Lewis acid-mediated alkylations of N,O-acetals and applications to the total syntheses of alkaloids

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**LEWIS ACID-MEDIATED ALKYLATIONS OF *N*, *O*-
ACETALS AND APPLICATIONS TO THE TOTAL
SYNTHESIS OF ALKALOIDS**

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TABLE OF CONTENTS

ACKNOWLEDGEMENTS	i
TABLE OF CONTENTS	ii
ABSTRACT	v
PUBLICATIONS	vi
LIST OF ABBREVIATIONS	vii
CHAPTER 1: INTRODUCTION	1
1.1. Alkylations of monocyclic iminium ions to 2,6- <i>cis</i> - disubstituted-piperidine rings.	3
1.1.1. Alkylations of monocyclic <i>N</i> -iminium ions arising from oxazolopiperidone synthon.	3
1.1.2. Alkylations of monocyclic <i>N</i> -acyliminium ions arising from α -alkyloxyl carbamates.	6
1.1.3. Alkylations of monocyclic <i>N</i> -acyliminium ions arising from imino glycal.	12
1.1.4. Alkylations of monocyclic <i>N</i> -sulfonyliminium ions.	14
1.2. Alkylations of monocyclic iminium ions to 2,6- <i>trans</i> - disubstituted-piperidine rings.	17
1.3. Alkylations of bicyclic iminium ions to 2,6- <i>trans</i> -disubstituted- piperidine rings.	19
1.4. Summary	22
1.5. Aim of present work	23

CHAPTER 2: LEWIS ACID-MEDIATED ALKYLATIONS	25
OF CYCLIC <i>N,O</i>-ACETAL	
2.1. Introduction	26
2.1.1. Alkylations of acyclic iminium ions	27
2.1.2. Summary	34
2.1.3. Aim of present work	34
2.2. Results and discussion	35
2.2.1. The preparation of cyclic <i>N,O</i> -acetals	35
2.2.2. The alkylations of cyclic <i>N,O</i> -acetals	38
2.2.3. The stereochemistry of alkylations of substituted cyclic <i>N,O</i> -acetals	43
2.3. Summary	47
CHAPTER 3: FORMAL SYNTHESSES OF	49
(-)-PORANTHEDIDINE AND <i>EPI</i>-ISOMER	
3.1. Introduction	50
3.1.1. Previous work on the synthesis of porantheridine	50
3.1.2. Aim of present work	57
3.2. Results and discussion	59
3.2.1. The first approach to (-)- porantheridine	59
3.2.2. The second approach to (-)-porantheridine	79
3.3. Summary	84
CHAPTER 4: TOTAL SYNTHESIS OF (-)-SEDININE	86

4.1. Introduction	87
4.1.1. Previous work on the total synthesis of sedinine	87
4.1.2. Aim of present work	91
4.2. Results and discussion	93
4.2.1. The first approach to sedinine	93
4.2.2. The second approach to sedinine	111
4.3. Summary	121
CHAPTER 5: EXPERIMENTAL SECTION	123
REFERENCES	203
APPENDIX	215
A.1. X-ray crystallography data	215
A.2. Chiral HPLC analysis	219
A.3. Select NMR spectra	221

ABSTRACT

Chapter one describes a literature overview of studies on the cyclic iminium ion chemistry and its use in the synthesis of 2,6-disubstituted piperidine derivatives.

Chapter two describes the facile synthesis of cyclic *N,O*-acetals and Lewis acid-mediated alkylation of these acetals with allyltrimethylsilane *via* acyclic iminium ion chemistry, giving homoallylic amine derivatives efficiently.

In Chapter three, we describe the successful syntheses of porantheridine **3-1** and its C8-epimer **3-59**, employing silver-catalyzed allene cyclization to generate a *cis*-isoxazolidine intermediate and Lewis acid-mediated alkylation of *N,O*-acetals to generate substituted piperidine rings. The generation of *trans* and *cis*-2,6-disubstituted piperidine can be rationalized by consideration of the different conformations of monocyclic *N*-acyl iminium ion **3-55** and bicyclic *N*-acyl iminium ion **3-64**.

In Chapter four, the first asymmetric synthesis of the sedum alkaloid sedinine **4-2** has been successfully achieved, employing silver-catalyzed allene cyclization and ring closing metathesis to form a bicyclic *N,O*-acetal **4-33**. Alkylation of this acetal with silyl enol ether **4-47** under Lewis acidic conditions was exclusively *trans* selective, leading to the natural product after reduction. On the other hand, conversion of the bicyclic *N,O*-acetal **4-33** to a semicyclic *N,O*-acetal **4-17** resulted in no stereoselectivity during such a reaction. Compared to the porantheridine synthesis, the contrasting results also can be rationalized by consideration of the conformation of the iminium ions.

PUBLICATIONS

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- Bates, R. W.; Boonsombat, J.; **Lu, Y.**; Nemeth, J. A.; Sa-Ei, K.; Song, P. Cai, M. P.; Cranwell, P. B.; Winbush, S. *N,O*-heterocycles as synthetic intermediate, *Pure and Applied Chemsitry* **2008**, 80, 681.

CONFERENCES POSTER PRESENTATIONS

- **Lu Yongna**, Roderick, W. Bates*, Studies towards the cyclic peptide mimics derived from *N*-acylisatins. International Symposium on Catalysis and Fine Chemicals 2007, Nanyang Technological University, Singapore, poster presentation, December 16 - 21, **2007**.
- **Lu Yongna**, Roderick, W. Bates*, Total syntheses of Porantheridine and Sedinine, 239th ACS National Meeting & Exposition, Moscone Center, San Francisco, USA, poster presentation, March 21-25, **2010**.

ABBREVIATION

Å	angstrom
Ac	acetyl
Acac	acetylacetonyl
Alloc	allyloxycarbonyl
App	apparent
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
b.p.	boiling point
Bz	benzoyl
Cbz	benzyloxycarbonyl
COSY	correlated spectroscopy
conc.	concentrated
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undecane
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium
DMSO	dimethyl sulfoxide
Dr	diastereoisomeric ratio
EDA	ethylene diamine
ee	enantiomeric excess
eq.	equivalent
Et	ethyl
Fmoc	Fluorenylmethyloxycarbonyl
h	Hour(s)

HRMS	High Resolution Mass Spectrometry
IR	Infra-red spectroscopy
<i>J</i>	Coupling constant
K-Selectride	Potassium tri- <i>sec</i> -butylborohydride
LDA	Lithium diisopropylamide
Lit.	Literature
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
Me	methyl
MOM	Methoxymethyl
m.p.	melting point
MS	mass spectrometry
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
<i>n</i> -Bu	butyl
<i>n</i> -Pr	propyl
Ns	<i>ortho</i> -nitrobenzenesulfonyl
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	4-Methylbenzenesulfonic acid
q	quartet
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
SEM	2-(Trimethylsilyl)ethoxymethyl
SES	β -Trimethylsilylethanesulfonyl
t	triplet
<i>t</i>	tertiary
TBDMS	<i>tert</i> -butyldimethylsilyl
<i>tert</i>	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMG	tetramethylguanidine
TMS	trimethylsilyl

CHAPTER 1

INTRODUCTION

The piperidine ring is a common moiety in a large number of natural products and biologically active compounds.¹ Among these naturally occurring piperidine alkaloids are (+)-prosopinine and (-)-deoxoprosophylline, isolated from *Prosopis Africana*, which exhibit antibiotic and anesthetic properties (Figure 1.1).² On the other hand, (+)-Cermizine D, a cernuane-type *Lycopodium* alkaloid possess cytotoxicity against murine lymphoma L1210 cells with an IC₅₀ of 7.5 $\mu\text{g/mL}$.³

Figure 1.1: Examples of piperidine alkaloids.

A huge number of stereoselective strategies⁴ to synthesize functionalized piperidines have been employed such as Michael-type conjugate addition reaction⁵, aminocyclization⁶, Mannich-type intramolecular cyclization⁷, reductive amination⁸ and aza-Diels-Alder reaction⁹.

One convenient access to functionalized piperidines is the Lewis acid-mediated alkylation of cyclic *N*-substituted iminium ions with nucleophilic species (NuY, Y= SiR₃, SnR₃ and metal) and this has attracted our attention (Scheme 1.1).¹⁰ On the basis of the structural characteristics, it can be classified into three groups: simple iminium ions (**1-1a**), *N*-acyliminium ions (**1-1b**) and *N*-sulfonyliminium ions (**1-1c**). Axial attack of nucleophile to the most favored half chair conformer **1-2** leads to

carbon-carbon bond formation *via* a chair transition state. Since a wide range of substituents can be introduced at different positions of piperidine ring, only the stereoselective routes to 2,6-disubstituted piperidine moieties are summarized herein.

Scheme 1.1: Iminium ion chemistry to piperidine ring.

1.1. Alkylations of monocyclic *N*-substituted iminium ions to 2,6-*cis*-disubstituted-piperidines

1.1.1. Alkylations of monocyclic *N*-substituted iminium ions arising from oxazolopiperidone synthon

We begin our review from alkylations of monocyclic *N*-substituted iminium ions, giving 2,6-*cis*-disubstituted-piperidines.

Husson and co-workers¹¹ employed (-)-2-cyano-6-oxazolopiperidine synthon **1-4**, which showed different reactivities of the C-2 (α -amino nitrile) and C-6 (α -amino ether) moieties (Scheme **1.2**). The alkylation of the anion of synthon **1-1** with *n*-PrBr

gave compound **1-5** as a single isomer with the assistance of the chiral auxiliary attached to the nitrogen. Reductive removal of cyano group provided compound **1-6** as a single isomer in 70-77% yield.

Scheme 1.2: Husson's synthetic route to (+)-dihydropinidine **1-9**.

They put forward the origin of the high stereoselectivity observed in the reaction of **1-5** to **1-6** (Scheme 1.3). Selective elimination of the cyano group by the complexation with silver ion generated iminium ion **1-7** only. Subsequent axial attack by hydride (H^-) to the half-chair conformer **1-7** from the top face gave the target compound **1-6**.¹¹

Scheme 1.3: The origin of stereoselectivity.

Thus the cyano group (CN) acts as both an electron withdrawing group to stabilize the anion and as a leaving-group to generate an iminium ion intermediate **1-7**. A second alkylation of compound **1-6** provided the 2,6-*cis*-disubstituted piperidine **1-8** with high diastereoselectivity ($dr > 95:5$) via the same axial attack of CH_3MgI to iminium ion

intermediate (Scheme 1.4). (+)-dihydropinidine **1-9** was then obtained by treatment with 70% H₂SO₄.

Scheme 1.4: Husson's synthetic route to (+)-dihydropinidine **1-9**.

Amat and co-workers¹² utilized a similar oxazolopiperidone synthon **1-12** as Husson¹¹ reported, which was prepared by alkylation of bicyclic lactam **1-10** and Red-Al reduction of compound **1-11** (Scheme 1.5). A subsequent alkylation of amina **1-12** with propylmagnesium bromide led to the 2,6-*cis*-disubstituted piperidine **1-13** exclusively. Dihydropinidine was then obtained by hydrogenation in 65% yield.

Scheme 1.5: Synthetic route to (+)-dihydropinidine **1-9**.

Compared to Husson's¹¹ synthetic route to (+)-dihydropinidine, in this strategy it is

easier to remove the chiral auxiliary attached to the nitrogen atom by hydrogenation. The above methodology¹² was also expanded to the syntheses of bicyclic quinolizidine **1-14**, substituted indolizidines **1-15**, and **1-16** (Scheme 1.6). Single isomers were obtained in all cases by alkylations with different Grignard reagents derived from 1,3-dioxolane or dioxane, followed by reductive amination under acidic conditions.

Scheme 1.6: Syntheses of quinolizidine **1-14**, indolizidines **1-15** and **1-16**.

1.1.2. Alkylation of monocyclic *N*-acyliminium ions arising from α -alkoxy carbamates

It was found that alkylations of monocyclic *N*-acyliminium ions arising from α -alkoxy carbamates could also lead to the 2,6-*cis*-disubstituted-piperidines as well.

Tanaka and co-workers¹³ employed α -methoxylated carbamate **1-18**, which was prepared by anodic oxidation from L-lysine ester **1-17** to synthesize sedamine **1-21** (Scheme 1.7). The carbamate **1-18** is a powerful precursor to an iminium ion. Treatment of 6-methoxypipicolate **1-18** with trimethylsilyloxystyrene **1-19** in the presence of titanium tetrachloride gave the 2,6-*cis*-disubstituted pipicolates **1-20** in 60-68% yield with good diastereoselectivity (*dr* = 10:1).

Scheme 1.7: Tanaka's synthetic route to sedamine **1-21**.

Shono and co-workers¹⁴ utilized the same α -methoxylated carbamates **1-18** to synthesize (+)-*N*-methylconiine **1-23** (Scheme 1.8). TiCl₄-mediated alkylation of compound **1-18** with allyltrimethylsilane followed by hydrogenation over palladium on carbon gave the 2,6-*cis*-disubstituted piperidine **1-22** in 68% yield exclusively.

Scheme 1.8: Schono's synthetic route to (+)-*N*-methylconiine **1-23**.

Hootelé and co-workers¹⁵ also employed anodic oxidation of **1-24** to provide a similar synthetic precursor, α -methoxylated carbamates **1-25** to synthesize sedinone **1-28** (Scheme 1.9). Alkylation of precursor **1-25** with silyl enol ether **1-31** in the presence of TiCl₄ led to 2,6-*cis*-disubstituted piperidine **1-27** in 70% yield with good

diastereoselectivity ($dr = 9:1$).

Scheme 1.9: Hootel's synthetic route to (-)-sedinone **1-28**.

In order to avoid the 1,2-interaction between the *N*-methoxycarbonyl group and C-6 side chain, the half-chair conformer **1-29** was most favored with the axial orientation of C-6 side chain (Scheme **1.10**). The stereoelectronically controlled axial attack of the nucleophile to the conformer **1-29** from the top face led to 2,6-*cis*-disubstitution piperidine *via* chair-like transition state, despite the fact that nucleophilic attack is on same face on bulky substituent, α to *N* atom. Stereoelectronic control thus overrides the steric bias.¹⁵

Scheme 1.10: Origin of stereochemistry.

The α -methoxylated carbamate **1-25** could also act as a precursor to the synthesis of (-)-sedacrine **1-33**, which bears a double bond in the piperidine ring¹⁵ (Scheme 1.11). Elimination of methanol from compound **1-25** gave the enecarbamate **1-30** in 96% yield. The key intermediate **1-31** was then obtained by iodomethoxylation with iodine in methanol, followed by dehydrohalogenation via treatment of DBU. The alkylation with silyl enol ether **1-26** in the presence of titanium chloride yielded the 2,6-*cis*-disubstituted piperidine **1-32** in 64% yield with good diastereoselectivity (*dr* = 9:1). The *trans*-stereochemistry was then obtained after equilibration in methanol.

Scheme 1.11: Hootelé's synthetic route to (-)-sedacrine **1-33**.

On the other hand, Ojima and co-workers¹⁶ employed hydroformylation of homoallylic amine **1-36** to synthesize a similar synthetic precursor, **1-37** to complete the synthesis of (-)-deoxoprosopphylline **1-40** (Scheme 1.12). The precursor **1-37** underwent alkylation with allylsilane **1-38** in the presence of boron trifluoride-diethyl etherate to afford the 2,6-*cis*-disubstituted piperidine **1-39** exclusively.

Scheme 1.12: Ojima's synthetic route to (-)-deoxoprosopphylline **1-40**.

Pilli and co-workers¹⁷ reported a new method to synthesize the α -ethoxylated carbamate **1-42** derived from the reduction of piperidinone **1-41** to synthesize decahydroquinoline **1-45** (Scheme 1.13). Treatment of **1-42** with allyl tri-*n*-butyltin in the presence of boron trifluoride-diethyl etherate yielded the 2,6-*cis*-disubstituted piperidine **1-44** in 64% yield, with good diastereoselectivity (*dr* = 89:7:4).

Scheme 1.13: Pilli's synthetic route to decahydroquinoline **1-45**.

Given the very small coupling constant (~ 0 Hz) between H-2 and H-3 of the major isomer **1-44**, the two allylic groups might adopt the pseudoaxial orientation due to

allylic A^{1,3} interaction between the *tert*-butyl carbamate group and the allyl substituent at C-2 (Scheme 1.14). This suggested the *trans* orientation of the two allylic groups.¹⁷

Scheme 1.14: ¹H NMR characterization of compound **1-44**.

Pilli and co-workers¹⁸ also applied the above methodology to the synthesis of quinolizidine **1-50**, involving a similar precursor, α -ethoxylated carbamate **1-47** embodying C-3 substitution (Scheme 1.15). The precursor **1-47** was treated with silyl enol ether **1-48** in the presence of trimethylsilyl triflate to afford 2,6-*cis*-disubstituted piperidine **1-49** exclusively. On the basis of NOE studies, the substituents at C-2, C-3 and C-6 of compound **1-49** adopted axial orientations to relieve allylic A^{1,3} strain.

Scheme 1.15: Pilli's synthetic route to quinolizidine **1-50**.

Blaauw and co-workers¹⁹ reported the *N*-acyliminium ion chemistry of compound **1-51**, containing a C-3 substituent (Scheme 1.16). Due to the restricted rotation of N-C=O bond, the stereochemistry was determined after removal of the Cbz group. Treatment of *N,O*-acetal **1-51** with a range of nucleophiles in the presence of 2 equiv $\text{BF}_3 \cdot \text{OEt}_2$ or 10 mol% of $\text{Sn}(\text{OTf})_2$ followed by hydrogenation, afforded the 2,6-*cis*-disubstituted-piperidines exclusively *via* pseudoaxial attack. However, the small nucleophile TMS-CN gave a 1.7:1 mixture of diastereoisomers.

Scheme 1.16: Blaauw's *N*-acyliminium ion chemistry of compound **1-51**.

1.1.3. Alkylations of monocyclic *N*-acyliminium ions arising from imino glycals.

One particular approach that caught our attention was the alkylation of monocyclic α,β -unsaturated *N*-acyliminium ions, resulting in the 2,6-*cis*-disubstituted-piperidines.

Shipman and co-workers²⁰ employed the intermediate imino glycal **1-54**, which was

prepared from d-glucal **1-53**, to synthesize (+)-deoxoprosophylline **1-40** (Scheme 1.17). The key step involved was iminium ion chemistry similar to Ojima's strategy.¹⁶ However, the precursor was the imino glycal not the α -alkoxy carbamate. The $\text{BF}_3 \cdot \text{OEt}_2$ -mediated alkylation of imino glycal **1-54** with allylsilane **1-38**, followed by the deprotection of *N*-Fmoc group led to the 2,6-*cis*-disubstituted piperidine **1-55** in 78% yield with high diastereoselectivity (*dr* = 9:1). The stereochemistry was determined by NOE experiments.

Scheme 1.17: Shipman's synthetic route to (+)-deoxoprosophylline: (+)-**1-40**.

A possible mechanism is shown in Scheme 1.18. Two conformations **1-56a** and **1-56b** would exist in solution. Due to the steric interaction between the C-6 acetoxymethyl group and the *N*-Fmoc group in conformation **1-56a**, conformation **1-56b** is much preferred. The nucleophile attacks from the top face under stereoelectronic control, leading to 2,6-*cis*-diastereoselectivity.

Scheme 1.18: Proposed origin of stereoselectivity.

1.1.4. Alkylation of monocyclic *N*-sulfonyliminium ions to 2,6-*cis*-disubstituted piperidines

In parallel with the approaches above, alkylations of monocyclic *N*-sulfonyliminium ions also proceeded in a similar way as the *N*-acyliminium ions, giving the 2,6-disubstituted-piperidines exclusively.

Speckamp and co-workers²¹ employed the key intermediate **1-58** as a precursor to *N*-sulfonyliminium ion **1-59**, which was derived from *N*-tosyl-6-ethoxy-2-piperidinone **1-57**, to synthesize deoxoprosophylline **1-40** (Scheme 1.19). Compared to *N*-acyliminium ions, the preparation of the *N*-sulfonyliminium ion involves multiple steps including methoxycarbonylation and *N*-tosylenamide hydroboration. However, with the bulkier *N*-Ts protecting group, the product could be found with higher diastereoselectivity, and well resolved NMR spectra that are free of rotamers.

Treatment of *N*-sulfonyliminium ion **1-58** with allylsilane **1-38** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ yielded 2,6-*cis*-disubstituted piperidine **1-40** exclusively.

Scheme 1.19: Speckamp's synthetic route to desoxoprosophylline **1-40**.

A possible mechanism is shown in Scheme **1.20**. Due to 1,2-interaction between the C2-siloxymethyl substituent and the *N*-tosyl group, the iminium ion **1-59** adopted the most stable conformation **1-61b** rather than conformation **1-61a**. Stereoelectronically controlled axial attack of the nucleophile **1-38** to conformer **1-61b** led to the 2,6-*cis*-disubstituted piperidine **1-60** exclusively in a similar way to *N*-acyliminium ions.

Scheme 1.20: Proposed origin of stereoselectivity.

Zhou and co-workers²² utilized similar *N*-sulfonyliminium ion chemistry reported by Speckamp²¹ to synthesize (+)-desoxoprosophylline **1-40** (Scheme 1.21). The key difference was the use of an Achmatowicz reaction to form the synthetic precursor **1-63** containing C5-substitution. TiCl_4 -mediated allylation of **1-63** with allyltrimethylsilane led to the 2,6-*cis*-disubstituted piperidine **1-64** in 67% yield exclusively.

Scheme 1.21: Speckamp's synthetic route to (+)-desoxoprosophylline (**1-40**).

Craig and co-workers²³ reported a systematic study of the preparation and alkylation of 2-alkyl-1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines **1-66**, starting from sulfonylactal **1-65**. The alkylation of key intermediate **1-66** was achieved efficiently with Lewis acidic organometallic reagents (Me_3Al , Et_2AlCl), or compounds **1-66** with an allylsilane or a silyl enol ether in the presence of tin tetrachloride afforded 2,6-*cis*-disubstituted products **1-67** exclusively in high yield (up to 99%). The stereochemistry arose from the nucleophilic attack on the less sterically hindered face of the *N*-sulfonyliminium ions in a similar way to Shipman's report²⁰.

L. A.: Me_3Al , Et_2AlCl , SnCl_4 ,

Yield: 70-99%

Nu: MeAl_3 , Et_2AlCl , $\text{TMSCH}_2\text{CHCH}_2$, $\text{TBSOC}(\text{CH}_2)t\text{-Bu}$

R: CH_2Ph , *i*-Pr, *i*-Bu, $\text{CH}_2\text{OSiPh}_2t\text{-Bu}$,

Scheme 1.22: Craig's *N*-sulfonyliminium ion chemistry.

1.2. Alkylations of monocyclic *N*-acyliminium ions to *trans*-2,6-disubstituted piperidines

In some cases, alkylation of monocyclic *N*-acyliminium ions can result in 2,6-*trans*-disubstituted piperidines.

One good example that illustrated this result was the work reported by Ojima and co-workers^{24a}. They employed a hydroformylation¹⁶ of compound **1-68** to synthesize the synthetic precursor, α -ethoxylated carbamate **1-69**, of the iminium ion intermediate (Scheme 1.23). However, when alkylation of α -ethoxylated carbamate **1-69** was carried out with *n*-BuCu:BF₃ complex, the 2,6-*trans*-disubstituted piperidine **1-70** was obtained exclusively. Moreover, the *trans*-isomer **1-70** could be converted to the thermodynamically more stable *cis*-**1-71** by facile epimerization with LiHMDS.

Scheme 1.23: Synthetic route to 2,6-*trans*-disubstituted piperidine **1-70** and 2,6-*cis*-disubstituted piperidine **1-71**.

Based on Wistrand's^{24b,c} suggestion, the origin of the *trans*-stereoselectivity is outlined in Scheme 1.24. Chelation of a copper species between the carbonyl group of ester and the nitrogen atom would provide copper complex **1-72**. The nucleophilic butyl group (*n*-BuCu) could adopt a preferred attack (less steric hindrance) from the bottom face to generate the *trans*-selectivity. Nevertheless, Wistrand's results show that the ester group is the cause of the *trans*-selectivity.

Scheme 1.24: the origin of *trans*-stereochemistry.

Thus, Ojima and co-workers¹⁶ employed the above alkylations with copper (I) complex to synthesize (+)-prosopinine **1-79** (Scheme 1.25). The required copper reagent **1-77** was derived from the reaction of alkyl bromide **1-75** with lithium metal and copper(I)

bromide in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. The chelation-controlled alkylation of α -ethoxylated carbamate **1-74** led to the 2,6-*trans*-disubstituted piperidine **1-78** exclusively in a similar way to Wistrand's report^{24b,c}.

Scheme 1.25: Ojima's synthetic route to (+)-prospinine **1-79**.

1.3. Alkylations of bicyclic *N*-acyliminium ions to 2,6-*trans*-disubstituted piperidines

The most common method for the synthesis of 2,6-*trans*-disubstituted piperidines is the alkylations of bicyclic *N*-acyliminium ions with nucleophiles.

Hootelé and co-workers²⁵ explored a novel and convenient method to synthesize 2,6-*trans*-piperidines, employing bicyclic α -methoxylated carbamate **1-84** as a starting material (Scheme 1.26). The precursor **1-84** was derived from nitron **1-80** via 1,3-dipolar cycloaddition (*exo/endo* = 99:1) and anodic oxidation. Treatment of

bicyclic α -methoxylated carbamate **1-84** with a silyl enol ether in the presence of titanium tetrachloride afforded 2,6-*trans*-disubstituted piperidine **1-85** exclusively in 55-58% yield *via* a bicyclic *N*-acyliminium ion intermediate.

Scheme 1.26: Hootel's synthetic route to *trans* piperidine alkaloids.

A possible mechanism is shown in Scheme 1.27. The cyclic carbamate constrains the C-2 side chain in a pseudoequatorial orientation. Thus, the conformer **1-86** of the bicyclic *N*-acyliminium ion is most favored in solution. The preferred axial attack of nucleophile from bottom face then led to a 2,6-*trans*-disubstituted-piperidine **1-84**.

Scheme 1.27: Proposed origin of stereochemistry.

Lhommet and co-workers²⁶ carried out a systematic study on the alkylation to 2,6-*trans*-disubstituted piperidines *via* bicyclic *N*-acyliminium ions (Table 1.1).

Treatment of iminium precursor **1-87** with a range of nucleophiles (allyltrimethylsilane, cyanotrimethylsilane, silyl enol ethers, silyl ketene acetals, furan and indole) under Lewis acidic conditions (TiCl_4 and TMSOTf) afforded 2,6-*trans*-disubstituted piperidines **1-89a-g** exclusively. The origin of *trans*-stereochemistry is the same as that proposed by Hootel²⁴, arising from axial attack on the bicyclic iminium ions.

Table 1.1: Alkylations of iminium precursor **1-87** with various nucleophiles.

Entry	Lewis acid	Nu.	R	Yield (%)
1	TiCl_4			86 (1-89a)
2	TiCl_4	TMSCN	CN	72 (1-89b)
3	TiCl_4			70 (1-89c)
4	TMSOTf			91 (1-89d)
5	TMSOTf			95 (1-89e)
6	TMSOTf			56 (1-89f)
7	<i>p</i> TSA			78 (1-89g)

Based on the successful results obtained above, Takayama and co-workers^{2b,2c} applied this methodology to the synthesis of 2,6-*trans*-piperidines, (-)-cernuine and (+)-cermizine D, cermizine C, and senepodine G, using the same key intermediate **1-92** (Scheme 1.28). TiCl₄-mediated alkylations of aminoacetal **1-91** with allyltrimethylsilane yielded 2,6-*trans*-disubstituted-piperidine **1-92** exclusively.

Scheme 1.28: Takayama's synthetic route to (-)-cernuine, (+)-cermizine D, cermizine C and senepodine G.

1.4. Summary

In summary, the alkylation of iminium ions with nucleophiles is very useful for the stereo-controlled formation of 2,6-disubstituted piperidine rings. *Cis* and *trans*-2,6-disubstituted piperidine rings can be generated in excellent yield with excellent diastereoselectivity respectively, depending on different conformations of iminium ion intermediates. Secondly, the precursors to iminium ions are easily

prepared, generally derived from *N,O*-acetals. Moreover, a range of nucleophiles can be employed in this transformation including allyltrimethylsilane, cyanotrimethylsilane, silyl enol ethers, silyl ketene acetals, furan, indole and even nucleophilic metal reagents.

1.5. Aim of the present work

The powerful alkylation of cyclic *N*-acyl iminium ions inspired us to study the alkylation of acyclic *N*-acyl iminium ions further to provide optically active amino alcohols derivatives (Scheme 1.29).

Scheme 1.29: One aim in present work

On the other hand, since the alkylation of cyclic iminium ions is a facile route to 2,6-disubstituted piperidine rings, it also inspired us to exploit this methodology for the synthesis of piperidine alkaloids.

In particular, formation of isoxazolidines *via* allenic hydroxylamine cyclization provides a facile route to *syn*-1,3-amino alcohols (Scheme 1.30).²⁷ These amino alcohols could serve as starting material for *N,O*-acetals, the precursor to iminium ions. It is also a facile approach to highly functionalized heterocycles with high

diastereoselectivity. Moreover, one of the allenic double bonds still remains in the cyclization product, which can be further manipulated such as by olefin metathesis.

Scheme 1.30: Allenic cyclization.

Therefore, another two aims of our work are to apply the alkylations of *N*-acyliminium ions and allenic cyclizations to the total syntheses of piperidine alkaloids: (-)-porantheridine and (-)-sedinine (Figure 1.2).

Figure 1.2: Two target molecules investigated in present work.

CHAPTER 2

LEWIS ACID-MEDIATED ALKYLATIONS OF CYCLIC *N,O*-ACETALS

2.1. Introduction

The alkylation of cyclic *O,O*-acetals with silicon-containing nucleophiles under Lewis acidic conditions has evolved into a powerful approach to stereoselective carbon-carbon bond formation (Scheme 2.9).²⁸ The corresponding reactions of cyclic *N,O*-acetals, where the *N* atom bears an electron withdrawing protecting group (PG), have not, to our knowledge, been systematically studied. As summarized in Chapter 1, *N,O*-acetals are good synthetic precursors to iminium ion intermediates. The alkylation of cyclic iminium ion intermediates can be a very efficient method to synthesize 2,6-disubstituted piperidines with excellent diastereoselectivity. Hence, if the alkylation of cyclic *N,O*-acetals containing a protecting group worked well, it would provide a convenient route to 1,3-amino alcohols, which are common structural moieties in many bioactive compounds. Therefore, we maintained our interest in studying the acyclic iminium ion chemistry further, derived from cyclic *N,O*-acetals.²⁹

Scheme 2.1: Alkylation reactions of acetals.

2.1.1. Alkylations of acyclic iminium ions

Lectka and co-workers³⁰ reported the first enantioselective alkylation of acyclic *N,O*-acetals **2-1** in the presence of a chiral Cu(I)-based Lewis acid catalyst (Scheme 2.2). Treatment of acyclic *N,O*-acetals **2-1** with a range of nucleophiles **2-4a-d** using catalytic copper complex **2-2** led to products **2-5** in high yield (73-93%) with high enantioselectivity (up to 95%).

Scheme 2.2: Enantioselective alkylation reactions of acyclic *N,O*-acetals **2-1**.

They utilized ^1H NMR experiments to put forward a possible mechanism (Scheme 2.3).³⁰ The acetals **2-1** were first reacted with 1 equiv of silyl enol ether **2-4a** to generate the intermediate **2-6**. The intermediate **2-6** then coordinated to the copper catalyst **2-2** to generate another intermediate **2-7**, which was reacted with a second equiv of silyl enol ether **2-4a** to afford product **2-5a** with high enantioselectivity, due to the special steric environment of BINAP.

Scheme 2.3: Proposed mechanism for alkylation of *N,O*-acetals.

Kobayashi and co-workers³¹ reported systematic studies on the diastereoselective alkylation of semicyclic *N,O*-acetals *via* acyclic iminium ion intermediates (Scheme 2.4). Semicyclic *N,O*-acetals bearing 3-alkoxy substituents were treated with a range of nucleophiles **2-9a-d** in the presence of TMSOTf to afford 1,5-amino alcohols **2-10** in high yields (56-93%) with high 1,2-*syn*-diastereoselectivity (up to 94:6).

Scheme 2.4: Alkylation reactions of semicyclic *N,O*-acetals **2-8**.

The proposed origin of the stereochemistry is shown in Figure 2.1.³¹ For small alkoxy

groups at 3-position (OAc or OBn), transition state model **TS2-11** was proposed, with a hydrogen bond between the proton bound to the nitrogen atom and the 3-alkoxy group. A nucleophile would attack from the less sterically hindered side to form *syn*-product. In this case, the bulkier nucleophiles could lead to higher selectivity because of larger steric strain against the alkyl side chain. For bulky 3-alkoxy group (OTBDPS), transition state model **TS2-12** without hydrogen bonding was proposed. A nucleophile would attack from the opposite side of OTBDPS group to form *syn*-product. In this case, the smaller nucleophiles would lead to higher selectivity.

Figure 2.1: Assumed transition state models.

Hioki and co-workers³² reported intramolecular amidoalkylation to form *syn*-1,3-aminoalcohols (Scheme 2.5). The acyclic *N,O*-acetals **2-13** were reacted with various Lewis acids (SnCl₄, TiCl₄, BF₃·OEt₂) to yield *syn*-1,3-aminoalcohols **2-15** in high yield (77-95%) with excellent diastereoselectivity (up to 290:1). However, the intermolecular alkylation of analogues proceeded with low diastereoselectivity (*dr* = 1:1.1 to 2:1).

Scheme 2.5: Amidoalkylation of 3-siloxybutaniminium ions.

A possible transition state **2-16** is outlined in Figure 2.2. The Lewis acid coordinates with the oxygen of the ester group and oxygen of the siloxy group respectively. “The intramolecular attack of the allyl group to the iminium carbon from the side opposite to the methyl group (R^1 or R^2) leads to the excellent *syn*-selectivity.”³²

Figure 2.2: Possible transition state for *syn*-selectivity.

Hioki and co-workers³³ later studied the similar intramolecular amidoalkylation⁵ further. However, in this case, *anti*-1,2 or 1,3-aminoalcohols were obtained *via* the migration of a vinyl or a phenyl group from a siloxy group (Scheme 2.6). Treatment of acyclic *N,O*-acetals **2-17** with various Lewis acids afforded *anti*-1,2- and *anti*-1,3-aminoalcohols **2-20** with excellent diastereoselectivity (up to 1:300), *via* acyclic imines **2-18** or iminium ion intermediates **2-19**.

$R_1 = \text{Vinyl, Ph}; R_2 = \text{CH}_3, \text{Vinyl, Ph}$

LA : $\text{TiCl}_4, \text{SnCl}_4$ $n = 0$: Yield: 19-98%

$R_3 = \text{CH}_3, \text{Vinyl, Ph, } t\text{-Bu}; R_4 = \text{Bn, Et}$

$\text{BF}_3 \cdot \text{OEt}_2$

syn : *anti* = 1:17 -1:300

$X = \text{H, Bn}$

$n = 1$: Yield: 5-82%

syn : *anti* = 1:4.5 -1:140

Scheme 2.6: Amidoalkylation and migration of *N,O*-acetals **2-17**.

The possible transition states **TS2-21** and **TS2-22** can account for the *anti*-selectivity for 1,2 and 1,3-aminoalcohols respectively (Figure 2.3).³³ In order to reduce the steric hindrance between methyl group and *N*-Bn group, the five-membered ring **TS2-21** was preferred for 1,2-*anti*-aminoalcohols. **TS2-21** was also valid for phenyl migration. On the other hand, the chair like six-membered-ring **TS2-22** without “*gauche* interaction around C2 -C3 bond” was preferred for 1,3-*anti*-aminoalcohols.

Figure 2.3: Possible transition state for *syn*-selectivity.

A new kind of nucleophile, γ -oxygen substituted allylstannane **2-25** was explored by

Yamamoto and co-workers³⁴ in the alkylations of acyliminium ions **2-24** (Scheme 2.7). Treatment of acyclic *N,O*-acetals **2-23** with γ -oxygen substituted allyltin **2-25** in the presence of Lewis acids afforded the protected 1,2-*syn*-aminoalcohols **2-26** smoothly.

Scheme 2.7: Alkylations with γ -oxygen substituted allylstannane **2-25**.

Marshall and co-workers³⁵ reported an alkylation of γ -oxygen substituted allylstannanes, similar to Yamamoto's work³⁴ with semicyclic *N,O*-acetal **2-27** (Scheme 2.8). More detailed studies of the different allylic stannanes, including optically pure nucleophilic stannanes were also conducted. Racemic *Z*-allylic stannanes **2-28** were first treated with acyclic *N,O*-acetal **2-27** to provide protected 1,2-*syn*-aminoalcohols **2-29** with good diastereoselectivity (up to 86:14).

Scheme 2.8: Alkylation of *N,O*-acetals **2-27** with racemic allylic stannanes **2-28**.

The enantioenriched allylic stannanes **2-28** were then examined in this reaction (Scheme 2.9).³⁵ Allylic stannanes (*S*)-**2-28** were treated with various acyclic *N,O*-acetals **2-30** to provide optically active 1,2-*syn*-aminoalcohols **2-31** in good yields (65-91%), with excellent diastereoselectivity (up to 95:5).

Scheme 2.9: Alkylation of **2-30** with enantioenriched allylic stannanes (*S*)-**2-28**.

Quintard and co-workers³⁶ extended alkylations similar to Yamamoto's report³⁴ to other *N,O*-acetal substrates and other substituted allylic stannanes (Scheme 2.10). Acyclic *N,O*-acetals **2-32** were treated with racemic γ -oxygenated allyltins **2-33** (OTBS) in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to afford protected 1,2-*syn*-amino alcohols **2-34** with excellent diastereoselectivity (up to 100:0). The origin of the *syn*-stereochemistry was unclear.

Scheme 2.10: Alkylations with allylic stannanes **2-33**.

2.1.2. Summary

In summary, the alkylation of acyclic iminium ions, derived from semicyclic or acyclic *N,O*-acetals with various silicon-containing nucleophiles or allylic stannanes is an efficient method for the preparation of 1,2 or 1,3-amino alcohols. Both *syn* and *anti*-amino alcohols can be obtained with excellent diastereoselectivity.

2.1.3. Aim of present work

We became interested in this area following difficulties in generating a homoallylic secondary amine, in which one or more of the alkyl substituents were secondary. Several methods, such as reductive amination or amide reduction, would not have been suitable for our purpose as problems of alkene reduction or migration could be anticipated. It was believed that the alkylation of a cyclic *N,O*-acetal would directly deliver a homoallylic amine.

Therefore, the aim of present work is to devise a convenient methodology for the formation of cyclic *N,O*-acetals and study the alkylations of these cyclic *N,O*-acetals with allyltrimethylsilane in the presence of Lewis acids to form 1,2 or 1,3 amino alcohols, containing an allyl group (Scheme 2.11).

Scheme 2.11: Aim of present work.

2.2. Results and Discussion

2.2.1. The preparation of cyclic *N,O*-acetals

We began our study by investigating the preparation of cyclic *N,O*-acetals. Based on the reviews of literature reports,³⁷ cyclic *N,O*-acetals were usually synthesized under acidic conditions at high temperature (reflux in benzene or toluene) from amino alcohols and aldehydes. Most of the reports utilized PPTS, *p*TSA, CSA or acetic acid as Brønsted acid catalysts in their reactions. One method of preparation that caught our attention was the use of amberlyst-15. The exchange resin, amberlyst-15, as a catalyst, has an advantage over other catalysts. That is the simple workup by filtration, avoiding the need for any extraction. Thus, we employed amberlyst-15 as a Brønsted acid catalyst in our strategy. It was hoped that the acetalization with amberlyst-15 would proceed efficiently without any heating.

We employed protected amino alcohols **2-35a-f** bearing electron withdrawing groups (PG) as substrates for acetalizations, which were easily prepared under usual conditions.³⁸⁻⁴³ Thus, the acetalizations of protected amino alcohols **2-35a-f** were carried out with a range of aldehydes in the presence of amberlyst-15 and 4 Å molecular sieves in anhydrous dichloromethane at room temperature. 4 Å Molecular sieves made the reactions fast and drove them to completion by absorbing the water formed in the process. To our delight, the cyclic *N,O*-acetals **2-36a-l** were obtained in generally excellent yields after simple filtration and evaporation, and were used in the next step without further purification. The results are outlined in Table **2.1**.

Table 2.1: Preparation of six-membered cyclic *N,O*-acetals **2-36a-l**.^a

Entry	SM	R	PG	Product	Yield ^c
1	2-35a ³⁸	Me	Ts	2-36a	82
2	2-35a	Et	Ts	2-36b	99
3	2-35a	Ph	Ts	2-36c ⁴⁴	91
4 ^b	2-35a	H	Ts	2-36d ⁴⁵	94
5	2-35b ³⁹	Me	CO ₂ Me	2-36e ⁴⁶	85
6	2-35b	Et	CO ₂ Me	2-36f	87
7	2-35b	Ph	CO ₂ Me	2-36g	80
8	2-35b	<i>n</i> -C ₅ H ₁₁	CO ₂ Me	2-36h	76
9	2-35c ⁴⁰	Et	Alloc	2-36i	99
10	2-35d ⁴¹	Et	Cbz	2-36j	86
11	2-35e ⁴²	Et	Boc	2-36k	86
12	2-35f ⁴³	Et	Bz	2-36l	30 ^d

a: The reactions were carried out in anhydrous dichloromethane at r.t. for 2 h in the presence of amberlyst-15 and 4 Å molecular sieves; *b*: The reaction was stirred at r.t. overnight. *c*: The yield after filtration and evaporation. *d*: Isolated yield by column chromatography

As shown in Table **2.1**, the reaction conditions for cyclic *N,O*-acetals synthesis proved

to be compatible with almost all *N*-protecting groups employed: methoxycarbonyl (CO₂Me), tosyl (Ts), Cbz, Alloc and even Boc. This was surprising but gratifying, given the acid lability of the Boc group. However, when the *N*-benzoyl derivative was employed, only 30% of **2-36l** was obtained (entry 12).

The reaction conditions for acetalization also proved to be general for both aliphatic and aromatic aldehydes. Even paraformaldehyde led to the formation of the corresponding methylene acetal **2-36d** (entry 8), albeit at slower rate due to the insolubility of the polymeric paraformaldehyde in the reaction medium. In contrast, when the α,β -unsaturated aldehyde, crotonaldehyde was used, no acetal could be isolated. Only a low yield of an unstable acetal could be obtained using acetone.

Table 2.2: Preparation of five-membered *N,O*-acetals **2-38a-d**.^a

Entry	SM	R	PG	Product	Yield (%)
1	2-37a ⁴⁷	Me	Ts	2-38a	82
2	2-37a	Et	Ts	2-38b	99
3	2-37b ⁴⁸	Me	CO ₂ Me	2-38c	91
4	2-37b	Et	CO ₂ Me	2-38d	94

^a: The reactions were carried out in anhydrous dichloromethane at r.t. for 2 h in the presence of amberlyst-15 and 4 Å molecular sieves.

Next, we extended the optimum conditions to five-membered analogues **2-38a-d**. These reactions proceeded efficiently as well, yielding the *N,O*-acetals **2-38a-d** in generally excellent yields after simple filtration and evaporation (up to 99%).

Therefore, we explored a very convenient method for the syntheses of cyclic *N,O*-acetals, which were very easily handled at room temperature with simple workup process. With cyclic *N,O*-acetals in hand, we concentrated our attention on a systematic study of alkylations of cyclic *N,O*-acetals.

2.2.2. The alkylations of cyclic *N,O*-acetals

We began our studies by examining the effect of Lewis acids in alkylations, using six-membered *N,O*-acetal **2-36b** with an *N*-Ts group as the test substrate (Table 2.3). Alkylations of **2-36b** with allyltrimethylsilane were performed in the presence of Lewis acids in anhydrous dichloromethane. Among various Lewis acids tested, titanium tetrachloride (TiCl₄) was found to be most effective at -78 °C. The 1,3-amino alcohol **2-39b** was obtained in 99% yield after workup under basic conditions (entry 1). It was gratifying to find that the large excesses of Lewis acids and nucleophiles typically employed in the *O,O*-acetal chemistry²⁸ were unnecessary. As little as 1.2 equiv of TiCl₄ could be employed whilst still obtaining a good yield. Similar results (98% for **2-39b**) were also observed when tin tetrachloride (SnCl₄) was employed (entry 2). Meanwhile, the use of boron trifluoride etherate (BF₃·OEt₂) resulted in a mixture of 1,3-amino alcohol **2-39b** and acetal hydrolysis (entry 3). Similarly, when

trimethylsilyl triflate (TMSOTf) was employed, 30% of 1,3-amino alcohol **2-39b** was obtained, accompanied by acetal hydrolysis (entry 4). On the other hand, when indium trichloride (InCl_3) was used, none of product was obtained but the acetal hydrolysis was observed instead. In addition, the milder Lewis acids, titanium blend ($\text{Ti}(\text{Oi-Pr})_4/\text{TiCl}_4$), Cp_2TiCl_2 , $\text{Yb}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ and titanocene triflate reported by Bosnich⁴⁹, proved to be ineffective, with starting material recovered.

Table 2.3: Effect of Lewis acids.

2-36b $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Lewis acids, allylTMS}}$ **2-39b**

Entry	L.A.	Temperature (°C)	Time (h)	Yield (%)
1	TiCl_4	-78	0.5	99
2	SnCl_4	-78	0.5	98
3	$\text{BF}_3 \cdot \text{OEt}_2$	-78 to -20	18	33
4	TMSOTf	0	15	30

a: Reactions were carried out with acetal 1 eq. **2-36b**, 1.2 eq. allylTMS, 1.2eq. Lewis acid in CH_2Cl_2 .

With TiCl_4 as Lewis acid, different protecting groups (PG) on the nitrogen atom of the six-membered *N,O*-acetals were next investigated (Table 2.4). TiCl_4 -mediated alkylation of **2-36b** proceeded efficiently with allyltrimethylsilane at -78 °C, giving 1,3-amino alcohol **2-39b** quantitatively. These observations for *N*-tosyl protecting

group applied equally to *N*-methoxycarbonyl (CO₂Me) and *N*-alloc substrates, giving 1,3-amino alcohols **2-39f** and **2-39i** quantitatively (entries 2 and 3). However, the yields of **2-39j** and **2-39k** derived from the Cbz and Boc protected acetals were lower, but still within a useful range (entries 4 and 5). It is particularly notable that the *N*-Boc protecting group still survived a sequence of two acidic steps.

Table 2.4: Effect of protecting groups on nitrogen atom.

2-36b,f,i-k $\xrightarrow[\text{CH}_2\text{Cl}_2, -78\text{ }^\circ\text{C}, 0.5\text{ h}]{\text{TiCl}_4, \text{CH}_2=\text{CHSiMe}_3}$ **2-39b,f,i-k**

Entry	Acetals	PG	Products	Yield ^b (%)
1	2-36b	Ts	2-39b	99
2	2-36f	CO ₂ Me	2-39f	99
3	2-36i	Alloc	2-39i	98
4	2-36j	Cbz	2-39j	63 ^c
5	2-36k	Boc	2-39k	66 ^c

a: Reactions were carried out with acetal (1 eq.), allylTMS (1.2 eq.), Lewis acid (1.2eq.)

in dichloromethane at -78 °C for 0.5 h. *b*: Yield after normal work up. *c*: Isolated yield

The optimum conditions for alkylations, using titanium tetrachloride (TiCl₄) at low temperature (-78 °C) in anhydrous dichloromethane, proved to be clean and efficient for other *N,O*-acetals derived from aliphatic substrates (Table 2.5). 1,3-Amino

alcohols **2-39a,d,e,h** were obtained in high yields (up to 94%). The methylene acetal **2-36d** derived from paraformaldehyde also underwent efficient alkylation reaction (entry 2).

Table 2.5: Effect of substrates.^a

2-36a,d,e,h $\xrightarrow[\text{CH}_2\text{Cl}_2, -78\text{ }^\circ\text{C}, 0.5\text{ h}]{\text{TiCl}_4, \text{CH}_2=\text{CH-SiMe}_3}$ **2-39a,d,e,h**

Entry	SM	R	PG	Product	Yield ^b (%)
1	2-36a	Me	Ts	2-39a	82
2	2-36d	H	Ts	2-39d	94
3	2-36e	Me	CO ₂ Me	2-39e	85
4	2-36h	<i>n</i> -C ₅ H ₁₁	CO ₂ Me	2-39h	76 ^c

^a: Reactions were carried out with acetal (1 eq.), allylTMS (1.2 eq.), Lewis acid (1.2eq.) in dichloromethane at -78 °C for 0.5 h. ^b: Yield after normal work up. ^c: Isolated yield

On the other hand, alkylations of cyclic *N,O*-acetals **2-36c** and **2-36g** derived from benzaldehyde gave the homoallylic amines in lower yields, accompanied by by-products amino-ethers (Scheme 2.12). Alkylation of **2-36c** with allyltrimethylsilane in the presence of TiCl₄ in anhydrous dichloromethane at -78 °C led to a 2:1 mixture of **2-39c** and **2-39c'** in 48% yield after isolation by column chromatography. A 2:1 mixture of products **2-39g** and **2-39g'** was also obtained quantitatively under the same

conditions. The reason for this phenomenon is unclear, but maybe due to the additional stabilization of the iminium ion by the phenyl group lowering the energy difference between the alternative iminium and oxonium ion intermediates.

Scheme 2.12: Alkylations of *N,O*-acetals derived from aromatic substrates.

The above optimum conditions were then extended to the five-membered analogues **2-38a-d**. The results are outlined in Table 2.6. It was found that the optimum conditions for six-membered *N,O*-acetals applied equally to five-membered analogues, giving 1,2-amino alcohols **2-40a-d** in high yields (up to 92%).

Table 2.6: Alkylations of five-membered acetals **2-38a-d**.

Entry	SM	R	PG	Product	Yield
1	2-38a	Me	Ts	2-40a	92
2	2-38b	Et	Ts	2-40b	88
3	2-38c	Me	CO ₂ Me	2-40c	80
4	2-38d	Et	CO ₂ Me	2-40d	92

2.2.3. The stereochemistry of alkylations of substituted cyclic *N,O*-acetals

With the optimum conditions obtained, we then focused our attention on stereochemical outcome of the alkylations of cyclic *N,O*-acetals containing stereogenic centres. Four additional substrates **2-42a,b,c** and **2-44** were examined. The preparation of these four substrates is shown in Scheme 2.13. 1-Aminobutan-3-ol **2-41**⁵⁰ was prepared by reduction of the corresponding nitrile while 3-Aminobutan-1-ol **2-43**⁵¹ was prepared by Bouveault–Blanc reduction of ethyl 3-aminocrotonate. The protection of these amino alcohols was then carried out with tosyl chloride, allyl chloroformate and methyl chloroformate in the presence of triethylamine in anhydrous dichloromethane at room temperature to give the protected amino alcohols in high yields. The crude NMR spectra for these protected amino alcohols were clean after normal workup and they were used in the next step without further purification.

Scheme 2.13: *Reagent and Conditions:* (i) 1.2 eq. NEt₃, 1.0 eq. TsCl, ClCO₂Me or AllocCl, CH₂Cl₂, r.t., 6 h. **2-42a**, 90%; **2-42b**, 71%; **2-42c**, 72%; **2-44a**, 88%.

With the substituted substrates ready, we diverted our attention to the preparation of

cyclic *N,O*-acetals **2-45**. The amino alcohol derivatives **2-42** were treated with propionaldehyde, using the procedure we developed previously. With an *N*-tosyl group, cyclic *N,O*-acetals **2-45a** were obtained in 97% yield as a single diastereoisomer as judged from the ^1H NMR spectrum, which displayed a triplet at 5.49 ppm with a coupling constant of 7.4 Hz for the acetal proton. A 93:7 separable mixture of **2-45b** stereoisomers with an *N*-alloc protecting group on the nitrogen atom was also isolated in 76% yield after purification by column chromatography. In a similar way, a 9:1 separable mixture of **2-45c** stereoisomers with *N*-CO₂Me protecting group was obtained in 80% yield.

Table 2.7: Preparation of *N,O*-acetals **2-45a,b,c** possessing chirality.

Entry	SM	PG	Product1	Yield ^a (%)	Dr ^c (<i>trans</i> : <i>cis</i>)
1	2-42a	Ts	2-45a	97 ^b	100:0
2	2-42b	Alloc	2-45b	76	93:7
3	2-42c	CO ₂ Me	2-45c	80	90:10

a: Isolated yield. *b*: Yield after simple filtration and evaporation. *c*: Determined by ^1H NMR.

To our delight, a single crystal of **2-45a** was obtained from a mixture of dichloromethane and hexane, and the relative configurations of substituted *N,O*-acetal

2-45a was then determined by X-ray analysis. As shown in Figure 2.4, the ethyl substituent adjacent to the *N*-Ts moiety prefers an axial orientation and the methyl group prefers an equatorial orientation. The axial disposition of the ethyl group can be attributed to the bulk of the *N*-tosyl group. A similar axial preference for substituents near to an *N*-sulfonyl group has also been observed.⁵²

Figure 2.4: The X-ray structure of *trans*-isomer **2-45a**.

The alkylation was then tested using these two related methyl substituted six-membered ring *N,O*-acetals **2-45a,b** (Scheme 2.14). The reactions proceeded well as expected, giving the 1,3-amino alcohols in high yields (up to 87%). However, it was disappointing to find that the reaction proceeded with modest diastereoselectivity (*dr*: 2.3:1-1.7:1) as determined from the ¹H NMR spectrum. The two isomers were inseparable by column chromatography and we could not determine the stereochemistry. The low stereoselectivity may arise from the fact that the C5-methyl group is small and is located far away from the newly formed chiral center. Therefore, we concluded that these *N,O*-acetals have smaller impact on the stereoselectivity than

those *O,O*-acetals that possess two stereochemical centres, rather than the single chiral centre in this study.²⁸

Scheme 2.14: Alkylation of substituted cyclic *N,O*-acetals **2-45a,b**.

Using the optimum conditions, acetalization of substituted amino alcohol **2-44** proceeded well, giving the substituted cyclic *N,O*-acetals **2-47** as a single isomer in crude ¹H NMR spectrum. A triplet at 5.36 ppm with a coupling constant of 7.2 Hz was observed for the acetal proton. A single crystal of **2-47** was also obtained from a mixture of dichloromethane and hexane.

Scheme 2.15: The formation of substituted *N,O*-acetals **2-47**.

The X-ray analysis of **2-47** in Figure 2.5 illustrates that the ethyl substituent adjacent to the *N*-Ts moiety prefers an axial orientation in a similar way as acetal **2-45a**.⁵² It is interesting to note that the methyl group also prefers an axial orientation. Thus, the

substituents at C-2 and C-6 positions adopt a *cis*-orientation in a chair conformation with a 1,3-diaxial arrangement. In this case, the acetalization is identified to be *cis*-selective. This is again likely to be due to the bulk of the *N*-tosyl group.

Figure 2.5: The X-ray structure of substituted cyclic *N,O*-**2-47**.

The substituted cyclic *N,O*-acetal **2-47** was subjected to TiCl_4 -mediated alkylation. In a similar way as **2-45a,b**, an inseparable mixture of amino alcohols **2-48** was obtained in high yield (82%), but again, with modest diastereoselectivity ($dr = 1.8:1$) because of the small steric hindrance of C5-methyl group and far location from the newly formed chiral center.

Scheme 2.16: Alkylation of substituted cyclic *N,O*-acetals **2-47**.

2.3. Summary

In conclusion, we have successfully developed a convenient method for the preparation of cyclic *N,O*-acetals using amberlyst-15. The substituted cyclic *N,O*-acetals were also obtained with high diastereoselectivity. Moreover, the alkylations of cyclic *N,O*-acetals provided an efficient access to a wide range of protected homoallylic amines. The presence of stereogenic centers on the acetals did not, however, lead to efficient diastereoselective induction.

CHAPTER 3

FORMAL SYNTHESSES OF (-)-PORANTHERIDINE AND AN EPIMER

3.1. Introduction

Porantheridine, a tricyclic alkaloid, was first isolated from *Corymbosa porantherida*, a shrub native to New South Wales by Lamberton and co-workers in 1972.⁵³ Its absolute configuration in the form of the hydrobromide salt was found to be the structure of **3-1**, which was determined by X-ray diffraction (Figure **3.1**).⁵⁴ Four synthetic routes to this natural product have, to our knowledge, been reported.⁵⁵ Due to the challenging structural array, porantheridine makes an interesting target for further studies.

Figure 3.1: Absolute configuration of (-)-porantheridine **3-1**.

3.1.1. Previous total syntheses of (-)-porantheridine

The first stereoselective synthesis of racemic porantheridine **3-1** was reported by Gössinger and co-workers in 1980, starting from nitrone **3-2** (Scheme **3.1**).^{55a} The nitrone **3-2** was converted to nitrone **3-3** by addition of a Grignard reagent followed by oxidation with HgO, giving a 1:3 mixture of nitrones **3-3** and **3-4** with poor regioselectivity. The lack of regioselectivity was also observed in the synthesis of (±)-andrachamine reported by Carruthers and co-workers.⁵⁶ However, only the minor isomer **3-3** had the regiochemistry required for the synthesis of Porantheridine. To

achieve the synthesis of porantheridine, the minor isomer **3-3**, as a mixture of diastereoisomers, was subjected to 1,3-dipolar cycloaddition.

Scheme 3.1: Gössinger's total synthesis of ($\pm$)-porantheridine **3-1**.

The 1,3-dipolar cycloaddition of minor isomer **3-3** with pent-1-ene proceeded efficiently to afford isoxazolidine **3-5** as a mixture of diastereomers at the siloxy-bearing stereocenter (Scheme 3.2). The *N-O* bond was then cleaved by hydrogenation, affording the amino alcohol **3-6**. However, the configuration of the hydroxyl-bearing carbon did not match the stereochemistry of porantheridine. Thus, inversion of this stereocenter was achieved by Mitsunobu reaction, affording compound **3-7** in 65% yield. Removal of the TBS group was achieved by treatment with 10% HCl to afford another amino alcohol **3-8** in 91% yield. Finally, subsequent oxidation of the alcohol with Jones reagent and aminocyclization gave ($\pm$)-porantheridine **3-1** in 68% yield.

Scheme 3.2: Gössinger's total synthesis of (±)-porantheridine **3-1**.

The first enantioselective synthesis of (-)-porantheridine was reported by Comins and co-workers in 1993, starting from the chiral 1-acylpyridinium salt **3-9** (Scheme 3.3).^{55b} This strategy demonstrates the potential of metallo enolate addition to chiral 1-acylpyridinium salts⁵⁷ for the synthesis of piperidine rings. The pyridinium salt **3-9** was derived from 4-methoxy-3-(triisopropylsilyl)-pyridine and the chloroformate of (-)-8-phenylmenthol. It was found that the addition of zinc enolate **3-10** to chiral 1-acylpyridinium salts **3-9** proceeded well under steric approach control⁵⁸ to afford the dihydropyridone **3-11** in 89% yield with high diastereoselectivity (*de* = 92%). Stereoselective reduction with K-Selectride followed by removal of the chiral auxiliary afforded the hydroxydihydropyridone **3-12** in 89% yield with excellent diastereoselectivity (*de* > 96%). Compound **3-12** was then converted to bicyclic carbamate **3-13** in 84% yield using 1,1'-carbonyldiimidazole, followed by removal of

the TIPS group. Subsequent 1,4-addition proceeded well with Grignard reagent **3-14**, affording *trans*-**3-15** in 81% yield with high diastereoselectivity (*dr* = 90%) by axial attack. Two-step reductive deoxygenation of the ketone group of **3-15** provided the bicyclic piperidine **3-16** in 77% yield. After hydrolysis and deprotection of the acetal, the synthesis of (-)-porantheridine was accomplished in eight steps and 23% overall yield from pyridinium salt **3-9**.

Scheme 3.3: Comins's total synthesis of (-)-porantheridine **3-1**.

Lhommet and co-workers reported another stereoselective approach to (-)-porantheridine, derived from α -methoxy carbamate **3-17** (Scheme 3.4).^{55c} This strategy demonstrates the alkylation of α -methoxy carbamates *via* the corresponding

bicyclic *N*-acyl iminium ion intermediates. It was found that TMSOTf-mediated alkylation of α -methoxy carbamate **3-17** with silyl enol ether **3-18** proceeded efficiently with stereoelectronic control, yielding the 2,6-*trans*-disubstituted piperidine **3-19** exclusively. Removal of the ester group under basic conditions followed by reduction of the carbonyl group afforded the corresponding alcohols **3-20** and **3-21**. At this point, a range of reducing reagents were employed such as trialkylborohydride, NaBH₄, H₂/Raney-Ni, H₂/Pd-C, LiAlH(*t*-BuO)₃ and Red-Al. Trialkylborohydride (K-Selectride) or lithium triethylborohydride (Super-H) gave a 4:1 mixture of **3-20** and **3-21** in 90% yield as the best result.

Scheme 3.4: Lhommet's total synthesis of (-)-porantheridine **3-1**.

Benzyl protection of the hydroxyl group, hydrolysis and Cbz-protection of the nitrogen atom were then achieved, giving the alcohol **3-22** in 74% overall yield (Scheme 3.5). The alcohol was oxidized by Swern oxidation followed by Wittig reaction to afford alkene **3-23** in 85% overall yield. After tandem hydrogenation of the

double bond, *N*-Cbz group and *O*-Bn group, subsequent tandem ketal cleavage and aminocyclization afforded (-)-porantheridine in 47% overall yield. Hence, the asymmetric synthesis of (-)-porantheridine was accomplished in nine steps and 20% overall yield from α -methoxy carbamate **3-17**, readily available from L-lysine.

Scheme 3.5: Lhommet's total synthesis of (-)-porantheridine **3-1**.

Takahata and co-workers reported a novel synthetic route to (-)-porantheridine.^{55d,55e}

This strategy demonstrates aminocyclization and desymmetrization using iodocarbamation (Scheme 3.6). The aldehyde **3-24** was reacted with allylborane **3-25** to afford 1,5-diol **3-26** as a mixture of diastereoisomers in 74% yield, using a procedure reported by Brown and co-workers.⁵⁹ The diastereoselectivity was not confirmed at this point. Ditosylation followed by aminocyclization proceeded well to afford 2,6-*trans*-diallylpiperidine **3-27** in 61% overall yield, accompanied by 14% of meso-**3-27**. The benzyl-protecting group was then converted to a carbamate-protecting

group, giving compound **3-28** in 93% yield. To achieve monofunctionalization of the diallyl groups in **3-28**, hydroboration, dihydroxylation and Wacker oxidation were screened. However, they all resulted in a mixture of mono and difunctionalized products. Fortunately, the key step, intramolecular iodocarbamation was achieved by treatment with iodine, affording oxazolidinones **3-29** in 98% yield. The desymmetrization using iodocarbamation served to mask one alkene, thus allowing for selective oxidation of the other alkene

Scheme 3.6: Takahata's synthetic route to **3-29** via intramolecular iodocarbamation.

Treatment of oxazolidinones **3-29** with a three-step process (Sharpless asymmetric dihydroxylation (AD-mix- α), deprotection and *N*-carbamation) provided the diol **3-30** in 66% overall yield with modest diastereoselectivity (*dr* = 3:1) (Scheme 3.7). A sequential reaction of cyclic stannoxanation, primary alcohol tosylation and epoxidation proceeded well to give epoxide **3-31** in 92% overall yield. The ring-opening of epoxide **3-31** with a Grignard reagent in the presence of CuBr-SMe₂

provided the alcohol **3-32** in 76% yield. Oxidative cleavage with OsO₄, Wittig reaction and hydrogenation with Pd(OH)₂ afforded the keto alcohol **3-34** in 79% overall yield. The subsequent reaction with *n*-PrSLi followed by acetalization proceeded well, affording Comin's^{55b} synthetic intermediate **3-16** in 90% overall yield. Hence, Takahata and co-workers accomplished the formal synthesis of (-)-Porantheridine in 17 steps and 13% overall yield.

Scheme 3.7: Takahata's synthetic route to (-)-porantheridine **3-1**.

3.1.2. Aim of present work

This work focused on a novel synthetic route to (-)-porantheridine by employing the allenic cyclization to form a *cis*-isoxazolidine intermediate and the alkylation of

N-acyliminium ion intermediate to form a piperidine ring.

Following the retrosynthetic analysis outlined in Scheme 3.8, (-)-porantheridine **3-1** could be considered to arise from a tandem deprotection and intramolecular cyclization of piperidine **3-35**.^{55b,55c} Based on the summary in Chapter 1, a reasonable disconnection of bicyclic *N,O*-acetal **3-37** would lead to a 2,6-disubstituted-piperidine **3-36** by alkylation of allylsilane to an iminium ion intermediate. This disconnection reveals the relationship between porantheridine and the sedum alkaloids, although they come from different plant families. We decided to employ the intermediate, isoxazolidine **3-38** to introduce the amino alcohol moiety by the key allenic cyclization of **3-39**, which could be prepared from epichlorohydrin **3-40**. A similar cyclization was employed in the synthesis of sedamine⁶⁰ in our lab.

Scheme 3.8: Retrosynthetic analysis for the synthesis of (-)-porantheridine.

3.2. Results and Discussion

3.2.1. The first approach to (-)- porantheridine

The initial explorations in our strategy started from the synthesis of the key intermediate, isoxazolidine **3-38**, using the strategy explored for sedamine synthesis⁶⁰ in our lab. It began using commercially available (*S*)-epichlorohydrin **3-40** (Scheme **3.9**). Ring-opening with a Grignard reagent (EtMgBr) in the presence of copper (I) catalyst proceeded well, giving the alcohol **3-41** in 94% yield, using a procedure reported by Blechert and co-workers.⁶¹ Only one product arising from attack at the less hindered carbon of (*S*)-epichlorohydrin **3-40** was observed in the ¹H NMR spectrum, in which only one multiplet was observed at 3.78-3.75 ppm for the H-2 proton. Ring-closing of alcohol **3-41** under basic conditions (NaOH) in diethyl ether gave (*S*)-pentene oxide **3-42** as a colorless oil after purification by distillation.

The ring-opening of compound **3-42** with commercially available lithium acetylide-ethylenediamine complex in anhydrous DMSO led to terminal acetylene **3-43** in 80% yield, using a procedure reported by Voss and co-workers.⁶² The crude product was purified by distillation, which had to be carried out carefully due to the high volatility of **3-43**. In a similar way, only one ring-opening product arising from attack at less steric hindered carbon was obtained. The ¹H NMR spectrum displayed a doublet of doublet of doublets at 2.43 ppm with coupling constants of 16.7, 4.7, 2.7 Hz for one propargylic proton. Accordingly, a doublet of doublet of doublets at 2.31 ppm

with coupling constants of 16.7, 6.8, 2.7 Hz was characteristic of the other propargylic proton. We then focused our attention on the allenic cyclization of acetylene **3-43**.

Scheme 3.9: *Reagents and conditions:* (i) EtMgBr, CuCN, -78 °C to -20 °C, THF, 3 h, 94%; (ii) NaOH, Et₂O, r.t., 24 h, quant.; (iii) Lithium acetylide-EDA complex, DMSO, r.t., overnight, 80%.

“Allenes are three-carbon functional groups bearing a 1,2-diene moiety and they also act as potential precursors in organic synthesis for their unique reaction behavior, where the reactivity is spread over three contiguous carbon atoms.”⁶³ In particular, transition metal based intramolecular cyclization of allenes to functionalized heterocycles attracted our attention, which provided an efficient route to amino alcohol moieties (Scheme **3.10**).²⁷ We intended to apply the allenic cyclization to our strategy for porantheridine. To our knowledge, a variety of methods have been developed for the synthesis of allene functional groups,⁶⁴ including homologation from the terminal acetylenes,⁶⁵ Wittig type reactions,⁶⁶ and ortho ester-Claisen rearrangements.⁶⁷ Based on the sedamine synthesis⁸, we intended to employ the Searles-Crabbé homologation to synthesize allene derivative from terminal acetylene.

Scheme 3.10: Transition metal based allenic cyclization.

In this work, the transformation of terminal acetylene **3-43** was achieved efficiently through Searles-Crabbé homologation, affording the allenic alcohol **3-44** in 67% yield after purification by distillation under reduced pressure (Scheme 3.11). Due to its low boiling point, some allenic alcohol was lost in the process of removing 1,4-dioxane. In practice, it was not necessary for the allene to be rigorously purified because small amounts of 1,4-dioxane did not affect the following step. The ^1H NMR displayed two special peaks for the allene functional group. One triplet of triplets (apparent quintet) was observed at 5.10 ppm with coupling constant of 7.0 Hz for one proximal proton of allene. Another doublet of triplets was observed at 4.67 ppm with coupling constants of 7.0, 2.8 Hz for the two terminal protons of allene. The ^{13}C NMR spectrum also provided evidence for the allene moiety with a peak at 209.3 ppm. The IR spectrum of allenic alcohol **3-44** exhibited a special peak at 1956 cm^{-1} , which is the allene stretching vibration.

Scheme 3.11: *Reagents and conditions:* (i) $(\text{CH}_2\text{O})_n$, $i\text{-Pr}_2\text{NH}$, CuBr, 1,4-dioxane, reflux, overnight, 67%.

In order to obtain the *N*-heterocycle, the allenic alcohol **3-44** was intended to be converted to allenic hydroxylamine **3-45** by the Mitsunobu reaction.⁶⁸ The Mitsunobu reaction allows the conversion of primary and secondary alcohols to a variety of functional groups with the stereochemistry inverted.⁶⁹ A range of nucleophiles can be

employed such as carboxylic acids, hydrazoic acids, imides, phenols, phthalimide and *N*-hydroxyphthalimide.

In our strategy we chose *N*-hydroxyphthalimide (HONPhth) as the nucleophile⁶⁰. Hence, the allenic alcohol **3-44** was treated with *N*-hydroxyphthalimide (HONPhth) in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to afford the *N*-phthaloyl hydroxylamine **3-45** in 80% yield with excellent enantioselectivity (Scheme 3.12). The enantiomeric excess of compound **3-45** was determined to be 99% by chiral HPLC analysis (appendix A.2). The ¹H NMR displayed multiplet peaks at 7.90-7.71 ppm for the aromatic ring of the phthalimide moiety. The ¹³C NMR spectrum displayed a peak at 164.2 ppm, which was assigned to the carbonyl group of the phthalimide moiety. Cleavage of the phthaloyl group of **3-45** was carried out with hydrazine hydrate in dichloromethane. The reaction was complete in 15 minutes, giving the free hydroxylamine **3-46** quantitatively after simple filtration and evaporation. The aromatic ring protons were not observed in the NMR spectra. Characterization by ¹H NMR showed a broad singlet at 5.23 ppm for NH₂ group. The IR spectrum also exhibited a sharp peak at 3316 cm⁻¹ for N-H stretching bond.

Scheme 3.12: Reagents and conditions: (i) HONPhth, PPh₃, DIAD, THF, -15 °C, 1 h, 80%; (ii) H₂NNH₂·H₂O, CH₂Cl₂, r.t., 15 min, quant..

With hydroxylamine **3-46** in hand, we then diverted our attention to accomplish the synthesis of the isoxazolidines **3-38** by allenic cyclization. As discussed in Chapter one, allenic cyclization is a useful approach to highly functionalized heterocycles with high diastereoselectivity. Three principal mechanisms have been put forward.²⁷ One of them is shown in Scheme 3.13. Metal catalysts would coordinate with one of the allene double bonds to form the complexes I or II, generating an allylic cation transition state III for allene activation. The nucleophilic addition (X) would then give rise to the complex IV, which would undergo protodemetalation, generating product and regenerating catalyst (M^{n+}) for recycle.

Scheme 3.13: Possible mechanism for allenic cyclization.

Previous investigations in our lab have resulted in a highly diastereoselective allenic cyclization, which was utilized for the synthesis of sedamine.⁶⁰ The results are shown in Table **3.1**. The allenic cyclization of hydroxylamines **3-47** was carried out with 10-20 mol% of silver nitrate and tetramethylguanidine (TMG, 5-10%) in wet acetone in the absence of light. In the first attempt, using the free hydroxylamine **3-47a**, none of the desired product was observed in the ^1H NMR spectrum with the starting

material being recovered (entry 1). Later on, further attempts were carried out by introducing different protecting groups (Boc, Cbz and *o*-Ns) to the nitrogen atom. Among the *N*-protecting groups employed, *N*-Boc protected hydroxylamine **3-47b** was found to be most efficient due to the large steric hindrance, giving the isoxazolidines **3-48b** in 98% yield as a 7:1 inseparable mixture (entry 2). The stereochemistry was proved to be *cis* in all cases by NOE experiments. Therefore, we chose the bulky *N*-Boc protecting group for the free hydroxylamine **3-46** in our approach to porantheridine.

Table 3.1: Previous work for allenic cyclization in our lab.

Entry	Allene	PG	R	Yield ^c (%)	Dr ^d (<i>cis</i> : <i>trans</i>)
1	3-47a	H	Ph	0 (3-48a)	-
2	3-47b	Boc	Ph	98 (3-48b)	7.0:1
3	3-47c	Cbz	Ph	93 (3-48c)	5.0:1
4	3-47d	<i>o</i> -Ns	Ph	0 (3-48d)	-
5	3-47e	Boc	Me	83 (3-48e)	4.0:1

N-Boc protection of free hydroxylamine **3-46** was then carried out with di-*tert*-butyl dicarbonate ((Boc)₂O) under basic conditions (NaOH) to afford the product **3-39** in 98% yield after purification by column chromatography (Scheme **3.14**). The ¹H NMR

spectrum displayed a broad singlet at 7.12 ppm for NH group. A singlet was observed at 1.45 ppm, which was assigned as the protons of *N*-Boc group. The ^{13}C NMR spectrum provided the proof for the *N*-Boc group with peaks at 157.1 and 28.1 ppm.

Scheme 3.14: *Reagents and conditions:* (i) NaOH, (Boc) $_2$ O, CH $_2$ Cl $_2$ -H $_2$ O (v/v 1:1), r.t., overnight, 98%.

The next step was to convert the *N*-Boc protected hydroxylamine **3-39** to isoxazolidines **3-38** by using allenic cyclization. Based on the above work in our lab, we began our initial investigation using silver nitrate as metal catalyst. We studied the influence of the metal loading of silver nitrate. As shown in Table **3.2**, treatment of allene **3-39** with 5 mol% of silver nitrate resulted in an incomplete reaction by crude ^1H NMR analysis (entry 1). Our attempts to purify the crude reaction mixture by flash column chromatography failed as there is no difference in the R_f value of starting material and product. As a result, the diastereomeric ratio of products could not be determined due to the complex ^1H NMR spectrum. To achieve complete conversion, 10 mol% of silver nitrate and 5 mol% TMG were employed, and to our delight, isoxazolidines **3-38** were obtained in 93% yield (entry 2). Although the products were inseparable by column chromatography, the corresponding peaks were clearly identifiable in the crude ^1H NMR spectrum in which the diastereomeric ratio was determined to be 4.8:1 by integrating the double bond proton peaks. Next, we

investigated the minimum amount of silver nitrate required to achieve higher diastereoselectivity of isoxazolidines. Therefore, a set of reactions involving different metal loading from 10 mol% to 60 mol% was carried out (entries 2-5). The results showed that diastereoselectivity just changed slightly from 4.6:1 to 5.1:1. Due to the inseparability, the configuration of isoxazolidines **3-38** was not determined at this point. The major isomer was presumed, on the basis of our previous results⁶, to be the *cis* isomer. It was hoped that we would be able to determine the stereochemistry in the following few steps.

Table 3.2: Allenic cyclization of Hydroxylamine **3-39**.^a

Entry	Catalyst ^b	Loading (mol%)	Yield ^c (%)	Dr ^e (<i>cis</i> : <i>trans</i>)
1	AgNO ₃ , TMG	5, 2.5	30 ^d	ND
2	AgNO ₃ , TMG	10, 5	93	4.8:1
3	AgNO ₃ , TMG	20, 10	97	5.1:1
4	AgNO ₃ , TMG	40, 20	99	5.0:1
5	AgNO ₃ , TMG	60, 30	99	4.6:1

a: The reaction was carried out in wet acetone (acetone : water is 5:1, v/v); *b*: The metal loading of TMG is half that of AgNO₃; *c*: Isolated yield; *d*: Determined by ¹H NMR.

To our knowledge, a range of catalysts can be involved in transition metal based

cycloisomerisation of allenes such as silver, gold, palladium, or lanthanides.²⁷ We attempted to improve the diastereoselectivity of the allenic cyclization further, by using gold⁷⁰ and other silver⁷¹ catalysts, which are available in our lab (Table 3.2). Treatment of compound **3-39** with 5 mol% of gold(III) chloride in the presence of calcium carbonate resulted in isoxazolidine *cis*-**3-38** with modest diastereoselectivity (*dr* = 4.0:1), using a procedure reported by Dewey⁷² in our lab (entry 1). Gold(I) triflate complex⁷³ was also employed in this transformation, giving the product *cis*-**3-38** in 86% yield and low diastereoselectivity (*dr* = 2.6:1) (entry 2). The allenic cyclization using a gold(I) catalyst was less selective than using the gold(III) catalyst, probably due to the lesser steric demand of the linear gold(I).

Treatment of hydroxylamine **3-39** with silver(I) triflate in anhydrous dichloromethane also proceeded with modest diastereoselectivity (*dr* = 4.0:1 - 4.6:1) (entries 3 and 4). To our delight, a substantially improved diastereoselectivity (up to 11.5:1) was observed when silver(I) tetrafluoroborate in anhydrous dichloromethane was employed (entries 5-8). To our surprise, a dependence on silver loading was observed. The diastereoselectivity was increased with the decrease of silver loading from 60 mol% to 10 mol%.⁷⁴ However, a much lower loading of silver(I) tetrafluoroborate (5 mol%) resulted in an incomplete reaction (entry 9). The diastereoselectivity was not determined in this case, due to the inseparability of product and starting material. Thus, the optimum conditions proved to be the use of silver(I) tetrafluoroborate at a loading of 10 mol% to afford an inseparable mixture of diastereoisomers in high selectivity (*dr* = 11.5:1) (entry 8). The desired isoxazolidine was identifiable from the ¹H NMR

spectrum (appendix A.3). A doublet of doublet of doublets was observed at 5.82 ppm with coupling constants of 17.0, 10.0, 6.8 Hz, and another two doublets were observed at 5.21 and 5.06 ppm with coupling constants of 17.0 and 10.0 Hz respectively. These three peaks were characteristic of the double bond formed by allenic cyclization.

Table 3.3: Allenic cyclization of Hydroxylamine **3-39**.^a

Entry	Catalyst	Metal loading (mol%)	Yield ^c (%)	Dr ^d (<i>cis</i> : <i>trans</i>)
1	AuCl ₃ , CaCO ₃ , CH ₂ Cl ₂ , CH ₃ CN ^b	5	76	4.0:1
2	Ph ₃ PAuCl, AgOTf	10, 10	86	2.6:1
3	AgOTf	20	99	4.0:1
4	AgOTf	10	95	4.6:1
5	AgBF ₄	60	99	4.6:1
6	AgBF ₄	40	99	4.0:1
7	AgBF ₄	20	99	9.0:1
8	AgBF ₄	10	94	11.5:1
9	AgBF ₄	5	25	ND

a: The reactions were carried out in anhydrous dichloromethane; *b*: Concentration of acetonitrile in dichloromethane: 0.165M; *c*: Isolated yield; *d*: Determined by ¹H NMR.

Based on Gallagher's report,⁷⁵ we can propose a possible mechanism to account for *cis*-selectivity in our strategy. As shown in Scheme 3.14, the two transition states **3-49A** and **3-49B** can exist in solution. However, the 1,3-interaction exists between the C-3 residue and C-5 developing alkenyl function in transition state **3-49A** while the 1,3-interaction also exists between the C-3 residue and the *N*-Boc group in transition state **3-49B**. Given the large 1,3-interaction in transition state **3-49B** because of the bulky *N*-Boc group, transition state **3-49A** is much more stable. Thus, the minimization of adjacent 1,3-interactions led to the *cis*-3,5-disubstituted isoxazolidine **3-38**. However, the proposed mechanism cannot account for the increased diastereoselectivity with the decrease of metal loading of silver catalyst. The reason for this phenomenon is unclear. It is possible that a second less stereoselective mechanism operates that requires two or more silver ions, but further experiments are required for establishing this.

Scheme 3.14: Proposed mechanism for *cis*-selectivity of allenic cyclization.

With the easily available key intermediate **3-38** in hand, we progressed toward the

total synthesis of (-)-porantheridine **3-1**. Isoxazolidines are good precursors to 1,3-amino alcohols by cleavage of the *N,O*-bond. If the *N,O*-bonds in isoxazolidines **3-38** could be cleaved, an amino alcohol moiety of porantheridine would be obtained. A variety of methods have been developed for the reductive cleavage of isoxazolidines (*N,O*-bond), including catalytic hydrogenation over Raney-Ni,⁷⁶ reduction by Zn in acetic acid⁷⁷ and Na(Hg) amalgam in ethanol,⁷⁸ that all allow access to chiral amino alcohols. In particular, Cicchi and co-workers^{79a} first employed a mild and efficient method to cleave the *N-O* bond, using a combination of molybdenum hexacarbonyl [Mo(CO)₆] and sodium borohydride in wet acetonitrile.⁷⁹ Given that the isoxazolidines **3-38** contained a double bond, we planned to employ the reductive cleavage reported by Cicchi^{79a} in our strategy (Scheme **3.15**). This reaction proceeded well, affording the amino alcohols **3-50** in 85% yield. It could also be carried out with molybdenum hexacarbonyl only, but the reaction required longer reaction time and a slightly lower yield (80%) was obtained. NaBH₄ was used to reduce the formed Mo(II) to Mo(0) in the catalytic cycle. At this point, the two diastereoisomers **3-50** could be separated by column chromatography but the configurations still could not be determined. The major isomer **3-50** was directly subjected to next step.

Considering that one double bond of the original allene still remained, it was intended to employ cross-metathesis⁸⁰ to introduce one aldehyde or acetal for intramolecular acetalization. The cross-metathesis was then carried out with 1,1-diethoxybut-4-ene **3-51** in the presence of 5 mol% second generation Grubbs catalyst in refluxing dichloromethane to yield a 8:1 mixture of *E*-**3-52** and *Z*-**3-52** in 84% yield (Scheme

3.15). We utilized the procedure reported by Mayr and co-workers to synthesize the alkene **3-51**.⁸¹ Triethyl orthoformate was reacted with allyl trimethylsilane under Lewis acidic conditions (SnCl_4), affording the alkene **3-51** in 43% yield after isolation by careful distillation under reduced pressure (10 mmHg, 40 °C). The two isomers of **3-52** could be separated by column chromatography. The coupling constant of the two protons of double bond in *E*-**3-52** was about 15.6 Hz whereas the coupling constant of the two protons of double bond in *Z*-**3-52** was about 10.0 Hz. Actually, the two isomers need not be separated, and the mixture was subjected to the next hydrogenation.

Scheme 3.15: Reagents and conditions: (i) Mo(CO)_6 , NaBH_4 , $\text{CH}_3\text{CN-H}_2\text{O}$ (v/v, 7:1), reflux, overnight, 85%; (ii) 5 mol% Grubbs II, CH_2Cl_2 , reflux, overnight, 84%.

With both the amino alcohol and *O,O*-acetal functional groups in compounds **3-52**, we attempted to prepare the target cyclic *N,O*-acetal **3-37** by using intramolecular acetalization. The synthesis of cyclic *N,O*-acetal **3-37** is outlined in Scheme 3.16. Hydrogenation using palladium on carbon at atmospheric pressure was very efficient, affording acyclic acetal **3-53** in 95% yield after simple filtration and evaporation. The

^1H NMR spectrum displayed a triplet at 4.46 ppm with the coupling constant of 5.6 Hz for acetal proton and the ^{13}C NMR spectrum also displayed a distinctive peak at 102.2 ppm for the acetal carbon.

The intramolecular acetalization was then achieved by the treatment of **3-53** with PPTS catalyst in the presence of 4Å molecular sieves, giving the bicyclic *N,O*-acetal **3-37** in 69% yield (Scheme 3.16). The tetrahydropyridine **3-54** was also formed in 8% yield, along with recovery of starting material **3-53** in about 10% yield. To achieve complete conversion, a stronger acid (such as amberlyst-15) was employed. However, it resulted in lower yield (< 50%), due to the competing removal of the *N*-Boc group. On the other hand, use of higher temperatures (dichloromethane at reflux, toluene at reflux) resulted in increased proportions of by-product **3-54** (about 15%). Due to the restricted rotation of the *N*-C=O bond (*N*-Boc), the ^1H NMR and ^{13}C NMR spectra displayed doublets for all of the peaks. However, the disappearance of both the NH group and OEt groups in NMR spectra was clearly apparent. The disappearance of O-H and N-H stretches was also observed from the IR spectrum.

Scheme 3.16: *Reagents and conditions:* (i) 1 atm, H_2 , Pd/C, MeOH, r.t., 95%; (ii) PPTS, CH_2Cl_2 , r.t., 69%.

Based on the summary in Chapter 1, the cyclic *N,O*-acetal **3-37** was expected to be a precursor to the reactive iminium ion, which was a key intermediate in our strategy to introduce the 2,6-disubstituted piperidine. Thus, the stereoselective alkylation of bicyclic *N,O*-acetal **3-37** was carried out with allyltrimethylsilane in the presence of titanium tetrachloride (TiCl₄) at -78 °C in anhydrous dichloromethane. (Scheme **3.17**) An inseparable mixture of piperidines **3-36** was isolated in 64% yield, *via* iminium ion intermediate **3-55**. A small amount of starting material **3-53** was recovered (<15% yield), accompanied by the decomposition of the substrate. To achieve complete conversion, other Lewis acids such as boron trifluoride (BF₃·OEt₂) and trimethylsilyl triflate (TMSOTf) were also screened in this reaction. However, they resulted in low yields of product (about 20%), with a high proportion of decomposition side products. As is often the case, the ¹H NMR spectrum of the piperidine **3-36** showed broadening due to the restricted rotation of the N-C=O bond again. As the two isomers were also inseparable by column chromatography, the stereochemistry could not be thoroughly determined at this stage. However, the desired piperidines still could be identifiable from ¹H NMR spectrum. A multiplet was observed at 5.78-5.66 ppm and another multiplet was observed at 5.07-5.00 ppm. They were characteristic of the double bond newly introduced by alkylation. The ¹³C NMR spectrum displayed two peaks at 136.2 and 116.8 ppm, also assigned for the double bond.

To determine the stereochemistry, we attempted to convert the piperidines **3-36** into the bicyclic carbamates **3-56**, which were expected to show well resolved NMR spectra. This cyclization was then achieved by treatment with potassium *tert*-butoxide

in anhydrous THF, giving the bicyclic carbamates **3-56** quantitatively. Sufficient partial (but not complete) separation of the two isomers **3-56** could be achieved and sharp NMR spectra could be obtained. The diastereomeric ratio was found to be 9:1 from the crude ^1H NMR spectrum of the mixture (appendix A.3). In order to determine the stereochemistry of **3-56**, COSY and NOESY experiments were carried out (appendix A.3).

Scheme 3.17: Reagents and conditions: (i) TiCl₄, allylTMS, CH₂Cl₂, -78 °C, 64%; (ii) KO*t*-Bu, THF, 0 °C to r.t., quant.

The ^1H NMR spectrum displayed a multiplet at 5.83-5.73 ppm for internal alkene proton. Two doublets at 5.09 and 5.04 ppm with coupling constants of 17.2 and 9.6 Hz respectively were assigned as terminal alkene protons. The COSY spectrum allowed assignment of a doublet of triplets at 2.80 ppm and another doublet of triplets at 2.18 ppm as the allylic protons (H-a and H-b), due to the cross peaks with the alkene protons. The COSY spectrum also assigned a multiplet at 3.77 ppm for the H-8 proton

due to the cross peak between H-8 and allylic protons. As shown in the NOESY spectrum (Figure 3.2), the major isomer **3-56** was identified to be the undesired *cis*-isomer from the NOE correlation between H-8 and H-4, and the absence of an NOE correlation between H-4 and the allyl side chain. On the other hand, an NOE correlation was also observed between H-4 and H-3, which confirmed that the allenic cyclization of compound **3-48** was the *cis*-selective (Table 3.2 and 3.3). The minor isomer **3-56** was proved to be the desired *trans*-isomer **3-56** later.

Figure 3.2: NOESY spectrum of compound *cis*-**3-56**.

Based on the work of Hootelé¹³ and Speckamp,²⁰ a possible mechanism for the formation of the 2,6-*cis*-disubstituted piperidine derivative is shown in Scheme 3.18. Two conformations of the iminium ion **3-57A** and **3-57B** can exist in solution. Due to the strong interaction between the C-6 side chain and the *N*-Boc group in conformer **3-57B**, conformer **3-57A** with the existing side chain axial is preferred. If the nucleophile attacks from the top face of conformer **3-57A**, an equatorial approach will be adopted through a boat-like transition state, which is disfavored. Thus, the nucleophile only can adopt an axial approach by attacking from the bottom face of conformer **3-57A** via a chair-like transition state. Therefore, the preferred axial attack of allyltrimethylsilane to the conformer **3-57A** leads to the *cis*-major product whereas axial attack of allyltrimethylsilane to conformer **3-57B** leads to *trans*-minor product.

Scheme 3.18: Proposed mechanism of monocyclic iminium ion for *cis*-selectivity.

Nevertheless, the 2,6-*cis*-disubstituted-piperidine **3-36**, as a 9:1 mixture, was taken through to *epi*-porantheridine **3-59** by a simple sequence of reactions (Scheme 3.19).

Cross-metathesis⁸⁰ of piperidines **3-36** was carried out with (*E*)-pent-3-en-2-one⁸² in the presence of Grubbs II catalyst in refluxing dichloromethane, affording the unsaturated ketone **3-56** exclusively as *E*-isomer in 80% yield. The *E*-configuration was clearly identified from the ¹H NMR spectrum with the coupling constant of 15.8 Hz for the two protons of double bond. The two diastereoisomers (epimeric at C-6) still could not be separated at this point and were just used in next step. The hydrogenation of alkenes **3-58** over palladium on carbon at atmospheric pressure proceeded well, providing the saturated ketone **3-35** in 85% yield. To our delight, the two diastereoisomers could be separated and the diastereoisomeric ratio was found to be 9:1 after isolation by column chromatography, which is consistent with the ratio observed from the ¹H NMR of **3-56** (see above). The ¹H NMR spectrum of *cis*-isomer **3-35** displayed a singlet at 2.12 ppm for the methyl group connected to ketone. The ¹³C NMR spectrum displayed a peak at 208.6 ppm for the ketone functional group.

Scheme 3.19: Reagents and conditions: (i) 5 mol% Grubbs II, CH₂Cl₂, reflux, overnight, 80%. (ii) H₂, 1 atm, Pd/C, MeOH, r.t., 85%.

Considering *epi*-porantheridine as a tricyclic *N,O*-acetal, it was envisaged that a tandem deprotection and intramolecular cyclization would provide our target molecule (Scheme 3.20). It was found that use of trifluoroacetic acid resulted in the deprotection of *N*-Boc group efficiently and subsequent neutralization with saturated NaHCO_3 completed the synthesis of *epi*-porantheridine **3-59** in 90% yield. Only one isomer was observed in the crude ^1H NMR spectrum because of the nature of the fused rings. When six-membered rings fuse together, the *trans*-ring fusion is usually favored as it gives the most stable conformation of product. The ^1H NMR spectrum displayed a multiplet at 3.79-3.76 ppm for H-2 proton. Two multiplets at 2.50-2.47 ppm and 2.15-2.10 ppm were assigned as H-3 and H-6 protons. A singlet at 1.32 ppm was characteristic of the methyl group at C-9 position.

Scheme 3.20: Reagents and conditions: (i) TFA, CH_2Cl_2 , 0 °C to r.t., 90%.

In summary, we have completed the synthesis of the *epi*-porantheridine in 16 steps and 7% overall yield with high diastereoselectivity, by using the key allenic cyclization and alkylation of iminium ion chemistry. To achieve the synthesis of (-)-porantheridine, it was necessary to rethink the synthetic strategy.

3.2.2. The second approach to (-)-porantheridine

To achieve the synthesis of the natural product **3-1**, it was necessary to ensure that the key iminium ion intermediate **3-60** should adopt a conformation with the side chain equatorial so that the alkylation of the iminium ion would give the correct *trans*-selectivity (Scheme 3.21). We anticipated that linking of the side chain and the *N*-protecting group, for instance, by the formation of a cyclic carbamate as in Lhommet's report,²⁶ would lead to *trans*-selectivity *via* bicyclic iminium ion intermediate **3-61**. Thus, we began to modify our strategy to achieve the synthesis of (-)-porantheridine, starting from the amino alcohol derivative **3-35**.

Scheme 3.21: Origin of modified synthetic approach.

The amino alcohol derivative **3-35** was treated with potassium *tert*-butoxide in anhydrous THF, providing the cyclic carbamate **3-62** in 93% yield (Scheme 3.22). The ¹H NMR spectrum displayed a sharp triplet of doublet of doublets at 4.22 ppm with

coupling constants of 9.8, 5.0, 2.8 Hz for H-6. A singlet at 5.49 ppm was assigned as the proton of N-H group, which shifted to lower field compared to the starting material, due to the electronic effect of the carbamate moiety. The acetalization of the cyclic carbamate **3-62** proceeded well by the treatment with *p*TSA in ethanol, affording the semicyclic *N,O*-acetal **3-63** in 91% yield. Only a single isomer was observed in the crude ^1H NMR spectrum. One ethoxy group was missing from the ^1H NMR spectrum. The *N,O*-acetal proton was observed at 5.71 ppm, shifting to lower field compared to *O,O*-acetal. The stereochemistry at the acetal center was not determined, but it was predicted to be axial due to the anomeric effect. Based on the review in Chapter one, the semicyclic *N,O*-acetal **3-63** would act as a useful precursor to a bicyclic iminium ion intermediate. Therefore, the stereochemistry at the acetal center would not affect the following iminium ion chemistry.

Scheme 3.22: Reagents and conditions: (i) KO^t-Bu, THF, 0 °C to RT, 93%; (ii) *p*TSA, EtOH, RT, 91%.

The alkylation of *N,O*-acetal **3-63** proceeded smoothly by treatment with

allyltrimethylsilane in the presence of titanium tetrachloride in anhydrous dichloromethane at -78°C , affording the piperidine **3-56** in 89% yield, *via* iminium ion intermediate **3-64** (Scheme 3.23). Only single isomer was observed in the crude ^1H NMR spectra (appendix A.3). To determine the stereochemistry of single isomer **3-56**, COSY and NOESY experiments were carried out (appendix A.3).

Scheme 3.23: Reagents and conditions: (i) TiCl_4 , allylTMS, CH_2Cl_2 , -78°C , 89%.

In a similar way to *cis*-**3-56**, the ^1H NMR spectrum displayed a multiplet at 5.80-5.73 ppm for the internal alkene proton. The terminal alkene protons were observed as two doublets at 5.04 and 5.03 ppm with coupling constants of 17.0 and 9.5 Hz respectively. The COSY spectrum was used to assign a doublet of triplets at 2.44 ppm and another doublet of triplets at 2.24 ppm as the allylic protons (H-a and H-b), due to the cross peaks with alkene protons. The COSY spectrum also allowed assignment of a multiplet at 4.70-4.66 ppm for H-8 proton due to the cross peak with allylic protons. As shown in Figure 3.3, no NOE interaction was observed between H-4 and H-8 but a strong NOE interaction was observed between H-4 and the allylic protons (Ha, Ha') in

the NOESY spectrum. Therefore, the carbamate **3-56** was identified to be the desired *trans*-isomer. Additionally, a strong NOE interaction was also observed between H-3 and H-4 in single isomer **3-56**, which again confirmed that allenic cyclization of compound **3-39** proceeded with *cis*-selectivity.

Figure 3.3: NOESY spectrum of compound *trans*-**3-56**.

Based on the work of Hootelé²⁵ and Lhommet,²⁶ the proposed mechanism for *trans*-stereoselectivity in our strategy is shown in Scheme 3.24. The presence of a cyclic 6-membered carbamate forces the C-4 side chain into an equatorial orientation in the

N-acyliminium ion **3-64**. Thus, the conformation **3-65** should be most preferred in solution. The observed *trans*-stereoselectivity results from the stereoelectronically controlled axial attack of nucleophile to the thermodynamically preferred conformation **3-65**.

Scheme 3.24: Proposed mechanism of bicyclic iminium ion for *trans*-selectivity.

With piperidine *trans*-**3-56** in hand, we intended to accomplish the synthesis of porantheridine, using the same sequence of reactions as in the synthesis of *epi*-porantheridine. Cross-metathesis⁸⁰ of the piperidine *trans*-**3-56** proceeded efficiently with (*E*)-pent-3-en-2-one in the presence of Grubbs II catalyst in refluxing dichloromethane, giving *E*-unsaturated ketone **3-66** as a single isomer in 86% yield (Scheme 3.25). The *E*-configuration was assigned on the basis of the coupling constant of 15.7 Hz for the two protons of the double bond. Subsequent hydrogenation over palladium on carbon at atmospheric pressure afforded the saturated ketone **3-67** in 99% yield. The ketone functional group was identified from the IR spectrum with a strong peak at 1713 cm⁻¹ and the ¹³C NMR spectrum with a peak at 208.9 ppm. To obtain the target porantheridine, the carbamate ring should be converted to the free amino alcohol under basic conditions. Thus the ketone functional group of **3-67** should be protected first. The 1,3-dioxolane **3-68** was obtained in 96% yield by treatment with ethylene

available (*S*)-epichlorohydrin. In addition, we have shown that the sense of stereoselectivity of the addition to such *N*-acyl iminium ions can be controlled by choosing either an acyclic or an internal protecting group. The synthesis also illustrates the ease with which a functionalized *syn*-1,3-amino alcohol can be constructed using allene cyclization chemistry.

CHAPTER 4

TOTAL SYNTHESIS OF (-)-SEDININE

4.1. Introduction

For the past several decades, the *sedum* alkaloids have attracted considerable attention, due to their unique and challenging structural array, and their medicinal properties.⁸³ Sedamine, one of the *sedum* alkaloids, has been successfully synthesized in our lab using two different strategies.⁶⁰ Another alkaloid that attracted our interest to study further is (-)-sedinine, which is “two-armed” *sedum* alkaloid with the two substituents *trans* to each other. (-)-Sedinine was isolated from *sedum acre* in 1958 by Frank.⁸⁴ As shown in Figure 4.1, sedinine was first assigned as the structure of **4-1**.⁸⁵ However, Hootelé and co-workers reported the revised structure of sedinine **4-2** with a different location of the double bond, on the basis of X-ray diffraction⁸⁶ and NMR spectroscopy⁸⁷.

Figure 4.1: Structure of sedinine.

4.1.1. Previous work on the total synthesis of sedinine

A preliminary stereoselective synthesis of racemic sedinine **4-2** was reported by Natsume and Ogawa⁸⁸ in 1985, starting from a dihydropyridine derivative **4-3** which

was derived from the addition of an alkynyl Grignard reagent to pyridine (Scheme 4.1). A sequential reaction of sensitized photooxygenation, addition of ethyl vinyl ether and acetalization proceeded well, affording the 2,6-*cis*-disubstituted-piperidine **4-4** in 72% yield. However, the configurations of the hydroxyl-bearing stereocenter, the location of double bond and even the relative configuration of two substituents at C-2 and C-6 sites in **4-4** did not match the desired stereochemistry. Thus, inversion of the hydroxyl group was achieved by oxidation with Jones reagent and subsequent reduction with LiBH_4 , affording alcohol **4-5** in 56% yield. Reaction of alcohol **4-5** with HgSO_4 gave a 1:1 mixture of ketone **4-6** and hemiacetal **4-7** in 88% yield, followed by benzoylation of both isomers to afford the key intermediate **4-8** in 74% yield.

Scheme 4.1: Natsume's approach to ($\pm$)-sedinine.

Next, the stereoselective reduction of ketone **4-8** with $\text{Li}(t\text{BuO})_3\text{AlH}$ was followed by protection of the hydroxyl group with methoxymethyl chloride (MOMCl), giving a 4:1 mixture of diastereoisomers as the best result. Due to the incorrect location of the double bond, a sequence of deprotection, hydrogenation and mesylation was then carried out to afford the key intermediate **4-10** in 76% yield. The double bond was introduced at the desired location by elimination of MsO group under basic conditions (DBU), generating the piperidine **4-11** in 78% yield. Reduction of *N*-CO₂Me group followed by exchange of oxygen protecting groups provided 2,6-*cis*-disubstituted-piperidine **4-12** in 51% yield.

Scheme 4.2: Natsume's approach to (±)-sedinine.

To obtain the requisite 2,6-*trans*-substituted piperidine ring, the subsequent

epimerization was carried out by the retro-Michael-Michael reaction to afford the equilibrated mixture of **4-13** and **4-14**, which was directly subjected to the addition of PhMgBr in the presence of Bu₃P·CuI. The desired alcohol **4-15** was then obtained in 22% yield, accompanied by the formation of corresponding isomer **4-15'** in 19% yield and other byproducts in 16% yield. The epimerization of diastereoisomer **4-15'** to the desired product **4-15** was also achieved by Jones oxidization followed by the stereoselective reduction with Li(*t*BuO)₃AlH. Finally, removal of the protecting group of **4-15** gave the desired product (±)-sedinine quantitatively.

Scheme 4.3: Natsume's approach to (±)-sedinine.

In summary, Natsume accomplished the total synthesis of racemic sedinine, involving

a long and complex synthetic route. In particular, the chiral centers were introduced with low diastereoselectivity. To our knowledge, this is the only report of the synthesis of sedinine. With the continuing interest in the stereoselective synthesis of piperidines, sedinine makes an interesting target for us to study further due to the presence of a double bond in the piperidine ring.

4.1.2. Aim of present work

In Chapter 3 we demonstrated that the synthesis of porantheridine was successfully achieved using *N*-acyliminium ion chemistry to form a piperidine ring.⁸⁹ Thus, we attempted to utilize similar *N*-acyliminium ion chemistry to control the stereochemistry of the piperidine moiety of sedinine. A challenge in sedinine synthesis, not present in porantheridine synthesis is the introduction of a double bond in the piperidine ring.

According to the retrosynthetic analysis outlined in Scheme 4.4, sedinine **4-2** can be considered to arise from diastereoselective reduction of ketone **4-16**. Following the our research on the porantheridine synthesis, a 2,6-*trans*-piperidine moiety in ketone **4-16**, would arise from alkylation of bicyclic iminium ion intermediate derived from *N,O*-acetal **4-17**. Accordingly, the double bond in the piperidine ring was expected to be formed by ring-closing metathesis of diene **4-18**. As a cyclic *N,O*-acetal, compound **4-18** could be synthesized by acetalization, using the procedure discussed in Chapter 2.⁹⁰ The diene **4-18** was expected to be the *cis* isomer, which would be the correct

stereochemistry for ring closing metathesis. Isoxazolidine **4-19** could be readily prepared from racemic propylene oxide **4-20** using our optimum conditions for the allenic cyclization.^{60,89}

Scheme 4.4: Retrosynthetic analysis of sedinine.

4.2. Results and Discussion

4.2.1. The first approach to sedinine

The initial investigation in our approach to sedinine focused on the synthesis of the key intermediate, isoxazolidine **4-19**. Based on experience from the sedamine and porantheridine syntheses, we attempted to utilize the same sequence of reactions to synthesize the isoxazolidine **4-19** from propylene oxide (*S*)-**4-20** (Scheme 4.5). However, since (*S*)-**4-20** is very volatile (bp 35 °C) and difficult to handle, cyclic sulfate **4-21** was used instead.⁹¹ Cyclic sulfates have been described as “like epoxides only more reactive”⁹² and act as useful substitutes for epoxides.

Scheme 4.5: Retrosynthetic route to isoxazolidine **4-19**.

We intended to employ the most general method initially reported by Sharpless and co-workers⁹² to synthesize the cyclic sulfate **4-21**, which was derived from propylene glycol **4-22** (Scheme 4.6). However, commercially available propylene glycol in enantiomerically pure form is costly. To our delight, hydrolytic kinetic resolution (HKR)⁹³ resolved the above problem. The propylene glycol **4-22** could be synthesized efficiently from the cheap racemic epoxide **4-20**.

Scheme 4.6: Synthetic route to cyclic sulfate **4-21**.

Hydrolytic kinetic resolution (HKR), reported by Jacobsen and co-workers, provides a useful and efficient method for the synthesis of both highly enantiomerically enriched epoxides and 1,2-diols from cheap racemic epoxides, using chiral (salen)Co(III) complexes **4-23** (Jacobsen catalyst) (Scheme 4.7). The resulting epoxides and 1,2-diols are usually separated by simple distillation. The Jacobsen catalysts are available in both enantiomeric forms and only a low catalyst loading (0.2 to 2 mol%) is required in this resolution.

Scheme 4.7: Hydrolytic kinetic resolution reaction (HKR).

In our hands, the HKR of racemic propylene oxide **4-20** was carried out with 0.55 equiv of water in the presence of 0.2 mol% of (*R, R*)-Jacobsen' catalyst (Scheme **4.8**). The subsequent separation of propylene oxide (*R*)-**4-20** was achieved by evaporation and the residue was distilled again under reduced pressure, giving (+)-propylene glycol **4-22** in 41% yield. Next, formation of cyclic sulfate **4-21** was achieved efficiently by the "one-pot" process.⁹² The propylene glycol **4-22** was treated with thionyl chloride in refluxing dichloromethane for 1 h to generate the cyclic sulfite **4-24**, which was then directly subjected to the catalytic oxidation with ruthenium chloride and NaIO₄, providing the cyclic sulfate **4-21** in 93% yield after distillation under reduced pressure. All the NMR data were consistent with the literature values.⁹⁴

The nucleophilic opening of cyclic sulfate **4-21** was carried out with lithium acetylide, which was generated by treatment of acetylene gas with *n*-butyl lithium at -78 °C in anhydrous THF. The reaction proceeded cleanly, giving homopropargyl alcohol **4-25** after hydrolysis with a small amount of water (1 equiv) and concentrated sulfuric acid (0.3 equiv). Sharpless and co-workers found that the hydrolysis in this way gave the best result and fastest reaction.⁹⁵ In order to remove the acetone impurity from the inside of the cylinder, the acetylene gas was required to be passed through a cold trap at -78 °C (dry ice and acetone) prior to use. Due to the volatility of alcohol **4-25**, the THF solvent was removed slowly by normal distillation and subsequent distillation under reduced pressure [45 °C (oil bath) at 6 mmHg] provided the terminal alkyne **4-25** in 79% yield. Only one product arising from attack at the less steric hindered carbon of cyclic sulfate **4-21** was observed in the ¹H NMR spectrum, which displayed

a quartet of triplets at δ 3.98 ppm with coupling constants of 6.2, 5.4 Hz for the H-4 tertiary proton. A triplet at 2.07 ppm with a coupling constant of 2.6 Hz was characteristic of the alkynyl proton.

Scheme 4.8: *Reagents and Conditions:* (i) (*R, R*)-Jacobsen's catalyst, H₂O, r.t., overnight, 41%. (ii) a: SOCl₂, CH₂Cl₂, reflux, 0.5 h; b: RuCl₃, NaIO₄, CH₃CN-H₂O (v/v, 1:1), r.t., 93%. (iii) Lithium acetylide, -78 to 0 °C, THF; H₂O, *conc.* H₂SO₄, 79%.

With the terminal alkyne **4-25** in hand, we progressed towards the synthesis of isoxazolidine **4-19**. The rest of the reactions of the isoxazolidine synthesis proceeded well, in a similar way to the porantheridine synthesis. Searles-Crabbé homologation was achieved by treatment of terminal alkyne **4-25** with paraformaldehyde and diisopropylamine in the presence of copper bromide catalyst, affording the allenic alcohol **4-26** in 68% yield after distillation under reduced pressure [1 mmHg, 50 °C (oil bath)] (Scheme 4.9). The alcohol **4-26** was not rigorously purified due to its volatility. The principle impurity was residual reaction solvent (THF or 1,4-dioxane)

which did not interfere with the subsequent reaction. A characteristic peak at 1956 cm^{-1} in the IR spectrum and a peak at 209.4 ppm in the ^{13}C NMR spectrum also confirmed the formation of the allene functional group. Mitsunobu reaction of allenic alcohol **4-26** with *N*-hydroxyphthalimide also proceeded well, affording *N*-phthaloyl hydroxylamine **4-27** in 94% yield with the configuration inverted. The enantiomeric excess of **4-28** was determined to be 98.5% by chiral HPLC analysis (appendix A.2). Cleavage of the phthaloyl group with hydrazine hydrate gave the free hydroxylamine **4-28** in 95% yield after simple filtration and evaporation, which was used in the next step without further purification. The subsequent protection with di-*tert*-butyl dicarbonate ((*Boc*)₂O) under basic conditions (NaOH) provided the *N*-Boc hydroxylamine **4-29** in 86% yield after purification by column chromatography.

Scheme 4.9: *Reagents and Conditions:* (i) $(\text{CH}_2\text{O})_n$, *i*-Pr₂NH, CuBr, 1,4-dioxane, reflux, overnight, 68%; (ii) HONPhth, PPh₃, DIAD, THF, -15 °C, 1 h, 94%. (iii) H₂NNH₂·H₂O, CH₂Cl₂, r.t., 15 min, 95%; (iv) NaOH, (*Boc*)₂O, CH₂Cl₂-H₂O (v/v 1:1), r.t., overnight, 90%.

The following step is the allenic cyclization, which is also one of key steps in this approach. In Chapter 3, an interesting result was discovered in the allenic cyclization,

which is the increase of the diastereoselectivity with decrease of catalyst loading. The optimum conditions proved to be the use of silver tetrafluoroborate (AgBF_4) at a loading of 10 mol%. We planned to establish the relationship between the diastereoselectivity and metal loading. Thus, in this project, we intended to study the allenic reaction further, using silver tetrafluoroborate as catalyst.

A series of reactions were carried out at different metal loadings of AgBF_4 from 100 mol% to 5 mol% (Table 4.1). It is interesting to find that a significant dependence of the diastereoselectivity on catalyst loading was also observed. Fortunately, the diastereoselectivity was increased (up to 13.0:1) as the silver loading (from 100 to 10 mol%) was decreased (entries 1-7). The same effect as observed in the synthesis of isoxazolidine 3-38 appears to be operating. Much lower loadings of silver(I) tetrafluoroborate (8 mol% and 5 mol%) resulted in incomplete reactions (entries 8 and 9). Fortunately, the starting material **4-29** and product **4-19** could be separated by column chromatography. The diastereoselectivities were determined to be 8:1 and 4:1 respectively in the ^1H NMR spectra (entries 8 and 9). Thus, the use of 10 mol% of silver(I) tetrafluoroborate was found to give the best result, affording a 13:1 inseparable mixture of isoxazolidines **4-19** in 90% yield (entry 7, appendix A.3).

Again, the stereochemistry of the inseparable isomers **4-19** could not be determined on the basis of their ^1H NMR spectra at this point. The *cis*-diastereoselectivity of allenic cyclization was determined in the next step by X-ray diffraction of the minor amino alcohol derivative **4-30** (See below).

Table 4.1: Allenic cyclization of compound **4-29**.^a

Entry	Metal loading (mol%)	Yield ^b (%)	Dr ^c (<i>cis</i> : <i>trans</i>)
1	100	96	4.5:1
2	80	95	5.5:1
3	60	97	6.5:1
4	50	99	6.0:1
5	40	95	9.0:1
6	20	86	10.0:1
7	10	90	13.0:1
8	8	63	8.0:1
9	5	40	4.0:1

a: the reaction was carried out in anhydrous CH₂Cl₂ at room temperature;

b: Isolated yield; *c*: Determined by ¹H NMR spectrum.

The isoxazolidine **4-19**, as a mixture of isomers, was converted to the amino alcohols **4-30** in 85% yield by cleavage of the *N-O* bond, using a combination of molybdenum hexacarbonyl and sodium borohydride in wet acetonitrile (Scheme 4.7). The two diastereoisomers could also be separated by column chromatography, giving the major

isomer as a colorless oil and the minor isomer as a colorless solid. Gratifyingly, a single crystal of minor isomer **4-30** was successfully obtained from a mixture of dichloromethane and hexane.

Scheme 4.10: Reagents and Conditions: (i) $\text{Mo}(\text{CO})_6$, NaBH_4 , $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (v/v, 7:1), reflux, overnight, 85%.

The X-ray structure analysis in Figure 4.2 illustrated the minor isomer **4-30** was identified as *anti*-isomer, which proved that the major isomer matches the *syn*-stereochemistry of sedinine. Thus, the allenic cyclization was proved to be *cis*-diastereoselective again (see above, Table 4.1).

Figure 4.2: X-ray crystal structure of minor isomer **4-30**.

In the synthesis of sedamine⁶⁰ in our lab, it was found that ring closing metathesis (RCM) of diene **4-31** preceded efficiently with Grubbs I catalyst, generating a piperidine **4-32** with a double bond. These results inspired us to employ a similar ring closing metathesis (RCM) to introduce the double bond into sedinine in our approach.

Scheme 4.11: Synthetic route to sedamine.

We therefore decided to attach the second alkene partner of diene **4-18** by the acetalization of amino alcohol *syn*-**4-30** with acetal **4-34**, using the procedure developed in Chapter 2 (Scheme **4.12**).⁹⁰

Scheme 4.12: Proposed synthetic route to *N,O*-acetal **4-33**.

Earlier in Chapter 3, we described the synthesis of *O,O*-acetal **4-34**. However, the methods of preparation involved afforded the desired product **4-34** in low yield (43%) with difficult purification. Moreover, the commercially available acetal **4-34** is costly.

We were also concerned about alkene isomerisation under acidic acetalisation conditions. Hence, we decided to utilize acetal **4-37** instead of acetal **4-34** (Scheme 4.13). We believed that the target **4-37** would be provided efficiently in this simple approach from a less expensive and more stable starting material.

Reduction of ester **4-35** with DIBAL (1.3 eq.) at -78 °C in anhydrous dichloromethane afforded the aldehyde **4-36** quantitatively after normal workup.⁹⁶ The reaction temperature and the number of equivalents of DIBAL had to be controlled strictly to prevent over-reduction to the corresponding alcohol. Subsequent acetalization of aldehyde **4-36** in refluxing methanol afforded the acetal **4-37** in 88% yield.⁹⁷

Scheme 4.13: *Reagents and Conditions:* (i) DIBAL, CH₂Cl₂, -78 °C, 20 min, quant. (ii) NH₄Cl (trace), MeOH, reflux, 4 h, 88%.

With the starting materials ready, we proceeded to the acetalization of amino alcohol *syn*-**4-30** with acetal **4-37** under acidic conditions. However, this transformation was found to be a difficult task. Several reaction conditions were thus investigated, including reaction catalyst, solvent, temperature and time (Table 4.2). Our initial trial was carried out with amberlyst-15, using the procedure as described in Chapter 2. Unexpectedly, only a trace of the target product **4-38** was obtained after filtration and evaporation, and was accompanied by products resulting from decomposition of the

starting material via competing removal of the *N*-Boc group (entry 1).

Rae and co-workers^{37b} reported that acetalization could also be achieved with a weaker Brønsted acid such as PPTS in refluxing benzene. Due to the toxicity of benzene, we utilized toluene as solvent instead. Amino alcohol **syn-4-30** was treated with acetal **4-37** with PPTS in refluxing toluene for 3 h (entry 2). However, only a trace of the target product was observed in the ¹H NMR spectrum, and again significant decomposition of starting material was observed.

Thus, the optimization of the reaction temperature was carried out (entries 3 and 4). To our delight, when the reaction mixture was heated at 105 °C (oil bath) for 3 h, the cyclic *N,O*-acetals **4-38** were obtained in 73% yield (mixture of isomers), with good diastereoselectivity (*dr* = 6:1) as judged from the ¹H NMR spectrum (entry 3). It was thought that increasing the reaction time to overnight would improve the yield and diastereoselectivity of *N,O*-acetals **4-38**. However, to our surprise, only 20% of product was obtained along with products that presumably arise from decomposition of **4-38** (entry 5).

Therefore, with the use of PPTS in toluene at 105 °C for 3 h as optimum conditions, a 6:1 separable mixture of the target *N,O*-acetals was obtained in good yield. The ¹H NMR spectrum of major isomer **4-38** displayed a doublet of doublets at 5.16 ppm for the acetal proton (H-2). A multiplet was observed at 4.67-4.62 ppm for the H-4 proton. A doublet of doublet of quartets was characteristic of the H-6 proton with coupling constants of 10.3, 6.3, 6.3 Hz. Loss of the OH and NH peaks were observed in IR

spectrum.

Table 4.2: The acetalization for cyclic *N,O*-acetal **4-38**.^a

Entry	Reagent	Condition	Yield ^b (%)	Dr ^c
1	Amberlyst-15	CH ₂ Cl ₂ , rt	trace	-
2	PPTS	Toluene, reflux ^d , 3 h	traced	-
3	PPTS	Toluene, 105 °C ^d , 3 h	73	6.0:1
4	PPTS	Toluene, 85 °C ^d , 3 h	53	6.2:1
5	PPTS	Toluene, 105 °C ^d , overnight	20	6.0:1

a: 0.5 eq PPTS and 2.0 eq acetal **4-37** were used in this reaction; *b*: Isolated yield for two isomers;

c: Determined by NMR; *d*: Oil bath temperature.

2D NMR experiments (COSY, NOESY) for both isomers of acetals **4-38** were conducted to determine the stereochemistry. Unfortunately, the NOESY spectra generated were poorly resolved and hence, useful information to determine their configurations could not be obtained. In Chapter 2, it was found that acetalization of amino alcohol **2-41** proceeded well with propionaldehyde, giving the cyclic *N,O*-acetals **2-45** exclusively (Scheme **4.14**). The relative configuration was determined to be *cis* by X-ray diffraction, with two substituents adopting axial

orientations to relieve the steric hindrance with the *N*-Ts group. Thus, the major isomer **4-38** in this strategy was presumed to be generated in a similar way as **2-45**.

Scheme 4.14: Acetalization of aminol alcohol **2-41**.

In addition, Martin⁹⁸ reported that only *cis*-2,6-disubstituted *N*-acyl piperidine **4-40** is possible for the ring closing metathesis to afford the bridged azabicyclic compound **4-41** (Scheme 4.15). The two alkenyl groups at the C-2 and C-6 positions had to both adopt axial orientations in the chair conformer **4-40** in order to avoid the 1,2-interactions with *N*-acyl group in conformer **4-39**. Martin also suggested that if the two alkenyl groups are in *trans*-orientation in conformer **4-42**, the RCM would not occur, because they would be too far apart to react with one another. Hence, it was envisioned that the six-membered *N,O*-acetal **4-38** would proceed in a similar way as Martin's piperidine system.

Scheme 4.15: Most stable conformer **4-40** for ring closing metathesis.

Thus, we decided to proceed with the ring closing metathesis of major isomer **4-38** after elimination of HBr, hoping that the desired bibcyclic *N,O*-acetal would be obtained efficiently. Elimination of HBr was achieved by the treatment of major-**4-38** with potassium *tert*-butoxide, giving the desired cyclic *N,O*-acetal **4-18** in 89% yield (Scheme 4.16). The subsequent ring closing metathesis of major isomer **4-18** was carried out with 5 mol% of the first generation Grubbs catalyst (Grubbs I) in dichloromethane at reflux for 4 h. To our delight, the RCM proceeded efficiently, affording the target bicyclic *N,O*-acetal **4-33** in 84% yield, which proved that this major isomer **4-18** was the *cis*-isomer with pseudo-axial alkenyl groups. Accordingly, the acetalization of **4-38** in Table 4.2 was also proved to proceed with *cis*-diastereoselectivity (see above). A similar result was also observed when the RCM reaction was carried out with 2 mol% of second generation Grubbs complex (Grubbs II). The reaction was complete in a shorter time (2 h). Only two double bond protons were observed in the ^1H NMR spectrum with a multiplet at 5.93-5.60 ppm.

Scheme 4.16: *Reagents and Conditions:* (i) KOtBu, THF, 0 °C - r.t., 89% (ii) 5 mol% Grubbs I or 2 mol% Grubbs II, CH₂Cl₂, reflux, 4 h, 84%.

With the *N,O*-acetal **4-33** in hand, we next focused our attention on the iminium ion chemistry. Based on our experience with porantheridine in Chapter 3,⁸⁹ it could be expected that alkylation of monocyclic iminium ion **4-43** with a nucleophile would proceed with *cis*-selectivity (Scheme 4.17). Meanwhile, the alkylation of bicyclic iminium ion **4-44** with a nucleophile would provide *trans*-selectivity instead. Hence, since *trans*-selectivity matches the stereochemistry of sedinine, we decided to convert the bicyclic *N,O*-acetal **4-33** into bicyclic carbamate **4-17**.

Scheme 4.17: Proposed alkylations of monocyclic iminium ion **4-41** and bicyclic iminium ion **4-42**.

The bicyclic *N,O*-acetal **4-33** was then treated with PPTS in methanol at -10 °C, giving the semicyclic *N,O*-acetal **4-45** in 88% yield (Scheme 4.18). However, at higher temperatures including room temperature, the reaction resulted in a mixture of the desired product and unwanted diene **4-46**. Again, the diastereoselectivity could not be determined by ¹H NMR spectroscopy as the line broadening was observed, due to the

restricted rotation of the $N\text{-C=O}$ bond. The semicyclic N,O -acetal **4-45** was directly subjected to the cyclization reaction under basic conditions using $\text{KO}t\text{-Bu}$ in anhydrous THF. The desired bicyclic carbamate **4-17** was obtained in 50% yield, accompanied by recovered starting material. Only one isomer was observed in the crude ^1H NMR spectrum. Considering that the bicyclic carbamate **4-17** acted as a precursor to an iminium ion intermediate in next step, determination of the configuration of the newly formed chiral center was considered to be unnecessary. A multiplet at 6.02-5.98 was observed for one of the alkene proton. A doublet of triplets was observed at 5.77 ppm with the coupling constants of 9.6, 2.4 Hz for the other alkene proton. A triplet at 5.55 ppm with a coupling constant of 3.3 Hz was characteristic of the acetal proton.

Scheme 4.18: *Reagents and Conditions:* (i) PPTS, MeOH, -10 to 0 °C, 5 h, 88%; (ii). $\text{KO}t\text{Bu}$, THF, -10 °C, 50%; (iii) PPTS, MeOH, r.t.

With bicyclic iminium ion precursor **4-17** in hand, the alkylation was then carried out with silyl enol ether **4-47**⁹⁹ in the presence of tin tetrachloride at -78 °C in anhydrous

dichloromethane (Scheme 4.19). The reaction proceeded well to afford products **4-16** in 68% yield, accompanied by recovered starting material in 15% yield. However, the diastereomeric ratio was found to be 1:1 after isolation by flash column chromatography. To achieve complete conversion and good diastereoselectivity, other Lewis acids were also investigated. Treatment with TiCl_4 led to a 1:1 mixture of desired products in 50% yield, accompanied by the formation of byproduct **4-46** in 10% yield and the recovery of starting material in 15% yield. Treatment of TMSOTf , $\text{BF}_3 \cdot \text{OEt}_2$ and SnCl_2 resulted in total decomposition of the reaction mixture as judged by crude ^1H NMR spectrum. Further attempts using $\text{Cp}_2\text{Ti}(\text{OTf})_2$ and $\text{Yb}(\text{OTf})_3$ were also unsuccessful, with the recovery of starting material.

Scheme 4.19: Reagents and conditions: (i) SnCl_4 , CH_2Cl_2 , -78°C , 68%.

As shown in Scheme 4.20, we postulated the origin of stereochemistry. The conformer **4-48** might be the most stable conformation in solution, in which the cyclic carbamate constrained the C-2 side chain in a pseudoequatorial orientation. Given the four

sp^2 -hybridized atoms in the ring, the conformer **4-48** is substantially planar, with no stereoelectronic or steric bias favoring either face. Therefore, the enol ether could attack the C=N bond from either top face or bottom face without stereoelectronic effects. Thus, the nucleophilic attack from the top face led to *trans*-isomer while the nucleophilic attack from the bottom face led to *cis*-isomer.

Scheme 4.20: Possible mechanism for non-stereoselectivity of bicyclic iminium ion.

Compared to the synthesis of porantheridine in Chapter 3,⁸⁹ we found that the alkylations of bicyclic iminium ion proceeded in a very different way. The alkylations of bicyclic iminium ion **3-64** with a nucleophile led to *trans*-selectivity exclusively under stereoelectronic control (axial attack) (Scheme **4.21**). However, the alkylation of bicyclic iminium ion **4-44** with nucleophile led to non-selectivity under steric control. This result has prompted us to conduct further studies to obtain *trans*-selectivity that matched the stereochemistry of sedinine. Thus, we went back to cyclic *N,O*-acetal **4-33**, studying the alkylation of monocyclic iminium ion intermediate **4-43**.

Scheme 4.21: Comparison of alkylation of iminium ion intermediates in two systems.

4.2.2. The second approach to sedinine

Alkylation of cyclic *N,O*-acetal **4-33** was then carried out with silyl enol ether **4-47** in the presence of tin tetrachloride at -78°C in anhydrous dichloromethane (Scheme 4.22). The 2,6-disubstituted piperidine **4-49** was isolated as a single isomer in 60% yield after purification by column chromatography, with recovered starting material (15%). To improve the reaction yield, TiCl_4 was also employed. However, the desired product was obtained in lower yield (40%), accompanied by the formation of byproduct **4-46** in 10% yield. A doublet at 7.97 ppm with a coupling constant of 7.5 Hz, a triplet at 7.56 ppm with a coupling constant of 7.5 Hz and a triplet at 7.46 ppm with a coupling constant of 7.5 Hz were characteristic of the aromatic protons in the ^1H NMR spectrum. The ^{13}C NMR displayed a distinctive peak at 198.5 ppm for the ketone carbonyl carbon.

2D NMR experiments (COSY, NOESY) for piperidine **4-49** were conducted to determine the stereochemistry. The COSY spectrum led to assignment of the multiplet at 3.94-3.87 ppm as the signal corresponding to H-2' proton (cross peak with methyl group). However, the NOESY spectrum did not give any useful information, as signals for the two protons at C-2 and C-6 positions in compound **4-49** overlapped as a multiplet at 4.46-4.42 ppm. To determine the stereochemistry, cyclization with potassium *tert*-butoxide was employed again to convert compound **4-49** to the corresponding bicyclic carbamate **4-16**, which would be expected to show a well resolved NMR spectrum. To our delight, the carbamate **4-16** was isolated as a colorless solid and the single crystal of compound **4-16** was obtained from a mixture of dichloromethane and hexane.

Scheme 4.22: *Reagents and conditions:* (i) SnCl_4 , silyl enol ether **4-47**, -78°C , CH_2Cl_2 , 60%. (ii) $\text{KO}^t\text{-Bu}$, THF, 0°C -r.t., 35%.

As shown in Figure **4.3**, X-ray analysis revealed that the two substituents at C-2 and

C-6 positions of the piperidine ring of compound **4-16** adopted a *trans*-orientation, which proved that the alkylation of monocyclic iminium ion intermediate **4-43** preferred *trans*-selectivity. The COSY spectrum allowed for assignment of H-8 proton as the doublet of triplets at 5.32 ppm with the coupling constants of 6.8, 6.8 Hz by the cross peaks with H-1' protons. A quartet of triplets at 4.37 ppm with the coupling constants of 6.2, 6.2 Hz was assigned as H-3 proton by the cross peak with the methyl group signal.

Figure 4.3: X-ray single crystal structure of compound *trans*-**4-16**.

We believe the origin of the unusual *trans*-stereoselectivity (Scheme **4.23**) can be attributed to the presence of the ring alkene. The resulting flattening of the ring of the iminium ion **4-43** ensures that neither of transition states are chair-like, hence, the absence of any stereoelectronic bias. However, the C-2 oxypropyl substituent is

compelled to adopt a pseudo-axial orientation to avoid steric hindrance with the *N*-Boc group in conformer **4-50**. Thus, the pseudo-axial oxypropyl substituent shields one face of the iminium ion intermediate and compels the silyl enol ether to approach from the opposite face. This results in the remarkably high selectivity in favor of the *trans*-isomer.

Scheme 4.23: Proposed Origin of Stereochemistry.

As shown in Scheme **4.24**, this *trans*-selectivity is in contrast to the results reported by Shipman¹⁸ and Craig.²¹ Shipman and co-workers found *cis*-selective addition to dihydropyridinium ion **1-56b**, which also contained two double bonds in pyridine rings. In those cases, the alkenes had an α,β -relationship to the iminium ions. However, in our case, with α,β,γ -relationship, the confirmation of the iminium ion **4-43** must be different.

Scheme 4.24: Alkylation of monocyclic iminium ion intermediates in two systems.

With the correct stereochemistry of *trans*-**4-49** in hand, we concentrated our attention on completion of the synthesis of sedinine. The next step was the asymmetric reduction of ketone **4-49** to corresponding alcohol. A number of methods have been developed for the asymmetric reduction of a prochiral ketone to optically active alcohol. The chirality could be introduced by either substrate control or reagent control.

Stoltz and co-workers¹⁰⁰ reported a model study by using DIBAL (Scheme 4.25). The ketone **4-51** was asymmetrically reduced to the corresponding alcohols **4-52** with high *anti*-selectivity (*dr* = 11:1) by the substrate control.

Scheme 4.25: Stoltz's DIBAL reduction.

They proposed the possible steric origin of the asymmetric reduction (Scheme 4.26).¹⁰⁰

The Lewis-acidic metal first coordinated with the substrate to form a eight-membered ring. The most stable twist-boat conformer **TB-53** and boat-chair **BC-53** would exist in solution by computational studies. The anionic hydride attacked from α -face with less steric hindrance, affording **TB-54** and **BC-54** respectively. Thus, after aqueous work-up, the *anti*-selectivity was then obtained.

Scheme 4.26: The stereochemical origin of the asymmetric reduction.

Our substrate, *trans*-**4-49**, is partially similar to Stoltz's model study. Thus, we believed that the asymmetric reduction in our strategy would proceed with *anti*-selectivity too via substrate control. The asymmetric reduction of ketone *trans*-**4-49** was then carried out with a range of chelation-controlled reducing reagents including aluminum hydrides ($LiAl(Ot-Bu)_3H$,^{88,101} Red-Al¹⁰² and DIBAL¹⁰⁰) and boron hydride (K-Selectride)¹⁰³. The results are outlined in Table 4.3. It was found that DIBAL was most efficient, giving a 4.5:1 separable mixture of target alcohols in

99% yield (entry 4).

^1H NMR spectrum of major-**4-55** displayed two broad singlets for the two hydroxyl groups at 3.31 and 2.80 ppm respectively. A doublet of triplets was observed at 4.65 ppm with the coupling constants of 9.4, 3.7 Hz for H-2' proton. A doublet of triplets at 4.36 ppm with the coupling constants of 5.9, 5.9 Hz was characteristic of H-2 proton. A doublet of doublet of triplets at 4.01 ppm with the coupling constants of 8.3, 4.2, 4.2 Hz was assigned as H-6 proton. A multiplet at 3.87-3.83 ppm was observed for H-2'' proton.

Table 4.3: Reduction of ketone **4-49** to corresponding alcohols.

Entry	Reagent	Condition	Yield ^a (%)	Dr ^c (anti:syn)
1	3.0 eq. K-Selectride	THF, 0 °C	80	1.5:1
2	3.0 eq. LiAl(Ot-Bu) ₃ H	THF, -78 °C	99 ^b	1.1:1
3	1.0 eq. Red-Al	CH ₂ Cl ₂ , -78 °C	60	2.7:1
4	2.5 eq. DIBAL	CH ₂ Cl ₂ , -78 °C	99 ^b	4.5:1

a: Isolated yield; *b*: Crude NMR spectra are clear without any purification; *c*: Determined by ^1H NMR.

To achieve high diastereoselectivity, a well known reducing reagent, the Corey-Bakshi-Shibata Oxazaborolidine (CBS-catalyst) was employed, changing from substrate control to reagent control.¹⁰⁴ Corey and co-workers first explored the CBS-H catalyst^{104a} and later did a systematic study on the optimization of CBS-R catalysts,^{104e} bearing different boron substituents. The substituted CBS catalysts were found to be less-sensitive to moisture, and can be easily handled and stored. On the other hand, the use of substituted CBS catalysts afforded the corresponding alcohols in excellent yield and short reaction time. Based on literature reports,^{104c, 104e} the absolute configuration of alcohols was predictable, generating either enantiomer with excellent selectivity (Scheme 4.27). The (*R*)-CBS catalyst will lead to *S*-configuration of the newly formed alcohol, which matches the stereochemistry of sedinine. Therefore, we employed the (*R*)-CBS-Me catalyst in our strategy.

Scheme 4.27: Predictable CBS reduction.

The asymmetric reduction of prochiral ketone **4-49** was then carried out with reducing reagent BH_3SMe_2 in the presence of (*R*)-CBS-Me in anhydrous THF at $-10\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$

(Scheme 4.28). However, it was found that the reaction did not work well under the usual conditions (0.05 eq CBS catalyst, 0.7 eq. borane), and the starting material was recovered. Quallich and co-workers^{104c} suggested that if substrate **4-49** contained a nitrogen atom, the borane can not only coordinate with the catalyst but also with the nitrogen atom in the substrate. “Once coordinated, the amine-borane **4-56** was inert under the reaction conditions.”^{104c} To make this reaction work well, more catalyst and borane were used. To our delight, the asymmetric reduction proceeded well with 4 equivalents of reducing reagent $\text{BH}_3\cdot\text{SMe}_2$ in the presence of 0.2 equivalent of (*R*)-CBS-Me, giving the target alcohol **4-55** in 92% yield as a single isomer as judged from the ^1H NMR spectrum. The single isomer was same as the major isomer obtained with use of DIBAL in ^1H NMR spectrum. On the basis of the literature reports, we predicted that the single isomer was the *anti*-isomer that we wanted.

Scheme 4.28: Reagents and conditions: (i) 4 eq. $\text{BH}_3\cdot\text{SMe}_2$, 0.2 eq. (*R*)-CBS-Me, THF, -10 to 0 °C, 92%.

The final step was to convert the *N*-Boc group to *N*-methyl group, by using the usual conditions with LiAlH_4 in refluxing THF.¹⁰⁰ The target molecule sedinine **4-2** was obtained in 40% yield, accompanied by the formation of byproduct **4-58** in 30% yield (Scheme 4.29). To improve the yield of the reaction, Red-Al in refluxing toluene was also investigated. However, sedinine was obtained in 50% yield, accompanied by the formation of **4-58** in 30% yield. To our delight, the alane-dimethyl ethylamine complex in refluxing THF provided the target molecular in 70% yield, giving the byproduct **4-58** in 15% yield. This byproduct **4-58** appears to be formed by C-N fission from intermediate **4-57**, perhaps due to the bulk of the piperidine fragment, whereas C-O fission gives sedinine **4-2**.

Scheme 4.29: *Reagents and conditions:* (i) LiAlH_4 , THF, reflux, 24 h, 40%. (ii) Red-Al, toluene, reflux, 6 h, 50%. (iii) alane-dimethyl ethylamine, THF, reflux, 70%.

The NMR spectroscopic data of sedinine **4-2** were consistent with those reported in literatures^{86,87} (Table 4.4).

Table 4.4: Compared physical and spectral data for sedinine **4-2**.

	Literature ^{86,87}	Our synthetic data	
Optical Rotation	$[\alpha]_D^{20}$ -98 (<i>c</i> 1.9, MeOH)	$[\alpha]_D^{20.3}$ -97.19 (<i>c</i> 0.57, MeOH)	
Melting Point	120-121 °C	118-120 °C	
¹ H NMR	300 MHz, CDCl ₃	500 MHz, CDCl ₃	
	5.75 (H-4, 10.3, 5.6, 2.2, 2.0) 5.56 (H-3, 10.3, 4.0, 2.2, 1.7) 4.80 (H-2', 9.4, 4.4) 4.01 (H-2'', 9.7, 6.2, 3.2) 3.28 (H-6, 11, 7.8, 6.1, 4.1) 3.18 (H-2, 10, 4, 3.3, 2.2, <1) 1.97 (H-5, 18.2, 11, 2.2, 2) 1.95 (H-1'', 14.3, 9.4, 7.8) 1.84 (H-5, 18.2, 5.6, 4.1, 1.7) 1.69 (H-1', 14.6, 10, 9.7) 1.68 (H-1'', 14.3, 6.1, 4.4) 1.50 (H-1', 14.6, 3.3, 3.2) 1.20 (H-3'', 6.2)	5.75 (H-4, 10.3, 5.3, 1.7) 5.56 (H-3, 10.3, 3.9, 1.9) 4.81 (H-2', 9.3, 4.5) 4.01 (H-2'', 9.4, 6.2, 3.2) 3.28 (H-6, 12, 6.0, 6.0) 3.18 (H-2, 10.3) 2.00-1.92 (H-5 + H-1'', multiplet) 1.83 (H-5, 18.0, 4.5) 1.72-1.65 (H-1' + H-1'', multiplet) 1.50 (H-1', 14.5, 3.3) 1.18 (H-3'', 6.2)	
¹³ C NMR	CDCl ₃	100 MHz, CDCl ₃	$\Delta\delta$
	72.9 (C-2') 68.6 (C-2'') 62.6 (C-2) 49.3 (C-6) 42.1 (C-1') 40.7 (C-1'') 34.7 (<i>N</i> -Me) 24.4 (C-5) 23.8 (C-3'')	73.1(C-2') 68.7(C-2'') 62.7(C-2) 49.2(C-6) 42.1(C-1') 40.6 (C-1'') 34.6 (<i>N</i> -Me) 24.3 (C-5) 23.8 (C-3'')	+0.2 +0.1 +0.1 -0.1 0 -0.1 -0.1 -0.1 0

4.3. Summary

In summary, a convenient asymmetric synthesis of sedinine **4-2**, one of the most complex *sedum* alkaloids, has been successfully accomplished in 14 steps and 6%

overall yield, starting from commercially available propylene glycol **4-22**. To our knowledge, this is the second synthesis of sedinine and the first asymmetric synthesis. In addition, we employed the allenic hydroxylamine cyclization and ring closing metathesis to form a key bicyclic *N,O*-acetal, containing a double bond. The excellent diastereoselectivity in the alkylation to monocyclic *N*-acyl iminium ion shows that inclusion of an alkene in the ring is an additional strategy for switching from *cis* to *trans* addition, due to the steric control.

CHAPTER 5

EXPERIMENTAL SECTION

5.1. General Methods

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran was distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane and acetonitrile were dried by distillation from CaH₂ immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received.

Analytical TLC was carried out on precoated plates (silica gel 60, F254). Column chromatography was performed with silica gel 60 (230–400 mesh).

¹H NMR spectra were recorded on a Bruker Advance DPX at 300, 400 or 500 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in ppm and coupling constants *J* are recorded in Hz. Multiplicities are recorded as singlet (s), broad singlet (brs), doublet (d), broad doublet (brd), triplet (t), quartet (q), multiplet (m).

Mass spectra were recorded on a Finnigan LCQ DECA XP MAX Ultra instrument or Finnigan Polaris Q, GCMS XP mass spectrometer. High resolution mass spectra were recorded on a Waters Q-Tof premier instrument or Finnigan MAT95XP instrument. Infrared spectra were recorded on a Shimadzu IR Prestige-21 FTIR or a Bruker

Alpha-E FTIR.

Melting points were determined on a OptiMelt MPA 100 and were uncorrected.

Optical rotations were recorded on an Jasco P-1030 polarimeter and are given with units of $10^{-1}\text{degcm}^2\text{g}^{-1}$. The angles of rotations were measured at wavelength of 589 nm.

Enantiomeric excess was determined by chiral HPLC analysis, performed on a Shimadzu HPLC and Daicel Chemical Industries Chiralcel OD-H column or OJ-H column, eluting with IPA/hexane.

5.2. Experimental Section for Chapter 2

GP1: General Procedure for *N*-Protected amino alcohols

Tosyl chloride (1.05 mmol) was added slowly to a solution of free amino alcohol (1 mmol) and triethylamine (1.2 mmol) in CH₂Cl₂ (10 mL) at 0 °C. Then the reaction was allowed to warm to room temperature and stirred for 6 h further. Water was added and the mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the protected amino alcohol, which was used without purification.

N-(3-Hydroxybutyl)-4-methylbenzenesulfonamide (2-42a)

Yield 90 %; colourless solid.

¹H NMR (400 MHz, CDCl₃) δ 7.75 (2H, d, J = 8.1 Hz, Ar), 7.31 (2H, d, J = 8.1 Hz, Ar), 5.08 (1H, br, NH), 3.94-3.91 (1H, m, CH), 3.19-3.15 (1H, m, CH₂N), 3.03-3.00 (1H, m, CH₂N), 2.43 (3H, s, Ar-CH₃), 1.68-1.52 (2H, m, NCH₂-CH₂-CHO), 1.17 (3H, d, J = 6.2 Hz, CH₃-CH).

¹³C NMR (75 MHz, CDCl₃) δ 143.1 (Ar), 136.5 (Ar), 129.5 (2C, Ar), 126.8 (2C, Ar), 65.8, 40.4, 37.5, 23.2, 21.3.

IR (nujol) 3282, 1598, 1157, 816, 663 cm⁻¹.

MS m/z 244 [M+H]⁺, 184 (39%), 155 (base peak), 91 (98%).

HRMS m/z calcd. for $C_{11}H_{17}O_3NS$ $[M]^+$ 243.0924, found 243.0929.

Methyl 3-hydroxybutylcarbamate (2-42b)

Yield 72%; colourless oil.

1H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, br, $\underline{NH}$), 3.91-3.87 (1H, m, $\underline{CH}$), 3.67 (3H, s, OCH_3), 3.54-3.46 (1H, m, $\underline{CH_2N}$), 3.20-3.16 (1H, m, $\underline{CH_2N}$), 2.60 (1H, br, OH), 1.66-1.52 (2H, m, $NCH_2-\underline{CH_2}-CHO$); 1.22 (3H, d, $J = 6.3$ Hz, $\underline{CH_3CH}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7 (C=O), 65.0, 51.8, 38.6, 37.7, 23.1.

IR (neat) 3367, 1697 cm^{-1} .

MS m/z 148 $[M+H]^+$, 129 (29%), 114 (68%), 88 (base peak).

HRMS m/z calcd. for $C_6H_{13}O_3N$ $[M]^+$ 147.0890, found 147.0887.

Allyl 3-hydroxybutylcarbamate (2-42c)

Yield 71%; colourless oil.

1H NMR (300 MHz, $CDCl_3$) δ 5.90 (1H, ddt, $J = 17.1, 10.5, 5.7$ Hz, $\underline{CH=CH_2}$), 5.30 (1H, dd, $J = 1.5, 17.1$ Hz, $\underline{CH_2=CH}$), 5.21 (1H, dd, $J = 1.2, 10.5$ Hz, $\underline{CH_2=CH}$), 5.08 (1H, br, $\underline{NH}$), 4.56 (2H, d, $J = 5.7$ Hz, $\underline{CH_2-CH=CH_2}$), 3.90-3.84 (1H, m, $\underline{CH}$), 3.52-3.47 (1H, m, NCH_2), 3.22-3.15 (1H, m, NCH_2), 1.69-1.51 (2H, m, $CHCH_2CH_3$), 1.21 (3H, d, $J = 6.0$ Hz, $\underline{CHCH_3}$).

^{13}C NMR (75 MHz, CDCl_3) δ 157.0 (C=O), 132.7 (CH=CH), 117.3 (CH=CH), 65.3, 65.1, 38.6, 37.8, 23.1.

IR (neat) 3420, 2965, 2932, 2874, 1694 cm^{-1} .

MS m/z 174 $[\text{M}+\text{H}]^+$, 156 (24%), 114 (36%), 88 (52%), 58 (base peak).

HRMS m/z calcd. for $\text{C}_8\text{H}_{15}\text{O}_3\text{N} [\text{M}]^+$ 173.1046, found 173.1042.

***N*-(4-Hydroxybutan-2-yl)-4-methylbenzenesulfonamide (2-44)**

Yield 68 %; colourless solid; m.p. 58-59 $^{\circ}\text{C}$.

^1H NMR (300 MHz, CDCl_3) δ 7.77 (2H, d, J = 8.1 Hz, Ar), 7.29 (2H, d, J = 8.1 Hz, Ar), 4.74 (1H, d, J = 8.2 Hz, NH), 3.89-3.81 (1H, m, CH), 3.66-3.49 (2H, m, CH_2O), 2.43 (3H, s, ArCH_3), 2.18 (1H, t, J = 5.2 Hz, OH), 1.76-1.65 (1H, m, $\text{NCH-CH}_2\text{-CH}_2\text{O}$), 1.51-1.42 (1H, m, $\text{NCH-CH}_2\text{-CH}_2\text{O}$), 1.00 (3H, d, J = 6.6 Hz, $\text{CH}_3\text{-CH}$).

^{13}C NMR (125 MHz, CDCl_3) δ 143.4 (Ar), 137.8 (Ar), 129.7 (2C, Ar), 127.0 (2C, Ar), 59.1, 47.5, 39.4, 21.7, 21.5.

IR (nujol) 3171, 1317, 918, 665 cm^{-1} .

MS m/z 244 $[\text{M}+\text{H}]^+$, 198 (base peak), 155 (74%), 91 (59%).

HRMS m/z calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_3\text{NS} [\text{M}]^+$ 243.0924, found 243.0925.

GP2: General Procedure for the synthesis of Cyclic *N,O*-Acetals Using Amberlyst-15

The acetaldehyde (1.2 mmol) was added to a solution of protected amino alcohol (1 mmol) in CH_2Cl_2 (10 mL) with trace of amberlyst-15 and 4 Å molecular sieves at room temperature. The mixture was stirred at room temperature for 2 h and then filtered through celite, washing with CH_2Cl_2 . The filtrate was evaporated *in vacuo* to give the acetal, which was used in the next step without purification.

2-Methyl-3-tosyloxazolidine (2-38a)

Yield 100 %; colourless solid; m.p. 129-131 °C.

^1H NMR (300 MHz, CDCl_3) δ 7.74 (2H, d, $J = 8.1$ Hz, Ar), 7.34 (2H, d, $J = 8.1$ Hz, Ar), 5.17 (1H, q, $J = 5.5$ Hz, CH), 3.90 (1H, dt, $J = 8.1, 5.7$ Hz, CH_2O), 3.47-3.32 (3H, m, $\text{CH}_2\text{O} + \text{CH}_2\text{N}$), 2.44 (3H, s, ArCH_3), 1.48 (3H, d, $J = 5.5$ Hz, $\text{CH}_3\text{-CH}$).

^{13}C NMR (100 MHz, CDCl_3) δ 144.1 (Ar), 134.2 (Ar), 129.9 (2C, Ar), 127.8 (2C, Ar), 88.5 (CHCH_3), 65.2, 46.6, 22.1, 21.6.

IR (nujol) 1340, 1167, 673 cm^{-1} .

MS m/z 240 $[\text{M-H}]^+$, 226 (92%), 155 (82%), 91 (base peak).

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_3\text{NS}$: C, 54.75; H, 6.27; N, 5.80, Found: C, 54.61; H, 6.22; N, 5.78.

2-Ethyl-3-tosyloxazolidine (2-38b)

Yield 81%; colourless solid; m.p.: 71-72 °C.

^1H NMR (300 MHz, CDCl_3) δ 7.74 (2H, d, $J = 8.1$ Hz, Ar), 7.33 (2H, d, $J = 8.1$ Hz, Ar), 5.06 (1H, dd, $J = 4.5, 6.4$ Hz, CH), 3.84 (1H, ddd, $J = 8.2, 6.4, 4.2$ Hz, CH_2O), 3.24-3.55 (3H, m, $\text{CH}_2\text{N} + \text{CH}_2\text{O}$), 2.44 (3H, s, ArCH_3), 1.88-1.65 (2H, m, $\text{CH}_3\text{-CH}_2$); 0.97 (3H, t, $J = 7.2$ Hz, $\text{CH}_3\text{-CH}_2$).

^{13}C NMR (75 MHz, CDCl_3) δ 144.1 (Ar), 134.2 (Ar), 129.9 (2C, Ar), 127.7 (2C, Ar), 92.5 (OCHN), 65.1, 46.6, 28.5, 21.5, 8.5.

IR (nujol) 1342, 1165, 673 cm^{-1} .

MS m/z 254 $[\text{M-H}]^+$, 226 (base peak), 155 (92%), 91 (96%).

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_3\text{NS}$: C, 56.45; H, 6.71; N, 5.49, Found: C, 56.41; H, 6.72; N, 5.49.

3-Methoxycarbonyl-2-methyloxazolidine (2-38c)

Yield 73%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.23 (1H, q, $J = 5.3$ Hz, CH), 4.11-4.04 (1H, m, CH_2O), 3.87 (1H, dd, $J = 7.3, 1.3$ Hz, CH_2O), 3.72 (3H, s, OCH_3), 3.73-3.58 (1H, m, CH_2N), 3.45-3.37 (1H, m, CH_2N), 1.41-1.40 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$).

^{13}C NMR (100 MHz, CDCl_3) δ 154.0 (C=O), 86.1 (OCHN), 65.4, 52.4, 44.5, 20.0.

IR (neat) 1701, 1458, 1394, 771 cm^{-1} .

MS m/z 144 $[\text{M-H}]^+$, 130 (base peak).

HRMS m/z calcd. for $\text{C}_6\text{H}_{10}\text{O}_3\text{N}$ $[\text{M-H}]^+$ 144.0655, found 144.0654.

3-Methoxycarbonyl-2-ethyloxazolidine (2-38d)

Yield 87%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 5.09 (1H, dd, $J = 6.3, 2.5$ Hz, CH), 4.90-4.83 (1H, m, CH_2O), 4.09-4.02 (1H, m, CH_2O), 3.72 (3H, s, OCH_3), 3.73-3.68 (1H, m, CH_2N), 3.40-3.32 (1H, m, CH_2N), 1.83-1.60 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$); 0.92 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 154.2 (C=O), 90.0 (OCHN), 65.3, 52.3, 44.9, 26.5, 7.9;

IR (neat) 1712, 1454, 1382, 769 cm^{-1} .

MS m/z 158 $[\text{M-H}]^+$, 130 (base peak).

HRMS m/z calcd for $\text{C}_7\text{H}_{12}\text{O}_3\text{N}$ $[\text{M-H}]^+$ 158.0812, found 158.0813.

2-Methyl-3-tosyl-1,3-oxazinane (2-34a)

Yield 82%; colourless solid; m.p. 92-93 $^\circ\text{C}$.

^1H NMR (400 MHz, CDCl_3) δ 7.78 (2H, d, $J = 8.2$ Hz, Ar), 7.30 (2H, d, $J = 8.2$ Hz, Ar), 5.62 (1H, q, $J = 6.3$ Hz, CH), 3.89 (1H, dt, $J = 3.3, 11.4$ Hz, CH_2O), 3.71-3.67 (1H, m, CH_2O), 3.59-3.51 (2H, m, CH_2N), 2.43 (3H, s, ArCH_3), 1.55 (3H, d, $J = 6.3$ Hz, $\text{CH}_3\text{-CH}$), 1.40-1.24 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$).

^{13}C NMR (75 MHz, CDCl_3) δ 143.3 (Ar), 138.1 (Ar), 129.7 (2C, Ar), 127.4 (2C, Ar), 80.8, 59.5, 39.4, 23.5, 21.5, 17.3.

IR (nujol) 1340, 1153, 858, 760, 665 cm^{-1} .

MS m/z 254 $[\text{M-H}]^+$, 240 (base peak), 155 (64%), 91 (68%).

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_3\text{NS}$: C, 56.45; H, 6.71; N, 5.49, Found: C, 56.30; H, 6.66; N, 5.47.

2-Ethyl-3-tosyl-1,3-oxazinane (2-34b)

Yield 100 %; colourless solid; m.p. 53-54 $^{\circ}\text{C}$.

^1H NMR (400 MHz, CDCl_3) δ 7.79 (2H, d, $J = 8.1$ Hz, Ar), 7.30 (2H, d, $J = 8.1$ Hz, Ar), 5.38 (1H, t, $J = 7.2$ Hz, CH), 3.84-3.72 (2H, m, CH_2O), 3.52-3.40 (2H, m, CH_2N), 2.42 (3H, s, ArCH_3), 2.03-1.88 (2H, m, $\text{CH}_3\text{-CH}_2$), 1.35-1.28 (1H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 1.14 (1H, brd, $J = 13.4$ Hz, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 0.95 (3H, t, $J = 7.4$ Hz, $\text{CH}_3\text{-CH}_2$).

^{13}C NMR (75 MHz, CDCl_3) δ 140.8 (Ar), 135.8 (Ar), 127.2 (2C, Ar), 125.0 (2C, Ar), 82.4 (OCHN), 56.4, 36.6, 20.5, 20.3, 19.1, 7.0.

IR (nujol) 1338, 1155, 964, 875, 663 cm^{-1} .

MS m/z 268 $[\text{M-H}]^+$, 240 (base peak), 155 (80%), 91 (88%).

Anal. Calcd. for $\text{C}_{13}\text{H}_{19}\text{O}_3\text{NS}$: C, 57.97; H, 7.11; N, 5.20, Found: C, 58.14; H, 7.32; N, 5.00.

2-Phenyl-3-tosyl-1,3-oxazinane (2-34c) ⁴⁴

Yield 91%; colourless solid.

^1H NMR (300 MHz, CDCl_3) δ 7.90 (2H, d, $J = 8.3$ Hz, Ar), 7.51-7.34 (7H, m, Ar), 6.69 (1H, s, CH), 3.84 (1H, dd, $J = 14.5, 4.2$ Hz, CH_2O), 3.72 (1H, td, $J = 12.0, 2.8$ Hz, CH_2N), 3.59 (1H, dd, $J = 11.6, 4.2$ Hz, CH_2O), 3.31 (1H, td, $J = 14.1, 2.8$ Hz, CH_2N), 2.46 (3H, s, ArCH_3), 1.49-1.32 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$).

^{13}C NMR (75 MHz, CDCl_3) δ 143.6 (Ar), 138.1 (Ar), 136.1 (Ar), 129.8 (2C, Ar), 129.0 (2C, Ar), 128.2, 127.6 (2C, Ar), 127.2 (2C, Ar), 83.7 (OCHN), 60.0, 39.8, 23.1, 21.6.

3-Tosyl-1,3-oxazinane (2-34d)⁴⁵

Yield 94%; colourless solid.

^1H NMR (400 MHz, CDCl_3) δ 7.78 (2H, d, $J = 8.1$ Hz, Ar), 7.32 (2H, d, $J = 8.1$ Hz, Ar), 4.94 (1H, s, CH_2), 3.71 (2H, t, $J = 5.3$ Hz, CH_2O), 3.53 (2H, t, $J = 5.7$ Hz, CH_2N), 2.44 (3H, s, ArCH_3), 1.35 (2H, tt, $J = 5.5, 5.5$ Hz, $\text{CH}_2\text{-CH}_2\text{-CH}_2$).

^{13}C NMR (75 MHz, CDCl_3) δ 143.4 (Ar), 136.8 (Ar), 129.5 (2C, Ar), 127.3 (2C, Ar), 78.1 (OCH_2N), 67.1, 44.1, 23.3, 21.2.

3-Methoxycarbonyl-2-methyl-1,3-oxazinane-3-carboxylate (2-36e)⁴⁶

Yield 85%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 5.68 (1H, q, $J = 6.2$ Hz, CH), 4.03-3.91 (2H, m, CH_2O), 3.71 (3H, s, OCH_3), 3.73-3.66 (1H, m, CH_2N), 3.23 (1H, dt, $J = 12.6, 3.8$ Hz, CH_2N), 1.88-1.82 (1H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$); 1.58-1.53 (1H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 1.44 (3H, d, $J = 6.2$ Hz, CH_3CH).

^{13}C NMR (100 MHz, CDCl_3) δ 154.9 (C=O), 79.1 (OCHN), 59.6, 52.6, 36.9, 25.3, 15.9.

IR (neat) 1694, 1445, 1279, 770 cm^{-1} .

MS m/z 158 $[\text{M-H}]^+$, 144 (base peak), 88 (39%).

HRMS m/z calcd. for $\text{C}_7\text{H}_{12}\text{O}_3\text{N}$ $[\text{M-H}]^+$ 158.0812, found 158.0814.

3-Methoxycarbonyl-2-ethyl-1,3-oxazinane (2-36f)

Yield 87%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.42 (1H, t, $J = 7.2$ Hz, CH), 4.06 (1H, dd, $J = 13.5, 5.2$ Hz, CH_2O), 3.89 (1H, dt, $J = 11.6, 3.5$ Hz, NCH_2), 3.71 (3H, s, OCH_3), 3.69-3.66 (1H, m, CH_2O), 3.17 (1H, dt, $J = 12.9, 3.5$ Hz, CH_2N), 2.04-1.87 (2H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 1.85-1.37 (2H, m, CH_3CH_2), 0.91 (3H, t, $J = 7.4$ Hz, CH_3CH).

^{13}C NMR (75 MHz, CDCl_3) δ 155.3 (C=O), 83.4 (NCHO), 59.4, 37.1, 25.3, 22.0, 9.1.

IR (neat) 2966, 2876, 1701, 1450, 1279, 768 cm^{-1} .

MS m/z 174 $[\text{M+H}]^+$, 144 (base peak), 88 (24%).

HRMS m/z calcd. for $\text{C}_8\text{H}_{15}\text{O}_3\text{N}$ $[\text{M}]^+$ 173.1046, found 173.1045.

3-Methoxycarbonyl-2-phenyl-1,3-oxazinane (2-36g)

Yield 80%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.43-7.31 (5H, m, Ar), 6.73 (1H, s, CH), 4.17 (1H, brd, $J = 11.0$ Hz, CH_2O), 3.78 (3H, s, OCH_3), 3.76-3.68 (2H, m), 3.08 (1H, td, $J = 13.1$, 3.1 Hz, CH_2N), 2.39-1.96 (1H, m, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 1.38 (1H, brd, $J = 13.1$ Hz, $\text{CH}_2\text{-CH}_2\text{-CH}_2$).

^{13}C NMR (75 MHz, CDCl_3) δ 156.1 (C=O), 136.7 (Ar), 128.9 (2C, Ar), 128.0 (Ar), 126.9 (2C, Ar), 82.2 (OCHN), 60.4, 53.0, 38.3, 25.4.

IR (neat) 1709, 1456, 1026, 721 cm^{-1} .

MS m/z 221 $[\text{M}]^+$, 162 (76%), 105 (62%), 144 (base peak), 155 (64%), 91 (68%).

HRMS m/z calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_3\text{N}$ $[\text{M}]^+$ 221.1046, found 221.1042.

3-Methoxycarbonyl-2-pentyl-1,3-oxazinane (2-36h)

Yield 76%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 5.47 (1H, t, $J = 7.1$ Hz, CH), 4.03 (1H, dd, $J = 13.5$, 4.5 Hz, CH_2O), 3.87 (1H, td, $J = 11.6$, 3.6 Hz, NCH_2), 3.68 (3H, s, OCH_3), 3.70-3.61 (1H, m, CH_2O), 3.15 (1H, td, $J = 13.1$, 3.6 Hz, NCH_2), 1.92-1.81 (2H, m, $\text{CH-CH}_2\text{-CH}_2$), 1.74-1.68 (1H, m, $\text{OCH}_2\text{-CH}_2\text{-CH}_2\text{N}$), 1.49 (1H, td, $J = 10.6$, 2.5 Hz,

OCH₂-CH₂-CH₂N), 1.29-1.15 (6H, m), 0.87 (3H, t, $J = 3.7$ Hz, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 155.2 (C=O), 82.2 (NCHO), 59.4, 52.6, 37.1, 31.4, 28.8, 25.3, 24.4, 22.5, 13.9.

IR (neat) 1703, 1449, 1410, 1277, 770 cm⁻¹.

MS m/z 216 [M+H]⁺, 144 (base peak).

HRMS m/z calcd. for C₁₂H₂₂O₃N [M+H]⁺ 216.1594, found 216.1598.

3-Allyloxycarbonyl-2-ethyl-1,3-oxazinane (2-36i)

Yield 100%; colourless oil.

¹H NMR (300 MHz, CDCl₃) δ 5.93 (1H, ddt, $J = 17.1, 10.5, 5.4$ Hz, CH=CH₂), 5.46 (1H, t, $J = 7.1$ Hz, CH), 5.29 (2H, dd, $J = 17.1, 1.5$ Hz, CH₂=CH), 5.21 (2H, dd, $J = 10.5, 1.5$ Hz, CH₂=CH), 4.61 (2H, dd, $J = 5.4, 1.4$ Hz, CH₂-CH=CH₂), 4.08 (1H, dd, $J = 13.6, 5.4$ Hz, OCH₂), 3.90 (1H, td, $J = 11.6, 3.5$ Hz, NCH₂), 3.74-3.69 (1H, m, OCH₂), 3.18 (1H, td, $J = 13.0, 3.5$ Hz, NCH₂), 2.00-1.76 (2H, m, CH₂CH₃), 1.59-1.56 (2H, m, CH₂CH₂CH₂), 0.92 (3H, t, $J = 7.5$ Hz, CH₂CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 154.5 (C=O), 132.9 (CH=CH₂), 117.4 (CH=CH₂), 83.4 (OCHN), 66.0, 59.5, 37.1, 25.3, 22.1, 9.2.

IR (neat) 1694, 1441, 1416, 1016, 766 cm⁻¹.

MS m/z 200 [M+H]⁺, 170 (base peak), 126 (16%), 98 (36%), 70 (18%).

HRMS m/z calcd. for C₁₀H₁₈O₃N [M+H]⁺ 200.1821, found 200.1273.

3-Benzoyloxy carbonyl-2-ethyl-1,3-oxazinane (2-36j)

Yield 86 %; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.36-7.33 (5H, m, Ar), 5.48 (1H, t, $J = 7.1$ Hz, CH), 5.15 (2H, s, CH_2Ph), 4.10 (1H, dd, $J = 13.5, 5.1$ Hz, OCH_2), 3.89 (1H, td, $J = 11.6, 3.6$ Hz, NCH_2), 3.73-3.69 (1H, m, OCH_2), 3.19 (1H, td, $J = 13.0, 3.6$ Hz, NCH_2), 1.97-1.85 (2H, m, CH_3CH_2), 1.83-1.78 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.58-1.50 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 0.90 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 154.6 (C=O), 136.6 (Ar), 128.5 (2C, Ar), 128.0 (Ar), 127.8 (2C, Ar), 83.5 (OCHN), 67.1, 59.5, 37.2, 25.3, 22.1, 9.2.

IR (neat) 1697, 1454, 1418, 1016, 698 cm^{-1} .

MS m/z 250 $[\text{M}+\text{H}]^+$, 220 (46%), 176 (50%), 91 (base peak).

HRMS m/z calcd. for $\text{C}_{14}\text{H}_{19}\text{O}_3\text{N}_1$ $[\text{M}]^+$ 249.1359; found 249.1358.

3-tert-Butoxycarbonyl 2-ethyl-1,3-oxazinane (2-36k)

Yield 86%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.39 (1H, t, $J = 7.1$ Hz, CH), 4.03 (1H, dd, $J = 13.7, 5.1$ Hz, OCH_2), 3.87 (1H, td, $J = 11.6, 3.6$ Hz, NCH_2), 3.71-3.68 (1H, m, OCH_2), 3.09 (1H, td, $J = 13.2, 3.6$ Hz, NCH_2), 1.92-1.78 (2H, m, CH_3CH_2), 1.55-1.44 (2H, m,

$\text{CH}_2\text{-CH}_2\text{CH}_2$), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.90 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz, CDCl_3) δ 153.9 (C=O), 83.3 (OCHN), 79.8, 59.4, 36.6, 28.3 (3C, Boc), 25.3, 22.0, 9.2.

IR (neat) 1694, 1477, 1458, 1411, 1366, 1155 cm^{-1} .

MS m/z 216 $[\text{M}+\text{H}]^+$, 186 (24%), 130 (65%), 116 (50%), 86 (base peak).

HRMS m/z calcd. for $\text{C}_{11}\text{H}_{21}\text{O}_3\text{N}$ $[\text{M}]^+$ 215.1516, found 215.1523.

3- Benzoyl-ethyl-1,3-oxazinan (2-36l)

Yield 30 %; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.40 (5H, m, Ar), 5.42 (1H, br, CH), 4.20 (1H, br, OCH_2), 3.96 (1H, td, $J = 11.8, 3.2$ Hz, NCH_2), 3.77 (1H, dd, $J = 11.7, 5.3$ Hz, OCH_2), 3.25 (1H, td, $J = 13.2, 3.2$ Hz, NCH_2), 2.11-2.01 (2H, m, CH_3CH_2), 1.99-1.82 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.58-1.54 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 0.88 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz, CDCl_3) δ 170.5 (C=O), 135.9 (Ar), 129.7 (Ar), 128.5 (2C, Ar), 126.8 (2C, Ar), 77.2 (OCHN), 59.5, 39.9, 38.0, 25.8, 21.9, 9.2.

IR (neat) 2968, 2936, 2876, 1643, 1600, 1446, 1417, 1283, 880, 702 cm^{-1} .

MS m/z 220 $[\text{M}+\text{H}]^+$, 190 (68%), 105 (base peak).

HRMS m/z calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{N}$ (M) $^+$ 219.1254; found 219.1251.

***trans*-2-Ethyl-6-methyl-3-tosyl-1,3-oxazinane (2-45a)**

Yield 97%; colourless solid; m.p. 80-82 °C.

^1H NMR (400 MHz, CDCl_3) δ 7.80 (2H, d, $J = 8.1$ Hz, Ar), 7.30 (2H, d, $J = 8.1$ Hz, Ar), 5.49 (1H, t, $J = 7.4$ Hz, OCHN), 3.86-3.81 (1H, m, CH_2N), 3.79-3.74 (1H, m, OCH-CH₃), 3.45-3.41 (1H, m, CH_2N), 2.43 (3H, s, ArCH₃), 2.03-1.84 (2H, m, CH-CH₂-CH₃), 1.14 (1H, brd, $J = 13.4$ Hz, CH-CH₂-CH₂); 0.96 (3H, t, $J = 7.4$ Hz, CH₃-CH₂), 0.89 (3H, d, $J = 6.0$ Hz, CH₃-CH).

^{13}C NMR (100 MHz, CDCl_3) δ 143.2 (Ar), 138.1 (Ar), 129.4 (2C, Ar), 127.6 (2C, Ar), 84.8 (OCHN), 63.6, 38.9, 29.8, 23.0, 21.6, 21.4, 9.56.

IR (nujol) 1335, 1157, 675 cm^{-1} .

MS m/z 282 $[\text{M-H}]^+$, 254 (base peak), 155 (51%), 91 (45%).

Anal. Calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_3\text{NS}$: C, 59.34; H, 7.47; N, 4.94, Found: C, 59.33; H, 7.53; N, 4.83.

***trans*-3-Allyloxycarbonyl-2-ethyl-6-methyl-1,3-oxazinane (*trans*-2-45b)**

Yield 71%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.91 (1H, ddd, $J = 17.1, 10.5, 5.4$ Hz, CH₂=CH), 5.54 (1H, br, OCHN), 5.27 (1H, dd, $J = 17.1, 1.5$ Hz, CH₂=CH), 5.18 (1H, dd, $J = 10.5, 1.5$ Hz, CH₂=CH), 4.59 (2H, d, $J = 5.4$ Hz, CH₂CH=CH₂), 4.14-4.11 (1H, m, CH₂N),

3.97-3.86 (1H, m, CH₃-CHO), 3.15-3.11 (1H, m, CH₂N), 1.99-1.94 (1H, m, CH₂-CH₃), 1.79 (1H, br, CH₂-CH₃), 1.52-1.46 (2H, m, CH-CH₂-CH₂), 1.14 (3H, d, *J* = 6.0 Hz, CH₃CH), 0.89 (3H, t, *J* = 7.5 Hz, CH₃-CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 154.8 (C=O), 133.0 (CH=CH₂), 117.2 (CH=CH₂), 88.0 (OCHN), 69.7, 65.7, 37.6, 32.8, 27.2, 21.6, 8.9.

IR (neat) 2972, 2936, 2878, 1697, 766 cm⁻¹.

MS *m/z* 214 [M+H]⁺, 184 (base peak), 98 (48%), 70 (28%).

HRMS *m/z* calcd. for C₁₁H₂₀O₃N [M+H]⁺ 214.1438, found 214.1446.

***cis*-3-Allyloxycarbonyl-2-ethyl-6-methyl-1,3-oxazinane (*cis*-2-45b)**

Yield 5%; colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 5.92 (1H, ddd, *J* = 17.2, 10.6, 5.2 Hz, CH₂=CH), 5.29 (1H, d, *J* = 17.2 Hz, CH₂=CH), 5.20 (1H, d, *J* = 10.6 Hz, CH₂=CH), 4.94 (1H, t, *J* = 5.6 Hz, OCHN), 4.90 (2H, d, *J* = 5.2 Hz, OCH₂CH=CH₂), 3.75 (1H, ddd, *J* = 13.3, 7.5, 3.6 Hz, CH₂N), 3.65-3.57 (1H, m, CH₃-CHO), 3.32 (1H, ddd, *J* = 14.2, 8.2, 6.4 Hz, CH₂N), 1.97-1.88 (1H, m, CH₂-CH₃), 1.83-1.72 (2H, m), 1.53-1.45 (1H, m, CH-CH₂-CH₂), 1.22 (3H, d, *J* = 6.0 Hz, CH₃CH), 0.94 (3H, t, *J* = 7.2 Hz, CH₃-CH₂).

¹³C NMR (125 MHz, CDCl₃) δ 154.4 (C=O), 133.0 (CH=CH₂), 117.3 (CH=CH₂), 83.1 (OCHN), 66.0, 64.3, 37.2, 32.6, 22.0, 21.8, 9.4.

***trans*-3-Methoxycarbonyl-2-ethyl-6-methyl-1,3-oxazinane (*trans*-2-45c)**

Yield 72%; colourless oil; ^1H NMR (400 MHz, CDCl_3) δ 5.53 (1H, br, OCHN), 4.15 (1H, br, CH_2N), 3.95-3.90 (1H, m, $\text{CH}_3\text{-CH}$), 3.70 (3H, s, OCH_3), 3.12 (1H, br, CH_2N), 1.97-1.92 (1H, m, $\text{CH}_2\text{-CH}_3$); 1.77-1.74 (1H, m, $\text{CH}_3\text{-CH}_2$), 1.50-1.43 (2H, m, $\text{CH-CH}_2\text{-CH}_2$), 1.15 (3H, d, $J = 6.1$ Hz, CH_3CH), 0.90 (3H, t, $J = 7.4$ Hz, $\text{CH}_3\text{-CH}_2$). ^{13}C NMR (100 MHz, CDCl_3) δ 155.1 (C=O), 83.0 (OCHN), 64.1, 52.5, 37.1, 32.5, 22.0, 21.7, 9.2.

IR (neat) 1703, 1450, 1410, 768 cm^{-1} .

MS m/z 186 $[\text{M-H}]^+$, 158 (base peak), 104 (59%), 88 (60%), 55 (39%).

HRMS m/z calcd. for $\text{C}_9\text{H}_{16}\text{O}_3\text{N}$ $[\text{M-H}]^+$ 186.1125, found 186.1120.

***cis*-3-Methoxycarbonyl-2-ethyl-6-methyl-1,3-oxazinane (*cis*-2-45c)**

Yield 8%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 4.90 (1H, t, $J = 6.0$ Hz, OCHN), 3.74-3.67 (1H, m, CH_3CHO), 3.69 (3H, s, OCH_3), 3.65-3.58 (1H, m, CH_2N), 3.32 (1H, ddd, $J = 13.6, 9.2, 6.4$ Hz, CH_2N), 1.95-1.86 (1H, m, $\text{CH}_2\text{-CH}_3$), 1.82-1.72 (2H, m), 1.52-1.44 (1H, m, $\text{CH-CH}_2\text{-CH}_2$), 1.21 (3H, d, $J = 6.4$ Hz, CH_3CH), 0.94 (3H, t, $J = 7.6$ Hz, $\text{CH}_3\text{-CH}_2$).

***cis*-2-Ethyl-4-methyl-3-tosyl-1,3-oxazinane (2-47)**

Yield 86%; colourless solid; m.p. 115-116 °C.

^1H NMR (400 MHz, CDCl_3) δ 7.76 (2H, d, $J = 8.1$ Hz, Ar), 7.29 (2H, d, $J = 8.1$ Hz, Ar), 5.36 (1H, t, $J = 7.2$ Hz, OCHN), 4.02-3.96 (1H, m, CH_3CHN), 3.86 (1H, td, $J = 11.4, 3.1$ Hz, CH_2O), 3.30 (1H, dt, $J = 12.0, 4.4$ Hz, CH_2O), 2.42 (3H, s, ArCH_3), 2.04-1.90 (2H, m, $\text{CH}_2\text{-CH}_3$), 1.52-1.40 (1H, m, $\text{CH-CH}_2\text{-CH}_2$); 1.43 (3H, d, $J = 7.1$ Hz, $\text{CH}_3\text{-CH}$), 1.18 (1H, dd, $J = 13.6, 2.8$ Hz, $\text{CH-CH}_2\text{-CH}_2$); 0.99 (3H, d, $J = 7.4$ Hz, $\text{CH}_3\text{-CH}_2$).

^{13}C NMR (100 MHz, CDCl_3) δ 143.2 (Ar), 137.6 (Ar), 129.6 (2C, Ar), 127.2 (2C, Ar), 84.9 (OCHN), 55.6, 46.5, 28.0, 27.9, 22.8, 21.5, 10.2.

IR (nujol) 1331, 1155, 814, 667 cm^{-1} .

MS m/z 284 $[\text{M}+\text{H}]^+$, 254 (base peak), 173 (26%), 155 (43%), 91 (41%).

HRMS m/z calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3\text{NS}$ $[\text{M}-\text{H}]^+$ 282.1158, found 282.1155.

GP3: General Procedure for the Ring–Opening Reaction of Cyclic *N,O*-Acetal Using Lewis Acids in CH_2Cl_2

TiCl_4 (1.2 mmol, 1M in toluene) was added to a cooled (-78 °C) solution of cyclic *N,O*-acetal (1.0 mmol) and allyltrimethylsilane (1.2 mmol) dropwise in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was stirred at -78 °C for 0.5 h. The reaction

mixture was quenched with a saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo* to give the amino alcohol.

***N*-(3-Hydroxypropyl)-4-methyl-N-(pent-4-en-2-yl) benzenesulfonamide (2-39a)**

Yield 82%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.70 (2H, d, $J = 8.1$ Hz, Ar), 7.28 (2H, d, $J = 8.1$, Ar), 5.68-5.54 (1H, m, $\text{CH}_2=\text{CH}$), 5.02 (1H, d, $J = 7.8$ Hz, $\text{CH}_2=\text{CH}$), 5.01 (1H, d, $J = 6.2$ Hz, $\text{CH}_2=\text{CH}$), 3.93 (1H, tq, $J = 6.8, 6.8$ Hz, CHN), 3.75 (2H, t, $J = 6.8$ Hz, OCH_2), 3.41-3.30 (2H, m, NCH_2), 2.41 (3H, s, ArCH_3), 2.27-2.06 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.84 (2H, tt, $J = 6.8$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.00 (3H, d, $J = 6.8$ Hz, CH_3CH).

^{13}C NMR (75 MHz; CDCl_3) δ 143.2 (Ar), 137.8 (Ar), 134.8 ($\text{CH}=\text{CH}_2$), 129.7 (2C, Ar), 127.0 (2C, Ar), 117.4 ($\text{CH}=\text{CH}_2$), 59.2, 53.9, 40.2, 39.9, 34.0, 21.5, 18.4.

IR (neat) 3524, 2972, 2930, 1599, 1456, 1337, 1153, 658 cm^{-1} .

MS m/z 256 [$\text{M}-\text{CH}_2\text{CH}=\text{CH}_2$], 212 (base peak), 155 (25%), 91 (28%).

HRMS m/z calcd. for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{NS}$ 256.1002 [$\text{M}-\text{CH}_2\text{CH}=\text{CH}_2$] $^+$, found 256.1005.

***N*-(Hex-5-en-3-yl)-N-(3-hydroxypropyl)-4-methyl benzenesulfonamide (2-39b)**

Yield 99%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.71 (2H, d, $J = 8.3$ Hz, Ar), 7.28 (2H, d, $J = 8.3$, Ar), 5.58-5.53 (1H, m, $\text{CH}_2=\text{CH}$), 4.95 (1H, d, $J = 15.6$ Hz, $\text{CH}_2=\text{CH}$), 4.94 (1H, d, $J = 11.5$ Hz, $\text{CH}_2=\text{CH}$), 3.75 (2H, t, $J = 6.3$ Hz, OCH_2), 3.62 (1H, tt, $J = 7.3$ Hz, CHN), 3.28-3.22 (2H, m, NCH_2), 2.42 (3H, s, ArCH_3), 2.22-2.01 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.83 (2H, tt, $J = 6.3, 6.3$ Hz, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.57-1.50 (1H, m, CH_3CH_2), 1.38-1.25 (1H, m, CH_3CH_2), 0.79 (3H, t, $J = 7.3$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz; CDCl_3) δ 143.1 (Ar), 137.9 (Ar), 135.1 ($\text{CH}=\text{CH}_2$), 129.5 (2C, Ar), 127.1 (2C, Ar), 117.2 ($\text{CH}=\text{CH}_2$), 60.3, 59.5, 40.4, 38.1, 34.0, 25.8, 21.5, 11.4.

IR (neat) 3524, 2966, 2936, 2877, 1599, 1456, 1383, 1334, 1153, 658 cm^{-1} .

MS m/z 270 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]^+$, 226 (45%), 155 (38%), 91 (60%).

HRMS m/z calcd. for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{NS}$ 270.1158 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]^+$, found 270.1158.

***N*-(3-Hydroxypropyl)-4-methyl-*N*-(1-phenylbut-3-enyl) benzenesulfonamide (2-39c)**

Yield 32%; colourless oil.

^1H NMR (300 MHz; CDCl_3) δ 7.71 (2H, d, $J = 8.3$ Hz, Ar), 7.31-7.24 (7H, m, Ar), 5.63-5.49 (1H, m, $\text{CH}=\text{CH}_2$), 5.06-5.01 (1H, m, PhCH), 4.96-4.91 (2H, m, $\text{CH}=\text{CH}_2$), 3.53-3.46 (2H, m, CH_2O), 3.24- 3.18 (2H, m, CH_2N), 2.88-2.78 (1H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.41 (3H, s, Ar), 2.40-2.33 (1H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.03 (1H, br, OH), 1.47-1.36 (2H,

m, CH₂CH₂CH₂).

¹³C NMR (100 MHz, CDCl₃) δ 143.3 (Ar), 137.8 (2C, Ar), 134.2 (CH=CH₂), 129.7(2C, Ar), 128.5 (2C, Ar), 128.4 (2C, Ar), 128.0 (Ar), 127.2 (2C, Ar), 117.7 (CH=CH₂), 60.2, 59.0, 40.8, 35.2, 32.9, 21.5.

IR (neat) 3524, 3065, 2947, 2878, 1599, 1454, 1335, 1157, 662 cm⁻¹.

MS *m/z* 318 [M-CH₂CH=CH₂]⁺, 91 (base peak).

HRMS *m/z* calcd. for C₁₇H₂₀O₃NS 318.1158 [M-CH₂CH=CH₂]⁺, found 318.1159.

***N*-(But-3-enyl)-*N*-(3-hydroxypropyl)-4-methylbenzenesulfonamide (2-39d)**

Yield 94%; colourless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.67 (2H, d, *J* = 8.1 Hz, Ar), 7.28 (2H, d, *J* = 8.1 Hz, Ar), 5.68-5.55 (1H, m, CH₂=CH), 5.00-4.93 (2H, m, CH₂=CH), 3.66 (2H, t, *J* = 6.3 Hz, OCH₂), 3.19 (2H, t, *J* = 6.3 Hz, NCH₂), 3.14-3.09 (2H, m, NCH₂), 2.35 (3H, s, ArCH₃), 2.22 (2H, ddd, *J* = 15.0, 7.5, 7.5 Hz, CH₂CH=CH₂), 1.69 (2H, tt, *J* = 6.3, 6.3 Hz, OCH₂CH₂CH₂N).

¹³C NMR (75 MHz; CDCl₃) δ 143.3 (Ar), 136.4 (Ar), 134.5 (CH=CH₂), 129.7 (2C, Ar), 127.0 (2C, Ar), 117.1 (CH=CH₂), 58.7, 48.3, 45.1, 33.2, 31.2, 21.4.

IR (neat) 3437, 2930, 2876, 1641, 1599, 1458, 1155, 918 cm⁻¹.

MS *m/z* 284 [M+H]⁺, 242 [M-CH₂CH=CH₂]⁺, 198 (base peak), 155 (20%), 91 (22%).

HRMS *m/z* calcd. for C₁₁H₁₆O₃NS 242.0845 [M-CH₂CH=CH₂]⁺, found 242.0838.

Methyl 3-hydroxypropyl(pent-4-en-2-yl)carbamate (2-39e)

Yield 85%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.73-5.63 (1H, m, $\text{CH}_2=\text{CH}$), 5.04 (1H, d, $J = 17.8$ Hz, $\text{CH}_2=\text{CH}$), 5.03 (1H, d, $J = 9.3$ Hz, $\text{CH}_2=\text{CH}$), 3.67 (3H, s, OCH_3), 3.62-3.47 (3H, m, $\text{CH}_2\text{O}+\text{CHN}$), 3.31 (2H, br, CH_2N), 2.32-2.19 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.68 (2H, br, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.16 (3H, d, $J = 6.9$ Hz, CH_3CH).

^{13}C NMR (75 MHz; CDCl_3) δ 158.3 (C=O), 135.1 ($\text{CH}=\text{CH}_2$), 117.1 ($\text{CH}=\text{CH}_2$), 59.0, 58.8, 52.5, 40.3, 39.4, 32.6, 18.9.

IR (neat) 3435, 2955, 2930, 2874, 1694, 1057 cm^{-1} .

MS m/z 202 $[\text{M}+\text{H}]^+$, 160 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]$ (58%), 116 (base peak), 84 (24%).

HRMS m/z calcd. for $\text{C}_{10}\text{H}_{19}\text{O}_3\text{N}$ 201.1359 $[\text{M}]^+$, found 201.1359.

Methyl hex-5-en-3-yl(3-hydroxypropyl)carbamate (2-39f)

Yield 99%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.77-5.65 (1H, m, $\text{CH}_2=\text{CH}$), 5.04 (1H, d, $J = 17.2$ Hz, $\text{CH}_2=\text{CH}$), 5.02 (1H, d, $J = 9.3$ Hz, $\text{CH}_2=\text{CH}$), 3.92 (1H, br, NCH), 3.71 (3H, s, OCH_3), 3.72-3.60 (3H, m, $\text{CH}_2\text{O}+\text{NHCH}$), 3.36-3.17 (2H, m, CH_2N), 2.30-2.26 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.72-1.58 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.56-1.50 (2H, m, CH_3CH_2), 0.88

(3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (100 MHz; CDCl_3) δ 158.8 (C=O), 135.2 ($\text{CH}=\text{CH}_2$), 117.1 ($\text{CH}=\text{CH}_2$), 60.2, 59.0, 52.7, 40.6, 38.0, 32.4, 26.0, 11.2.

IR (neat) 3439, 3076, 2961, 2875, 1693, 1060, 916, 773 cm^{-1} .

MS m/z 216 $[\text{M}+\text{H}]^+$, 174 (67%), 142 (32%), 130 (base peak).

HRMS m/z calcd. for $\text{C}_{11}\text{H}_{20}\text{O}_3\text{N}_1$ 214.1438 $[\text{M}-\text{H}]^+$, found 214.1440.

Methyl 3-hydroxypropyl(1-phenylbut-3-enyl)carbamate (2-39g)

Yield 67%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.28-7.33 (5H, m, Ar), 5.84-5.71 (1H, m, $\text{CH}_2=\text{CH}$), 5.29 (1H, brs, NCH), 5.14 (1H, d, $J = 17.3$ Hz, $\text{CH}_2=\text{CH}$), 5.08 (1H, d, $J = 10.2$ Hz, $\text{CH}_2=\text{CH}$), 3.71 (3H, s, OCH_3), 3.41 (2H, t, $J = 5.7$ Hz, CH_2O), 3.27-3.20 (2H, m, CH_2N), 2.78-2.72 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.65-1.35 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR (75 MHz; CDCl_3) δ 158.0 (C=O), 139.5 (Ar), 134.7 ($\text{CH}=\text{CH}_2$), 128.5 (3C, Ar), 128.0 (Ar), 127.8 (Ar), 117.6 ($\text{CH}=\text{CH}_2$), 59.0, 58.6, 52.9, 40.1, 35.3, 32.1.

IR (neat) 3443, 2954, 1672, 1469, 1447, 1404, 1057, 702 cm^{-1} .

MS m/z 264 $[\text{M}+\text{H}]^+$, 222 (74%), 118 (72%), 121 (52%), 91 (base peak).

HRMS m/z calcd. for $\text{C}_{15}\text{H}_{21}\text{O}_3\text{N}$ 263.1516 $[\text{M}-\text{H}]^+$, found 263.1507.

Methyl 3-hydroxypropyl(non-1-en-4-yl)carbamate (2-39h)

Yield 76%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 5.71-5.64 (1H, m, $\text{CH}_2=\text{CH}$), 5.02 (1H, d, $J = 17.9$ Hz, $\text{CH}_2=\text{CH}$), 5.01 (1H, d, $J = 8.5$ Hz, $\text{CH}_2=\text{CH}$), 4.01-3.83 (1H, m, CHN), 3.69 (3H, s, OCH_3), 3.69-3.57 (2H, m, CH_2O), 3.37-3.14 (2H, m, NCH_2), 2.29-2.19 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.67-1.69 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.48-1.46 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 1.27-1.25 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 0.86 (3H, t, $J = 6.6$ Hz, CH_3CH_2).

^{13}C NMR (100 MHz; CDCl_3) δ 158.8 (C=O), 135.2 ($\text{CH}=\text{CH}_2$), 117.1 ($\text{CH}=\text{CH}_2$), 59.0, 57.2, 52.7, 40.0, 38.2, 33.1, 32.5, 31.6, 26.2, 22.6, 14.0.

IR (neat) 3418, 2954, 2928, 2858, 1694, 1061, 914, 773 cm^{-1} .

MS m/z 258 $[\text{M}+\text{H}]^+$, 216 (76%), 184 (44%), 172 (48%), 102 (base peak).

HRMS m/z calcd. for $\text{C}_{14}\text{H}_{27}\text{O}_3\text{N}$ 257.1985 $[\text{M}]^+$, found 257.1982.

***N*-(2-Hydroxyethyl)-4-methyl-N-(pent-4-en-2-yl) benzenesulfonamide (2-40a)**

Yield 92%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.63 (2H, d, $J = 8.1$ Hz, Ar), 7.21 (2H, d, $J = 8.1$, Ar), 5.60-5.50 (1H, m, $\text{CH}_2=\text{CH}$), 4.99 (1H, d, $J = 13.5$ Hz, $\text{CH}_2=\text{CH}$), 4.98 (1H, d, $J = 7.2$ Hz, $\text{CH}_2=\text{CH}$), 3.96 (1H, tq, $J = 6.8, 6.8$ Hz, CHN), 3.82-3.73 (2H, m, OCH_2), 3.18-3.10 (2H, m, NCH_2), 2.70 (1H, br, OH), 2.33 (3H, s, ArCH_3), 2.15 (1H, ddd, $J =$

13.6, 6.8, 6.8 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.06 (1H, ddd, $J = 13.6, 6.8, 6.8$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 0.87 (3H, d, $J = 6.8$ Hz, CH_3CH).

^{13}C NMR (100 MHz; CDCl_3) δ 143.4 (Ar), 137.0 (Ar), 134.7 ($\text{CH}=\text{CH}_2$), 129.6 (2C, Ar), 127.1 (2C, Ar), 117.4 ($\text{CH}=\text{CH}_2$), 62.6, 53.9, 45.1, 39.8, 21.4, 18.0.

IR (neat) 3524, 2976, 2930, 1597, 1456, 1337, 1153, 658 cm^{-1} .

MS m/z 284 $[\text{M}+\text{H}]^+$, 242 (base peak), 155 (42%), 91 (62%), 70 (98%).

HRMS m/z calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3\text{NS}$ 282.1158 $[\text{M}-\text{H}]^+$, found 282.1144.

***N*-(Hex-5-en-3-yl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (2-40b)**

Yield 88%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 7.73 (2H, d, $J = 8.1$ Hz, Ar), 7.30 (2H, d, $J = 8.1$, Ar), 5.65-5.56 (1H, m, $\text{CH}_2=\text{CH}$), 4.95 (1H, d, $J = 16.2$ Hz, $\text{CH}_2=\text{CH}$), 4.94 (1H, d, $J = 11.1$ Hz, $\text{CH}_2=\text{CH}$), 3.77 (2H, td, $J = 5.9, 3.0$ Hz, OCH_2), 3.69 (1H, tt, $J = 7.2, 7.2$ Hz, CHN), 3.19 (2H, td, $J = 5.9, 2.2$ Hz, NCH_2), 2.43 (3H, s, ArCH_3), 2.13 (1H, ddd, $J = 14.4, 7.2, 7.2$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.98 (1H, ddd, $J = 14.4, 7.2, 7.2$ Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.57- 1.48 (1H, m, CH_3CH_2), 1.33-1.23 (1H, m, CH_3CH_2), 0.83 (3H, t, $J = 7.2$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz; CDCl_3) δ 143.4 (Ar), 137.3 (Ar), 135.0 ($\text{CH}=\text{CH}_2$), 129.8 (2C, Ar), 127.3 (2C, Ar), 117.4 ($\text{CH}=\text{CH}_2$), 62.6, 60.5, 45.6, 37.8, 25.8, 21.5, 11.3.

IR (neat) 3524, 2966, 2933, 2877, 1597, 1456, 1383, 1335, 1155, 658 cm^{-1} .

MS m/z 298 $[M+H]^+$, 256 (base peak), 155 (45%), 116 (44%), 91 (62%), 84 (85%).

HRMS m/z calcd. for $C_{15}H_{22}O_3NS$ 296.1315 $[M-H]^+$, found 296.1320.

Methyl 2-hydroxyethyl(pent-4-en-2-yl)carbamate (2-40c)

Yield 80%; colourless oil.

1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, br, $CH_2=CH$), 5.05 (1H, d, $J = 14.4$ Hz, $CH_2=CH$), 5.04 (1H, d, $J = 7.5$ Hz, $CH_2=CH$), 4.11 (1H, br, $HOCH_2$), 3.69 (5H, br, OCH_3+CH_2OH+NH), 3.35-3.28 (2H, m, CH_2N), 2.27-2.18 (2H, m, $CH_2CH=CH_2$), 0.88 (3H, d, $J = 7.4$ Hz, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (C=O), 135.0 ($CH_2=CH$), 117.3 ($CH_2=CH$), 63.5, 52.7, 52.3, 45.8, 39.3, 18.8.

IR (neat) 3410, 1702, 1453 cm^{-1} .

MS m/z 188 $[M+H]^+$, 146 (base peak), 114 (28%), 70 (26%).

HRMS m/z calcd. for $C_9H_{18}O_3N$ 188.1281 $[M+H]^+$, found 188.1273.

Methyl hex-5-en-3-yl(2-hydroxyethyl)carbamate (2-40d)

Yield 92%; colourless oil.

1H NMR (300 MHz, $CDCl_3$) δ 5.72-5.68 (1H, m, $CH_2=CH$), 5.03 (1H, d, $J = 11.2$ Hz,

$\text{CH}_2=\text{CH}$), 5.00 (1H, d, $J = 9.2$ Hz, $\text{CH}_2=\text{CH}$), 3.88-3.84 (1H, m, CH_2OH), 3.69-3.63 (5H, m, $\text{OCH}_3+\text{CH}_2\text{OH}+\text{NH}$), 3.30-3.20 (2H, m, CH_2N), 2.30-2.18 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.50-1.47 (2H, m, CH_3CH_2), 0.88 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz, CDCl_3) δ 159.4, 135.0, 117.2, 63.2, 58.5, 52.8, 45.9, 37.8, 25.9, 11.0.

IR (neat) 3437, 2965, 1712, 1469 cm^{-1} .

MS m/z 202 $[\text{M}+\text{H}]^+$, 160 (base peak), 128 (82%), 84 (24%).

HRMS m/z calcd. for $\text{C}_{10}\text{H}_{19}\text{O}_3\text{N}_1$ 201.1359 $[\text{M}]^+$, found 201.1359.

Allyl hex-5-en-3-yl(3-hydroxypropyl)carbamate (2-39i)

Yield 98%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.89 (1H, ddt, $J = 17.1, 10.2, 5.4$ Hz, $\text{OCH}_2\text{CH}_2=\text{CH}$), 5.76-5.63 (1H, m, $\text{CHCH}_2\text{CH}_2=\text{CH}$), 5.26 (1H, d, $J = 17.1$ Hz, $\text{OCH}_2\text{CH}_2=\text{CH}$), 5.17 (1H, d, $J = 10.2$ Hz, $\text{OCH}_2\text{CH}_2=\text{CH}$), 5.04-4.98 (2H, m, $\text{CHCH}_2\text{CH}_2=\text{CH}$), 4.58 (2H, d, $J = 5.4$ Hz, $\text{OCH}_2\text{CH}_2=\text{CH}$), 3.91-3.75 (1H, m, CHN), 3.56 (2H, m, CH_2OH), 3.31-3.13 (2H, m, CH_2N), 2.30-2.21 (2H, m, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 1.77-1.66 (2H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.53 (2H, dt, $J = 14.4, 7.2$ Hz, CH_3CH_2), 0.85 (3H, t, $J = 7.2$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz, CDCl_3) δ 157.8 (C=O), 135.2 ($\text{CH}=\text{CH}_2$), 132.9 ($\text{CH}=\text{CH}_2$), 117.4 ($\text{CH}=\text{CH}_2$), 117.1 ($\text{CH}=\text{CH}_2$), 66.1, 60.2, 59.0, 40.7, 38.0, 32.4, 26.1, 11.2.

IR (neat) 3435, 2965, 2932, 2875, 1672, 1059, 916, 733 cm^{-1} .

MS m/z 242 $[\text{M}+\text{H}]^+$, 200 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]$, base peak, 156 (68), 142 (48%), 112 (48%), 72 (42%).

HRMS m/z calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_3\text{N}$ 240.1594 $[\text{M}-\text{H}]^+$, found 240.1588.

Benzyl hex-5-en-3-yl(3-hydroxypropyl)carbamate (2-39j)

Yield 63%; colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.36 (5H, m, Ar), 5.69-5.62 (1H, m, $\text{CH}_2=\text{CH}$), 5.15 (2H, s, CH_2Ph), 4.98 (1H, d, $J = 17.6$ Hz, $\text{CH}_2=\text{CH}$), 4.97 (1H, d, $J = 9.2$ Hz, $\text{CH}_2=\text{CH}$), 4.97 (1H, s, $\text{CH}_2=\text{CH}$), 3.94-3.81 (1H, m, NCH), 3.65-3.53 (2H, t, $J = 5.7$ Hz, CH_2O), 3.36-3.19 (2H, m, CH_2N), 2.29-2.24 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.76-1.69 (1H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.59-1.50 (2H, m, CH_3CH_2), 0.85 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (75 MHz, CDCl_3) δ 158.1 (C=O), 136.6 (Ar), 135.2 ($\text{CH}=\text{CH}_2$), 128.5 (2C, Ar), 128.1 (Ar), 128.0 (Ar), 127.8 (Ar), 117.2 ($\text{CH}=\text{CH}_2$), 67.4, 60.4, 59.0, 40.7, 38.0, 32.4, 26.1, 11.2.

IR (neat) 3428, 2965, 2934, 2876, 1693, 1643, 1454, 1418, 1344, 1057, 698 cm^{-1} .

MS m/z 292 $[\text{M}+1]^+$, 250 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]$ (26%), 206 (40%), 91 (base peak).

HRMS m/z for $\text{C}_{18}\text{H}_{20}\text{O}_3\text{N}$ 250.1438 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]^+$, found 250.1436.

***tert*-Butyl hex-5-en-3-yl(3-hydroxypropyl)carbamate (2-39k)**

Yield 66%; colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 5.76-5.67 (1H, m, $\text{CH}_2=\text{CH}$), 5.03 (1H, d, $J = 10.8$ Hz, $\text{CH}_2=\text{CH}$), 5.01 (1H, d, $J = 7.2$ Hz, $\text{CH}_2=\text{CH}$), 4.02-3.91 (1H, m, NCH), 3.61-3.52 (2H, m, CH_2O), 3.31-3.05 (2H, m, CH_2N), 2.28-2.21 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.78-1.66 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.65-1.55 (2H, m, CH_3CH_2), 1.45 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.87 (3H, t, $J = 7.4$ Hz, CH_3CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 157.6 (C=O), 135.5 ($\text{CH}=\text{CH}_2$), 116.9 ($\text{CH}=\text{CH}_2$), 80.1, 59.6, 58.8, 40.6, 38.1, 32.4, 28.4, 26.3, 11.3.

IR (neat) 3429, 2968, 2932, 2876, 1694, 1366, 1165 cm^{-1} .

MS m/z 258 $[\text{M}+\text{H}]^+$, 216 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]$ (6%), 116 (base peak), 72 (58%).

HRMS m/z calcd. for $\text{C}_{11}\text{H}_{22}\text{O}_3\text{N}$ 216.1594 $[\text{M}-\text{CH}_2\text{CH}=\text{CH}_2]^+$, found 216.1590.

(Hex-5-en-3-yl)-N-(3-hydroxybutyl)-*p*-toluene sulfonamide (2-46a) (mixture of isomers)

Yield 87%; colourless oil.

^1H NMR (400 MHz) δ 7.69 (4H, d, $J = 8.3$ Hz, Ar), 7.27 (4H, d, $J = 8.3$ Hz, Ar), 5.54-5.60 (0.58H, m, $\text{CH}_2=\text{CH}$), 5.42-5.34 (1H, m, $\text{CH}_2=\text{CH}$), 4.99-4.87 (3H, m, $\text{CH}_2=\text{CH}$), 3.95-3.93 (2H, m), 3.60-3.58 (2H, m), 3.36-3.29 (2H, m), 3.15-3.09 (2H, m),

2.42 (6H, s, ArCH₃), 2.17-2.08 (2H, m), 1.92-1.77 (2H, m), 1.64-1.35 (8H, m), 1.26-1.19 (6H, m), 0.86 (3H, t, $J = 7.3$ Hz, CH₃CH₂), 0.69 (1.8H, t, $J = 7.3$ Hz, CH₃CH₂).

¹³C NMR (100 MHz, CDCl₃) δ 143.0 (2C, Ar), 137.8 (2C, Ar), 135.2 (CH=CH₂), 135.0 (CH=CH₂), 129.5 (2C, Ar), 129.4 (2C, Ar), 127.1 (2C, Ar), 127.0 (2C, Ar), 117.1 (2C, CH=CH₂), 65.0, 60.2 (2C), 40.5, 40.4, 40.3 (2C), 38.9, 37.4, 26.4, 25.1, 23.4 (2C), 21.4, 11.3 (2C).

Allyl hex-5-en-3-yl(3-hydroxybutyl)carbamate (2-46b) (mixture of isomers)

Yield 74%; colourless oil; ¹H NMR (400 MHz) δ 5.94-5.88 (1H, m, OCH₂CH=CH₂), 5.76-5.63 (1H, m, CHCH₂CH=CH₂), 5.31-5.19 (2H, m, OCH₂CH=CH₂), 5.05-4.99 (2H, m, CHCH₂CH=CH₂), 4.58 (2H, brd, $J = 4.9$ Hz, OCH₂CH=CH₂), 4.92-3.56 (3H, m), 3.19-3.00 (1H, m), 2.30-2.23 (2H, m, CHCH₂CH=CH₂), 1.70-1.43 (2H, m), 0.91-0.83 (3H, m, CH₃CH₂).

***N*-(Hex-5-en-3-yl)-*N*-(1-methyl-3-hydroxypropyl)-ptoluenesulfonamide (2-48)**

(mixture of isomers)

Yield 82%; colourless oil.

¹H NMR (400 MHz) δ 7.76-7.74 (4H, m, Ar), 7.29-7.27 (4H, m, Ar), 5.75-5.66 (1H, m,

CH₂=CH), 5.60-5.53 (1H, m, CH₂=CH), 5.09-4.95 (3H, m, CH₂=CH), 3.89-3.87 (1H, m), 3.85-3.77 (2H, m), 3.60-3.54 (1.5H, m), 3.12-3.09 (1.5H, m), 2.53-2.49 (2H, m), 2.42 (6H, s, ArCH₃), 2.34-2.30 (1H, m), 1.86-1.60 (6H, m), 1.18-1.13 (4.5H, m), 0.89 (1.6H, t, *J* = 7.4 Hz, CH₃CH₂), 0.77 (3H, t, *J* = 7.4 Hz, CH₃CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 142.8 (Ar), 142.7 (Ar), 139.4 (Ar), 139.2 (Ar), 136.1 (CH=CH₂), 135.6 (CH=CH₂), 129.4 (4C, Ar), 127.3 (2C, Ar), 127.2 (2C, Ar), 117.0 (2C, CH=CH₂), 60.0, 59.9, 59.4, 59.2, 50.0, 49.9, 39.6, 38.9, 38.6, 38.3, 27.0, 26.4, 21.4 (2C), 19.5, 19.3, 12.2, 12.0.

5.3. Experimental Section for Chapter 3

(*S*)-1-Chloropentan-2-ol (3-41).⁶¹

A trace of I₂ was added to a suspension of magnesium (0.77 g, 32.3 mmol) in Et₂O (16 mL). The mixture was heated at reflux until the color disappeared. Bromoethane was then added dropwise over 0.5 h, keeping the reaction mixture refluxing. After completion of addition, the mixture was heated at reflux for 1 h further. The resulting solution of ethylmagnesium bromide was added dropwise to a solution of (*R*)-epichlorohydrin (2.0 g, 21.6 mmol) **3-40** and CuCN (0.19 g, 2.16 mmol) in anhydrous THF (30 mL) at -78 °C. The mixture was warmed to -20 °C over 3 h and was quenched with a saturated NH₄Cl solution. The two layers were separated and the

aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford (*S*)-1-chloro-pentan-2-ol **3-41** as a yellowish oil (2.5 g, 94%) which was used without further purification.

$[\alpha]_{\text{D}}^{22.1} +1.0$ (*c* 2.7, CHCl₃), $[\alpha]_{\text{D}}^{24} -19.7$ (*c* 1.5, MeOH), [ref.61 $[\alpha]_{\text{D}}^{20} +1.1$ (*c* 2.9, CHCl₃)].

¹H NMR (300 MHz, CDCl₃) δ 3.84-3.80 (1H, m, CHOH), 3.64 (1H, dd, *J* = 11.1, 3.2 Hz, CH₂Cl), 3.48 (1H, dd, *J* = 11.1, 7.2 Hz, CH₂Cl), 2.12 (bs, 1H, OH), 1.58–1.39 (4H, m, CH₂CH₂), 0.95 (3H, t, *J* = 7.0 Hz, CH₃).

All data is consistent with those reported in literature.⁶¹

(*S*)-1,2-epoxypentane (3-42).⁶¹

Powdered NaOH (2.7 g, 68.6 mmol) was added to a solution of (*S*)-1-chloropentan-2-ol **3-41** (1.5 g, 12.2 mmol) in Et₂O (20 mL). The mixture was stirred vigorously for 24 h and water (20 mL) was added. After separation of the two layers, the aqueous layer was extracted with Et₂O (3 x 30 mL) and the combined organic layers were dried over anhydrous Na₂SO₄ and filtered through celite. Removal of the solvent by distillation through a 10 cm Vigreux-column afforded (*S*)-1,2-epoxypentane **3-42** (1.8 g) as a light yellow oil, which was used without further purification.

(S)-Hept-1-yn-4-ol (3-43).⁶²

Lithium acetylide-EDA complex (4.8 g, 52.3 mmol) was added to a solution of (*S*)-1,2-epoxypentane **3-42** (1.8 g, 20.9 mmol) in anhydrous DMSO (25 mL) at room temperature. The reaction mixture was stirred overnight (15 h) at room temperature. After quenching with ice slowly, the basic reaction mixture was neutralized by 2.0 M H₂SO₄ solution and was then extracted with Et₂O (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered through celite. The Et₂O solvent was removed slowly by normal distillation and the subsequent distillation under reduced pressure gave (*S*)-hept-1-yn-4-ol (2.34 g, 80%) as a colorless oil.

$[\alpha]_{\text{D}}^{25.2}$ -25.4 (*c* 2.0, MeOH), (ref.⁶² $[\alpha]_{\text{D}}$ -27.2 (*c* 1.1, MeOH)).

¹H NMR (300 MHz, CDCl₃) δ 3.78-3.75 (1H, m, CHOH), 2.43 (1H, ddd, *J* = 16.7, 4.7, 2.7 Hz, CH₂C $\equiv$ CH), 2.31 (1H, ddd, *J* = 16.7, 6.8, 2.7 Hz, CH₂C $\equiv$ CH), 2.05 (1H, t, *J* = 2.7 Hz, C $\equiv$ CH), 1.92 (1H, brd, *J* = 4.7 Hz, OH), 1.63-1.22 (4H, m, CH₃CH₂CH₂), 0.94 (t, *J* = 7.1 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 80.9(C $\equiv$ CH), 70.7 (C $\equiv$ CH), 69.6, 38.3, 27.3, 18.8, 13.9

All data is consistent with those reported in literature.⁶²

(S)-Octa-6,7-dien-4-ol (3-44).

Diisopropylamine (6.8 mL, 48.6 mmol) was added to a mixture of (*S*)-hept-1-yn-4-ol **3-43** (2.72 g, 24.3 mmol), paraformaldehyde (1.46 g, 48.6 mmol) and copper (I) bromide (1.15 g, 8.0 mmol) in dioxane (80 mL) at room temperature. The reaction was heated at reflux overnight (10 h) and then cooled to room temperature. Air was bubbled through the reaction mixture for 0.5 h. The reaction mixture was then filtered through celite, washing with Et₂O (3 x 15 mL). The filtrate was concentrated *in vacuo* to give a brown oil. The crude product was purified by distillation under reduced pressure to give (*S*)-octa-6,7-dien-4-ol **3-44** (2.05g, 67%) as a colourless oil.

$[\alpha]_D^{24.4}$ -5.2 (*c* 1.5, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.10 (1H, tt, *J* = 7.0, 7.0 Hz, CH=C=CH₂), 4.67 (2H, dt, *J* = 7.0, 2.8 Hz, CH=C=CH₂), 3.67-3.65 (1H, m, CHOH), 2.23-2.15 (1H, m, CH₂CH=C=CH₂), 2.12-2.03 (1H, m, CH₂CH=C=CH₂), 1.97 (1H, d, *J* = 3.4 Hz, OH), 1.47-1.27 (4H, m, CH₃CH₂-CH₂), 0.90 (3H, t, *J* = 6.8 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 209.3 (CH=C=CH₂), 86.3 (CH=C=CH₂), 74.6 (CH=C=CH₂), 70.8, 38.8, 36.4, 18.8, 14.0.

IR (neat) 3401, 2959, 1956 cm⁻¹.

MS *m/z* 149 [M+Na]⁺; HRMS *m/z* calcd. for C₈H₁₅O [M+H]⁺ 127.1123, found 127.1117.

2-((*R*)-Octa-6,7-dien-4-yloxy)isoindoline-1,3-dione (**3-45**).

A solution of diisopropyl azodicarboxylate (0.89 mL, 4.48 mmol) in THF (2 mL) was

added to a solution of (*S*)-octa-6,7-dien-4-ol **3-44** (0.47 g, 3.73 mmol), triphenylphosphine (1.17 g, 4.48 mmol) and *N*-hydroxyphthalimide (0.73 g, 4.48 mmol) in THF (8 mL) dropwise at -15 °C. The reaction mixture was stirred at -15 °C for 1 h. After evaporation of the solvent, the residue was subjected to purification by flash chromatography (EtOAc : Hexane = 1 : 9) to afford *N*-phthaloyl hydroxylamine **3-45** (0.81 g, 80%) as a colourless oil.

$[\alpha]_D^{23.8} +48.4$ (*c* 1.1, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 7.90-7.79 (2H, m, Ar), 7.76-7.71 (2H, m, Ar), 5.24 (1H, tt, *J* = 7.0, 7.0 Hz, CH=C=CH₂), 4.65 (2H, dt, *J* = 7.0, 2.9 Hz, CH=C=CH₂), 4.30 (1H, tt, *J* = 5.7, 5.7 Hz, CHON), 2.44-2.24 (2H, m, CH₂CH=C=CH₂), 1.80-1.50 (4H, m, CH₂CH₂), 0.96 (3H, t, *J* = 7.2 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 209.3 (CH=C=CH₂), 164.2 (2C, C=O), 134.3 (2C, Ar), 129.0 (2C, Ar), 123.4 (2C, Ar), 87.1 (CH=C=CH₂), 85.3 (CH=C=CH₂), 74.8, 34.3, 31.9, 18.3, 14.0.

IR (neat) 2961, 2936, 2872, 1956, 1789, 1732, 1468 cm⁻¹.

MS *m/z* 272 [M+H]⁺; HRMS *m/z* calcd. for C₁₆H₁₈O₃N [M+H]⁺ 272.1287, found 272.1286.

Chiral HPLC: Chiralcel OD-H (hexane / *i*-PrOH = 99 / 1, flow rate 0.30 mL / min, λ = 230 nm), *t*_R(minor) = 45.6 min, *t*_R(major) = 48.6 min; 99% ee.

(*R*)-Octa-6,7-dien-4-hydroxylamine (3-46).

Hydrazine monohydrate (0.54 mL, 11.1 mmol) was added to a solution of the *N*-phthaloyl hydroxylamine **3-45** (0.75 g, 2.77 mmol) in CH₂Cl₂ (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min and was filtered through celite, washing with Et₂O (3 x 8 mL). The filtrate was concentrated *in vacuo* to give hydroxylamine **3-46** (0.39 g, 100%) as a colourless oil, which was used without further purification.

$[\alpha]_D^{24} +29.2$ (*c* 1.3, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.23 (2H, brs, ONH₂), 5.10 (1H, tt, *J* = 7.0, 7.0 Hz, CH=C=CH₂), 4.67 (2H, dt, *J* = 7.0, 2.8 Hz, CH=C=CH₂), 3.59 (1H, tt, *J* = 6.0, 6.0 Hz, CHONH₂), 2.30-2.24 (2H, m, CH₂CH=C=CH₂), 1.47-1.23 (4H, m, CH₂CH₂), 0.92 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 209.3 (CH=C=CH₂), 86.1 (CH=C=CH₂), 83.0 (CH=C=CH₂), 74.2, 34.4, 31.7, 18.7, 14.1; IR (neat) 3316, 2959, 2934, 1956 cm⁻¹; MS *m/z* 142 [M+H]⁺; HRMS *m/z* calcd. for C₈H₁₆ON [M+H]⁺ 142.1232, found 142.1239.

***N*-tert-Butoxycarbonyl (*R*)-octa-6,7-dien-4-amine (3-39).**

Powered sodium hydroxide (0.41 g, 10.20 mmol) was added to a solution of the hydroxylamine **3-46** (0.60 g, 4.26 mmol) and di-*tert*-butyl dicarbonate (1.17 mL, 5.10 mmol) in CH₂Cl₂-H₂O (15 mL-15 mL) at room temperature. The reaction mixture was stirred at room temperature overnight and extracted with EtOAc (3 x 8 mL). The

combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to provide *N*-protected hydroxylamine **3-39** as a colourless oil (1.0 g, 98%).

$[\alpha]_{\text{D}}^{24.1} +40.8$ (c 1.3, CHCl_3).

^1H NMR (300 MHz, CDCl_3) δ 7.12 (1H, brs, NH), 5.12 (1H, tt, $J = 7.0, 7.0$, $\text{CH}=\text{C}=\text{CH}_2$), 4.63 (2H, dt, $J = 7.0, 2.8$ Hz, $\text{CH}=\text{C}=\text{CH}_2$), 3.77 (1H, tt, $J = 5.6, 5.6$ Hz, CHO), 2.31-2.24 (2H, m, $\text{CH}_2\text{CH}=\text{C}=\text{CH}_2$), 1.57-1.22 (4H, m, CH_2CH_2), 1.45 (9H, s, Boc), 0.89 (3H, t, $J = 7.2$ Hz, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 209.3 ($\text{CH}=\text{C}=\text{CH}_2$), 157.1 ($\text{C}=\text{O}$), 85.7 ($\text{CH}=\text{C}=\text{CH}_2$), 84.7 ($\text{CH}=\text{C}=\text{CH}_2$), 81.3, 74.4, 34.1, 31.5, 28.1 (3C, Boc), 18.5, 14.1.

IR (neat) 3319, 2980, 2961, 2934, 2873, 1956, 1748 cm^{-1} .

MS m/z 264 $[\text{M}+\text{Na}]^+$; HRMS m/z calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_3\text{NNa}$ $[\text{M}+\text{Na}]^+$ 264.1576, found 264.1568.

(3R,5R)-tert-Butyl 5-propyl-3-vinylisoxazolidine-2-carboxylate (3-38).

AgBF_4 (16.3 mg, 0.083 mmol) was added to a solution of the *N*-protected hydroxylamine **3-39** (0.2 g, 0.83 mmol) in dry CH_2Cl_2 (6 mL) at room temperature. The reaction mixture was stirred at room temperature in the absence of light for 8 h and filtered through celite. The filtrate was washed with sat. NaHCO_3 solution and

brine and dried over anhydrous Na_2SO_4 . After filtration through celite, the filtrate was then evaporated *in vacuo* to give the residue, which was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to afford a inseparable mixture of *trans*-**3-38** and *cis*-**3-38** (*trans*: *cis* = 1:11.5, 0.188 g, 94%) as a colourless oil.

cis-**3-38**: ^1H NMR (500 MHz, CDCl_3) δ 5.82 (1H, ddd, J = 17.0, 10.0, 6.8 Hz, $\text{CH}=\text{CH}_2$), 5.21 (1H, d, J = 17.0 Hz, $\text{CH}=\text{CH}_2$), 5.06 (1H, d, J = 10.0 Hz, $\text{CH}=\text{CH}_2$), 4.56 (1H, td, J = 7.2, 7.2 Hz, CHN), 3.86-3.83 (1H, m, CHO), 2.52 (1H, ddd, J = 13.1, 7.2, 5.8 Hz, CHCH_2CH), 1.68-1.60 (2H, m), 1.54-1.33 (3H, m), 1.45 (9H, s, Boc), 0.91 (3H, t, J = 7.2 Hz, CH_3).

^{13}C NMR (125 MHz, CDCl_3) δ 157.5 (C=O), 137.8 ($\text{CH}=\text{CH}_2$), 114.1 ($\text{CH}=\text{CH}_2$), 81.6, 81.0, 62.1, 41.2, 34.2, 28.1 (3C), 19.2, 13.8.

IR (neat) 2976, 2965, 1732 cm^{-1} .

MS m/z 242 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_3\text{NNa}$ $[\text{M}+\text{Na}]^+$ 264.1576, found 264.1573.

***tert*-Butyl (3*R*,5*R*)-5-hydroxyoct-1-en-3-ylcarbamate (*syn*-**3-50**) and *tert*-butyl ((3*S*,5*R*)-5-hydroxyoct-1-en-3-yl)carbamate (*anti*-**3-50**)**

$\text{Mo}(\text{CO})_6$ (0.24 g, 0.89 mmol) was added to a solution of isoxazolidines **3-38** (0.20 g, 0.56 mmol) in $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (14 mL-2 mL). The mixture was stirred at room temperature for 15 min and NaBH_4 (25 mg, 0.67 mmol) was added in one portion.

The reaction mixture was heated at 90 °C overnight and cooled to room temperature. The suspension was filtered through celite, washing with Et₂O (3 x 8 mL). The filtrate was then concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to give *syn*-**3-50** (0.16 g, 78%) and *anti*-**3-50** (14 mg, 7%).

syn-**3-50**: colorless oil; $[\alpha]_D^{24.8}$ -16.0 (*c* 1.1, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.77 (1H, ddd, *J* = 17.0, 10.4, 6.1 Hz, CH=CH₂), 5.19 (1H, d, *J* = 17.0 Hz, CH=CH₂), 5.10 (1H, d, *J* = 10.4 Hz, CH=CH₂), 4.71 (1H, brs, NH), 4.24 (1H, brs, CHNH), 3.71 (1H, brs, CHOH), 1.64-1.59 (2H, m, CHCH₂CH), 1.48-1.33 (4H, m, CH₂CH₂), 1.45 (9H, s, Boc), 0.91 (3H, t, *J* = 6.9 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 155.5 (C=O), 138.9 (CH=CH₂), 114.7 (CH=CH₂), 79.5, 69.4, 51.3, 42.6, 40.0, 28.3 (3C), 18.7, 14.0.

IR (neat) 3442, 3345, 2974, 2930, 2872, 1694 cm⁻¹.

MS *m/z* 266 [M+Na]⁺; HRMS *m/z calcd.* for C₁₃H₂₅O₃NNa [M+Na]⁺ 266.1732, found 266.1729.

anti-**3-50**: colourless solid; m.p.: 46-47 °C; $[\alpha]_D^{24.8}$ +6.1 (*c* 1.1, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 5.83 (1H, ddd, *J* = 17.0, 10.5, 5.4 Hz, CH=CH₂), 5.18 (1H, d, *J* = 17.0 Hz, CH=CH₂), 5.10 (1H, d, *J* = 10.5 Hz, CH=CH₂), 4.75 (1H, d, *J* = 8.8 Hz, NH), 4.42 (1H, brs, CHN), 3.59 (1H, brs, CHOH), 1.64-1.51 (2H, m, CHCH₂CH), 1.48-1.33 (4H, m), 1.45 (9H, s, Boc), 0.90 (3H, t, *J* = 6.7 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 156.7 (C=O), 138.5 (CH=CH₂), 114.4 (CH=CH₂), 79.5, 67.2, 49.3, 43.4, 39.1, 28.3 (3C, Boc), 19.0, 14.0.

***tert*-Butyl (*E*,5*R*,7*R*)-1,1-diethoxy-7-hydroxydec-3-en-5-ylcarbamate (*E*-3-52) and *tert*-butyl ((5*R*,7*R*,*Z*)-1,1-diethoxy-7-hydroxydec-3-en-5-yl)carbamate (*Z*-3-52).**

A solution of Grubbs II catalyst (87 mg, 5 mol%) in CH₂Cl₂ (5 mL) was added to a refluxing solution of compound **3-50** (0.5 g, 2.06 mmol) and 1,1-diethoxybut-3-ene **3-51**⁸¹ (1.10 mL, 6.17 mmol) in CH₂Cl₂ (5 mL) in four portions *via* syringe over 1 h. The mixture was heated at reflux overnight and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc : Hexane = 2 : 8) to provide *E*-3-52 (0.55 g, 75%) and *Z*-3-52 (70 mg, 9%) as colourless oils.

E-3-52: $[\alpha]_{\text{D}}^{24.8} +3.6$ (*c* 1.1, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 5.59 (1H, dt, *J* = 15.6, 6.8 Hz, CH=CHCH₂), 5.48 (1H, dd, *J* = 15.6, 6.4 Hz, CH=CHCH₂), 4.72 (1H, br, NH*Boc*), 4.46 (1H, t, *J* = 5.7 Hz, CH(OEt)₂), 4.21 (1H, br, CHNH), 3.66-3.58 (3H, m, CHOH+OCH₂CH₃), 3.49-3.44 (2H, m, OEt), 2.33 (2H, dd, *J* = 6.8, 6.8 Hz, CH=CHCH₂), 1.60 (2H, dd, *J* = 6.3, 6.3 Hz, CHCH₂CH), 1.48-1.33 (4H, m, CH₂CH₂), 1.40 (9H, s, *Boc*), 1.17 (6H, t, *J* = 7.1 Hz, CH(OCH₂CH₃)₂), 0.88 (3H, t, *J* = 6.9 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 155.4 (C=O), 133.4 (CH=CHCH₂), 125.7 (CH=CHCH₂), 102.2 (CH(OEt)₂), 79.3, 76.6, 61.2 (2C), 50.5, 42.9, 39.9, 36.8, 28.3 (3C), 18.7, 15.2 (2C), 13.9.

IR (neat) 3443, 3350, 2974, 2930, 2874, 1694 cm⁻¹.

MS (m/z) 382 $[M+Na]^+$; HRMS m/z calcd. for $C_{19}H_{37}O_5NNa$ $[M+Na]^+$ 382.2569, found 382.2566.

Z-3-52: $[\alpha]_D^{21.9}$ -54.9 (c 1.0, $CHCl_3$).

1H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, dt, $J = 10.0, 5.6$ Hz, $CH=CHCH_2$), 5.25 (1H, dd, $J = 10.0, 10.0$ Hz, $CH=CHCH_2$), 4.61 (1H, br, NH), 4.54 (1H, dd, $J = 4.0, 4.0$ Hz, $CH(OEt)_2$), 4.51 (1H, brs, CHN), 3.71-3.45 (5H, m, $CHOH+2OCH_2CH_3$), 3.00 (1H, brs, $CHCH_2CH$), 2.72 (1H, dt, $J = 14.0, 8.3$ Hz, $CH=CHCH_2$), 2.42 (1H, brs, $CHCH_2CH$), 1.69 (1H, ddd, $J = 14.0, 10.0, 4.0$ Hz, $CH=CHCH_2$), 1.48-1.28 (4H, m, CH_2CH_2), 1.40 (9H, s, Boc), 1.18 (6H, td, $J = 7.0, 3.0$ Hz, $CH(OCH_2CH_3)_2$), 0.87 (3H, t, $J = 6.7$ Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2 ($C=O$), 132.3 ($CH=CHCH_2$), 126.3 ($CH=CHCH_2$), 102.2 ($CH(OEt)_2$), 79.1, 68.0, 62.5, 60.6, 46.0, 43.0, 39.9, 32.5, 28.3 (3C, Boc), 18.9, 15.1, 15.0, 14.0.

IR (neat) 1689 cm^{-1} .

MS m/z 382 $[M+Na]^+$; HRMS m/z calcd. for $C_{19}H_{37}O_5NNa$ $[M+Na]^+$ 382.2569, found 382.2568.

***tert*-Butyl (5*S*,7*R*)-1,1-diethoxy-7-hydroxydecan-5-ylcarbamate (3-53).**

A suspension of alkenes **3-52** (0.24 g, 0.67 mmol), palladium on carbon (10%) (35.5 mg, 0.033 mmol) and a trace of calcium carbonate in MeOH (10 mL) was stirred at

room temperature for 3 h under H₂ (1 atm). The reaction mixture was filtered through celite, washing with MeOH (5 x 5 mL). The filtrate was concentrated to give product **3-53** (0.23 g, 95%) as a colourless oil.

$[\alpha]_D^{24}$ -6.5 (*c* 2.3, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 4.61 (1H, brs, NHBoc), 4.46 (1H, t, *J* = 5.6 Hz, $\underline{\text{CH}}(\text{OEt})_2$), 3.59-3.51 (4H, m, $\underline{\text{CHN}}+\underline{\text{CHOH}}+\underline{\text{OCH}_2\text{CH}_3}$), 3.49-3.44 (2H, m, $\underline{\text{OCH}_2\text{CH}_3}$), 2.45 (1H, m, OH), 1.79-1.36 (21H, m), 1.19 (6H, t, *J* = 7.1 Hz, $\underline{\text{CH}}(\text{OCH}_2\underline{\text{CH}_3})_2$), 0.91 (3H, t, *J* = 6.5 Hz, $\underline{\text{CH}_3}$).

¹³C NMR (75 MHz, CDCl₃) δ 156.0 (C=O), 102.7 ($\underline{\text{CH}}(\text{OEt})_2$), 79.4, 70.0, 61.1, 60.9, 49.3, 43.6, 39.8, 35.9, 33.4, 28.4 (3C, Boc), 21.0, 18.8, 15.3 (2C, $\underline{\text{OCH}_2\text{CH}_3}$), 14.0.

IR (neat) 3443, 3343, 2974, 2932, 2872, 1694 cm⁻¹.

MS *m/z* 384 [M+Na]⁺; HRMS *m/z* calcd. for C₁₉H₃₉O₅NNa [M+Na]⁺ 384.2711, found 384.2726.

(1*S*,3*R*,5*S*)-tert-Butyl 3-propyl-2-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate

(3-37) and (S)-tert-butyl 2-((R)-2-hydroxypentyl)-3,4-dihydropyridine-1(2H)

-carboxylate (3-54)

PPTS (0.36 g, 1.44 mmol) was added to a solution of compound **3-53** (0.52 g, 1.44 mmol) in CH₂Cl₂ (10 mL) at room temperature. The mixture was stirred at room

temperature for 14 h. After water was added, the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo* to afford the crude product which was purified by flash chromatography (EtOAc : Hexane = 1 : 4) to provide the cyclic *N,O*-acetal **3-37** (0.27 mg, 69%) and tetrahydropyridine **3-54** (33 mg, 8%) as colourless oils.

Compound **3-37**: $[\alpha]_{\text{D}}^{23.1} -6.7$ (*c* 1.5, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ (mixture of rotamers) 5.78 (brs) and 5.66 (brs) (1H, OCHN), 4.45 (brd, $J = 11.6$ Hz) and 4.32 (brd, $J = 11.6$ Hz) (1H, HCNBoc), 3.37-3.31 (1H, m, CHO), 2.18-2.20 (2H, m), 1.79-1.60 (3H, m), 1.47 (9H, s, Boc), 1.43-1.34 (7H, m), 0.90 (3H, t, $J = 7.0$ Hz, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ (mixture of rotamers) 154.7 (C=O), 80.1 and 79.8 (OCHN), 79.0 and 77.8, 67.3 and 67.2, 44.9 and 43.3, 37.1 and 37.0, 35.2 and 34.6, 30.7 and 30.6, 30.5 and 30.3, 28.3 (3C, Boc), 18.6 and 18.5, 14.1 and 14.0, 13.6.

IR (neat) 2957, 2936, 2870, 1697 cm^{-1} .

MS m/z 269 $[\text{M}]^+$; HRMS m/z calcd. for $\text{C}_{15}\text{H}_{27}\text{O}_3\text{N} [\text{M}]^+$ 269.1985, found 269.1969.

Compound **3-54**: ^1H NMR (300 MHz, CDCl_3) δ 6.63 (1H, d, $J = 8.5$ Hz, BocNCH=CH), 4.85-4.82 (1H, m, BocNCH=CH), 4.51 (1H, brd, $J = 11.6$ Hz, CHNBoc), 4.30 (1H, d, $J = 3.2$ Hz, OH), 3.39-3.33 (1H, m, CHOH), 2.08-1.99 (2H, m, $\text{CH}_2\text{CH=CH}$), 1.90-1.78 (1H, m), 1.75-1.65 (2H, m), 1.53-1.15 (5H, m), 1.49 (9H, s, Boc), 0.89 (3H, t, $J = 6.9$ Hz, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 152.9 (C=O), 124.4 (BocNCH=CH), 105.3

(BocNCH=CH), 81.1, 69.7, 47.9, 39.9, 39.8, 28.3 (3C, Boc), 25.7, 19.0, 17.5, 14.0.

IR (neat) 1700, 1650 cm^{-1} .

MS m/z 292 $[\text{M}+\text{Na}]^+$; HRMS m/z calcd. for $\text{C}_{15}\text{H}_{27}\text{O}_3\text{NNa}$ $[\text{M}]^+$ 292.1889, found 292.1886.

(2*R*,6*S*)-tert-Butyl 2-allyl-6-((*R*)-2-hydroxypentyl)piperidine-1-carboxylate (3-36**).**

TiCl_4 (1 M in toluene, 0.67 mL, 0.67 mmol) was added to a cooled ($-78\text{ }^\circ\text{C}$) solution of cyclic *N,O*-acetal **4** (0.15 g, 0.56 mmol) and allyltrimethylsilane (0.11 mL, 0.67 mmol) in CH_2Cl_2 (8 mL). After stirring at $-78\text{ }^\circ\text{C}$ for 1 h, the reaction mixture was quenched with saturated NaHCO_3 solution at this temperature and then allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to provide an inseparable mixture of *trans*-**36** and *cis*-**3-36** (0.10 g, 64%) as colourless oils.

cis-**3-36** ^1H NMR (300 MHz, CDCl_3) δ 5.78-5.66 (1H, m, $\text{CH}=\text{CH}_2$), 5.07-5.00 (2H, m, $\text{CH}=\text{CH}_2$), 4.17-4.09 (2H, brs, $\text{CHN}(\text{Boc})+\text{CHOH}$), 3.50-3.46 (1H, m, NBocCH), 2.27-2.22 (2H, m, $\text{CH}_2\text{CH}=\text{CH}$), 1.83-1.33 (21H, m), 0.91 (3H, t, $J = 6.9\text{ Hz}$, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 155.8 (C=O), 136.2 ($\text{CH}=\text{CH}_2$), 116.8 ($\text{CH}=\text{CH}_2$), 79.9,

70.0, 50.3, 47.7, 44.2, 40.1, 39.0, 28.7, 28.5 (3C), 26.6, 18.9, 14.1, 13.7.

IR (neat) 3431, 2954, 2934, 2870, 1660 cm^{-1} .

MS m/z 312 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{18}\text{H}_{33}\text{O}_3\text{NNa}$ $[\text{M}+\text{Na}]^+$ 334.2358, found 334.2344.

(3*R*,4*aS*,8*R*)-8-Allyl-3-propylhexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-56).

$t\text{BuOK}$ (7.1 mg, 0.063 mmol) was added to a solution of peiperidine **3-36** (13 mg, 0.042 mmol) in THF (7 mL) at 0 °C. The mixture was allowed to warm to room temperature and it was stirred for 4 h. The mixture was quenched with saturated NH_4Cl solution and extracted with CHCl_3 (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was purified by flash chromatography (EtOAc : Hexane = 1 : 4) to provide an inseparable mixture of *cis*-**3-56** and *trans*-**3-56** (10.1 mg, 100%, *cis*-**3-56**:*trans*-**3-56** = 9:1) as colourless oils.

cis-**3-56**: ^1H NMR (400 MHz, CDCl_3) δ 5.83-5.73 (1H, m, $\text{CH}=\text{CH}_2$), 5.09 (1H, d, J = 17.2 Hz, $\text{CH}=\text{CH}_2$), 5.04 (1H, d, J = 9.6 Hz, $\text{CH}=\text{CH}_2$), 4.21-4.25 (1H, m, CHOH), 3.79-3.74 (1H, m, $\text{CHNCH}_2\text{CH}=\text{CH}_2$), 3.55 (1H, tt, J = 12.0, 4.0 Hz, NCH), 2.80 (1H, dt, J = 13.4, 4.8 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.18 (1H, dt, J = 13.4, 9.6 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.94 (1H, ddd, J = 13.4, 4.6, 2.2 Hz, $\text{HOCHCH}_2\text{CHN}$), 1.84-1.36 (11H, m), 0.92 (3H, t, J =

7.2 Hz, CH_3CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 153.3 ($\text{NC}=\text{O}$), 135.7 ($\text{CH}=\text{CH}_2$), 116.7 ($\text{CH}=\text{CH}_2$), 75.4, 54.1, 51.3, 38.1, 37.2, 35.7, 29.5, 22.9, 17.9, 16.4, 13.8.

IR (neat) 2956, 2935, 2873, 1666 cm^{-1} .

MS m/z 238 $[\text{M}+\text{H}]^+$.

trans-**3-56**: see below.

(2*S*,6*R*)-tert-Butyl 2-((*R*)-2-hydroxypentyl)-6-((*E*)-4-oxopent-2-enyl)piperidine-1-carboxylate (3-58).

A solution of Grubbs II catalyst (8 mg, 5 mol%) in CH_2Cl_2 (2 mL) was added to a refluxing solution of piperidine **3-36** (56 mg, 0.18 mmol) and 3-buten-2-one (53 μL , 0.54 mmol) in CH_2Cl_2 (2 mL) in four portions via syringe over 1 h. The mixture was heated at reflux overnight and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc : Hexane = 1 : 4) to provide *trans*-**3-58** (51mg, 80%) as a colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 6.73 (1H, dt, J = 15.8, 7.7 Hz, $\text{CH}_2\text{CH}=\text{CH}$), 6.07 (1H, d, J = 15.8 Hz, $\text{CH}_2\text{CH}=\text{CH}$), 4.25 (2H, brs, $\text{CHN}^{\text{Boc}}+\text{CHOH}$), 3.54-3.51 (1H, m, NBocCH), 2.44-2.38 (2H, m, $\text{CH}_2\text{CH}=\text{CH}$), 2.22 (3H, s, $\text{C}=\text{OCH}_3$), 1.76-1.33 (21H, m), 0.91 (3H, t, J = 6.8 Hz, CH_3CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 198.4 ($\text{C}=\text{OCH}_3$), 155.4 ($\text{C}=\text{O}$, Boc), 144.9 ($\text{CH}_2\text{CH}=\text{CH}$), 132.9 ($\text{CH}_2\text{CH}=\text{CH}$), 80.2, 69.6, 49.5, 47.5, 44.0, 40.0, 37.8, 28.4 (3C, Boc), 27.4, 27.0, 26.1, 18.8, 14.0, 13.7.

IR (neat) 3447, 2957, 2932, 2860, 1655, 1643 cm^{-1} .

MS m/z 376 $[\text{M}+\text{Na}]^+$; HRMS m/z calcd. for $\text{C}_{20}\text{H}_{35}\text{O}_4\text{NNa}$ $[\text{M}+\text{Na}]^+$ 376.2464, found 376.2452.

(2*S*,6*R*)-tert-Butyl-2-((*R*)-2-hydroxypentyl)-6-(4-oxopentyl)piperidine-1-carboxylate (*cis*-3-35) and (2*S*,6*S*)-tert-butyl 2-((*R*)-2-hydroxypentyl)-6-(4-oxopentyl)piperidine-1-carboxylate (*trans*-3-35).

A suspension of alkene **3-58** (51 mg, 0.14 mmol) and palladium on carbon (10%) (8 mg, 5 mol%) in MeOH (5 mL) was stirred at room temperature for 2 h under H_2 (1 atm). The reaction mixture was filtered through celite, washing with MeOH (5 x 3 mL). The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc : Hexane = 2 : 8) to afford *cis*-**3-35** (35 mg, 77%) and *trans*-**3-35** (4 mg, 8%) as colourless oils.

cis-**3-35**: $[\alpha]_{\text{D}}^{24}$ -27.1 (c 1.6, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 4.18 (1H, brs, CHOH), 4.04 (1H, brs, CHNBoc), 3.51 (1H, brs, NBocCH), 2.46-2.43 (2H, m, $\text{CH}_2\text{C}=\text{OCH}_3$), 2.12 (3H, s, $\text{C}=\text{OCH}_3$), 1.55-1.35 (25H, m), 0.91 (3H, t, J = 6.8 Hz, CH_3CH_2).

^{13}C NMR (125 MHz, CDCl_3) δ 208.6 ($\text{C}=\text{OCH}_3$), 155.9 ($\text{C}=\text{O}$, Boc), 79.9, 69.9, 50.4, 47.8, 44.3, 43.4, 40.0, 34.0, 29.9, 29.3, 28.4 (3C), 27.4, 21.3, 18.9, 14.1, 13.9.

IR (neat) 3447, 2957, 2932, 2860, 1655, 1643 cm^{-1} .

MS m/z 378 $[\text{M}+\text{Na}]^+$; HRMS m/z calcd. for $\text{C}_{20}\text{H}_{37}\text{O}_4\text{NNa}$ $[\text{M}+\text{Na}]^+$ 378.2620, found 378.2615.

trans-**3-35**: ^1H NMR (500 MHz, CDCl_3) δ 3.92-3.89 (1H, brs, CHOH), 3.72-3.68 (1H, brs, CHNBoc), 3.59-3.56 (1H, brs, NBocCH), 2.48-2.44 (2H, m, $\text{CH}_2\text{C}=\text{OCH}_3$), 2.14 (3H, s, $\text{C}=\text{OCH}_3$), 1.81-1.76 (2H, m), 1.73-1.70 (2H, m), 1.65-1.33 (12H, m), 1.46 (9H, s, Boc), 0.91 (3H, t, $J = 7.0$ Hz, CH_3CH_2).

^{13}C NMR (125 MHz, CDCl_3) δ 208.8 ($\text{C}=\text{OCH}_3$), 155.9 ($\text{C}=\text{O}$, Boc), 79.9, 70.0, 51.8, 49.5, 44.1, 43.4, 40.1, 33.6, 29.9, 28.5 (3C), 25.2, 23.6, 21.2, 18.9, 14.1, 13.5.

(2*R*,3*aS*,6*aR*,9*aS*)-Decahydro-9*a*-methyl-2-propyl-2*H*-[1,3]oxazino[2,3,4-*de*]quinoline (3-59).

Trifluoroacetic acid (0.46 mL) was added to a solution of *cis*-**3-35** (23 mg, 0.062 mmol) in CH_2Cl_2 (4 mL) at 0 $^\circ\text{C}$. The reaction mixture was warmed to room temperature and stirred for 2 h. The volatiles were evaporated and the residue was partitioned between aqueous NaHCO_3 and CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried

over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford the crude product which was purified by column chromatography (MeOH:CH₂Cl₂ = 1 : 9) to give product **3-59** (13 mg, 90%) as a colourless oil.

$[\alpha]_D^{24} +6.0$ (*c* 0.8, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 3.80-3.76 (1H, m, OCH), 2.50-2.47 (1H, m, CHN), 2.15-2.10 (1H, m, CHN), 1.55-1.22 (18H, m), 1.32 (3H, s, CH₃C), 0.88 (3H, t, *J* = 7.0 Hz, CH₂CH₃).

¹³C NMR (125 MHz, CDCl₃) δ 86.5 (OCHN), 67.8, 55.2, 51.9, 39.6, 39.2, 38.6, 34.4, 34.2, 33.8, 23.5, 20.8, 18.4, 14.1, 11.6.

IR (neat) 2930, 2868, 2799 cm⁻¹.

MS *m/z* 238 [M+H]⁺; HRMS *m/z* calcd. for C₁₅H₂₈ON [M+H]⁺ 238.2171, found 238.2164.

(4*S*,6*R*)-4-(4,4-Diethoxybutyl)-6-propyl-1,3-oxazinan-2-one (3-62).

^tBuOK (83.0 mg, 7.38 mmol) was added to a solution of compound **3-53** (178 mg, 4.92 mmol) in THF (7 mL) at 0 °C. The mixture was allowed to warm to room temperature and it was stirred at room temperature for 4 h. The mixture was quenched with saturated NH₄Cl solution and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was

purified by flash chromatography (EtOAc : Hexane = 3 : 7) to provide cyclic carbamate **3-62** (133 mg, 93%) as a colourless oil.

$[\alpha]_D^{24} +5.7$ (*c* 1.3, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 5.49 (1H, brs, NH), 4.46 (1H, t, *J* = 5.5 Hz, CH(OEt)₂), 4.22 (1H, tdd, *J* = 9.8, 4.7, 2.8 Hz, HC-6), 3.63 (2H, qd, *J* = 7.1, 9.3 Hz, OCH₂CH₃), 3.51-3.40 (3H, m, CHNH + OCH₂CH₃), 1.96 (1H, ddt, *J* = 13.5, 4.7, 1.5 Hz, OCHCH₂CHN), 1.70-1.34 (11H, m), 1.20 (6H, t, *J* = 7.1 Hz, CH(OCH₂CH₃)₂), 0.93 (3H, t, *J* = 7.3 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 154.8 (O=CNH), 102.5 (CH(OEt)₂), 76.8, 61.2, 61.1, 50.8, 37.2, 36.0, 33.3, 33.1, 20.0, 17.9, 15.3(2C), 13.8.

IR (neat) 2961, 2932, 2874, 2243, 1697 cm⁻¹.

MS *m/z* 310 [M+Na]⁺; HRMS *m/z* calcd. for C₁₅H₂₉O₄NNa [M+Na]⁺ 310.1994, found 310.1989.

(3*R*,4*aS*)-8-ethoxy-3-propylhexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-63).

p-TsOH (0.48 g, 2.39 mmol) was added to a solution of compound **3-62** (133 mg, 0.48 mmol) in EtOH (5 mL) at room temperature. The mixture was stirred at room temperature for 4h. Saturated aqueous NaHCO₃ (5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in*

vacuo. The residue was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to provide *trans*-**3-63** (0.11 g, 91%) as a single isomer and as a colourless solid.

m.p. 57-59 °C; $[\alpha]_D^{23.6} +30.0$ (c 1.7, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 5.71 (1H, br, NCHOEt), 4.14-4.07 (1H, m, CHO), 3.56-3.39 (3H, m, CHN +OCH₂CH₃), 2.07-1.42 (12H, m), 1.18 (3H, t, J = 7.0 Hz, OCH₂CH₃), 0.93 (3H, t, J = 7.0 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 154.1 (NC=O), 80.3 (NCHOEt), 75.0, 62.4, 49.1, 37.0, 35.3, 33.1, 29.9, 17.9, 17.6, 15.1, 13.9.

IR (neat) 2957, 2936, 2874, 1694, 1422 cm⁻¹.

MS m/z 264 [M+Na]⁺; HRMS m/z calcd. for C₁₃H₂₃O₃NNa [M+Na]⁺ 264.1576, found 264.1567.

(3*R*,4*aS*,8*S*)-8-Allyl-hexahydro-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one
(*trans*-3-56).

To a solution of *N,O*-acetal **3-63** (48 mg, 0.21 mmol) and allyltrimethylsilane (0.10 mL, 0.63 mmol) in CH₂Cl₂ (5 mL) was added TiCl₄ (0.63 mmol, 0.63 mL of 1 M solution in toluene) via syringe at -78 °C. After stirring at -78 °C for 0.5 h, the reaction mixture was quenched at this temperature with saturated NaHCO₃ and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford the

crude product. The crude product was purified by flash chromatography (EtOAc : Hexane = 2 : 8) to provide *trans*-**3-56** (44 mg, 89%) as a colourless oil.

$[\alpha]_D^{24.4} +6.9$ (*c* 2.0, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 5.80-5.73 (1H, m, CH=CH₂), 5.04 (1H, d, *J* = 17.0 Hz, CH=CH₂), 5.03 (1H, brd, *J* = 9.5 Hz, CH=CH₂), 4.70-4.66 (1H, m, NCHCH₂CH=CH₂), 4.03 (1H, tt, *J* = 5.2, 5.2 Hz, CH₂CHO), 3.37 (1H, tdd, *J* = 11.4, 5.2, 2.9 Hz, NCHCH₂CHO), 2.44 (1H, dt, *J* = 13.8, 8.3 Hz, CH₂CH=CH₂), 2.24 (1H, dt, *J* = 13.8, 6.8 Hz, CH₂CH=CH₂), 1.99 (1H, ddd, *J* = 13.8, 5.2, 1.5 Hz, NCHCH₂CHO), 1.79-1.76 (1H, m, NCHCH₂CHO), 1.66-1.12 (10H, m), 0.92 (3H, t, *J* = 7.2 Hz, CH₃CH₂).

¹³C NMR (125 MHz, CDCl₃) δ 154.0 (C=O), 135.3 (CH=CH₂), 117.0 (CH=CH₂), 74.2, 49.7, 49.3, 36.8, 35.7, 34.8, 33.3, 27.0, 18.1, 17.8, 13.8.

IR (neat) 2957, 2934, 2872, 1687 cm⁻¹.

MS *m/z* 237 [M]⁺; HRMS *m/z* calcd. for C₁₄H₂₃O₂NNa [M+Na]⁺ 260.1623, found 260.1618.

(3*R*,4*aS*,8*S*)-Hexahydro-8-((*E*)-4-oxopent-2-enyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-66).

A solution of Grubbs II catalyst (11 mg, 5 mol%) in CH₂Cl₂ (2 mL) was added to a refluxing solution of *trans*-**3-56** (60 mg, 0.25 mmol) and 3-buten-2-one (74 μ L, 0.76 mmol) in CH₂Cl₂ (2 mL) in four portions *via* syringe over 1 h. The mixture was heated

at reflux overnight and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc : Hexane = 3 : 7) to provide *trans*-**3-66** (68 mg, 96%) as a single isomer and as a colourless oil.

$[\alpha]_D^{24}$ -2.6 (*c* 1.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 6.74 (1H, ddd, *J* = 15.7, 8.7, 6.5 Hz, CH=CHCOCH₃), 6.02 (1H, d, *J* = 15.7 Hz, CH=CHCOCH₃), 4.84-4.78 (1H, m, NCH-8), 4.01-3.94 (1H, m, CHO), 3.34 (1H, tdd, *J* = 11.3, 5.0, 2.9 Hz, NCH-4), 2.63 (1H, dt, *J* = 13.9, 8.7 Hz, CH₂CH=CH), 2.24 (1H, dt, *J* = 13.9, 6.5 Hz, CH₂CH=CH), 2.24 (3H, s, C=OCH₃), 1.99 (1H, ddd, *J* = 11.2, 5.2, 1.5 Hz, NCHCH₂CHO), 1.82-1.12 (11H, m), 0.89 (3H, t, *J* = 7.2 Hz, CH₃CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 198.8 (C=OCH₃), 153.9 (NC=O), 144.7 (CH=CHC=OCH₃), 133.7 (CH=CHC=OCH₃), 74.6, 49.6, 49.4, 36.8, 35.5, 33.9, 33.1, 27.5, 26.2, 18.1, 17.8, 13.7.

IR (neat) 2957, 2936, 2874, 1674, 1429 cm⁻¹.

MS *m/z* 302 [M+Na]⁺; HRMS *m/z* calcd. for C₁₆H₂₅O₃NNa [M+Na]⁺ 302.1732, found 302.1737.

(3*R*,4*aS*,8*S*)-Hexahydro-8-(4-oxopentyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-67).^{55d}

A suspension of alkene **3-66** (68 mg, 0.24 mmol) and palladium on carbon (10%) (13 mg, 5 mol%) in MeOH (5 mL) was stirred at room temperature for 2 h under H₂ (1

atm). The reaction mixture was filtered through celite, washing with MeOH (5 x 2 mL). The combined organic filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc : Hexane = 3 : 7) to afford product **3-67** (68 mg, 99%) as colourless oil.

$[\alpha]_D^{24} +16.8$ (*c* 1.0, CHCl₃) [ref.55d $[\alpha]_D^{26} +9.67$ (*c* 0.76, CHCl₃)].

¹H NMR (300 MHz, CDCl₃) δ 4.59-4.54 (1H, m, CHO), 4.10-4.05 (1H, m, CHNCH), 3.40 (1H, tdd, *J* = 11.3, 5.4, 2.8 Hz, CHNCH), 2.56-3.39 (2H, m, CH₂C=O), 2.11 (3H, s, CH₃C=O), 2.02 (1H, ddd, *J* = 13.6, 5.4, 1.6 Hz, NCHCH2CHO), 1.62-1.45 (15H, m), 0.91 (3H, t, *J* = 7.2 Hz, CH₃CH₂).

¹³C NMR (75 MHz, CDCl₃) δ 208.9 (CH₂C=O), 154.2 (NC=O), 74.5, 50.0, 49.0, 42.8, 36.9, 35.8, 33.6, 30.0, 29.2, 27.7, 20.0, 18.2, 17.8, 13.9.

IR (neat) 2934, 2872, 1713, 1674, 1429 cm⁻¹.

MS *m/z* 282 [M+H]⁺; HRMS *m/z* calcd. for C₁₆H₂₈O₃N [M+H]⁺ 282.2069, found 282.2061.

(3*R*,4*aS*,8*S*)-Hexahydro-8-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-68). ^{55b,55d}

A mixture of compound **3-67** (68 mg, 0.24 mmol), ethylene glycol (66 μ L, 1.21 mmol), and *p*-toluenesulfonic acid monohydrate (9.6 mg, 0.048 mmol) in benzene (5 mL) was heated at reflux overnight using a Dean–Stark apparatus. Saturated NaHCO₃ was

added to the mixture. The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc : Hexane = 3 : 7) to yield **3-68** (75 mg, 96%) as a colourless oil.

$[\alpha]_{\text{D}}^{24.1} +10.4$ (*c* 1.1, CHCl_3) [ref.55d $[\alpha]_{\text{D}}^{26} +10.0$ (*c* 0.25, CHCl_3), ref.55b $[\alpha]_{\text{D}} +10.3$ (*c* 1.96, CHCl_3)].

^1H NMR (300 MHz, CDCl_3) δ 4.58-4.56 (1H, m, NCH-8), 4.08-4.03 (1H, m, CHO), 3.90 (4H, s, $\text{OCH}_2\text{CH}_2\text{O}$), 3.38 (1H, tdd, $J = 11.3, 5.5, 2.9$ Hz, NCH-4), 2.01 (1H, ddd, $J = 13.6, 5.5, 2.9$ Hz, NCHCH_2CHO), 1.80-1.11 (17H, m), 1.31 (3H, s, CCH_3), 0.91 (3H, t, $J = 6.9$ Hz, CH_3CH_2).

^{13}C NMR (100 MHz, CDCl_3) δ 154.0 (C=O), 110.0(CCH_3), 74.4, 64.6 (2C, $\text{OCH}_2\text{CH}_2\text{O}$), 50.5, 49.2, 38.8, 36.9, 35.8, 33.7, 29.8, 27.2, 23.8, 20.7, 18.2, 17.9, 13.8. IR (neat) 2936, 2872, 1672, 1427 cm^{-1} .

MS m/z 326 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{18}\text{H}_{32}\text{O}_4\text{N}$ $[\text{M}+\text{H}]^+$ 326.2331, found 326.2333.

5.4. Experimental Section for Chapter 4

(*S*)-Propane-1,2-diol (**4-22**).^{93c}

Acetic acid (33 μ L, 0.57 mmol) was added to a solution of (*R,R*)-**4-23** (0.17 g, 0.2 mol%) in toluene (1.5 mL) at room temperature. The reaction mixture was stirred open to the air for an hour at room temperature. The color changed from red to dark-brown. After concentration *in vacuo*, the catalyst (*R,R*)-**4-23**·OAc was obtained as a brown solid. Racemic propylene oxide **4-20** (10.0 mL, 142.7 mmol) was added to the resulting catalyst in one portion at room temperature. The reaction mixture was cooled to 0 °C and water (1.4 mL, 78.5 mmol) was added dropwise over 15 min. The reaction mixture was then warmed to room temperature and was stirred for 14 h further. Propylene oxide (*R*)-**4-20** was removed by evaporation and the residue was distilled again under reduced pressure, giving the (*S*)-propylene glycol **4-22** (4.4 g, 41%) as a colourless oil.

$$[\alpha]_{\text{D}}^{22.3} +23.9 \text{ (} c \text{ 7.5, H}_2\text{O)} \text{ [ref. 105 } [\alpha]_{\text{D}}^{23} +20.7 \text{ (} c \text{ 7.5, H}_2\text{O)}]$$

(*S*)-4-methyl-1,3,2-dioxathiolane 2,2-dioxide (4-21).⁹⁴

Thionyl chloride (11.5 mL, 0.16 mol) was added dropwise to a solution of (*S*)-propylene glycol **4-22** (10 g, 0.13 mol) in CH₂Cl₂ (80 mL) at room temperature. After completion of addition, the reaction mixture was heated at reflux for 1 h and then cooled to 0 °C. Acetonitrile (50 mL), water (80 mL), ruthenium trichloride trihydrate (27 mg, 0.13 mmol) and sodium periodate (42 g, 0.2 mol) were added sequentially. The reaction mixture was warmed to room temperature and stirred for a

further 1 h. After extraction with Et₂O (3 x 20 mL), the combined organic layers were washed with sat. NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the crude product as a yellowish oil. The crude product was purified by distillation (80 °C (oil bath) at 0.5 mmHg) to give the cyclic sulfate **4-21** (16.3 g, 90%) as a colourless oil.

$[\alpha]_D^{24.5} +20.0$ (*c* 3.7, CH₂Cl₂) [ref. 94 $[\alpha]_D^{23} +16.5$ (*c* 0.16, CH₂Cl₂)].

¹H NMR (300 MHz, CDCl₃) δ 5.18- 5.07 (1H, m, CH₃CH), 4.73 (1H, dd, *J* = 8.5, 5.8 Hz, CH₂), 4.31 (1H, t, *J* = 8.5 Hz, CH₂), 1.61 (3H, d, *J* = 6.3 Hz, CH₃CH)

¹³C NMR (75 MHz, CDCl₃) δ 79.6, 74.0, 17.7.

All data are consistent with these reported in literature.⁹⁴

(*S*)-Pent-4-yn-2-ol (**4-25**).^{94,106}

Acetylene gas was bubbled through THF (130 mL) at -78 °C for 0.5 h. *n*-BuLi in hexane (1.6 M, 54 mL, 87.0 mmol) was added dropwise over 0.5 h at -78 °C under nitrogen. After addition, the clear solution was stirred for 1 h at -78 °C. Then cyclic sulphate **4-21** (10 g, 72.5 mmol) in THF (30 mL) was added *via* cannula. The reaction mixture was stirred at -78 °C for 1.5 h, then allowed to warm to room temperature and stirred for 1 h further. Concentrated sulfuric acid (1.2 mL) and water (1.2 mL) were added and the cloudy mixture was stirred for 0.5 h. Powdered NaHCO₃ and water (2 mL) were added to neutralize the acidic solution. The reaction mixture was dried over

anhydrous Na_2SO_4 and filtered through celite, washing with Et_2O (3 x 20 mL). Removal of the solvent by simple distillation at atmospheric pressure and subsequent distillation under reduced pressure [about 45 °C (oil bath) at 6 mmHg] gave (*S*)-pent-4-yn-2-ol **4-25** (4.80 g, 79%) as a colourless oil.

$[\alpha]_{\text{D}}^{23} +17.9$ (*c* 1.2, CHCl_3) [ref. 106 $[\alpha]_{\text{D}}^{23} +17.5$ (*c* 0.16, CHCl_3)].

^1H NMR (500 MHz, CDCl_3) δ 3.98 (1H, qt, $J = 6.2, 5.4$, CHOH), 2.41 (1H, ddd, $J = 16.6, 5.0, 2.6$ Hz, CH_2C), 2.32 (1H, ddd, $J = 16.6, 6.6, 2.6$ Hz, CH_2C), 2.07 (1H, t, $J = 2.6$ Hz, $\text{C}\equiv\text{CH}$), 1.27 (3H, d, $J = 6.2$ Hz, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 80.8 ($\text{C}\equiv\text{CH}$), 70.8 ($\text{C}\equiv\text{CH}$), 66.2, 28.9, 22.2.

IR (neat) 3300, 2240 cm^{-1} .

All data are consistent with these reported in literature.^{94,105}

(*S*)-Hexa-4,5-dien-2-ol (4-26).

Diisopropylamine (13.1 mL, 93.3 mmol) was added to a suspension of (*S*)-pent-4-yn-2-ol **4-25** (3.92 g, 46.7 mmol), paraformaldehyde (2.80 g, 93.3 mmol) and copper (I) bromide (2.20 g, 15.4 mmol) in 1,4-dioxane (80 mL). The reaction mixture was heated at reflux overnight and then cooled to room temperature. Air was bubbled through the reaction mixture for 0.5 h and the reaction mixture was then filtered through celite, washing with Et_2O (3 x 10 mL). The combined filtrates were concentrated *in vacuo* to give the crude product as a brown oil. The crude product was

purified by distillation under reduced pressure [50 °C (oil bath), 1 mmHg] to give (*S*)-hexa-4,5-dien-2-ol **4-26** (3.22 g, 68%) as a colourless oil.

$[\alpha]_D^{23} +9.0$ (*c* 1.3, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 5.12 (1H, tt, *J* = 7.0, 7.0 Hz, CH=C=CH₂), 4.72 (2H, dt, *J* = 7.0, 2.8 Hz, CH=C=CH₂), 3.9-3.84 (1H, m, CHOH), 2.23-2.08 (2H, m, CH₃-CH-CH₂), 1.68 (1H, brd, OH) 1.17 (3H, d, *J* = 6.2 Hz, CH₃).

¹³C NMR (125 MHz, CDCl₃) δ 209.4 (CH=C=CH₂), 86.2 (CH=C=CH₂), 74.8 (CH=C=CH₂), 67.1, 38.2, 22.6.

IR (neat) 2970, 2909, 1956 cm⁻¹.

HRMS *m/z* *calcd.* for C₆H₁₀ONa [M+Na]⁺ 121.0627, found 121.0629.

(*R*)-2-(Hexa-4,5-dien-2-yloxy)isoindoline-1,3-dione (4-27).

A solution of diisopropyl azodicarboxylate (4.6 mL, 23.3 mmol) in THF (10 mL) was added to a solution of (*S*)-hexa-4,5-dien-2-ol **4-26** (1.9 g, 19.4 mmol), triphenylphosphine (6.1 g, 23.3 mmol) and *N*-hydroxyphthalimide (3.8 g, 23.3 mmol) in THF (60 mL) dropwise at -20 °C. The reaction mixture was stirred at -20 °C for 3 h. After evaporation of the solvent, the residue was subjected to purification by flash chromatography (EtOAc : Hexane = 1 : 9) to give the *N*-phthaloyl hydroxylamine **4-27** (4.4 g, 94%) as a colourless solid.

$[\alpha]_D^{23} +18.5$ (*c* 1.1, CHCl₃). m.p.: 60-61 °C.

^1H NMR (500 MHz, CDCl_3) δ 7.84-7.82 (2H, m, Ar), 7.76-7.74 (2H, m, Ar), 5.22 (1H, tt, $J = 7.0, 7.0$ Hz, $\text{CH}=\text{C}=\text{CH}_2$), 4.68 (2H, dt, $J = 7.0, 2.8$ Hz, $\text{CH}=\text{C}=\text{CH}_2$), 4.44 (1H, qt, $J = 6.2, 6.2$ Hz, CHO), 2.23-2.08 (2H, m, $\text{CH}_3\text{-CH-CH}_2$), 2.55-2.32 (2H, m, $\text{CH}_3\text{-CH-CH}_2$), 1.39 (3H, d, $J = 6.2$ Hz, CH_3).

^{13}C NMR (125 MHz, CDCl_3) δ 209.4 ($\text{CH}=\text{C}=\text{CH}_2$), 164.2 (2C, $\text{C}=\text{O}$), 134.4 (2C, Ar), 128.9 (2C, Ar), 123.5 (2C, Ar), 85.2 ($\text{CH}=\text{C}=\text{CH}_2$), 83.7 ($\text{CH}=\text{C}=\text{CH}_2$), 75.0, 33.9, 18.3.

IR (neat) 1953, 1729 cm^{-1} .

MS m/z 244 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{14}\text{H}_{14}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 244.0975, found 244.0974.

(R)-O-(Hexa-4,5-dien-2-yl)hydroxylamine (4-28).

Hydrazine monohydrate (2.0 mL, 41.2 mmol) was added to a solution of the N-phthaloyl hydroxylamine **4-27** (2.5 g, 10.3 mmol) in dichloromethane (30 mL) at room temperature. The reaction mixture was stirred at room temperature for 0.5 h and then filtered through celite, washing with Et_2O (3 x 10 mL). The filtrate was concentrated *in vacuo* to give the free hydroxylamine **4-28** (1.1 g, 95%) as a colourless oil, which was used without further purification.

$[\alpha]_{\text{D}}^{23} +10.7$ (c 1.4, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 5.09 (1H, tt, $J = 7.0, 7.0$ Hz, $\text{CH}=\text{C}=\text{CH}_2$), 4.67 (2H, dt,

$J = 7.0, 2.8$ Hz, $\text{CH}=\text{C}=\text{CH}_2$), 3.73 (1H, qt, $J = 6.2, 6.2$ Hz, CHONH_2), 2.35-2.11 (2H, m, CH_2), 1.17 (3H, d, $J = 6.2$ Hz, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 209.3 ($\text{CH}=\text{C}=\text{CH}_2$), 86.1 ($\text{CH}=\text{C}=\text{CH}_2$), 79.3 ($\text{CH}=\text{C}=\text{CH}_2$), 74.4, 33.8, 18.3.

IR (neat) 3317, 1956 cm^{-1} .

HRMS m/z calcd. for $\text{C}_6\text{H}_{12}\text{NO}$ $[\text{M}+\text{H}]^+$ 114.0919, found 114.0919.

***N*-tert-Butoxycarbonyl (*R*)-hexa-4,5-dien-2-hydroxylamine (4-29).**

Powered sodium hydroxide (1.02 g, 25.4 mmol) was added to a solution of the free hydroxylamine **4-28** (1.1 g, 10.6 mmol) and di-*tert*-butyl dicarbonate (2.68 mL, 11.7 mmol) in dichloromethane-water (25 mL-25 mL) at room temperature. The reaction mixture was stirred at room temperature overnight and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to give the crude product as a light yellow oil. Purification by flash chromatography (EtOAc : Hexane = 1 : 9) provided *N*-protected hydroxylamine **4-29** as a colourless oil (1.87 g, 90%).

$[\alpha]_{\text{D}}^{24.1} +40.8$ (c 1.3, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 7.01 (1H, brs), 5.13 (1H, tt, $J = 7.0, 7.0$, $\text{CH}=\text{C}=\text{CH}_2$), 4.68 (2H, dt, $J = 7.0, 2.8$ Hz, $\text{CH}=\text{C}=\text{CH}_2$), 3.95 (1H, qt, $J = 6.2, 6.2$ Hz, CHO), 2.39-2.33 (1H, m, CH_2), 2.23-2.18 (1H, m, CH_2), 1.48 (9H, s, Boc), 1.23 (3H, d, $J =$

6.2 Hz, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 209.4 ($\text{CH}=\text{C}=\text{CH}_2$), 157.1 ($\text{C}=\text{O}$), 85.7 ($\text{CH}=\text{C}=\text{CH}_2$), 84.7 ($\text{CH}=\text{C}=\text{CH}_2$), 81.6, 81.0, 74.6, 33.6, 28.2 (3C, Boc), 18.0.

IR (neat) 3319, 2980, 1957, 1716 cm^{-1} .

MS m/z 236 $[\text{M}+\text{Na}]^+$; HRMS m/z calcd. for $\text{C}_{11}\text{H}_{19}\text{O}_3\text{NNa}$ $[\text{M}+\text{Na}]^+$ 236.1263, found 236.1271.

(5R)-tert-Butyl 5-methyl-3-vinylisoxazolidine-2-carboxylate (4-19).

AgBF_4 (91 mg, 0.47 mmol) was added to a solution of the *N*-protected hydroxylamine **4-29** (1.0 g, 4.7 mmol) in dried CH_2Cl_2 (25 mL) at room temperature. The reaction mixture was stirred at room temperature in the absence of light for 8h and was filtered through celite, washing with Et_2O (3 x 10 mL). The combined filtrates were washed with sat. NaHCO_3 solution and brine and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was then evaporated *in vacuo* to give the residue which was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to afford a inseparable mixture of *trans*-**4-19** and *cis*-**4-19** (*trans*-**4-19**: *cis*-**4-19** = 1:13, 0.90 g, 90%) as a colourless oil .

cis-**4-19**: ^1H NMR (300 MHz, CDCl_3) δ 5.77 (1H, ddd, J = 17.0, 10.1, 6.9 Hz, $\text{CH}=\text{CH}_2$), 5.17 (1H, d, J = 17.0 Hz, $\text{CH}=\text{CH}_2$), 5.17 (1H, d, J = 10.1 Hz, $\text{CH}=\text{CH}_2$), 4.52 (1H, td, J = 7.2, 7.2 Hz, $\text{NCHCH}=\text{CH}_2$), 3.95 (1H, ddq, J = 9.9, 6.2, 5.7 Hz, CH_3CHO), 2.51 (1H, ddd, J = 14.0, 8.3, 5.7 Hz, CH_2), 1.60 (1H, ddd, J = 12.0, 9.9, 7.2

Hz, CH_2), 1.45 (9H, s, Boc), 1.27 (3H, d, $J = 6.2$ Hz, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 157.1 (C=O), 137.9 ($\text{CH}=\text{CH}_2$), 115.1 ($\text{CH}=\text{CH}_2$), 81.4, 76.9, 62.4, 42.7, 34.4, 27.9 (3C, Boc), 17.4.

IR (neat) 2979, 2936, 1701 cm^{-1} .

MS m/z 236 $[\text{M}+\text{Na}]^+$, 114 (42%); HRMS m/z calcd. for $\text{C}_{11}\text{H}_{19}\text{O}_3\text{NNa}$ $[\text{M}+\text{Na}]^+$ 236.1263, found 236.1252.

***tert*-Butyl ((3*R*, 5*R*)-5-hydroxyhex-1-en-3-yl)carbamate (*syn*-4-30) and *tert*-butyl ((3*S*, 5*R*)-5-hydroxyhex-1-en-3-yl)carbamate (*anti*-4-30).**

$\text{Mo}(\text{CO})_6$ (2.0 g, 7.51 mmol) was added to a solution of isoxazolidines **4-19** (1.0 g, 4.69 mmol) in $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (49 mL-7 mL). The mixture was stirred at room temperature for 15 min and NaBH_4 (90 mg, 2.38 mmol) was added in one portion. The reaction mixture was heated at reflux overnight and cooled to room temperature. The suspension was filtered through celite, washing with Et_2O (3 x 10 mL). The filtrate was then concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography ($\text{EtOAc} : \text{Hexane} = 1 : 9$) to give *syn*-4-30 (0.78 g, 78%) and *anti*-4-30 (60 mg, 6%) both as colourless oils.

syn-4-30: $[\alpha]_{\text{D}}^{22} -21.4$ (c 1.2, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 5.78 (1H, ddd, $J = 17.0, 10.5, 6.2$ Hz, $\text{CH}=\text{CH}_2$), 5.19 (1H, d, $J = 17.0$, $\text{CH}=\text{CH}_2$), 5.11 (1H, d, $J = 10.5$ Hz, $\text{CH}=\text{CH}_2$), 4.68 (1H, brs,

NHBoc), 4.23 (1H, brs, CHNH), 3.93 (1H, qt, $J = 6.2, 6.2$ Hz, CHOH), 1.64 (2H, dd, $J = 6.2, 6.2$ Hz, CHOHCH₂CNH), 1.39 (9H, s, Boc), 1.23 (3H, d, $J = 6.2$ Hz, CH₃CHOH).

¹³C NMR (100 MHz, CDCl₃) δ 155.6 (C=O), 138.8 (CH=CH₂), 114.7 (CH=CH₂), 79.6, 65.7, 51.2, 44.3, 28.3 (3C, Boc), 23.8.

IR (neat) 3333, 2976, 2933, 1683 cm⁻¹.

MS m/z 238 [M+Na]⁺, 216 ([M+1]⁺, 12%), 116 (38%); HRMS m/z calcd. for C₁₁H₂₁NO₃Na [M+Na]⁺ 238.1419, found 238.1412.

anti-**4-30**: [α]_D^{21.4} -2.4 (c 1.36, CHCl₃). m. p.: 52-55 °C.

¹H NMR (400 MHz, CDCl₃) δ 5.83 (1H, ddd, $J = 17.0, 11.0, 5.3$ Hz, CH=CH₂), 5.19 (1H, d, $J = 17.0$, CH=CH₂), 5.12 (1H, d, $J = 11.0$ Hz, CH=CH₂), 4.69 (1H, brs, NHBoc), 4.40 (1H, brs, CHNH), 3.84 (1H, qt, $J = 6.2, 6.2$ Hz, CHOH), 1.68-1.61 (2H, m, CHOHCH₂CNH), 1.45 (9H, s, Boc), 1.21 (3H, d, $J = 6.2$ Hz, CH₃CHOH).

¹³C NMR (100 MHz, CDCl₃) δ 156.7 (C=O), 138.4 (CH=CH₂), 114.5 (CH=CH₂), 80.0, 63.7, 49.3, 45.1, 28.3 (3C, Boc), 22.9.

IR (neat) 3356, 2976, 2832, 1687 cm⁻¹.

MS m/z 238 [M+Na]⁺; HRMS m/z calcd. for C₁₁H₂₁NO₃Na [M+Na]⁺ 238.1419, found 238.1413.

(2*S*,4*R*,6*R*)-*tert*-Butyl 2-(3-bromopropyl)-6-methyl-4-vinyl-1,3-oxazinane-3-carboxylate (*cis*-**4-38**) and (2*R*,4*R*,6*R*)-*tert*-butyl 2-(3-bromopropyl)-6-methyl-4-vinyl-1,3-oxazinane-3-carboxylate (*trans*-**4-38**).

A mixture of protected amino alcohol *syn*-**4-30** (0.4 g, 1.86 mmol), dimethyl acetal **4-37** (1.1 g, 5.58 mmol) and PPTS-resin (50% by weight) in anhydrous toluene was heated at 105 °C for 3.0 h. The reaction mixture was cooled to room temperature and filtered through celite, washing with Et₂O (3 x 8 mL). The combined filtrates were removed *in vacuo* to give a pale yellow oil. The residue was purified by flash chromatography (EtOAc: Hexane = 5: 95) to afford *cis*-**4-38** (0.39 g, 63%) and *tran*-**4-38** (65 mg, 10%) both as colourless oils.

cis-**4-38**: $[\alpha]_D^{22}$ -23.7 (*c* 1.0, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 5.98 (1H, ddd, *J* = 17.1, 10.3, 6.8 Hz, CH=CH₂), 5.16 (1H, dd, *J* = 6.2, 3.8 Hz, OCHN); 5.12 (1H, d, *J* = 17.1 Hz, CH=CH₂), 5.06 (1H, *J* = 10.3 Hz, CH=CH₂), 4.67-4.62 (1H, m, NCHCH=CH₂), 3.57 (1H, ddq, *J* = 10.3, 6.3, 6.3 Hz, CH₃CHO), 3.41-3.31 (2H, m, CH₂Br), 2.10-2.07 (1H, m), 1.96-1.85 (3H, m), 1.75-1.65 (1H, m), 1.61-1.55 (1H, m), 1.47 (9H, s, Boc), 1.22 (3H, d, *J* = 6.3 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 154.0 (C=O), 140.9 (CH=CH₂), 114.7 (CH=CH₂), 85.0 (NCHO), 80.3, 68.1, 50.8, 36.2, 36.0, 33.6, 28.8, 28.4(3C, Boc), 22.1.

IR (neat) 1689 cm⁻¹.

MS *m/z* 370 [M+Na]⁺, 348 ([M+H]⁺, 60%), 248 (100%); HRMS *m/z* calcd. for C₁₅H₂₆NO₃BrNa [M+Na]⁺ 370.0994, found 370.0998.

tran-**4-38**: $[\alpha]_D^{22}$ +2.8 (*c* 1.6, CHCl₃).

^1H NMR (300 MHz, CDCl_3) δ 6.01 (1H, ddd, $J = 17.1, 10.3, 6.2$ Hz, $\text{CH}=\text{CH}_2$), 5.35 (1H, dd, $J = 8.9, 3.5$ Hz, OCHN), 5.06 (1H, d, $J = 17.1$ Hz, $\text{CH}=\text{CH}_2$), 5.02 (1H, $J = 10.3$ Hz, $\text{CH}=\text{CH}_2$), 4.28 (1H, dt, $J = 6.2, 6.2$ Hz, $\text{NCHCH}=\text{CH}_2$), 4.03 (1H, qdd, $J = 6.3, 6.3, 6.3$ Hz, CH_3CHO), 3.53-3.40 (2H, m, CH_2Br), 2.10-1.92 (5H, m), 1.66-1.57 (1H, m), 1.43 (9H, s, Boc), 1.22 (3H, d, $J = 6.3$ Hz, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 154.0 ($\text{C}=\text{O}$), 140.3 ($\text{CH}=\text{CH}_2$), 113.0 ($\text{CH}=\text{CH}_2$), 82.5, 80.2, 63.3, 52.7, 35.9, 33.5, 30.1, 28.9, 28.4 (3C, Boc), 22.8.

IR (neat) 1687 cm^{-1} .

MS m/z 370 $[\text{M}+\text{Na}]^+$, 348 $[\text{M}+\text{H}]^+$, 60%, 248 (100%); HRMS m/z calcd. for $\text{C}_{15}\text{H}_{26}\text{NO}_3\text{BrNa}$ $[\text{M}+\text{Na}]^+$ 370.0994, found 370.1008.

(2*S*,4*R*,6*R*)-tert-Butyl 2-allyl-6-methyl-4-vinyl-1,3-oxazinane-3-carboxylate (4-18).

KOt-Bu (0.20 g, 1.77 mmol) was added to a solution of compound *cis*-**4-38** (0.41 g, 1.18 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 2.0 h further. The mixture was then quenched with saturated NH_4Cl solution and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was purified by flash chromatography ($\text{EtOAc} : \text{Hexane} = 5 : 95$) to provide diene **4-18** (0.28 g,

89%) as a colourless oil.

$[\alpha]_D^{22}$ -14.5 (c 1.8, CHCl_3).

^1H NMR (500 MHz, CDCl_3) δ 6.01 (1H, ddd, $J = 17.3, 10.3, 6.7$ Hz, $\text{CH}=\text{CH}_2$), 5.83 (1H, ddt, $J = 17.2, 10.2, 7.1$ Hz, $\text{CH}=\text{CH}_2$), 5.21 (1H, dd, $J = 7.8, 4.3$ Hz, OCHN); 5.14-5.04 (4H, m, $2\text{CH}=\text{CH}_2$), 4.75-4.71 (1H, m, $\text{NCHCH}=\text{CH}_2$), 3.66 (1H, ddq, $J = 10.3, 6.3, 6.3$ Hz, CH_3CHO), 2.54-2.52 (1H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.46-2.41 (1H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 2.19 (1H, ddd, $J = 13.8, 9.1, 4.7$ Hz, OCHCH_2CHN), 1.96-1.85 (3H, m), 1.75-1.65 (1H, m), 1.61-1.55 (1H, m), 1.46 (9H, s, Boc), 1.23 (3H, d, $J = 6.3$ Hz, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 154.1 ($\text{C}=\text{O}$), 141.1 ($\text{CH}=\text{CH}_2$), 134.0 ($\text{CH}=\text{CH}_2$), 117.2 ($\text{CH}=\text{CH}_2$), 114.5 ($\text{CH}=\text{CH}_2$), 85.5, 80.2, 68.2, 50.8, 42.0, 36.4, 28.4 (3C, Boc), 22.1.

IR (neat) 1694 cm^{-1} .

MS m/z 267 $[\text{M}]^+$; HRMS m/z calcd. for $\text{C}_{15}\text{H}_{25}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 290.1732, found 290.1732.

(1*S*,3*R*,5*R*)-tert-Butyl 3-methyl-2-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylate (4-33).

A solution of Grubbs I catalyst (43 mg, 5 mol%) in CH_2Cl_2 (5 mL) was added to a refluxing solution of diene **4-18** (0.28 g, 1.05 mmol) in CH_2Cl_2 (5 mL) in four portions

via syringe over 0.5 h. The mixture was heated at reflux for an additional 3.5 h and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc : Hexane = 1 : 9) to provide bicyclic *N,O*-acetal **4-33** (0.21 g, 84%) as a colourless oil.

$[\alpha]_{\text{D}}^{20.7}$ -146.2 (c 1.03, CHCl_3).

^1H NMR (400 MHz, CDCl_3) δ 5.93-5.60 (3H, m, $\text{CH}=\text{CH}$, OCHN), 4.53 (1H, ddd, J = 16.5, 9.6, 5.4 Hz, $\text{NCHCH}=\text{CH}$), 3.58 (1H, ddq, J = 11.0, 5.5, 5.5 Hz, CH_3CHO), 2.35-2.07 (3H, m), 1.48 (9H, s, Boc), 1.41-1.30 (1H, m), 1.16 (d, J = 5.5 Hz) and 1.15 (d, J = 5.5 Hz) (3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 154.2 and 153.7 ($\text{C}=\text{O}$), 130.4 and 129.8 ($\text{CH}=\text{CH}$), 121.3 and 120.8 ($\text{CH}=\text{CH}$), 80.1 and 80.0, 78.4, 63.2 and 62.9, 45.3 and 43.7, 36.6 and 35.8, 32.0 and 31.9, 28.2 and 28.1, 20.7 and 20.6.

IR (neat) 1632 cm^{-1} .

MS m/z 239 $[\text{M}]^+$, 207 (100%), 179 (95%); HRMS m/z calcd. for $\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 262.1419, found 262.1429.

(2*R*)-tert-Butyl 5,6-dihydro-2-((*R*)-2-hydroxypropyl)-6-methoxypyridine-1(2*H*)-carboxylate (4-45).

PPTS (79 mg, 0.31 mmol) was added to a solution of *N,O*-acetal **4-33** (0.15 g, 0.63 mmol) in MeOH (10 mL) at -10 °C. The reaction mixture was warmed to 0 °C and

stirred at 0 °C for 5 h. the reaction mixture was quenched with saturated NaHCO₃ solution and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc : Hexane = 2 : 8) to afford semicyclic *N,O*-acetal **4-45** (0.15 g, 88%) as a colourless oil.

$[\alpha]_D^{20.3}$ -185.5 (*c* 1.8, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 5.78-5.38 (3H, m, CH=CH and OCHN), 4.46 (1H, brs, NCHCH=CH₂), 3.87 (1H, brs, CH₃CHO), 3.25 (3H, s, OMe), 2.37-2.28 (2H, m, CH2CH=CH₂), 1.74 (1H, dd, *J* = 6.0, 6.0 Hz, CH2CHOH), 1.45 (9H, s, Boc), 1.15 (3H, d, *J* = 6.0 Hz, CH3).

¹³C NMR (100 MHz, CDCl₃) δ 154.6 (C=O), 126.7 and 126.1 (CH=CH), 120.1 and 119.3 (CH=CH), 80.7 and 80.3, 79.5, 65.5 and 64.7, 55.3 and 55.0, 48.8, 45.3, 30.4, 28.3 (3C), 24.0.

IR (neat) 1660 cm⁻¹.

MS *m/z* 294 [M+Na]⁺; HRMS *m/z* calcd. for C₁₄H₂₅NO₄Na [M+Na]⁺ 294.1681, found 294.1668.

(3*R*,4*aR*)-4,4*a*,7,8-Tetrahydro-8-methoxy-3-methylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (4-17).

KOt-Bu (75 mg, 0.66 mmol) was added to a solution of compound **4-45** (0.18 g, 0.66

mmol) in THF (10 mL) at -10 °C and was stirred at this temperature for 10 min. The mixture was then quenched with saturated NH₄Cl solution and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was purified by flash chromatography (EtOAc : Hexane = 1 : 1) to provide product **4-17** (65 mg, 50%) as a colourless oil.

$[\alpha]_D^{22}$ -41.1 (*c* 2.1, CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 6.02-5.98 (1H, m, CH=CH) 5.77 (1H, dt, *J* = 9.6, 2.4 Hz, CH=CH), 5.55 (1H, t, *J* = 3.3 Hz, OCHN), 4.58 (1H, ddq, *J* = 11.2, 6.2, 6.2 Hz, CH₃CHO), 3.99-3.94 (1H, m, NCHCH=CH₂), 3.39 (3H, s, OMe), 2.58 (1H, ddd, *J* = 16.2, 6.9, 2.3 Hz, CH₂CH=CH₂), 2.28-2.22 (1H, m, CH₂CHO), 2.14 (1H, ddd, *J* = 13.4, 2.3, 2.3 Hz, CH₂CH=CH₂), 1.73 (1H, aq.q, *J* = 12.0 Hz, CH₂CHO), 1.43 (3H, d, *J* = 6.2 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 154.3 (C=O), 126.8 (CH=CH), 125.2 (CH=CH), 82.0, 75.5, 56.7, 49.7, 37.4, 29.4, 22.0.

IR (neat) 1670 cm⁻¹.

MS *m/z* 220 [M+Na]⁺, 179 (100%); HRMS *m/z* calcd. for C₁₀H₁₅NO₃Na [M+Na]⁺ 220.0950, found 220.0944.

(3*R*,4*aR*,8*S*)-3-Methyl-8-(2-oxo-2-phenylethyl)-4,4*a*,7,8-tetrahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (*trans*-4-16) and **(3*R*,4*aR*,8*R*)-3-methyl-8-(2-oxo-2-phenylethyl)-4,4*a*,7,8-tetrahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (*cis*-4-16).**

SnCl₄ (1 M in CH₂Cl₂, 36 μL, 0.036 mmol) was added to a cooled (-78 °C) solution of *N,O*-acetal **4-17** (6 mg, 0.03 mmol) and (1-phenylvinyl)oxy)trimethylsilane (20 μL, 0.09 mmol) in CH₂Cl₂ (3 mL) *via* syringe. After stirring at -78 °C for 1 h, the reaction mixture was quenched with saturated NaHCO₃ solution at this temperature and then allowed to warm to room temperature. The reaction mixture was then extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was purified by flash chromatography (EtOAc : Hexane = 2 : 8) to provide *cis*-**4-16** (3 mg, 34%) as a colourless oil and *trans*-**4-16** (3 mg, 34%) as a colourless solid.

cis-**4-16**: ¹H NMR (500 MHz, CDCl₃) δ 8.03 (2H, d, *J* = 7.4 Hz, Ar), 7.55 (1H, t, *J* = 7.4 Hz, Ar), 7.45 (2H, t, *J* = 7.4 Hz, Ar), 5.87-5.92 (1H, m, CH=CH), 5.66 (1H, d, *J* = 9.7 Hz, CH=CH), 4.38 (1H, qt, *J* = 6.2, 6.2 Hz, CHO), 4.22-4.17 (2H, m), 3.94 (1H, dd, *J* = 17.3, 5.0 Hz, CH₂C=OPh), 3.38 (1H, dd, *J* = 17.3, 8.2 Hz, CH₂C=OPh), 2.57-2.51 (1H, m), 2.18 (2H, dd, *J* = 13.5, 4.6 Hz, CH₂CH=CH), 1.58-1.51 (1H, m), 1.35 (3H, d, *J* = 6.2 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 198.5 (C=OPh), 153.6 (NC=O), 136.9 (Ar), 133.1 (Ar), 128.6 (2C, Ar), 128.5 (CH=CH₂), 128.3 (2C, Ar), 127.4 (CH=CH₂), 71.5, 54.0, 52.0,

41.9, 36.7, 28.8, 20.6.

IR (neat) 1673 cm^{-1} .

MS m/z 286 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{17}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 286.1443, found 286.1439.

trans-**4-16**: m.p.: 147-150 $^{\circ}\text{C}$.

^1H NMR (400 MHz, CDCl_3) δ 7.95 (2H, d, $J = 7.6$ Hz, Ar), 7.56 (1H, t, $J = 7.6$ Hz, Ar), 7.46 (2H, t, $J = 7.6$ Hz, Ar), 5.83 (1H, dd, $J = 10.1, 6.0$ Hz, $\text{CH}=\text{CH}$), 5.59 (1H, d, $J = 10.1$ Hz, $\text{CH}=\text{CH}$), 5.32 (1H, dt, $J = 6.8, 6.8$ Hz, CHNCH), 4.68 (1H, app. d, $J = 11.8$ Hz, CHN), 4.37 (1H, qt, $J = 6.2, 6.2$ Hz, CHO), 3.27 (1H, dd, $J = 14.8, 8.4$ Hz, $\text{CH}_2\text{C}=\text{OPh}$), 3.19 (1H, dd, $J = 14.8, 6.6$ Hz, $\text{CH}_2\text{C}=\text{OPh}$), 2.56 (1H, dd, $J = 6.2, 2.3$ Hz), 2.07-2.04 (2H, m, $\text{CH}_2\text{CH}=\text{CH}$), 1.60-1.51 (1H, m), 1.36 (3H, d, $J = 6.2$ Hz, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 197.9 ($\text{C}=\text{OPh}$), 152.9 ($\text{NC}=\text{O}$), 136.6 (Ar), 133.3 (Ar), 128.7 (2C, Ar), 128.2 (2C, Ar), 125.9 ($\text{CH}=\text{CH}_2$), 124.0 ($\text{CH}=\text{CH}_2$), 71.9, 48.8, 45.5, 40.3, 35.9, 28.2, 21.0.

IR (neat) 1670 cm^{-1} .

MS m/z 286 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{17}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 286.1443, found 286.1434.

(2*R*,6*S*)-tert-Butyl 2-((*R*)-2-hydroxypropyl)-6-(2-oxo-2-phenylethyl)-5,6-dihydro

-pyridine-1(2H)-carboxylate (4-49).

SnCl₄ (1 M in CH₂Cl₂, 0.55 mL, 0.55 mmol) *via* syringe was added to a cooled (-78 °C) solution of cyclic *N,O*-acetal **4-33** (110 mg, 0.46 mmol) and (1-phenylvinyl)oxy)trimethylsilane (0.56 mL, 2.8 mmol) in CH₂Cl₂ (8 mL). After stirring at -78 °C for 0.5 h, the reaction mixture was quenched with saturated NaHCO₃ solution and then allowed to warm to room temperature. The reaction mixture was then extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo* to afford the crude product, which was purified with flash chromatography (EtOAc : Hexane = 2 : 8) to provide ketone **4-49** (100 mg, 60%) as a colourless oil.

$[\alpha]_D^{19.5}$ -101.4 (*c* 1.27, CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 7.97 (2H, d, *J* = 7.5 Hz, Ar), 7.56 (1H, t, *J* = 7.5 Hz, Ar), 7.46 (2H, t, *J* = 7.5 Hz, Ar), 5.97 (1H, dd, *J* = 9.4, 4.5 Hz, CH=CH), 5.82 (1H, dt, *J* = 9.4, 4.4 Hz, CH=CH), 4.46-4.42 (2H, m, CHNCH), 3.94-3.87 (1H, m, CHOH), 3.37 (1H, br, CH₂C=O), 3.28 (H, dd, *J* = 41.7, 8.8 Hz, CH₂C=O), 2.28-2.21 (2H, m, CH₂CH=CH), 2.01 (1H, ddd, *J* = 14.2, 9.3, 5.2 Hz, HOCHCH₂), 1.66 (1H, ddd, *J* = 13.7, 7.4, 3.1 Hz, HOCHCH₂), 1.45 (9H, s, Boc), 1.20 (3H, d, *J* = 6.3 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 198.5 (C=O^{Ph}), 155.2 (NC=O), 136.8 (Ar), 133.0 (Ar), 130.3 (CH=CH₂), 128.5 (2C, Ar), 128.0 (2C, Ar), 124.1 (CH=CH₂), 80.2, 66.0, 51.4, 48.1, 44.9, 42.4, 28.3(3C), 28.2, 24.1.

IR (neat) 1674, 1597, 1580, 1449 cm⁻¹.

MS *m/z* 382 [M+Na]⁺, 360 ([M+H], 47%).

HRMS m/z calcd. for $C_{21}H_{29}NO_4Na$ $[M+Na]^+$ 382.1994, found 382.1980.

(3*R*,4*aR*,8*S*)-3-methyl-8-(2-oxo-2-phenylethyl)-4,4*a*,7,8-tetrahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (*trans*-4-16).

KOt-Bu (9 mg, 0.075 mmol) was added to a solution of compound **4-49** (18 mg, 0.05 mmol) in THF (5 mL) at 0 °C and the mixture was warmed to room temperature. The mixture was stirred at room temperature for 1 h, then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered through celite and concentrated *in vacuo* to afford the crude product. The crude product was purified by flash chromatography (EtOAc : Hexane = 1 : 1) to provide product (5 mg, 35%) as a colourless solid. The NMR data is consistent with that of *trans*-4-16 (See above).

(2*R*,6*S*)-tert-Butyl 6-((*S*)-2-hydroxy-2-phenylethyl)-2-((*R*)-2-hydroxypropyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (*anti*-4-55) and (2*R*,6*S*)-tert-butyl 6-((*R*)-2-hydroxy-2-phenylethyl)-2-((*R*)-2-hydroxypropyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (*syn*-4-55).

DIBAL (1M in cyclohexane, 0.97 mL, 0.97 mmol) was slowly added to a solution of

compound (70 mg, 0.19 mmol) in CH₂Cl₂ (5 mL) at -78 °C *via* syringe over 5 min. The reaction mixture was stirred at -78 °C for 2 h and then warmed to -40 °C for 0.5 h. Then methanol (0.5 mL) and water (0.5 mL) were added subsequently to quench the reaction. It was allowed to warm to room temperature for 0.5 h, dried over anhydrous Na₂SO₄ and stirred for 10 min further. After filtration through celite and evaporation, the residue was purified with flash chromatography (EtOAc : Hexane = 2 : 8) to provide *syn*-**4-55** (14 mg, 18%) and *anti*-**4-55** (56 mg, 82%) as colourless oils.

anti-**4-55**: $[\alpha]_D^{20.2}$ -118.9 (*c* 1.27, CHCl₃).

¹H NMR (300 MHz, CDCl₃) δ 7.35-7.21 (5H, m, Ar), 5.89 (1H, ddd, *J* = 9.9, 4.6, 1.2 Hz, CH=CH), 5.81 (1H, dt, *J* = 9.9, 4.1 Hz, CH=CH), 4.65 (1H, dt, *J* = 9.4, 3.7 Hz, PhCH₂OH), 4.36 (1H, dt, *J* = 5.9, 5.9 Hz, CH=CHCH₂N), 4.01 (1H, ddt, *J* = 8.3, 4.2, 4.2 Hz, CH₂N), 3.87-3.83 (1H, m, CH₃CH₂OH), 3.31 (1H, brs, OH), 2.80 (1H, brs, OH), 2.26-2.21 (2H, m, CH₂CH=CH), 2.07-1.98 (2H, m), 1.90 (1H, ddd, *J* = 14.0, 9.1, 5.1 Hz), 1.58 (1H, ddd, *J* = 14.0, 7.4, 3.3 Hz), 1.48 (9H, s, Boc), 1.18 (3H, d, *J* = 6.2 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 155.9 (C=O), 144.8 (Ar), 130.5 (CH=CH₂), 128.4 (2C, Ar), 127.3 (Ar), 125.7 (2C, Ar), 124.4 (CH=CH₂), 80.5, 72.3, 66.2, 51.7, 49.4, 44.7, 44.3, 28.5(3C, Boc), 28.0, 24.1.

IR (neat) 3393, 1652, 1475, 1454, 1400 cm⁻¹.

MS *m/z* 362 [M+H]⁺, 384 ([M+Na], 48%); HRMS *m/z* calcd. for C₂₁H₃₂NO₄ [M+H]⁺ 362.2331, found 362.2332.

syn-**4-55**: ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.21 (5H, m, Ar), 5.84-5.81 (2H, m,

CH=CH), 4.63 (1H, dd, $J = 10.4, 2.6$ Hz, PhCHOH), 4.50-4.46 (1H, m, CH=CHCHN), 4.13-4.05 (1H, m, CH₃CHOH), 4.03-3.93 (1H, m, CH=CHCH₂CHN), 2.30 (1H, ddd, $J = 13.7, 10.3, 2.8$ Hz, CH₂CH=CH), 2.20-2.15 (1H, m), 2.06-1.95 (1H, m), 1.82-1.59 (3H, m), 1.44 (9H, s, Boc), 1.21 (3H, d, $J = 6.2$ Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ 156.6 (C=O), 144.6 (Ar), 129.9 (CH=CH₂), 128.3 (2C, Ar), 127.1 (Ar), 125.7 (CH=CH₂), 125.6 (2C, Ar), 80.8, 70.4, 67.1, 53.1, 48.5, 43.9, 43.6, 29.6, 28.5(3C), 24.3.

IR (neat) 3365, 1666, 1454, 1400 cm⁻¹.

MS m/z 362 [M+H]⁺, 384 ([M+Na], 38%); HRMS m/z calcd. for C₂₁H₃₂NO₄ [M+H]⁺ 362.2331, found 362.2321.

(2*R*,6*S*)-tert-Butyl-6-((*S*)-2-hydroxy-2-phenylethyl)-2-((*R*)-2-hydroxypropyl)-5,6-dihydro-1*H*-pyridine-1(2*H*)-carboxylate (*anti*-4-55)

(*R*)-CBS-Me (34 μ L, 0.033 mmol) was added to a solution of BH₃·SMe₂ (48 μ L, 0.50 mmol) in anhydrous THF (2 mL) at room temperature. The reaction mixture was stirred for 15 min and cooled to -10 °C for 5 min. A solution of the ketone **4-49** (60 mg, 0.167 mmol) in THF (2 mL) was added dropwise by cannula. The reaction mixture was stirred at -10 °C for 20 min and warmed to 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and quenched with methanol (2 mL) and stirred at room temperature for 15 min. After evaporation, the residue was purified by flash chromatography

(EtOAc : Hexane = 2 : 8) to give *anti*-**4-55** (55 mg, 92%) as a colourless oil.

(*R*)-1-((2*R*,6*S*)-1,2,5,6-Tetrahydro-6-((*S*)-2-hydroxy-2-phenylethyl)-1-methylpyridin-2-yl)propan-2-ol (4-2) and (*R*)-1-((2*R*,6*S*)-6-((*S*)-2-hydroxy-2-phenylethyl)-1,2,5,6-tetrahydropyridin-2-yl)propan-2-ol (4-57).

Alane-*N,N*-dimethylethylamine (0.5 M in toluene, 0.83 mL, 0.42 mmol) was added to a solution of compound **4-55** (30 mg, 0.083 mmol) in anhydrous THF (5 mL) at room temperature. The mixture was then heated at reflux for 5 h and was cooled to 0 °C. Water was added cautiously and dropwise. The reaction mixture was extracted with CHCl₃ (3 x 5 mL), dried over anhydrous Na₂SO₄, filtered through celite and concentrated *in vacuo*. The residue was purified by flash chromatography (basic Al₂O₃, MeOH : CH₂Cl₂ = 2 : 98) to give sedinine **4-2** (16 mg, 70%) as a colourless solid and byproduct **4-57** (4 mg, 15%) as a yellowish oil.

Sedinine 4-2: [α]_D^{20.4} -97.2 (*c* 0.57, MeOH) [ref. 86 [α]_D²⁰ -98 (*c* 1.9, MeOH)]. m.p.: 118-120 °C [ref. 86: 120-121 °C].

¹H NMR (500 MHz, CDCl₃) δ 7.42 (2H, d, *J* = 7.6 Hz, Ar), 7.34 (1H, t, *J* = 7.6 Hz, Ar), 7.27 (2H, t, *J* = 7.6 Hz, Ar), 5.75 (1H, ddd, *J* = 10.3, 5.3, 1.7 Hz, CH=CH), 5.56 (1H,

ddt, $J = 10.3, 3.9, 1.9$ Hz, $\text{CH}=\text{CH}$), 4.81 (1H, dd, $J = 9.3, 4.5$ Hz, $\text{PhCH}\underline{\text{O}}\text{H}$), 4.01 (1H, dqd, $J = 9.4, 3.2, 3.2$ Hz, $\text{CH}_3\text{CH}\underline{\text{O}}\text{H}$), 3.28 (1H, ddt, $J = 12.0, 6.0, 6.0$ Hz, $\text{CH}\underline{\text{N}}$), 3.18 (1H, brd, $J = 10.3$ Hz, $\text{CH}\underline{\text{N}}$), 2.35 (3H, s, CH_3N), 2.00-1.92 (2H, m), 1.83 (1H, dt, $J = 18.0, 4.5$ Hz, $\text{CH}_2\text{CH}=\text{CH}$), 1.72-1.65 (2H, m), 1.50 (1H, dt, $J = 14.5, 3.3$ Hz, $\text{CH}_3\text{CHOHCH}_2$), 1.18 (3H, d, $J = 6.2$ Hz, CH_3).

^{13}C NMR (100 MHz, CDCl_3) δ 145.0 (Ar), 128.4 (2C, Ar), 127.5, 127.4, 125.9 (2C, Ar), 125.0 ($\text{CH}=\text{CH}_2$), 73.1, 68.6, 62.7, 49.2, 42.0, 40.6, 34.6, 24.3, 23.8.

MS m/z 276 $[\text{M}+\text{H}]^+$, 246 (36%); HRMS m/z calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 276.1964, found 276.1961.

4-57: ^1H NMR (300 MHz, CDCl_3) δ 7.42-7.19 (5H, m, Ar), 5.81-5.75 (1H, m, $\text{CH}=\text{CH}$), 5.68-5.64 (1H, m, $\text{CH}=\text{CH}$), 4.90 (1H, dd, $J = 9.0, 4.6$ Hz, $\text{PhCH}\underline{\text{O}}\text{H}$), 4.00 (1H, dqd, $J = 9.3, 6.0, 3.2$ Hz, $\text{CH}_3\text{CH}\underline{\text{O}}\text{H}$), 3.60 (1H, brd, $J = 9.7$ Hz, $\text{CH}\underline{\text{N}}$), 3.12 (1H, ddt, $J = 9.4, 9.4, 4.6$ Hz, $\text{CH}\underline{\text{N}}$), 2.34-1.47 (6H, m), 1.20 (3H, d, $J = 6.0$ Hz, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ 144.8 (Ar), 129.8 (Ar), 128.4 (2C, Ar), 127.5 ($\text{CH}=\text{CH}_2$), 125.9 (2C, Ar), 125.1 ($\text{CH}=\text{CH}_2$), 73.0, 68.2, 52.7, 46.4, 44.4, 41.0, 31.0, 24.0.

MS m/z 262 $[\text{M}+\text{H}]^+$; HRMS m/z calcd. for $\text{C}_{16}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 262.1807, found 262.1801

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APPENDIX

A.1. X-ray crystallography data

Table 1. Crystal data and structure refinement for **2-45a**.

Identification code	2-45a	
Empirical formula	C ₁₄ H ₂₁ N O ₃ S	
Formula weight	283.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 25.4697(10) Å	$\alpha = 90^\circ$.
	b = 8.2707(3) Å	$\beta = 112.799(2)^\circ$.
	c = 15.0401(6) Å	$\gamma = 90^\circ$.
Volume	2920.70(19) Å ³	
Z	8	
Density (calculated)	1.289 Mg/m ³	
Absorption coefficient	0.225 mm ⁻¹	
F(000)	1216	
Crystal size	0.22 x 0.20 x 0.16 mm ³	
Theta range for data collection	1.73 to 30.49°.	
Index ranges	-36 ≤ h ≤ 36, -10 ≤ k ≤ 11, -21 ≤ l ≤ 21	
Reflections collected	14008	
Independent reflections	4342 [R(int) = 0.0286]	
Completeness to theta = 30.49°	97.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9648 and 0.9521	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4342 / 0 / 245	
Goodness-of-fit on F ²	1.069	
Final R indices [I > 2σ(I)]	R1 = 0.0408, wR2 = 0.1132	
R indices (all data)	R1 = 0.0529, wR2 = 0.1241	
Largest diff. peak and hole	0.437 and -0.238 e.Å ⁻³

Table 1. Crystal data and structure refinement for **2-47**.

Identification code	2-47	
Empirical formula	C ₁₄ H ₂₁ N O ₃ S	
Formula weight	283.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.4160(3) Å	$\alpha = 90^\circ$.
	b = 11.6034(4) Å	$\beta = 92.908(2)^\circ$.
	c = 16.6499(7) Å	$\gamma = 90^\circ$.
Volume	1430.89(10) Å ³	
Z	4	
Density (calculated)	1.315 Mg/m ³	
Absorption coefficient	0.230 mm ⁻¹	
F(000)	608	
Crystal size	0.25 x 0.20 x 0.16 mm ³	
Theta range for data collection	2.14 to 30.51°.	
Index ranges	-10 ≤ h ≤ 10, -15 ≤ k ≤ 16, -23 ≤ l ≤ 23	
Reflections collected	15576	
Independent reflections	4338 [R(int) = 0.0266]	
Completeness to theta = 30.51°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9641 and 0.9447	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4338 / 0 / 256	
Goodness-of-fit on F ²	1.045	
Final R indices [I > 2σ(I)]	R1 = 0.0345, wR2 = 0.0963	
R indices (all data)	R1 = 0.0423, wR2 = 0.1018	
Largest diff. peak and hole	0.391 and -0.245 e.Å ⁻³

Table 1. Crystal data and structure refinement for minor-4-30.

Identification code	4-30	
Empirical formula	C ₁₁ H ₂₁ N O ₃	
Formula weight	215.29	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.3087(3) Å	α = 90°.
	b = 10.4384(4) Å	β = 90°.
	c = 13.4289(5) Å	γ = 90°.
Volume	1304.86(8) Å ³	
Z	4	
Density (calculated)	1.096 Mg/m ³	
Absorption coefficient	0.079 mm ⁻¹	
F(000)	472	
Crystal size	0.40 x 0.40 x 0.36 mm ³	
Theta range for data collection	2.66 to 29.68°.	
Index ranges	-11 ≤ h ≤ 12, -14 ≤ k ≤ 14, -17 ≤ l ≤ 18	
Reflections collected	11324	
Independent reflections	2081 [R(int) = 0.0377]	
Completeness to theta = 29.68°	98.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9722 and 0.9692	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2081 / 0 / 141	
Goodness-of-fit on F ²	1.169	
Final R indices [I > 2σ(I)]	R1 = 0.0487, wR2 = 0.1304	
R indices (all data)	R1 = 0.0706, wR2 = 0.1709	
Absolute structure parameter	-10(10)	
Largest diff. peak and hole	0.270 and -0.332 e.Å ⁻³

Table 1. Crystal data and structure refinement for *trans*-**4-16**.

Identification code	4-16	
Empirical formula	C ₁₇ H ₁₉ N O ₃	
Formula weight	285.33	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.5279(6) Å	α = 90°.
	b = 10.4994(7) Å	β = 90°.
	c = 18.0253(11) Å	γ = 90°.
Volume	1424.69(17) Å ³	
Z	4	
Density (calculated)	1.330 Mg/m ³	
Absorption coefficient	0.091 mm ⁻¹	
F(000)	608	
Crystal size	0.36 x 0.08 x 0.07 mm ³	
Theta range for data collection	2.26 to 30.88°.	
Index ranges	-10 ≤ h ≤ 5, -15 ≤ k ≤ 15, -25 ≤ l ≤ 25	
Reflections collected	10233	
Independent reflections	2545 [R(int) = 0.0395]	
Completeness to theta = 30.88°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9937 and 0.9679	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2545 / 0 / 191	
Goodness-of-fit on F ²	1.083	
Final R indices [I > 2σ(I)]	R1 = 0.0389, wR2 = 0.0968	
R indices (all data)	R1 = 0.0511, wR2 = 0.1139	
Largest diff. peak and hole	0.371 and -0.317 e.Å ⁻³	

A.2. Chiral HPLC Analysis

Chiral HPLC analysis for compound **3-45: 2-((R)-Octa-6,7-dien-4-yloxy) isoindoline-1,3-dione**

Time: 2008Sep291757
 LNY-1
 Chiral column: OD-H
 Eluent: 99% hexane 1%IPA
 Flow rate: 0.3 mL/min

PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	46.397	170692263	1821057	48.278	52.380
2	49.230	182869563	1655555	51.722	47.620
Total		353561827	3476612	100.000	100.000

Time: 2008Sep291758
 LNY-RAC
 Chiral column: OD-H
 Eluent: 99% hexane 1%IPA
 Flow rate: 0.3 mL/min

PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.603	989326	14463	0.235	0.477
2	48.600	419814765	3016761	99.765	99.523
Total		420804091	3031224	100.000	100.000

Chiral HPLC analysis for compound **4-27: (R)-2-(Hexa-4,5-dien-2-yloxy)isoindoline -1,3-dione**

Time: 2009Apr281358
 Reaction name:
 Substrate:
 Sample name: lny-2-rac
 Catalyst:
 Solvent:
 Temperature:
 Chiral column: OJ-H
 Eluent: 99% hexane 1%IPA
 Flow rate: 0.3mL/min

PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	57.787	15448643	113740	44.255	48.496
2	61.357	19459744	120796	55.745	51.504
Total		34908388	234536	100.000	100.000

Time: 2009Apr281359
 Reaction name:
 Substrate:
 Sample name: lny-2
 Catalyst:
 Solvent:
 Temperature:
 Chiral column: OJ-H
 Eluent: 99% hexane 1%IPA
 Flow rate: 0.3mL/min

PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	57.098	600916	7941	0.357	0.715
2	60.685	167806486	1102827	99.643	99.285
Total		168407402	1110768	100.000	100.000

A.3. Selective NMR spectra

¹H NMR spectrum of (3*R*,5*R*)-*tert*-Butyl 5-propyl-3-vinylisoxazolidine-2-carboxylate (3-38) (CDCl₃, 500MHz)

¹³C NMR spectrum of (3*R*,5*R*)-*tert*-Butyl 5-propyl-3-vinylisoxazolidine-2-carboxylate (3-38) (CDCl₃, 125MHz)

¹H NMR spectrum of (3*R*,4*aS*,8*R*)-8-Allyl-3-propylhexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (*cis*-3-56) (CDCl₃, 500MHz)

COSY spectrum of (3*R*,4*aS*,8*R*)-8-Allyl-3-propylhexahydropyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (*cis*-3-56) (CDCl₃, 400MHz)

¹H NMR spectrum of (2R,3aS,6aR,9aS)-Decahydro-9a-methyl-2-propyl-2H-[1,3]oxazino 2,3,4-de]quinolizine (3-59) (CDCl₃, 400MHz)

¹³C NMR spectrum of (2R,3aS,6aR,9aS)-Decahydro-9a-methyl-2-propyl-2H-[1,3]oxazino 2,3,4-de]quinolizine (3-59) (CDCl₃, 125MHz)

¹H NMR spectrum of **(3R,4aS,8S)-8-Allyl-3-propylhexahydropyrido[1,2-c][1,3]oxazin-1(3H)-one (trans-3-56)** (CDCl₃, 500MHz)

COSY spectrum of **(3R,4aS,8S)-8-Allyl-3-propylhexahydropyrido[1,2-c][1,3]oxazin-1(3H)-one (cis-3-56)** (CDCl₃, 125MHz)

¹H NMR spectrum of (3*R*,4*aS*,8*S*)-Hexahydro-8-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-68) (CDCl₃, 300MHz)

¹³C NMR spectrum of (3*R*,4*aS*,8*S*)-Hexahydro-8-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)-3-propylpyrido[1,2-*c*][1,3]oxazin-1(3*H*)-one (3-68) (CDCl₃, 100MHz)

¹H NMR spectrum of (5R)-tert-Butyl 5-methyl-3-vinylisoxazolidine-2-carboxylate (4-19) (CDCl₃, 300 MHz)

¹³C NMR spectrum of (5R)-tert-Butyl 5-methyl-3-vinylisoxazolidine-2-carboxylate (4-19) (CDCl₃, 75 MHz)

¹H NMR spectrum of (R)-1-((2R,6S)-1,2,5,6-Tetrahydro-6-((S)-2-hydroxy-2-phenylethyl)-1-methylpyridin-2-yl)propan-2-ol (4-2) (CDCl₃, 500 MHz)

¹³C NMR spectrum of (R)-1-((2R,6S)-1,2,5,6-Tetrahydro-6-((S)-2-hydroxy-2-phenylethyl)-1-methylpyridin-2-yl)propan-2-ol (4-2) (CDCl₃, 100 MHz)