycloaddition

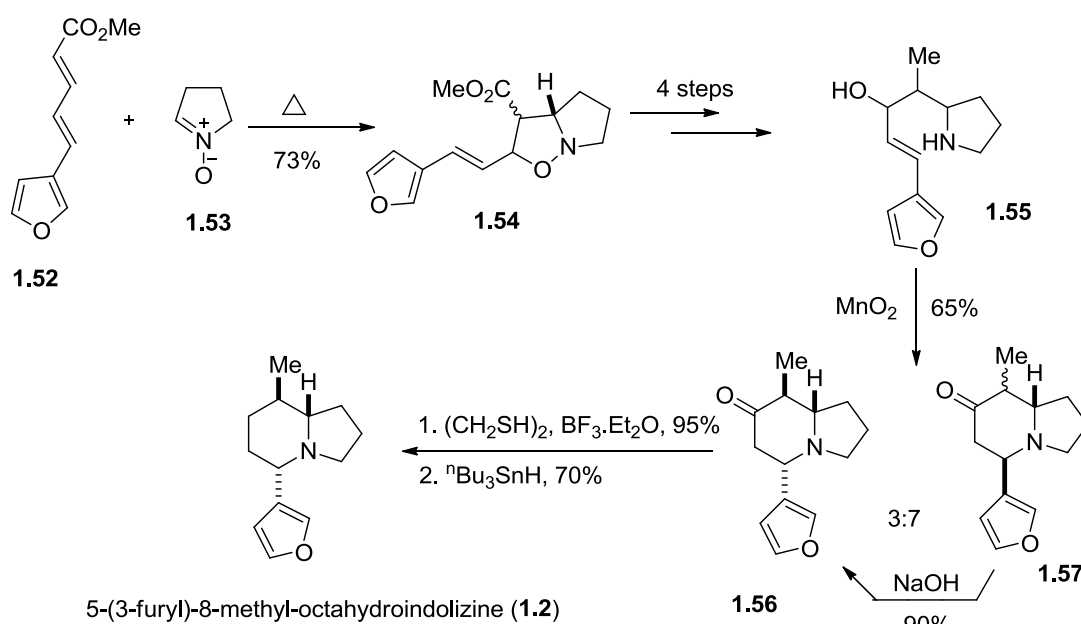


(-)-deoxynupharidine (**1.4**) (-)-*epi*-deoxynupharidine

Scheme 1-11

The Diels-Alder cycloaddition is a powerful method to construct six-membered rings, and can be extended to heterocyclic systems. The design of the diene and the dienophile will greatly affect the stereochemistry of the product formed. Fowler and Hwang reported an intramolecular Diels-Alder reaction which could eventually lead to the synthesis of deoxynupharidine (**1.4**) (Scheme 1-11). The key intermediate **1.49**, which was derived from (*R*)-citronellene **1.48**, was subjected to heat in order to form

an α,β -unsaturated imine which could function as a hetero-diene in a cycloaddition to form lactams **1.50** and **1.51** in a ratio of 3:1. It was suggested that the cycloaddition went through an *exo* transition state, with an equatorial methyl group, giving the major product as there is less steric hindrance.¹⁶ Lactams **1.50** and **1.51** were hydrogenated selectively from the β face, then the diastereomers were separated and converted to (-)-deoxynupharidine (**1.4**) and its epimer. In this work, the two fused piperidine rings of the (-)-deoxynupharidine was formed simultaneously and effectively *via* nicely designed acyclic intermediate **1.49**.

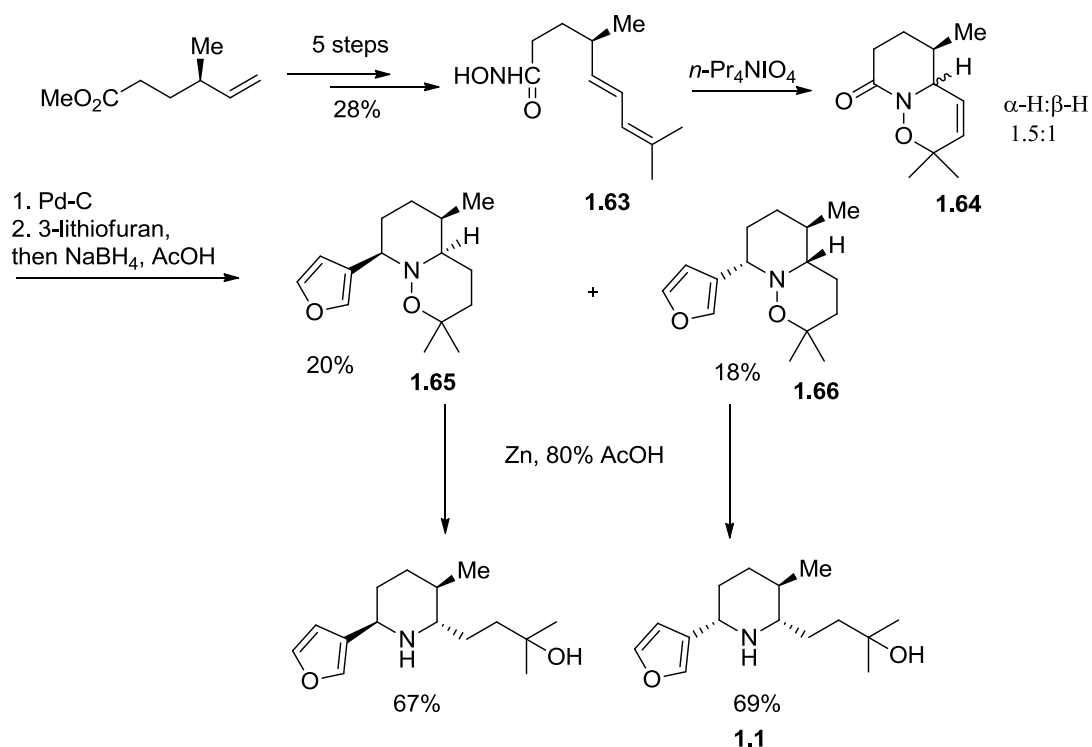
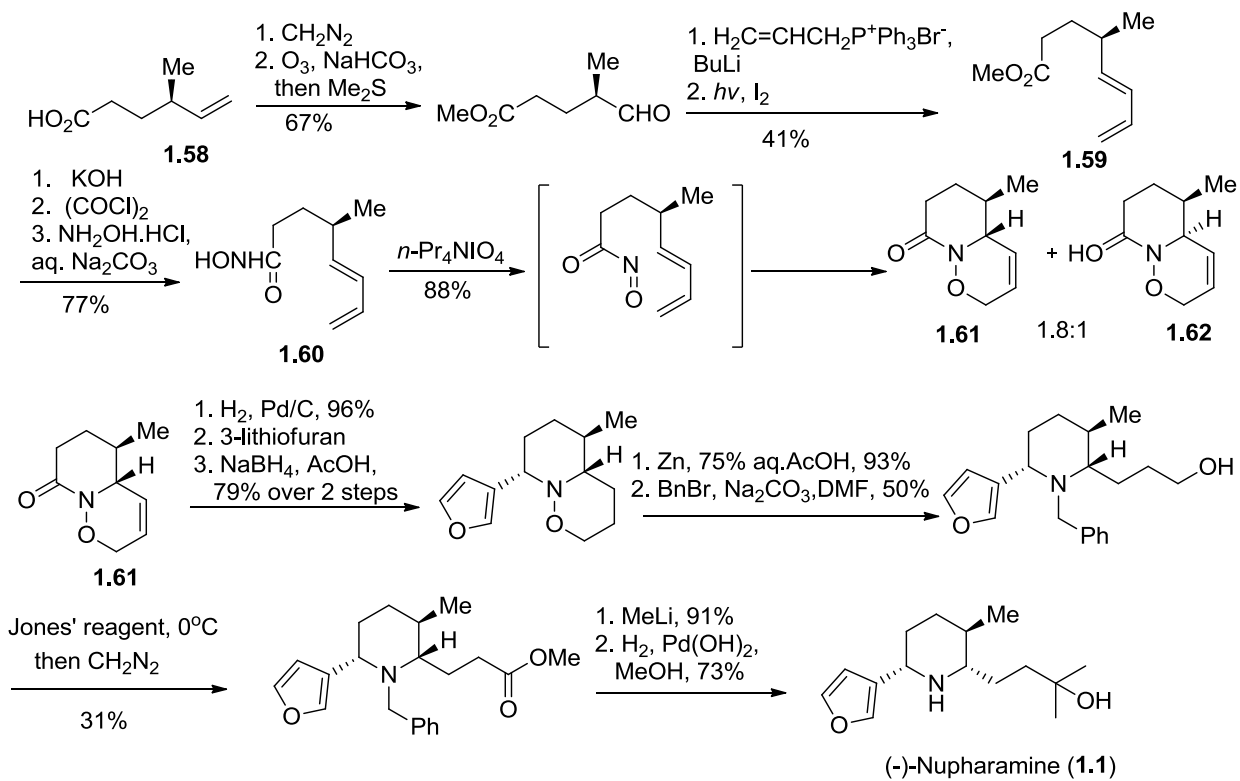


Scheme 1-12

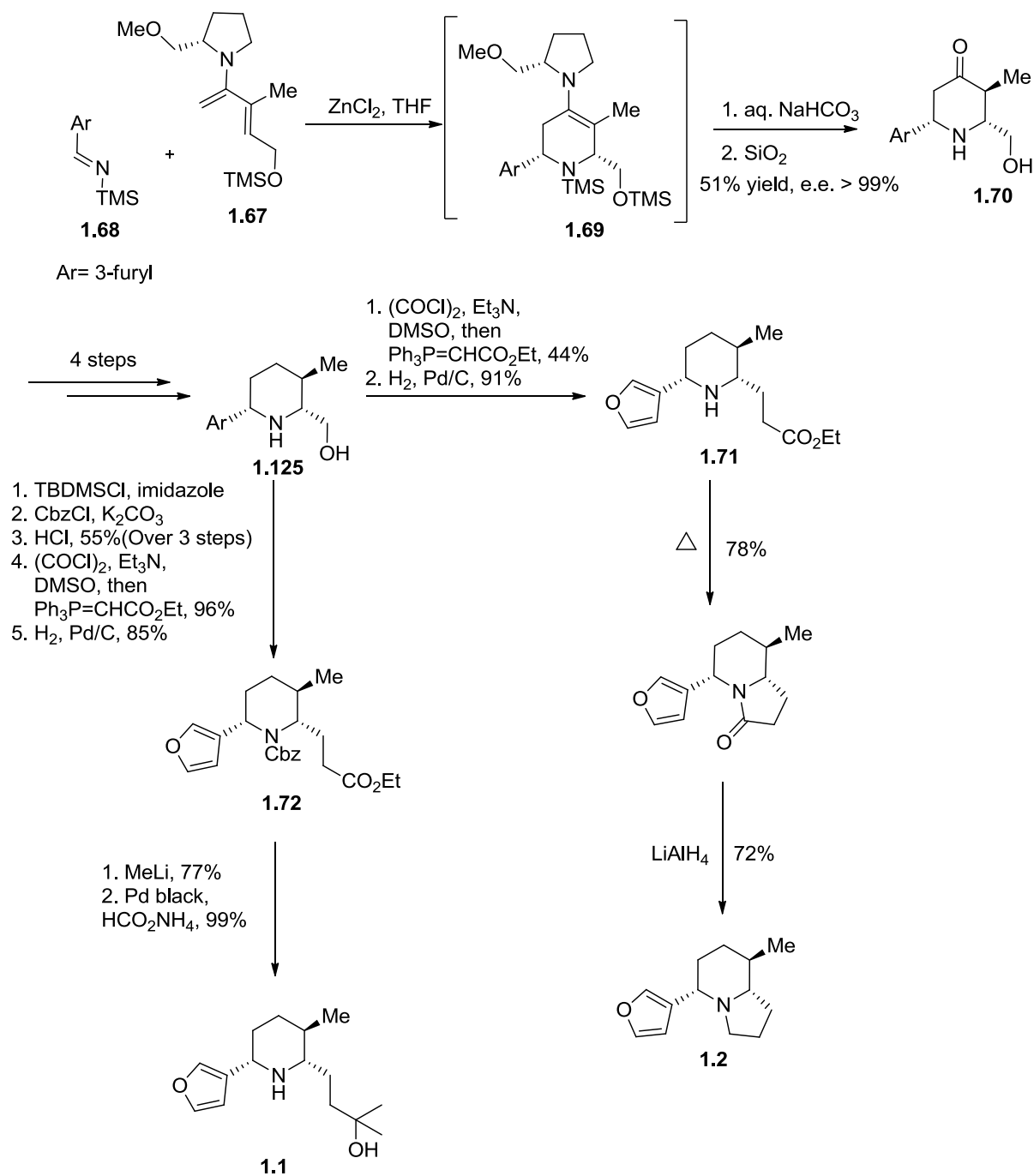
Tufariello and Dyszlewski synthesised 5-(3-furyl)-8-methyl-octahydroindolizine by a nitronium **1.53** 1,3-dipolar cycloaddition with 1,4-disubstituted-but-1,3-diene **1.52** as key step to form bicyclic isoxazolidine **1.54** as a diastereoisomeric mixture which was converted to amine **1.55** (Scheme 1-12). Upon oxidation of alcohol **1.55**, 6-*endo* Michael addition occurred to give a mixture of piperidinones **1.56** and **1.57**. Piperidinone **1.57** was epimerised to the desired piperidinone **1.56** through

equilibration by a retro-Michael-Michael process and enolisation in the presence of NaOH, which was then transformed to the racemic natural product **1.2** by a modification of the Mozingo method.¹⁷ The authors had achieved the synthesis of the racemic unnamed bicyclic nuphar alkaloid **1.2** with a relatively short sequence steps (9 steps including the epimerisation of piperidinone **1.57**).

An asymmetric intramolecular nitroso Diels-Alder was employed by Kibayashi and co-workers in the total synthesis of (-)-nupharamine (**1.1**) and (+)-3-*epi*-nupharamine (Scheme 1-13). Diene **1.59** was synthesised through four synthetic steps from carboxylic acid **1.58**, derived from (*R*)-citronellol, and converted to diene **1.60** which underwent an intramolecular hetero-Diels-Alder reaction to form lactams **1.61** and **1.62** with selectivity of 1.8:1. The *trans*-adduct was the major product. The desired lactam was then transformed to (-)-nupharamine (**1.1**) through a total of 15 synthetic steps starting from carboxylic acid **1.58** with an overall yield of 1%. For shorter alternative route (9 steps starting from carboxylic acid **1.58**) for the synthesis of (-)-nupharamine **1.1**, the Diels-Alder reaction of the corresponding nitroso compound with a *gem*-dimethyl diene, **1.63**, was also studied. The intramolecular cycloaddition gave an inverted *cis/trans* ratio of 1.5:1. The mechanistic reason for this phenomenon remains unclear. The diastereoisomeric mixture of lactams **1.64** was then converted to piperidines **1.65** and **1.66** which led to the synthesis (-)-nupharamine (**1.1**) and its epimer by N-O bond cleavage with overall yields of 4% and 3% respectively.¹⁸ Two synthetic ways of (-)-nupharamine (**1.1**) had been investigated but unfortunately the key step, the hetero Diels-Alder reaction, does not give good selectivity in either case.



Scheme 1-13



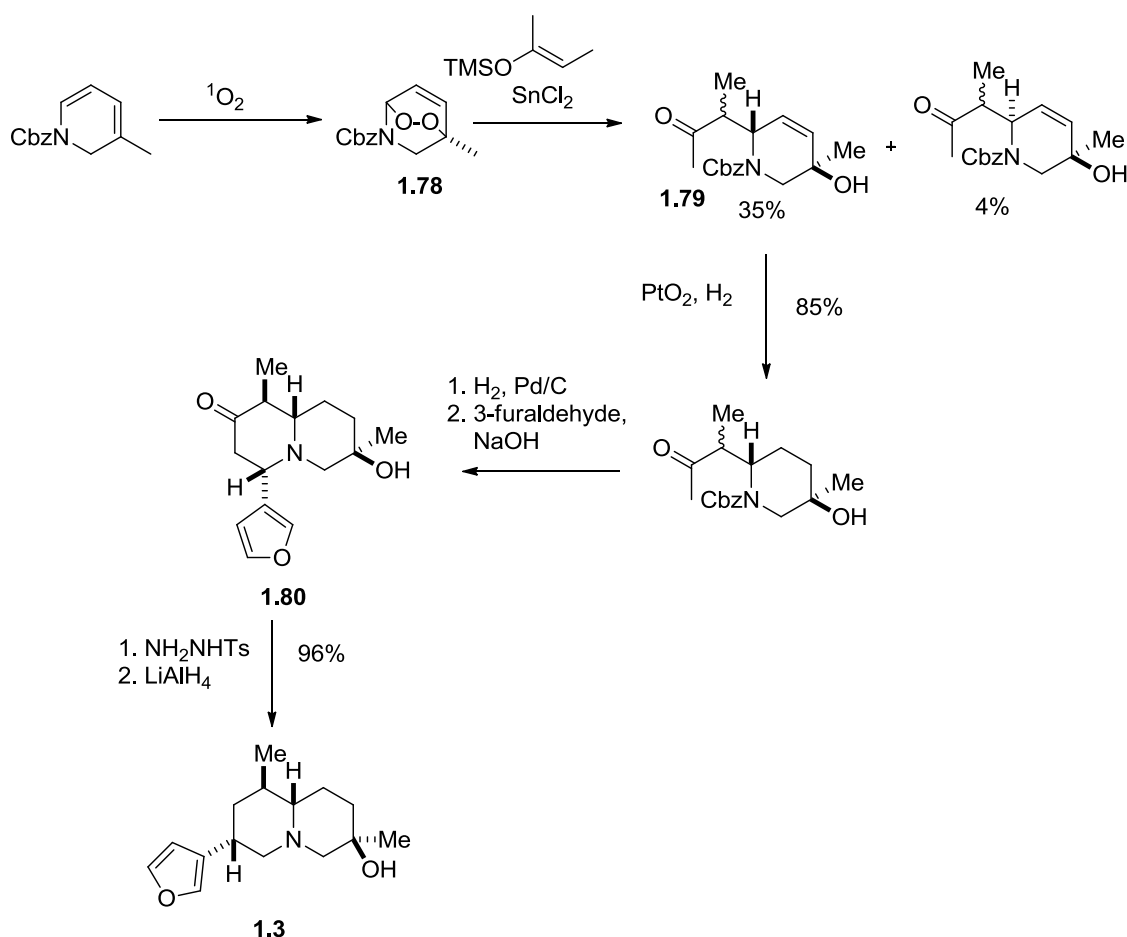
Scheme 1-14

The first asymmetric synthesis of (-)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (1.2) along with an enantioselective synthesis of (-)-nupharamine (1.1) was completed by Barluenga and co-workers *via* a common intermediate 1.125 (Scheme 1-14). The three stereogenic centres of the nuphar

alkaloids were established by the hetero Diels-Alder reaction of chiral diene **1.67** and imine **1.68** which formed intermediate **1.69**, followed by deprotection to form piperidinone **1.70**. Piperidine **1.71**, which was derived from piperidine alcohol **1.125**, was converted to the unnamed bicyclic natural product **1.2** *via* thermolytic cyclisation and reduction by LiAlH_4 . As for the synthesis of nuphramine (**1.1**), piperidine **1.125** was converted carbamate to ester **1.72**. The carbamate was reacted with MeLi to form a tertiary alcohol which was then finally deprotected to provide the natural product **1.1**.¹⁹ Barluenga and co-workers had demonstrated a very efficient way of introducing three substituents of the piperidine ring with the right stereoconfiguration in *via* asymmetric hetero Diels-Alder that led to the synthesis of two nuphar alkaloids.

cycloaddition did not proceed as well as expected, giving a low yield of piperidine **1.76** with a mixture of side products. An alternative route was designed to form racemic piperidine **1.76** which enabled further studies on the synthesis. Piperidine **1.76** was transformed to bicyclic compound **1.77**, which is a common immediate to access several of the alkaloids.²⁰ Low yield of the [3+3] formal cycloaddition had become the limitation to this synthetic route. Otherwise, this work will be another elegant method to access to different nuphar alkaloids.

4. SnCl₂ mediated reaction of endo peroxides

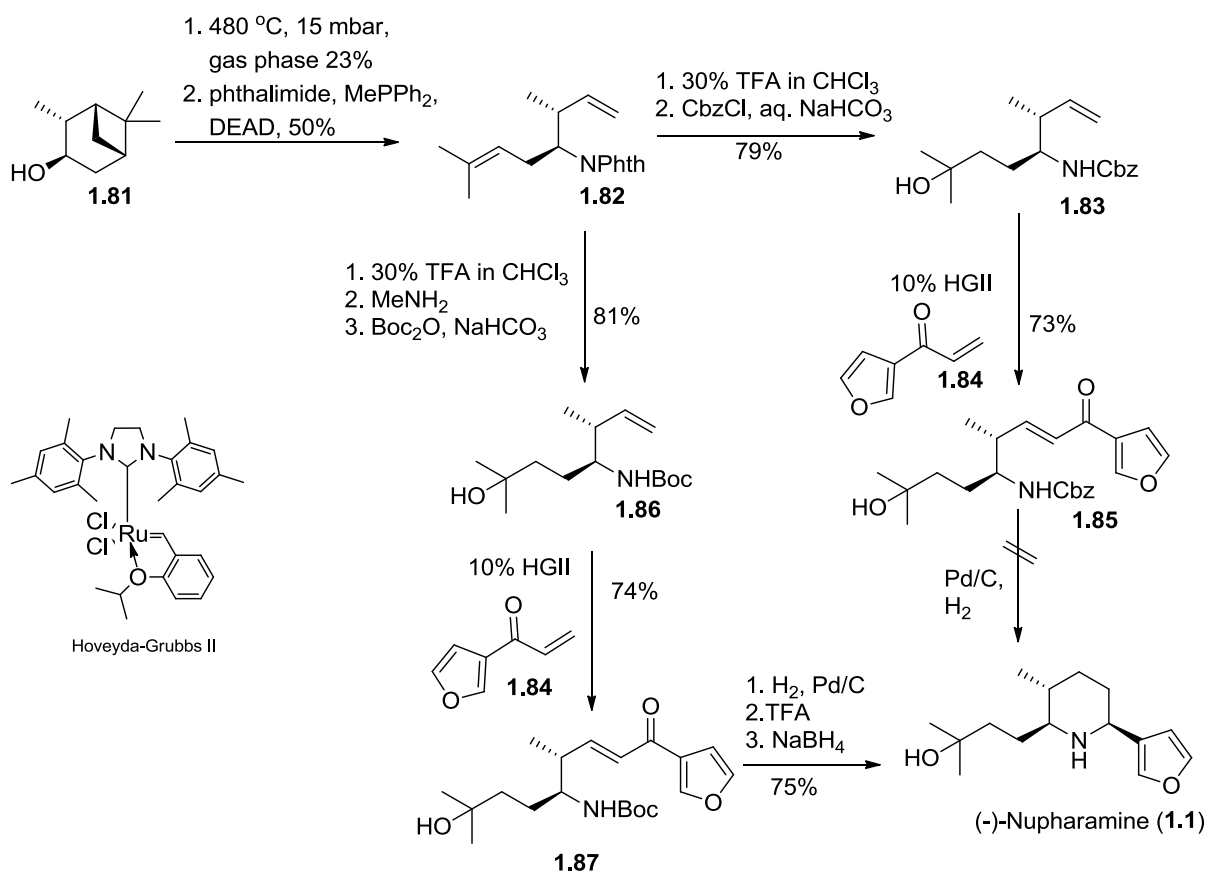


Scheme 1-16

Natsume and Ogawa reported the first racemic stereoselective synthesis of nupharolutine (**1.3**) by employing the $SnCl_2$ -mediated reaction of endoperoxide **1.78**

formed by the Diels-Alder reaction of singlet oxygen with a 1,2-dihydropyridine (Scheme 1-16).²¹ In the presence of SnCl₂, 2-trimethylsilyloxy-2-butene, employed as the nucleophile, attacked from the direction opposite to the peroxide to form piperidine **1.79**. SnCl₂ is likely to act as both Lewis acid and reducing agent. Piperidine **1.79** underwent hydrogenation, protection, and then condensation with 3-furaldehyde to form piperidinone **1.80**. The carbonyl group on piperidinone **1.80** was converted to a tosylhydrazone to undergo Bamford-Stevens reaction, which, upon reduction with LiAlH₄, gave nupharolutine (**1.3**).²² The SnCl₂ mediated reaction was shown to be an interesting method of functionalizing the piperidine ring. However, the low yield of this reaction has become the limitation to the natural product synthesis despite the short synthetic route.

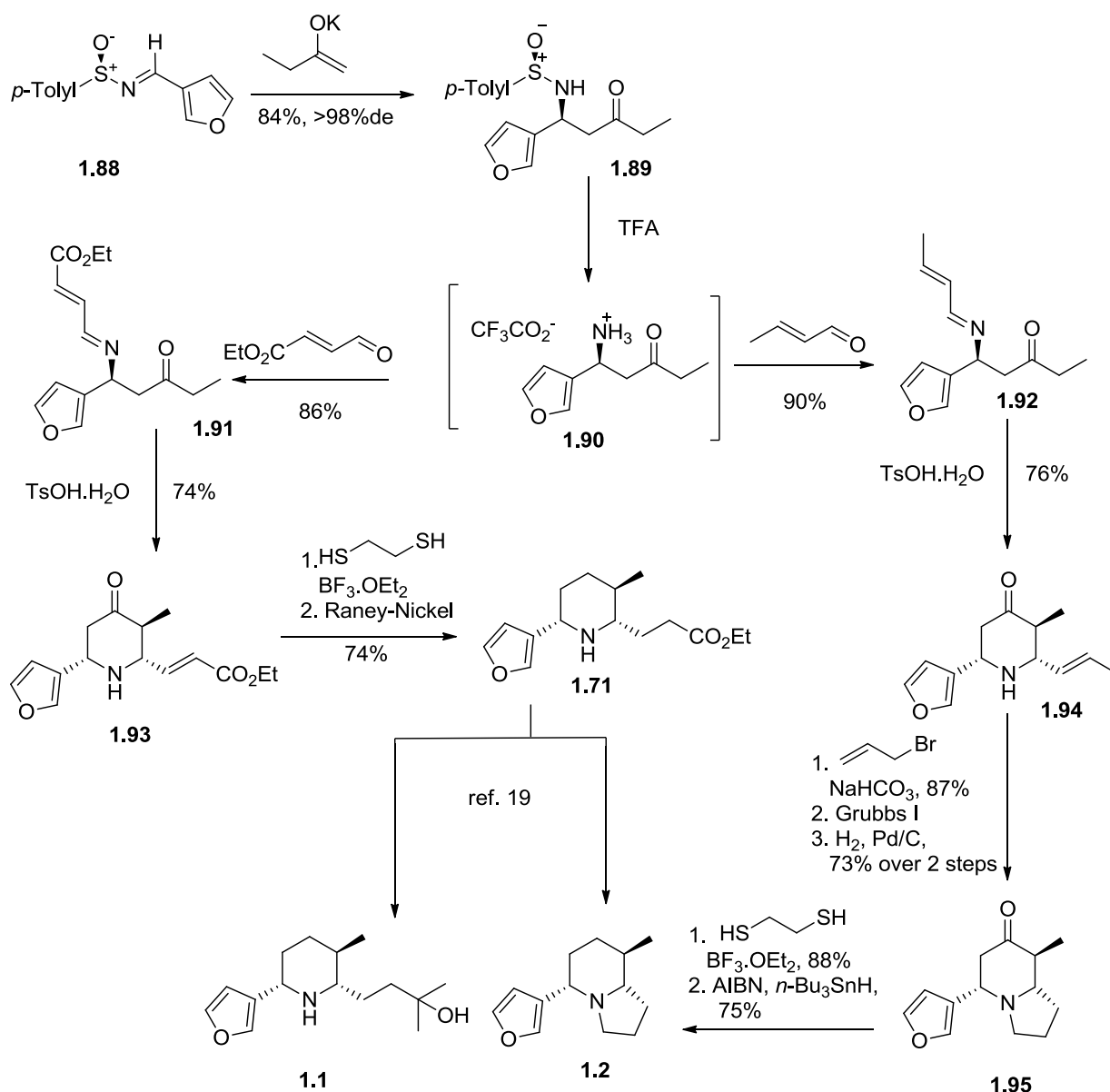
5. Cross Metathesis



Scheme 1-17

Undoubtedly metathesis has become a powerful tool in total synthesis.²³ Blechert and Gebauer have reported an elegant short synthesis of (-)-nupharamine (**1.1**) from the pyrolysis of (+)-isopinocampheol **1.81**, employing cross metathesis and reductive amination as key steps (Scheme 1-17). Phthalimide **1.82** was converted to Cbz protected amine **1.83** which was then subjected to cross metathesis with furyl alkene **1.84** using the Hoveyda-Grubbs second generation catalyst to form alcohol **1.85**. However, reduction and deprotection of the alkene **1.85** also resulted in reduction of the furyl group. To overcome this problem, phthalimide **1.82** was converted to Boc-protected amine **1.86**, then subjected to cross metathesis with furyl alkene **1.84** to form alcohol **1.87**. The effect of the different protecting groups, Boc and Cbz, was not explained. The alkene of alcohol **86** was successfully reduced and deprotected to form imine which was then reduced in a stereoselective manner to obtain (-)-nupharamine (**1.1**).²⁴ Short asymmetric synthesis of (-)-nupharamine (**1.1**) had been illustrated. However, high catalyst loading of the cross metathesis catalyst has become the drawback of this synthetic route design. It is unclear why such a loading is required and may be unnecessary, particularly if better catalysis are employed.

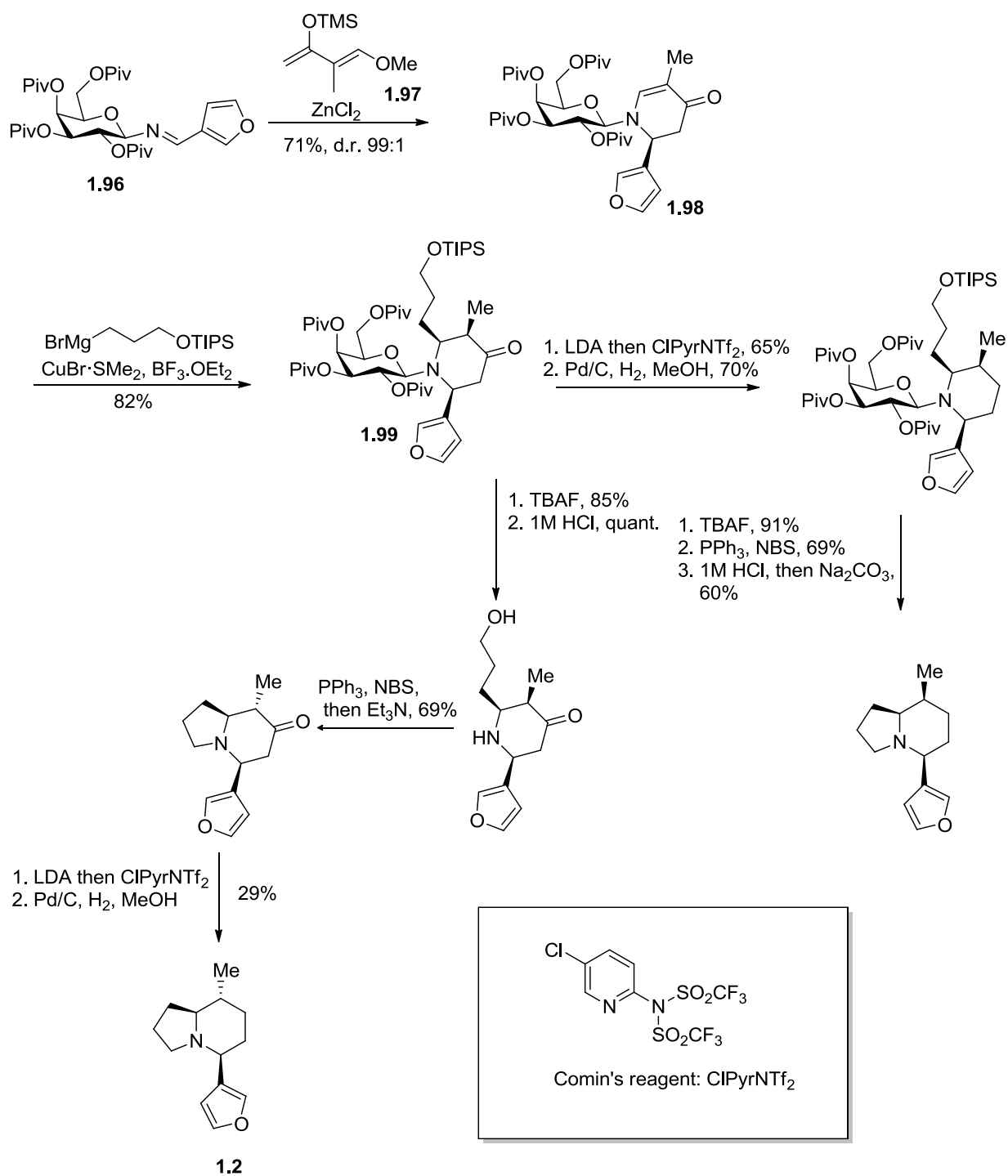
6. Intramolecular Mannich Reaction



Scheme 1-18

Since the discovery of the Mannich reaction, many studies have been carried out to improve its utility in synthesis. In particular, Davis has pioneered the use of chiral sulfoximines to control stereochemistry. Davis and Santhanaraman synthesised (-)-nupharamine (**1.1**) and the unnamed alkaloid (-)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**1.2**) *via* intramolecular Mannich reactions as key steps

(Scheme 1-18). Sulfoximine **1.88**, which was derived from readily available (*R*)-(-)-*p*-toluenesulfinamide, was converted to amino ketone **1.89**, and deprotected under acidic condition to form ammonium salt **1.90**. Reaction with two different aldehydes led to the formation of imines **1.91** and **1.92** respectively. The imines then underwent Mannich cyclisation in the presence of TsOH to form piperidinones **1.93** and **1.94**, which were isolated as single isomers. Piperidinone **1.93** was then converted to piperidine **1.71**, which is the same as the intermediate reported by Barluenga,¹⁹ and could be converted to both (-)-Nupharamine (**1.1**) and (-)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**1.2**).¹⁷ Piperidinone **1.94** was allylated and underwent ring closing metathesis with the Grubbs I catalyst. Then, hydrogenation of the double bond gave ketone **1.95**. Removal of the ketone group was done by formation of thiol ketal followed followed by desulfization with tributyltin hydride in the presence of AIBN as initiator, to give (-)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**1.2**).²⁵ The Barluenga intermediate **1.71** was synthesised in only 6 synthetic steps with excellent diastereoselectivity introduced by the sulfoximines and exceptional stereoelectronic control of the Mannich reactions.

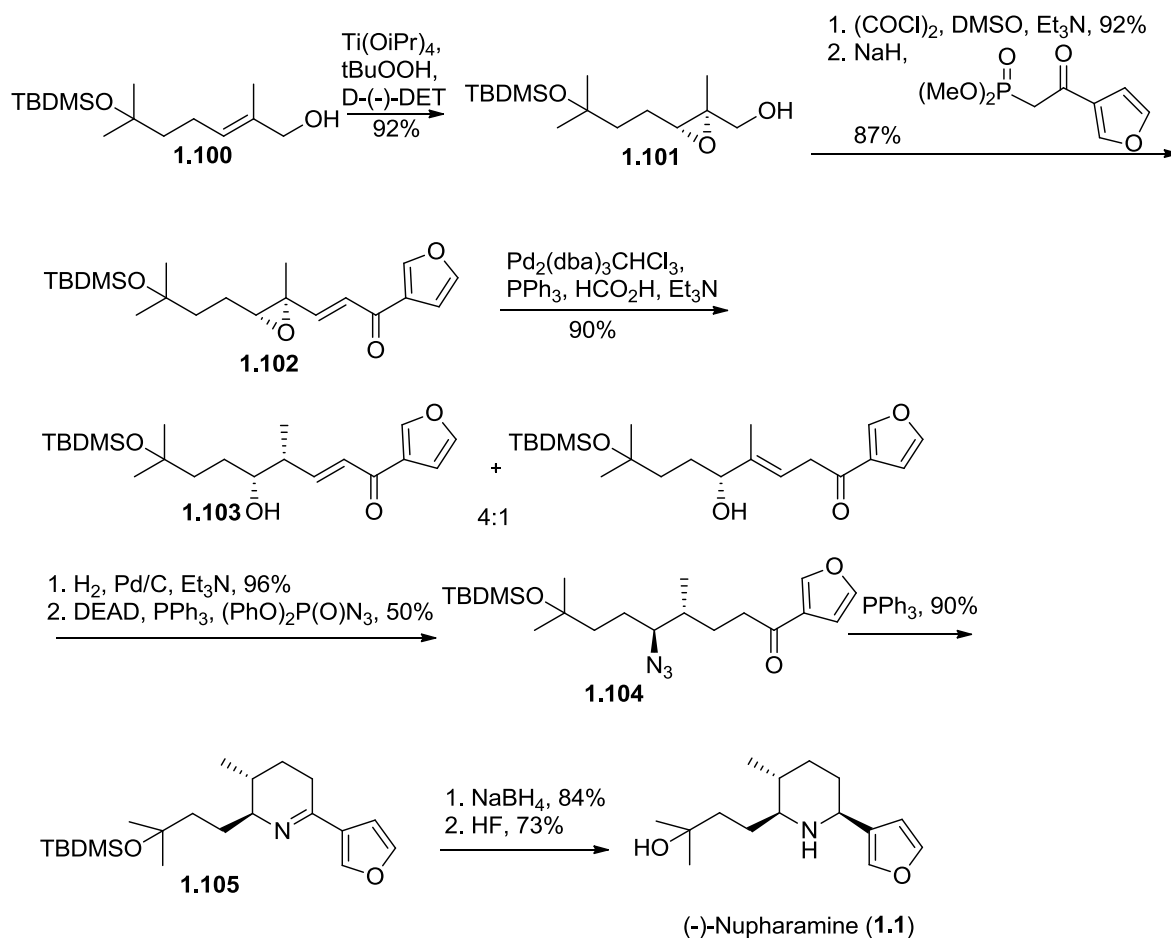


Scheme 1-19

The use of chiral auxiliaries is indeed a very powerful tool for introducing chirality to achiral molecules. Kunz and co-workers employed galactosylamine as a chiral auxiliary in their synthesis of (-)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine

(**1.2**) and its epimer (Scheme 1-19). The imine **1.96** underwent a domino Mannich-Michael reaction with Danishefsky's diene **1.97** giving piperidinone **1.98** with a very high diastereoselectivity after acidic work up. Then piperidinone **1.98** was submitted to diastereoselective 1,4-addition of a Grignard reagent to establish the two *syn* stereocentres on piperidinone **1.99**. The highly functionalized piperidinone **1.99** was then transformed to the natural products **1.2** with removal of the superfluous ketone group by Comins' method as one of the steps.²⁶ Kunz and co-workers had shown a good example on the application of chiral auxiliary in natural product synthesis. Chiral auxiliary is an excellent method to introduce chirality, however, it requires stoichiometric amount which can be less preferable as compared to chiral catalysts which usually require low catalyst loading.

7. Pd mediated hydrogenolysis

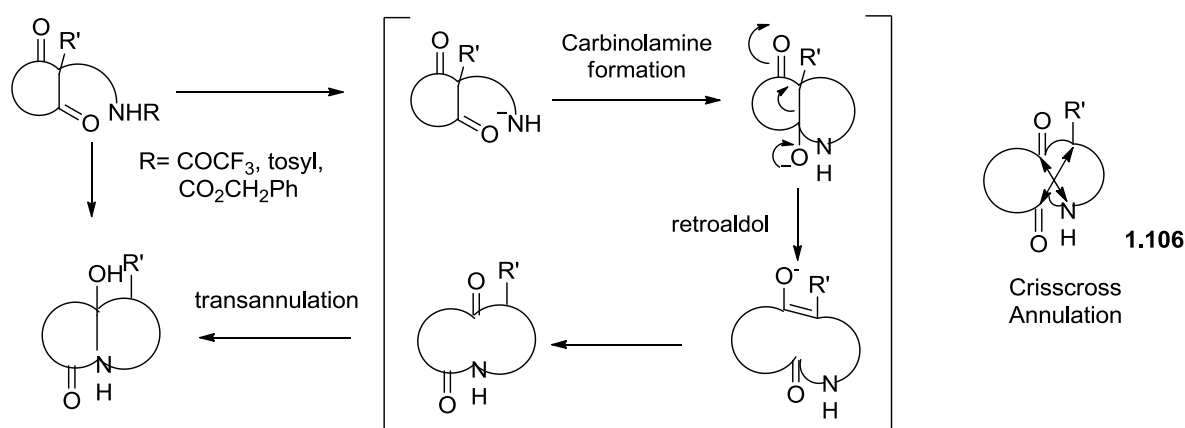


Scheme 1-20

An asymmetric synthesis of (-)-nupharamine (**1.1**) was also achieved by Shimizu and Yamazaki in a rather short route (Scheme 1-20). The synthesis was initiated by Sharpless asymmetric epoxidation of allylic alcohol **1.100** to introduce the enantiopure epoxide **1.101**. Then a couple of transformations provided key intermediate **1.102**, which underwent palladium catalysed hydrogenolysis of alkene epoxide in the presence of formic acid to form homoallylic alcohol **1.103** with reasonable regioselectivity of 4:1 *via* a π -allyl palladium intermediate. This reaction ensures the correct stereochemistry of the methyl group as the hydride will be delivered directly

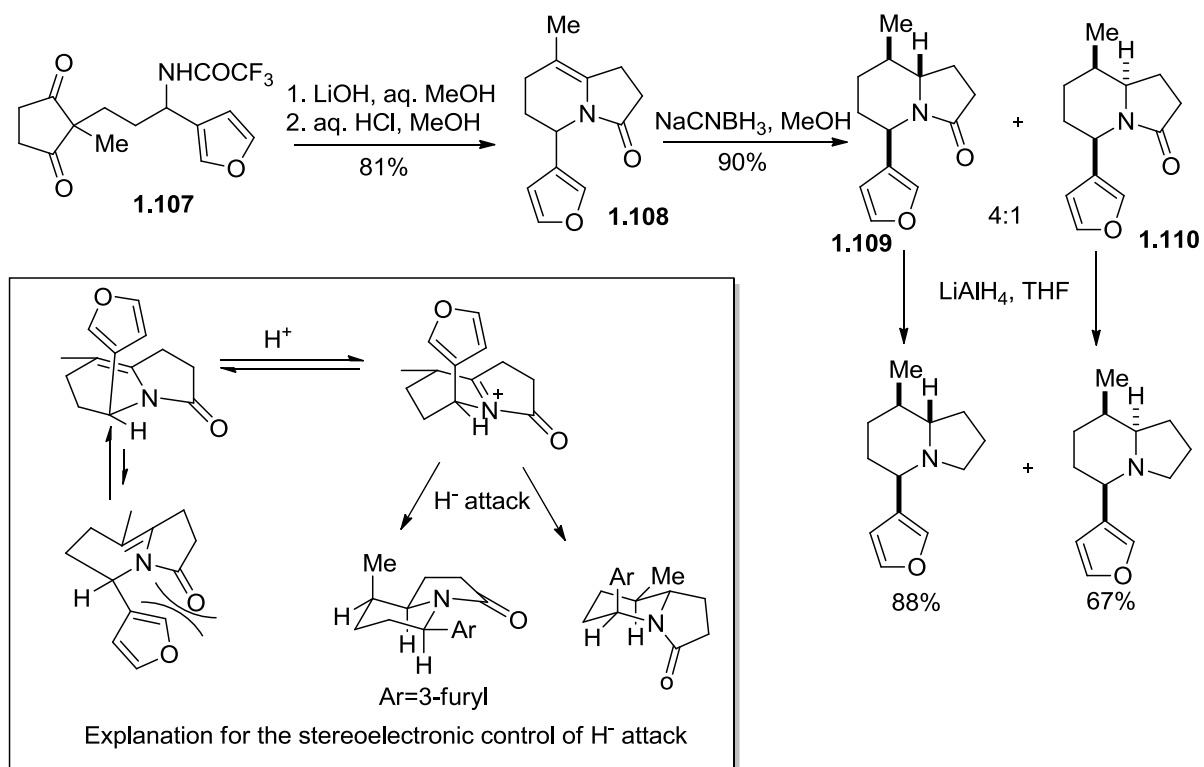
from the Pd which was opposite to the epoxide. Alcohol **1.103** was then reduced and underwent a Mitsunobu reaction to form azide **1.104**, which was cyclised via an aza-Wittig reaction to form imine **1.105**. Subsequently, imine **1.105** was reduced selectively and deprotected with HF to form (-)-nupharamine (**1.1**).²⁷ The synthesis of (-)-nupharamine **1.1** was achieved in 9 steps with a good overall yield of 17%.

8. Criss-cross annulation



Scheme 1-21

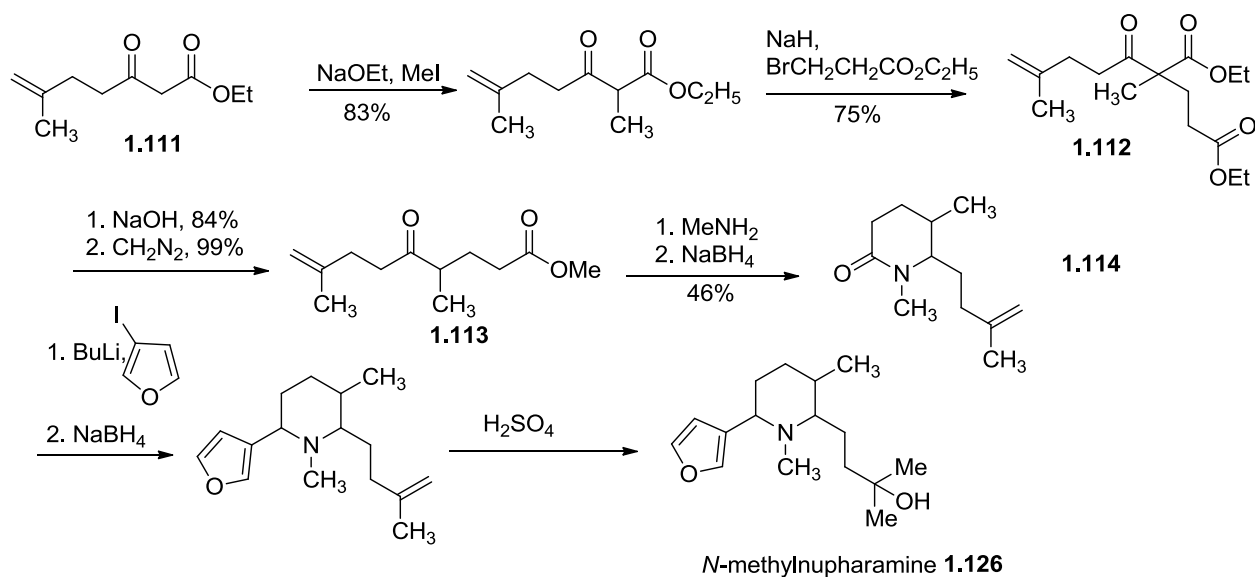
Ban and co-workers introduced the concept of criss-cross annulation, which involves the formation of a carbinolamine, followed by a retro aldol reaction and transannulation to form pyrrolizidines and indolizidines. It was simplified by the authors as depicted by molecule **1.106** (Scheme 1-21).



Scheme 1-22

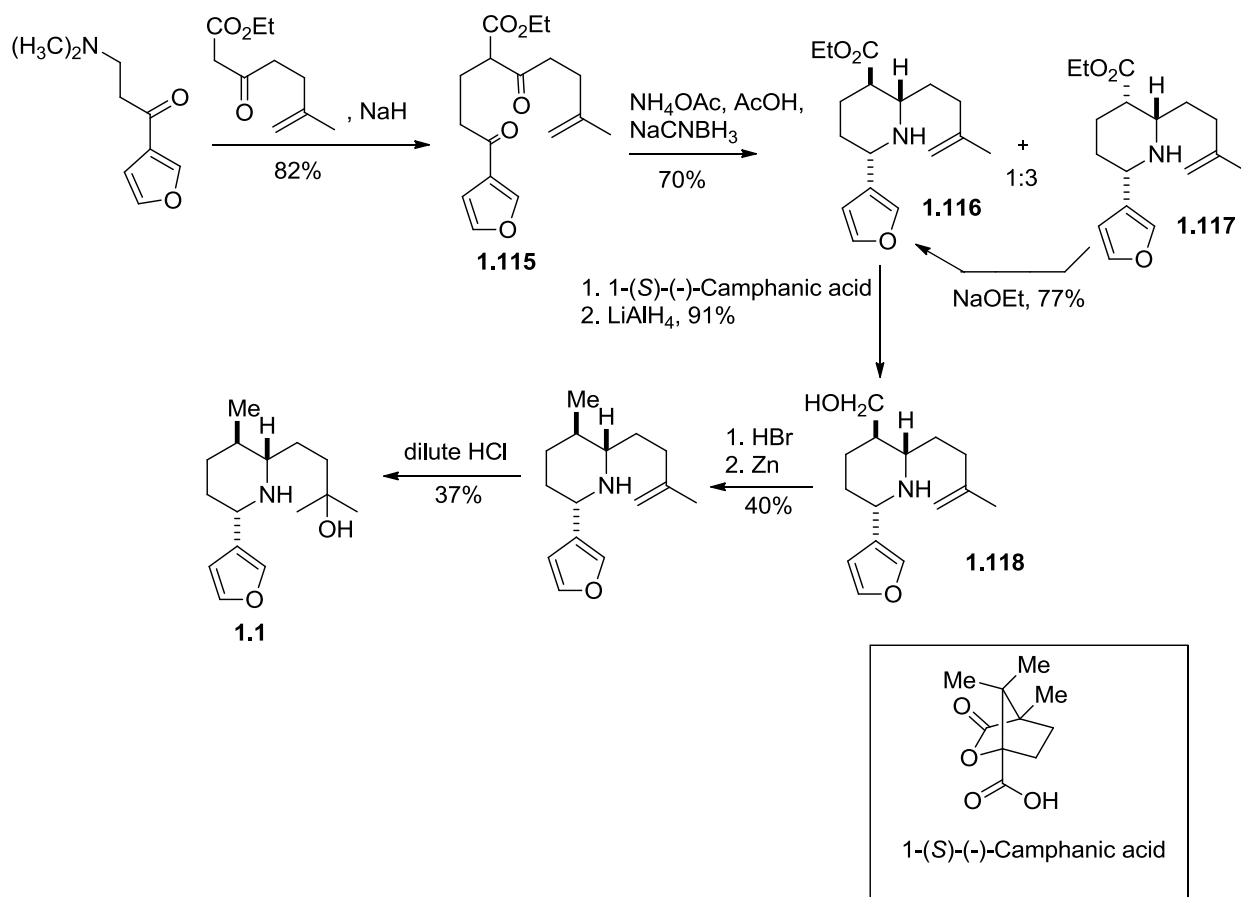
Dione **1.107** underwent criss-cross annulation in the presence of LiOH, followed by HCl to form lactam **1.108** (Scheme 1-22). The enamine was then reduced under stereoelectronic control, applying the concept of $A^{(1,3)}$ strain to provide lactams **1.109** and **1.110** in a ratio of 4:1. The lactams were further reduced to provide the racemic epimers of indolizine nuphar alkaloid **1.2**.²⁸ The authors reported that both of the synthesised diastereomers had almost the same mass spectra to those reported by Ohloff for the natural product²⁹ and no other spectroscopic data of the natural alkaloid was reported for further comparison.

9. Miscellaneous Synthesis Methods



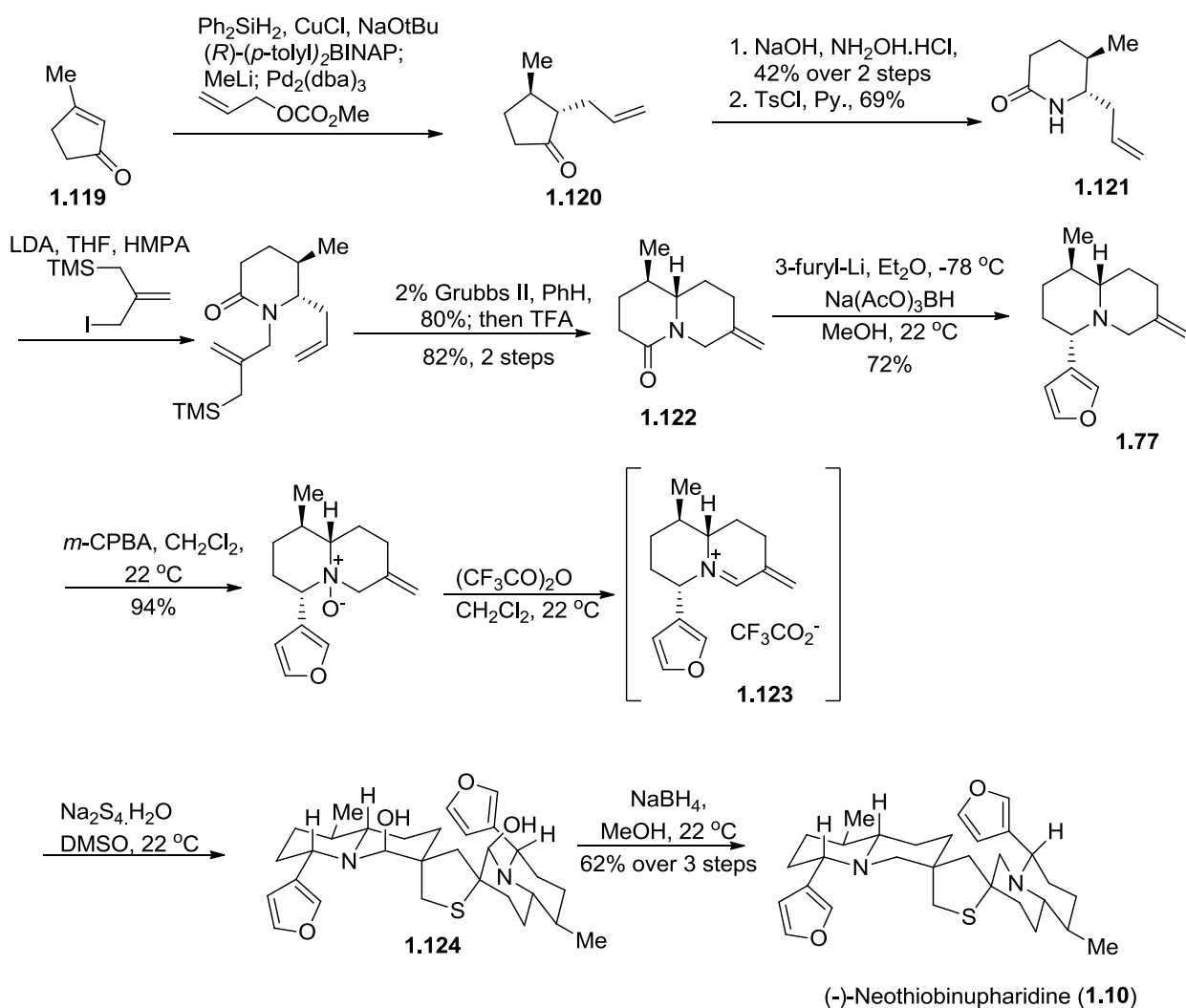
Scheme 1-23

N-Methylnupharamine **1.126** and its diastereomers were synthesised by Matsutani and co-workers starting from β -ketoester **1.111**, derived from methallyl chloride by the method of Crombie.³⁰ β -Ketoester **1.111** was doubly alkylated to provide ester **1.112**, which was transformed to keto ester **1.113**. The keto ester **1.113** was treated with methylamine to form an imine which underwent double reductive amination to form lactam **1.114**. Lactam **1.114** was then converted to a mixture of *N*-methylnupharamine **1.126** and its diastereomers which were separated through chromatography. The isolated fraction of the diastereometer mixture carrying the racemic mixture of the *N*-Methylnupharamine **1.126** was identified by comparison with the methylated natural nupharamine (Scheme 1-23).³¹ Chirality and stereochemical control were not emphasized in this synthesis, leading to the formation of mixtures of diastereomers.



Scheme 1-24

The stereoselective synthesis of (-)-nupharamine (**1.1**) was achieved by Leniewski and Szychowski by condensation of 1,4-diketone **1.115** followed by stereoselective reductive amination to form mixtures of amines **1.116** and **1.117**. The amine **1.116** with the desired relative stereochemistry was found to be the minor product. However, the undesired amine **1.117** could be isomerized to the desired amine on treatment with NaOEt. The piperidine **1.116** was resolved with 1-(*S*)-(-)-Camphanic acid to obtain enantiopure alcohol amine **1.118** which was converted to (-)-nupharamine (**1.1**) (Scheme 1-24).³² This synthesis provides a good classical example of the use of chiral resolution through recrystallization of the diastereomers that formed from the reaction between racemic mixtures with enantiopure resolving agents.

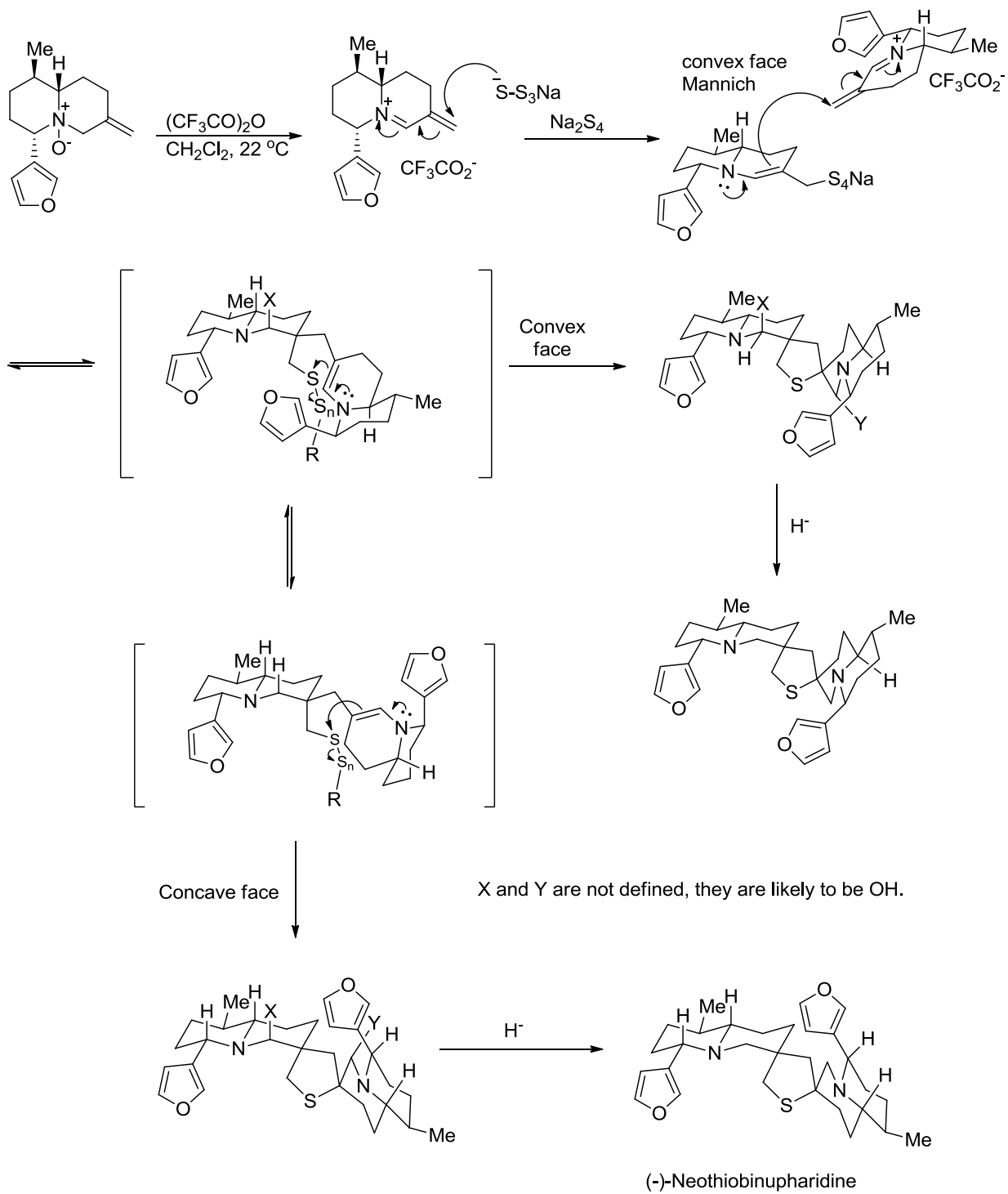


Scheme 1-25

Recently, Jansen and Shenvi reported the first asymmetric synthesis of (-)-neothiobinupharidine and the shortest synthesis of the nuphar quinolizidine monomer (Scheme 1-25). The synthesis began with a combination of Buchwald's conjugate addition³³ to the cyclopentenone **1.119** and a modified Tsuji-Trost allylation giving ketone **1.120** with high diastereoselectivity (d.r. > 10:1) and high enantioselectivity (e.e 95%). This procedure effectively introduces two chiral centres, and thus, leads to a short synthesis of the nuphar alkaloids. Cyclopentenone **1.120** was converted to an oxime which underwent Beckmann rearrangement to form lactam **1.121** with the

expected regioselectivity. Vanderwal's allylsilane-RCM methodology was applied to convert lactam **1.121** to quinolizidine **1.122** with an exocyclic methylene.³⁴ These five steps could be achieved on a multigram scale (3.4 g). The 3-furyl moiety was introduced by a modification of Fowler's procedure¹⁶ and reduction was carried out with sodium triacetoxyborohydride to provide indolizidine **1.77**, which is also an intermediate reported by Harrity and co-workers in their nuphar alkaloid synthesis.²⁰ Oxidation of indolizidine **1.77** followed by elimination with trifluoroacetic anhydride generated iminium ion **1.123**, which was then dimerized with sodium tetrasulfide in DMSO to give dimer **1.124** with high diastereoselectivity (10:1). Finally the dimer was reduced with sodium borohydride to provide (-)-Neothiobinupharidine (**1.10**).³⁵

The mechanism of the dimerization is not fully understood. It has been suggested that an iminium ion is generated and trapped by a sulphide nucleophile to generate an enamine. The enamine then adds to a second iminium ion. This addition is to the "convex" face of the enamine, which is well precedented for Nuphar alkaloids. The newly formed enamine then counter-attacks onto sulphur to form the tetrahydrothiophene bridge. The reaction occurs on the concave face, in contrast to the initial attack. This may be under stereoelectronic control as it corresponds to axial thiolation. Why the diastereoselectivity of this step varies with solvent and the amount of sulphide remain to be explained. The crude mixtures produced by the dimerization were reduced with sodium borohydride to convert the remaining iminium ions or hemiaminals to the amine (Scheme 1-26). The elegant synthesis of (-)-neothiobinupharidine by Jansen and Shanvi could be considered the most efficient synthesis among the nuphar alkaloids reported to date.



Scheme 1-26

Conclusions

In conclusions, various synthesis strategies of Nuphar alkaloids were discussed. However, more efficient and flexible methods should be developed in constructing these interesting alkaloids.

CHAPTER 2:

Studies on the Synthesis of

Nuphar Alkaloids

Chapter 2: Studies on the Synthesis of Nuphar Alkaloids

2.1 Introduction

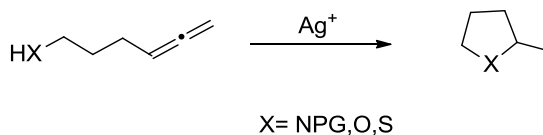
2.2 Allenic hydroxylamine cyclisation and its early applications in total synthesis

2.3 Alkene Cross Metathesis

2.4 Synthesis of Nuphar Alkaloids

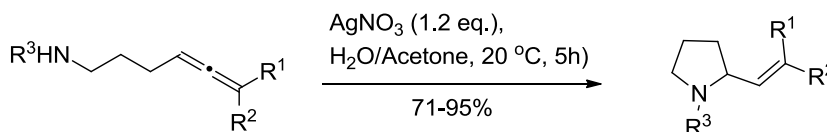
2.1 Introduction

Introduction



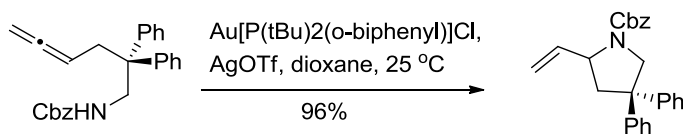
Scheme 2-1 General Claisen Cyclization

Since Claisen's serendipitous discovery of the allenic amine cyclization on a silver contaminated gas chromatography column, extensive work has been done on this and related reactions.³⁶ The cyclization reactions mainly used protected amine, oxygen or sulphur as the nucleophile and are normally catalysed by silver, gold or palladium (Scheme 2-1).³⁷



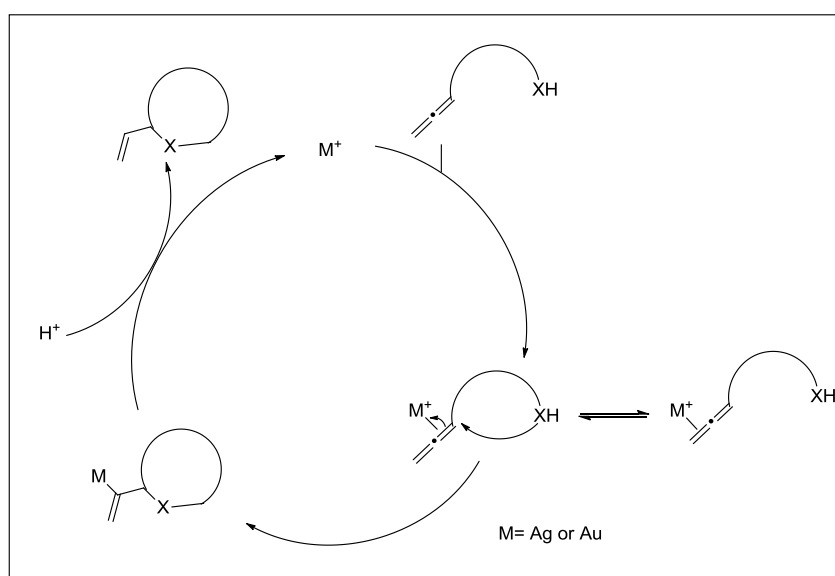
Scheme 2-2

Arseniyadis and Goré reported the *exo*-cyclization of the allenic amine by using high catalyst loading of silver nitrate (1.2 eq.) to obtain pyrrolidines. In the same work, they discovered that the silver catalysed cyclization could be achieved under ambient conditions with higher yields as compared to HgCl₂ that gave lower yields (35-70%) and required higher temperatures (60 °C), longer reaction times (12 hrs), as well as a Hg-C cleavage work up (Scheme 2-2).³⁸



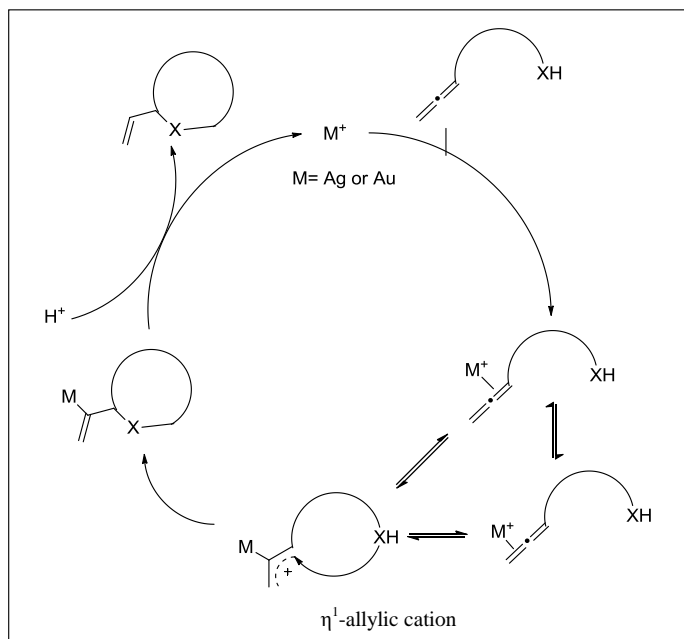
Scheme 2-3

On the other hand, Widenhoefer and co-workers have shown that the *exo*-cyclisation could be achieved by using gold(I) catalyst, Au[P(*t*Bu)₂(*o*-biphenyl)]Cl (5 mol%), in the present of AgOTf (5 mol%) at 25 °C for 5-45 minutes (Scheme 2-3).³⁹



Scheme 2-4 Proposed Mechanism for silver/gold catalyzed allenic cyclisation

The proposed mechanism of the metal catalyzed allenic cyclisation involved the coordination of the metal ion on the allene, followed by intramolecular nucleophilic attack and finally protonolysis to obtain the desired cyclised product (Scheme 2-4). The metal ion may coordinate to either of the allene double bonds, but these η^1 -complexes are believed to be in equilibrium.



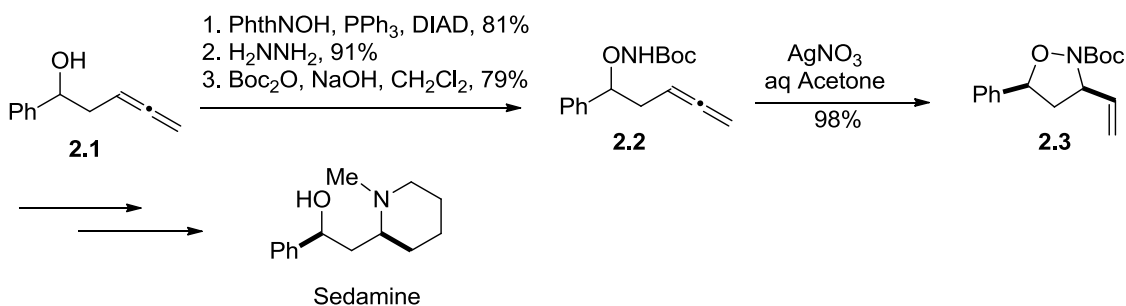
Scheme 2-5 Alternative proposed mechanism

Alternatively, Widenhoefer and co-workers proposed the involvement of a η^1 -allylic cation, which could be a reactive intermediate or transition state during the allene coordination (Scheme 2-5).

Tethered nitrogen has shown to be useful in the total synthesis of natural products, in which the nitrogen is being tethered temporarily by either a group or a covalent bond and undergoes intramolecular cyclofunctionalisation.⁴⁰ Bates and co-workers used hydroxylamines as tethered nitrogen nucleophiles to undergo Claisen cyclisation with silver salts as catalyst.⁴¹ This type of cyclisation has been shown to be useful as the reaction was done under very mild conditions and often gives high regio- and stereoselectivity. Besides that, careful design of the substrates could lead to a variety of building blocks which are useful as total synthesis intermediates and bioactive molecules. Some examples of the application of silver and gold catalysed cyclisation in total synthesis will be discussed in the next section.

2.2 Allenic hydroxylamine cyclisation and its early applications on total synthesis

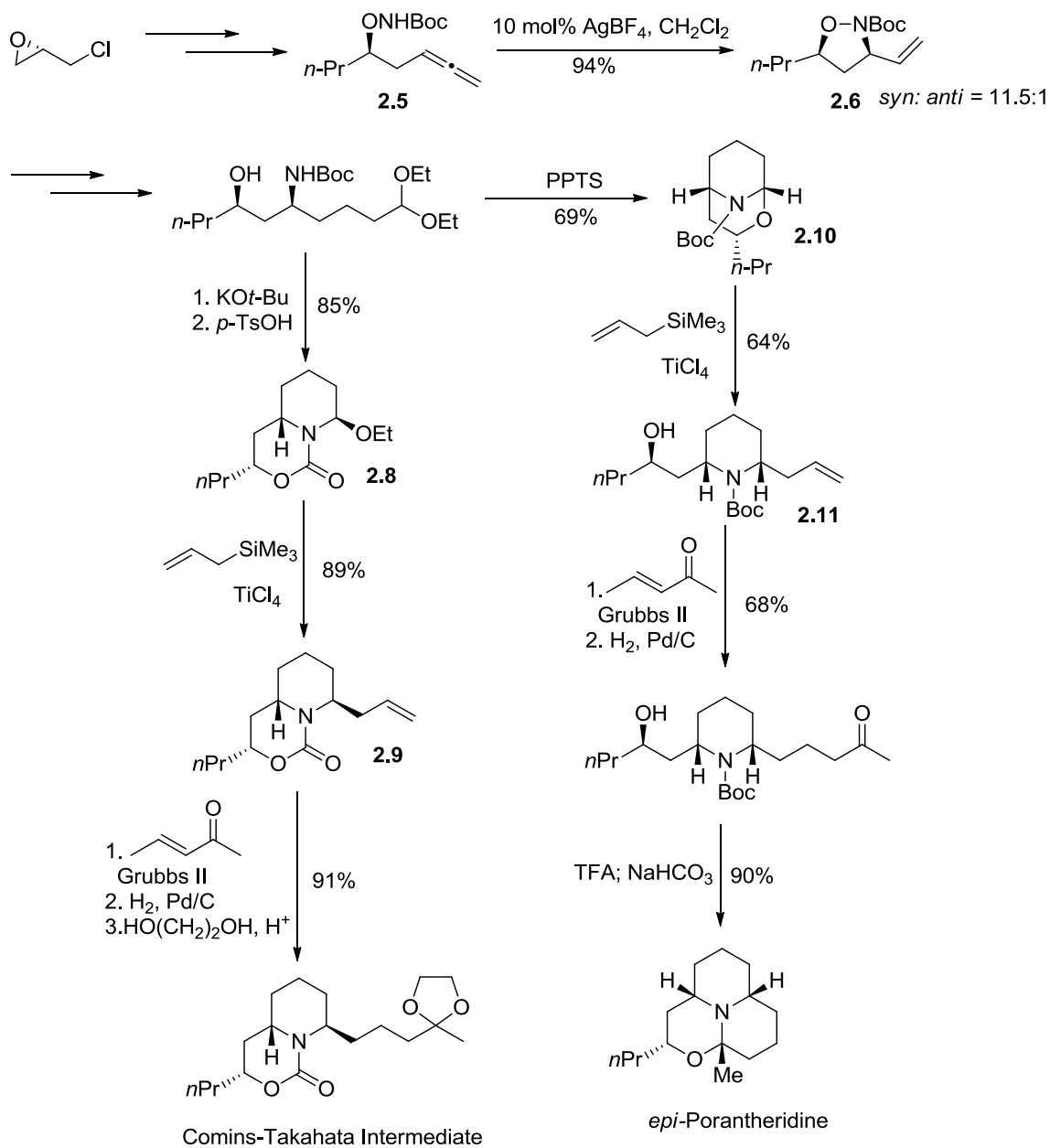
Synthesis of Sedamine



Scheme 2-6

Bates and co-workers reported the first allenic hydroxylamine cyclisation that led to the synthesis of Sedamine, which can be considered a ‘benchmark molecule to demonstrate synthetic methodology’ (Scheme 2-6). The allenic hydroxylamine was synthesised from the allenic alcohol **2.1** via a sequence of Mitsunobu reaction, dephthaloylation and Boc protection. The allenic hydroxylamine **2.2** cyclised under mild conditions with silver nitrate to give the isoxazolidine **2.3** with reasonable selectivity (7:1) and good yield (98%). The allenic hydroxylamine with Cbz as the protecting group gave slightly lower selectivity (5:1); when the *o*-nosyl group was used as the protecting group, no reaction was observed. The isoxazolidine then could be converted to Sedamine.⁴¹

Formal synthesis of Porantherdine and total synthesis of its epimer

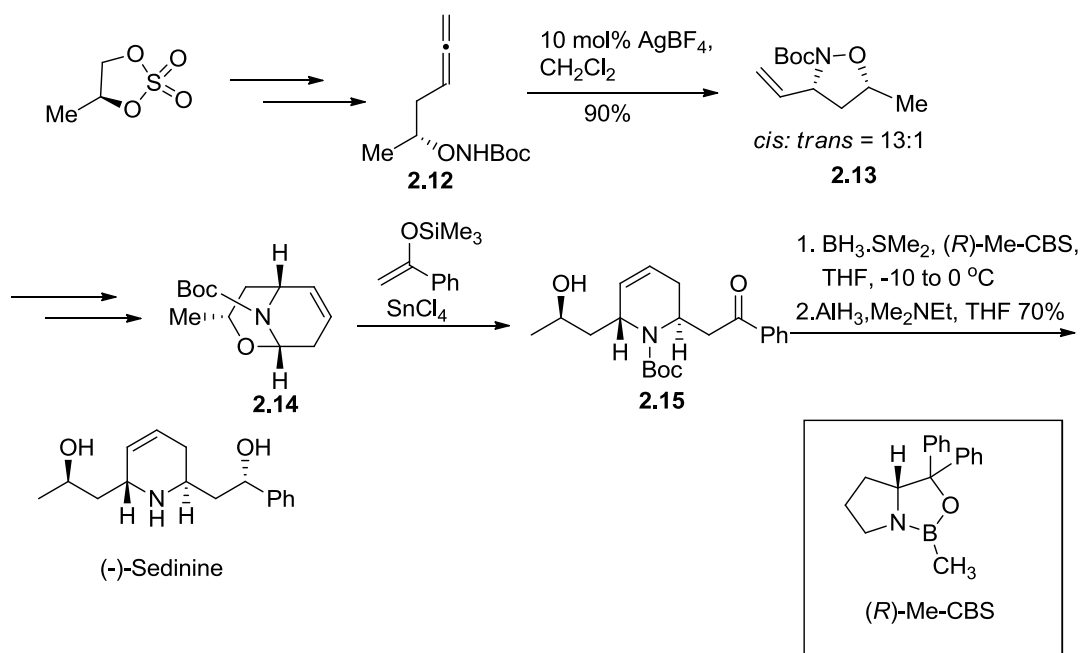


Scheme 2-7

The allenic hydroxylamine **2.5**, which was derived from commercially available (*S*)-epichlorohydrin, was cyclised with silver tetrafluoroborate as the catalyst giving 1,3-*syn* substituted isoxazolidine **2.6**. Cyclisation using different silver salts give different diastereoselectivity results and this suggests that there is a counter ion effect that

affects the reaction. The isoxazolidine was then converted to aminals **2.8** and **2.10**, which underwent Lewis acid mediated Sakurai-type allylation to form alkene **2.9** and **2.11** respectively. The two alkenes then could lead to the Comins-Takahata intermediate of porantheridine synthesis and total synthesis of *epi*-porantheridine (Scheme 2-7).⁴²

Total synthesis of Sedinine

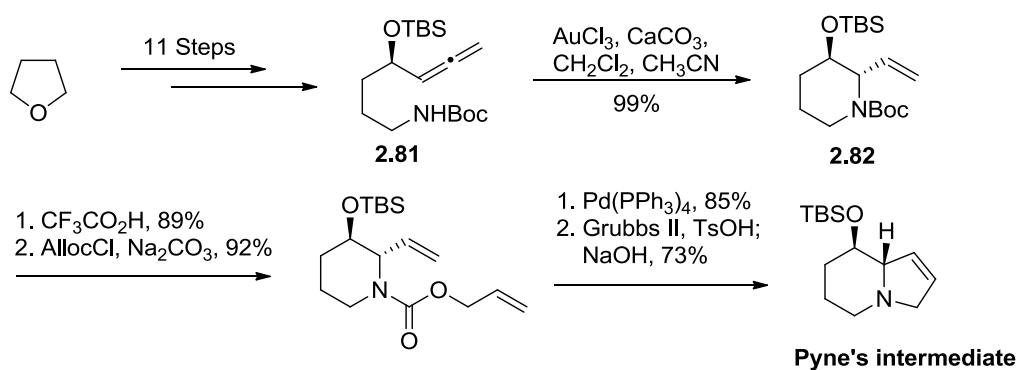


Scheme 2-8

Sedinine is one of the more challenging *sedum* alkaloids and had previously been the subject of a single, racemic, synthesis. Bates and Lu applied silver catalyzed allenic hydroxylamine cyclisation as one of the key steps during the synthesis of this alkaloid (Scheme 2-8). The allenic hydroxylamine **2.12**, which was derived from (*S*)-propylene glycol, underwent cyclisation with silver tetrafluoroborate to form the isoxazolidine **2.13** with the *cis* isomer as the major product. It was found that the optimum loading of the catalyst was 10 mole % and other amounts of loading would result in either a decrease of the yield or the diastereoselectivity. The reason behind this phenomenon

remains interesting and unsolved as the reaction mechanism could be much more complicated than expected. The isoxazolidine was then converted to the fused bicyclic amination **2.14** which underwent Lewis acid mediated stereoselective addition of the silyl enol ether to provide hydroxypiperidine **2.15**. Finally the ketone underwent asymmetric reduction with CBS catalyst and reduction with alane to give Sedinine, completing the first asymmetric synthesis of this compound.⁴³

Formal Synthesis of Swainsonine

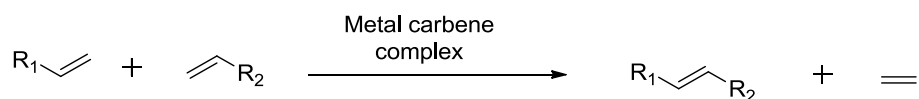


Scheme 2-9

Bates and Dewey started the formal synthesis of Swainsonine from THF, which underwent 11 synthetic steps to form amino allene **2.81**. The amino allene was cyclized with AuCl_3 to form amino alkene **2.82** with near quantitative yield and complete diastereoselectivity. Attempts of the cyclisation using silver(I) nitrate and the (triphenylphosphine)gold(I) chloride-silver triflate led to recovery of starting material. Introduction of calcium carbonate to the reaction was found to be able to prevent formation of hydrogen chloride due to trace amounts of moisture and thus avoiding the deprotection of TBS that led to formation of 5-*endo*-cyclisation by the oxygen and returning of starting material. Furthermore, acetonitrile was added as co-solvent as it increases the solubility and stability of the gold(III). Amino alkene **2.82** was then

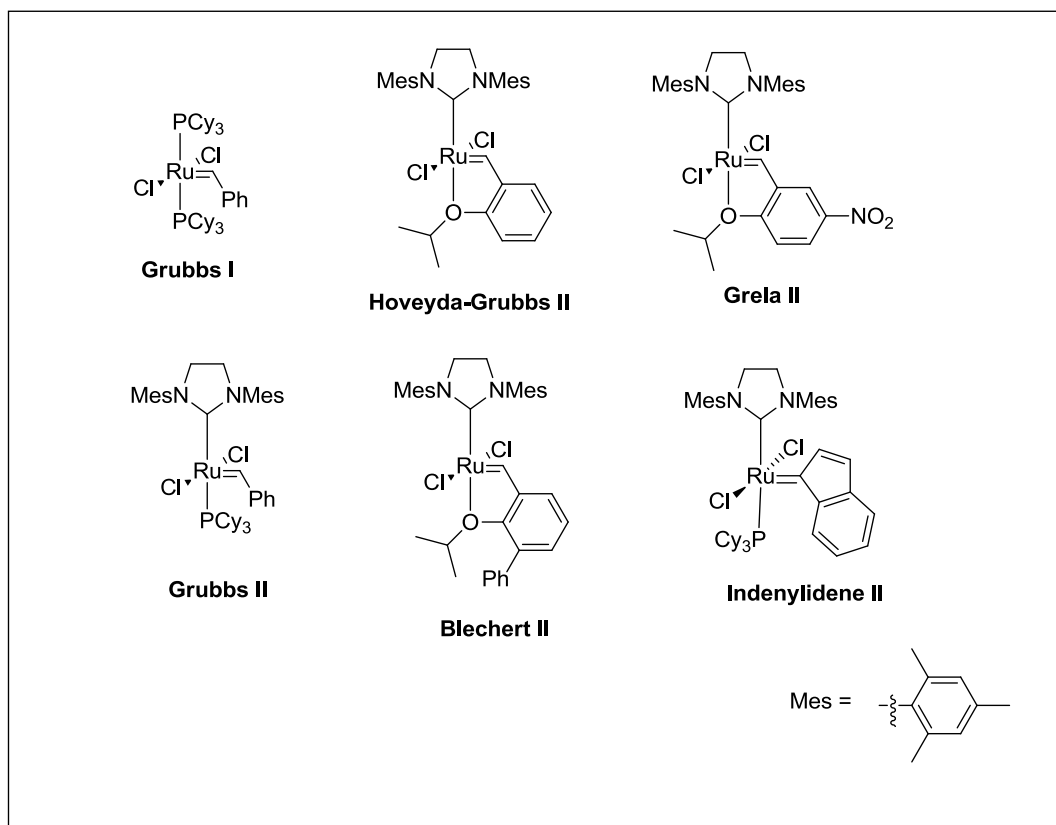
converted in multiple steps to Pyne's intermediate for the formal synthesis of Swainsonine (Scheme 2-9).⁴⁴

2.3 Alkene Cross Metathesis



Scheme 2-10

Alkene Cross-metathesis refers to the intramolecular exchange of two alkenes fragments to form a more substituted alkene by generating ethylene as a by product in the presence of metal carbene complexes (Scheme 2-10). The first examples of olefin metathesis, the conversion of propylene to 2-butene and ethylene in the Philips triolefin process, was a cross-metathesis reaction.⁴⁵ In terms of the synthesis of complex molecules, Ring Closing Metathesis (RCM) was developed first. Cross-metathesis followed later, perhaps because the early catalysts are less effective for this process.

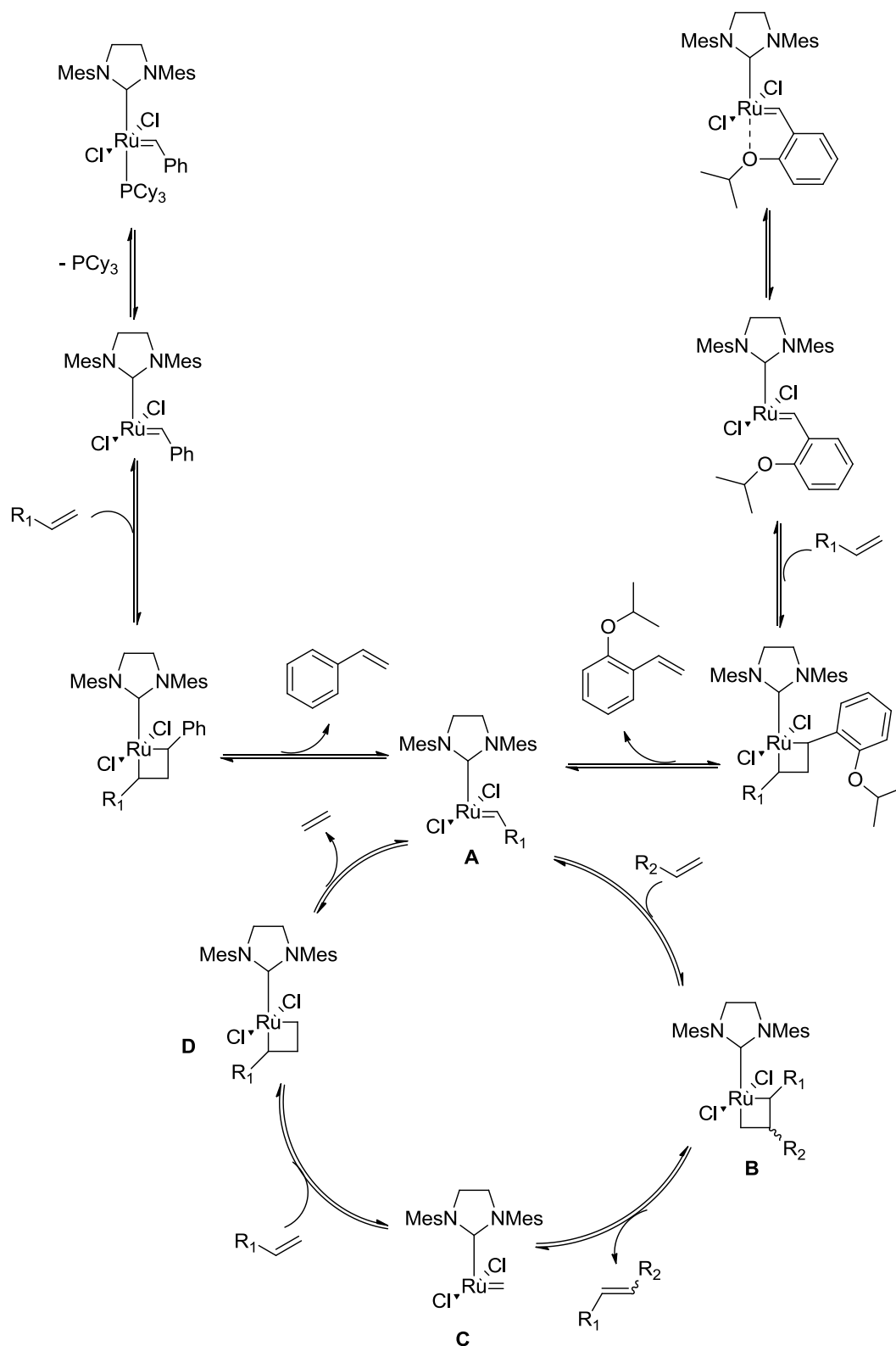


Scheme 2-11 Selected commonly used Cross Metathesis pre-catalyst

Several precatalysts for cross-metathesis reaction have been developed over the years. The choice of catalyst used for the reaction remains empirical and substrate dependant. The Grubbs II catalyst is often the first choice. The Grubbs I catalyst is useful for cross-metathesis only in special cases.

The proposed catalytic cycle of cross-metathesis is illustrated (Scheme 2-12). The mechanism begins with the dissociation of the ligand, tricyclohexylphosphine, for Grubbs II and dissociation of oxygen from the isopropyl group on Hoveyda-Grubbs II. The mechanism of cross metathesis involved the formation of a metalacyclobutane intermediate from the stepwise [2+2] cycloaddition of the metal carbene to the alkenes. The metalacyclobutane will collapse in a concerted manner to give aryl alkene and form metal carbene **A**. Subsequently another cycloaddition will occur with the alkene

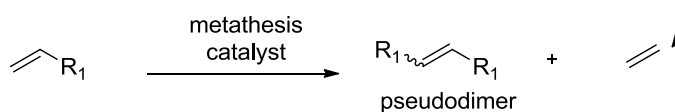
carrying fragment R_2 . Then a new substituted alkene will be formed upon the collapse of the metalacyclobutane **B** to generate metal carbene **C**, which is considered as the active catalyst for cross metathesis. As the formation of the different species in the catalytic cycle is reversible, the reaction generally proceeds towards the formation of the thermodynamically most stable product.



Scheme 2-12 Proposed Mechanism of Cross-Metathesis by Ruthenium type carbene complexes

Cross metathesis enjoys a number of advantages and has emerged as a powerful synthetic tool. Firstly, cross-metathesis reactions are atom economical as technically ethylene is the sole by product. The major alternative alkene forming reactions, such as the Wittig reaction, tend to generate significant by product, such as triphenylphosphine oxide and purification of the product can be troublesome. There is a wide selection of cross-metathesis substrates that are generally less expensive and readily available or can be synthesised easily. For other olefination reactions, such as the Wittig and Horner-Wadsworth-Emmons reactions, the ylid and the phosphonate respectively need be to synthesised. Low catalyst loading of 1-5 mol% are usually required for metathesis. Cross-metathesis reactions can be very appealing when it involves electron-deficient alkene as it is complementary to conventional method such as Horner-Wadsworth-Emmons, Wittig and Heck reactions.⁴⁶

However, there are several limitations to this useful reaction. Self-metathesis of alkene to form pseudo-dimers can be a problem that leads to a mixture of products. Cross-metathesis involving highly substituted alkenes or sterically hindered alkenes might not lead to the desired product. Therefore, choice of the alkenes is crucial to obtain the desired target molecules.



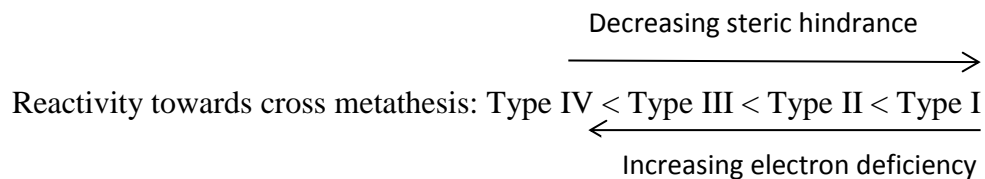
Scheme 2-13 Pseudo-dimerisation of alkenes in Cross Metathesis

Grubbs *et al.* have categorized the alkenes into four different types (Type I, II, III, IV) as a guideline based on the reactivity of alkenes towards formation of pseudo-dimers and participation in cross metathesis (Table 2A). Alkenes that do not fall under these

categories are those that will deactivate the catalyst.⁴⁷ This is a useful simplification however some alkenes may fall at or near the Type boundaries.

Type	Description
I	Alkenes that will undergo fast pseudodimerization and the pseudodimers are able to undergo another cross metathesis with the other counter- part alkenes. Examples of alkenes: terminal alkenes, allyl silanes, allyl boronate esters
II	Alkenes that will form pseudo-dimers more slowly than the Type I alkene and the pseudo-dimers can only partially participate in the subsequent cross metathesis. Examples of alkenes: acrylates, vinyl ketone, acrolein
III	Alkenes that will not form pseudo-dimers but are able to undergo cross metathesis with Type I and Type II alkenes. Examples of alkenes: 1,1-disubstituted alkene, non-bulky trisubstituted alkenes, phenyl vinyl sulfides
IV	Spectator alkenes that will only react in cross metathesis in the presence of certain catalysts and do not cause any inhibition to the catalytic activity on the other alkenes. Examples of alkene: protected trisubstituted allyl alcohols, vinyl nitro alkenes

Table 2A: Different Types of Alkenes



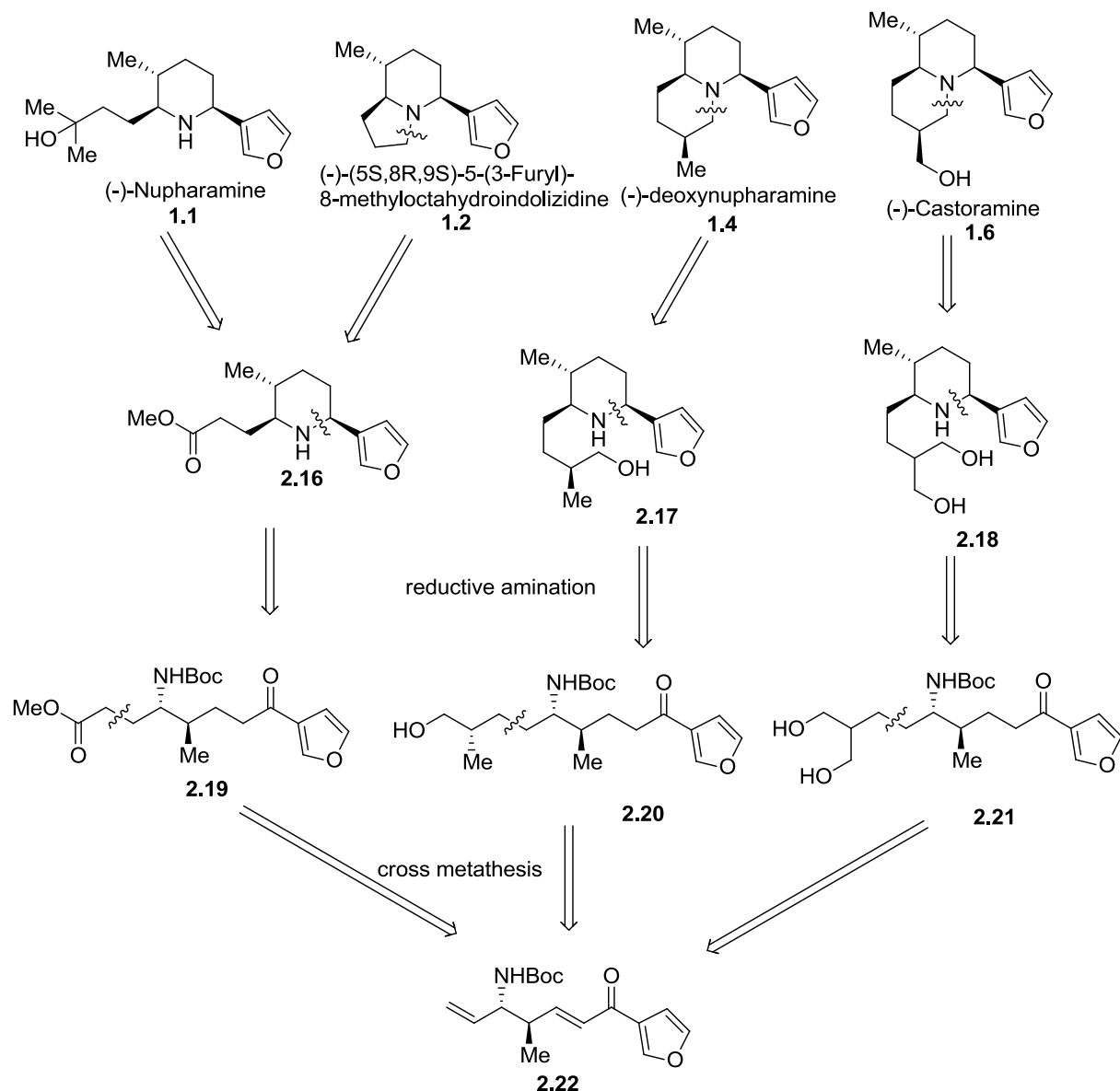
Scheme 2-14

Generally, the reactivity of olefins increases from Type IV alkenes, those that are sterically hindered and electron poor alkenes, to Type I alkenes, which are electron rich and sterically unhindered (Scheme 2-14). Cross metathesis reaction between two Type I alkenes will result in statistical distributions of products and pseudo-dimers unless one of the alkenes is in great excess (10 eq.) to obtain high yield of desired product. Cross metathesis reactions often work well between Type II or Type III alkenes and Type I alkenes to obtain desired product as Type II and Type III alkenes form pseudo-dimers slowly and the Type I alkenes' pseudodimers can undergo secondary metathesis with the Type II or Type III alkenes.

Application of cross metathesis in natural product synthesis has gained increasing popularity over the last decades. Some examples of cross metathesis in natural product synthesis²³ can be found in the Chapter 1 of this thesis.

2.4 Synthesis of Nuphar alkaloids

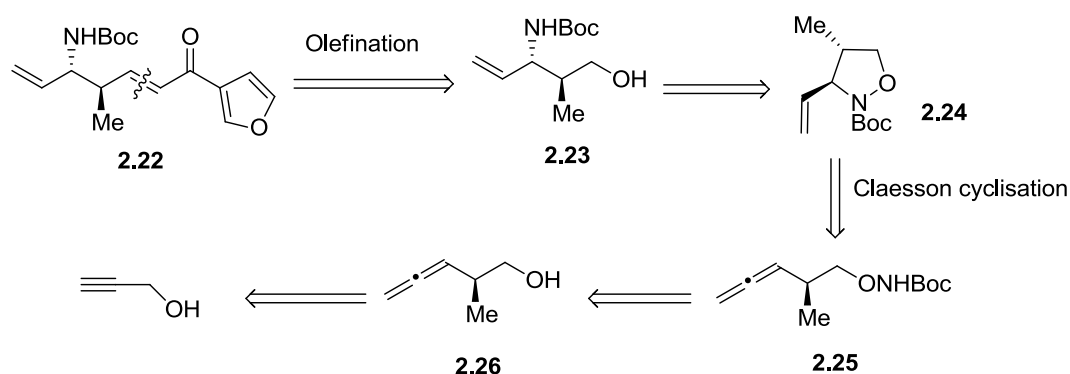
Retrosynthetic analysis



Scheme 2-15 Retrosynthetic analysis

Nupharamine (**1.1**), (3-furyl)-8-methyloctahydroindolizidine (**1.2**), deoxynupharamine (**1.4**) and castoramine (**1.6**), share three stereocenters with the same configuration on the piperidine ring. Thus, we proposed that the four alkaloids could be synthesised *via* a common intermediate. Nupharamine (**1.1**) and (3-furyl)-8-methyloctahydroindolizidine (**1.2**) were simplified to ester **2.16**. Castoramine (**1.6**) and

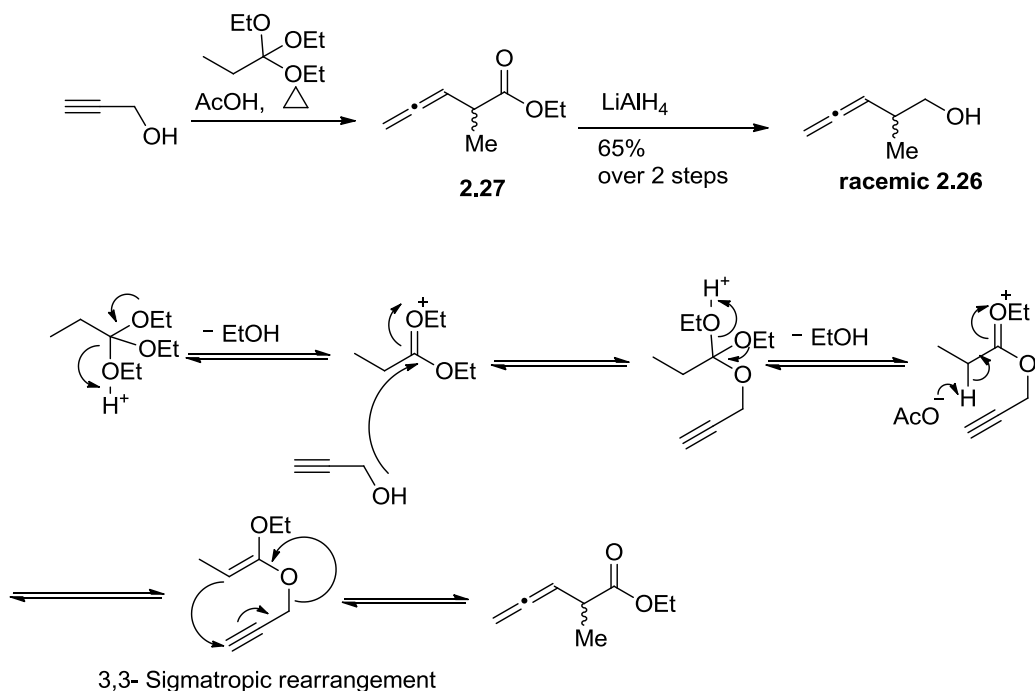
deoxynupharamine (**1.4**) were disconnected to compound **2.17** and compound **2.18** *via* nucleophilic cyclisation. Then the three compounds could be disconnected *via* reductive amination and condensation to compound **2.19**, **2.20** and **2.21** respectively. Cross metathesis could be done through diene **2.22** which is the common intermediate that can lead to different synthetic routes of the alkaloids (Scheme 2-15).



Scheme 2-16

Diene **2.22** can be further disconnected at the internal alkene with olefination or conversion of alcohol to good leaving group, followed by alkylation, to amino alcohol **2.23** which was derived from Claesson cyclisation product **2.24** of allenic hydroxylamine **2.25**. In the previous work of hydroxylamine cyclisation, the substituent is at the position α to the hydroxy group, which lead to the formation of *syn* 1,3 disubstituted isoxazolidine. However, the effect of the substituent at position β to the hydroxy group has not been studied. The allenic hydroxylamine **2.25** could be derived from the functional group interconversion of allenic alcohol **2.26** that could be formed from propargyl alcohol (Scheme 2-16).

Synthesis of the common intermediate

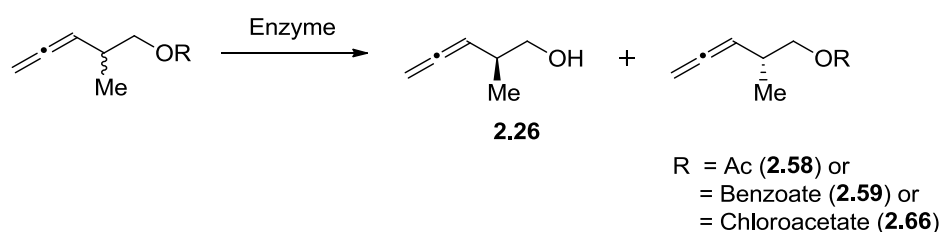


Scheme 2-17 Mechanism for the formation of allenic ester

The synthesis of diene started with the acid catalysed Johnson-Claisen rearrangement of propargyl alcohol and triethyl orthopropionate to form allenic ester **2.27** (Scheme 2-17), which could be synthesised on a 100 g scale.^{48,50} The ester obtained was contaminated with a small amount of ethyl propionate. However, the ¹H NMR spectrum was consistent with the data reported by Ohta and co-workers.⁴³ With the easy access to the starting material, dynamic kinetic resolution was applied during the synthesis of nuphar alkaloids. Enzymatic dynamic kinetic resolution is a selective reaction, hydrolysis for our case, on one of the enantiomers of substrate by an enzyme faster than the other enantiomer. In principal, a selective enzyme will give enantiopure product if the reaction is stopped when the yield reached 50%. The kinetic resolution of secondary alcohols is well known, but rare for primary alcohols.⁴⁹ The difficulty results from the chiral centre being more distant from the reactive site. The ester **2.27**

was reduced to alcohol **2.26** using LiAlH₄ and then converted to esters which subjected to high throughput screening and optimization to obtain the enantiomerically enriched alcohol. High throughput screening is a screening technique in which a substrate is subjected to many reagents or conditions or both at once in 96-well plates. Then upon work up, all the reactions will be assayed to identify by HPLC, GC or another method which group of mixtures gives the best result, which is a hit. Then the hit condition will be further optimized to obtain the desired result.

- **Enzymatic Kinetic resolution**

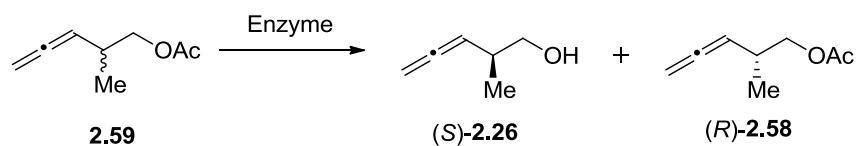


Scheme 2-18

Acetate **2.58**, chloroacetate **2.66** and benzoate **2.59** were synthesised from allenic alcohol **2.26** for the enzymatic kinetic resolution screening (Scheme 2-18). Acetate **2.58** was studied as it was previously employed by Ohta and co-workers.⁴³ Chloroacetate **2.66** was studied as it could be an advantage for work up as the unresolved chloroacetate could be reacted with triphenyl phosphine and dissolved in the aqueous layer during extraction. Benzoate **2.59** was chosen as a study candidate due to its lipophilic character. Stability tests were done on the three esters by stirring in potassium phosphate buffer solutions overnight at pH 6, 7 and 8. To our disappointment, the chloroacetate was hydrolysed to form the alcohol **2.26** even in the absence of enzyme. This ester was not, therefore, studied further. The acetate and benzoate esters, however, were stable. High throughput screening (HTS) of acetate

and benzoate with different type of enzymes were carried out. The results are summarised and discussed below.

HTS screening for Acetate



Entry	Enzyme	Conversion %	e.e. (%) of alcohol (5hr)
1	Lipase 003	74	8
2	Lipase 006	29	76
3	Lipase AN	28	6
4	Lipase A	69	0
5	Lipase PS	99	N.D.
6	Lipase P1	100	41 [#]
7	Lipase P2	100	81 [#]
8	Lipase PC	10	N.D.
9	Lipase PF	99	N.D.
10	Lipase RS	55	53
11	Lipase C1	91	N.D.
12	Lipase CA isoform A	59	35
13	Lipase CA isoform B	99	N.D.
14	Lipase MM	90	N.D.
15	Esterase 001	56	N.D.
16	Esterase 003	80	N.D.

17	Esterase 004	100	N.D.
18	Esterase 005	100	N.D.
19	Esterase 007	62	63
20	Esterase 008	77	9
21	Esterase 009	83	N.D.
22	Esterase 011	91	N.D.
23	Acylase 001	78	0
24	NZP 101	73	68
25	NZP 102	17	30
26	NZP 103	8	5
27	NZP 104	3	N.D.
28	NZP 105	3	N.D.
29	NZP 106	2	N.D.
30	Lipase AS1	74	20
31	Lipase AS2	100	N.D.
32	Lipase 005	98	N.D.
33	Lipase C2	98	N.D.
34	Esterase 002	100	N.D.

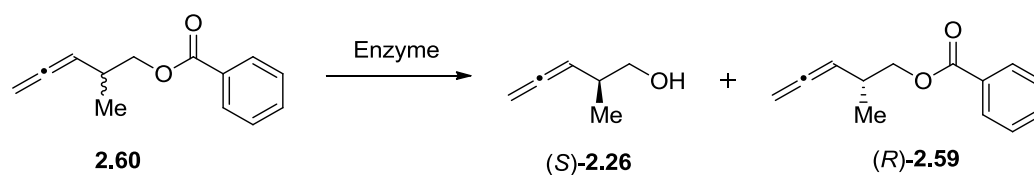
Table 2B Enzymes screening for allenic acetate.

Experimental error from the software error

Previously, Ohta and co-workers reported that Amano lipase PS does not hydrolyse the acetate to provide alcohol with good e.e.⁵⁰ We screened through a group of enzymes in the hope of obtaining a better enzyme for the kinetic resolution but none of the hydrolases give satisfactory e.e. that could be worked on further. Some of the

enzymes were totally unselective while some were not reactive towards the substrates. Enantiomeric excess of enzymatic reactions that gave very high yields, >80%, were not determined as the enzymes are thus shown to be non selective and too reactive. Enantiomeric excess for reactions with low yields, <30%, were not determined as it was assumed that the enzymes are not reactive enough for the substrates (Table 2B).

HTS of benzoate and optimization



Entry	Enzyme	Conversion	e.e. of alcohol (%)
1	Lipase 003	86	12
2	Lipase 005	66	9
3	Lipase 006	0	N.D.
4	Lipase AS1	0	N.D.
5	Lipase AS2	41	86
6	Lipase A	4	N.D.
7	Lipase AN	0	N.D.
8	Lipase C1	0	N.D.
9	Lipase C2	92	11
10	Lipase P1	70	83
11	Lipase P2	47	89
12	Lipase PC	0	N.D.
13	Lipase PF	37	40

14	Lipase PS	65	10
15	Lipase RS	13	N.D.
16	Lipase CA isoform A	0	N.D.
17	Lipase CA isoform B	0	N.D.
18	Lipase MM	0	N.D.
19	Esterase 001	19	28
20	Esterase 003	87	16
21	Esterase 004	91	10
22	Esterase 005	5	N.D.
23	Esterase 007	3	N.D.
24	Esterase 008	0	N.D.
25	Esterase 009	20	0
26	Esterase 011	0	N.D.
27	Acylase 001	0	N.D.
28	NZP 101	0	N.D.
29	NZP 102	0	N.D.
30	NZP 103	0	N.D.
31	NZP 104	0	N.D.
32	NZP 105	0	N.D.
33	NZP 106	0	N.D.

Table 2C Enzymes screening for allenic benzoate

We then carried out similar screening with the benzoate (Table 2C). To our delight, enzyme AS 2 and lipase P2 from the enzyme screening showed good conversion and selectivity.

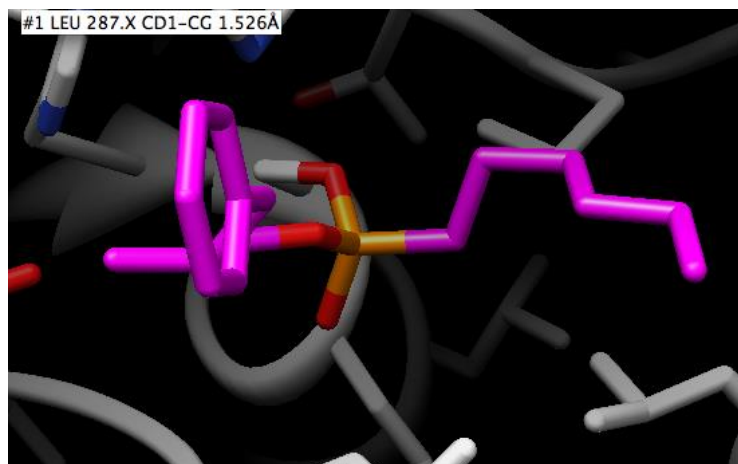
Entry	Enzyme	e.e. (%) of alcohol (12hr)
1	Amano Lipase PS	82%
2	Lipase P2	80%

Table 2D e.e. Comparison between Amano Lipase and Lipase P2⁵¹

A separate reaction was also carried out with Amano lipase PS from Sigma Aldrich, which is readily available (Table 2D). To our delight, Amano lipase PS from Aldrich was found to have similar reactivity as lipase P2 towards the hydrolysis of benzoate **2.59** providing good conversion and good selectivity of 82% e.e.

Amano Lipase PS is a hydrolase enzyme which is extracted from the bacteria *Pseudomonas Cepacia* (also known as *Burkholderia Cepacia*). This enzyme has been shown to be reactive towards secondary alcohols and often used in the kinetic resolution of secondary alcohols *via* hydrolysis.⁴² To our delight, Amano Lipase PS has shown stereoselectivity in hydrolyzing allenic benzoate **2.59**, which is a primary allenic alcohol derivative.

We were interested to understand the great improvement of enantioselectivity as the ester group changes from acetate to benzoate. The crystal structure of Amano lipase PS (1HQD) from the Protein Data Bank (PDB) was studied (Scheme 2-19).⁵² It was found that the binding pocket of the enzyme is very lipophilic. The substrate is surrounded by many aliphatic side chain of the peptide. Therefore a more lipophilic ester is a more suitable substrate to be hydrolysed by the enzymes. Benzoate is more lipophilic than acetate. Hence, the enzymatic kinetic resolution of benzoate gave better conversion as well as the enantioselectivity as benzoate can fit into the enzyme binding pocket better.



Scheme 2-19 Crystal structure of the binding pocket of Amano Lipase Enzyme

Hence, several allenic esters with different aromatic group and an aliphatic chain were screened with Amano lipase PS, lipase P2 and lipase AS2. Hexanoyl was chosen because of the long aliphatic chain. Nicotinate and Picolinate esters were synthesised in the hope of using acid/base extraction to remove the unreacted esters after the enzymatic reaction. Toluate and *p*-methoxybenzoate were chosen to examine the effect of increased size (Table 2E).

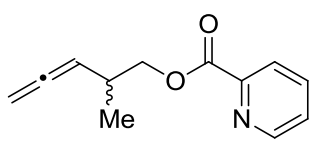
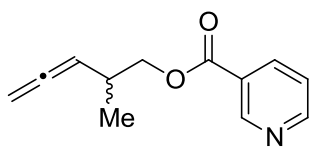
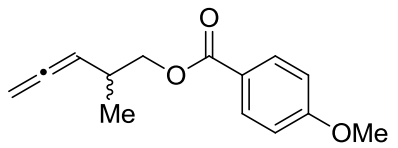
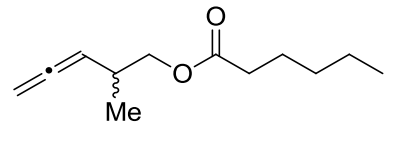
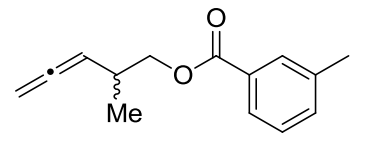
Aromatic esters	e.e. (%) of alcohol		
	Amano Lipase PS	Lipase P2	Lipase AS2
Picolinate 2.61 	65	63	64
Nicotinate 2.62 	68	65	68
4-methoxybenzoate 2.63 	52*	81	71
Hexanoate 2.64 	6*	5	5
<i>m</i>-toluate 2.65 	8*	52	35

Table 2E Screening of different allenic ester with different aromatic group for 19hr using Amano Lipase PS

Note: *e.e. was determined for 3hrs

Unfortunately, none of the esters with different aromatic groups and longer aliphatic alkyl chains give better e.e. than allenic benzoate ester. The hexanoyl ester shows almost no selectivity by the enzymes (Table 2E). This implies that the benzene ring is

important and probably benzoate fits better into the binding pocket of the enzymes than the rest of the aromatic rings.

DOE Experiments

Run	Factor 1 A: temperature (°C)	Factor 2 B: pH	Factor 3 C: Substrate (g/L)	Factor 4 D: CH ₃ CN (%)	Response 1 Conversion (%)	Response 2 e.e (%)
1	55	8	2.0	5	93	69 [#]
2	40	7	3.5	10	79	78
3	40	7	3.5	10	72	79
4	25	6	5.0	15	53	87
5	25	8	5.0	5	66	88
6	55	6	2.0	15	77	79
7	25	6	2.0	5	56	80
8	55	8	5.0	15	40	83
9	25	8	2.0	15	46	85
1	40	7	3.5	10	60	81
11*	40	7	3.5	10	68	73
12	55	6	5.0	5	49	82

Table 2F D.O.E reactions conducted for 19h. Note:* reaction was carried out for 45hrs

experimental error

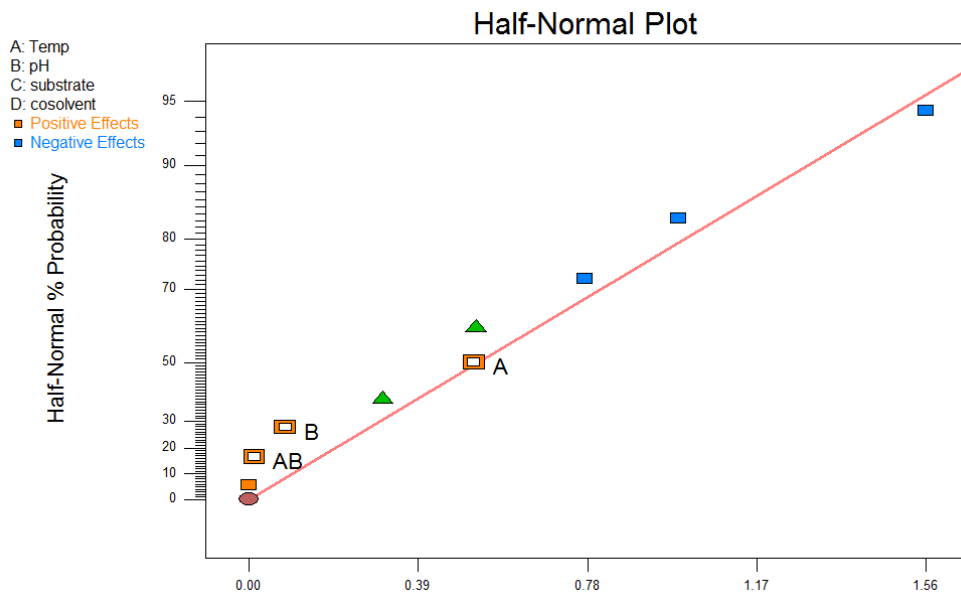
Design of Experiments (DOE) is a statistical design of experiments by using “Multivariant approach”, in which more than one variable of the reaction is changed

rather than the traditional approach as variables are not independent. The design of the experiments can be achieved by the software Design Expert. Experiments with a combination of variables and some control experiments will be generated and studied. Quantifiable variables that affect the reactions and the correlation between variables can be predicted from the 3-D graphs that are plotted based on the results that obtained from the generated reactions. Based on this, further reactions could be planned to obtain the desired results. To optimize the reaction, DOE was applied to generate a mixture of different reaction conditions to be screened with temperature, pH, organic co-solvent %, substrate loading as parameters. Temperature and pH were studied as the reactivity of enzymes is normally highly dependent on these factors. Amount of co-solvent was included as it is important for the solubility of the benzoate. The substrate loading was included to identify the amount that can be included in the reactions without affecting the e.e. of the product obtained (Table 2F).

Analysis of DOE Results

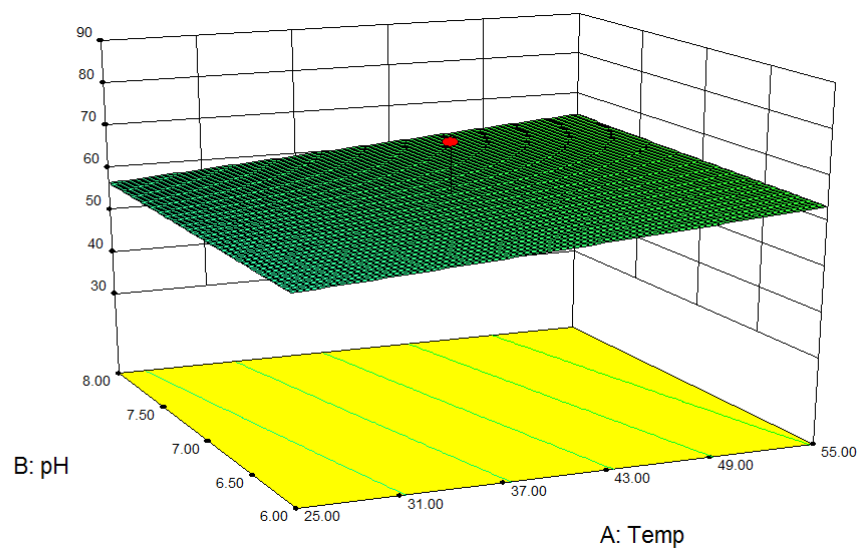
Half-Normal Plot or Half-Normal Probability Plot is used in Design Expert to quantify the estimated effects of the different variables statistically which assist researcher in identifying variables which are important and variables that are dependent on each other.

Conversion



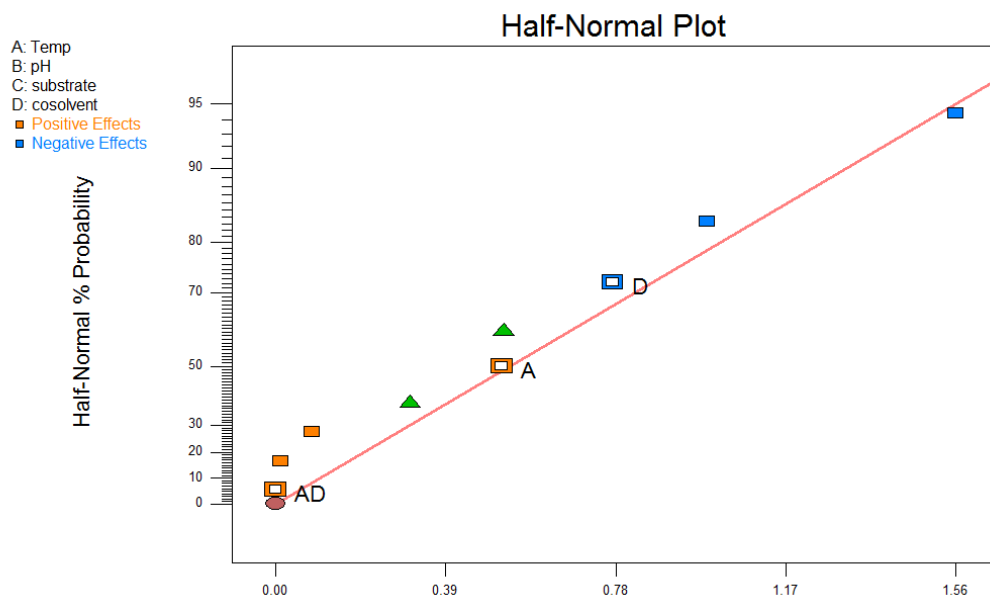
Graph 2-1

By taking account of the variables that affect the conversion of the hydrolysis, temperature and pH individually as well as together have positive effect on the reaction (Graph 2-1).



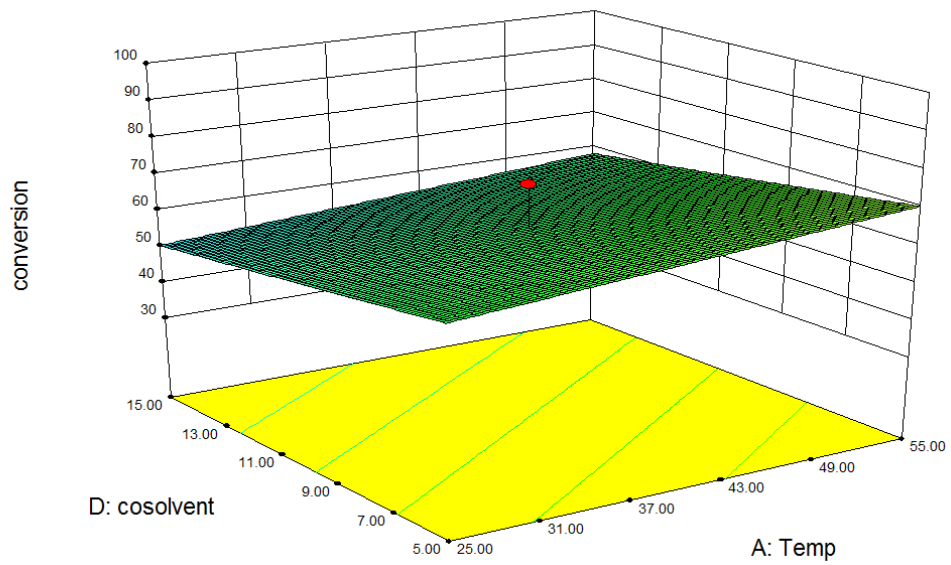
Graph 2-2

The 3D graph from analysis shown that, higher pH and temperature will increase the conversion. However, only 50% yield is desired as it is a kinetic resolution, only 50% of the enantiopure compound from the racemic mixture should react (Graph 2-2).



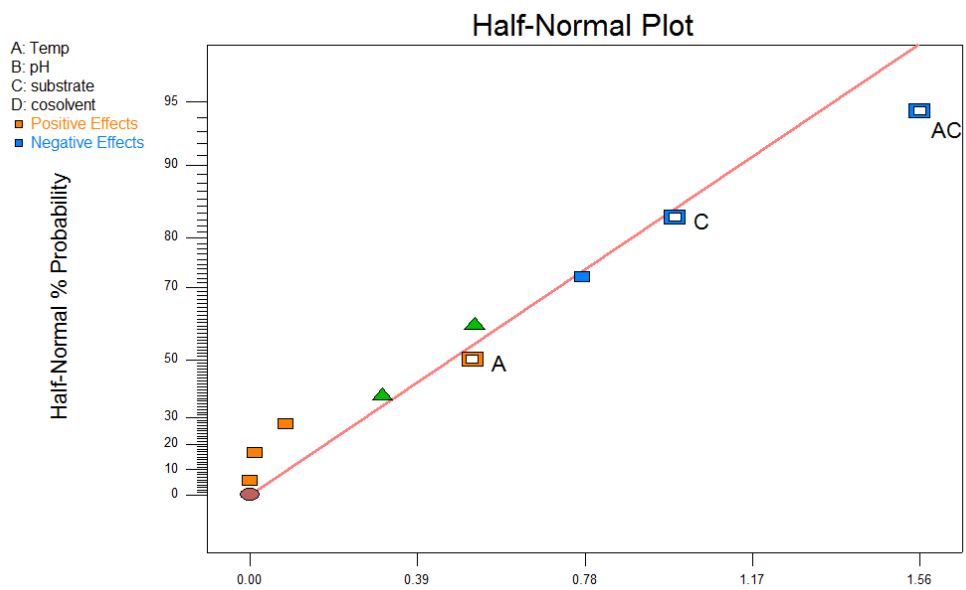
Graph 2-3

Temperature and co-solvent together will cause effect to the reaction but not the co-solvent itself (Graph 2-3).



Graph 2-4

The analysis showed that higher temperature and lower amount of co-solvent will increase the conversion of the reaction while a higher loading of co-solvent and lower temperature will decrease the conversion of the hydrolysis (Graph 2-4).

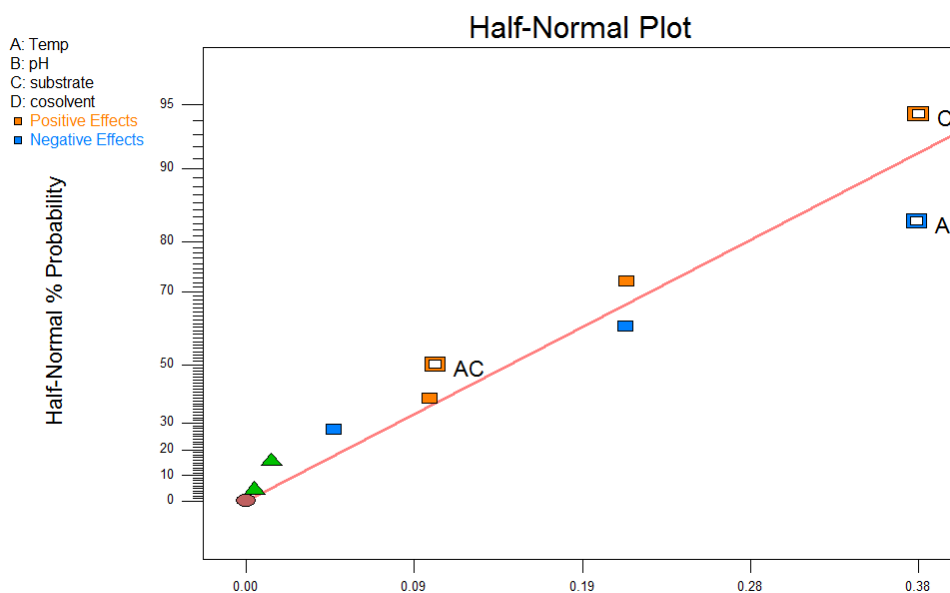


Graph 2-5

The analysis indicated that concentration of the substrate and its combination with temperature did not give strong effects on the reaction (Graph 2-5).

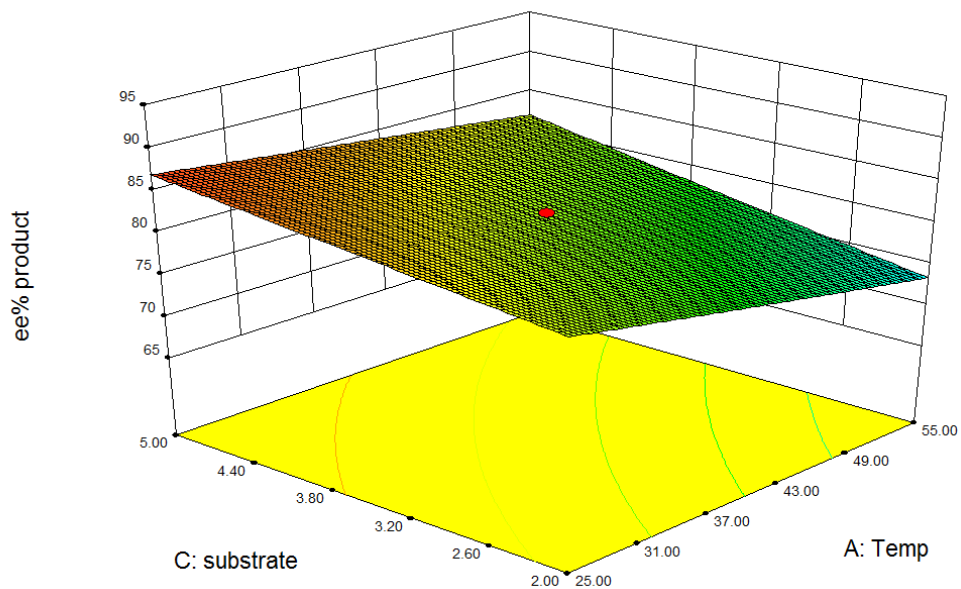
Besides looking into the effects that will affect the conversion of the kinetic resolution, we need to take into account the effects that will influence the enantioselectivity of the reaction.

e.e.



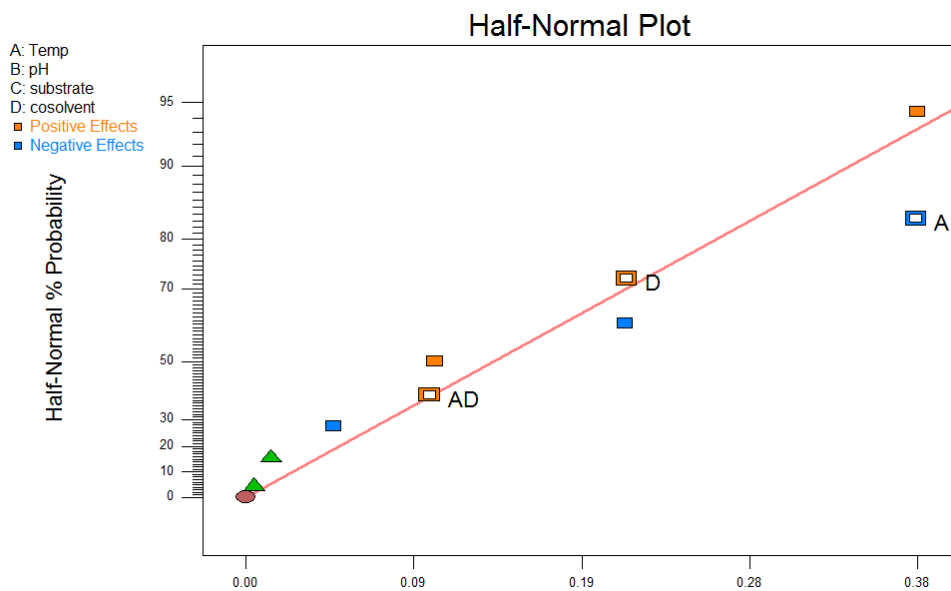
Graph 2-6

Temperature and combination with substrate will affect the e.e. of the resolution (Graph 2-6).



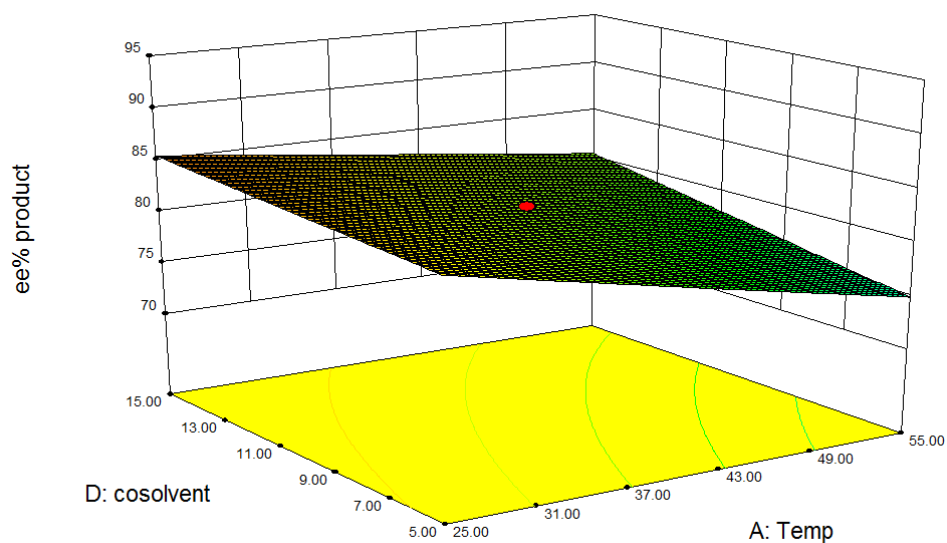
Graph 2-7

The analysis indicated that high concentration of substrate and lower temperature will increase the e.e. Higher temperature and higher substrate concentration will not increase the e.e. of the reaction (Graph 2-7).



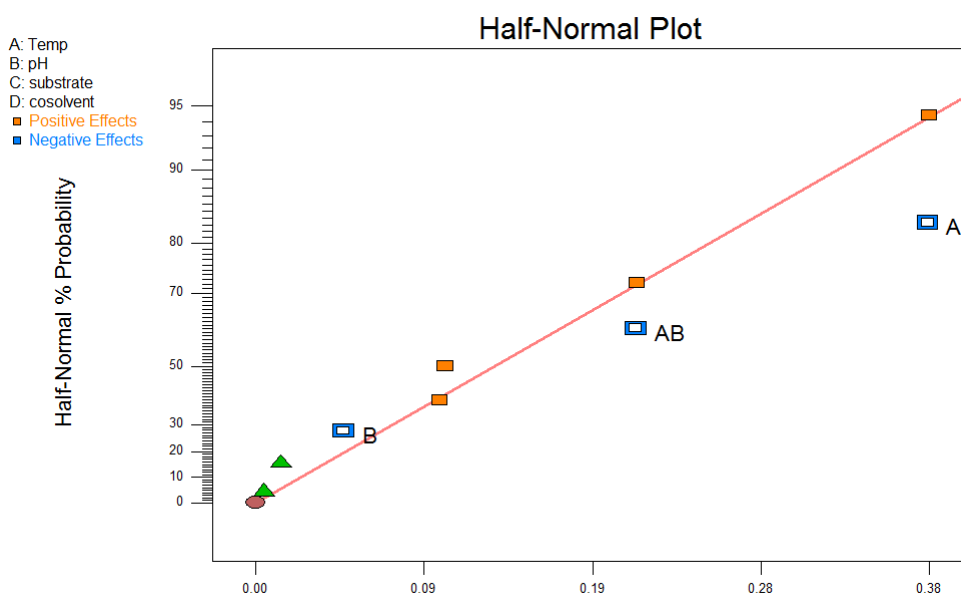
Graph 2-8

The amount of co-solvent added and combination of effect with temperature will affect the e.e. (Graph 2-8).



Graph 2-9

As the reaction temperature is reduced and the co-solvent proportion is increased; there will be an increase in the e.e. of the product. When the temperature of the reaction increases and more co-solvent is added, e.e. of the product will decrease (Graph 2-9).

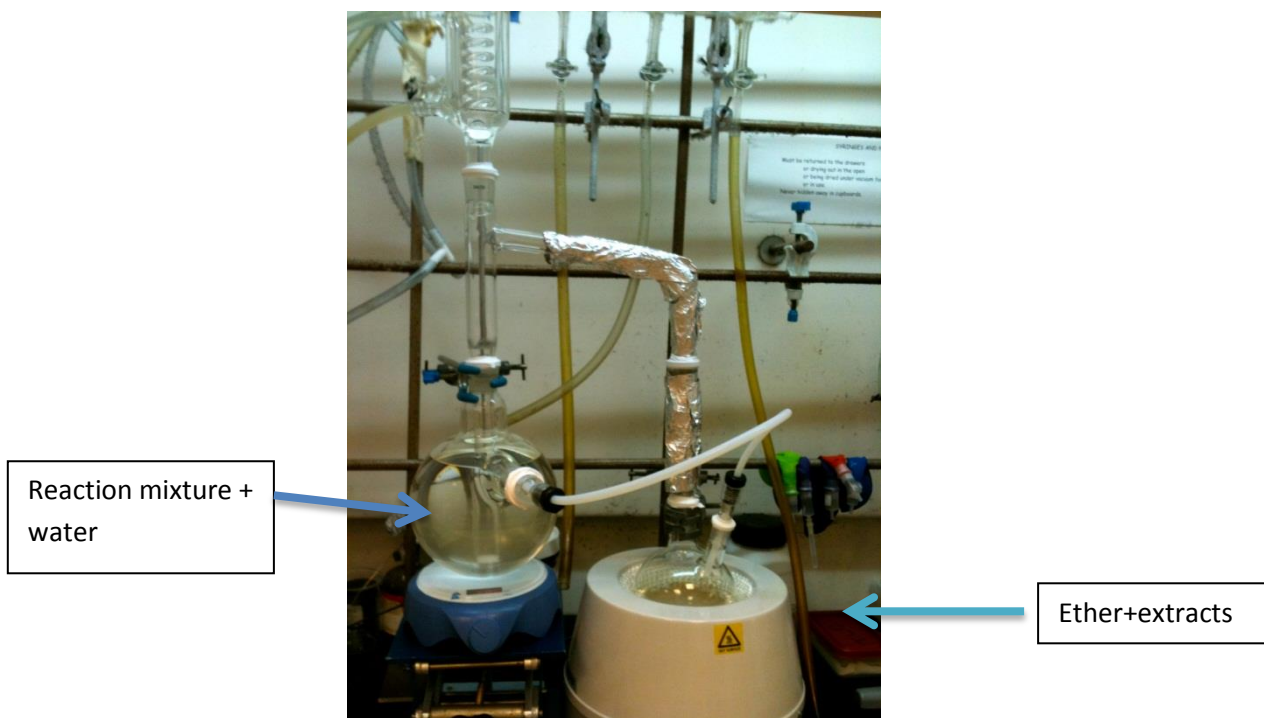


Graph 2-10

From the analysis, it shows that pH and temperature and their combination do not affect the e.e. of the reaction (Graph 2-10).

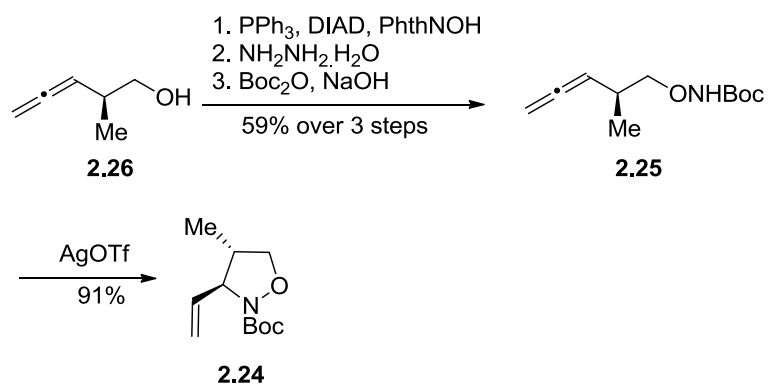
In summary, the variables affect the conversion and e.e. differently. However, the data obtained did not give an excellent DOE model which could be used to make good predictions and suggestions of best reaction condition. We decided to pick the conditions giving the best result from the DOE experiments to move on our synthesis.

With the best result from DOE experiments, the reaction was scaled up from 5 mL to 500 mL. However, the reaction did not proceed as well as in small scale; a significant decrease in yield (10%) and e.e. (60%) was observed. Through careful observation, it was found that mass transfer was the problem. The benzoate does not have good solubility in the reaction mixture. Hence, normal stirring is not effective enough for good mass transfer. Poor mass transfer will cause a prolonged reaction time and inefficient entry of the desired enantiomer to reaction with the enzymes and cause reduction in the enantioselectivity.



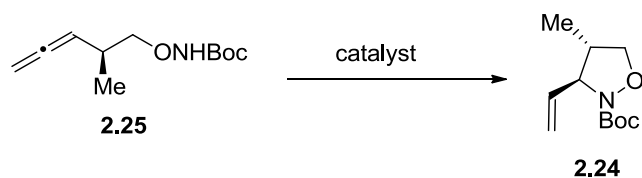
Scheme 2-20 Continuous Extractor

When an over-head stirrer was used, good selectivity (80% e.e) and reasonable yield (34%) could be achieved as the stirring is more vigorous and thorough. As the alcohol has good solubility in water, normal extraction with a separating funnel was unable to provide the alcohol in good yield. The reaction mixture of the enzyme kinetic resolution was extracted with Et_2O with a continuous extractor (Scheme 2-20) which improved the yield from 10% to 34%.



Scheme 2-21

The resolved alcohol **2.26** was subjected to a Mitsunobu reaction⁵³ to give phthalimide, which was then cleaved with hydrazine to provide the corresponding hydroxylamine. The hydroxylamine was then protected as a *t*-butyl carbamate, which gives better selectivity from previous studies in the group. The carbamate **2.25** was then subjected to Claesson cyclisation to form isoxazolidine **2.24** (Scheme 2-21).



Entry	Catalyst (mol%)	Solvent	<i>trans/cis</i>	Yield ⁵⁴
1	AgNO ₃ (20)	Acetone-H ₂ O = (5:1)	1.7:1	45%
2	AuPPh ₃ Cl/AgOTf = 1:1.8 (5%)	CH ₂ Cl ₂	1.8:1	23% (NMR)
3	AuCl ₃ (4)	CH ₂ Cl ₂	1.7:1	9%
4	Ag ₂ O (20)	CH ₂ Cl ₂	1.2:1	70%(NMR)
5	Ag ₂ O (26)	Acetone-H ₂ O = (5:1)	1:3.9	29%(NMR)
6	AgOTs (20)	CH ₂ Cl ₂	1.6:1	39%(NMR)
7	Argentated Silica (20)	CH ₂ Cl ₂	7:1	23%
8	AgSbF ₆ (20)	CH ₂ Cl ₂	-	N.R
9	AgBF ₄ (35)	CH ₂ Cl ₂	10:1	46%
10	AgOTf (20)	Acetone-H ₂ O	1:1	96%
11	AgOTf (20)	CH₂Cl₂	22:1	91%
12	HBF ₄ (30)	CH ₂ Cl ₂	-	0

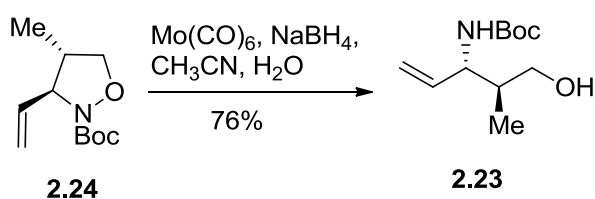
Table 2G Catalyst screening of Claisen cyclisation

Several silver and gold catalysts were screened (Table 2G). The catalysts were selected from readily available catalysts as well as commonly used catalysts for Claesson Cyclisation. The reaction using silver nitrate in aqueous acetone (entry 1) was initially attempted as it is the earliest conditions reported in the group. However, the selectivity was poor. Both gold(I)⁵⁵ (entry 2) and gold(III)⁵⁶ (entry 3) gave incomplete reactions and poor selectivity. Silver tetrafluoroborate (entry 9) was tried as it is one of the most commonly used catalysts for Claesson cyclisation and it gave reasonably good selectivity. All of the reactions gave the *trans* isomer as the major product except for silver oxide (entry 5) in which the selectivity was reversed. The reason for this remains unclear. We think that it might be due to the heterogeneous nature of the reaction. Hence, an investigation was done with argentated silica⁵⁷ as the catalyst (entry 7). To our disappointment, the selectivity of the cyclisation was not as anticipated. Strangely, cyclisation with silver hexafluoroantimonate (entry 8) only gave recovery of starting material.

The highest selectivity was obtained using silver triflate in anhydrous dichloromethane (entry 11). The cyclisation is highly efficient, where excellent 91% yield and good diastereoselectivity of 22:1 could be obtained and the reaction could be carried out on a 7.0 mmole scale. In contrast, the same silver salt in aq. Acetone gave no selectivity (entry 10). In fact, the high selectivity was obtained using silver triflate from a brand new bottle. When the reaction was repeated, the selectivity fell. It was realised that this was due to absorption of moisture by the hygroscopic silver triflate during handling. The high level of selectivity could be restored by running the reaction in the presence of activated molecular sieves.

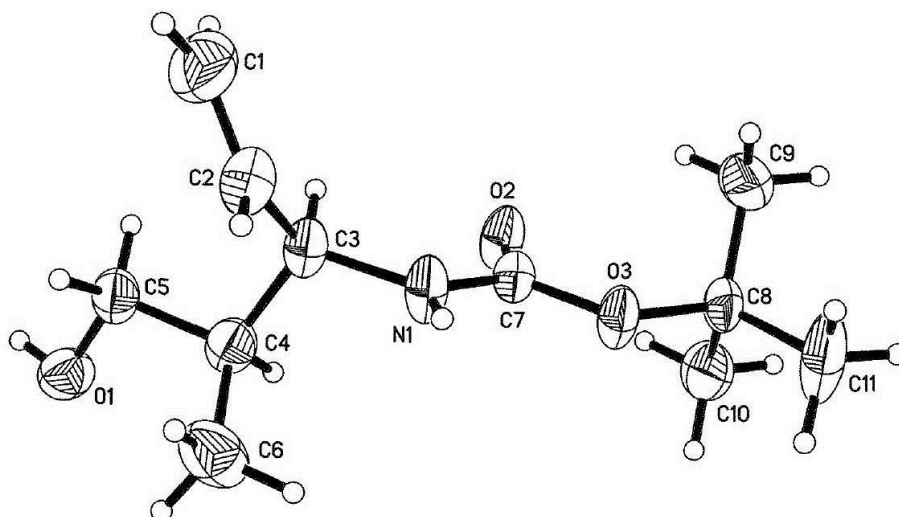
It was found that different counter ions of silver(I) salts greatly affect the selectivity of the cyclisation. This implies that the mechanism of the cyclisation is much more

complicated than the proposed mechanism. In addition, the presence of water significantly reduced the selectivity of the cyclisation. It is known that water molecules coordinate to organometallic silver complexes.⁵⁸ Thus, it can be speculated that the hydrated silver ion could affect the mechanism of the reaction. A control experiment with tetrafluoroboric acid (entry 12) was done and no reaction was observed. Thus, we can conclude that the Claesson cyclisation is silver mediated instead of proton mediated.

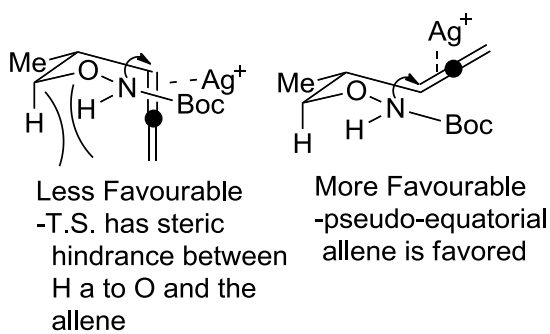


Scheme 2-22

At this point of the synthesis, the relationship between the two stereo centres was not known. To our delight, when the N-O bond was cleaved with molybdenum hexacarbonyl⁵⁹ to provide amino alcohol **2.23**, the product was crystalline (Scheme 2-22). X-ray crystallography showed that the two stereo centres are *anti* to each other (Scheme 2-23). This leads to the conclusion that the major product of the allenic hydroxylamine cyclisation was *trans*, which is the stereochemistry required for the nuphar alkaloids synthesis. Based on the screening, we propose the transition state of the cyclisation that leads to the formation of major *trans* product. Steric hindrance is probably one of the factors that influence the selectivity of the cyclisation (Scheme 2-24). Cyclisation of allenic hydroxylamine **2.25** with the methyl group at the position α to the allene gave major *trans* product, which is different from the previous findings when the substituent is at the position β to the allene that led to the formation of major *cis* product.

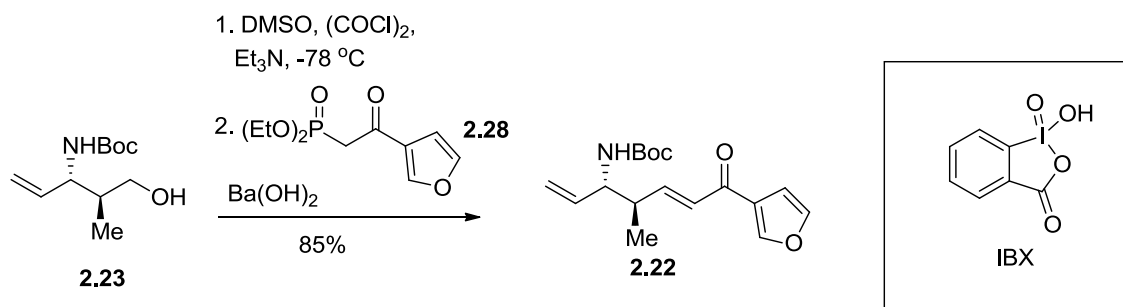


Scheme 2-23 X-ray Structure of amino alcohol 2.23



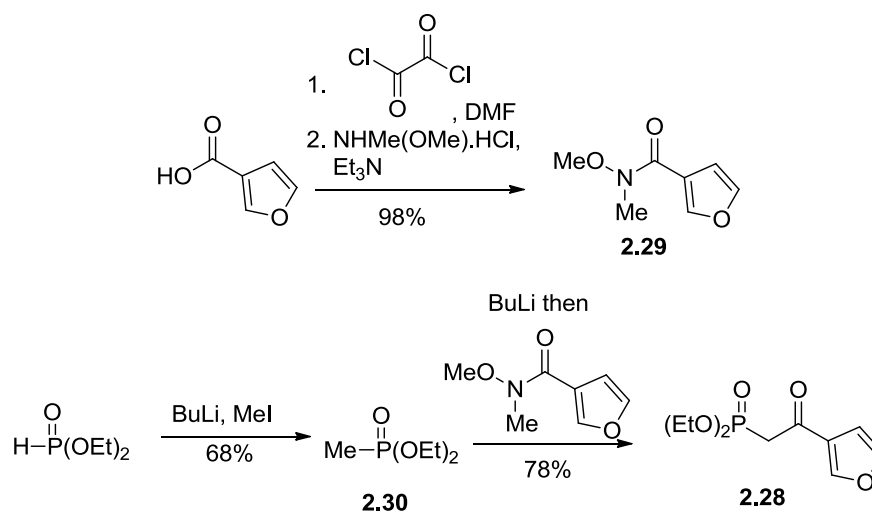
Scheme 2-24 Proposed Transition State of the Allenic Cyclisation

Initially, the alcohol of the amino alcohol **2.23** was converted to good leaving group (Br^- and I^-) so that alkylation could be done to install the keto furan. However, the activated amino alcohols were either unstable or unable to be isolated.⁶⁰



Scheme 2-25 Formation of the diene 2.22

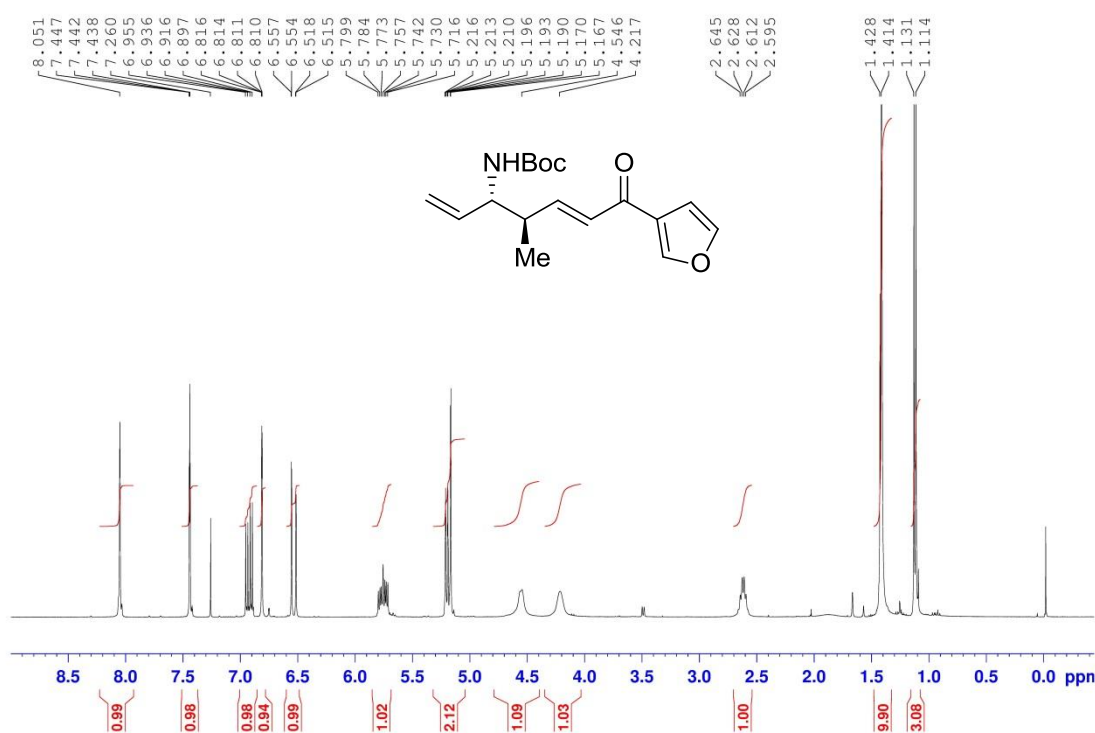
Instead of making a new C-C single bond, formation of a C=C double bond might be easier. Initially, oxidation of amino alcohol **2.23** was done with IBX but this resulted in partial epimerization, which might be due to the acidity of the IBX. Amino alcohol **2.23** underwent Swern oxidation⁶¹ to give aldehyde without epimerization as the reaction was done under very mild conditions. Aldehyde was then coupled with phosphonate **2.28** to form diene **2.22** (Scheme 2-25).



Scheme 2-26 Formation of phosphonate 2.28

Phosphonate ester **2.28** was synthesised from methylphosphonate **2.30**, which underwent nucleophilic substitution with the Weinreb amide **2.29** derivative of 3-furoic acid (Scheme 2-26).

Horner-Wadsworth-Emmons (HWE) olefination using $\text{Ba}(\text{OH})_2$ ⁶² was found to be superior to the Masamune-Roush conditions, (DBU as base with addition of LiCl),⁶³ which gave incomplete reaction and partial epimerization (Scheme 2-25). This might be due to $\text{Ba}(\text{OH})_2$ being a very mild base with low solubility in THF. Therefore, it was good enough to deprotonate the phosphonate but did not epimerize the aldehyde or the diene **2.22**. Thus, the common intermediate could be synthesised with control of relative and absolute stereochemistry.



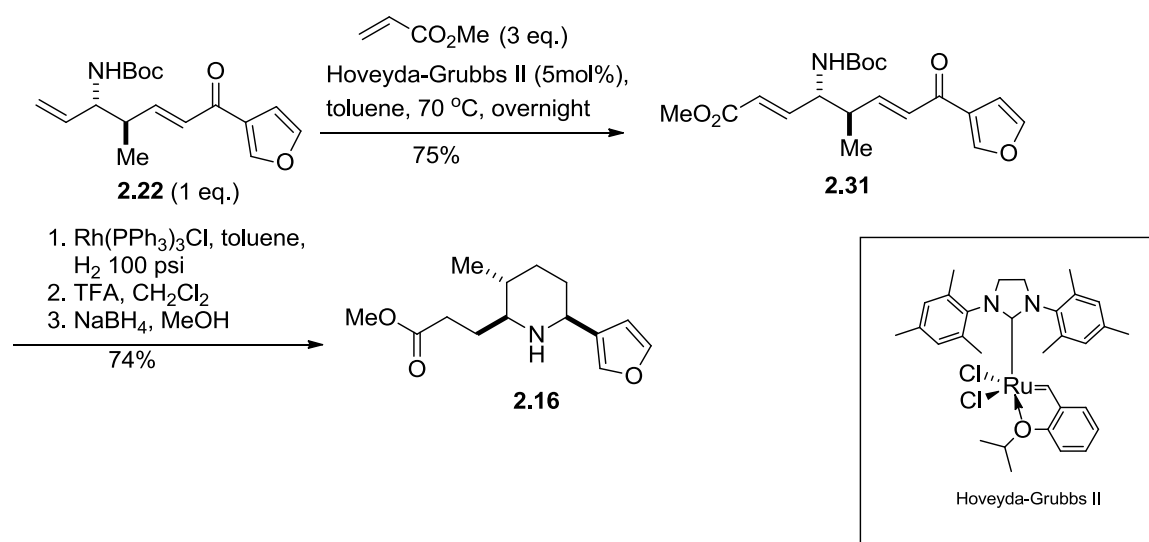
Scheme 2-27 ¹H NMR spectrum of diene **2.22**

The structure of diene **2.22** was determined by NMR (Scheme 2-27). The signal at the 5.78 ppm, which has the multiplicity of ddd ($J = 5.5, 10.1, 16.5$ Hz) corresponds to the proton of the internal carbon of the terminal alkene. The signals at 5.20 ppm and 5.22 ppm correspond to the terminal protons of the terminal alkene. The internal alkene had

signals at 6.55 ppm and 6.84 ppm which is due to the electron withdrawing effect of the carbonyl group. The coupling constants of both signals (15.6 Hz) confirmed that the internal alkene is an *E*-alkene. The proton which appears as a multiplet with a chemical shift of 4.26 ppm is attached to the carbon that is bonded to nitrogen. The signal at 2.66 ppm is due to the proton which shares the same carbon as the methyl group.

Synthesis of (±)-nupharamine and (±)-(5*S*,8*R*,9*S*)-5-(3-furyl)-

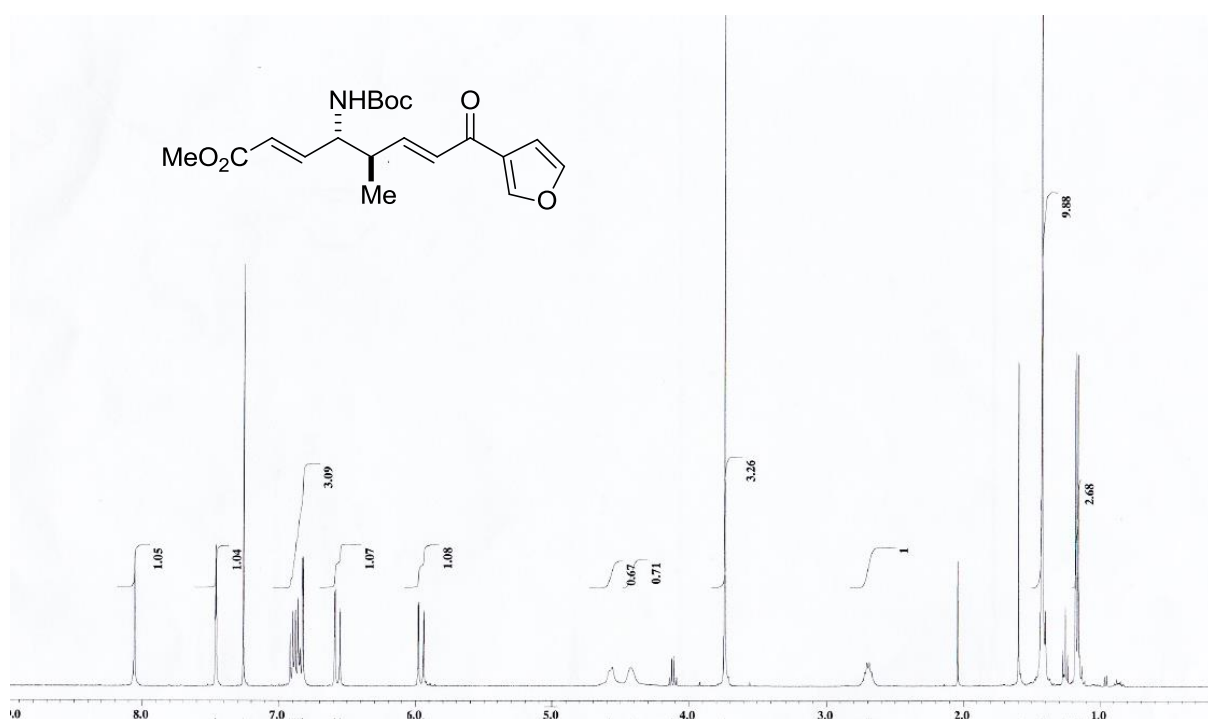
8-methyloctahydroindolizidine



Scheme 2-28

Nupharamine (**1.1**) and bicyclic nuphar alkaloid (**1.2**) were synthesized in racemic form as this work was carried out prior to the studies of enzymatic kinetic resolution of the allenic ester (Scheme 2-28). For the racemic synthesis of nupharamine (**1.1**) and the alkaloids (3-furyl)-8-methyloctahydroindolizidine (**1.2**), the diene **2.22** underwent cross-metathesis with methyl acrylate by using the Hoveyda-Grubbs II catalyst. Previous studies using Grubbs II as the catalyst resulted in poor yields and formation

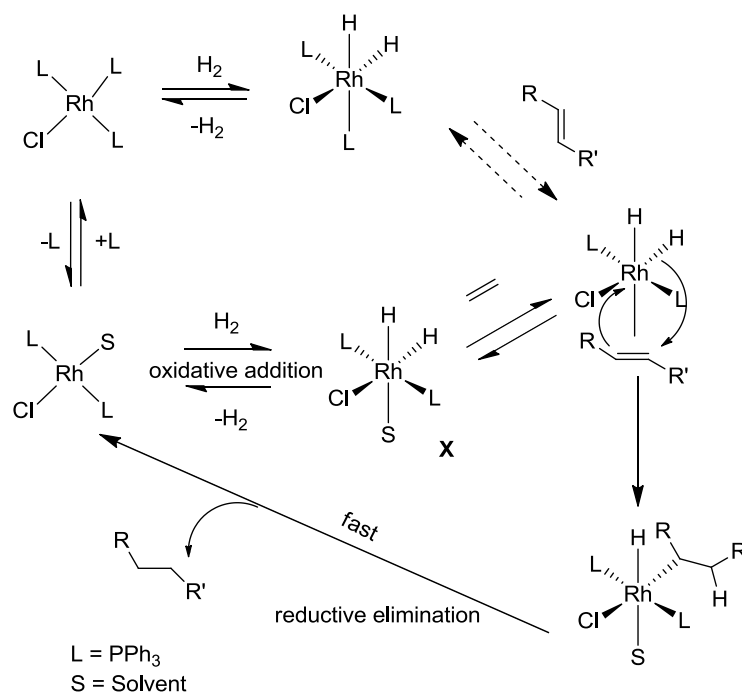
of the pseudo-dimer of the diene **2.22**. Hoveyda-Grubbs II catalyst had been shown to be a more robust catalyst with a longer reaction life time which is *via* stabilization by the oxygen atom of the isopropoxide of the catalyst. The longer reaction time might enable the pseudo-dimer of the diene to re-enter the catalytic cycle and drives forwards the formation of desired alkene **2.31**. Grela has shown that the catalyst works well at 70 °C in toluene.⁶⁴ The cross-metathesis reaction was also done with a continuous flow of nitrogen to purge the ethylene that is formed during the reaction and hence prolong the life time of the catalyst as well as driving the reaction towards the formation of the desired product. With the conditions above, the cross metathesis proceeded successfully giving diene ester **2.31** with good yield of 75%. No reaction at the internal alkene was observed.



Scheme 2-29 ¹H NMR spectrum of diene ester **2.31**

From the proton NMR spectrum (Scheme 2-29), it is observed that the signal of the terminal alkene at 5.20, 5.22 and 5.78 disappeared and new signals appeared at 5.92 ppm and 6.77 ppm, which correspond to the alkene that formed from cross metathesis.

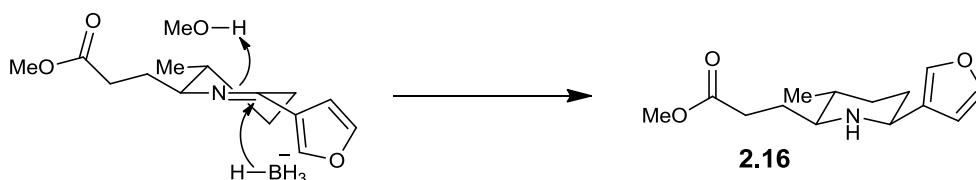
Use of the standard heterogeneous catalyst Pd/C was tried for the hydrogenation of the diene ester **2.31**, but reduction of furan ring was also observed. A homogeneous catalyst was considered for the reduction. The diene was then reduced using Wilkinson's catalyst under a moderate pressure of 100 psi to give the saturated ester in excellent yield. This is rather unusual, as most reductions using Wilkinson's catalyst only require atmospheric pressure and there are few reports using moderate pressure.⁶⁵ At atmospheric pressure, the hydrogenation gave partial and incomplete reduction of the diene ester **2.31**.



Scheme 2-30 Catalytic cycle of Wilkinson's hydrogenation

From the catalytic cycle, it can be suggested that, under high pressure, the equilibrium is shifted to the formation of the dihydride active species **X** and thus increases the rate of the rate determining step (Scheme 2-30).

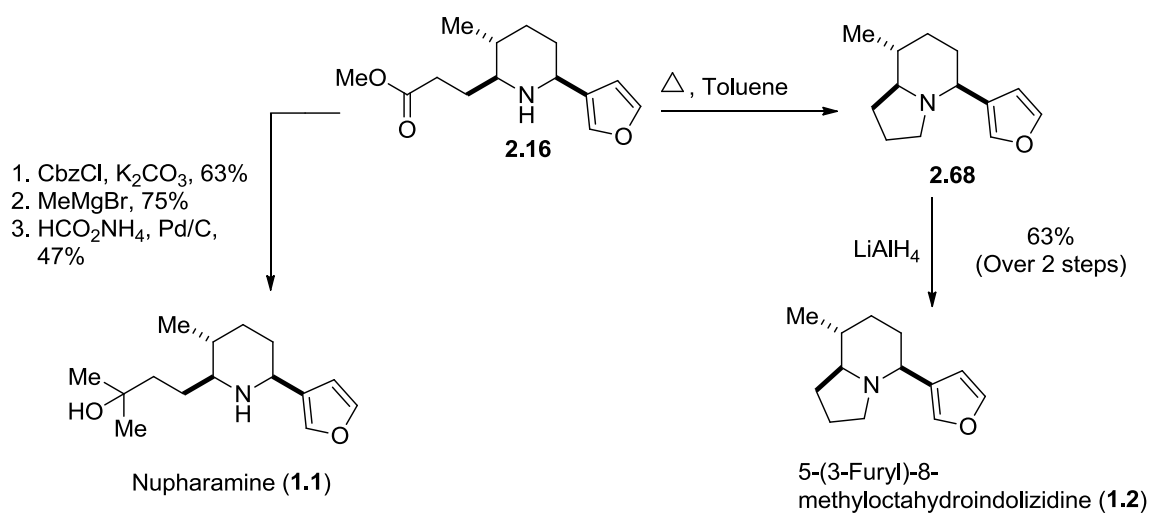
With the saturated compound in hand, the amine was deprotected with trifluoroacetic acid and, upon basic work up, it underwent intramolecular condensation forming an imine (Scheme 2-28).



Scheme 2-31 Stereoelectronic Control Reductive Amination

Then the reductive amination was done under stereoelectronic control, in which the hydride was delivered from the axial direction and lead to the formation of the amine *via* a chair transition state, to give ester **2.16** as a single diastereomer (Scheme 2-31).²⁴

The NMR data of the piperidine methyl ester **2.16** agrees with the results reported by Barluenga for a similar compound with an ethyl ester.



Scheme 2-32

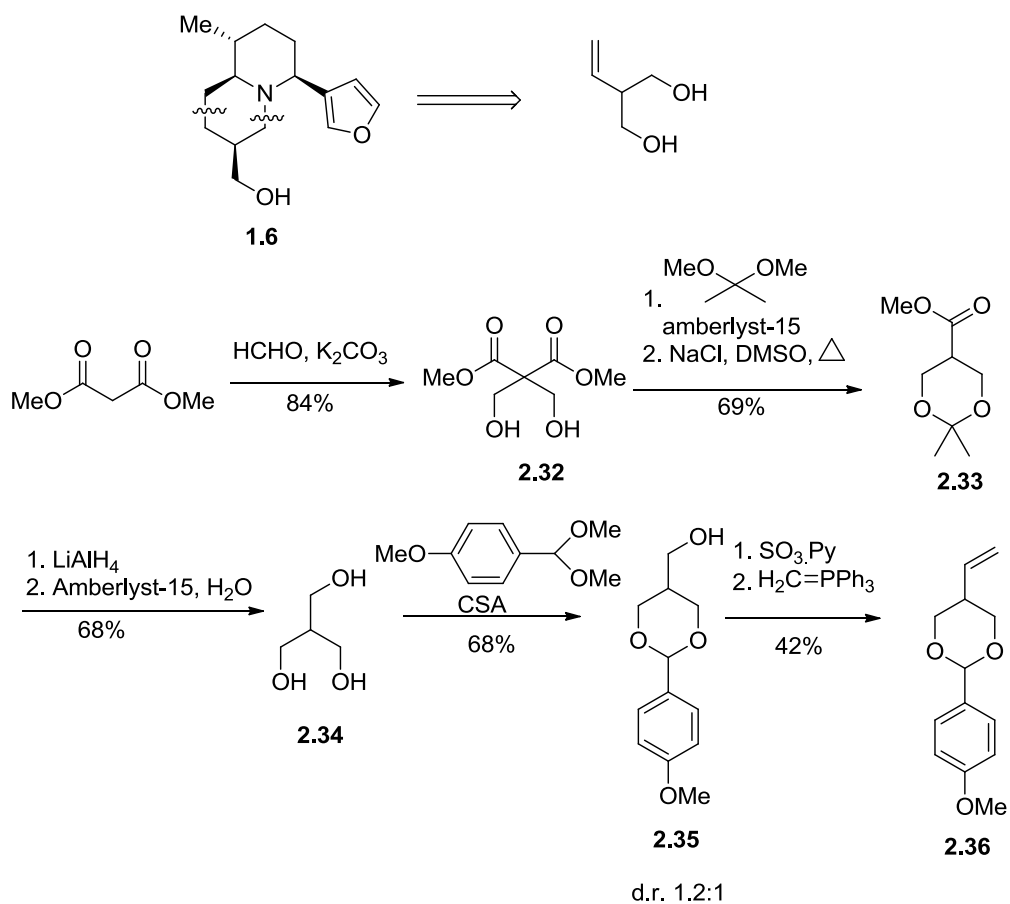
Synthesis of nupharamine and 5-(3-furyl)-8-methyloctahydroindolizidine

The ester could be converted to nupharamine (**1.1**) and 5-(3-furyl)-8-methyloctahydroindolizidine (**1.2**) as reported by Barluenga (Scheme 1-4).¹⁹ The ester **2.16** was cyclised to form the lactam under thermal conditions and reduced to form the unnamed alkaloid **1.2**. The ester **2.16** was protected as a benzyl carbamate, followed by reaction with MeMgBr to form a tertiary alcohol. Finally, the amine was deprotected to form nupharamine (**1.1**).¹⁹ Direct treatment of ester **2.16** with excess methyl magnesium bromide on unprotected amino ester **2.16** led to the formation of lactam **2.68** (Scheme 2-32), rather than nupharamine **1.1**.

In short, we have achieved the synthesis of the unnamed nuphar alkaloid **1.2** and nupharamine (**1.1**) by using the allenic hydroxylamine cyclisation and cross metathesis as key steps. These two alkaloids were synthesised in the racemic forms to show that amine **2.16** could lead to the natural products in the same manner as the common intermediate reported by Barluenga.¹⁹ We then continued our studies by using the

diene **2.22** which serves as a common intermediate to synthesise deoxynupharidine (**1.4**) and castoramine (**1.6**).

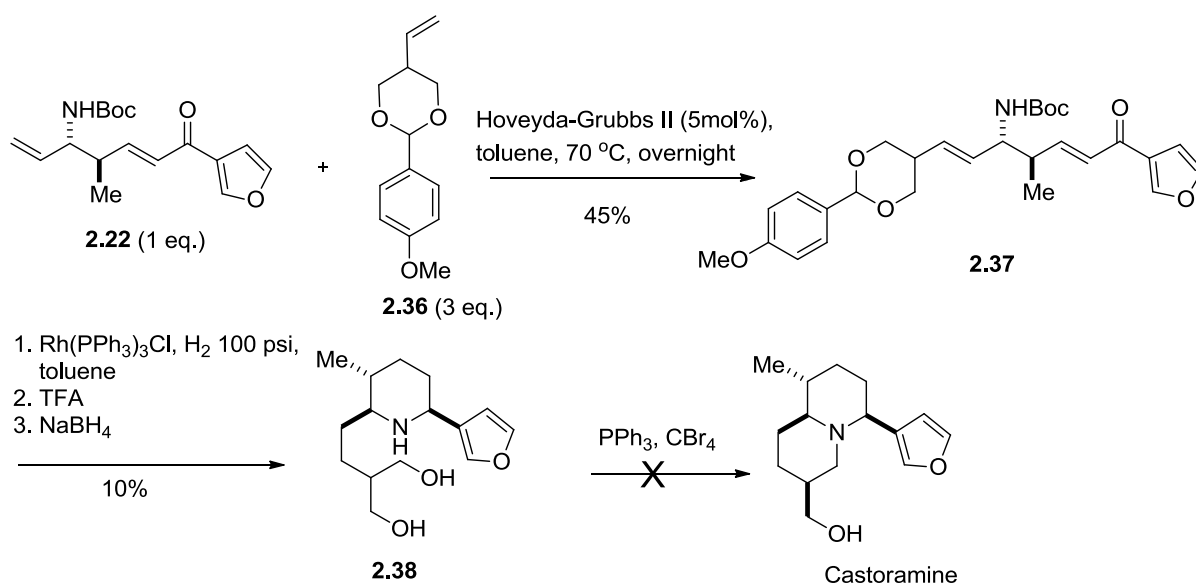
Attempted Synthesis of Castoramine



Scheme 2-33 Formation of alkene **2.36**

For the synthesis of castoramine (**1.6**) according to our retrosynthesis (Scheme 2-15), it was required to carry out a cross-metathesis of the common diene intermediate **2.22** with a derivative of 2-(hydroxymethyl)but-3-enol. One hydroxy group of this fragment would be used for ring closure and the other would become the hydroxymethyl group present in the natural product.

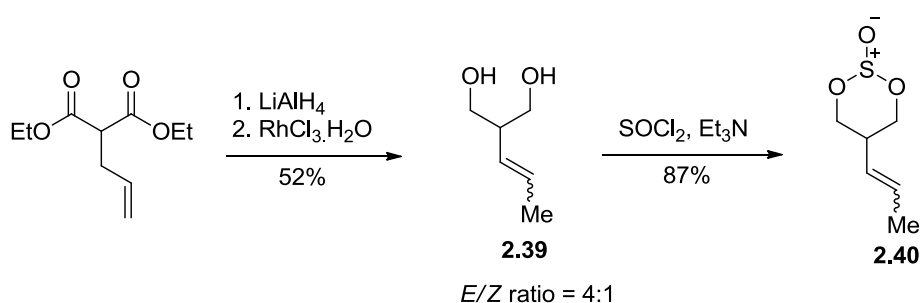
Synthesis of the metathesis coupling alkene started with the reaction of dimethylmalonate with formaldehyde to form diol **2.32**,⁶⁶ which was protected to form an acetonide. The malonate of the acetonide underwent Krapcho decarboxylation to form monoester **2.33**.⁶⁷ The aldehyde of the corresponding dimethyl acetonide had been reported to be unstable and polymerised easily.⁶⁸ Therefore the ester was reduced and the acetonide was hydrolysed to form triol **2.34**.⁶⁹ Triol **2.34** is commercially available but it is expensive as compared to the synthetic precursors. The triol **2.34** was then protected as its *p*-methoxybenzylidene acetal **2.35**, as a mixture of stereoisomers, followed by oxidation of the remaining alcohol to an aldehyde using a protocol reported by Lee and co-workers, then Wittig olefination to give alkene **2.36** (Scheme 2-33).⁶⁰



Scheme 2-34

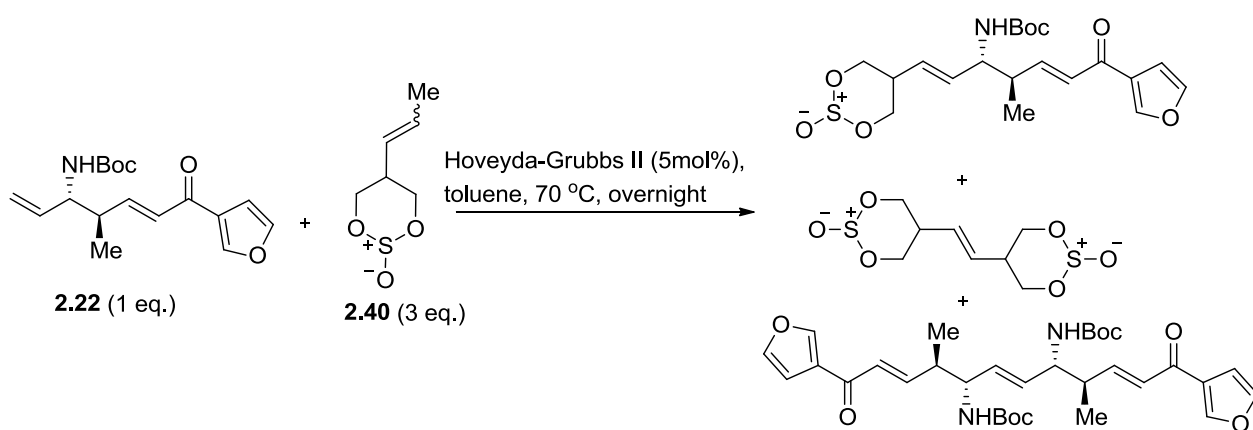
The diene **2.22** was then subjected to cross-metathesis with alkene **2.36** to form diene **2.37**⁷⁰ in a moderate yield (45%) with 3 equivalent of the alkene **2.36**. The diene **2.37** was reduced with Wilkinson's catalyst, followed by global deprotection. Basic work

up and reduction with NaBH_4 gave the piperidine **2.38**. However, only a low yield of 10% was obtained over 3 steps. This might be due to high water solubility of the diol amine that formed during deprotection and was therefore lost during the work up process. Diol **2.38** was subjected to Appel conditions but unfortunately no desired product was obtained, and no identifiable compounds could be isolated during purification (Scheme 2-34).



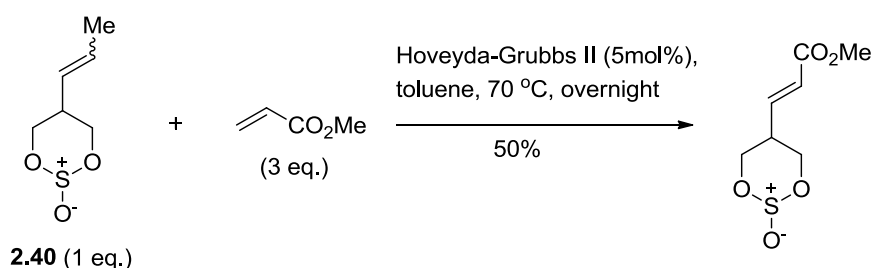
Scheme 2-35 Formation of cyclic sulfite **2.40**

We considered that the corresponding cyclic sulfite **2.40** could be a useful metathesis partner. The cyclic sulfite moiety would both protect the diol and activate it for final cyclisation.⁷¹



Scheme 2-36

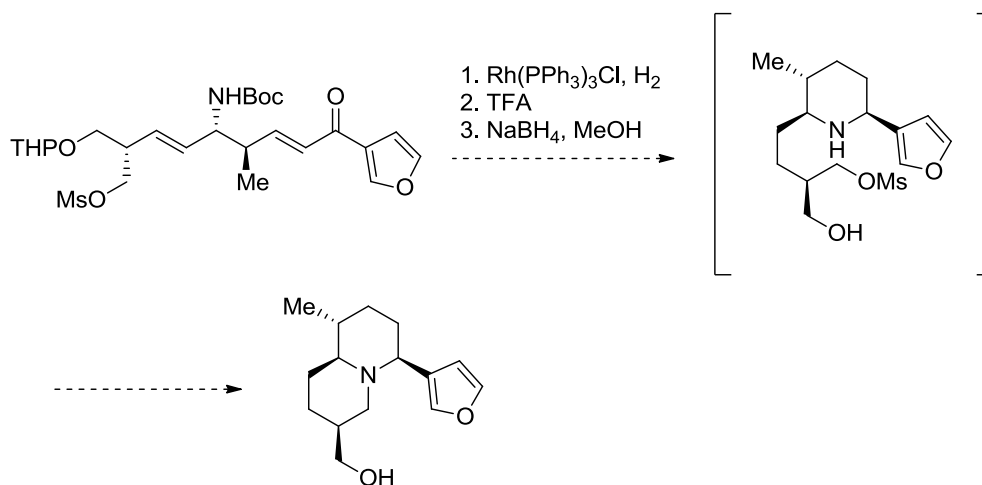
The synthetic route of making the cross-metathesis partner was rather long and low yielding. Hence, the strategy of making the alkene needed to be improved to a shorter route. Synthesis of cyclic sulfite **2.40** was planned instead of the corresponding cyclic sulfate as sulfonyl chloride which would be required to form the cyclic sulphate. This compound is too reactive and hazardous to be shipped. Besides that, oxidation of cyclic sulfites to sulfates is normally done with RuO₄ or KMnO₄ which will also cleave the alkene. There is an extra methyl group on the designed alkene instead of terminal alkene but this should promote the cross metathesis by reducing the formation of the cyclic sulfate pseudo-dimer. Diethylallyl malonate was reduced to the diol⁷² then isomerized using rhodium trichloride in ethanol to give internal alkene **2.39**⁷³ as a single regioisomer but as a mixture of stereoisomers with an *E/Z* ratio of 4:1. Diol **2.39** was reacted with SOCl₂ to form cyclic sulfite **2.40** as a diastereomeric mixture (Scheme 2-35). Cross-metathesis of diene **2.22** with cyclic sulfite **2.40** resulted in a poor yield and the formation of both possible pseudo-dimers. The subsequent hydrogenation with Wilkinson's catalyst did not proceed well with only partial reduction and recovery of starting material (Scheme 2-36).



Scheme 2-37

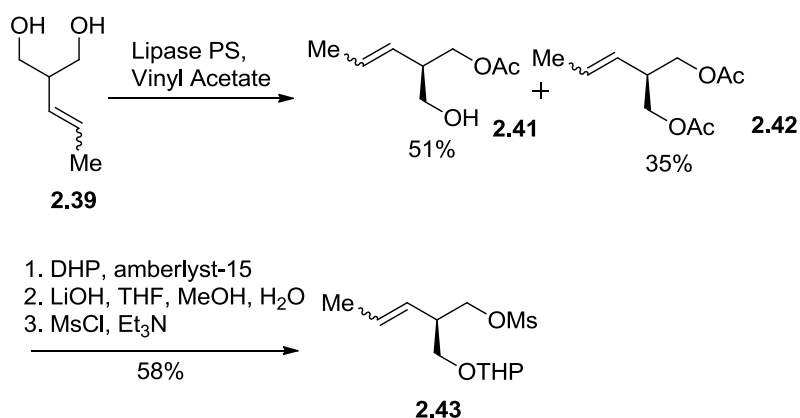
To study the reactivity of the cyclic sulphite **2.40** in cross-metathesis, methyl acrylate and the cyclic sulfite **2.40** were subjected to cross metathesis reaction but only a moderate yield of 50% was obtained (Scheme 2-37). This is possibly due to the lone

pair on the sulfur atom of cyclic sulfite deactivating both the Hoveyda-Grubbs II and Wilkinson's catalysts.



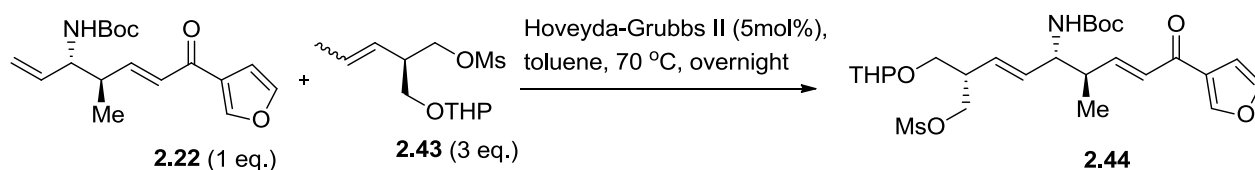
Scheme 2-38

In search of solution to the above problem, an acyclic alkene with one activated alcohol derived from the desymmetrized diol was synthesised. This is to ensure the cyclisation to form the second ring of castoramine gives the correct stereochemistry. The leaving group, mesyl, was installed on the alkene before the cross metathesis as the mesylate has been shown to be stable (Scheme 2-38).



Scheme 2-39

Enzymatic desymmetrization of diol **2.39** was employed to give acetate **2.41**.⁷⁴ The alcohol was protected as its THP ether and subsequently hydrolysis of the ester gave the alcohol. The alcohol was mesylated to form sulfonate **2.43**. The e.e. of the desymmetrization was not determined as our plan was to synthesize the alkene to try the cross metathesis on the diene **2.22** (Scheme 2-39).

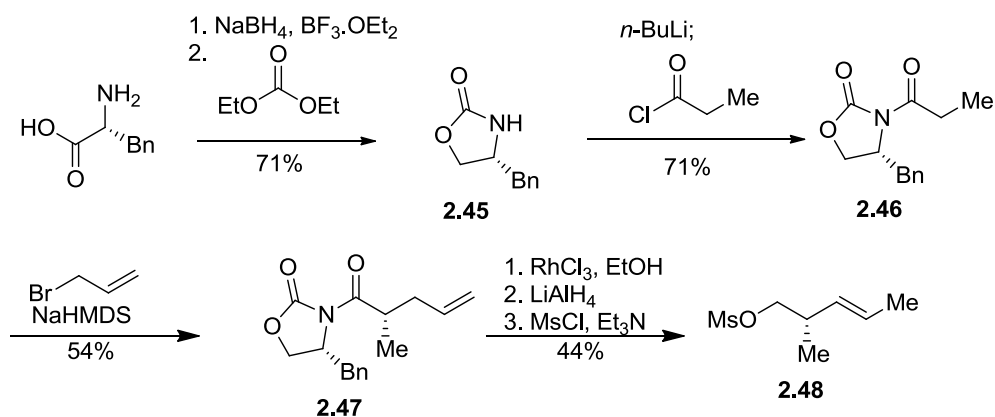


Scheme 2-40

It was observed that cross-metathesis between diene **2.22** and alkene sulfonate **2.34** gave only a trace amount of the product **2.44** with decomposition observed. It was suspected that this was due to the formation of traces of acid from the mesylate. No desired product was formed when acid scavenger 2,6-*di*-*tert*-butyl methyl pyridine was added (Scheme 2-40).

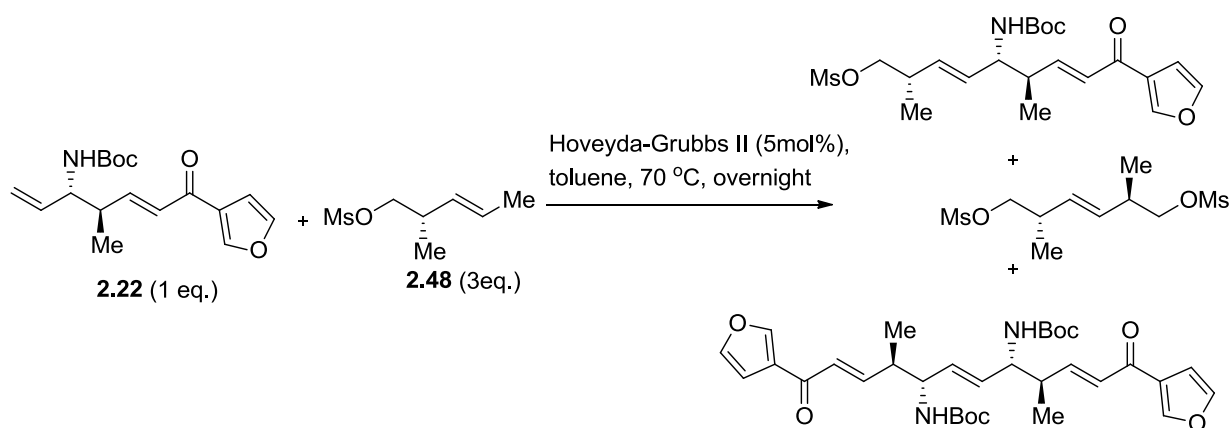
Attempted Synthesis of Deoxynupharidine

For the synthesis of deoxynupharidine (**1.4**), a simpler alkene for cross-metathesis is required, as compare to the synthesis of castoramine. However, asymmetric synthesis of the alkene for cross-metathesis is essential to obtain the natural product with the correct stereoconfiguration.



Scheme 2-41

To prepare the cross-metathesis coupling alkene, Evans' chiral auxiliary chemistry was employed. This is a very useful method in asymmetric synthesis as the new stereogenic centre can be controlled by the stereoconfiguration of the substituent on the oxazolidinone and the formation of the auxiliary is from the easily available amino acid, D-phenylalanine.⁷⁵ Oxazolidinone **2.45** was acylated with propionyl chloride to form amide **2.46**.⁷⁶ The amide **2.46** was allylated under Hovey's conditions⁷⁷ to give alkene **2.47** as a single diastereomer. Subsequently the alkene was isomerized to the internal alkene as single isomer with RhCl_3 . The oxazolidinone was cleaved by reduction with LiAlH_4 to produce an alcohol which was mesylated to form sulfonate **2.48**. This is the desired metathesis partner for the synthesis of deoxynupharidine (Scheme 41).

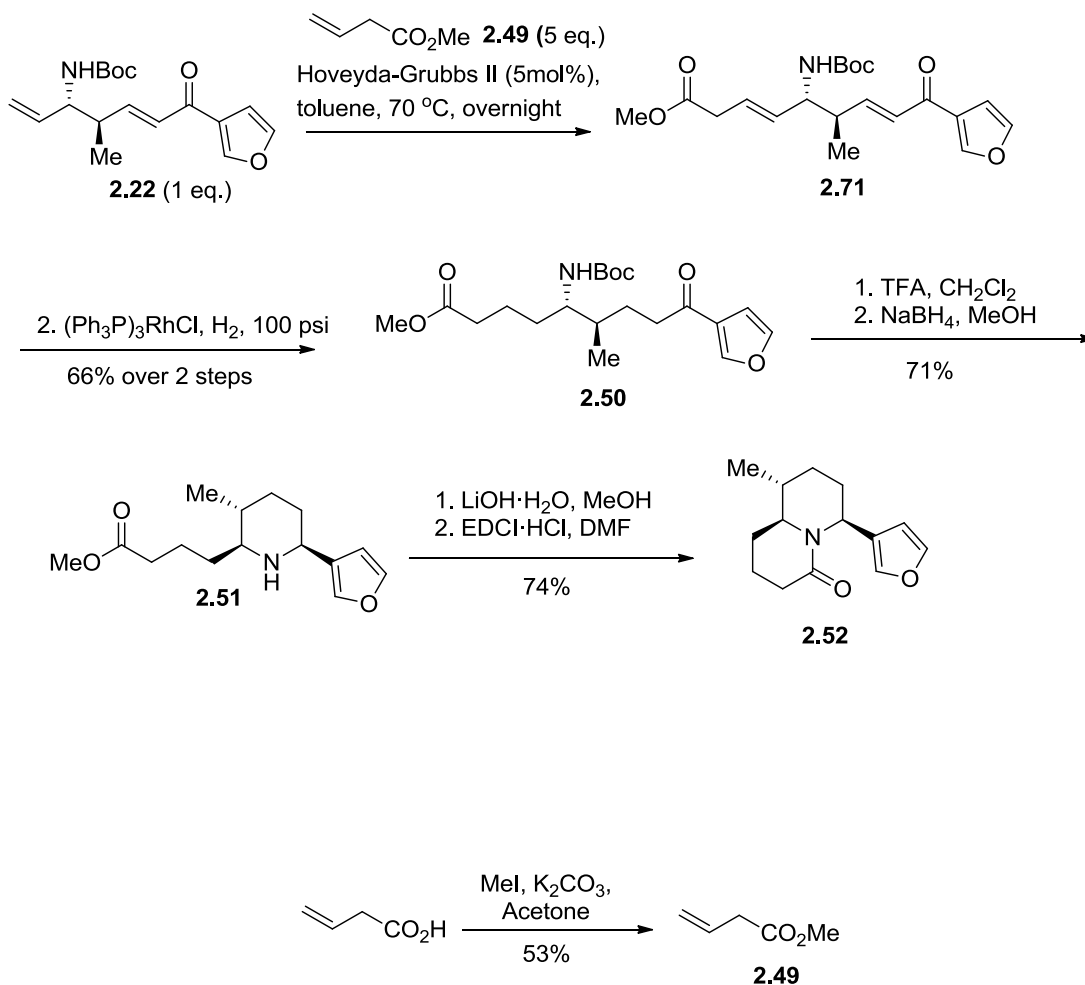


Scheme 2-42

Employing the similar strategy, diene **2.22** and sulfonate **2.48** were subjected to the same cross-metathesis conditions. To our disappointment, only trace amounts of product were obtained and decomposition was observed. This is probably due to the long reaction time which might have caused the decomposition of sulfonate, while a short reaction time did not give desired product in good yield. The formation of pseudo-dimers of the both alkene **2.22** and **2.48** might be due to both alkene being sterically hindered (Scheme 2-42).

To our disappointment, the cross-metathesis was shown to be much more challenging than expected. Therefore, a brand new strategy needed to be planned.

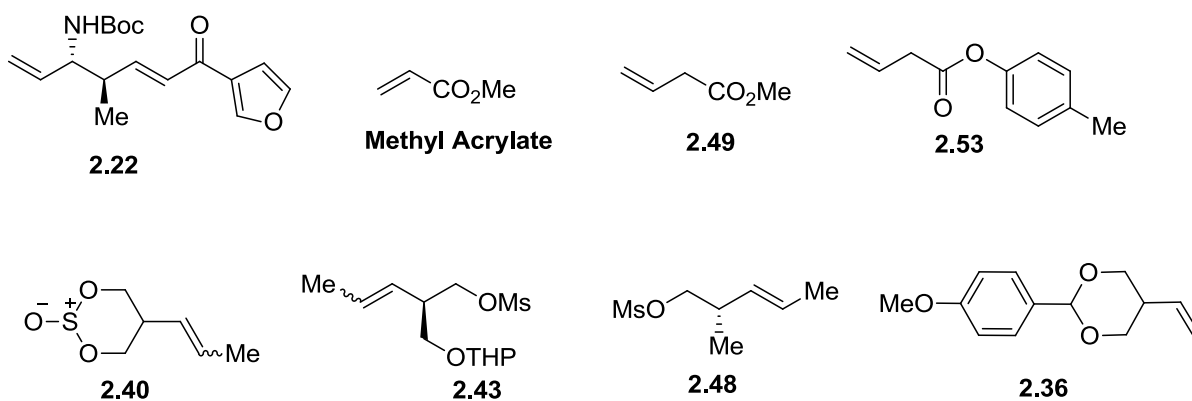
Synthesis of Deoxypharidine and Castoramine *via* a common intermediate



Scheme 2-43

Based on the observations, we concluded that the diene **2.22** is not very reactive in cross metathesis. The cross-metathesis reaction only works well if the partner is not sterically hindered such as methyl acrylate. So a strategy to reduce the steric hindrance of the cross metathesis partner, such as using methyl but-3-enoate **2.49**, with introduction of the substituent at a later stage of the synthesis was planned. We employed the same strategy as we used for piperidine **2.16**. Methyl but-3-enoate **2.49**, which was synthesised by methylation of the 3-butenoic acid,⁷⁸ was used, and to our delight, the cross-metathesis reaction proceeded successfully and in good yield to give

diene ester **2.71** with an *E/Z* ratio of 5:1. The diene ester **2.71** was reduced then converted to a piperidine in a similar way as discussed previously to give ester **2.51**. The intramolecular lactamization to form the 6-membered ring *via* thermolysis did not yield the desired product even by heating at 210 °C or under microwave conditions. This was surprising as for formation of the 5-membered ring in the synthesis of the unnamed indolizidine nuphar alkaloid **1.2** was reported by Barluenga and co-workers and reproduced in this work (Scheme 2-34). The lactamization could be achieved by heating at reflux in toluene. It is surprising that the higher homolog is so unreactive. To achieve lactamization, the ester was hydrolysed with LiOH. The lithium salt was submitted directly to EDCI coupling to give lactam **2.52** as isolation of amino acids can be difficult (Scheme 2-43).⁷⁹

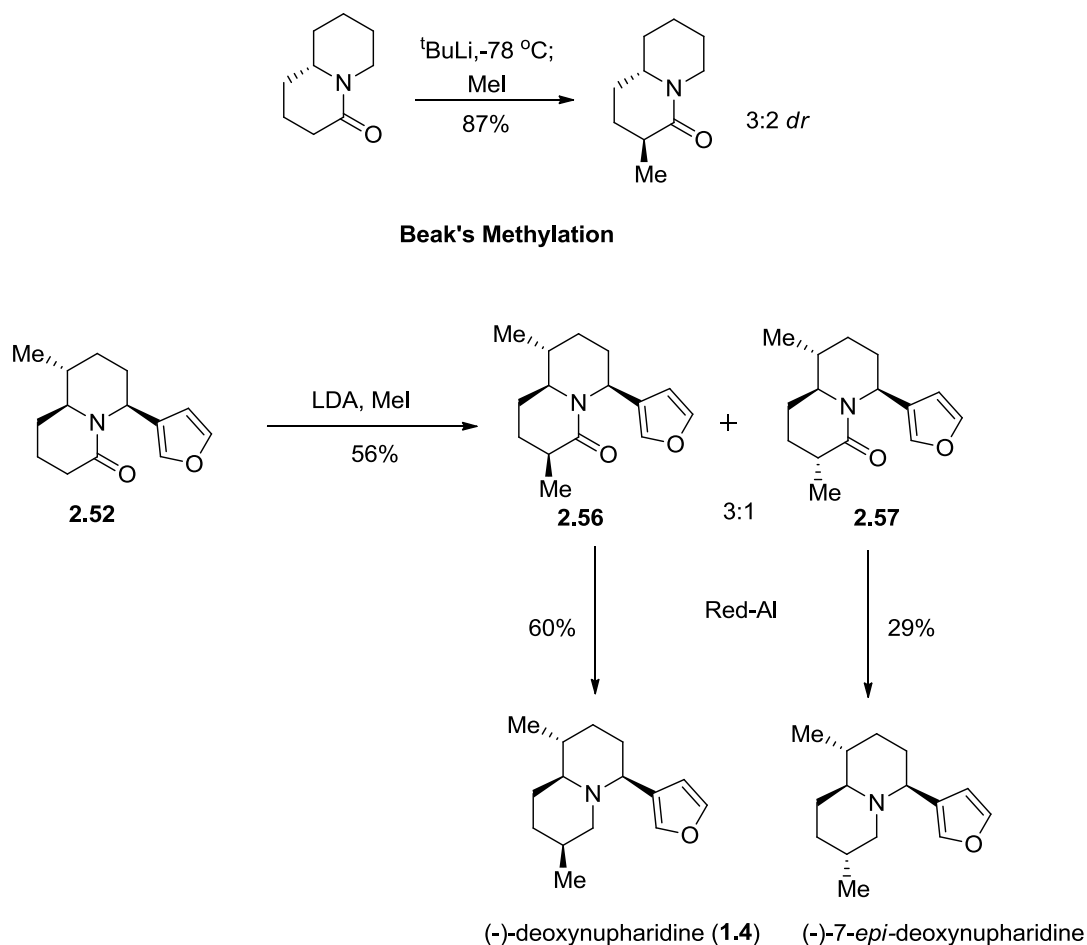


Scheme 44 Alkenes studied for Cross-Metathesis

From the various attempts of the cross-metathesis, diene **2.22** seems to behave like a Type II alkene. Firstly, diene **2.22** underwent cross metathesis with methyl acrylate, methyl but-3-enoate **2.49** and *p*-cresol but-3-enoate **2.53** to give desired products with good yields. On the other hand, mixture of pseudodimers and desired product were obtained when diene **2.22** underwent cross-metathesis with cyclic sulphite **2.40**, mesylate **2.48** and alkene **2.36**. This had shown that the pseudodimer of diene **2.22** was not consumed during the reaction.

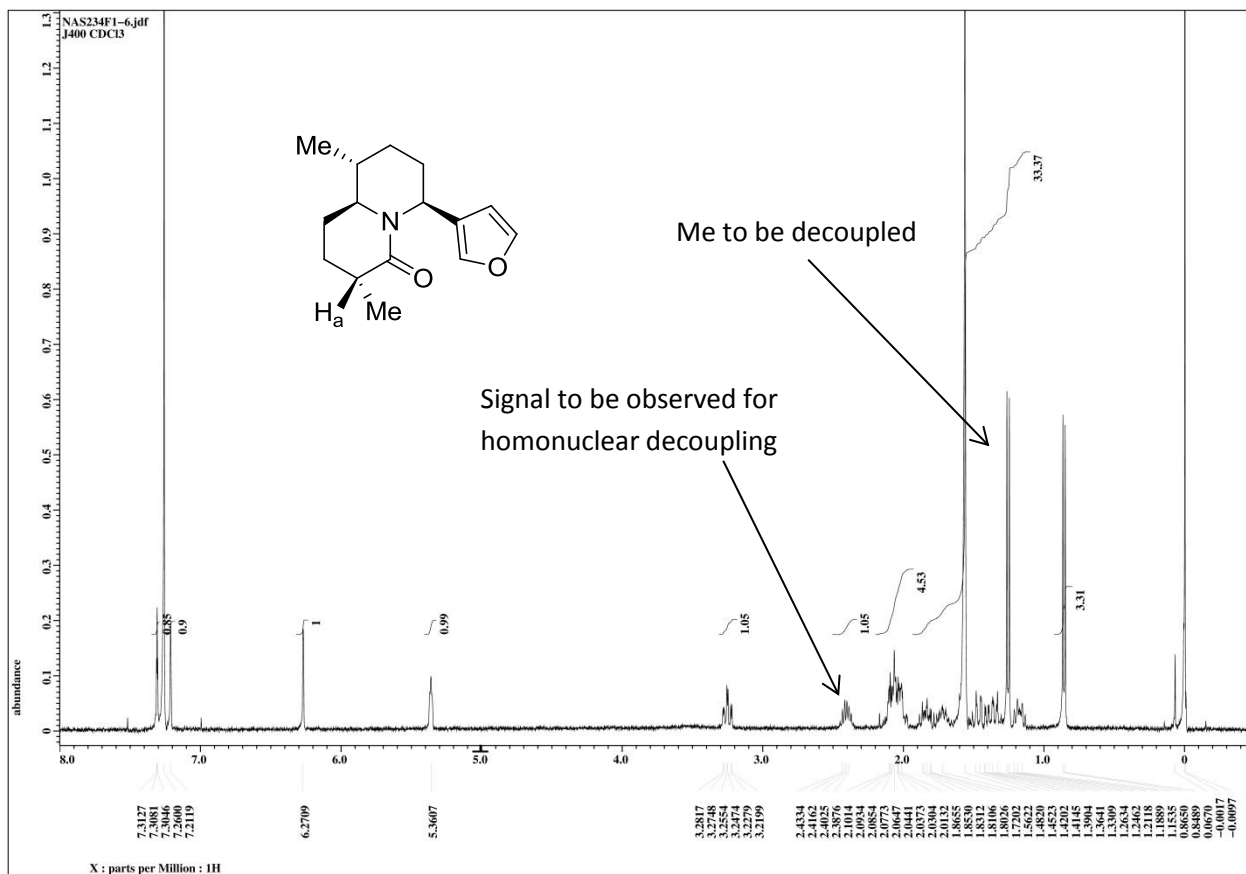
Methyl acrylate is a Type II alkenes because small amount of pseudo-dimers were isolated from the cross-metathesis reactions with diene **2.22**. Methyl but-3-enoate **2.49** and *p*-Cresol but-3-enoate **2.53** can be considered as Type I alkenes as they are not sterically hindered and underwent cross metathesis well with diene **2.22**. It is very likely that the pseudodimer of alkene **2.49** and **2.53** underwent secondary cross-metathesis during the reaction with diene **2.22**. Mesylate **2.48** and alkene **2.36** fell under the category of Type II alkene as they are electron rich alkene but hindered and statistical mixture of products was formed during cross-metathesis reaction with diene **2.22**. Mesylate **2.43** could not be categorised as it decomposed and inhibited the metathesis reactions. Cyclic sulfite **2.40** is hard to classify because coordination of the

sulphur atom to the ruthenium centre of the catalysts might have occurred during the cross-metathesis with diene **2.22**.⁸⁰

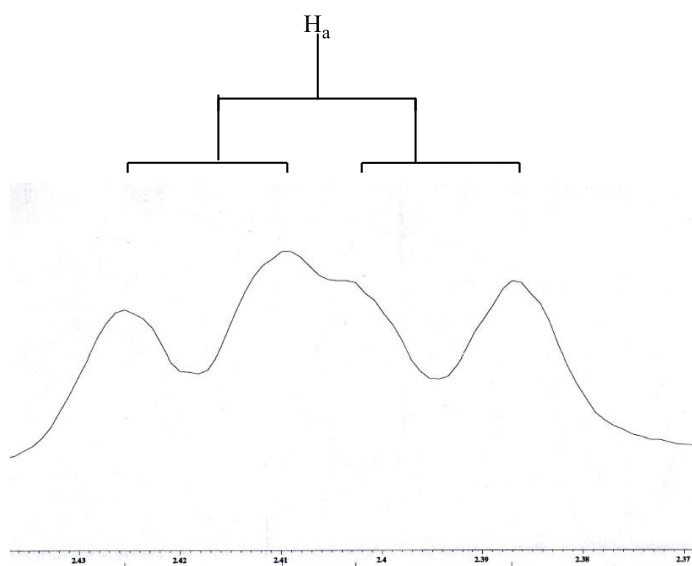


Scheme 2-45 Formation of (-)-deoxynupharidine and its epimer

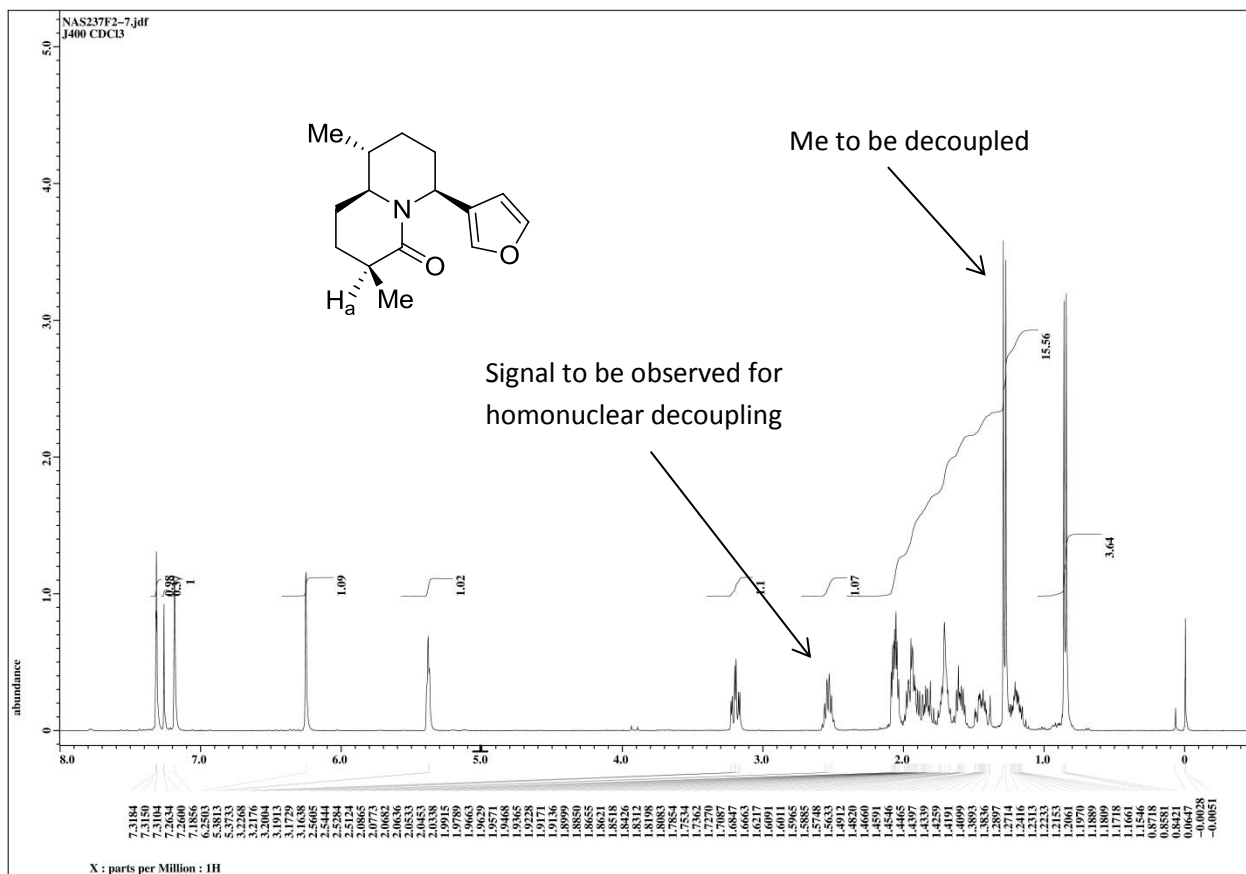
The lactam **2.52** was methylated with moderate 3:1 diastereoselectivity by treatment with LDA followed by methylation. Beak and co-workers reported a similar methylation of a bicyclic lactam but the determination of the stereochemistry of the product obtained was not discussed (Scheme 2-45).⁸¹ The configuration of our methylated products was determined by homonuclear decoupling experiments.



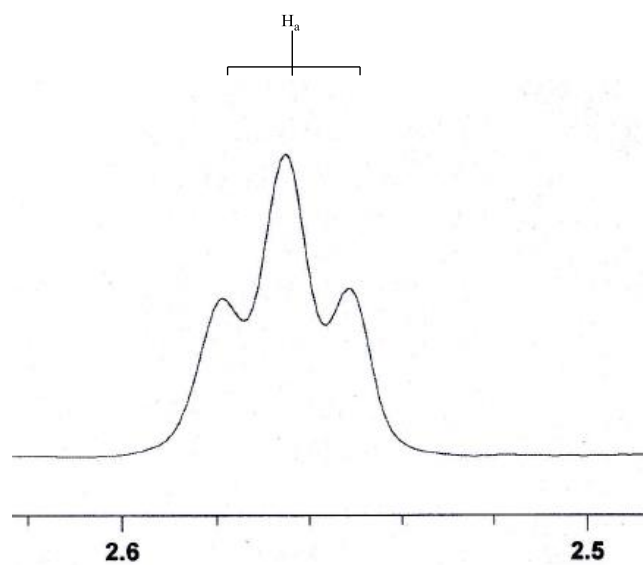
Scheme 2-46 NMR Spectrum of equatorial product, lactam 2.57 (minor)



Scheme 2-47 Homodecoupling signal of the H_a on lactam 2.57

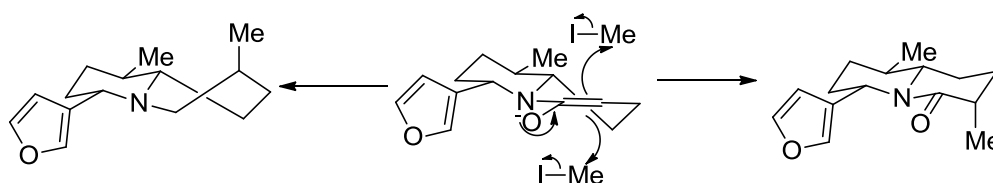


Scheme 2-48 NMR Spectrum of axial product, lactam 2.56 (major)



Scheme 2-49 Homodecoupling signal of the H_a on lactam 2.56

The stereochemistry of saturated six membered rings can often be determined by analysis of coupling constants, provided that the ring adopts a chair conformation. In the case of the methylated compounds, this was not directly possible as proton H_a appeared as a multiplet in both isomers (Scheme 2-46 & 2-48). Homonuclear decoupling experiments were, therefore, carried out. For each isomer, irradiation of the signal due to the methyl group α to the amide carbonyl resulted in the desired simplification. For the major **2.56** isomer, H_a now appeared to be a triplet ($J = 5.5$ Hz) (Scheme 2-49). This is consistent with an axial methyl group as the observed coupling constants are consistent with equatorial-equatorial and equatorial-axial relationships, but not an axial-axial relationship for the vicinal coupling constants. On the other hand, the signal for H_a for the minor **2.57** isomer simplified to a double doublet with coupling constants of 9.2 and 6.2 Hz (Scheme 2-47). These are consistent with axial-axial and axial-equatorial relationships respectively.



Scheme 2-50

The axial product was obtained as the major product because when the enolate reacts with methyl iodide from the bottom face, it will be *via* a chair transition state. Thus the axial product is, therefore, stereoelectronically preferred. However, when the enolate reacts with methyl iodide from the top face, the reaction will proceed *via* a less favorable twist-boat transition state (Scheme 2-50).⁸²

Then lactams **2.56** and **2.57** was reduced with Red-Al to give (-)-deoxynupharidine (**1.4**) and its epimer respectively. Initial attempts of the reduction with LiAlH₄ gave epimerized product with a mixture of unknown side products.

(-)-deoxynupharidine⁸³

Comparison of Spectroscopic Data of Synthesised (-)-Deoxynupharidine with the Literature

Spectroscopic Data	Literature data ^{15,16}	Our Synthetic data
[α] ₂₀ ^D	-105 (<i>c</i> 2.5, MeOH)	-163 (<i>c</i> 0.6, MeOH)
¹ H NMR	270 MHz (CDCl ₃)	400 MHz (CDCl ₃)
	7.33 (m, 1H) 7.25 (br s, 1H) 6.38 (br d, <i>J</i> = 1.3 Hz, 1H) 2.96 (dd, <i>J</i> = 6.1, 6.9 Hz, 1H) 2.63 (ddd, <i>J</i> = 1.5, 2.8, 11.4 Hz, 1H) 1.82 (dd, <i>J</i> = 3.1, 11.4 Hz, 1H) 1.24-1.77 (m, 10H) 1.04-1.20 (m, 1H) 0.99 (d, <i>J</i> = 6.9 Hz, 3H) 0.88 (d, <i>J</i> = 6.4 Hz, 3H)	7.33 (m, 1H) 7.25 (m, 1H) 6.38 (br d, <i>J</i> = 1.2 Hz, 1H) 2.90-2.94 (m, 1H) 2.62-2.65 (m, 1H) 1.81 (dd, <i>J</i> = 3.0, 11.3 Hz, 1H) 1.00-1.79 (m, 11H) 0.99 (d, <i>J</i> = 6.8 Hz, 3H) 0.88 (d, <i>J</i> = 6.4 Hz, 3H)

Table 2H

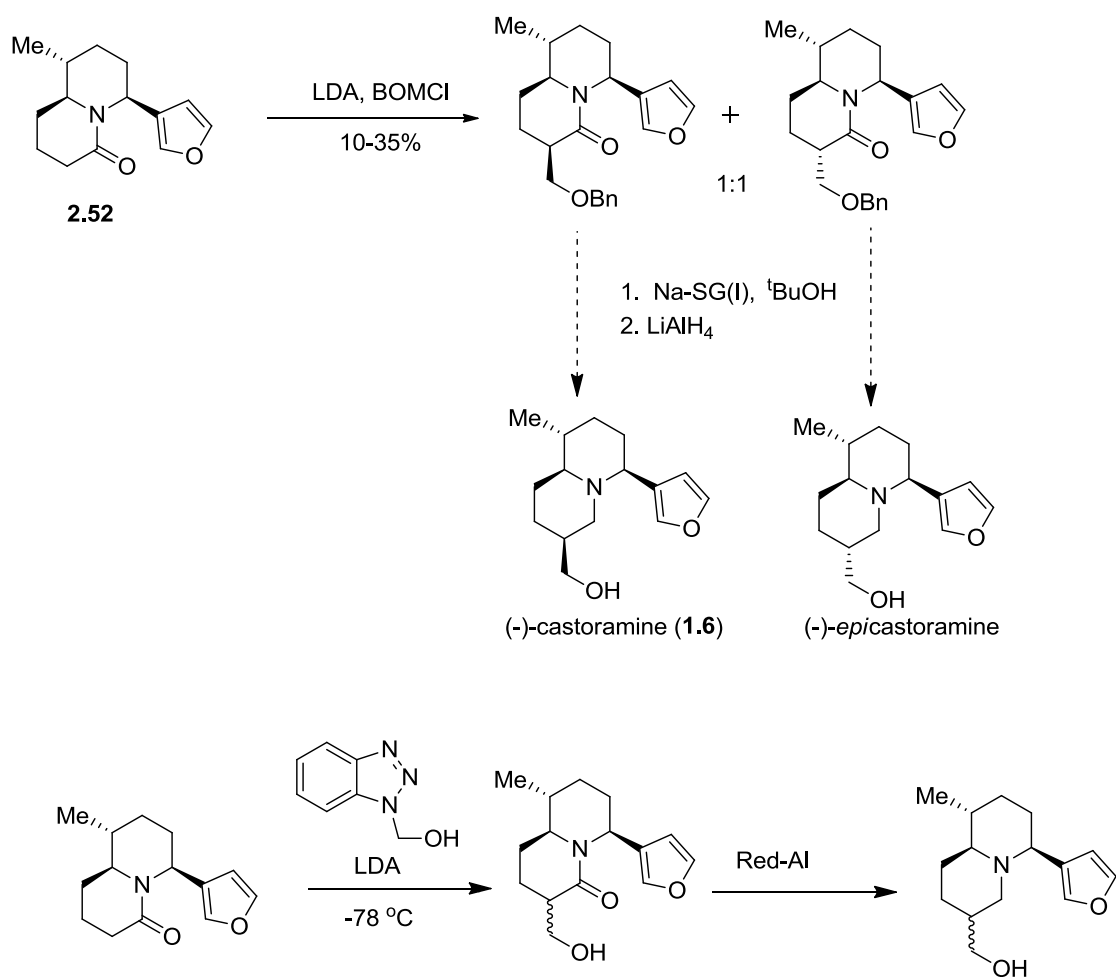
(-)-*epi*-deoxynupharidine⁸⁴

**Comparison of Spectroscopic Data of Synthesised (-)-7-*epi*-Deoxynupharidine
with the Literature**

Spectroscopic Data	Literature data¹³	Our Synthetic data
¹³ C NMR	67.8 MHz (CDCl ₃)	100 MHz (CDCl ₃)
	19.2 19.9 30.1 31.1 33.5 34.0 34.9 36.4 60.9 61.3 69.3 109.6 128.9 139.5 142.8	19.0 19.9 30.0 30.7 33.6 34.1 35.0 36.4 60.9 61.3 69.4 109.7 128.8 139.6 142.6
¹ H NMR	270 MHz (CDCl ₃)	400 MHz (CDCl ₃)
	7.35 (m, 1H) 7.29 (dd, <i>J</i> = 0.7, 1.5 Hz, 1H) 6.43 (br d, <i>J</i> = 1.2 Hz, 1H) 2.89 (dd, <i>J</i> = 3.3, 10.5 Hz, 1H) 2.81 (ddd, <i>J</i> = 2.1, 3.5, 11.2 Hz, 1H) 1.90-1.99 (m, 1H) 1.61-1.82 (m, 4H) 1.09-1.58 (m, 6H) 0.76-0.95 (m, 1H) 0.90 (d, <i>J</i> = 6.3 Hz, 3H) 0.73 (d, <i>J</i> = 6.6 Hz, 3H)	7.35 (m, 1H) 7.30 (m, 1H) 6.42 (m, 1H) 2.89 (dd, <i>J</i> = 2.8, 11.0 Hz, 1H) 2.80 (dt, <i>J</i> = 2.3, 11.4 Hz, 1H) 1.90-1.99 (m, 1H) 1.00-1.80 (m, 10H) 0.76-1.00 (m, 1H) 0.89 (d, <i>J</i> = 6.4 Hz, 3H) 0.73 (d, <i>J</i> = 6.8 Hz, 3H)

Table 2-I

The ^1H spectra of (-)-deoxynupharidine and both ^1H and ^{13}C NMR spectra of (-)-7-*epi*-deoxynupharidine matched the data reported in the literature (Table 2H & 2I). However, the specific optical rotation value for deoxynupharidine deviates from the reported values in the literature but the sign agrees. This deviation might be due to trace amount of acid and also that the measurement was carried out with small amount of sample (1.6 mg) which can cause greater experimental error (Table 2H).



Scheme 2-51

For the castoramine (**1.6**), lactam **2.52** was alkylated with BOMCl. However, the alkylation yield was poor (35%) and could not be improved further.⁸⁵ Alkylation was also carried out with formaldehyde, which was generated *in situ* by deprotonation of benzotriazolyl methanol.⁸⁶ Paraformaldehyde was not used in the reaction as pyrolysis of paraformaldehyde to form formaldehyde gas is a dangerous procedure. To our disappointment, the reaction proceeded with a lower yield of 15% and gave an inseparable mixture of diastereomers. The small amount of diastereomers (2 mg) obtained was then reduced with Red-Al to give a trace amount of castoramine (**1.6**) and its epimer as an inseparable mixture (Scheme 2-51).

Conclusion

In conclusion, we have successfully achieved the synthesis of (\pm)-nupharamine (**1.1**) and (\pm)-(3-furyl)-8-methyloctahydroindolizidine (**1.2**) as well as the total synthesis of (-)-deoxynupharidine (**1.4**) and its epimer with silver mediated allenic hydroxylamine cyclisation and cross metathesis as key steps, which extends the scope of the allenic hydroxylamine chemistry. The advantage of our synthetic route is that most of the steps were carried out under mild conditions. Besides that, the common intermediate of the synthesis route will enable easy access to the other Nuphar alkaloids. However, the cross metathesis step of the diene is sensitive. This is a limitation of the route. In addition, our synthetic route involves more reaction steps and is less efficient as compare to the synthetic strategy recently reported by Shenvi and Jansen.³⁴

CHAPTER 3:

Towards the Total Synthesis of Cernuine

Chapter 3

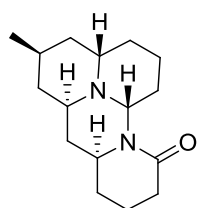
3.1 Introduction

3.2 Early synthesis of Cernuine

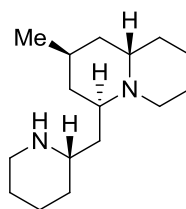
3.3 Towards the total synthesis of Cernuine

3.1 Introduction

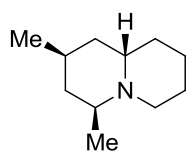
Cerluine, a cerluane-type *Lycopodium* alkaloid, was isolated from the club moss *Lycopodium Cernuum*,⁸⁷ which was found in both Jamaica and Okinawa Prefecture, Japan. Cerluine was first isolated in 1948 by Marion and Manske⁸⁸ but the structure was only elucidated by Ayer and co-workers in 1967 by analysis of coupling constants in the ¹H NMR spectrum and comparison of the CD spectra to those of related alkaloids.⁸⁹ Many *Lycopodium* alkaloids possess interesting biological activity but the activity of Cerluine is yet to be studied further. (-)-Cerluine possesses a fused tetracyclic ring system with an aminal moiety which is rare among *Lycopodium* alkaloids. The interesting structure and synthetic challenge of (-)-cerluine have triggered our great interest to synthesis this molecule with the opportunity to apply iminium ion chemistry and face the challenge of *syn* 1,3-diamine synthesis based on our existing 1,3-aminoalcohol strategies.



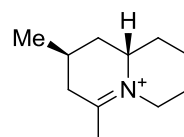
(-)-Cerluine (3.1)



(+)-Cermizine D (3.2)



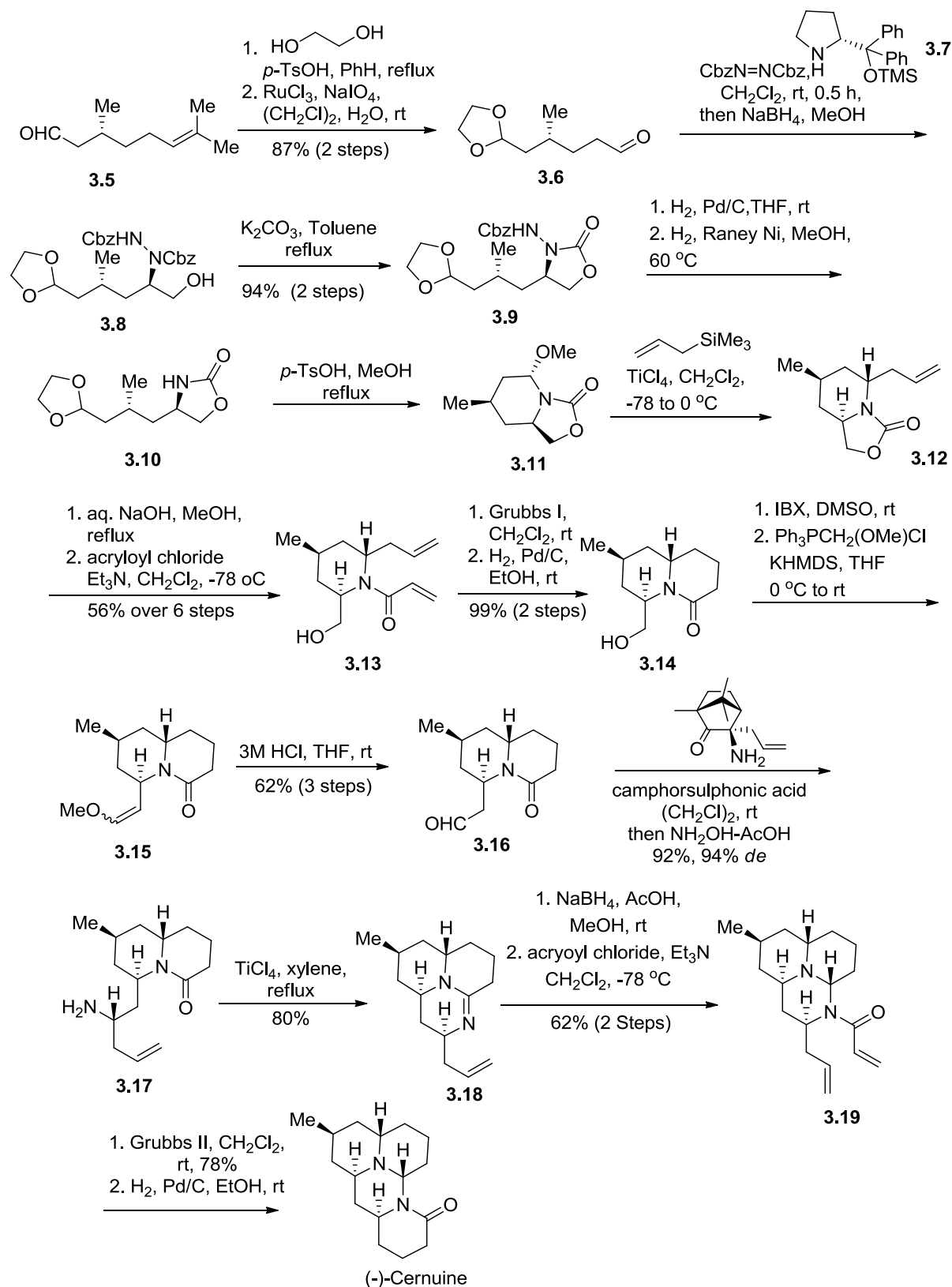
Cermizine C (3.3)



Senepodine G (3.4)

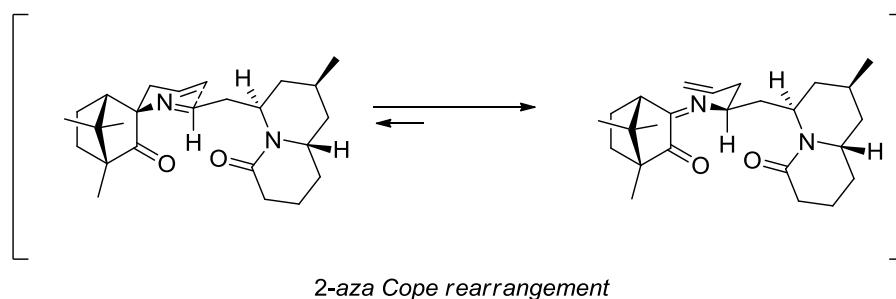
Scheme 3-1 Cerluane-type *Lycopodium* Alkaloids

3.2 First synthesis of Cernuine



Scheme 3-2 Synthetic route to (-)-Cernuine by Takayama and co-workers

Takayama and co-workers started their synthesis of cernuine with aldehyde **3.5** derived from chiral pool compound (+)-citronellal (Scheme 3-2). The aldehyde **3.5** was protected and the alkene was cleaved under a protocol developed by Yang and Zhang, to form aldehyde **3.6**.⁹⁰ The aldehyde underwent amination with catalyst **3.7** and followed by selective reduction with NaBH₄ and, upon heating with potassium carbonate in anhydrous toluene, formed oxazolidinone **3.9**, which upon reduction and treatment with *p*-TsOH gave aminal **3.11**. Stereoelectronically controlled Hosomi-Sakurai allylation of aminal **3.11** gave alkene **3.12**, which was hydrolysed, followed by acylation of amine to form diene **3.13**. Diene **3.13** underwent ring closing metathesis with the Grubbs-I catalyst to form an alkene which was reduced to lactam **3.14**, a common intermediate that can also lead to the synthesis of (+)-cernizine C (**3.3**) and (-)-Senepodine G (**3.4**). The alcohol of lactam **3.14** was oxidized with IBX and underwent olefination to form alkene **3.15** which upon hydrolysis gave aldehyde **3.16**.

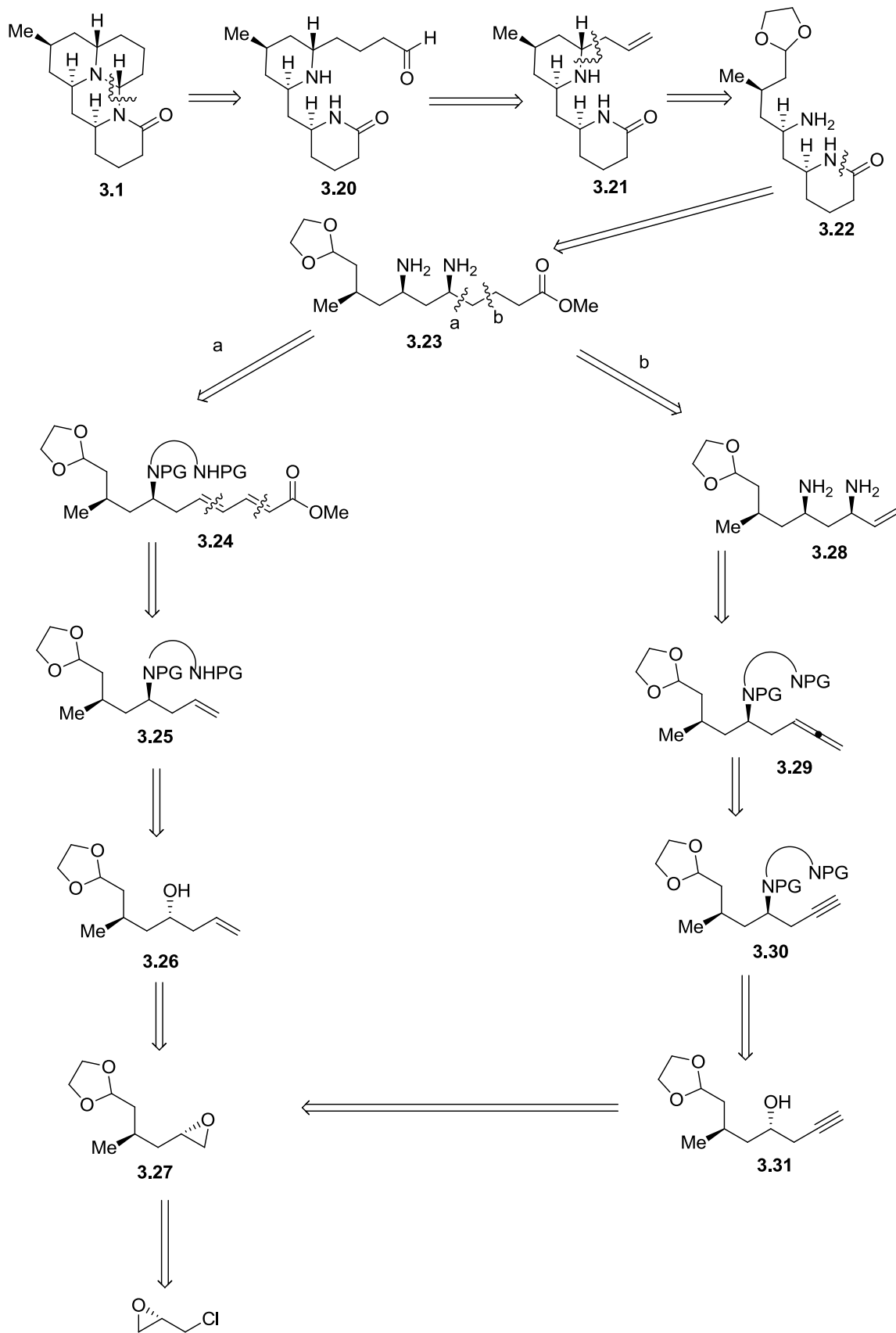


Scheme 3-3 Proposed Mechanism for the formation of **3.17**

The aldehyde **3.16** underwent aminoallylation transfer *via* a 2-aza Cope rearrangement developed by Kobayashi and co-workers to form amino alkene **3.17**,⁹¹ which is a common intermediate that led to the synthesis of (+)-Cernizine D (**3.2**) (Scheme 3-3). Upon heating amino alkene **3.17** at reflux with TiCl₄, the third ring of Cernuine and also amidine **3.18** was formed. Stereoelectronically controlled reduction of amidine **3.18** gave aminal **3.19**. The aminal was acylated with acryloyl chloride

then underwent ring closing metathesis, followed by hydrogenation to obtain (-)-cernuine (**3.1**).

In short, Takayama and co-workers developed a versatile route to access to different types of cernuane alkaloids with 12 synthetic steps to obtain the common intermediate from citronellal.⁹² Effective installation of chiral centre was achieved by the utilization of organocatalysis and stereoelectronically controlled reactions.



Scheme 3-4 Retrosynthetic Analysis for (-)-Cernuine

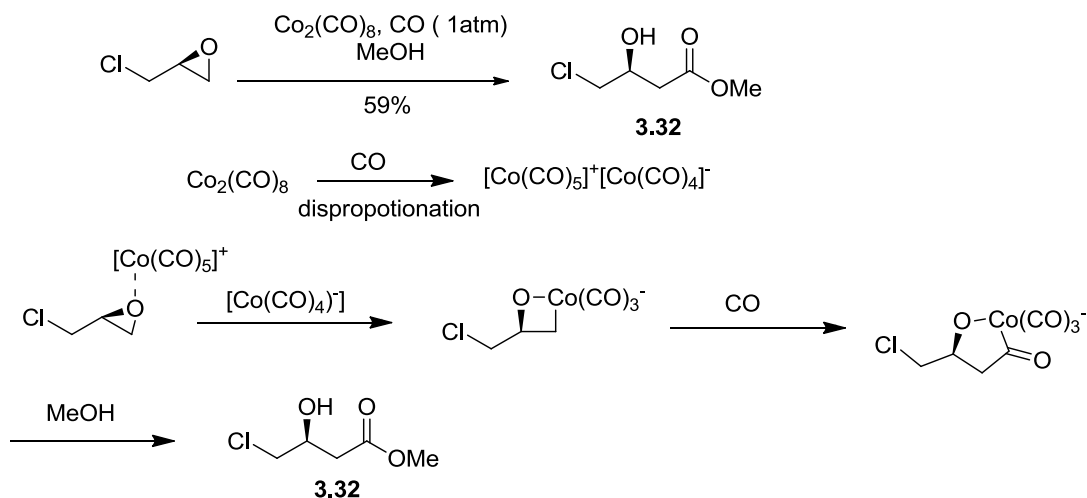
3.3 Towards the Synthesis of Cernuine

Retrosynthetic analysis

Our plan for the synthetic route of (-)-Cernuine (**3.1**) is to include the formation of the *syn* 1,3-diamine, *via* a tether, so that the formation of one N-C bond is directed by the other.

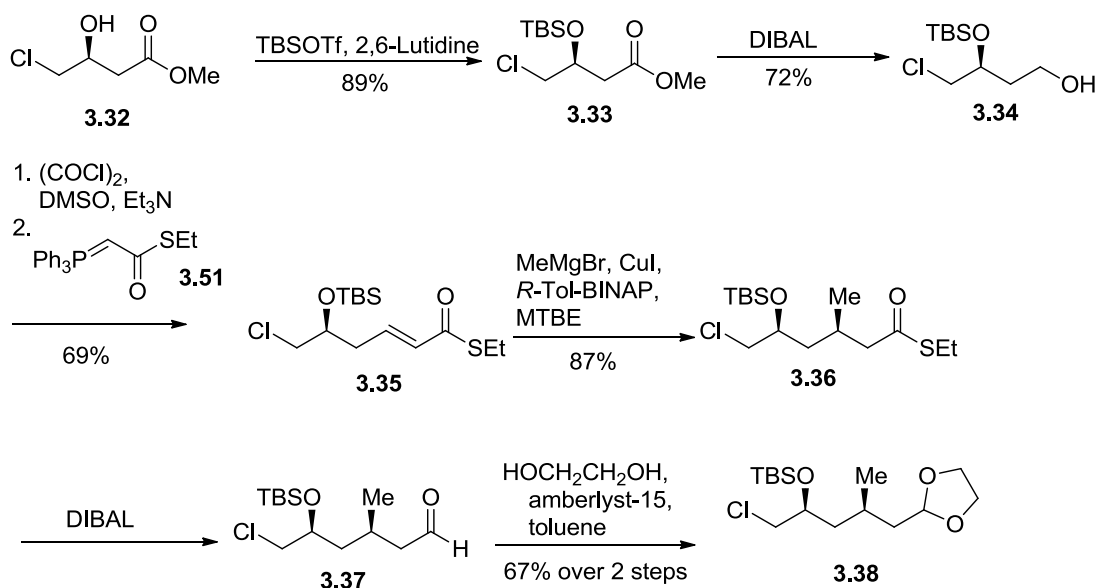
Cernuine is disconnected so that the aminal comes from the condensation of aldehyde **3.20** which can be formed from hydroformylation of alkene **3.21**. Alkene **3.21** can be disconnected *via* the stereoelectronic control allylation of the iminium ion. Disconnection at the lactam **3.22** would lead to diamine **3.23** which could be further disconnected *via* two strategies. For strategy (a), the diamine could be formed from the 1,6- conjugated addition of the tethered amine **3.24**. The diene could be disconnected *via* Wittig olefination and cross metathesis. The tethered amine **3.25** could be formed from Mitsunobu reaction of the alcohol **3.26** which is derived from the ring opening of epoxide **3.27**. As for strategy (b), the diamine was disconnected *via* cross metathesis and the diamine **3.28** could be formed from the metal mediated cyclisation of the tethered amino allene **3.29**. The allene **3.29** could be synthesised *via* Searles-Crabbé homologation of alkyne **3.30** which could be disconnected to epoxide **3.27**. The epoxide **3.27** could be derived from (*S*)-epichlorohydrin (Scheme 3-4). These two strategies were studied as we intended to install the two N atoms of the natural product simultaneously *via* a tethered procedure. Besides that, formation of *syn* 1,3-diamine is not extensively studied in the literature and yet many natural products possess the *syn* 1,3-diamine in their structure.

Synthesis



Scheme 3-5 Formation of alcohol 3.32 and Proposed Mechanism of Carbonylation by Denmark

The synthesis of Cernuine began with the formation of alcohol **3.32**, which was derived from the carbonylation of the commercially available enantiopure (*S*)-epichlorohydrin by Denmark's protocol.⁹³ It was proposed that dicobalt octacarbonyl will disproportionate in the presence of a Lewis base. The cobalt cation will activate the epoxide and the anion will react with the epoxide to form an organo-cobalt ate species. Then insertion of the carbon monoxide will form cobalt acyl complex and reaction with the MeOH will cause the release of the chlorohydrin ester. This method had shown to be atom economical, easy to scale up with reasonable yield (59%) and can be handled under ambient conditions (Scheme 3-5).



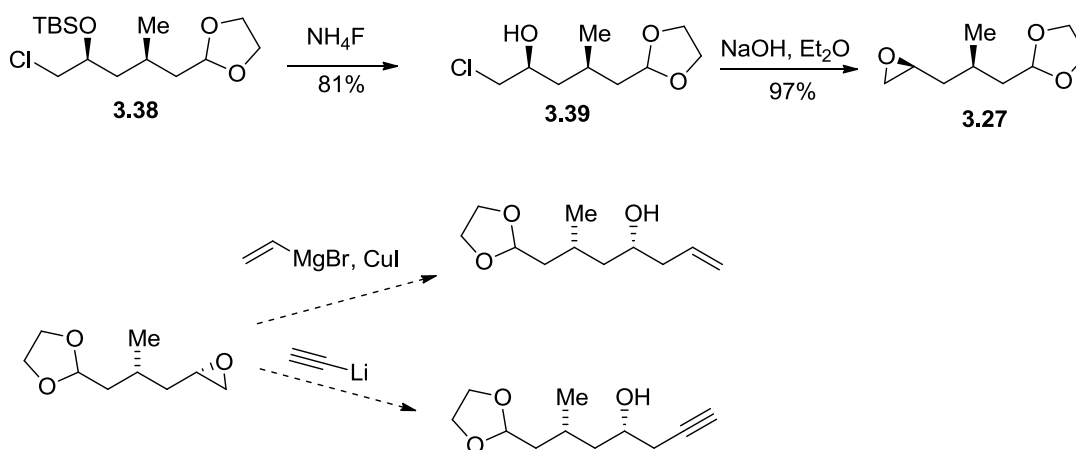
Scheme 3-6

The alcohol **3.32** was then protected as a silyl ether **3.33** with TBSOTf in the presence of 2,6-lutidine. Reduction of the ester **3.33** with 1 equivalent of DIBAL was expected to give the corresponding aldehyde, but when a stoichiometric amount of DIBAL at -78 °C was added for the reduction of ester **3.33**, a mixture of starting material, aldehyde and alcohol was obtained. The ester **3.33**, therefore, was reduced with excess DIBAL to form alcohol **3.34**. The alcohol **3.34** underwent Swern oxidation to form the aldehyde which was then reacted with the ylid **3.51**. The thioester containing ylid **3.51** was used instead of an oxygen ester ylid as Feringa's asymmetric methylation in a later step would require the thioester. Swern oxidation was employed as it is a very mild oxidizing condition that will not affect the TBS group.

The α,β -unsaturated thioester **3.35** was subjected to Feringa's asymmetric methylation⁹⁴ giving ester **3.36** as a 20:1 separable mixture of diastereomers and in excellent yield (87%). This strategy was employed based on the previous synthesis of Mintlactone in this laboratory.⁹⁵ It is a good method for introducing a chiral centre with good diastereoselectivity. The thioester was then reduced with DIBAL to obtain

aldehyde **3.37**. In this instance, the reduction works well to give the desired aldehyde **3.37**.

Aldehyde **3.37** was protected with ethylene glycol with amberlyst-15 as acid and toluene as solvent *via* Dean-Stark distillation. No deprotection of the TBS was observed. The amount of nucleophile present was too low because ethylene glycol is not soluble in toluene and the protection of aldehyde proceeds much faster. For deprotection of TBS, the nucleophile will attack the Si centre and this happen readily in a polar solvent (Scheme 3-6).



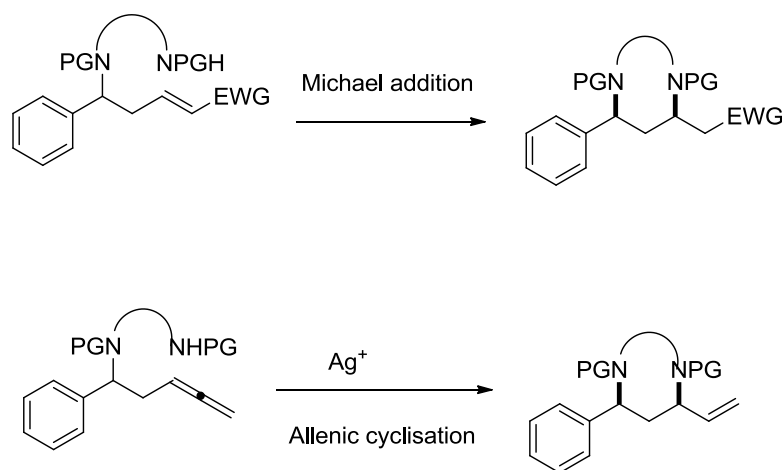
Scheme 3-7

The silyl ether **3.38** was then deprotected with NH_4F under reflux with methanol to form chlorohydrin **3.39**. The advantage of using NH_4F is the easy work up in which the reaction mixture is preabsorbed onto silica after the reaction and subjected to flash chromatography for purification.⁹⁶ This is a good alternative to TBAF, which can cause purification problems especially when a polar product is formed after the reaction. Chlorohydrin **3.39** was treated with NaOH to form epoxide **3.27**. The epoxide **3.27** is a useful precursor that can lead to two different possible synthetic pathway of the synthesis by either reacting with vinyl magnesium bromide or lithium

acetylide to give important precursors for the formation of the *syn* 1,3-diamine moiety (Scheme 3-7).

Model studies for the formation of *syn* 1,3-diamine

Tethered nitrogen has been widely used in natural product synthesis. The nitrogen is tethered temporarily to another atom in the substrate by either a group of atoms or even a single covalent bond. The tether will be removed or cleaved at a later stage of the synthesis, after cyclofunctionalisation. The use of tethered nitrogen on sp^2 carbon will normally lead to sterecontrolled formation of 1,2- or 1,3- difunctionalized product *via* 5 or 6 member ring intermediate. As the tether ensures that the cyclofunctionalisation is intramolecular, it is possible to exercise control over the regio- and stereochemistry of the product.³⁷

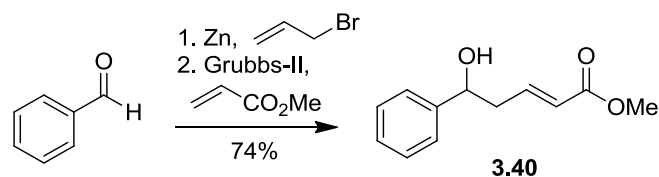


Scheme 3-8

We designed a model study of the formation of the 1,3-diamine with starting materials derived from benzaldehyde. The *syn* 1,3-diamine was proposed to form *via* a tether

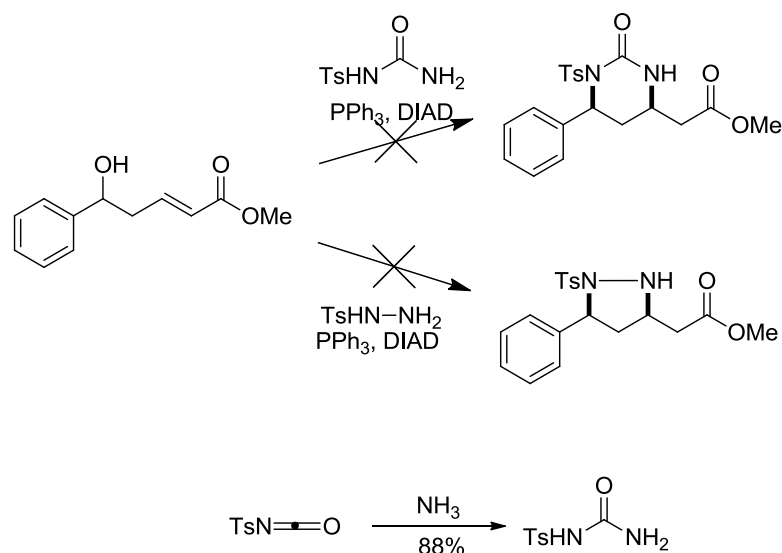
which can be a group such as carbonyl or even a single bond through Michael addition or allenic cyclisation (Scheme 3-8).

Formation *via* Michael addition



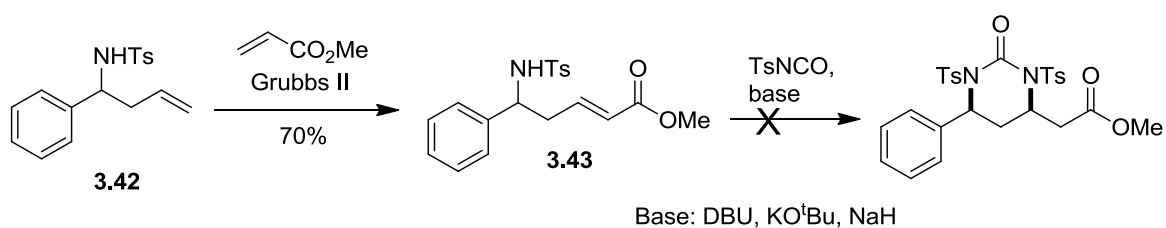
Scheme 3-9

We started the studies of the formation of the 1,3-amine via intramolecular Michael addition, which is a simpler version to the proposed intramolecular 1,6-addition. Benzaldehyde was subjected to Barbier reaction with allyl bromide and then cross metathesis with methyl acrylate to form the α,β -unsaturated ester **3.40** (Scheme 3-9).



Scheme 3-10

Ester **3.40** was then subjected to Mitsunobu condition with tosyl urea or tosyl hydrazine but no desired product was obtained and only starting material was recovered. This might be due to the anion of the tosyl urea formed being too stabilised and insufficiently nucleophilic to form desired the products. Initial formation of tosyl urea posed some challenges as direct formation of the compound from urea is very difficult as the nitrogen on the urea is not nucleophilic and thus could not react with tosyl chloride.⁹⁷ An attempt was made by reacting tosyl isocyanate with ammonia formed from a mixture of potassium carbonate and ammonium chloride. However, it was found that *p*-toluene sulphonamide was formed during the reaction as the ammonium chloride contains water. Finally, tosyl urea was formed from the reaction of ammonia in dioxane and tosyl isocyanate (Scheme 3-10).⁹⁸



Scheme 3-11

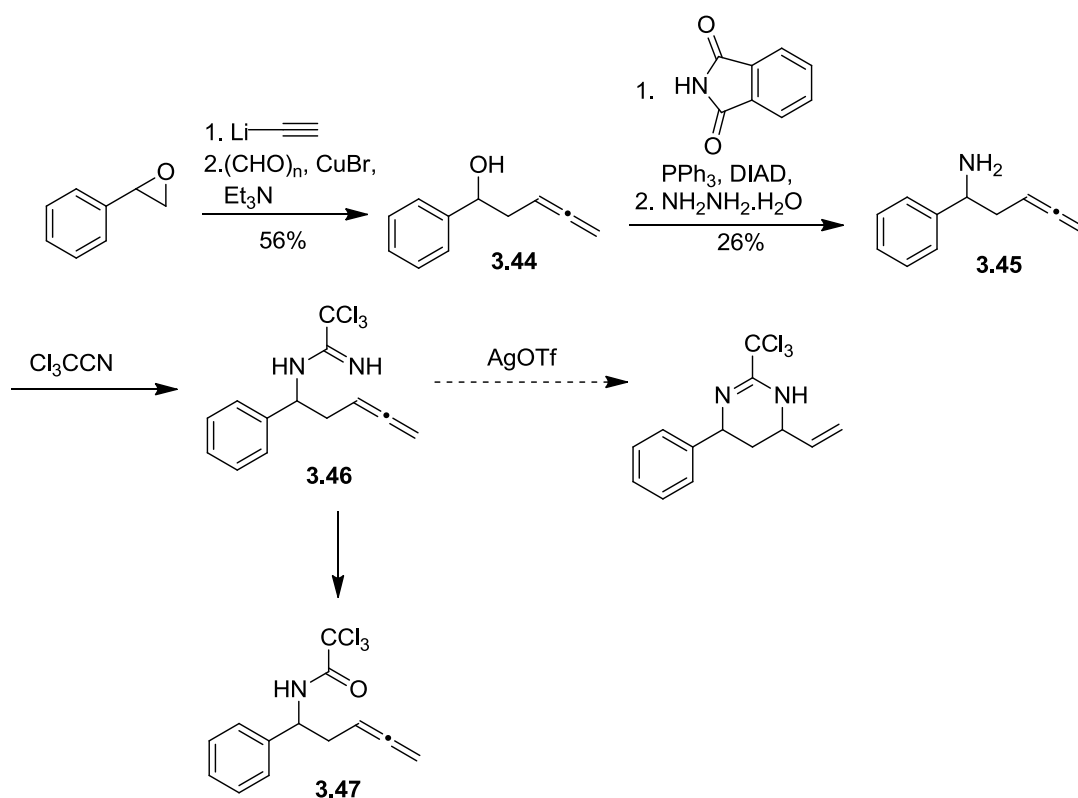
As the introduction of the tether directly has found to be difficult, we planned to install the first nitrogen and then use tandem tosyl urea formation and cyclisation to form the 1,3-diamine.

Alkene **3.42** underwent cross metathesis with methyl acrylate to form α,β -unsaturated ester **3.43**. The ester **3.43** was reacted with tosyl isocyanate in the presence of different type of base such as DBU, TMG, NaH and KO^tBu. However, no desired product was obtained and starting material was recovered (Scheme 3-11).

Alternatively, a strategy for formation of 1,3-diamine via silver mediated allene cyclisation was attempted.

Formation of 1,3-diamine *via* silver mediated allenic cyclisation

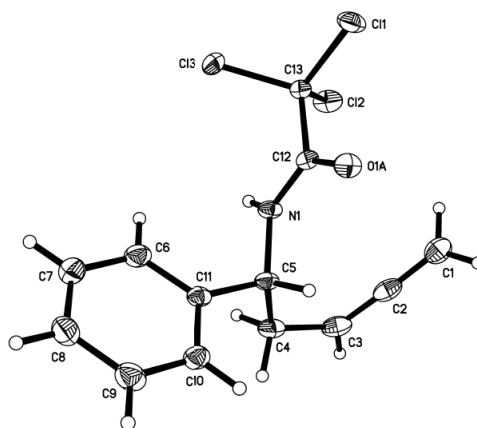
We also planned to employ a strategy similar to the formation of 1,3-amino alcohols *via* allenic cyclisation of hydroxylamines, which was discussed in the previous chapter. We planned to use trichloromethylamidine as a tether to study the allenic cyclisation.



Scheme 3-12

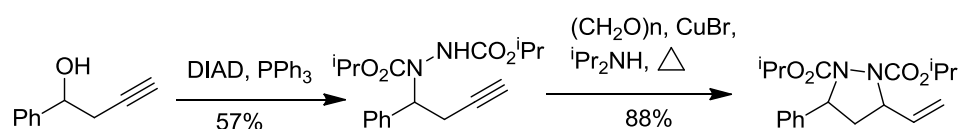
Styrene oxide was treated with lithium acetylide to form the alkyne⁹⁹ which underwent Searles-Crabbé homologation¹⁰⁰ to form allene **3.44**. The alcohol underwent Mitsunobu reaction followed by dephthaloylation to form amine **3.45** which was reacted with trichloroacetonitrile to form amidine **3.46**. The amidine **3.46** was treated

silver triflate but no reaction was observed. To our disappointment, X-ray crystallography and further support result from HRMS¹⁰¹ showed that it is amide **3.47** instead of amidine (Scheme 3-12).



Scheme 3-14 X ray structure of amide 3.47

The amide **3.47** might be formed from the hydrolysis of the amidine **3.46** during purification by flash chromatography. The failure of the amide **3.47** to cyclise might be due to the electron withdrawing nature of the trichloromethyl group (Scheme 3-14).



Scheme 3-15

Recently, our group has serendipitously discovered a one pot homologation and copper mediated allenic cyclisation of hydrazine alkyne could lead to the formation of the 1,3-diamine. The relative stereochemistry of the two chiral centres was not determined at this moment. Further studies will need to be done in the future (Scheme 3-15).¹⁰²

In conclusions, a precursor for the key reaction, 1,3-diamine formation, that could lead to the synthesis of cernuine was synthesised. The precursor contains two stereogenic centres and represents an important and challenging fragment. Different diazocarboxylate derivatives will be employed so that easy deprotection of the hydrazine can be achieved and the relative stereochemistry could be determined.

CHAPTER 4:

Experimental Section

4.1 General Methods

All the anhydrous and oxygen sensitive reactions were carried out under a N₂ atmosphere. All glass apparatus for anhydrous reactions was dried in an oven (120 °C) and cooled under vacuum. Anhydrous toluene was distilled from sodium metal under nitrogen. Anhydrous THF and Et₂O were distilled from sodium metal and benzophenone under nitrogen. MTBE, DMSO (under reduced pressure) and CH₂Cl₂ were distilled from CaH₂ under nitrogen. All the other solvents and reagents were commercial and used as received.

¹H NMR spectra were recorded on Bruker Advance DPX at 300, 400, or 500 MHz or JEOL ECA 400 MHz using deuterated solvents (CDCl₃ or CD₃OD). ¹³C NMR spectra were recorded on the same instruments at 75, 100 or 125 MHz. Chemical Shifts (δ) were recorded in ppm and coupling constant *J* were in Hz.

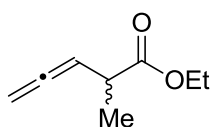
Mass spectra were recorded out on a Finnigan LCQ DECA XP MAX Ultra instrument or a Finnigan Polaris Q, GCMS XP mass spectrometer. High Resolution Mass Spectroscopy (HRMS) experiments were carried on a Waters Q-Tof premier instrument.

Infrared spectra were recorded either neat, or as nujol mull on NaCl or KBr plate on a Shimadzu IR Prestige-21 FTIR or a Bruker Alpha-E FTIR.

Specific optical rotations were recorded on a Jasco-1030 polarimeter and are given with units of 10⁻¹degcm²g⁻¹. The angles of rotations were measured at wavelength of 589 nm.

Enantiomeric excess was determined by chiral HPLC analysis which was performed on a Agilent HPLC and Daicel ID column, eluting with IPA/hexane. Conversion determined by HPLC was performed on a Agilent HPLC using Agilent Poroshell EC C18 column, eluting with acetonitrile and water. Enantiometric excess determined by Chiral GC was performed on Agilent GC, using Restek 13112 column.

4.2 Experimental for Chapter 2



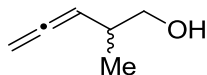
(±)-2-Methyl-penta-3,4-dienoic acid ethyl ester (2.27)

A mixture of propargyl alcohol (19.5 mL, 330 mmole), triethyl orthopropionate (120 mL, 599 mmole) and acetic acid (2.3 mL, 40 mmole) was heated with a Dean-Stark trap at 150 °C for 5 hours. The mixture was cooled to room temperature and a small amount of 2 M hydrochloric acid (aq.) was added. The mixture was stirred for 30 minutes then was taken up in dichloromethane and washed with saturated aqueous sodium bicarbonate. The mixture was dried over MgSO₄ and concentrated to give ester **2.27** as yellow liquid (48.91 g, 349 mmole, quant.) containing a trace amount of ethyl propionate acid. The ester **2.27** can be purified *via* flash column chromatography eluting with 10% ethyl acetate/ hexane to give ester as pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ 1.23-1.27 (5H, m), 3.07-3.13 (1H, m), 4.12 (2H, q, *J* = 7.1 Hz), 4.79 (2H, dd *J* = 3.0, 6.5 Hz), 5.31 (1H, app. q, *J* = 7.0 Hz)

¹³C NMR (75 MHz, CDCl₃) δ 14.2, 16.4, 38.7, 60.7, 77.1, 90.7, 174.3, 208.0

Data agrees with those of the literature.⁵⁰



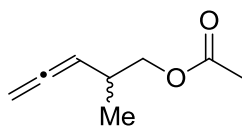
(±)-2-Methyl-penta-3,4-dien-1-ol (2.26)

A solution of ester **2.27** (10 g, 10.2 mmole) in Et₂O (300 mL) was cooled in an ice bath. Lithium aluminium hydride (2.98 g, 78.74 mmole) was added portionwise to the mixture under a constant flow of nitrogen. The reaction mixture was stirred for 2 hours. The mixture was quenched cautiously with wet Et₂O and water was added dropwise until effervescence ceased. The mixture was stirred for 30 minutes then and filtered. The filter cake was washed 3 times with ethyl acetate and the filtrate was concentrated. The residue was purified *via* distillation (cold finger, 6 mm Hg, 30 °C) to give alcohol **2.26** as colorless oil (4.58 g, 46.7 mmole, 65%).

¹H NMR (300 MHz, CDCl₃) δ 1.00 (3H, d, *J* = 7.0 Hz), 2.27-2.37 (1H, m, CH), 3.46 (2H, m), 4.71 (2H, dd, *J* = 3.0, 5.5 Hz) 5.07 (1H, app. q, *J* = 6.5 Hz)

¹³C NMR (75MHz, CDCl₃) δ 16.3, 35.5, 67.4, 75.9, 92.6, 207.9

Data agrees with those of the literature.⁵⁰



(±)- 2-Methylpenta-3,4-dien-1-yl acetate (2.59)

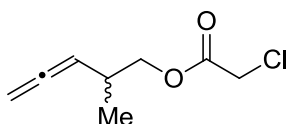
A solution of the allenic alcohol **2.26** (2 g, 20.4 mmole) in CH₂Cl₂ (30 mL) was allowed to stand over molecular sieves (4Å), and the transferred *via* cannula to a flask containing K₂CO₃ (4.22 g, 30.6 mmole). Acetic anhydride (2.2 mL, 22.4 mmole) was added and followed by few crystals of DMAP. The mixture was stirred overnight then filtered through celite. The filtrate was washed with aqueous 2 M HCl and saturated

aqueous sodium bicarbonate. The combined organic layers was dried over MgSO₄ and concentrated. Then the crude was purified by flash chromatography on silica eluting with 5-10% ethyl acetate/ hexane to give allenic acetate **2.59** as colorless oil (2.26 g, 16 mmole, 78%).

¹H NMR (400 MHz, CDCl₃) δ 1.05 (3H, d, *J* = 6.8 Hz), 1.56 (1H, br), 2.05 (3H, s), 2.45-2.55 (1H, m), 3.93 (1H, dd, *J* = 6.4, 10.8 Hz), 3.98 (1H, dd, *J* = 6.4, 10.8 Hz), 4.75 (2H, dd, *J* = 3.2, 6.9 Hz), 5.10 (1H, app. q, *J* = 6.4 Hz)

¹³C NMR (100 MHz, CDCl₃) δ 16.6, 20.8, 32.0, 68.5, 76.2, 92.1, 170.9, 207.9

Data agrees with those of the literature.⁵⁰



(±)-2-Methylpenta-3,4-dien-1-yl 2-chloroacetate (2.66)

The chloroacetate was prepared using the procedure described for acetate **2.59** using:

Allenic alcohol **2.26** (1.5 g, 15.3 mmole), chloroacetic anhydride (2.87 g, 16.8 mmole), DMAP (93 mg, 0.76 mmole), K₂CO₃ (3.17 g, 22.9 mmole); Yield: Yellow oil (1.89 g, 10.9 mmole, 71%)

IR (NaCl) v/cm⁻¹ 2968, 1956, 1746

¹H NMR (400 MHz, CDCl₃) δ 1.06 (3H, d, *J* = 6.9 Hz), 2.50-2.59 (1H, m), 4.06-4.12 (4H, m), 4.75 (2H, dd, *J* = 3.0, 6.7 Hz), 5.08 (app. q, *J* = 6.6 Hz)

¹³C NMR (75MHz, CDCl₃) δ 16.6, 32.1, 40.8, 70.1, 76.6, 91.7, 167.3, 208.1

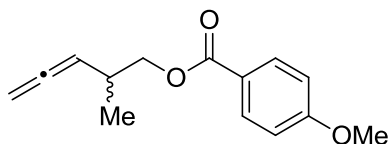
MS GCMS m/z $[M-CH_3]^+$ 159; HRMS m/z calcd. for $C_8H_{11}O_2^{35}ClNa$ $[M+Na]^+$
197.0345, found 197.0350

General procedure of esterification with acyl chloride

Formation of acid chloride

Oxalyl chloride (853 μ L, 9.78 mmole) was added to carboxylic acid (1.2 eq., 4.89 mmole) in CH_2Cl_2 (10 mL) under nitrogen. 1 Drop of DMF was added and the reaction mixture was stirred until effervescence ceased. The mixture was then concentrated and used for subsequent esterification.

Alcohol **2.26** (400 mg, 4.1 mmole) was dissolved in CH_2Cl_2 (8 mL) then transferred *via* cannula to the mixture of triethylamine (1.14 mL, 8.2 mmole) and DMAP (25 mg, 0.2 mmole). The acid chloride in CH_2Cl_2 (5 mL) was added dropwise to the mixture and it was stirred overnight. Water was added to the reaction mixture followed by ammonium chloride then extracted twice with CH_2Cl_2 . The organic layer was washed with 2N HCl and saturated aqueous sodium bicarbonate. The organic layer was dried over $MgSO_4$ then concentrated under reduce pressure. The ester was then purified by distillation (cold finger, Pressure and temperature depends on the ester)



(±)-2-Methylpenta-3,4-dien-1-yl 4-methoxybenzoate (2.63)

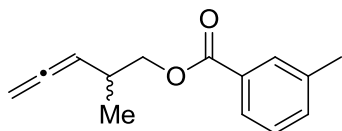
p-methoxybenzoic acid (744 mg); Yield: yellow oil (657 mg, 2.82 mmole, 69%)

IR (NaCl) ν/cm^{-1} 2970, 1956, 1712, 1606

^1H NMR (400 MHz, CDCl_3) δ 1.13 (3H, $J = 6.8$ Hz), 2.60-2.70 (1H, m), 3.86 (3H, s), 4.16 (1H, dd, $J = 6.4, 10.8$ Hz), 4.20 (1H, dd, $J = 6.4, 10.8$ Hz), 4.74 (2H, dd, $J = 3.0, 6.9$ Hz), 5.19 (1H, app. q, $J = 6.5$ Hz)

^{13}C NMR (75MHz, CDCl_3) δ 16.8, 32.4, 55.4, 68.7, 76.3, 92.2, 113.6, 122.8, 131.6, 163.3, 166.2, 208.0

MS GCMS m/z $[\text{M}]^+$ 232; HRMS m/z calcd. for $\text{C}_{14}\text{H}_{17}\text{O}_3$ 233.1178, found 233.1175



(±)-2-Methylpenta-3,4-dien-1-yl 3-methylbenzoate (2.65)

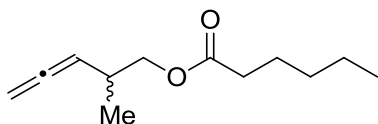
3-methylbenzoic acid (665 mg), Yield: yellow oil (390 mg, 1.8 mmole, 44%)

IR (NaCl) ν/cm^{-1} 2927, 2118, 1759, 1506

^1H NMR (400 MHz, CDCl_3) δ 1.15 (3H, d, $J = 6.8$ Hz), 2.41 (3H, s), 2.64-2.72 (1H, m), 4.17 (1H, dd, $J = 6.7, 10.7$ Hz), 4.22 (1H, dd, $J = 6.7, 10.7$ Hz), 4.75 (2H, dd, $J = 3.0, 6.7$ Hz), 5.18 (1H, app. q, $J = 6.5$ Hz), 7.29-7.40 (2H, m), 7.83-7.86 (2H, m)

^{13}C NMR (75MHz, CDCl_3) δ 16.8, 21.3, 32.4, 68.9, 76.4, 92.2, 126.7, 238.2, 130.1, 130.2, 133.6, 138.1, 166.7, 208.1

MS GCMS m/z $[\text{CH}_3\text{C}_6\text{H}_5]^+$ 91, $[\text{CH}_3\text{C}_6\text{H}_5\text{CO}]^+$ 119, $[\text{M}]^+$ 216; HRMS m/z calcd. for $\text{C}_{14}\text{H}_{17}\text{O}_2$ 217.1229, found 217.1230



(±)-2-Methylpenta-3,4-dien-1-yl hexanoate (2.64)

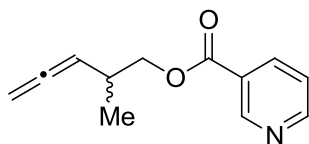
Hexanoyl chloride (684 μL , 4.89 mmole), Yield: colorless oil (584 mg, 2.96 mmole, 73%)

IR (NaCl) ν/cm^{-1} 2958, 1956, 1738, 1638

^1H NMR (400 MHz, CDCl_3) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.05 (3H, d, $J = 6.8$ Hz), 1.25-1.35 (4H, m), 1.62 (2H, quintet, $J = 7.5$ Hz), 2.30 (2H, t, $J = 7.5$ Hz), 2.48-2.51 (1H, m), 3.95 (2H, dd, $J = 6.7, 10.7$), 4.73 (2H, dd, $J = 3.0, 6.7$ Hz), 5.11 (1H, app. q, $J = 6.6$ Hz)

^{13}C NMR (75MHz, CDCl_3) δ 13.9, 16.7, 22.3, 24.7, 31.3, 32.3, 34.3, 68.3, 76.3, 92.2, 173.8, 207.9

MS GCMS m/z $[\text{CH}_3(\text{CH}_2)_4]^+$ 71, $[\text{CH}_3(\text{CH}_2)_4\text{CO}]^+$ 99, $[\text{M}]^+$ 196; HRMS m/z calcd. for $\text{C}_{12}\text{H}_{21}\text{O}_2$ $[\text{M}+\text{H}]^+$ 197.1542, found 197.1545



(±)-2-Methylpenta-3,4-dien-1-yl nicotinate (2.62)

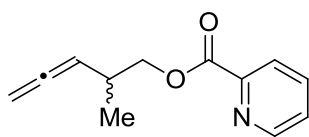
Nicotinic acid (602 mg); Yield: Yellow oil (538 mg, 2.64 mmole, 65%)

IR (NaCl) ν/cm^{-1} 2970, 1956, 1724, 1591

^1H NMR (400 MHz, CDCl_3) δ 1.14 (3H, d, $J = 6.8$ Hz), 2.64-2.71 (1H, m), 4.22 (1H, dd, $J = 6.5, 10.7$ Hz), 4.27 (1H, dd, $J = 6.5, 10.7$ Hz), 4.75 (2H, dd, $J = 3.0, 6.7$ Hz), 5.18 (1H, app. q, $J = 6.6$ Hz), 7.38 (1H, ddd, $J = 0.4, 4.8, 7.6$ Hz), 8.28 (1H, dt, $J = 2.0, 8.0$ Hz), 8.76 (1H, dd, $J = 1.6, 4.8$ Hz), 9.22 (1H, br-s)

^{13}C NMR (75 MHz, CDCl_3) δ 16.8, 32.3, 69.3, 92.0, 123.3, 126.2, 137.0, 150.9, 153.4, 165.1, 208.0

MS GCMS m/z [Nic^+] 78, [Nic^+] 106, [Nic^+] 124, $[\text{M}]^+$ 203; HRMS m/z calcd. for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 204.1021, found 204.1025



(±)-2-Methylpenta-3,4-dien-1-yl picolinate (2.61)

Picolinic acid (468 mg); Yield: Yellow oil (538 mg, 2.29 mmole, 56%)

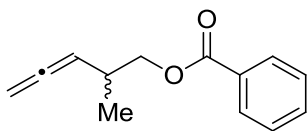
IR (NaCl) ν/cm^{-1} 2970, 1956, 1714, 1585

^1H NMR, 400 MHz (CDCl_3) δ 1.14 (3H, d, $J = 6.8$ Hz), 2.70-2.77 (1H, m), 4.26 (1H, dd, $J = 7.0, 10.7$ Hz), 4.34 (1H, dd, $J = 7.0, 10.7$ Hz), 4.74 (2H, dd, $J = 3.0, 6.6$ Hz),

5.21 (1H, app. q, $J = 6.6$ Hz), 7.45-7.48 (1H, m), 7.82 (1H, dt, $J = 1.6, 8.0$ Hz), 8.10 (1H, d, $J = 7.8$ Hz), 8.77 (1H, dd, $J = 0.6, 4.7$ Hz)

^{13}C NMR (75 MHz, CDCl_3) δ 16.8, 32.2, 69.8, 76.5, 92.0, 125.1, 126.8, 136.9, 148.1, 150.0, 165.0, 208.1

MS GCMS m/z [C_6H_5] $^+$ 78, [$\text{C}_6\text{H}_5\text{O}$] $^+$ 106; HRMS m/z calcd. for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 204.1021, found 204.1017



(±)-2-Methylpenta-3,4-dien-1-yl benzoate (2.59)

Alcohol **2.26** (8.0 g, 81.5 mmole), benzoyl chloride (10.4 mL, 89.5 mmole), DMAP (100 mg, 0.82), triethylamine (17 mL, 122 mmole); Yield: colorless oil (14.99 g, 74.2 mmole, 91%)

IR (NaCl) ν/cm^{-1} 2968, 1956, 1721, 1600, 1450

^1H NMR (300 MHz, CDCl_3) δ 1.15 (3H, d, $J = 6.8$ MHz), 2.64-2.71 (1H, m), 4.18 (1H, dd, $J = 6.8, 10.8$ Hz), 4.26 (1H, dd, $J = 6.4, 10.8$ Hz), 4.77 (2H, dd, $J = 2.8, 6.4$ Hz), 5.21 (1H, app. q, $J = 6.8$ Hz), 7.45(2H, t, $J = 7.6$ Hz), 7.55 (1H, $J = 7.2$ MHz), 8.04 (2H, $J = 1.6, 7.2$ Hz)

^{13}C NMR (75 MHz, CDCl_3) δ 208.0, 166.5, 132.9, 130.3, 129.6, 128.3, 92.2, 68.9, 32.4, 16.8

MS GCMS m/z [C_6H_5] $^+$ 77.11, HRMS m/z calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_2$ $[\text{M}+\text{H}]^+$ 203.1072, found 203.1074

High Throughput Screening

0.1 M pH 7 potassium phosphate buffer solution (330 μL) was added from a micropipette to each (34 for acetate **2.58** and 33 for benzoate **2.59**) well of the 96 well plate followed by enzymes (50 μL , 8mg/mL in 0.1 M pH 7 potassium phosphate buffer solution). The acetate **2.58** or benzoate **2.59** (20 μL , 40mg/mL in CH_3CN) was then added to each mixture and the mixture was shaken for 24 hour. Each reaction mixture was quenched with CH_3CN (400 μL), shaken for minutes then centrifuged for 10 minutes.

For determination of conversion *via* HPLC: 50 μL of each quenched reaction was diluted with CH_3CN 150 μL then submitted for assay.

For determination e.e. *via* Chiral GC: Extraction was done by diluting aliquots 100 μL of each quenched reaction with 300 μL of MTBE then shaken for 10 minutes and centrifuged for 10 minutes. 200 μL of the organic layer from each extracted reaction mixture was submitted for assay.

DOE Experiments

Buffer solution was added to the 20 mL vial and was warmed to the desired temperature with stirring. Acetonitrile was added to the buffer solution and the pH was adjusted to the desired pH by addition of 6 M HCl or 2 M NaOH. Enzyme stock solution was added followed by benzoate and the reaction mixture was stirred for 24 hour and quenched with 5mL CH_3CN . The conversion and e.e. determination were conducted as described in high throughput screening section.

Measured density of benzoate **2.59**: 1.024 g/cm^3

For Run 1:

Temperature: 55 °C

CH₃CN: 0.25 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 8 potassium phosphate buffer solution)

Buffer solution: 4.25 mL (0.1 M pH 7 potassium phosphate buffer solution)

Benzoate **2.59**: 9.77 µL

For Run 2, 3, 10, 11:

Temperature: 40 °C

CH₃CN: 0.50 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 7 potassium phosphate buffer solution)

Buffer solution: 4.00 mL (0.1 M pH 7 potassium phosphate buffer solution)

Benzoate **2.59**: 17.09 µL

For Run 4:

Temperature: 25 °C

CH₃CN: 0.75 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 6 potassium phosphate buffer solution)

Buffer solution: 3.75 mL (0.1 M pH 6 potassium phosphate buffer solution)

Benzoate **2.59**: 24.41 µL

For Run 5:

Temperature: 25 °C

CH₃CN: 0.25 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 8 potassium phosphate buffer solution)

Buffer solution: 4.25 mL (0.1 M pH 8 potassium phosphate buffer solution)

Benzoate **2.59**: 24.41 µL

For Run 6:

Temperature: 55 °C

CH₃CN: 0.75 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 6 potassium phosphate buffer solution)

Buffer solution: 3.75 mL (0.1 M pH 7 potassium phosphate buffer solution)

Benzoate **2.59**: 9.77 μ L

For Run 7:

Temperature: 25 °C

CH₃CN: 0.25 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 6 potassium phosphate buffer solution)

Buffer solution: 4.25 mL (0.1 M pH 6 potassium phosphate buffer solution)

Benzoate **2.59**: 9.77 μ L

For Run 8:

Temperature: 55 °C

CH₃CN: 0.75 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 8 potassium phosphate buffer solution)

Buffer solution: 3.75 mL (0.1 M pH 7 potassium phosphate buffer solution)

Benzoate **2.59**: 24.41 μ L

For Run 9:

Temperature: 25 °C

CH₃CN: 0.75 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 8 potassium phosphate buffer solution)

Buffer solution: 3.75 mL (0.1 M pH 8 potassium phosphate buffer solution)

Benzoate **2.59**: 9.77 μ L

For Run 12:

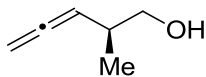
Temperature: 55 °C

CH₃CN: 0.25 mL

Enzyme stock: 0.5 mL (10g/L in 0.1 M pH 6 potassium phosphate buffer solution)

Buffer solution: 4.25 mL (0.1 M pH 7 potassium phosphate buffer solution)

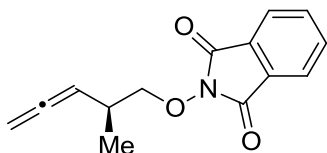
Benzoate **2.59**: 24.41 μ L



(S)-2-Methyl-penta-3, 4-dien-1-ol (2.26)

Acetonitrile (25mL) was added to pH 8 phosphate buffer solution (425 mL) and the pH was adjusted to 8. Amano Lipase PS (500mg) was dissolved in pH 8 potassium phosphate buffer (50 mL) and added to the acetonitrile-buffer solution mixture. The mixture was stirred for 5 minutes. Benzoate **2.59** (2.5 g, 12.0 mmole) was added and the mixture was stirred vigorously with an overhead stirrer for 24 hours. THF (100 mL) and aqueous saturated aqueous sodium bicarbonate (100 mL) were added to the mixture and it was stirred for 30 minutes. The mixture was filtered through celite and extracted with Et₂O using a continuous-extractor for 8 hours. The ether layer was dried over mixture of sodium bicarbonate and sodium sulfate then filtered and concentrated under reduced pressure at room temperature. The residue was purified by flash chromatography on silica gel eluting with 5-20% ether-pentane to give alcohol **2.26** (400 mg, 4.1 mmole, 34%) as a colorless oil.

$[\alpha]_D^{23}$ -34.2 (*c* 0.45, CHCl₃); lit.⁵⁰ $[\alpha]_D^{21}$ -43.9 (*c* 1.08, CHCl₃)



(S)-2-((2-Methylpenta-3,4-dien-1-yl)oxy)isoindoline-1,3-dione (2.78)

Alcohol **2.26** (5.4 g, 55 mmole) was dissolved in THF (200 mL) and allowed to stand over molecular sieves (4Å). The solution was added *via* cannula to a mixture of *N*-hydroxyphthalimide (13.3 g, 82.5 mmole) and triphenyl phosphine (21.6 g, 82.5 mmole). A solution of DIAD (14.3 mL, 82.5 mmole) in THF (10 mL) was added dropwise to the mixture at 0 °C. The mixture was stirred overnight. The mixture was pre-absorbed on silica then purified by flash chromatography on silica gel eluting with 0-5% ethyl acetate/ hexane to give phthalimide **2.78** as colorless solid (10.3 g, 31 mmole, 76%).

m.p. 49-53 °C

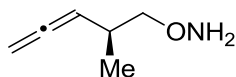
IR ν/cm^{-1} 2971, 2937, 1953, 1786, 1725

^1H NMR (300 MHz, CDCl_3) δ 1.21 (3H, d, $J = 7.0$ MHz), 2.66-2.73 (1H, m), 4.02 (1H, dd, $J = 7.5, 9.0$ Hz), 4.16 (1H, m), 4.77 (2H, dd, $J = 3.0, 7.0$ Hz), 5.29 (1H, app. q, $J = 6.5$ Hz), 7.73-7.75 (2H, m), 7.82-7.85 (2H, m)

^{13}C NMR (75 MHz, CDCl_3) δ 16.6, 31.7, 76.6, 82.5, 92.0, 123.5, 129.0, 134.5, 163.4, 207.9

MS HRMS m/z calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}$ $[\text{M}+\text{H}]^+$ 212.1075, found 212.1079

$[\alpha]_{\text{D}}^{23} -35.3$ (c 0.31, CHCl_3)

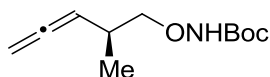


(S)-O-(2-Methylpenta-3,4-dien-1-yl)hydroxylamine (2.79)

Hydrazide monohydrate (14mL, 28.9 mmole) was added to a solution of phthalimide **2.78** (11.7 g, 48.1 mmole) in CH₂Cl₂ (300 mL). The mixture was stirred for 1 hr, filtered then concentrated to give the hydroxylamine **2.79** as a colorless oil. The crude product was used directly in the next step.

¹H NMR 300 MHz (CDCl₃) δ 1.10 (3H, d, *J* = 7.0 MHz), 2.55-2.65 (1H, m), 3.00 (1H, br), 4.04 (1H, dd, *J* = 6.5, 9.5 Hz), 4.13 (1H, dd, *J* = 3.0, 7.0 Hz), 4.79 (2H, dd, *J* = 3.0, 7.0 Hz), 5.12 (1H, app. q, *J* = 6.5 Hz)

¹³C NMR, 75 MHz δ 16.6, 31.5, 76.0, 80.5, 93.0, 208.0



(S)-tert-Butyl (2-methylpenta-3,4-dien-1-yl)oxycarbamate (2.25)

Water (150 mL), NaOH (3.57 g, 89 mmole) and Boc₂O (11.1 mL, 53.5 mmole) were added sequentially to a solution of the hydroxylamine **2.79** (9.50 g, 44.5 mmole) in dichloromethane (150 mL). The mixture was stirred overnight then extracted twice with dichloromethane. The organic layer was dried over MgSO₄, concentrated and purified by flash chromatography on silica gel eluting with 5% ethyl acetate/ hexane to give hydroxylamine **2.25** as a colorless oil. (8.77 g, 37.3 mmole, 77%)

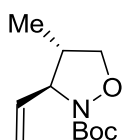
IR ν/cm⁻¹ 3290, 2977, 2932, 2875, 1955, 1717

^1H NMR (300 MHz, CDCl_3) δ 1.05 (3H, d, $J = 6.8$ Hz), 1.47 (9H, s), 2.51-2.58 (1H, m), 3.69 (1H, dd, $J = 7.0, 9.5$ Hz), 3.76 (1H, dd, $J = 7.0, 9.5$ Hz), 4.73 (2H, dd, $J = 3.2, 6.5$ Hz), 5.16 (1H, app. q, $J = 6.5$ Hz)

^{13}C NMR (75 MHz, CDCl_3) δ 16.7, 28.2, 31.5, 76.3, 81.2, 81.7, 92.5, 156.9, 207.9

MS LCMS m/z $[\text{M}+\text{Na}]^+$ 236, GCMS m/z $[\text{C}(\text{CH}_3)^+]$ 57, HRMS calcd. m/z for $\text{C}_{11}\text{H}_{19}\text{NO}_3$ $[\text{M}+\text{Na}]^+$ 236.1263, found 236.1264

$[\alpha]_{\text{D}}^{23} -42.9$ (c 0.17, CHCl_3)



(3S, 4S)-tert-Butyl 4-methyl-3-vinylisoxazolidine-2-carboxylate (2.24)

Hydroxylamine **2.25** (1.50 g, 7.0 mmole) was dissolved in CH_2Cl_2 (5 mL) and allowed to stand over molecular sieves (4Å). The solution added *via* cannula to a solution of silver triflate (0.039 g, 1.52 mmole) in CH_2Cl_2 (20 mL) with containing molecular sieves (4Å). The mixture was stirred overnight then filtered through a pad of silica gel. The filtrate was concentrated to give isoxazolidine **2.24** as a colorless oil (1.37 g, 6.4 mmole, 91%).

Major isomer:

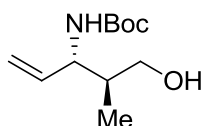
IR ν/cm^{-1} 2977, 2935, 2876, 1730

^1H NMR (300 MHz, CDCl_3) δ 1.08 (3H, d, $J = 6.8\text{Hz}$), 1.45 (9H, s, ^tBu), 2.37-2.45 (1H, m), 3.41 (1H, t, $J = 8.3\text{Hz}$), 3.93 (1H, t, $J = 6.9\text{ Hz}$), 4.10 (1H, t, $J = 7.2\text{ Hz}$), 5.13 (1H, d, $J = 10.1$), 5.22 (1H, d, $J = 17.0\text{ Hz}$), 5.76 (1H, ddd, $J = 7.2, 10.2, 16.8\text{ Hz}$)

^{13}C NMR (75 MHz, CDCl_3) δ 14.5, 28.2, 43.8, 69.1, 75.0, 81.8, 115.8, 136.7, 157.0

MS LCMS m/z $[\text{M}+\text{Na}]^+$ 236, GCMS $[\text{M}-\text{Boc}+\text{H}]^+$ 113, $[\text{Bu}]$ 57 ; HRMS m/z calcd. for $\text{C}_{11}\text{H}_{19}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 236.1263, found 236.1264

$[\alpha]_{\text{D}}^{24} +48.7$ (c 0.3, CHCl_3)



***tert*-Butyl ((3*S*,4*S*)-5-hydroxy-4-methylpent-1-en-3-yl)carbamate (2.23)**

Molybdenum hexacarbonyl (170 mg, 0.64 mmole) and NaBH_4 (120 mg, 3.17 mmole) were added to a solution of the isoxazolidine **2.24** (419 mg, 1.97 mmole) in acetonitrile:water (10:1) (8.8 mL). The mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature then air was bubbled through it for 30 minutes. The mixture was filtered, concentrated and purified by flash chromatography on silica gel eluting with 5-20% ethyl acetate/ hexane to give hydroxylamine as a colorless solid (322 mg, 1.50 mmole, 76%) .

m.p. 74-79 $^\circ\text{C}$

IR ν/cm^{-1} 3290, 2976, 1670

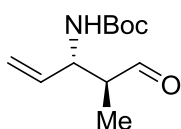
^1H NMR (300 MHz, CDCl_3) δ 1.00 (3H, d, $J = 6.8\text{ Hz}$), 1.45 (9H, s), 1.60-1.65 (1H, m), 3.49 (1H, d, $J = 3.4, 11.5\text{ Hz}$), 3.72 (1H, d, $J = 3.4, 11.6\text{ Hz}$), 4.06 (2H, dd, $J = 8.0,$

15.5 Hz), 5.18 (1H, d, $J = 10.5$ Hz), 5.23 (1H, d, $J = 17.0$ Hz), 5.77 (1H, ddd, $J = 6.5$, 10.5, 17.0 Hz)

^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 28.2, 39.5, 55.2, 64.1, 79.5, 115.9, 136.9, 156.3

MS LCMS m/z $[\text{M}+\text{H}]^+$ 238; HRMS calcd. m/z for $\text{C}_{11}\text{H}_{21}\text{NO}_3\text{Na}[\text{M}+\text{Na}]^+$ 238.1419, found 238.1417

$[\alpha]_{\text{D}}^{23} -3.3$ (c 0.13, CHCl_3)

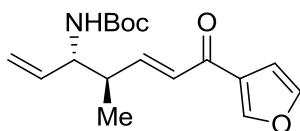


***tert*-Butyl ((3*S*,4*S*)-4-methyl-5-oxopent-1-en-3-yl)carbamate (**2.80**)**

A solution of oxalyl chloride (0.91 mL, 10.4 mmole) in THF (90 mL) was cooled to -78°C. DMSO (1.48 mL, 1.48 mmole) was added dropwise and the mixture was stirred for 5 minutes. Alcohol (1.89 g, 8.8 mmole) in THF (10 mL) was allowed to stand over molecular sieves (4Å) and then transferred *via* cannula to the reaction mixture and stirred for 15 minutes. Triethylamine (4.63 mL, 33.2 mmole) was added dropwise and the mixture was stirred for 30 minutes then warmed to room temperature. Water was added to the reaction mixture and it was extracted twice with Et_2O . The organic layer was dried over MgSO_4 and concentrated under reduced pressure to give the crude aldehyde **2.80** which was used directly in the next step.

IR ν/cm^{-1} 3337, 2978, 1694, 1506

^1H NMR (400 MHz, CDCl_3) δ 1.13 (3H, d, $J = 7.3$), 1.45 (s, 9H), 2.60-2.75 (1H, m), 4.40-4.50 (1H, m), 4.80-4.90 (1H, m), 5.21 (1H, d, $J = 10.5$ Hz), 5.24 (1H, d, $J = 17.4$ Hz), 5.78 (1H, ddd, $J = 6.0, 10.5, 16.9$ Hz), 9.67 (1H, s)



***tert*-Butyl ((3*S*,4*R*,*E*)-7-(furan-3-yl)-4-methyl-7-oxohepta-1,5-dien-3-yl)carbamate
(2.22)**

Ba(OH)₂ (830 mg, 4.84 mmole) was heated at 140°C for 3 hours with stirring then cooled to 70 °C . A solution of phosphonate (2.55 g, 11.4 mmole) in THF (30 mL) was added followed by addition of aldehyde **2.80** in THF (10 mL). Water (376 μL) was added to the mixture and it was heated at reflux overnight. The reaction mixture was cooled to room temperature then water was added and it was extracted twice with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated. The residue was purified *via* flash column chromatography on silica gel eluting with 5-10% ethyl acetate/ hexane to give diene **2.22** as a yellow solid. (2.24 g, 8.1 mmole, 85%).

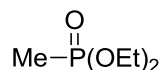
m.p. 83-86 °C

¹H NMR (400 MHz, CDCl₃) δ 1.15 (3H, d, *J* = 6.9 Hz), 1.46 (9H, s), 2.59-2.64 (1H, m), 4.26 (1H, CH), 4.54 (br, 1H), 5.20 (1H, d, *J* = 10.0 Hz), 5.22 (1H, d, *J* = 5.5 Hz), 5.78 (1H, ddd, *J* = 5.5, 10.1, 16.5 Hz), 6.55 (1H, d, *J* = 16.0 Hz), 6.84 (1H, d, *J* = 1.84 Hz), 6.9 (1H, dd, *J* = 7.8, 15.6 Hz), 7.48 (1H, d, *J* = 1.8 Hz), 8.09 (1H, s)

¹³C NMR (100 MHz, CDCl₃) δ 15.3, 28.3, 41.4, 56.3, 79.6, 109.0, 116.6, 127.8, 135.4, 136.3, 144.2, 147.1, 147.5, 148.5, 155.3

MS LCMS [M+H]⁺ 306; GCMS [M-Boc] 205; HRMS calcd. m/z for C₁₇H₂₄NO₄
306.1705, found 306.1698

[α]_D²³ +25 (c 0.24, CHCl₃)



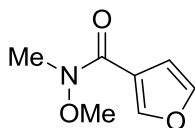
Diethyl methylphosphonate (2.30)

A suspension of sodium hydride (6.7 g, 174 mmole, 60% w/w in mineral oil) in THF (200 mL) was cooled in an ice bath. Diethyl phosphite (18.7 mL, 145 mmole) in THF (40 mL) was added dropwise from an addition funnel and the addition funnel was rinsed with THF (5 mL). The mixture was stirred for 1hr. Methyl iodide (13.0 mL, 209 mmole) in THF (40 mL) was then added dropwise from an additional funnel and rinsed with THF (5 mL). The mixture was stirred for 1 hr at room temperature. Water was added dropwise until effervescence ceased, then the mixture was filtered through celite and concentrated under reduced pressure. The residue was purified *via* distillation (cold finger 0.5 mmHg, 50 °C) to give phosphate **2.30** as a colorless oil (15.0 g, 98 mmole, 68%).

¹H NMR (400 MHz, CDCl₃) δ 1.32 (6H, t, *J* = 7.3 Hz), 1.45 (3H, *J* = 17.9), 4.00-4.20 (4H, m)

¹³C NMR (100 MHz, CDCl₃) δ 11.3 (d, *J* = 144.1), 16.0 (d, *J* = 6.7 Hz), 61.1 (d, *J* = 5.73 Hz)

Data agrees with those of the literature.¹⁰³



***N*-Methoxy-*N*-methylfuran-3-carboxamide (2.29)**

Oxalyl chloride (5.84 mL, 66.9 mmole) was added to a suspension of 3-furoic acid (5 g, 44.6 mmole) in CH₂Cl₂ (50 mL) followed by 1 drop of DMF. When effervescence ceased, the volatiles were removed under reduced pressure to give the crude acyl chloride. The acyl chloride was dissolved in CH₂Cl₂ (10 mL) then added *via* cannula to *N,O*-dimethylhydroxylamine·hydrochloride (8.7 g, 89.2 mmole). Triethylamine (37.3 mL, 267 mmole) was added dropwise then the mixture was stirred for 2 hr. Water and saturated aqueous ammonium chloride was added and the mixture was extracted twice with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. Ether (20 mL) was added. The mixture was filtered and concentrated to give Weinreb amide **2.29** as brown liquid (6.64 g, 43 mmole, 98 %). The crude product was used directly in the next step.

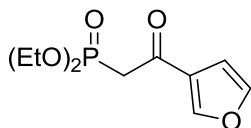
IR ν/cm^{-1} 3489, 3132, 2939, 1627, 1512

¹H NMR (400 MHz, CDCl₃) δ 3.34 (3H, s), 3.71 (3H, s), 6.87 (1H, d, $J = 1.36$ Hz), 7.42 (1H, t, $J = 1.36$ Hz), 8.02 (1H, d, $J = 0.9$ Hz)

¹³C NMR (100 MHz, CDCl₃) δ 32.8, 61.1, 111.3, 119.7, 142.6, 146.5, 163.1

MS LCMS m/z [M+H]⁺ 156, [M-NMe(OMe)] 95; HRMS calcd. m/z for C₇H₁₀NO₃

156.0661, found 156.0658



Diethyl (2-(furan-3-yl)-2-oxoethyl)phosphonate (2.28)

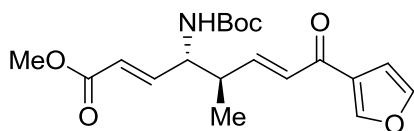
n-BuLi (48 mL, 71.6 mmole, 1.6M in hexane) was added dropwise to a solution of phosphate **2.30** (8.7 g, 57.3 mmole) in THF (100 mL) at -78°C The reaction mixture was stirred for 30 minutes. Weinreb amide **2.29** (6.6 g, 47.7 mmole) in THF (10 mL) was added dropwise and the mixture was warmed to room temperature and stirred for 2 hr. Water and saturated aqueous ammonium chloride was added. The mixture was extracted twice with ethyl acetate. The organic layer was dried over MgSO₄ then concentrated to give the crude phosphonate **2.28** as a brown liquid (10.0 g, 37 mmole, 78%).

IR ν/cm^{-1} 2983, 1674, 1161

¹H NMR (300 MHz, CDCl₃) δ 1.30 (6H, t, $J = 7.1$), 3.39 (2H, d, $J = 22.7$ Hz), 4.10-4.20 (4H, m), 6.80 (1H, t, $J = 1.2$ Hz), 7.43 (s, 1H), 8.16 (1H, s)

¹³C NMR (100 MHz, CDCl₃) δ 16.2 (d, $J = 5.72$ Hz), 40.6 (d, $J = 127.8$), 62.7, 108.8, 127.7, 144.2, 149.1, 185.6 (d, $J = 6.7$ Hz)

MS LCMS [M+H]⁺ 247; HRMS calcd. m/z for C₁₀H₁₅O₅NaP [M+Na]⁺ 269.0555, found 269.0560



(2E, 4S, 5R, 6E)-Methyl 4-((tert-butoxycarbonyl)amino)-8-(furan-3-yl)-5-methyl-8-oxoocta-2,6-dienoate (2.31)

Diene **2.22** (306 mg, 1.11 mmole) and methyl acrylate (300 μ L, 3.32 mmole) were dissolved in toluene (11 mL) and warmed to 70°C. Hoveyda-Grubbs II catalyst (35 mg, 0.05 mmole) was dissolved in toluene (1 mL) was added in 5 portions over 2.5 hrs. The mixture was stirred overnight at 70°C. Nitrogen was bubbled through the system during the reaction. The reaction mixture was cooled then toluene was partially removed under reduce pressure. Purification by flash chromatography on silica gel eluting with 5-20% ethyl acetate/ hexane gave the diene ester **2.31** as a yellow viscous oil (300 mg, 0.83 mmole, 75%).

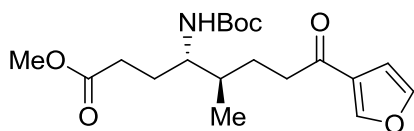
IR ν/cm^{-1} 3337, 2977, 1694, 1667, 1620, 1510

^1H NMR (400 MHz, CDCl_3) δ 1.15 (3H, d, $J = 6.8$ Hz), 1.41 (9H, s), 2.65-2.72 (1H, m), 3.72 (3H, s), 4.41 (1H, br-s), 4.67 (1H, br-s), 5.92 (d, $J = 14.2$), 6.55 (1H, d, $J = 15.6$ Hz), 6.82-6.84 (1H, m), 6.87 (1H, dd, $J = 7.8, 15.6$ Hz), 7.41 (1H, d, $J = 1.8$ Hz), 8.03 (1H, s)

^{13}C NMR (100 MHz, CDCl_3) δ 20.9, 28.2, 40.9, 51.6, 54.8, 80.0, 109.0, 121.9, 128.0, 128.8, 144.42, 146.12, 147.0, 147.5, 155.1, 166.3, 183.9

MS LCMS m/z $[\text{M}+\text{Na}]^+$ 386, HRMS calcd. m/z for $\text{C}_{19}\text{H}_{26}\text{NO}_6$ $[\text{M}+\text{H}]^+$ 364.1760, found 364.1759

$[\alpha]_{\text{D}}^{23}$ -20 (c 0.1, CHCl_3)



(4*S*,5*R*)-Methyl 4-((tert-butoxycarbonyl)amino)-8-(furan-3-yl)-5-methyl-8-oxooctanoate

(2.67)

A solution of Wilkinson's catalyst (56 mg, 0.06 mmole) and diene **2.31** (343 mg, 1.03 mmole) in toluene (7 mL) was stirred under hydrogen at 100 psi at room temperature overnight. The mixture was purified by flash chromatography on silica gel eluting with 5-20% ethyl acetate/ hexane to give ester **2.67** as a colorless viscous oil (347 mg, 1.03 mmole, 98%)

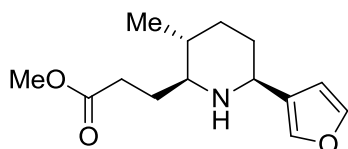
IR ν/cm^{-1} 3361, 2972, 1737, 1681, 1514

^1H NMR (400 MHz, CDCl_3) δ 0.93 (3H, d, $J = 6.4$ Hz), 1.42 (9H, s), 1.54-1.60 (3H, m), 1.86-1.90 (2H, m), 2.36-2.40 (2H, m), 2.71-2.82 (2H, m), 3.51-3.53 (1H, m), 3.67 (3H, s), 6.76 (1H, br-s), 7.44 (1H, br-s), 8.07 (1H, s)

^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 15.6, 26.7, 26.9, 28.4, 31.0, 37.2, 37.7, 51.7, 54.1, 60.4, 108.6, 127.6, 144.2, 147.4, 155.9, 174.3

MS LCMS m/z $[\text{M}+\text{Na}]^+$ 390, $[\text{M}+\text{H}]^+$ 368; HRMS calcd. m/z for $\text{C}_{19}\text{H}_{30}\text{NO}_6$ $[\text{M}+\text{H}]^+$ 368.2073, found 368.2072

$[\alpha]_{\text{D}}^{23}$ -4.0 (c 0.1, CHCl_3)



Methyl 3-((2*S*,3*R*,6*S*)-6-(furan-3-yl)-3-methylpiperidin-2-yl)propanoate (2.16)

Trifluoroacetic acid (9 mL, 118 mmole) was added to a solution of carbamate **2.67** (872 mg, 2.58 mmole) in CH₂Cl₂ (90 mL). The reaction mixture was stirred for 1 hr, then concentrated, dissolved in CH₂Cl₂ (30 mL) and washed with saturated aqueous NaHCO₃ solution. The organic layer was dried over MgSO₄ then concentrated. The residue was taken up in MeOH (20 mL).

Sodium borohydride (98 mg, 2.6 mmole) was added portionwise to the imine solution at 0 °C. The mixture was stirred for 1 hr at 0°C. The reaction mixture was warmed to room temperature then pre-absorbed on florisil. Purification by flash chromatography on florisil eluting with 10-30% ethyl acetate/hexane gave amine **2.16** as a colorless oil (490 mg, 1.95 mmole, 75%).

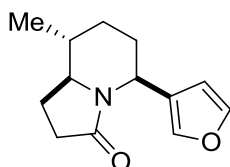
IR ν/cm^{-1} 3360, 2954, 1681

¹H NMR (400 MHz, CDCl₃) δ 0.90 (3H, d, $J = 6.0$ Hz), 1.18-1.22 (3H, m), 1.60-1.65 (2H, m), 1.83 (2H, m), 1.98-2.03 (1H, m), 2.30 (1H, dt, $J = 3.2, 8.6$ Hz), 2.42-2.45 (2H, m), 3.58 (1H, dd, $J = 2.7, 11.4$ Hz), 3.67 (3H, s), 6.4 (1H, s), 7.28-7.34 (2H, m)

¹³C NMR (100 MHz, CDCl₃) δ 18.4, 28.7, 30.3, 34.0, 34.3, 35.5, 51.5, 53.3, 62.4, 109.2, 129.6, 138.3, 142.7, 174.6

MS HRMS calcd. m/z for C₁₄H₂₁NO₃Na [M+Na]⁺ 274.1419, found 274.1413

$[\alpha]_{\text{D}}^{23}$ -8.0 (c 0.1, CHCl₃)

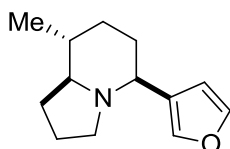


(±)-5-(furan-3-yl)-8-methylhexahydroindolizin-3(2H)-one (2.68)

A solution of ester **2.16** (202 mg, 0.8 mmole) in toluene (20 mL) was heated at reflux for 3hr. The toluene was removed under reduced pressure to give crude lactam **2.68** as yellow liquid (154 mg, 0.64 mmole, 80%).

¹H NMR (400 MHz, CDCl₃) δ 0.95 (d, *J* = 3H, d, 6.4 Hz), 1.17-1.91 (m, 6H), 2.16-2.39 (m, 3H), 3.11 (1H, dt, *J* = 6.0, 10.1 Hz), 4.40 (1H, dd, *J* = 4.1, 7.8 Hz), 6.36-6.38 (1H, m), 7.31 (1H, br-s), 7.35 (1H, br-s)

Data agrees with those of the literature.¹⁹



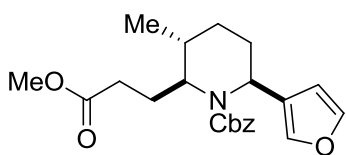
(±)-5-(Furan-3-yl)-8-methyloctahydroindolizine (1.2)

Lithium aluminium hydride (122 mg, 3.2 mmole) was added to a solution of lactam **2.68** (194mg, 0.8mmole) in THF (10mL). The mixture was heated at reflux for 2 hr. Water was added till effervescence ceased. The mixture was stirred for 30 minutes then filtered and concentrated. The residue was purified by flash chromatography on alumina eluting with 5-10% Methanol/dichloromethane to give indolizidine (**1.2**) as colorless oil (150 mg, 0.63 mmole, 79%).

^1H NMR (400 MHz, CDCl_3) δ 0.90 (3H, d, $J = 6.9$ Hz), 1.0-2.0 (11H, m), 2.85-2.92 (2H, m), 6.43 (1H, br-s), 7.32-7.34 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 142.6, 139.3, 128.2, 109.7, 71.4, 59.7, 53.1, 36.4, 34.1, 33.8, 29.0, 20.1, 18.8

Data agrees with those of the literature.¹⁹



(±)-Benzyl 6-(furan-3-yl)-2-(3-methoxy-3-oxopropyl)-3-methylpiperidine-1-carboxylate

(2.69)

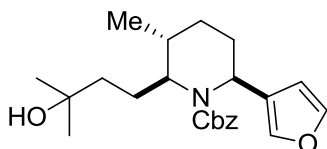
Saturated aqueous potassium carbonate (10 mL) was added to a solution of ester **2.16** (216 mg, 0.86 mmole) in acetonitrile (10 mL). Benzyl chloroformate (287 μL , 1.72 mmole) was added to the mixture and it was stirred overnight. The mixture was extracted twice with dichloromethane and the combined organic layers were dried over MgSO_4 . The combined organic extracts was concentrated and purified by flash chromatography on silica eluting with 10-20% ethyl acetate/hexane to give carbamate **2.69** as a colorless oil (208 mg, 0.54 mmole, 63%).

IR ν/cm^{-1} 2951, 1737, 1681

^1H NMR (400 MHz, CDCl_3) δ 1.06 (3H, d, $J = 7.0$ Hz), 1.35-2.11 (9H, m), 3.51 (3H, s) 4.00-4.03 (1H, m), 5.11 (1H, d, $J = 16.5$ Hz), 5.23 (1H, d, $J = 16.5$ Hz), 5.38 (1H, br-s), 6.32 (1H, br-s), 7.33 (7H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 18.7, 22.1, 29.5, 31.3, 45.3, 51.4, 56.6, 65.4, 67.3, 110.3, 127.0, 127.8, 128.0, 128.5, 136.7, 138.8, 143.0, 173.6

MS HRMS calcd. m/z for $\text{C}_{21}\text{H}_{26}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 372.1811, found 372.1823



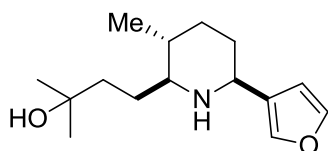
(±)-*N*-Benzyloxycarbonyl Nupharamine (**2.70**)

Methyl magnesium bromide (372 μL , 11.2 mmole) was added dropwise to a solution of carbamate **2.69** (208 mg, 0.54 mmole) in diethyl ether (30 mL) cooled in an ice bath. The mixture was heated at reflux for 2 hours. Reaction mixture was cooled to room temperature and saturated aqueous ammonium chloride was added. The mixture was diluted with ethyl acetate and extracted twice with ethyl acetate. The combined organic layers was dried over MgSO_4 , concentrated and purified by flash column chromatography on silica eluting with 10-20 % ethyl acetate/hexane to give amine **2.70** as colorless liquid (155 mg, 0.4 mmole, 75%).

^1H NMR (400 MHz, CDCl_3) δ 0.98 (3H, s), 0.95 (3H, s), 1.06 (3H, d, $J = 7.0$ Hz), 1.12-2.14 (9H, m), 3.99 (1H, br-s), 5.20 (2H, br-s), 5.38 (1H, br-s), 6.36 (1H, br-s), 7.28-7.40 (7H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 18.8, 21.7, 28.8, 29.1, 29.4, 31.4, 40.6, 45.2, 57.6, 67.2, 70.5, 110.8, 127.6, 128.0, 128.5, 136.8, 139.8, 142.5, 159.3

Data agrees with those of the literature.¹⁹



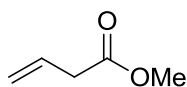
(±)-Nupharamine

MeOH (10 mL) was added to a mixture of alcohol **2.70** (77 mg, 0.23 mmole), 5% Pd/C (12 mg) and ammonium formate (85 mg, 1.34 mmole). The mixture was stirred overnight. The reaction mixture was filtered through celite then concentrated and purified by flash chromatography on alumina eluting with 10% methanol/dichloromethane to give Nupharamine as colorless liquid (27 mg, 0.11 mmole, 47%).

^1H NMR (400 MHz, CDCl_3) δ 0.94 (3H, d, $J = 6.9$ Hz), 1.19 (3H, s), 1.22 (3H, s), 1.45-2.04 (9H, m), 2.40 (1H, t, $J = 8.2$ Hz), 3.60-3.63 (1H, m), 6.42 (1H, br-s), 7.33-7.37 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 18.5, 28.4, 29.2, 30.2, 33.5, 33.8, 39.6, 53.0, 62.8, 68.8, 109.2, 138.4, 143.0

Data agrees with those of the literature.¹⁹



Methyl but-3-enoate (2.49)

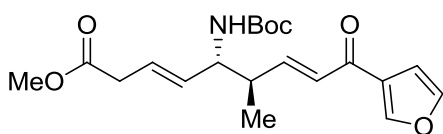
Vinyl acetic acid (3.2g, 38 mmole) was added to a suspension of K_2CO_3 (6.4g, 46 mmole) in acetone (60 mL) in an ice bath. The mixture was stirred for 30 minutes. MeI (3.60 mmole, 58 mmole) was added and the mixture was stirred for 6 hours. The reaction mixture was filtered through celite and the celite cake was washed with

ether. The volatiles were removed under reduced pressure at room temperature gave ester **2.49** as colorless liquid (2 g, 20 mmole, 53%).

^1H NMR (400 MHz, CDCl_3) δ 3.08 (2H, $J = 6.8$ Hz), 3.67 (3H, s), 5.12-5.16 (2H, m), 5.89 (1H, ddd, $J = 6.9, 10.1, 17.4$, Hz)

^{13}C NMR (100 MHz, CDCl_3) δ 30.5, 38.9, 51.8, 118.5, 130.2, 171.9

Data agrees with those of the literature.⁷⁸



(3E,5S,6R,7E)-Methyl-5-((tert-butoxycarbonyl)amino)-9-(furan-3-yl)-6-methyl-9-oxonona-3,7-dienoate (2.71)¹⁰⁴

Diene (625 mg, 2.00 mmole) and methyl ester **2.49** (100 mg, 10.0 mmole) were dissolved in toluene (20 mL) and warmed to 70°C. Hoveyda-Grubbs II catalyst (64 mg, 0.05 mmole) was dissolved in toluene (1 mL) then added in 5 portions over 2.5 hrs. The reaction mixture was stirred overnight. Nitrogen was bubbled through the system during the reaction. The reaction mixture was cooled then toluene was partially removed under reduced pressure. Purification by flash chromatography on silica gel eluting with 5-20% ethyl acetate/ hexane to give ester **2.71** as yellow solid (582 mg, 1.54 mmole, 77%)

m.p. 83-86 °C

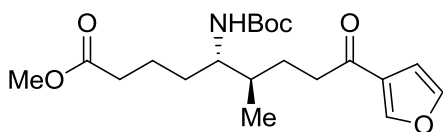
IR ν/cm^{-1} 3361, 2922, 1681, 1454

^1H NMR (400 MHz, CDCl_3) δ 1.11 (3H, d, $J = 6.8$ Hz), 1.42 (9H, s), 2.61-2.63 (1H, m), 3.08 (2H, d, $J = 6.9$ Hz), 3.67 (3H, s), 4.12 (1H, br-s), 4.54 (1H, br-s), 5.54 (1H,

dd, $J = 6.12, 15.4$ Hz), 5.71 (1H, dt, $J = 6.1, 15.2$ Hz), 6.54 (1H, d, $J = 15.5$ Hz), 6.82 (1H, t, $J = 2.0$ Hz), 6.91 (1H, dd, $J = 7.7, 15.6$ Hz), 8.07 (1H, s)

^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 15.8, 21.0, 28.3(2C), 37.4, 41.4, 51.9, 60.4, 109.1, 124.1, 127.9, 132.3, 144.2, 147.5, 148.3, 155.2, 171.1

MS GCMS m/z [MeO-C(=O)] $^+$ 73, [furan-C(=O)] $^+$ 95, [M- furan-C(=O)] $^+$ 282; HRMS m/z calcd. for $\text{C}_{20}\text{H}_{28}\text{NO}_6$ 378.1917, found 378.1918



(5*S*,6*R*)-Methyl 5-((*tert*-butoxycarbonyl)amino)-9-(furan-3-yl)-6-methyl-9-oxononanoate (2.50)

A solution of Wilkinson's catalyst (46 mg, 0.06 mmole) and diene **2.71** (188 mg, 0.5 mmole) in toluene (5 mL) was stirred under hydrogen at 100 psi at room temperature overnight. The mixture was purified by flash column chromatography on silica gel eluting with 5-20% ethyl acetate/ hexane to give ester **2.50** as a colorless viscous oil (165 mg, 0.43 mmole, 86%).

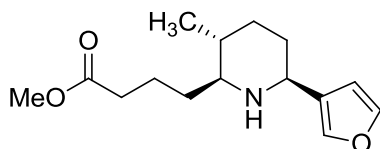
IR ν/cm^{-1} 3369, 2957, 2358, 1732, 1674, 1514

^1H NMR (400 MHz, CDCl_3) δ 0.90 (3H, d, $J = 6.8$ Hz), 1.31-1.83 (16H, m), 2.30-2.35 (2H, m), 2.70-2.82 (2H, m), 3.50 (1H, m), 3.66 (3H, s), 6.75 (1H, d, $J = 9.5$ Hz), 6.74 (1H, d, $J = 1.4$ Hz), 7.42 (1H, br-s), 8.05 (1H, br-s)

^{13}C NMR (100 MHz, CDCl_3) δ 15.7, 21.5, 26.7, 28.4, 31.0, 33.6, 36.8, 37.8, 51.5, 54.2, 79.1, 108.6, 127.6, 144.1, 147.2, 155.9, 173.9 195.1

MS GCMS m/z [MeO-C(=O)] $^+$ 73; HRMS m/z calcd. for $\text{C}_{20}\text{H}_{31}\text{NO}_6\text{Na}$ $[\text{M}+\text{H}]^+$ 404.2049,
found 404.2041

$[\alpha]_{\text{D}}^{22} +16.0$ (c 0.2, CHCl_3)



Methyl 4-((2*S*,3*R*,6*S*)-6-(furan-3-yl)-3-methylpiperidin-2-yl)butanoate (**2.51**)

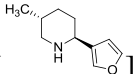
Trifluoroacetic acid (375 μL , 4.9 mmole) was added to a solution of carbamate **2.50** (123 mg, 0.34 mmole) in CH_2Cl_2 (4 mL). The reaction mixture was stirred for 2 hr then concentrated, dissolved in CH_2Cl_2 (30 mL) and washed twice with saturated aqueous NaHCO_3 solution. The combined organic layer was dried over MgSO_4 then concentrated. The residue was taken up in MeOH (4 mL).

Sodium borohydride (12.5 mg, 0.34 mmole) was added portionwise to the imine solution at 0 °C. The mixture was stirred for 1 hr at 0 °C. The mixture was warmed to room temperature then pre-absorbed on florisil. Purification by flash chromatography on florisil eluting with 10-30% ethylacetate/hexane gave amine **2.51** as a colorless oil (64 mg, 0.24 mmole, 71%).

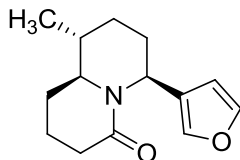
IR ν/cm^{-1} 3369, 2957, 2358, 1732, 1674, 1514

^1H NMR (400 MHz, CDCl_3) δ 0.87 (3H, d, $J = 6.2$ Hz), 1.28-1.84 (9H, m), 2.28-2.32 (3H, m), 3.57 (1H, dd, $J = 2.8, 14.9$ Hz), 3.66 (3H, s), 6.38-6.42 (1H, m), 6.74 (1H, d, $J = 1.4$ Hz), 7.34 (2H, m), 8.05 (1H, s)

^{13}C NMR (100 MHz, CDCl_3) δ 18.4, 21.0, 33.0, 33.9, 34.2, 34.4, 35.6, 51.5, 53.5, 62.9, 109.2, 129.5, 138.4, 142.7, 174.0

MS GCMS m/z []⁺ 164, [M]⁺ 265; HRMS m/z calcd. for C₁₅H₂₄NO₃ [M+H]⁺ 266.1756, found 266.1756

[α]_D²² +32.5 (*c* 0.27, CHCl₃)



(6S,9R,9aS)-6-(Furan-3-yl)-9-methylhexahydro-1H-quinolizin-4(6H)-one (2.52)

LiOH·H₂O (10 mg, 0.24 mmole) and H₂O (5.0 μ L, 0.28 mmole) were added to a solution of ester **2.51** (60 mg, 0.23 mmole) in MeOH (3 mL). The mixture was heated at reflux overnight. The mixture was cooled to room temperature and the volatiles were removed under reduced pressure. The residue was dissolved in DMF (3 mL). EDCI·HCl (65 mg, 0.34 mmole) was added and the mixture was stirred overnight. Water was added and reaction mixture was extracted with ethyl acetate. The organic layer was dried over MgSO₄, concentrated and purified *via* flash chromatography with silica eluting with 60% EtOAc/Hexane to give lactam **2.52** as colorless liquid (40 mg, 0.17 mmole, 74%).

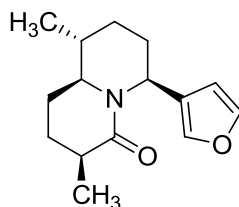
IR ν/cm^{-1} 2953, 2358, 1634, 1408

¹H NMR (400 MHz, CDCl₃) δ 0.86 (3H, d, *J* = 6.6 Hz), 1.18-1.34 (3H, m), 1.64- 2.10 (7H, m), 2.38-2.51 (2H, m), 3.24 (1H, dt, *J* = 3.4, 11.0 Hz), 5.39 (1H, br-s), 6.27 (1H, br-s), 7.21 (1H, br-s), 7.31 (1H, br-s)

¹³C NMR (100 MHz, CDCl₃) δ 18.6, 20.0, 24.1, 26.2, 28.0, 31.9, 32.2, 46.4, 59.0, 109.7, 127.8, 138.9, 142.5, 170.0

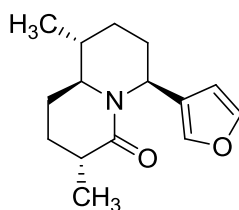
MS GCMS m/z $[M-CH_3]^+$ 216, $[M]^+$ 233; HRMS m/z calcd. for $C_{14}H_{20}NO_2$ $[M+H]^+$
234.1494, found 234.1499

$[\alpha]_D^{21}$ -117.4 (c 0.23, $CHCl_3$)



Major:

(3S,6S,9R,9aS)-6-(Furan-3-yl)-3,9-dimethylhexahydro-1H-quinolizin-4(6H)-one
(2.56)



Minor:

(3R,6S,9R,9aS)-6-(Furan-3-yl)-3,9-dimethylhexahydro-1H-quinolizin-4(6H)-one
(2.57)

LDA formation: A solution of iPr_2NH (15 μL , 0.11 mmole) in THF (110 μL) was cooled at 0 °C. $n-BuLi$ (65 μL , 0.1 mmole, 1.6 M solution in hexane) was added dropwise and the mixture was stirred for 30 minutes.

LDA was added dropwise to a solution of lactam **2.52** (21 mg, mmole) in THF (1 mL) at -78 °C and the mixture was stirred for 2 hrs. MeI (10 μL , 0.16 mmole) was added and the mixture was stirred overnight at -78 °C. MeOH and saturated aqueous

ammonium chloride were added. The mixture was warmed to room temperature and extracted twice with EtOAc. The organic layer was dried over MgSO₄, concentrated and purified by flash chromatography on silica eluting with 5-30% EtOAc/Hexane to give the major lactam as a colorless oil (10 mg, 0.04mmole, 44%) and the minor lactam as a colorless oil (3 mg, 0.012 mmole, 13%).

Major diastereomer:

IR ν/cm^{-1} 2954, 2357, 1643

¹H NMR (400 MHz, CDCl₃) δ 0.87 (3H, d, $J = 6.4$ Hz), 1.25 (3H, m), 1.1- 2.20 (10H, m), 2.35-2.45 (1H, m), 3.22 (1H, dt, $J = 3.2, 11.0$ Hz), 5.38 (1H, s), 7.19 (1H, br-s), 7.32 (1H, br-s)

¹³C NMR (100 MHz, CDCl₃) δ 17.8, 18.6, 24.3, 26.0, 28.2, 29.3, 32.4, 37.0, 46.8 59.4, 109.8, 128.0, 139.0, 142.4, 172.9

MS GCMS m/z , [M]⁺ 247; HRMS m/z calcd. for C₁₅H₂₂NO₂ [M+H]⁺ 248.1561, found 248.1653

$[\alpha]_{\text{D}}^{21} +43.3$ (c 0.03, CHCl₃)

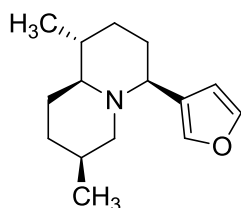
Minor diastereomer:¹⁰⁵

IR ν/cm^{-1} 2954, 2359, 1634

¹H NMR (400 MHz, CDCl₃) δ 0.85 (3H, d, $J = 5.5$ Hz), 1.21-2.08 (10 H, m), 1.28 (3H, d, $J = 7.3$ Hz), 2.51-2.54 (1H, m), 3.19 (1H, dt, $J = 3.6, 11.0$ Hz), 5.37-5.38 (1H, m), 6.25 (1H, br-s), 7.19 (1H, br-s), 7.32 (1H, br-s)

¹³C NMR (100 MHz, CDCl₃) δ 17.8, 18.6, 24.3, 26.0, 28.2, 29.3, 32.4, 37.0, 46.8, 59.4, 109.8, 128.0, 139.0, 142.4, 172.9

MS GCMS m/z , [M]⁺ 247; HRMS m/z calcd. for C₁₅H₂₂NO₂ [M+H]⁺ 248.1561, found 248.1655



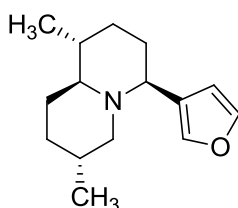
(-)-Deoxynupharidine

Red-Al (50 μL , 0.175 mmole, 70% in toluene) was added to a solution of lactam **2.57** (12 mg, 0.04 mmole) in THF (1 mL) and the mixture was heated at reflux for 30 minutes. Water was added cautiously and the mixture was extracted twice with chloroform. The combined organic layers was dried over MgSO₄ and concentrated. The crude product was purified by flash chromatography on neutral alumina eluting with 10-20% EtOAc/Hexane to give deoxynupharidine as colorless oil (6 mg, 0.026 mmole, 64%).

^1H NMR (400 MHz, CDCl_3) δ 0.88 (3H, d, $J = 6.4$ Hz), 0.99 (3H, d, $J = 6.8$ Hz), 1.00-1.79 (11H, m), 1.81 (1H, dd, $J = 3.0, 11.3$ Hz), 2.62-2.65 (1H, m), 2.90-2.94 (2H, m), 6.38 (1H, br- d, $J = 1.2$ Hz), 7.25 (1H, br-s), 7.33 (1H, br-s)

^{13}C NMR (100 MHz, CDCl_3) δ 17.2, 19.1, 25.6, 30.4, 33.8, 60.0, 69.5, 109.5, 139.0, 142.6

$[\alpha]_{\text{D}}^{22} -164$ (c 0.16, CHCl_3)

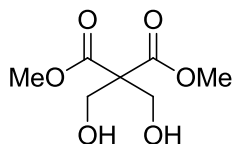


(-)-*epi*-7-Deoxynupharidine

Red-Al (50 μL , 0.175 mmole, 70% in toluene) was added to a solution of lactam **2.57** (6.8 mg, 0.028 mmole) in THF (1 mL) and the mixture was heated at reflux for 30 minutes. Water was added cautiously and the mixture was extracted twice with chloroform. The combined organic layers was dried over MgSO_4 and concentrated. The crude product was purified by flash chromatography on neutral alumina eluting with 10-20% EtOAc/Hexane to give 7-*epi*-deoxynupharidine as a colorless oil (2 mg, 0.008 mmole, 29%).

^1H NMR (400 MHz, CDCl_3) δ 0.73 (3H, d, $J = 6.8$ Hz), 0.89 (3H, d, $J = 6.4$ Hz), 0.76 (1H, m), 1.00-1.80 (10H, m), 1.90-1.99 (1H, m), 2.80 (1H, dt, $J = 2.3, 11.4$ Hz), 2.89 (1H, dd, $J = 2.8, 11.0$ Hz), 6.42 (1H, m), 7.30 (1H, br-s), 7.35 (1H, br-s)

^{13}C NMR (100 MHz, CDCl_3) δ 19.0, 19.9, 30.0, 30.7, 33.6, 34.1, 35.0, 36.4, 60.9, 61.3, 69.4, 109.7, 128.8, 139.6, 142.6



Dimethyl 2,2-bis(hydroxymethyl)malonate (**2.32**)

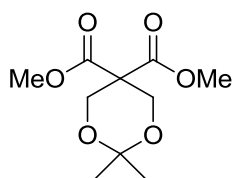
Dimethyl malonate (9.5 mL, 75.7 mmole) was added dropwise to a mixture of K_2CO_3 (606 mg, 6.06 mmole) and formaldehyde (12.2 mL, 151 mmole, 37% w/w aqueous), maintaining the temperature at 20-25 °C. The reaction mixture was stirred for 1 hr. The reaction mixture was saturated with NaCl. Saturated aqueous ammonium chloride was added and the mixture was extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude diol **2.32** as a colorless solid (12.22 g, 63.6 mmole, 84%).

IR ν/cm^{-1} 3505, 3444, 1721

1H NMR (300 MHz, $CDCl_3$) δ 3.76 (6H, s), 4.09 (4H, s)

^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 61.1, 63.6, 169.8

MS HRMS m/z calcd. for $C_7H_{12}O_6Na$ $[M+Na]^+$ 215.0532, found 215.0539



Dimethyl 2,2-dimethyl-1,3-dioxane-5,5-dicarboxylate (2.72)

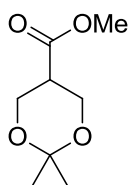
2,2-Dimethoxypropane (1.5 mL, 13.8 mmole) was added to a mixture of Amberlyst-15 (46 mg) and diol **2.32** (1.25 g, 6.5 mmole) in anhydrous acetone (20 mL) containing molecular sieves (4Å). The mixture was stirred overnight, then filtered through celite and concentrated to give the crude acetonide **2.72** as a yellow oil (2.45 g, 10.5 mmole, 94%).

IR ν/cm^{-1} 2996, 2958, 1720

^1H NMR (300 MHz, CDCl_3) δ 1.39 (6H, s), 3.76 (6H, s), 4.28 (4H, s)

^{13}C NMR, (100 MHz, CDCl_3) δ 23.5, 34.8, 53.4, 62.5, 98.6, 168.4

MS GCMS m/z $[\text{M}-\text{CH}_3]^+$ 217, HRMS m/z calcd. for $\text{C}_{10}\text{H}_{17}\text{O}_6$ $[\text{M}+\text{H}]^+$ 215.0532, found 215.0539



Methyl 2,2-dimethyl-1,3-dioxane-5-carboxylate (2.33)

A solution of dimethoxy acetonide **2.72** (2.02 g, 8.7 mmole) and NaCl (509 mg, 8.71 mmole) in DMSO (5mL) and water (450 μL) was heated at 130 $^\circ\text{C}$ overnight. Water was added and the mixture was extracted twice with diethyl ether. The combined

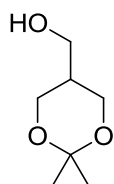
organic layers were dried over MgSO₄ and evaporated to give the mono ester **2.53** as yellow oil (1.10 g, 6.3 mmole, 73%).

IR ν/cm^{-1} 2994, 2955, 1729

¹H NMR (300 MHz, CDCl₃) δ 1.41 (3H, s), 1.42 (3H, s), 2.81 (1H, tt, $J = 5.5, 8.3$ Hz), 3.71 (3H, s), 4.00-4.10 (4H, m)

¹³C NMR, (100 MHz, CDCl₃) δ 21.1, 26.2, 39.9, 51.8, 60.4, 98.0, 171.2

MS HRMS m/z calcd. for C₈H₁₄O₄Na [M+Na]⁺ 197.0790, found 197.0782



(2,2-Dimethyl-1,3-dioxan-5-yl)methanol (2.73)

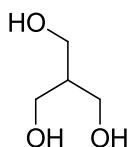
LiAlH₄ (522 mg, 12.6 mmole) was added portionwise to a solution of ester **2.33** (1g, 5.74 mmole) in Et₂O (50 mL) and the mixture was stirred for 2 hrs. Water was added dropwise until the effervescence eased. The mixture was filtered and concentrated to give crude alcohol **2.73** as brown oil (574 mg, 3.92 mmole, 68%).

IR ν/cm^{-1} 3420, 1372

¹H NMR (300 MHz, CDCl₃) δ 1.40 (3H, s), 1.44 (3H, s), 3.70-3.80 (4H, m), 4.00 (2H, dd, $J = 1.25, 12.46$)

¹³C NMR (100 MHz, CDCl₃) δ 23.1, 24.7, 36.5, 61.3, 61.8, 98.0

MS GCMS [M-OH]⁺, HRMS m/z calcd. for C₇H₁₄O₃Na [M+Na]⁺ 169.0841, found 169.0833

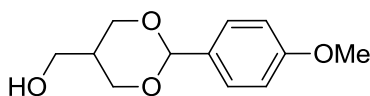


2-(Hydroxymethyl)propane-1,3-diol (**2.34**)¹⁰⁶

Amberlyst-15 (549 mg) and water (1.41 mL, 78.4 mmole) were added to a solution of the alcohol **2.73** (5.73 g, 39.2 mmole) in MeOH (50 mL). The mixture was stirred overnight then filtered and concentrated to give the triol as colorless liquid (4.3g, quant).

¹H NMR (300 MHz, MeOD) δ 1.74 (1H, sep, $J = 6.0$ Hz), 3.55 (6H, d, $J = 6.0$ Hz)

¹³C NMR (100 MHz, MeOD) δ 45.8, 60.2



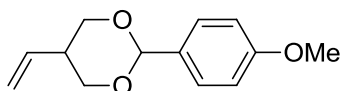
(2-(4-Methoxyphenyl)-1,3-dioxan-5-yl)methanol (**2.35**)

Triol **2.34** (1.06 g, 9.93 mmole) and (\pm)- camphor sulfonic acid were suspended in dichloromethane (20 mL). *p*-Methoxybenzaldehyde dimethyl acetal (1.8 mL, 10.4 mmole) was added and the mixture was heated at reflux overnight. The reaction mixture was filtered, concentrated and purified by flash chromatography on silica gel eluting with 0-20% ethyl acetate/ hexane to give alcohol **2.35** as colorless solid (1.43 g, 6.7 mmole, 68%).

¹H NMR (400 MHz, CDCl₃) δ 1.62-1.67 (1H, m), 2.33-2.39 (1H, m), 3.48 (1H, d, $J = 6.0$ Hz), 3.71-3.37 (1H, m), 3.79 (3H, s), 4.03-4.13 (2H, m), 4.21-4.30 (2H, m), 5.37 (1H, s), 5.46 (1H, s), 6.87-6.90 (2H, m), 7.37-7.42 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 36.5, 36.9, 55.3, 61.2, 61.9, 67.8, 69.6, 101.4, 101.8, 113.6, 113.6, 127.2, 127.3, 160.0

Data agrees with those of the literature.¹⁰⁷



2-(4-Methoxyphenyl)-5-vinyl-1,3-dioxane (**2.36**)

Alcohol **2.35** (1.38, 6.5 mmole) and sulfur trioxide.pyridine (1.07, 13 mmole) were dissolved in a mixture of DMSO (10 mL) and dichloromethane (50 mL). Triethylamine (3.62 mL, 26 mmole) was added and the mixture was stirred for 2 hr. The reaction mixture was diluted with EtOAc and water, then washed with saturated aqueous ammonium chloride. The organic layers was dried over MgSO_4 and concentrated to give the crude aldehyde which was used directly in the next step without purification.

Methyl triphenylphosphonium bromide (4.17g, 11.7 mmole) was suspended in THF (50 mL) and the mixture was cooled in an ice bath. *n*-BuLi (6.1 mL, 9.75 mmole, 1.6 M in hexane) was added dropwise to the mixture and it was stirred for 1 hr. The crude aldehyde in THF (15 mL) was added *via* cannula and the mixture was stirred for 1 hr. The mixture was pre-absorbed on silica then purified by flash chromatography on silica gel eluting with 0-10% ethyl acetate/ hexane to give alkene **2.36** as colorless oil (570 mg, 2.74 mmole, 42%).

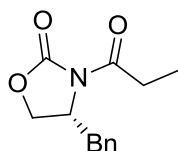
IR ν/cm^{-1} 2962, 2839, 1517

^1H NMR (400 MHz, CDCl_3) δ 2.17-2.19 (1H, m), 2.78-2.87 (1H, m), 3.70-3.74 (1H, m), 3.80 (3H, s), 4.10-4.24 (3H, m), 5.10-5.46 (3H, m), 5.50-5.52 (1H, m), 6.38 (1H, ddt, $J = 7.8, 10.4, 17.5$ Hz), 6.88-6.90 (2H, m), 7.40-7.42 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 38.5, 38.9, 55.3, 71.0, 71.2, 101.2, 101.7, 113.6, 116.0, 118.0, 127.3, 127.4, 130.8, 131.1, 133.6, 138.3, 160.0

MS GCMS $[\text{M}]^+$ 220; HRMS m/z calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 243.0997, found 243.0995

Data agrees with those of the literature.⁷⁶



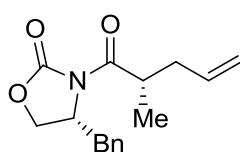
(R)-4-Benzyl-3-propionyloxazolidin-2-one (2.46)

n-BuLi (12.4 mL, 19.9 mmole, 1.6 M in hexane) was added dropwise to a solution of oxazolidinone **2.45** (3.22 g, 18.1 mmole) in THF (50 mL) at -78 °C. The mixture was stirred for 30 minutes. Propionyl chloride (1.73 mL, 19.9 mmole) was added dropwise and the mixture was stirred for 2 hours. The reaction mixture was warmed to room temperature. Saturated aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate twice. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over MgSO_4 and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-15% ethyl acetate/ hexane to give the imide **2.46** as viscous colorless oil (3g, 12.8 mmole, 71%).

^1H NMR (400 MHz, CDCl_3) δ 1.21 (t, $J = 7.4$ Hz, 3H), δ 2.76 (dd, $J = 9.6, 13.3$ Hz, 1H), δ 2.87-2.98 (m, 2H), δ 3.32 (dd, $J = 3.2, 13.4$ Hz, 1H), δ 4.15-4.23 (m, 2H), δ 4.64-5.30 (m, 1H), δ 7.25 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3) δ 8.3, 29.2, 37.9, 55.1, 66.2, 127.3, 128.9, 129.4, 135.3, 153.5, 174.1

Data agrees with those of the literature.⁷⁶



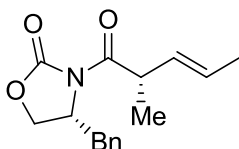
(R)-4-Benzyl-3-((S)-2-methylpent-4-enoyl)oxazolidin-2-one (2.47)

NaHMDS (15.3 mL, 15.3 mmole, 1M in THF) was added dropwise to a solution of imide **2.46** (3.25 g, 13.9 mmole) in THF (28 mL) at -78 °C and the mixture was stirred for 1 hr. Allyl bromide (41.6 mmole) was added dropwise and the mixture was stirred for 1 hr, then warmed to -40 °C and stirred overnight. Saturated aqueous ammonium chloride was added and the mixture was warmed to room temperature. The mixture was dilute with a small amount of water then extracted twice with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 0-15% ethyl acetate/hexane to give imide **2.47** as viscous colorless liquid (2.04 g, 7.46 mmole, 54%).

^1H NMR (400 MHz, CDCl_3) δ 1.19 (3H, d, $J = 6.8$ Hz), 2.20-2.27 (1H, m), 2.51-2.56 (1H, m), 2.70 (1H, dd, $J = 9.8, 13.3$ Hz), 3.30 (1H, dd, $J = 3.2, 13.3$ Hz), 3.84-3.89 (1H, m), 4.13-4.19 (2H, m), 4.65-4.70 (1H, m), 5.04-5.12 (2H, m), 5.80 (1H, ddt, $J = 7.0, 10.1, 17.1$ Hz), δ 7.20-7.35 (5H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 16.4, 37.1, 38.0, 38.1, 55.4, 66.0, 117.2, 127.3, 128.9, 129.4, 135.2, 135.3, 153.1, 176.5

Data agrees with those of the literature.¹⁰⁸



(R)-4-Benzyl-3-((S,E)-2-methylpent-3-enoyl)oxazolidin-2-one (2.74)

A solution of the alkene **2.47** (880 mg, 3.2 mmole) and rhodium trichloride hydrate (17 mg, 0.08 mmole) in a mixture of EtOH (6 mL) and H_2O (0.6 mL) was heated at reflux overnight under N_2 . The mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0-15% ethyl acetate/ hexane to give imide **2.74** as thick colorless liquid (660 mg, 2.41 mmole, 75%).

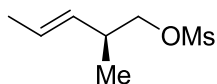
IR ν/cm^{-1} 2974, 1771, 1693

^1H NMR (400 MHz, CDCl_3) δ 1.27 (d, $J = 6.8$ Hz, 3H), δ 1.72 (3H, d, $J = 6.4$ Hz), δ 2.77 (1H, dd, $J = 9.2, 13.5$ Hz), δ 3.23 (1H, dd, $J = 3.3, 13.4$ Hz), δ 4.13-4.22 (1H, m), δ 4.41-4.45 (1H, m), δ 4.66-4.71 (1H, m), δ 5.74-5.57 (2H, m), δ 7.18-7.28 (5H, m).

^{13}C NMR (100 MHz, CDCl_3): δ 17.2, 18.0, 37.7, 40.5, 55.1, 65.9, 127.3, 127.8, 128.8, 129.5, 129.6, 135.2, 152.9, 175.2.

MS GCMS m/z : 273 (M^+); HRMS: m/z calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_3$ [$\text{M}+\text{H}$] $^+$ 274.1443, found 274.1441

$[\alpha]_{\text{D}}^{22} +11.0$ (c 0.155, CHCl_3)



(*S,E*)-2-Methylpent-3-en-1-yl methanesulfonate (2.43)

Lithium aluminium hydride (90 mg, 2.4 mmole) was added portionwise to a solution of oxazolidinone **2.74** (538 mg, 2.0 mmole) in Et₂O (10 mL). The mixture was stirred for 2 hrs then water was added cautiously until effervescence ceased. The mixture was stirred for 30 minutes then filtered and washed with 30 mL of diethyl ether. The filtrate was added *via* cannula to a flask containing a solution of triethylamine (548 μ L, 3.9 mmole) in CH₂Cl₂ (10mL) cooled in an ice bath. Methane sulfonyl chloride (377 μ L, 3.9 mmole) was added dropwise and the mixture was stirred for 2 hrs, then warmed to room temperature. Saturated aqueous ammonium chloride and water were added. The mixture was extracted twice with CH₂Cl₂. The combined organic layers were washed with saturated aqueous NaHCO₃ then dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel eluting with 15% ethyl acetate/ hexane to give alkene **2.43** as colorless liquid (211 mg, 1.18 mmole, 59%).

IR ν /cm⁻¹ 2968, 1354

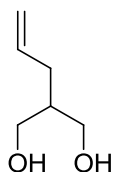
¹H NMR (400 MHz, CDCl₃): δ 1.05 (3H, d, J = 6.7Hz), δ 1.66 (3H, d, J = 6.2Hz), δ 2.52-2.56 (m, 1H), δ 2.97 (s, 3H), δ 3.95-4.11 (m, 2H), δ 5.27-5.33 (m, 1H), δ 5.52-5.58 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 16.6, 17.9, 36.4, 37.3, 74.0, 127.0, 131.0

MS GCMS: m/z : [M⁺] 179, [CH₃SO₂OCH₂⁺] 123; HRMS m/z calcd. for C₇H₁₅O₃S

[M+H]⁺ 179.0750, found 179.0742

$[\alpha]_{\text{D}}^{22} +12.6$ (c 0.46, CHCl_3)



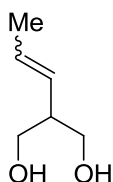
2-Allylpropane-1,3-diol (2.75)

Lithium aluminium hydride (4.8 g, 126 mmole) was suspended in diethyl ether (50 mL). A solution of allyl diethyl malonate (10 mL, 50.7 mmole) in diethyl ether (50 mL) was added dropwise to the mixture at 0 °C. The mixture was stirred overnight. Water was added cautiously until effervescence ceased. The mixture was filtered and the cake was washed with ethyl acetate (3 times) and concentrated. The residue was purified by flash chromatography on silica gel eluting with 10-70% ethyl acetate/hexane to give diol **2.75** as colorless liquid (4.43 g, 38.2 mmole, 75%).

^1H NMR (400 MHz, CDCl_3): δ 1.84 (1H, m), 2.05 (2H, m), 3.00 (2H, br), 3.60-3.66 (2H, m), 3.75-3.80 (2H, m), 5.02 (2H, m), 5.78 (1H, ddt, $J = 7.1, 10.1, 14.2$ Hz)

^{13}C NMR (100 MHz, CDCl_3): δ 32.5, 41.7, 65.8, 116.6, 136.2

Data agrees with those of the literature.⁷²



2-(Prop-1-en-1-yl)propane-1,3-diol (2.39)⁷³

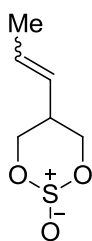
RhCl₃·H₂O (192 mg, 0.9 mmole) was added to a solution of diol **2.75** (4.27 g, 36.8 mmole) in EtOH/H₂O (10:1) (54 mL) and the mixture was heated at reflux under nitrogen overnight. The mixture was concentrated and purified by flash chromatography on silica eluting with 10-70% EtOAc/ Hexane to give diol **2.39** as a colorless liquid (2.95 g, 25.4 mmole, 69%).

Major isomer:

¹H NMR (400 MHz, CDCl₃): δ 1.68 (3H, d, *J* = 6.4 Hz), 2.43 (1H, app. sextet, *J* = 6.7 Hz), 3.67 (3H, s), 5.27 (1H, dd, *J* = 8.1, 15.5 Hz), 5.57-5.68 (1H, m)

¹³C NMR (100 MHz, CDCl₃): δ 18.2, 46.7, 65.0, 128.0, 129.0

Data agrees with those of the literature.



5-(Prop-1-en-1-yl)-1,3,2-dioxathiane 2-oxide (2.40)¹⁰⁹

Thionyl chloride (2.1 mL, 29.3 mmole) was added to a solution of diol **2.39** (2.88g, 24.4 mmole) in CH₂Cl₂ (70 mL) and the mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and saturated aqueous NaHCO₃ solution was added cautiously until the effervescence ceased. The organic layer was

separated and the aqueous layer was extracted twice with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , then filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 0-5% ethyl acetate/ hexane to give mixture of sulfoxide **2.40** as yellow liquid (3.45 g, 21.2 mmole, 87%) and as a mixture of diastereomers.

Isomer I:

IR ν/cm^{-1} 2947, 1188

^1H NMR (400 MHz, CDCl_3): δ 1.68 (3H, d, $J = 6.2$ Hz), 2.97-3.00 (1H, m), 3.70-3.74 (2H, m), 4.60 (2H, t, $J = 11.4$ Hz), 5.05-5.11 (1H, m), 5.60-5.65 (1H, m)

^{13}C NMR (100 MHz, CDCl_3): δ 18.1, 38.4, 60.4, 124.7, 131.1

MS HRMS m/z calcd. for $\text{C}_6\text{H}_{11}\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$: 163.0429, found 163.0435

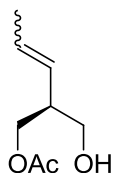
Isomer II:

IR ν/cm^{-1} 2947, 1188

^1H NMR (400 MHz, CDCl_3): δ 1.68 (3H, d, $J = 5.0$ Hz), 3.75-3.80 (4H, m), 5.24-5.30 (1H, m), 5.59-5.64 (1H, m)

^{13}C NMR (100 MHz, CDCl_3): δ 18.1, 38.4, 60.4, 124.7, 131.1

MS HRMS m/z calcd. for $\text{C}_6\text{H}_{11}\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 163.0429, found 163.0424



(S)-2-(Hydroxymethyl)pent-3-en-1-yl acetate (2.41)

Vinyl acetate (317 μL , 3.4 mmole) and Amano lipase PS (69 mg) were added sequentially to a solution of diol **2.39** (200 mg, 1.7 mmole) in THF (5 mL). The mixture was stirred overnight at room temperature then filtered through celite and concentrated. The mixture was purified by flash chromatography on silica eluting with 0-10% EtOAc/Hexane to give mono acetate **2.41** as colorless oil (137 mg, 0.86 mmole, 51%) and diacetate **2.42** as colorless oil (120 mg, 0.6 mmole, 35%).

Major isomer:

Monoacetate **2.41**:

IR ν/cm^{-1} 3466, 2956, 1739

^1H NMR (400 MHz, CDCl_3): δ 1.69 (3H, d, $J = 6.4$ Hz), 2.04 (3H, s), 2.51 (1H, app. sextet, $J = 7.0$ Hz), 3.51 (2H, m), 4.04-4.17 (2H, m), 5.23-5.33 (1H, m), 5.58-5.62 (1H, m)

^{13}C NMR (100 MHz, CDCl_3): δ 18.2, 20.8, 39.3, 44.5, 62.9, 64.5, 127.7, 129.3, 171.4

MS HRMS m/z calcd. for $\text{C}_8\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$ 159.1021, found 159.1025

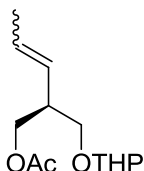
Diacetate **2.42**:

IR ν/cm^{-1} 2960, 1741

^1H NMR (400 MHz, CDCl_3): δ 1.66 (3H, d, $J = 6.4$ Hz), 2.02 (3H, s), 2.65 (1H, app. sextet, $J = 6.6$ Hz), 4.04-4.09 (4H, m), 5.25-5.31 (1H, m), 5.56-5.62 (1H, m)

^{13}C NMR (100 MHz, CDCl_3): δ 18.1, 20.8, 41.0, 64.3, 127.0, 129.0, 170.9

MS HRMS m/z calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 223.0946, found 223.0940



(2S)-2-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)pent-3-en-1-yl acetate (2.76)

Dihydropyran (138 μL , 1.52 mmole) was added to a mixture of acetate **2.41** (200 mg, 1.26 mmole) and amberlyst-15 (10 mg) in CH_2Cl_2 (5 mL). The mixture was stirred for 2 hours and filtered. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica eluting with 0-5% EtOAc/Hexane to give acetate **2.76** as colorless oil (290 mg, 1.2 mmole, 95%).

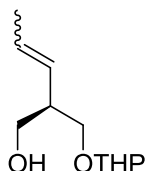
Major isomer:

IR v/cm^{-1} 2941, 1741

^1H NMR (400 MHz, CDCl_3) δ 1.65-1.68 (6H, m), 1.67 (3H, d, $J = 6.4$ Hz), 2.06 (3H, s), 2.63 (1H, app. sextet, $J = 6.9$ Hz), 3.33-3.40 (1H, m), 3.47-3.52 (1H, m), 3.70-3.73 (2H, m), 4.10-4.15 (2H, m), 4.50-4.58 (1H, m), 5.30-5.38 (1H, m), 5.50-5.60 (1H, m)

^{13}C NMR, 100 MHz (CDCl_3) δ 18.4, 19.2, 41.9, 61.8, 65.1, 67.6, 67.9, 98.6, 98.9, 128.0, 128.4, 171.1

MS GCMS m/z $[\text{THP}]^+$ 85 ; HRMS m/z calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 265.1416, found 265.1410



(2R)-2-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)pent-3-en-1-ol (2.77)

LiOH.H₂O (300 mg, 7.1 mmole) was added to a solution of acetate **2.76** (1.15 g, 4.76 mmole) in a mixture of THF (3.2 mL), MeOH (360 μ L) and water (1.28 mL). The mixture was stirred overnight. The reaction mixture was extracted twice with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated to give alcohol **2.77** as a colorless oil (704 mg, 3.5 mmole, 74%).

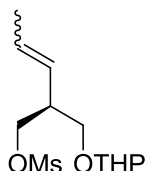
Major isomer:

IR ν/cm^{-1} 2941, 3416

¹H NMR (400 MHz, CDCl₃) δ 1.65-1.68 (6H, m), 1.67 (3H, d, $J = 6.4$ Hz), 2.06 (3H, s), 2.63 (1H, app. sextet, $J = 6.9$ Hz), 3.36-4.53 (6H, m), 4.53-4.54 (1H, m), 5.24-5.32 (1H, m), 5.50-5.61 (1H, m)

¹³C NMR (100 MHz, CDCl₃) δ 18.4, 19.2, 41.9, 61.8, 65.1, 67.6, 67.9, 98.6, 98.9, 128.0, 128.4, 171.1

MS GCMS m/z [THP]⁺ 85; HRMS m/z calcd. for C₁₁H₂₀O₃Na [M+Na]⁺ 223.1310, found 223.1306



(2S)-2-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)pent-3-en-1-yl methanesulfonate
(2.43)

Methanesulfonyl chloride (175 μ L, 2.3 mmole) was added dropwise to a solution of alcohol **2.76** (300 mg, 1.5 mmole) in CH_2Cl_2 (10 mL) cooled in an ice bath. Et_3N (420 μ L, 3.0 mmole) was added dropwise to the mixture. The mixture was stirred for 2 hours then warmed to room temperature. Saturated aqueous ammonium chloride solution was added and the mixture was extracted twice with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , concentrated and purified by flash chromatography on silica eluting with 10-15% EtOAc/Hexane to give sulfonate **2.43** as colorless oil (384g, 1.25 mmole, 83%).

Major isomer:

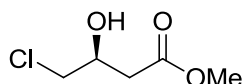
IR ν/cm^{-1} 2941, 1175

^1H NMR (400MHz, CDCl_3): δ 1.50-1.69 (9H, m), 2.96-3.00 (1H, m), 3.99 (3H, s), 3.45-3.48 (1H, m), 3.63-3.80 (1H, m), 4.17-4.29 (2H, m), 4.51-4.54 (1H, m), 5.30-5.35 (1H, m), 5.60-5.65 (1H, m)

^{13}C NMR (100MHz, CDCl_3): 18.0, 18.1, 19.3, 19.4, 25.3, 30.4, 37.0, 42.1, 42.2, 44.3, 62.0, 62.2, .667, 67.0, 70.1, 70.3, 98.7, 99.3, 125.9, 126.4, 129.1, 129.2

MS GCMS m/z [THP] $^+$ 85 ; HRMS m/z calcd. for $\text{C}_{12}\text{H}_{23}\text{O}_5\text{S}$ [M+H] $^+$ 279.1266, found 279.1275

Experimental for Chapter 3



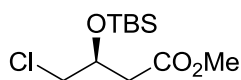
(S)-Methyl 4-chloro-3-hydroxybutanoate (3.32)

Co₂(CO)₈ (1.69 g, 4.94 mmole) was added to a flask which was then saturated with CO gas (balloon). Methanol (50 mL) was added to the mixture and it was stirred for 2 minutes. (*S*)-Epichlorohydrin (3.91 mL, 49.7 mmole) was added and the mixture was stirred for 24 hours. The mixture was diluted with Et₂O, filtered through a pad of silica and concentrated. The residue product was purified *via* flash chromatography eluting with 0-15% ethyl acetate/ hexane to give alcohol **3.32** as a colorless oil (4.49 g, 29.5 mmole, 59%).

¹H NMR (400 MHz, CDCl₃) δ 2.62-2.65 (2H, m), 3.60-3.65 (2H, m), 4.71 (3H, s), 4.24-4.27 (1H, m)

¹³C NMR (100 MHz, CDCl₃) δ 38.2, 48.1, 52.0, 67.9 172.1

Data agrees to those of the literature.⁹³



(S)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-4-chlorobutanoate (3.33)

2,6-Lutidine (5.62 mL, 52.4 mmole) and TBSOTf (6.62 mL, 28.8 mmole) were added sequentially to a solution of alcohol ester **3.32** (4g, 26.2 mmole) in CH₂Cl₂ (26 mL) at 0 °C. The mixture was stirred for one hour then warmed to room temperature. The

mixture was washed with 2N aq. HCl and saturated aqueous NaHCO₃ solution. The organic layers was dried over MgSO₄ then concentrated. The protected ester was purified by flash chromatography on silica gel eluting with 5% ethyl acetate/ hexane to give protected ester **3.33** as a pale yellow oil (5.52 g, 23.3 mmole, 89%).

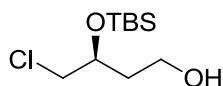
IR (KBr), ν/cm^{-1} 2929, 2360, 1741

¹H NMR (100 MHz, CDCl₃) δ 0.06 (3H, s), 0.11 (3H, s), 0.87 (9H, s), 2.51 (1H, dd, $J = 7.3, 15.2$ Hz), 2.70 (1H, dd, $J = 4.8, 15.2$ Hz), 3.50-3.55 (2H, m), 3.68 (3H, s), 4.27-4.33 (1H, m)

¹³C NMR (100 MHz, CDCl₃) δ 17.9, 25.6, 40.2, 48.0, 51.7, 69.5, 171.4

MS HRMS m/z calcd. for C₁₁H₂₄O₃³⁵ClSi [M+H]⁺ 267.1183, found 267.1186

$[\alpha]_{\text{D}}^{22}$ -66.5 (c 0.188, CHCl₃)



(S)-3-((tert-Butyldimethylsilyl)oxy)-4-chlorobutan-1-ol (3.34)

DIBAL (65.8 mL, 65.8 mmole, 1M in cyclohexanes) was added dropwise to a solution of ester **3.33** (9.04 g, 33.8 mmole) in CH₂Cl₂ (90 mL) at 0 °C. The mixture was stirred for an hour at 0 °C. Then the mixture was warmed to room temperature. Water was added until a jelly like mixture was formed. Solid Na₂SO₄ was added until the mixture could be stirred easily. The mixture was filtered and concentrated to give alcohol **3.34** as a colorless oil (5.08 g, 24.3 mmole, 72%).

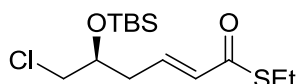
IR (KBr) ν/cm^{-1} 3439, 2929

^1H NMR (100 MHz, CDCl_3) δ 0.01 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.76-1.99 (2H, m), 3.48-3.50 (2H, m), 3.75-3.80 (2H, m), 4.06-4.09 (1H, m)

^{13}C NMR (100 MHz, CDCl_3) δ -4.9, -4.5, -2.97, 18.0, 25.7, 36.5, 47.9, 59.3, 70.9

MS HRMS m/z calcd. for $\text{C}_{10}\text{H}_{24}\text{O}_2^{35}\text{ClSi}$ $[\text{M}+\text{H}]^+$ 271.0955, found 271.0950

$[\alpha]_D^{21}$ -22.0 (c 0.118, CHCl_3)



(*S,E*)-*S*-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-6-chlorohex-2-enethioate (3.35)

DMSO (2.36 mL, 33.3 mmole) was added dropwise to a solution of oxalyl chloride (2.00 mL, 16.7 mmole) in CH_2Cl_2 (7 mL) at -78°C and the mixture was stirred for 5 minutes. Alcohol **3.34** (3.16 g, 13.2 mmole) in CH_2Cl_2 (5 mL) was added *via* cannula and the mixture was stirred for 10 minutes. Triethylamine (7.38 mL, 53.0 mmole) was added slowly and the mixture was stirred 15 minutes, then warmed to room temperature. Water was added and the mixture was extracted twice with CH_2Cl_2 , dried over MgSO_4 and concentrated to give aldehyde as a yellow oil, which was used in the next step directly.

The aldehyde was dissolved in CH_2Cl_2 (7 mL) and the thioylid $\text{Ph}_3\text{PCHCOSEt}$ **3.51**¹¹⁰ (5.95 g, 16.6 mmole) was added. The mixture was stirred overnight then pre-absorbed on silica and purified by flash chromatography on silica eluting with 5-10% ethyl acetate/ hexane to give thioester **3.35** as a yellow liquid (3.22 g, 9.12 mmole, 69%).

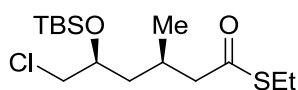
IR (KBr) ν/cm^{-1} 2929, 1670

^1H NMR (100 MHz, CDCl_3) δ 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.28 (2H, t, $J = 7.4$ Hz), 2.40-2.54 (2H, m), 2.94 (2H, q, $J = 7.4$ Hz), 3.38-3.45 (2H, m), 3.94-3.97 (1H, m), 6.17 (1H, d, $J = 15.6$ Hz), 6.85 (1H, dt, $J = 7.8, 15.3$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ -4.7, -4.6, 14.7, 18.0, 23.1, 25.7, 37.6, 47.7, 71.3, 131.5, 139.9, 189.8

MS GCMS m/z for $[\text{CH}_2=\text{C}(\text{SEt})]^+$ 115, $[\text{C}_4\text{H}_9\text{OTBS}]^+$ 193; HRMS m/z calcd. for $\text{C}_{14}\text{H}_{28}\text{O}_2^{35}\text{ClSi}$ $[\text{M}+\text{H}]^+$ 323.1268, found 323.1271

$[\alpha]_{\text{D}}^{22}$ -7.5 (c 0.21, CHCl_3)



(3R,5S)-S-Ethyl 5-((tert-butyldimethylsilyl)oxy)-6-chloro-3-methylhexanethioate
(3.36)

CuI (35 mg, mmole) and R-Tol-BINAP (173 g, 0.25mmole) were dissolved in CH_2Cl_2 (74 mL). The mixture was stirred for 2 hr. Freshly distilled MTBE (74 mL) was added to the mixture and it was cooled at -78 °C. MeMgBr (12.2 mL, 36.6 mmole, 3M in diethyl ether) was added slowly and the mixture was stirred for 5 minutes. Thioester **3.35** (3.2 g, 9.07 mmole) in MTBE (74 mL) was added slowly *via* cannula to the mixture and it was stirred overnight at -78 °C. Methanol (5 mL) and saturated aqueous NH_4Cl (5 mL) were added to the mixture which was then warmed to room temperature. The mixture was extracted twice with Et_2O . The combined organic layers were dried over MgSO_4 then concentrated and purified by flash chromatography on silica gel eluting with 2-5% ethyl acetate/ hexane to give thioester **3.36** as a colorless oil (2.9 g, 7.86 mmole, 87%).

Major diastereomer:

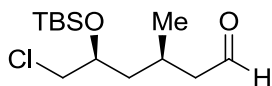
IR (KBr) ν/cm^{-1} 2957, 1687

^1H NMR (400 MHz, CDCl_3) δ 0.09 (6H, s), 0.89 (9H, s), 0.97 (3H, d, $J = 6.7$ Hz), 1.23 (2H, t, $J = 7.4$ Hz), 1.43-1.47 (1H, m), 1.57-1.64 (1H, m), 2.11-2.16 (1H, m), 2.33 (1H, dd, $J = 8.6, 14.6$ Hz), 2.59 (1H, dd, $J = 5.2, 14.6$ Hz), 2.86 (1H, q, $J = 7.4$ Hz), 3.42 (1H, dd, $J = 0.9, 5.4$ Hz), 3.85-3.88 (1H, m),

^{13}C NMR (100 MHz, CDCl_3) δ -4.6, -4.4, 14.8, 20.4, 23.3, 25.8, 27.4, 42.1, 48.7, 50.8, 70.6, 198.6

MS GCMS m/z for $[\text{M}-\text{SEt}]^+$ 277; HRMS m/z calcd. for $\text{C}_{15}\text{H}_{31}\text{O}_2^{35}\text{ClSiNa}[\text{M}+\text{Na}]^+$ 361.1400, found 361.1396

$[\alpha]_{\text{D}}^{22}$ -7.5 (c 0.21, CHCl_3)

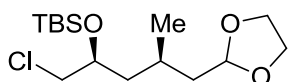


(3R,5S)-5-((*tert*-Butyldimethylsilyl)oxy)-6-chloro-3-methylhexanal (3.37)

DIBAL-H (8.35 mL, 8.35 mmole, 1M in cyclohexane) was added dropwise to a solution of thioester **3.36** (2.8 g, 7.59 mmole) in CH_2Cl_2 (15 mL) at -78°C . The mixture was stirred for 1 hr at -78°C . Water was added slowly to the mixture and it was warmed to room temperature. The mixture was stirred until a jelly-like mixture formed. Na_2SO_4 was added until all the jelly-like substance converted to crystals. The mixture was filtered and concentrated to give aldehyde **3.37** as a colorless oil which was used directly in the next step.

^1H NMR (100 MHz, CDCl_3) δ 0.08 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.01 (3H, d, $J = 6.5$ Hz), 1.53-1.61 (2H, m), 2.20-2.27 (2H, m), 2.48-2.51 (1H, m), 3.45 (1H, d, $J = 5.4$ Hz), 3.91 (1H, tt, $J = 5.3, 7.0$ Hz), 9.75 (1H, s)

^{13}C NMR (100 MHz, CDCl_3) δ -4.6, -4.3, 18.0, 20.9, 24.4, 25.8, 42.1, 48.5, 50.6, 70.5, 202.2



***tert*-Butyl(((2*S*,4*R*)-1-chloro-5-(1,3-dioxolan-2-yl)-4-methylpentan-2-yl)oxy)dimethylsilane (3.38)**

A mixture of aldehyde **3.37** (2.11 g, 7.57 mmole), ethylene glycol (2.08 mL, 37.8 mmole) and Amberlyst-15 (53 mg) in toluene (25 mL) was heated at reflux overnight. The reaction mixture was cooled, concentrated and purified by flash column chromatography on silica gel eluting with 20% ethyl acetate hexane to give dioxolane **3.38** as a colorless oil (1.635 g, 5.07 mmole, 67 %).

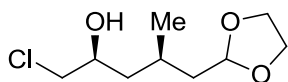
IR (KBr) ν/cm^{-1} 2951

^1H NMR (100 MHz, CDCl_3) δ 0.09 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 0.99 (3H, d, $J = 6.6$ Hz), 1.38-1.82 (5H, m), 3.43-3.46 (2H, m), 3.80-3.97 (4H, m), 4.90 (1H, t, $J = 5.2$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ -4.4, 18.6, 20.8, 25.8, 40.7, 43.1, 49.1, 64.6, 64.8, 70.7, 103.4

MS GCMS m/z for [$\text{C}_5\text{H}_9\text{O}_2$] $^+$ 73; HRMS m/z calcd. for $\text{C}_{15}\text{H}_{31}\text{O}_3^{35}\text{ClSiNa}$ $[\text{M}+\text{Na}]^+$ 345.1629, found 361.1620

$[\alpha]_D^{22} -7.0$ (c 0.53, CHCl_3)



(2*S*,4*R*)-1-Chloro-5-(1,3-dioxolan-2-yl)-4-methylpentan-2-ol (3.39)

A solution of silyl ether **3.38** (2.09 g, 6.47 mmole) and ammonium fluoride (3.50 g, 94.5 mmole) in MeOH (50 mL) was heated at reflux overnight. The reaction mixture was cooled, pre-absorbed on silica then purified by flash column chromatography on silica eluting with 20% ethyl acetate/ hexane to give alcohol **3.39** as a colorless oil (1.09 g, 5.2 mmole, 81%).

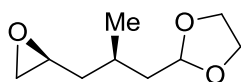
IR (KBr) ν/cm^{-1} 2955, 3441

^1H NMR (400 MHz, CDCl_3) δ 1.01 (3H, d, $J = 6.9$ Hz), 1.48-1.59 (3H, m), 1.71-1.75 (1H, m), 1.85-1.95 (1H, m), 2.63 (1H, d, $J = 5.0$ Hz), 3.46 (1H, dd, $J = 6.9, 11.0$ Hz), 3.58 (1H, dd, $J = 3.7, 11.0$ Hz), 3.81-3.98 (4H, m), 4.90 (1H, t, $J = 5.5$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ 21.1, 25.9, 39.8, 41.4, 50.5, 64.7, 64.8, 103.5

MS HRMS m/z calcd. for $\text{C}_{10}\text{H}_{18}\text{O}_3^{35}\text{Cl}[\text{M}+\text{H}]^+$ 221.0944, found 221.0947

$[\alpha]_D^{22} -8.0$ (c 0.46, CHCl_3)



2-((*R*)-2-Methyl-3-((*S*)-oxiran-2-yl)propyl)-1,3-dioxolane (3.27)

Solid sodium hydroxide (767 mg, 19.2 mmole) was added to a solution of chlorohydrin **3.39** (800 mg, 3.83 mmole) in Et_2O (38 mL). The mixture was stirred overnight at room temperature. Water was added to the reaction mixture and it was

extracted twice with Et₂O. The combined organic layers was dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica eluting with 10-20% ethyl acetate/hexane to give epoxide **3.39** as colorless oil (640 mg, 3.7 mmole, 97%).

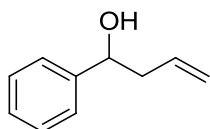
IR (KBr) ν/cm^{-1} 2955

¹H NMR (400 MHz, CDCl₃) δ 1.06 (3H, d, $J = 6.7$ Hz), 1.42-1.78 (4H, m), 1.91-1.98 (1H, m), 2.42-2.45 (1H, m), 2.74 (1H, t, $J = 6.2$ Hz), 2.92-2.95 (1H, m), 3.81-3.96 (4H, m), 4.91 (1H, t, $J = 6.8$ Hz)

¹³C NMR (100 MHz, CDCl₃) δ 20.4, 28.1, 40.0, 40.7, 46.8, 51.0, 64.6, 64.7, 103.4

MS HRMS m/z calcd. for C₉H₁₆O₃Na [M+Na]⁺ 195.0997, found 195.0995

$[\alpha]_{\text{D}}^{22} +5.0$ (c 0.22, CHCl₃)



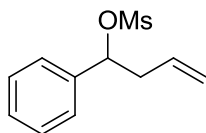
1-Phenylbut-3-en-1-ol (3.41)

Allyl bromide (5.1 mL, 58.9 mmole) was added to a mixture of benzaldehyde (5 g, 47.1 mmole), THF (10 mL) and sat. aq. ammonium chloride (50 mL). The mixture was cooled in an ice bath. Zinc dust (3.85 g, 58.9 mmole) was added portion wise to the mixture and it was stirred overnight. The mixture was extracted twice with ethyl acetate and washed with brine. The organic layers was dried over MgSO₄, filtered and concentrated to give allene alcohol **3.41** as a yellow oil (6.82, 46 mmole, 98%). The alcohol was used directly in the next step.

^1H NMR (400 MHz, CDCl_3) δ 2.02 (1H, br-s), 2.48-2.55 (2H, m), 4.73-4.76 (1H, dd, J = 5.4, 7.6 Hz, CH), 5.13-5.20 (2H, m), 5.76-5.87 (1H, m), 7.27-7.30 (5H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 43.6, 73.2, 118.1, 125.8, 127.4, 128.3, 134.4, 143.8

Data agrees with those of the literature.¹¹¹

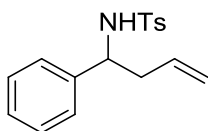


1-Phenylbut-3-en-1-yl methanesulfonate (3.48)¹¹²

Methanesulfonyl chloride (3.10 mL, 40.2 mmole) was added dropwise to the mixture of alcohol **3.41** (5.0 g, 33.5 mmole) and triethylamine (7 mL, 50.3 mmole) in dichloromethane (70 mL) at 0 °C. The mixture was stirred for 1 hr, warmed to room temperature and washed with ammonium chloride. The combined organic layers was dried over MgSO_4 and concentrated to give crude mesylate **3.48** as a yellow oil (6.84 g, 30.2 mmole, 90%), which was used directly in the next step.

^1H NMR (400 MHz, CDCl_3) δ 2.62-2.68 (1H, m, CH), 2.69 (3H, s, CH_3), 2.79-2.91 (1H, m, CH) 5.11-5.17 (2H, m), 5.52-5.56 (1H, dd, J = 6.0, 7.8 Hz), 5.71 (1H, ddt, J = 6.9, 10.2, 17.1 Hz), 7.27-7.41 (5H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 38.8, 41.0, 83.8, 118.9, 126.5, 128.6, 128.9, 131.9, 137.6



4-Methyl-N-(1-phenylbut-3-en-1-yl)benzenesulfonamide (3.42)

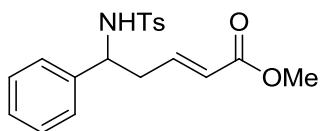
Sodium azide (1.5 g, mmole) was added to a solution of mesylate (6.8 g, 30 mmole) in DMF (70 mL). The mixture was stirred overnight at 60 °C. Water was added to the mixture and it was extracted twice with diethyl ether. The combined organic layers was dried over MgSO₄ and concentrated to give the crude azide as yellow liquid.

Acetic acid was added to a solution of azide in THF (60 mL). Zinc dust was added to the reaction mixture and it was sonicated for 5-8 hrs. The reaction mixture was filtered through celite and water was added. The mixture diluted with dichloromethane and washed with sat. aq. Sodium bicarbonate. The organic layer was dried over MgSO₄ then concentrated. *p*-Toluene sulfonyl chloride (4.62 g, 24.2 mmole) was added to a mixture of the crude amine and sodium carbonate (17.1g, 162 mmole) in dichloromethane (60 mL) and water (60 mL). The reaction mixture was stirred overnight and it was extracted twice with dichloromethane. The combined organic layer was dried over MgSO₄, concentrated and purified by flash chromatography eluting 10-25% ethylacetate/ hexane to give the sulphonamide **3.42** as a colorless solid (5.0 g, 16.6 mmole, 55%).

¹H NMR (400 MHz, CDCl₃) δ 2.37 (3H, s), 2.43-2.45 (2H, m), 4.37 (1H, t, *J* = 6.4 Hz), 5.03-5.08 (2H, m), 5.54-5.57 (1H, m), 7.05-7.19 (7H, m), 7.53-7.56 (1H, d, *J* = 8.3 Hz)

¹³C NMR (100 MHz, CDCl₃) δ 21.4, 41.8, 50.1, 119.3, 126.5, 127.1, 127.3, 128.3, 129.3, 133.0, 137.4, 140.3, 143.1

Data agrees with those of the literature.¹¹³



(E)-Methyl 5-(4-methylphenylsulfonamido)-5-phenylpent-2-enoate (3.43)

Sulfonamide **3.42** (947 mg, 1.66 mmole) and methyl acrylate were dissolved in toluene (17 mL). Grubbs-II catalyst (27 mg, 0.32 mmole) was dissolved in toluene (1 mL) and added to the mixture which was heated at 70 °C for overnight while nitrogen was bubbled through the reaction. The mixture was purified by flash column chromatography on silica eluting with 10-25% ethylacetate/ hexane to give alkene **3.43** as a colorless solid (420 mg, 1.17 mmole, 70%).

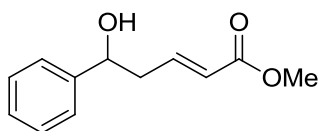
m.p. 93-98 °C

IR ν/cm^{-1} 3263, 2949, 1714, 1598, 1444

^1H NMR (400 MHz, CDCl_3) δ 2.38 (3H, s), 2.60-2.71 (2H, m), 3.69 (3H, s), 5.01 (1H, br), 5.77 (1H, d, $J = 16.0$ Hz), 6.64 (1H, dt, $J = 7.3, 15.6$ Hz), 7.01-7.05 (2H, m), 7.14-7.19 (5H, m), 7.55 (1H, d, $J = 8.3$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ 21.4, 39.8, 51.4, 56.9, 124.1, 126.3, 126.9, 127.1, 127.6, 128.2, 128.5, 129.2, 129.3, 139.5, 143.1, 143.3, 166.2

MS HRMS m/z calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_4\text{S}$ 382.1089, found 382.1083

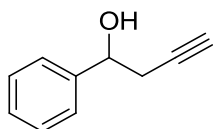


(E)-Methyl 5-hydroxy-5-phenylpent-2-enoate (3.40)

Alkene alcohol **3.41** (250 mg, 1.69 mmole) and methyl acrylate was dissolved in dichloromethane (4 mL). Grubbs-II catalyst (72 mg, 0.09 mmole) was dissolved in dichloromethane (2 mL) and added in 3 portions over 1.5 hrs to the mixture which was heated at reflux for 6 hrs. The reaction mixture was purified by flash chromatography on silica eluting with 10-25% ethyl acetate/ hexane to give alkene **3.40** as a brown oil (260 mg, 1.26 mmole, 75%).

^1H NMR (400 MHz, CDCl_3) δ 2.64 (2H, m), 3.71 (3H, s), 4.81 (1H, t, $J=5.1$ Hz, CH), 5.90 (1H, d, $J=15.7$ Hz), 6.96 (1H, dt, $J=7.3, 15.7$ Hz) 7.29-7.36 (5H, m)

Data agrees with those of the literature.¹¹⁴



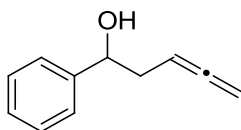
1-Phenylbut-3-yn-1-ol (3.49)

Styrene oxide (13.5 mL, 126 mmole) in DMSO (15 mL) was added dropwise to lithium acetylide (15.3 g, 166 mmole) in DMSO (105 mL) and the mixture was stirred overnight. The reaction mixture was poured into ice water and extracted twice with diethyl ether. The combined organic layers were dried over MgSO_4 and concentrated. The residue was purified by distillation (cold finger, 5 mmHg, 150 °C) to give alcohol **3.49** as a colorless oil (14.7 g, 100 mmole, 79%).

^1H NMR 400 MHz (CDCl_3) δ 2.09 (1H, t, $J = 2.8$ Hz), 2.36 (1H, br), 2.65 (2H, dd, $J = 2.3, 5.9$ Hz), 4.89 (1H, t, $J = 6.3$ Hz), 7.35 (5H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 28.1, 70.7, 71.9, 80.7, 125.6, 127.5, 128.1, 142.3

Data agrees with those of the literature.⁹⁹



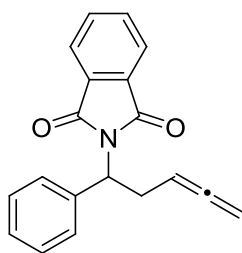
1-Phenylpenta-3,4-dien-1-ol (3.44)

Diisopropylamine (13.4 mL, 95.8 mmole) was added to a mixture of alkyne **3.49** (7.0 g, 48 mmole), paraformaldehyde (2.87 g, 95.8 mmole) and CuBr (2.06 g, 14.4 mmole) in 1,4-dioxane (140 mL). The mixture was heated at reflux under nitrogen overnight. The reaction mixture was cooled to room temperature and air was bubbled through for 30 minutes. The mixture was filtered through celite. Water was added to the filtrate and it was extracted twice with Et_2O . The organic layer was dried over MgSO_4 then concentrated. The residue was purified by distillation (cold finger, 5 mmHg, 150 °C) to give alcohol **3.49** as yellow oil (4.74 g, 29.6 mmole, 62%).

^1H NMR (400 MHz, CDCl_3) δ 2.11 (1H, m), 2.46 (2H, m), 4.72 (2H, dd, $J = 2.8, 6.9$ Hz), 4.80-4.82 (1H, m) 5.82 (1H, app. quintet, $J = 7.0$ Hz), 7.28-7.42 (5H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 38.1, 73.4, 74.6, 86.0, 125.7, 127.3, 128.1, 143.5, 209.2

Data agrees with those of the literature.¹¹⁵



2-(1-Phenylpenta-3,4-dien-1-yl)isoindoline-1,3-dione (**3.50**)

DIAD (295 μ L, 3.03 mmole) was added to a solution of triphenylphosphine (3.93 g, 1.5 mmole), *N*-Phthalimide (220 mg, 1.5 mmole) and alcohol **3.50** (200 mg, 1.25 mmole) in THF (5 mL) at 0 °C. The reaction mixture was stirred overnight, pre-adsorbed on silica and purified by flash column chromatography eluting with 10-20% ethylacetate/ hexane to give phthalimide **3.50** as a colorless solid (217 mg, 0.75 mmole, 60%)

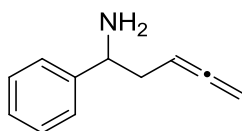
m.p. 86-91 °C

IR ν/cm^{-1} 1954, 1769, 1714

^1H NMR (400 MHz, CDCl_3) δ 2.87-2.94 (1H, m), 3.35-3.43 (1H, m), 4.49-4.60 (1H, m), 5.10 (1H, app. quintet, $J = 6.6$ Hz), 5.42 (1H, dd, $J = 6.0, 10.5$ Hz), 7.25-7.35 (3H, m), 7.53-7.56 (2H, m), 7.67-7.70 (2H, m), 7.79-7.82 (2H, m)

^{13}C NMR (100 MHz, CDCl_3) δ 30.1, 54.6, 75.4, 86.4, 123.2, 127.9, 128.0, 128.5, 131.8, 133.9, 139.2, 168.3, 209.2

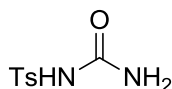
MS HRMS m/z calcd. for $\text{C}_{19}\text{H}_{16}\text{NO}_4$ 290.1181, found 290.1181



1-Phenylpenta-3,4-dien-1-amine (3.45)¹¹⁶

Hydrazine monohydrate (1 mL, 20.7 mmole) was added to a solution of phthalimide **3.50** (1.0 g, 3.5 mmole) in EtOH (7 mL). The mixture was heated at reflux for 30 minutes then cooled to room temperature. Diethyl ether was added to the reaction mixture which was filtered and concentrated to give the crude amine **3.45** as a colorless oil (240 mg, 1.5 mmole, 43%).

¹H NMR (400 MHz, CDCl₃) δ 2.27-2.44 (2H, m), 4.02 (1H, dd, *J* = 7.2, 10.6 Hz), 4.66-4.69 (1H, m), 5.08 (1H, app. quintet, *J* = 6.8 Hz), 7.23-7.35 (5H, m)



N-Carbamoyl-4-methylbenzenesulfonamide⁹⁸

Tosyl isocyanate (146 μL, 1.09 mmole) was added to a bold solution of ammonia in dioxane (2.62 mL, 1.31 mmole, 0.5M in dioxane) in THF (1 mL). The reaction mixture was then concentrated under reduced pressure to give tosyl urea as colorless solid (205 mg, 0.96 mmole, 88%).

IR ν/cm^{-1} 3460, 1748

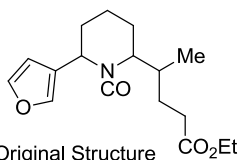
¹H NMR (400 MHz, CDCl₃) δ 2,43 (3H, s), 7.31 (2H, d, *J* = 8.3 Hz), 7.83 (2H, d, *J* = 8.3 Hz)

¹³C NMR (100 MHz, CDCl₃) δ 21.7, 126.4, 127.9, 129.7, 135.2, 145.7

MS HRMS *m/z* calcd. for C₈H₁₁N₂O₃S [M+H]⁺ 215.0490, found 215.0494

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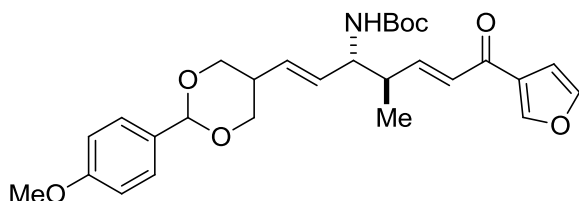


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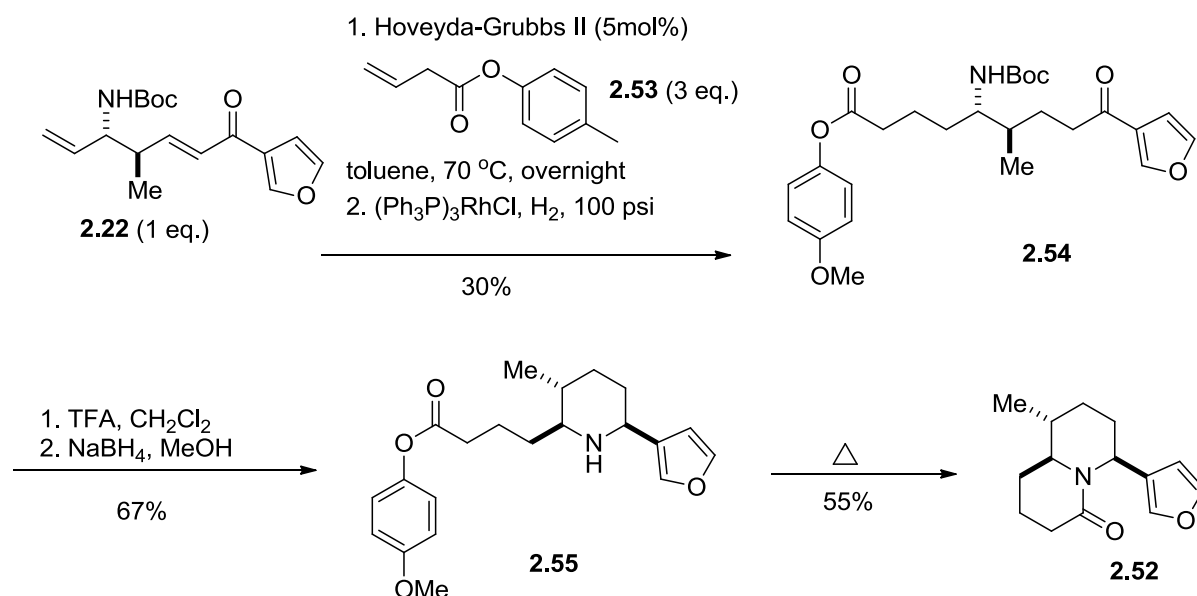
70



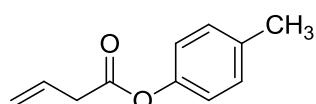
tert-Butyl ((1E,3S,4R,5E)-7-(furan-3-yl)-1-(2-(4-methoxyphenyl)-1,3-dioxan-5-yl)-4-methyl-7-oxohepta-1,5-dien-3-yl)carbamate (2.37)

¹H NMR (400MHz, CDCl₃) δ 1.12 (3H, d, *J* = 6.8 Hz), 1.42 (9H, s), 2.60-2.65 (1H, m), 3.79 (3H, s), 4.05-4.25 (5H, m), 4.53-4.62 (1H, m), 5.68 (1H, dd, *J* = 6.1, 15.6 Hz), 6.16 (1H, dd, *J* = 7.8, 15.7 Hz), 6.53 (1H, m), 6.80-6.98 (5H, m), 7.37-7.45 (3H, m), 8.00 (1H, br-s)

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At the same time, *p*-cresol butenoate ester **2.53**, which was formed from the coupling of butenoic acid and *p*-cresol, underwent cross-metathesis with diene **2.22**. This method was employed as *p*-cresol is a better leaving group than methoxy group which could be useful for lactamization at the later stage. Then the diene was then reduced to ester **2.54**. Unfortunately, the reductive amination step could not be up-scaled, *p*-methylphenoxide group was removed and reduced to alcohol during the reduction as *p*-methylphenoxide group is a much better leaving group than methoxy group. Amine **2.55** could be cyclised under thermolysis to give lactam **2.52**. But due to the poor yield during reductive amination, this route was not carried out further.

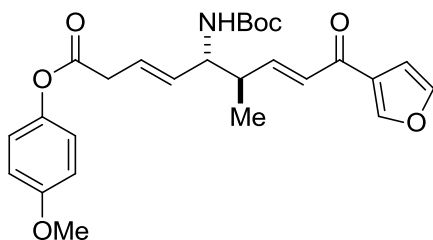


p-Tolyl but-3-enoate (**2.53**)

DCC (2.25 g, 13.9 mmole) was added to a mixture of 3-butenoic acid (990 μL , 11.6 mmole), *p*-cresol (1.46 mL, 13.9 mmole) and DMAP (142 mg, 0.58 mmole) in dichloromethane (12 mL). The reaction mixture was stirred overnight and filtered through celite. The celite cake was washed twice with dichloromethane. The filtrate was washed with 2N aqueous HCl and then saturated aqueous sodium bicarbonate. The organic layers was dried over MgSO_4 and concentrated the purified *via* flash column chromatography on silica eluting with 10% ethylacetate/ hexane to give ester as a colorless oil (2.17g, 12 mmole, 86%).

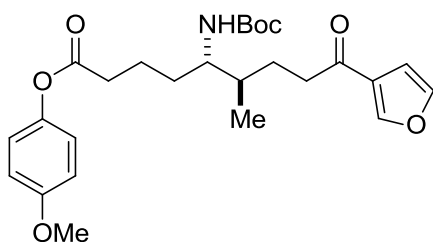
^1H NMR (400 MHz, CDCl_3) δ 2.34 (3H, s), 3.33 (2H, dt, $J = 1.4, 6.9$ Hz), 5.4 (1H, app. dq, $J = 1.3, 6.6$ Hz), 5.28 (1H, app. dq, $J = 1.4, 14.2$ Hz), 6.03 (1H, ddt, $J = 6.9, 10.1, 17.1$ Hz), 6.96 (2H, dd, $J = 2.0, 6.6$ Hz), 7.16 (2H, d, $J = 8.2$ Hz)

^{13}C NMR (100 MHz, CDCl_3) δ 20.8, 39.1, 119.1, 121.2, 129.6, 135.5, 146.7, 148.4, 170.2



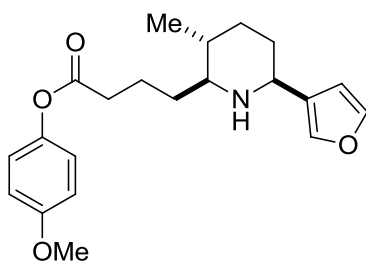
(3E,5S,6R,7E)-4-Methoxyphenyl 5-((tert-butoxycarbonyl)amino)-9-(furan-3-yl)-6-methyl-9-oxonona-3,7-dienoate (2.78)

^1H NMR (300 MHz, CDCl_3) δ 1.13 (3H, *d*, $J = 6.8$ Hz), 1.42 (9H, *s*), 2.32 (3H, *s*), 2.60-2.64 (1H, *m*), 3.32 (2H, *d*, $J = 6.8$ Hz), 4.25 (1H, *br*), 4.59 (1H, *br*), 5.62 (1H, *dd*, $J = 6.0, 15.2$ Hz), 5.80-5.85 (1H, *m*), 6.53 (1H, *d*, $J = 15.6$ Hz), 6.80-6.85 (1H, *m*), 6.90-6.95 (3H, *m*), 7.14 (2H, *d*, $J = 8.3$ Hz), 7.44 (1H, *br-s*), 8.06 (1H, *br-s*)



(5S,6R)-4-Methoxyphenyl 5-((tert-butoxycarbonyl)amino)-9-(furan-3-yl)-6-methyl-9-Oxononanoate (2.54)

^1H NMR (400 MHz, CDCl_3) δ 0.92 (3H, *d*, $J = 6.7$ Hz), 1.43 (9H, *s*), 1.15-1.86 (7H), 2.33 (3H, *s*), 2.50-3.00 (4H, *m*), 3.56-3.59 (1H, *m*), 4.42 (1H, *br d*, $J = 8.9$ Hz), 6.75 (1H, *d*, $J = 1.2$ Hz), 6.94 (2H, *d*, $J = 8.5$ Hz), 7.15 (2H, *d*, $J = 8.1$ Hz), 7.43 (1H, *br-s*), 8.05 (1H, *br-s*)



4-Methoxyphenyl 4-((2S,3R,6S)-6-(furan-3-yl)-3-methylpiperidin-2-yl)butanoate (2.55)

^1H NMR (400 MHz, CDCl_3) δ 0.90 (3H, *d*, $J = 6.4$ Hz), 1.00-2.00 (12H, *m*), 2.22-2.32 (1H, *m*), 2.34 (3H, *s*), 2.54-2.58 (1H, *m*), 3.60 (1H, *dd*, $J = 2.2$ Hz), 6.40 (1H, *br-s*), 6.94 (2H, *dd*, $J = 2.0, 6.8$ Hz), 7.16 (2H, *d*, $J = 8.3$ Hz), 7.35 (2H, *br-s*)

⁸⁰ All the other cross metathesis reactions that did not have the procedures at the experimental section follow the protocol of cross metathesis for the formation of alkene ester **2.31**.

⁸¹ Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056.

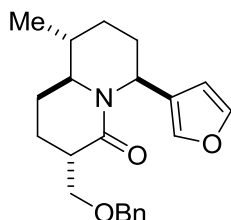
⁸² "Stereolectronic effects in Organic Chemistry" Delongchamps, P. *Pergamon, Oxford*, **1983**, page 274.

⁸³ Several signals were not shown in the ^{13}C NMR spectrum due to the low amount of sample submitted for the ^{13}C NMR experiment.

⁸⁴ The specific optical rotation was not measured as the lactam **2.57** from the

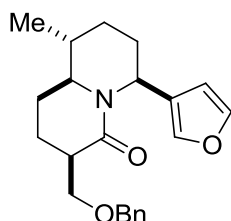
asymmetric synthesis was too little to carry out the decarbonylation as lactam **2.57** is a minor product of the methylation.

85



(3S,6S,9R,9aS)-3-((benzyloxy)methyl)-6-(furan-3-yl)-9-methylhexahydro-1H-quinolizin-4(6H)-one

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.86 (3H, d, $J = 6.4$ Hz), 1.10-1.40 (2H, m), 1.50-1.70 (2H, m), 2.61-2.63 (1H, m), 3.25 (dt, $J = 2.8, 10.9$ Hz), 3.82 (2H, m), 4.52 (1H, d, $J = 11.9$ Hz), 4.56 (1H, d, $J = 12.4$ Hz), 5.36 (1H, br-s), 6.27 (1H, br-s), 7.10-7.40 (6H, m)



(3R,6S,9R,9aS)-3-((benzyloxy)methyl)-6-(furan-3-yl)-9-methylhexahydro-1H-quinolizin-4(6H)-one

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.88 (3H, d, $J = 6.3$ Hz), 1.10-1.21 (9H), 2.67-2.70 (1H, m), 3.18 (1H, dt, $J = 3.2, 10.5$ Hz), 3.78 (1H, dd, $J = 3.7, 9.2$ Hz), 3.87 (1H, dd, $J = 6.8, 8.7$ Hz), 4.54 (2H, s), 5.38 (1H, br-s), 6.24 (1H, br-s), 7.1-7.4 (6H, br-s)

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- ¹¹⁶ The compound was not fully characterized as it does not contribute further to the studies.

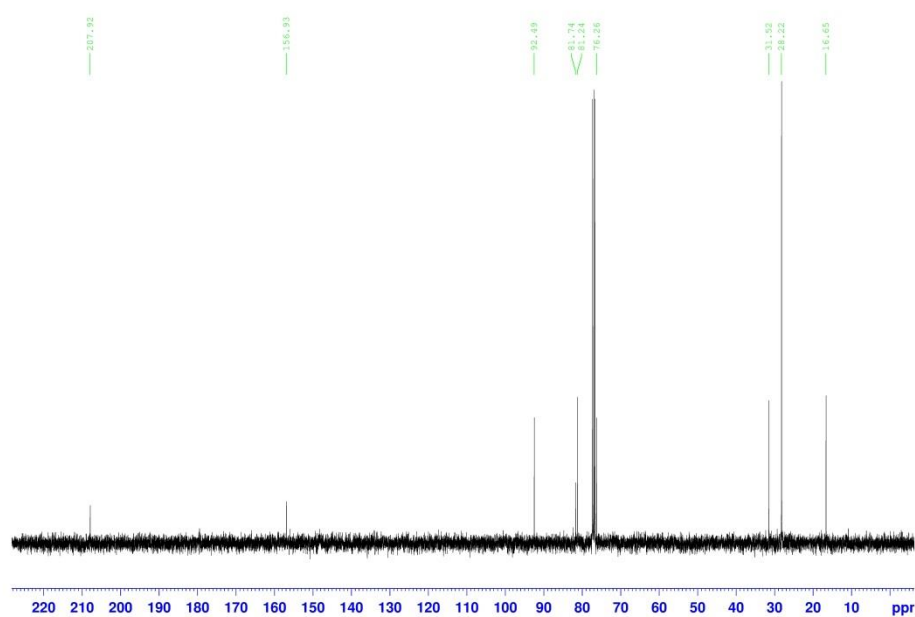
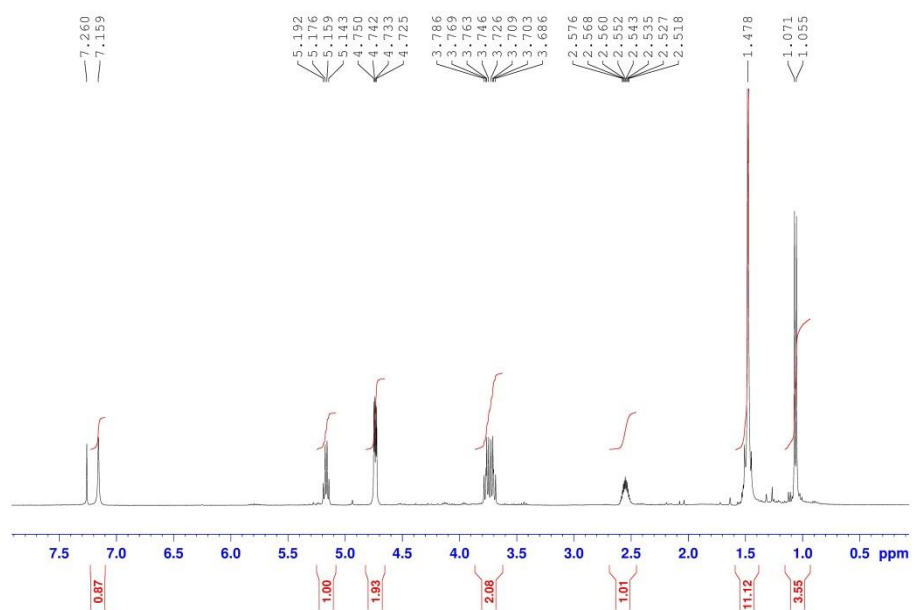
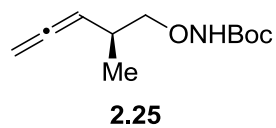
Appendix:

A.1 Selected NMR Spectra

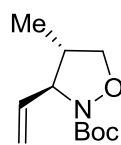
A.2 Chiral HPLC Data

Selected NMR Spectra

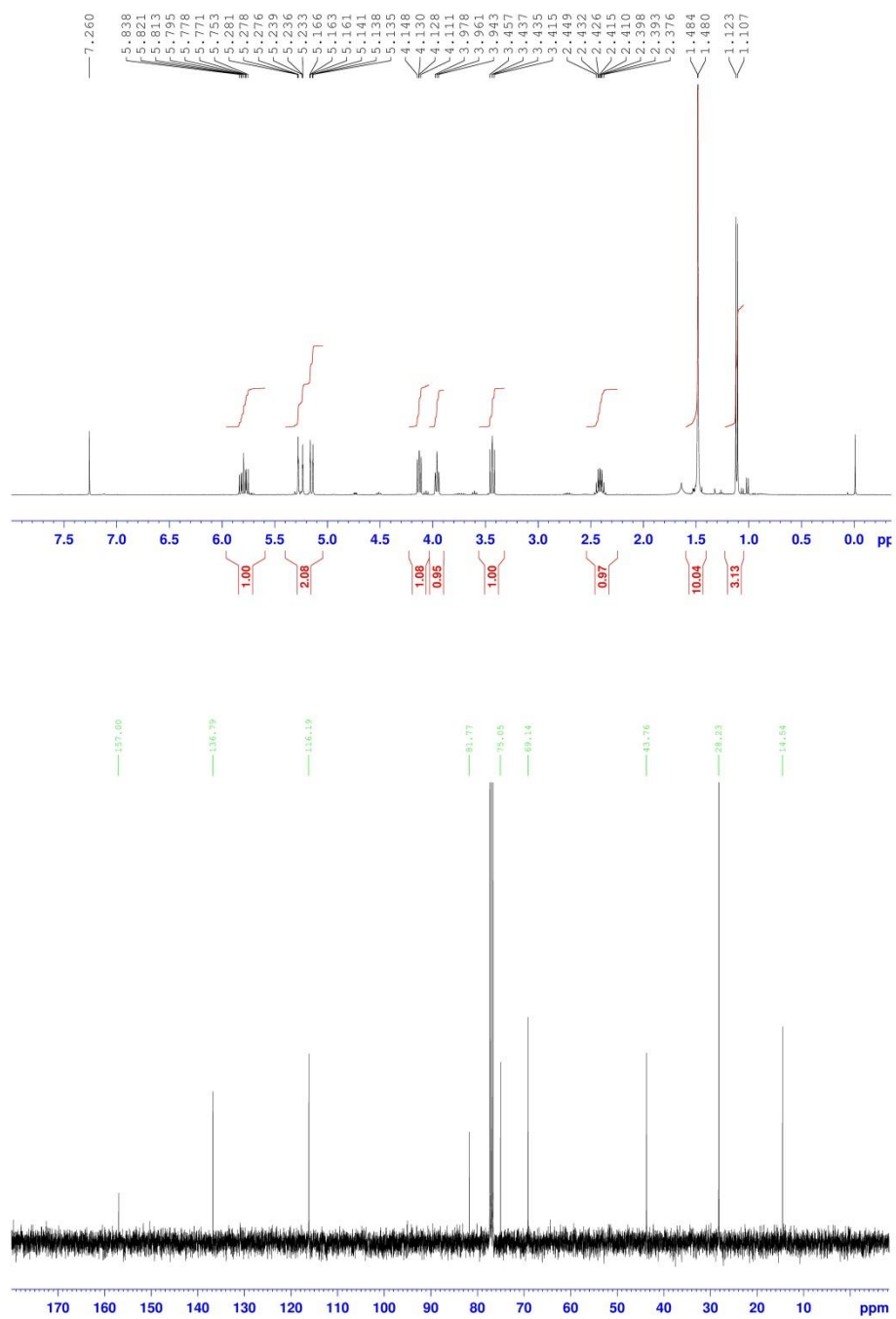
^1H NMR and ^{13}C NMR Spectra for



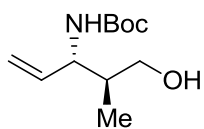
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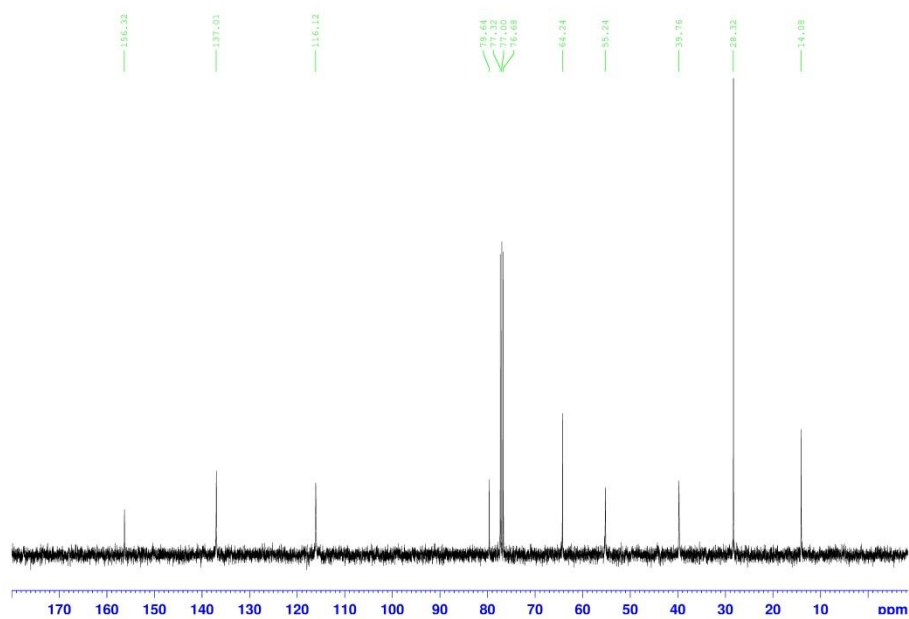
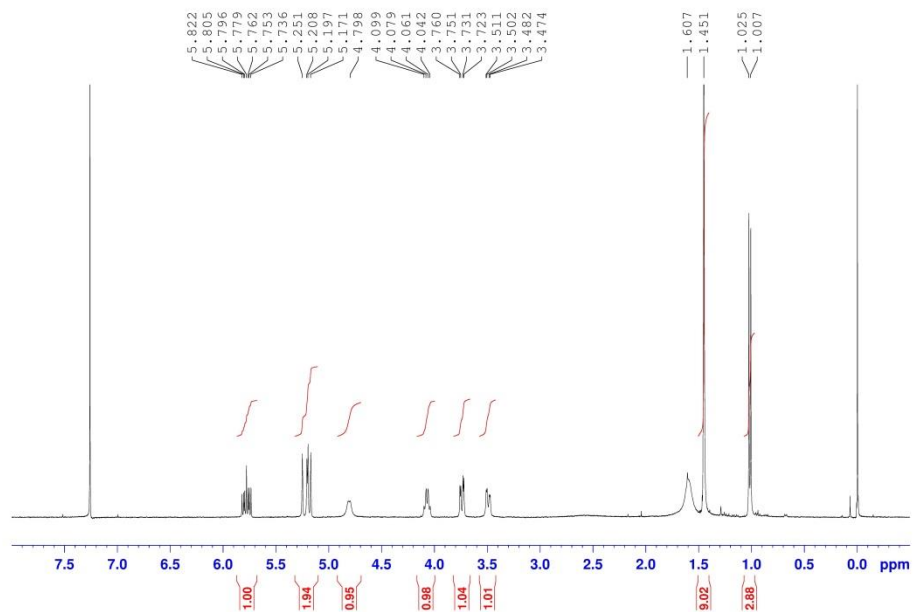
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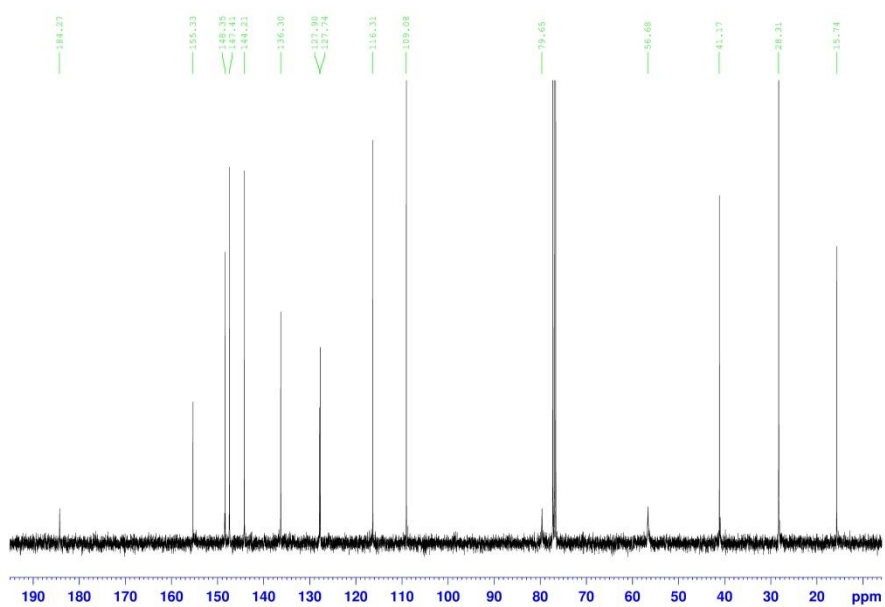
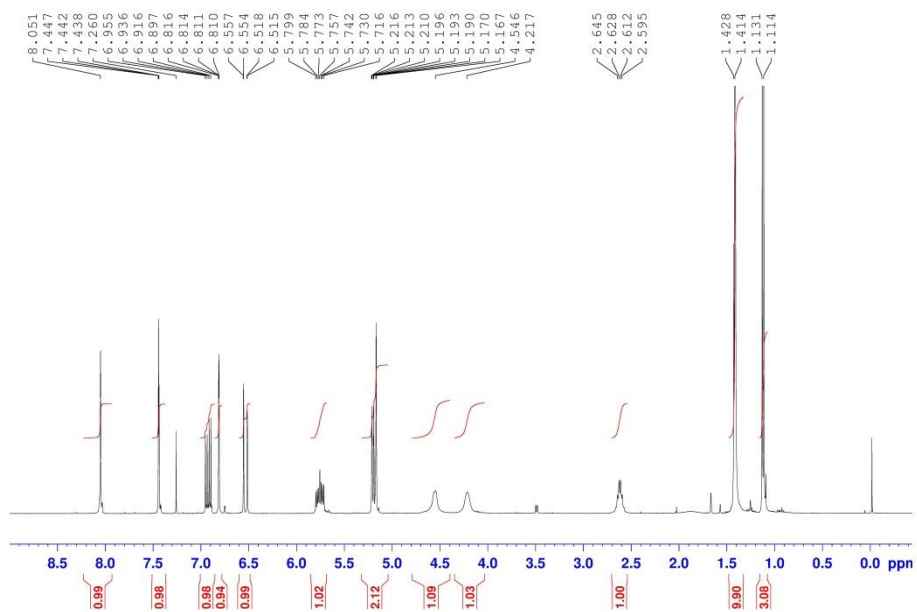
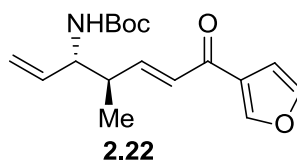
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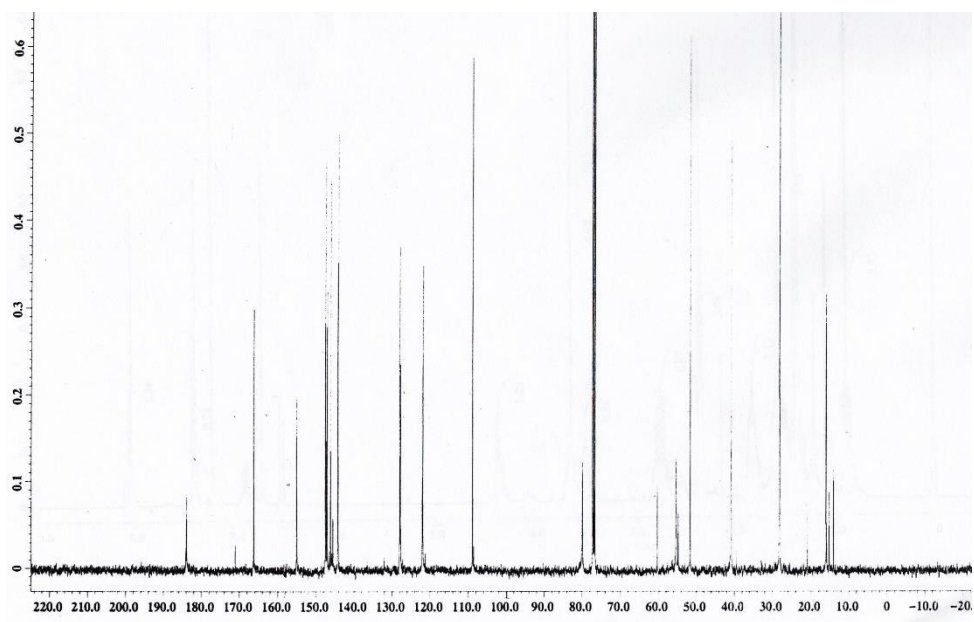
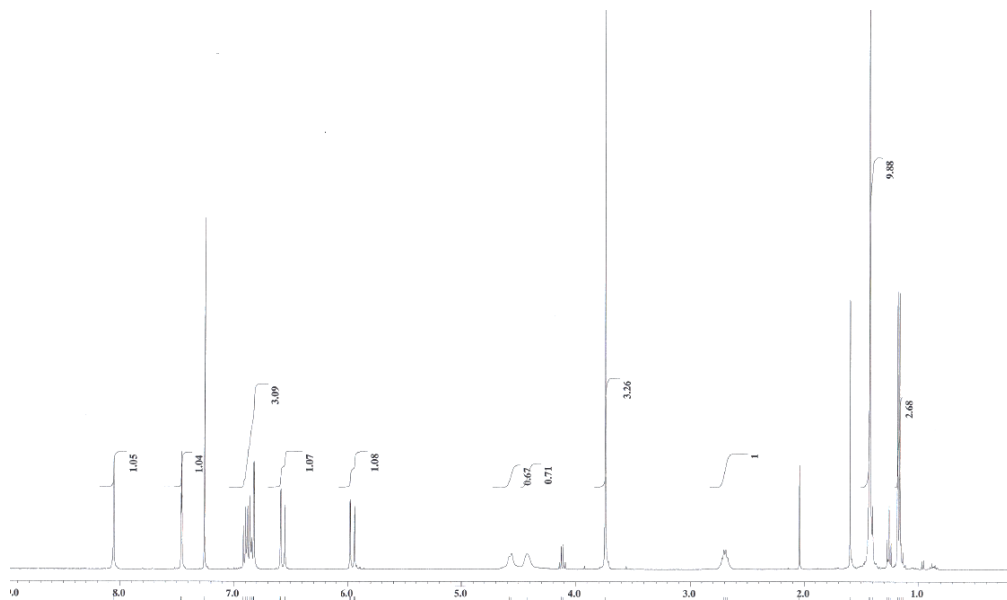
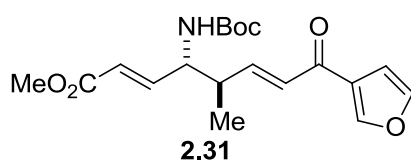
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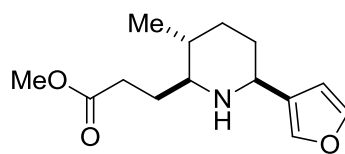
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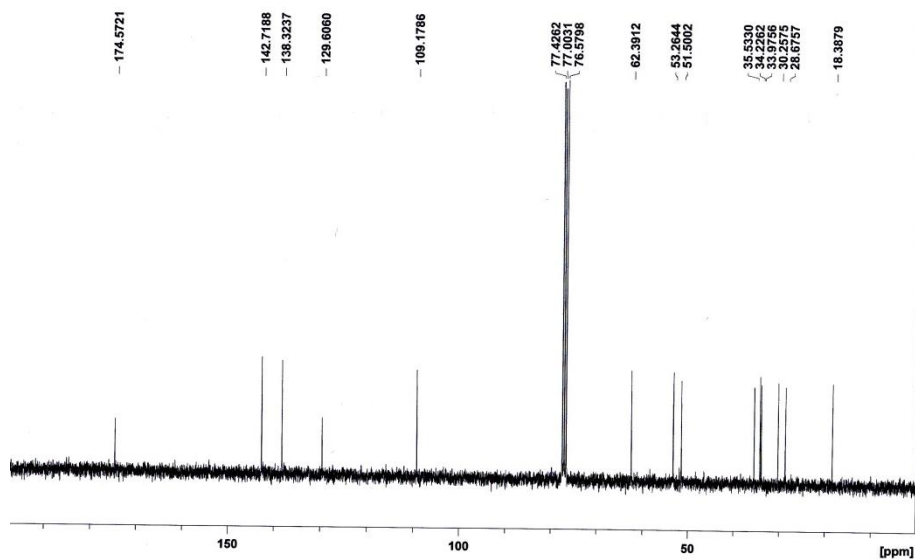
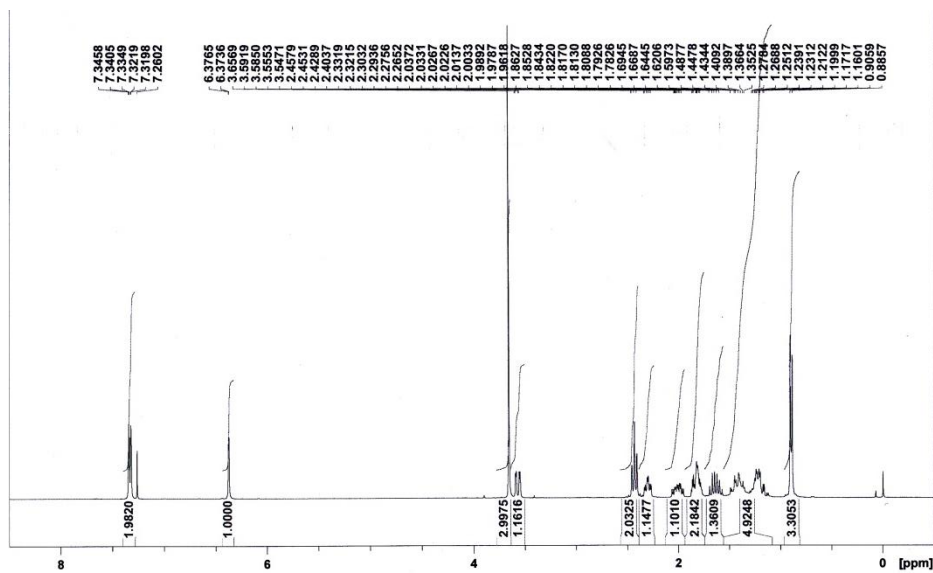
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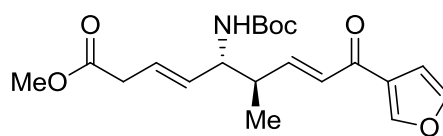
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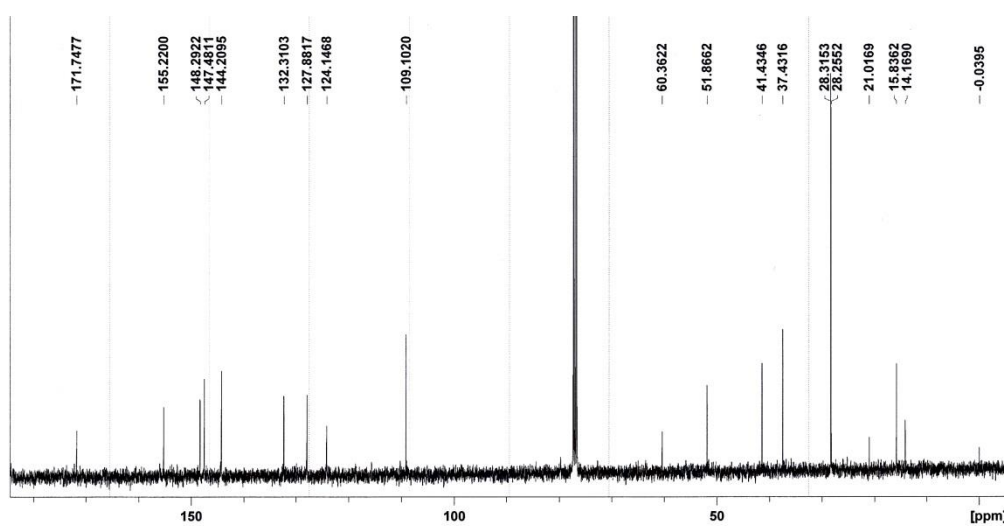
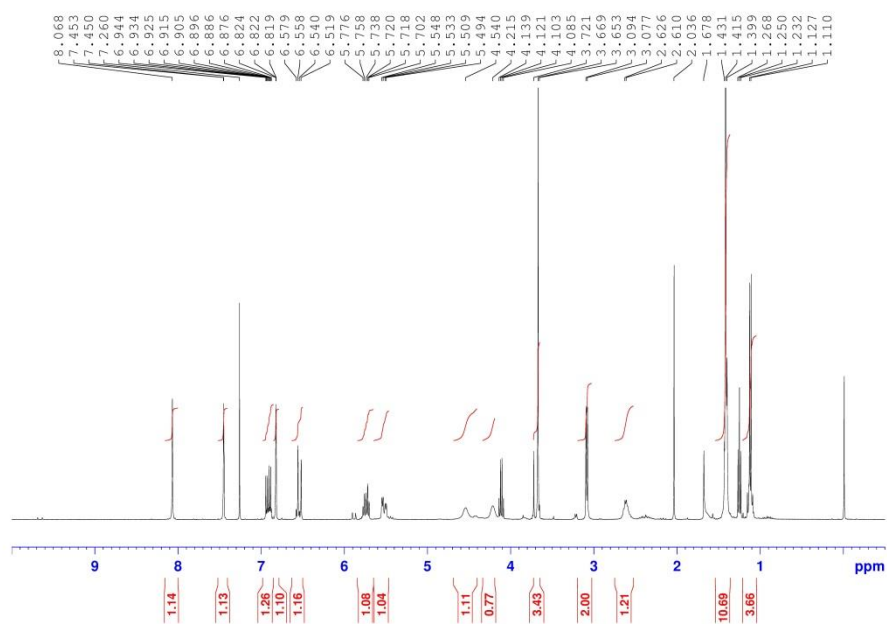
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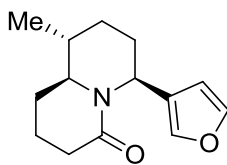
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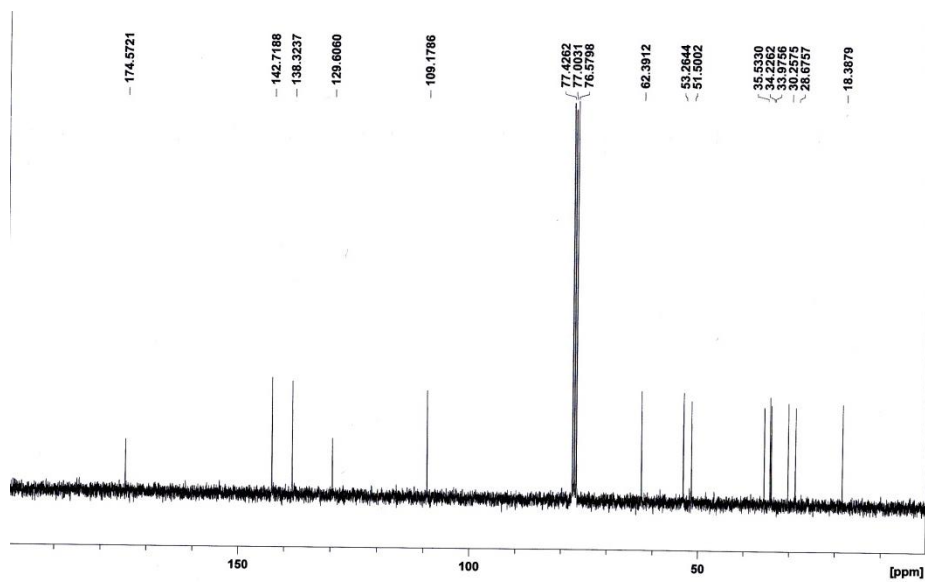
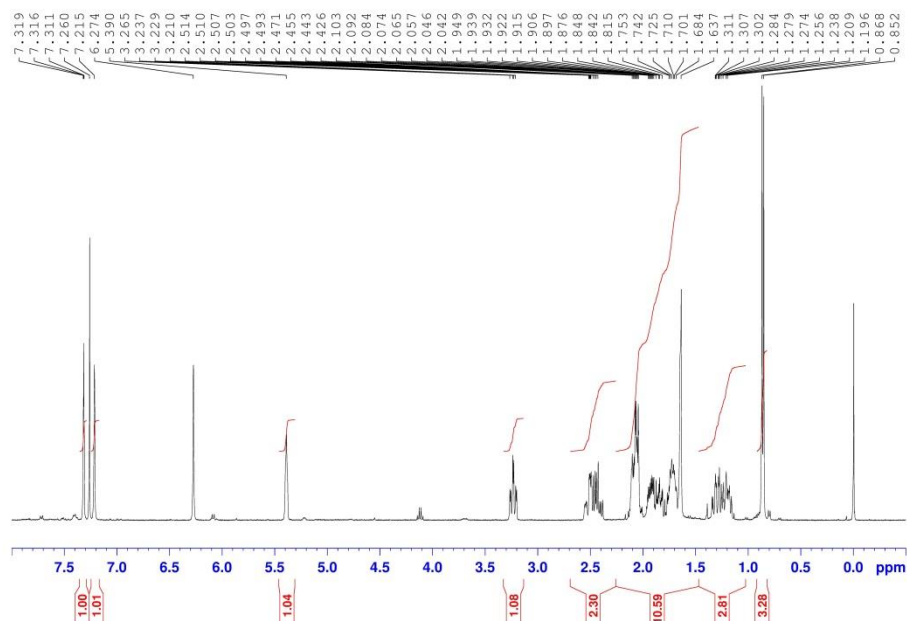
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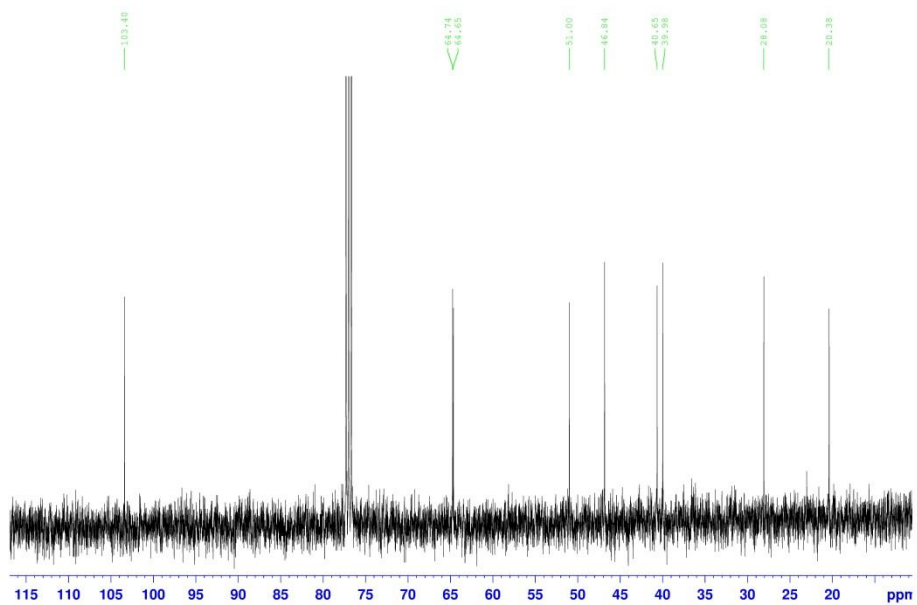
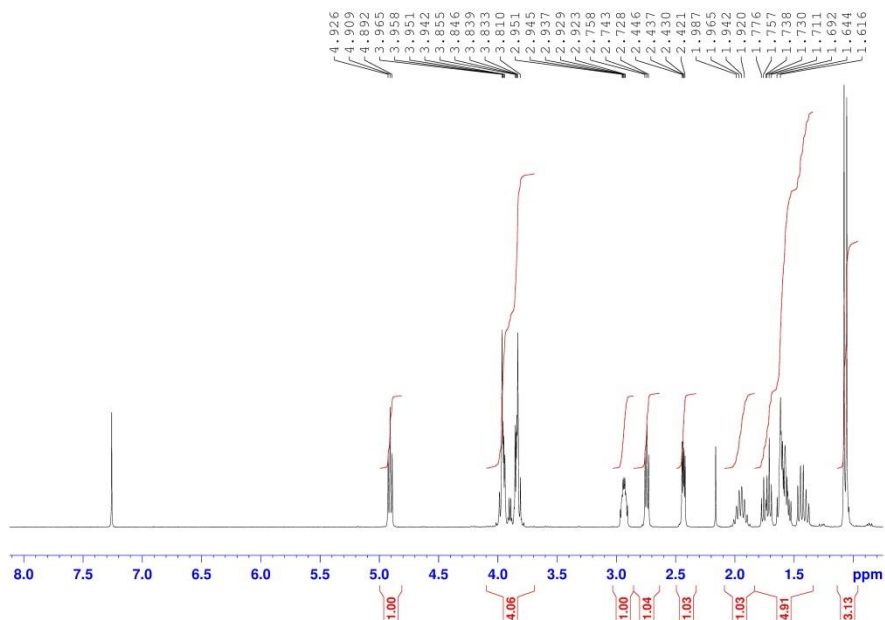
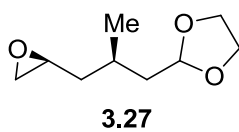
¹H NMR and ¹³C NMR Spectra for



2.52



^1H NMR and ^{13}C NMR Spectra for



Normal phase HPLC-UV chiral separation of racemic

2-((2-methylpenta-3,4-dien-1-yl)oxy)isoindoline-1,3-dione (2.78)

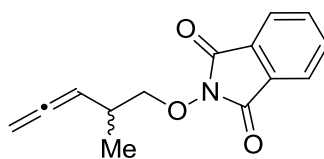
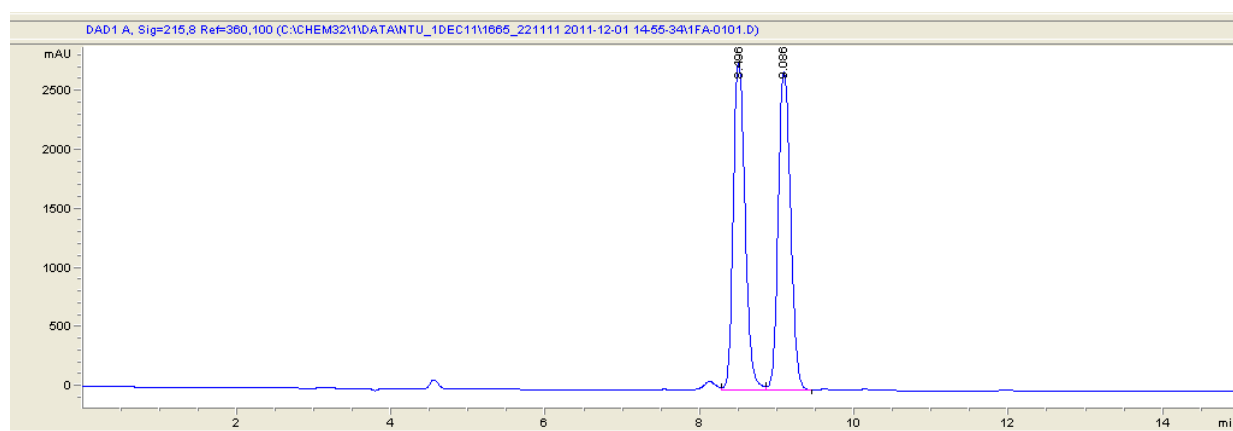


Table 1: Chromatographic conditions

Column	Daicel ID 250x4.6mm, 5um
Mobile Phase	80% Hexane/ 20% Isopropanol (isocratic)
Flow rate	1.0 mL/min (52bar)
Column Temperature	25 °C
Injection Volume	5 µL
Detection wavelength	215nm
Total Runtime	15 min

Figure 1: Chromatogram from Method 1



Sample: 1mg/ mL in isopropanol

Enantiomeric Peak 1: 8.5 minute, Enantiomeric Peak 2: 9.1 minute