2-AZA-[3,3]-Sigmatropic rearrangement and AZA-PRINS cyclization and their applications in total synthesis of (-)-indolizidine-209B and (-)-perhydrohistrionicotoxin

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(-)-PERHYDROHISTRIONICOTOXIN**

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Doctor of Philosophy

2010

To my teachers,

friends

and family.

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Summary

Two novel C-C bond formation methodologies, i.e. 2-aza-[3,3]-sigmatropic rearrangement and aza-Prins cyclization, were developed for the synthesis of linear homoallylic hydroxylamines and 2,3,6-trisubstituted piperidines respectively. These two nitrogen-containing compounds are useful building blocks in many natural products. The applications of these methodologies were then demonstrated in the total syntheses of both (–)-indolizidine 209B and (–)-perhydrohistrionicotoxin.

Based on our group's previous development of 2-oxocarbenium-[3,3]-sigmatropic rearrangement and oxocarbenium-Prins cyclization, we extend the chemistry to the iminocarbenium moiety. Hence, the following 2-aza-[3,3]-sigmatropic rearrangement was successful using camphorsulfonic acid in isopropanol.

Enantiomeric excess is up to 99% with up to 80% yield. This reaction works well with enolizable aliphatic aldehydes, hence, it complements many of current imine allylations which work exclusively for nonenolizable aldehyde. Mechanism studies also disclosed that the enantiomeric excess decreases dramatically in [3,3]-sigmatropic rearrangement of simple homoallylic nitrones. Stereochemical study showed that the product was obtained with retention of stereochemistry.

The homoallylic nitrone can be readily converted to homoallylic amine, a known versatile synthon. Also, the nitrone can be converted to hydroxyl amine, which is an excellent precursor in the synthesis of nitrones and a good starting materials for 1,3-dipolar cycloadditions. Hence, this method provides an efficient and convenient access to linear

homoallylic amines and hydroxylamines under environmentally benign and mild reaction conditions.

In the aza-Prins cyclization, the piperidine-core is obtained smoothly in up to 86% yield when a readily obtained nitron was subjected to acetyl bromide at ambient temperature.

Various substituents are demonstrated, including both aromatic and aliphatic, bulky and non-bulky side chains. This aza-Prins also afforded the tri-substituted piperidine, hence extending the scope of current aza-Prins cyclizations. In all cases, simple olefins are sufficient for the cyclization to occur. Furthermore, no homo-couple product was obtained. All the products are obtained exclusively as the cross-coupling product. In addition, the optical purity of the piperidine product is largely preserved, as demonstrated in a subsequent total synthesis. Mechanistic studies later led to a proposed explanation of the abrupt and unusual change in bromide's axial/equatorial selectivity.

These two methodologies were then applied in the total syntheses of (–)-indolizidine 209B and (–)-perhydrohistrionicotoxin.

The aza-Prins cyclization was applied in the total synthesis of (–)-indolizidine 209B, and it provided the piperidine core and established all the relative stereochemistry required. The total synthesis was accomplished in seven steps with 8.5% yield.

The 2-aza-[3,3]-sigmatropic rearrangement was applied in the total synthesis of (-)-perhydrohistrionicotoxin, where it provided an efficient and rapid access to the key nitronium intermediate in high optical purity.

The total synthesis of (-)-perhydrohistrionicotoxin was established in nine steps with 14% overall yield.

List of Abbreviations

δ	chemical shift
Δ	heating
$\uparrow\downarrow$	reflux
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
AcBr	acetyl bromide
AcOH	acetic acid
Ac ₂ O	acetic anhydride
AllylBr	allylbromide
aq	aqueous
br s	broad singlet
Bz	benzoyl
<i>t</i> -bu	tert-butyl
calcd	calculated
cat	catalytic
Cbz	benzyloxycarbonyl
C-C	carbon-carbon
CDCl ₃	deuterated chloroform
CSA	camphorsulfonic acid
CH ₂ Cl ₂	dichloromethane
CHCl ₃	chloroform
cm ⁻¹	inverse centimeter

d	doublet
DCC	1,3-dicyclohexylcarbodiimide
dd	doublets of doublet
ddd	doublets of doublets of doublet
<i>de</i>	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublets of triplet
dq	doublets of quartet
dqd	doublets of quartets of doublet
<i>ee</i>	enantiomeric excess
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atomic bombardment
FTIR	Fourier transform infrared spectroscopy

Gly	glycine
g	gram
h	hour
H	hydrogen
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HPMA	hexamethylphosphoramidate
HMPT	hexamethylphosphorous triamide
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constants
kg	kilogram
LDA	lithium diisopropylamide
M	concentration (mol/dm ⁻³)
M ⁺	parent ion peak (mass spectrum)
m	multiplet
Me	methyl
MeCN	acetonitrile
MeOH	methanol

mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)
NaHMDS	Sodium hexamethyl disilazide
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu	<i>n</i> -butyl
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
obs.	Observed
OTf	trifluoromethanesulfonate
p	page
PBr ₃	phosphorus tribromide
PCC	pyridinium chlorochromate
Pd / C	palladium on carbon
Ph	phenyl
PhH	benzene
PhMe	toluene

ppm	parts per million
q	quartet
qd	quartets of doublet
qdd	quartets of doublets of doublet
rt.	room temperature
RBF	round bottom flask
R_f	retention factor
s	singlet
sat	saturated
s-Bu	<i>sec</i> -Butyl
t	triplet
<i>t</i> -Bu	<i>tert</i> -butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TEAB	triethylammonium bromide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
T.S.	transition state
Vol	volume

CHAPTER 1
INTRODUCTION
AND
SYNTHESIS OF HYDROXYLAMINES

Background: Cascade reaction

1.1.1 Cascade reactions in total synthesis

Cascade reactions are popular in many total syntheses of natural product. They can provide rapid syntheses of complex molecules from simple precursors with great efficiency and elegance.¹

A cascade reaction involves a series of consecutive fast organic transformation, including C-C bonds forming reactions. As a result, it dramatically speeds up the overall synthesis, often with high atom economy and without the need of workup and isolation of intermediates. It usually proceeds *via* highly reactive intermediates as the driving force for the subsequent domino reactions.

Among its application in many total syntheses, cascade reaction have been efficiently demonstrated on alkaloids. For instance, Larry Overman has demonstrated the syntheses of alkaloids, with reactive imino species as intermediates. In the classic example shown in Scheme 1.1, he demonstrated an elegant domino reaction in following sequence: iminium formation, Cope rearrangement, followed by intramolecular Mannich reaction.²

Scheme 1.1 Larry Overman tandem reaction

- 1 For reviews and references of cascade reaction, see (a) Denmark, S. E.; Thorarensen, A., *Chem. Rev.* **1996**, *96*, 137. (b) Malacria, M., *Chem. Rev.* **1996**, *96*, 289. (c) Padwa, A.; Weingarten, M. D., *Chem. Rev.* **1996**, *96*, 223. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J., *Chem. Rev.* **1996**, *96*, 195. (e) Tietze, L. F., *Chem. Rev.* **1996**, *96*, 115. (f) Winkler, J. D., *Chem. Rev.* **1996**, *96*, 167. (g) Eilbracht, P.; Barfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A., *Chem. Rev.* **1999**, *99*, 3329. (h) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C., *Chem. Rev.* **2005**, *105*, 1001. (i) Tietze, L. F.; Kinzel, T.; Brazel, C. C., *Acc. Chem. Res.* **2009**, *42*, 367. (j) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.*, **2005**, 22.

In this alkaloid synthesis, the [3,3]-sigmatropic rearrangement proceeded under surprisingly mild reaction conditions. This is attributed to the formation of an iminium intermediate, since the charged nitrogen intermediate bears the beneficial effect of lowering the activation energy of the sigmatropic rearrangement.^{2,3}

1.1.2 Total synthesis of alkaloid via cascade reactions involving novel oxyiminium species.

Based on the prior experience with employing oxocarbenium [3,3]-sigmatropic rearrangement and intramolecular oxocarbenium Prins cyclization, we envisage that the oxyiminium intermediates may enable these reactions in a similar manner. The oxyiminium intermediates, instead of their iminium counterparts, were chosen as we expect they should provide different, if not improved, in scope and yield over the current iminium involving [3,3]-sigmatropic rearrangement and Prins cyclization. Furthermore, with the choice oxyiminium intermediate for the cascade reaction, we envisage that this cascade reaction may include 1,3-dipolar cycloaddition. (Scheme 1.2)

Scheme 1.2 Cascade reaction with oxyiminium intermediate

2 For examples of reaction involving charge species, see, Overman, L. E. *Acc. Chem. Res.* **1992**, 25, 352.

3 (a) Seebach, D.; Hidber, A. *Chimia* **1983**, 37, 449. (b) Giese, B. *Angew. Chem., Int. Ed.* **1977**, 16, 125.

1.2. Chemistry involved in the cascade reactions

1.2.1. Background: Our methodologies for the syntheses of homoallylic alcohols, substituted pyran and furan.

With the aim of pursuing greener and more efficient chemical transformations, our group has successfully developed methodologies for the synthesis of branched homoallylic amines,⁴ and both branched and linear homoallylic alcohols (Scheme 1.3).⁵

Scheme 1.3 Synthesis of homoallylic alcohols

Homoallylic alcohols are versatile intermediates.⁶ For instance, we have demonstrated that homoallylic alcohols are readily converted into various substituted furan and pyran, *via* Prins cyclization and intramolecular Ene reaction (Scheme 1.3).^{7,8}

4 (a) Loh, T. P.; Ho, D. S. C.; Xu, K. C.; Sim, K. Y. *Tetrahedron Lett.* **1997**, 38, 865. (b) Loh, T. P.; Lye, P. L.; Wang, R. B.; Sim, K. Y. *Tetrahedron Lett.* **2000**, 41, 7779. (c) Li, H.; Cheng, H. S.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, 48, 2209.

5 (a) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, 40, 2921. (b) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Tet. Lett.* **2001**, 42, 8705. (c) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc.* **2001**, 123, 2450-2451. (d) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, 42, 8701. (e) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *Org. Lett.* **2002**, 4, 2389. (f) Loh, T. P.; Lee, C. L. K.; Tan, K. T. *Org. Lett.* **2002**, 4, 2985. (g) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, 125, 2958. (f) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, 125, 4990. (g) Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, 125, 13042.

1.2.2. Oxyiminium as key intermediate for the cascade

Hence, we would like to explore the chemistry of hydroxyimino carbenium in the similar manner with the oxocarbenium chemistry. With the protonated nitron and acylated nitron identified as the key oxyiminium intermediates, these nitrones can be obtained by direct condensation of aldehyde, **1**, and hydroxylamine, **2** (Scheme 1. 3). While the synthesis of aldehydes is well established, the synthesis of homoallylic hydroxylamines, **2**, is relatively less explored.

Scheme 1.4 Formation of protonated and acylated nitrones.

1.3. Synthesis of branched homoallylic hydroxylamines --- The starting materials.

Reports on the synthesis of homoallylic hydroxylamines via allylation⁹ are limited, in contrast to the numerous reports on the syntheses of homoallylic amines.^{10,11} Hence, we developed the following methods for the synthesis of homoallylic hydroxylamines.

6 For reviews, see (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, 93, 2207. (b) Hall, D. G.; Kennedy, J. W. *J. Angew. Chem. Int. Ed.* **2003**, 42, 4732. (c) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, 47, 258.

7 (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, 7, 4491. (b) Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2006**, 47, 1641.

8 (a) Loh, T. P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett.* **2001**, 3, 2669.

9 (a) Ritson, D. J.; Cox, R. J.; Berge, J. *Org. Biomol. Chem.* **2004**, 2, 1921. (b) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1987**, 3, 215.

10 For reviews, see (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, 93, 2207. (b) Hall, D. G.; Kennedy, J. W. *J. Angew. Chem. Int. Ed.* **2003**, 42, 4732. (c) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, 47, 258.

1.3.1. Allylation of “acylated nitron” with allyltributylstannane

We envisage that homoallylic hydroxylamines can be obtained *via* an acyclic transition state (Scheme 1.5).

Scheme 1.5 Allylation of nitron *via* acyclic mechanism.

We anticipate that chirality can be induced into the homoallylic hydroxylamine if a chiral auxiliary, e.g. Mannose derivative¹², is employed (Scheme 1.6).

Scheme 1.6 Mannose derivative as chiral auxiliary.

The nitron with Mannose auxiliary can be obtained using known methods.¹²

11 (a) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis* Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, **1991**, 975. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (c) Merino, P.; Tejero, T.; Delso, J. I.; Mannucci, V. *Curr. Org. Synth.* **2005**, 2, 479.

12 Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J.D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, 59, 6103.

1.3.2 Results and discussion

The desired homoallylic hydroxylamine product, **2**, was obtained *via* two step reaction from a known nitron (Scheme 1.7).

Scheme 1.7 Mannose derivative as chiral auxiliary.

In the first step, the desired allylated product **4** was obtained smoothly when the AcBr was added dropwise into a solution of nitron (1 equiv) and crotyltributyltin (4 equiv, *E/Z* = 66:33) in DCM at -78°C .¹³ After workup and recrystallization or column chromatography, the major isomer was obtained cleanly as a single isomer. The absolute stereochemistry of this isomer **4** was confirmed by X-ray Crystallography (Scheme 1.8).

Scheme 1.8 X-ray structure of **4**.

¹³ The isomers of product **4** were obtained in the ratio of (1.7 : 10.2 : 7.6 : **80.5**) as determined by HPLC.

This allylated product **4** was then hydrolysed with LiOH, followed by the removal of the chiral auxiliary in a one-pot reaction, to afford desired product **2** in 71% yield over two steps.

1.3.3 Conclusion

In conclusion, the starting material, homoallylic hydroxylamine **2**, was successfully obtained *via* a presumably acyclic pathway. The scopes and limitations of this method are currently being explored by our group.

1.4 Conclusion

We plan to develop methodologies involving oxyiminium intermediates that allow rapid syntheses of alkaloid *via* cascade reactions, building upon our prior experience in the facile synthesis of pyran skeleton with oxocarbenium Prins cyclization and the synthesis of linear homoallylic alcohols in high optical purity with 2-oxocarbenium-[3,3]-sigmatropic rearrangement. Hence, a convenient synthesis of homoallylic hydroxylamines was developed, thus providing the essential starting materials for the desired nitrone which can be readily obtained *via* the condensation of the homoallylic hydroxylamine and an aldehyde.

CHAPTER 2

2-AZA-[3,3]-SIGMATROPIC REARRANGEMENT

CHAPTER 2 SYNTHESIS OF LINEAR HOMOALLYLIC HYDROXYLAMINES VIA [3,3]-SIGMATROPIC REARRANGEMENT

2.1 Introduction

Linear homoallylic alcohols/amines are versatile and useful building blocks for many natural product syntheses. Among the strategies, 2-oxocarbenium-[3,3]-sigmatropic rearrangement is arguably one of the most convenient and the most efficient methods for the synthesis of linear homoallylic alcohols with high optical purity.¹⁴

Herein, we extend this chemistry to the synthesis of linear homoallylic hydroxylamines.¹⁵

2.1.1 Background

Homoallylic amines are versatile synthons in synthetic chemistry since the allyl group can be readily converted into a wide variety of synthetically useful compounds.¹⁰ Among the many methods available, enantioselective allylation of imines is one of the most straight forward and efficient methods to obtain enantiomeric enriched homoallylic amines.^{10,11} However, enantioselective imine allylation has its drawbacks as the allylation of enolizable imines can be complicated with side reactions (Scheme 2.1).^{11b-c} Furthermore, the allylations were mostly γ -regioselective, affording branched homoallylic amines. As far as we know, there has been no report on the α -regioselective imine allylation with good enantioselectivity.

14 (a) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (b) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701. (c) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 4990. (d) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (e) Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J.; *J. Am. Chem. Soc.* **2000**, *122*, 1310. (f) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (g) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (h) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.

15 Cheng, H. S.; Seow, A. H.; Loh, T. P. *Org. Lett.* **2008**, *10*, 2805.

CHAPTER 2 SYNTHESIS OF LINEAR HOMOALLYLIC HYDROXYLAMINES VIA [3,3]-SIGMATROPIC REARRANGEMENT

Scheme 2.1 Challenges in imines allylation.

2.1.2 Our aim

Based on our recent work on 2-oxocarbenium-[3,3]-sigmatropic rearrangement in the synthesis of linear homoallylic alcohols (Scheme 2.2),¹⁴ we envisage that the 2-aza-[3,3]-sigmatropic rearrangement of the corresponding nitrones, easily obtained from hydroxylamines, will afford the synthetically versatile linear homoallylic hydroxylamines/nitrones.¹⁶

Scheme 2.2 2-oxocarbenium-[3,3]-sigmatropic rearrangement

Herein, we report a synthesis of linear homoallylic nitrones using the branched homoallylic nitron generated *in situ* from aldehyde and branched homoallylic hydroxylamines.

16 (a) Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, 72, 1518. For a review: (b) Przheval'skii, N. M.; Grandberg, I. I. *Usp. Khim.* **1987**, 56, 814. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, 25, 352. (d) Wuts, P. G. M.; Jung, Y. W. *J. Org. Chem.* **1988**, 53, 1957. (e) Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, 128, 11038.

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2.2 Results

2.2.1 Optimization of reaction condition

Initial studies were done by subjecting the readily available branched homoallylic hydroxylamine **II-2** with hydrocinnamaldehyde **II-1a** in the presence of Lewis acids or Brønsted acids under various reaction conditions. The results are summarized in Table 2.1.

Table 2.1 rearrangement of branched homoallylic nitrones generated in situ to form linear homoallylic nitrones.

Entry	II-2 /equiv (<i>Syn:Anti</i>)	Acid /0.2 equiv	Solvent	Time /h	Yield ^a /%
1	3.0 (50:50)	In(OTf) ₃ ^b	CH ₂ Cl ₂	4	70
2	3.0 (50:50)	CSA	CH ₂ Cl ₂	5	85
3^c	1.1 (50:50)	CSA	CH₂Cl₂	5	81
4	1.1 (50:50)	CSA	MeOH	72	5
5	1.1 (50:50)	CSA	THF	12	54
6 ^d	1.1 (100:0)	CSA	<i>i</i> PrOH	7	80
7 ^e	1.1 (0:100)	CSA	<i>i</i> PrOH	4	82
8 ^f	1.1 (50:50)	-	<i>i</i> PrOH	120	0

[a] Isolated yield. [b] 0.1 equiv of In(OTf)₃ was used. [c] ¹H NMR monitoring showed that the rate of reaction of the *anti* isomer is faster than that of the *syn* isomer. [d] *Syn* isomer of **II-2** was used. [e] *Anti* isomer of **II-2** was used. [f] No acid was added.

This reaction worked well in the presence of Lewis acids or Brønsted acid catalysts to afford the desired product in moderate to good yield (Table 2.1). The reaction was found to proceed smoothly under both protic and aprotic solvents (Table 2.1, entries 2-7). To our surprise, regardless of the stereo geometry of the starting material **II-2**, all the products were obtained exclusively as the *E*-isomers. This result is in contrast to the reaction involving the 2-oxocarbenium-[3,3]-sigmatropic rearrangement.¹⁴

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2.2.2 Scope and limitations

With these results in hand, we proceeded to investigate the asymmetric version of this new hydroxylaminoallylation reaction. A readily available optically pure starting material *syn-R-II-2*,¹³ was subjected to the optimized reaction conditions.

Table 2.2 asymmetric synthesis of nitrones.

$\text{R}-\text{CHO} + \text{Ph}-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}=\text{CH}_2 \xrightarrow[\text{rt}]{\text{cat CSA, } i\text{PrOH}}$
 $\text{R}-\text{CH}(\text{O}-\text{N}^+\text{Ph})-\text{CH}_2-\text{CH}=\text{CH}_2$

II-1 ***syn-R-II-2*** **II-3**

Entry	R-	Product	Time /h	Yield ^{a,b} /%	ee /%
1		II-3a	7	80	99
2		II-3b	24	95	98
3		II-3c	12 (Δ48) ^c	86	94
4	Ph-	II-3d	12 (Δ72) ^d	88	92
5		II-3e	12	72	97
6		II-3f	12	74	98
7		II-3g	36	70	97
8 ^e		II-3a^f (<i>S</i> -isomer)	4	82	99

[a] Isolated yield. [b] Absolute stereochemistry was confirmed by matching chiral HPLC data with known product. [c] Heated at 50 °C for 48 h after 12 h at rt [d] Heated at 50 °C for 72 h after 12 h at rt [e] *anti-R-II-2* was used in place of *syn-R-II-2*. [f] *S*-isomer was obtained.

In all cases, the desired linear homoallylic nitrones were obtained in good yields with excellent enantioselectivities. Even with enolizable aldehydes, the products were obtained in good yields with excellent enantioselectivities of up to 99% ee (Table 2.2, entries 1-2 and 5-7). The rate of the reaction was affected by the steric bulkiness of the aldehydes. While the reactions with primary and secondary aldehydes proceeded smoothly at room

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temperature, the reactions involving tertiary and aromatic aldehydes were very slow at room temperature and heating was necessary to drive the reactions to completion.

2.3 Discussion

2.3.1 Comparison with 2-oxocarbenium-[3,3]-sigmatropic rearrangement

Remarkably, the only product obtained, **II-3''**, possessed *E*-geometry, which stereochemically corresponded to the minor product, **II-3o''**, in the 2-oxocarbenium-[3,3]-sigmatropic rearrangement.¹⁴ The *Z*-product **II-3'** was not observed although it stereochemically corresponded to the major product in the 2-oxocarbenium-[3,3]-sigmatropic rearrangement (Scheme 2.3). The *E*-geometry of one of the products, **II-3d** was confirmed by X-ray crystallography. The absolute stereochemistry of this compound was determined by comparing HPLC retention times.¹⁷

Scheme 2.3 2-aza- and 2-oxocarbenium-[3,3]-sigmatropic rearrangements.¹⁴

Furthermore, when the [3,3]-sigmatropic rearrangement of optically active homoallylic nitron **N1** was studied, it was found that the enantiomeric excess of product **N2**

¹⁷ **3dx** was attained from **3d**. The HPLC retention time match well with the literature value. Aggarwal, V. K.; Guang, Y. F.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642. See Supporting Information for detail.

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dropped significantly (Scheme 2.4). This observation differed from a previous report on 2-aza-[3,3]-sigmatropic rearrangement,^{16e} where the enantiomeric excess was maintained.^{16d}

Scheme 2.4 2-aza-[3,3]sigmatropic rearrangement

2.3.2 Proposed mechanism

Hence, the following transition states were proposed to account for the outcome in the absolute stereochemistry and exclusive *E* selectivity (Scheme 2.5), based on the fact that oximes readily go through both the chair and boat conformers in their Zimmermann-Taxler transition states.¹⁸

Scheme 2.5. Proposed mechanism

While the [3,3]-sigmatropic rearrangement of nitronium *anti-II-4* clearly goes through the most stable chair transition state, the rearrangement of *syn-II-4* has to proceed *via* the

18 Hoffmann, R. W.; Endesfelder, A. Liebigs Ann. Chem. 1987, 215.

CHAPTER 2 SYNTHESIS OF LINEAR HOMOALLYLIC HYDROXYLAMINES VIA [3,3]-SIGMATROPIC REARRANGEMENT

boat transition state, thus avoiding the unfavorable 1,3-diaxial interaction, to afford the *E*-isomer. The stereochemistry of the methyl group is crucial in determining the conformer of the transition states and hence directed the stereochemical outcome of this [3,3]-sigmatropic rearrangement.

2.4 Homoallylic hydroxylamines as versatile synthons

We have also demonstrated the versatility of the homoallylic nitron **II-3a** (Scheme 2.6).

Scheme 2.6 Synthetic applications of nitron.

It can be readily converted into linear homoallylic amine **II-6**, which is widely used in organic synthesis.¹¹ More importantly, **II-3a** can be readily converted into homoallylic hydroxylamine **II-5**, a valuable synthon which can easily be transformed into a diverse array of nitrones for various 1,3 dipolar reactions.¹⁹

2.5 Conclusion

In conclusion, a direct access to linear homoallylic nitrones has been realized under very mild reaction conditions affording good yields and excellent enantioselectivities. Also, the homoallylic nitron was shown to be readily converted into both homoallylic amine and homoallylic hydroxylamine, which are useful and versatile synthons.

19 For examples on intramolecular 1,3-dipolar cycloaddition, see (a) Looper, R. E.; Williams, R. M. *Angew. Chem. Int. Ed.* 2004, 43, 2930. (b) Budzinska, A.; Wojciench, S. *Tetrahedron*, **2001**, 57, 2021. (c) Lumma, Jr., W. C. *J. Am. Chem. Soc.* **1969**, 91, 2920.

CHAPTER 3

PRINS CYCLIZATION

3.1. Introduction

3.1.1 Piperidines Synthesis and Aza-Prins Cyclization

Piperidines are common and important structural motifs of many natural products. Therefore, they continue to be important targets for asymmetric synthesis due to their significant biological properties and their often scarce availability from natural sources. Hence, many strategies are developed for the synthesis of piperidines, including reductive aminations, ring-closing metathesis, cycloaddition, and etc.²⁰ Compared to these strategies in efficiency, Prins cyclization offers an attractive and quick access to piperidines, since it convergently constructs the piperidines core, with the formation of a C–N bond and a C–C bond with the establishment of many stereogenic centers in a single step (Scheme 3.1).

Scheme 3.1 Prins Cyclization

3.1.2 Scopes and limitations of current Aza-Prins Cyclization

However, current aza-Prins cyclizations are less commonly employed in the construction of piperidines since most of them required activated alkene, e.g. α -silylated olefin and are typically conducted under harsh reaction conditions.²¹ Furthermore, it is only limited to the synthesis of monosubstituted^{21h} or disubstituted^{21a-g} piperidine.

20 (a) Buffat, M. G. P. *Tetrahedron* **2004**, 60, 1701. (b) Pearson, M. S. M.; Mathe-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159. (c) Baliah, V.; Jeyraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, 83, 379. (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, 13, 1781. (e) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, 58, 5957.

21 (a) Wuts, P. G. M.; Jung, Y. W. *J. Org. Chem.* **1988**, 53, 1957. (b) Ciblat, S.; Besse, P.; Canet, J. L.; Troin, Y.; Veschambre, H.; Gelas, J. *Tetrahedron-Asymmetry* **1999**, 10, 2225. (c) Wu, X. D.; Khim, S. K.; Zhang,

3.2. Results and Discussion

Based on our recent development of oxocarbenium Prins cyclization,²² we herein report a novel aza-Prins cyclization for the synthesis of piperidines and its application in the total synthesis of (–)-indolizidine 209B.

3.2.1 Optimization of reaction condition

In the attempt of developing an aza-Prins cyclization using simple olefin, screenings of various reaction conditions with different combination of substrates were carried out. Initial effort in using various allylic amine derivatives and aldehydes was not successful. Later, imines and their derivatives were used instead (Table 3.1). Although simple imine does not yield the desired cyclized product (Table 3.1, entry 1-2), nitron was found to be a good substrate for the Prins cyclization in the presence of either acetyl bromide (Table 3.1, entry 5-6) or acetic anhydride and magnesium bromide (Table 3.1, entry 3). It was also found that other *O*-protecting reagents like Ac₂O with DMAP or TMSBr did not favor the Prins Cyclization (Table 3.1, entries 7–8).

X. M.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (d) Khim, S. K.; Wu, X. D.; Mariano, P. S. *Tetrahedron Lett.* **1996**, *37*, 571. (e) Rutjes, F.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127. (f) Castro, P.; Overman, L. E.; Zhang, X. M.; Mariano, P. S. *Tetrahedron Lett.* **1993**, *34*, 5243. (g) Yang, T. K.; Teng, T. F.; Lin, J. H.; Lay, Y. Y. *Tetrahedron Lett.* **1994**, *35*, 3581. (h) Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 3837.

22 (a) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491. (b) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387. (c) Chan, K. P.; Ling, Y. H. Loh, T. P. *Chem. Comm.* **2007**, 939. (d) Zhang, W. C.; Viswanathan, G. S.; Li, C. J. *Chem. Comm.* **1999**, 291. (e) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627.

CHAPTER 3

AZA-PRINS CYCLIZATION

Table 3.1: Optimization of Reaction condition

Entry	X	Product N-R	Condition	T / °C	Yield ^a /%(III-3 _{eq} :III-3 _{ax})
1 ^b	N	—	A	r.t.	0
2 ^b	N	—	A	r.t.	0
3	N ⁺ —O [−]	N-OAc	A	r.t.	55 (74 : 26)
4 ^c	N ⁺ —O [−]	N-OBz	B	r.t.	45 (28 : 72) ^d
5	N ⁺ —O [−]	N-OAc	B	r.t.	82 (12 : 88)
6	N ⁺ —O [−]	N-OAc	B	0	57 (21 : 79)
7 ^e	N ⁺ —O [−]	N-OAc	B	r.t.	0
8 ^f	N ⁺ —O [−]	N-OH	B	r.t	5 (< 20 : 80)

^a isolated yield. ^b imine was used in place of nitrones ^c BzCl was used place of AcBr. ^d 4-Chloro substituted product was obtained. ^e Ac₂O, DMAP was used in place of AcBr. ^f TMSBr was used in place of AcBr. Condition A: Ac₂O (1.0 equiv) was added into a mixture of MgBr₂ (1.0 equiv), nitrone **III-2** (1.0 equiv) and CH₂Cl₂. Condition B: AcBr (1.5 equiv) was added into a solution of nitrone **III-2** in CH₂Cl₂.

The relative stereochemistry of the product was confirmed by NOESY correlation and X-ray crystallography.²³

Unexpectedly, it was found that selectivity of bromide was reversed from equatorial (III-3_{eq}) to axial (III-3_{ax}) position when the reaction conditions were changed.²⁴

²³ For X-ray structure, refer to supporting information.

²⁴ For similar observation in oxocarbenium Prins cyclization see, Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, 126,9904.

3.2.2 Scopes and limitations

The optimized condition (Table 3.1, entry 4) was applied to various substrates including aliphatic and aromatic nitrones (Table 3.2). In all cases, the desired product was obtained smoothly at room temperature within 1h, affording 4-axial bromide as major product.

Table 3.2: Prins Cyclization of various nitrones

Entry	R ₁	R ₂	R ₃	Product	Yield ^a /% (III-3 _{eq} :III-3 _{ax})
1		Ph-	H	III-3a	55 (9 : 91)
2		Ph-	H	III-3b	49 (10 : 90)
3		Ph-	H	III-3c	68 (3 : 97)
4	Ph-	Ph-	H	III-3d	82 (12 : 88)
5		Ph-	H	III-3e	65 (15 : 85)
6		Ph-	H	III-3f	68 (6 : 94)
7		Ph-	H	III-3g	65 (> 2 : 98)
8	Ph-		H	III-3a	65 (12 : 88)
9			H	III-3h	55 (64 : 36)
10			H	III-3i	60 (68 : 32)
11	Ph-	Ph-	Me	III-3j	86 (56 : 44)
12		Ph-	Me	III-3h	75 (26 : 74)

^a isolated yield. Reaction Condition: AcBr (1.5 equiv) was added into a solution of nitrone III-2 in CH₂Cl₂.

The reaction condition was general, affording desired Prins product in moderate to good yield.

In comparison, nitrones with aromatic R_1 (Table 3.2, entries 4-5, 8 and 11) generally afforded higher yield than those with aliphatic R_1 (Table 3.2, entries 1-3, 6-7, 9-10 and 12). However, those with aliphatic R_2 (Table 3.2, entries 8-10) afforded higher yield than those with aromatic R_2 (Table 3.2, entry 1-7).

3.3 Mechanistic Study

3.3.1 Origin of axial/equatorial selectivity

In order to gain more insight into the reaction, the reason for the unexpected shift in bromide's axial-equatorial selectivity (Table 3.1, entry 3 and 5) was studied carefully in the following experiments (Table 3.3).

Table 3.3: Study on the selectivity of bromide

Entry	Yield ^a /%	Selectivity III-3 _{eq} :III-3 _{ax}	Conditions addition, (rxn mixture)
1 ^b	82	12: 88	AcBr, (III-2)
2	70	68 :32	AcBr, (III-2, MgBr ₂)
3 ^c	55	74 :26	Ac ₂ O, (III-2, MgBr ₂)
4	79	11: 89	III-2, (MgBr ₂ , excess Ac ₂ O) ^d
5	30	77 :33	III-2, (excess MgBr ₂ , Ac ₂ O)

^a isolated yield. ^b Table 1, entry 5. ^c Table 1, entry 3. ^d MgBr₂ (2.0 equiv), Ac₂O (2.5 equiv) ^e MgBr₂ (10 equiv) Ac₂O (2.5 equiv)

Firstly, when a mixture of MgBr_2 and nitron was subjected to the addition of AcBr , the selectivity was abruptly reversed to favor equatorial **III-3_{eq}** instead of **III-3_{ax}** (Table 3.3, entry 1–2). On the other hand, similar abrupt change of selectivity was also observed for the reactions involving MgBr_2 and Ac_2O (Table 3.3, entry 3–5). Although adding Ac_2O into mixture of MgBr_2 and **III-2** favored **III-3_{eq}** (Table 3.3, entry 3), adding **III-2** into a mixture of MgBr_2 (2.0 equiv) and Ac_2O (2.5 equiv) favored axial **III-3_{ax}** (Table 3.3, entry 4). Furthermore, under the same condition with amount of MgBr_2 increased to 10 equivalent, the selectivity reversed, again, to favor equatorial **III-3_{eq}** (Table 3.3, entry 5).

3.3.2 Proposed Reaction Mechanism

Based on this information, the mechanism of this Prins cyclization is proposed as shown in Scheme 3.2. Firstly, the acylating agent, AcBr , formed by mixing MgBr_2 and Ac_2O , reacted with the nitron **III-2**, to provide the intimate ion pair.²⁵ Pro-axial addition of this bromide yielded the axial adduct **III-3_{ax}**. (Table 3, entry 1, 4) In the event of presence of excess MgBr_2 , bromide binds to MgBr_2 , forming less nucleophilic $(\text{MgBr}_2)_n \cdot \text{Br}^-$, which can favor the nucleophilic attack through the lower energy level equatorial pathway.²⁴

Scheme 3.2 Proposed mechanism for axial /equatorial selectivity

²⁵ Sreen, R. A. *Acc. Chem. Res.* **1973**, 6, 46.

3.4 Conclusion

In conclusion, we have developed a convergent and convenient aza-Prins cyclization for the synthesis of piperidines. A mechanism was also proposed to account for the axial/equatorial selectivity.

Its application in the total synthesis of (–)-indolizidine 209B is discussed in the next chapter.

CHAPTER 4

TOTAL SYNTHESIS OF

(–)-INDOLIZIDINES 209 B

4.1. Total Synthesis of (–)-Indolizidine 209B

4.1.1. Indolizidines in Natural Products

Indolizidines are bicyclo-[4.2.0] amines, having a tertiary amine located between the two fused rings. The carbon atoms on indolizidine are numbered according to the following sequence.

Indolizidine structures are commonly featured in many alkaloids. Many of these alkaloids contain alkyl sub-chains at 5- and/or 8- positions. Isolated from various sources including ants, frogs, fungi and plants, they usually exhibit phytotoxic, insecticidal, antibacterial and fungicidal bioactivities. Some examples of these alkaloids are shown below.

4.1.2. Isolation and Bioactivities of (–)-Indolizidine 209B

(–)-Indolizidine 209B is a member of the dendrobatid alkaloids isolated from the skin secretions of neotropical frogs.²⁶

²⁶ For isolation of (–)-indolizidine 209B see: Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon*, **1987**, 26, 1023.

indolizidine 209B

It possesses an interesting chemical structure containing two subchains, i.e. 5-pentyl and 8-methyl on its indolizidine core and three stereogenic centers.

It exhibits pharmacological and medicinal activity as a non-competitive blocker of nicotine receptor channels. (–)-Indolizidine 209B belongs to a series of 8-methyl-5-substituted indolizidines that inhibits the binding of a non-competitive blocking agent, (–)-perhydrohistrionicotoxin, to muscle-type nicotinic acetylcholine receptor channels, in membranes from Torpedo electroplax. These 5,8-disubstituted indolizidines appear to represent an atypical and potent class of non-competitive blockers for muscle-type and ganglionic nicotinic receptor channels.²⁷

4.2. Syntheses of (–)-Indolizidine 209B

Due to its appealing bioactivity and interesting structures, (–)-Indolizidine 209B has attracted the attention of many synthetic organic chemists over the past decades. The work done on its formal and total syntheses, is summarized below in chronological order.

4.2.1. Total synthesis by Marazano

In 1991, Marazano reported a total synthesis of (–)-indolizidine 209B.²⁸ The piperidine was derived from the reduction of pyridines, with the chirality controlled using a chiral auxiliary. However, the desired diastereoisomer is only the minor product. Hence, purification of the diastereomers is needed and the overall yield is significantly reduced.

²⁷ Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1213.

²⁸ Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc. Chem. Commun.* **1991**, *9*, 625.

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TOTAL SYNTHESIS OF (–)-INDOLIZIDINE 209B

4.2.2. Total synthesis by Andrew Holmes

In 1991, Holmes performed a total synthesis *via* an intramolecular 1,3-dipolar cycloaddition.²⁹

4.2.3. Total synthesis by Chihiro Kibayashi

Kobayashi's total synthesis was reported in 1992.³⁰ Starting from known starting materials,³¹ the piperidine core was constructed with a nitroso Diels Alder reaction in the key step.

29 Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. J. *Org. Chem.* **1991**, 56, 1393.

30 Shishido, Y.; Kibayashi, C. J. *Org. Chem.* **1992**, 57, 2876.

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TOTAL SYNTHESIS OF (–)-INDOLIZIDINE 209B

4.2.4. Total synthesis by Jeffrey Aubé

In 1993, Aubé's group reported a total synthesis of (–)-indolizidine 209B where the piperidine core was obtained *via* Schmidt rearrangement.³²

31 (a) Cernigliaro, G. J.; Kocienski, P. J. *J. Org. Chem.* **1977**, 42, 3622. (b) Wihama, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. P. *J. Am. Chem. Soc.* **1982**, 104, 4708.

32 Aube, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, 35, 1141.

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4.2.5. Total synthesis by Isao Shimizu

In 1993, Shimizu *et al.* reported a total synthesis of (–)-indolizidine.³³ The chirality was established *via* Sharpless epoxidation while the piperidine core was obtained *via* reductive amide formation.

4.2.6. Formal synthesis by Takefumi Momose

In 1994, Momose *et al.* reported a formal synthesis of (–)-indolizidine 209B^{34a} which utilized either lipase-catalysed hydrolysis or trans-esterification of a meso bicyclo-amine developed by his lab.^{34b}

33 Satake, A.; Shimizu, I. *Tetrahedron Asymmetry* **1993**, 2, 1405.

34 (a) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, 59, 943. (b) Momose, T.; Toyooka, N.; Jin, M. *Tetrahedron Lett.* **1992**, 33, 5389.

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4.2.7. Formal synthesis by Charles Jefford

In 1995, Jefford *et al.* reported a formal synthesis, ending at Holmes' alcohol.³⁵ The indolizidine core was attained *via* an intramolecular Friedel-Craft reaction on a pyrrole.

35 Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511.

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4.2.8. Total synthesis by Peter Somfai

In 1995, Somfai *et al.* reported another total synthesis of (–)-indolizidine 209B.³⁶ The piperidine core was obtained after an intramolecular S_N2' addition of an enolate to the allylic aziridine.

4.2.9. Total synthesis by Gérard Lhommet

In 1998, Lhommet's group reported a total synthesis of (–)-indolizidine 209B.³⁷ A chiral auxiliary provided the basis of this asymmetric synthesis, with the piperidine skeleton obtained *via* a reductive amine formation.

36 Aehman, J.; Somfai, P. *Tetrahedron* **1995**, 51, 9747.

37 Bardou, A.; Celerier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1998**, 39, 5189.

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4.2.10. Total synthesis by Thomas Back

In 2000, Back *et al.* reported a total synthesis of (–)-indolizidine 209B³⁸ via a stepwise 4 + 2 piperidine core formation, using a starting material containing two chiral centres.

4.2.11. Formal synthesis by Joseph Michael

In 2000, Micheal *et al.* reported a formal synthesis of (–)-indolizidine 209B.³⁹ Starting from a chiral amine, this synthesis ended at the Holmes' indolizidines²⁹ in more than ten steps.

38 Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543.

39 Michael, J. P.; Gravestock, D. J. *Chem. Soc. Perkin Trans.1* **2000**, *12*, 1919.

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4.2.12. Total synthesis by Lanny Liebeskind

In 2001, Liebeskind *et al.* reported a total synthesis based on a methodology developed by his group.⁴⁰ Starting from chiral piperidines obtained via lipase-catalysed kinetic resolution, the diastereoselective methodology established the desired chirality of the three substituents on the piperidine core.

40 Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477.

4.3. Our synthetic strategy

Despite the many reported total and formal syntheses of (–)-indolizidine 209B, they generally suffered from long synthetic pathway. We would like to improve the convergence the current total synthesis of (–)-indolizidine 209B, by using our methodologies described in previous chapters.

We plan to construct all the three chiral centres in (–)-indolizidine 209B using our methodology developed in Chapter 3 (Scheme 4.1).

Scheme 4.1 Synthetic strategy

It was envisaged that the relative stereochemistry can be established *via* Prins cyclization while the absolute stereochemistry can be established by our allyl-transfer methodology (from Chapter 1 and 2) (Scheme 4.1).

4.4. Retrosynthetic Analysis

With this plan in mind, the (–)-indolizidine 209B is as shown in Scheme 4.2. First it can be attained from alcohol *via* known procedures.⁴⁰ The alcohol in turn can be obtained *via* the reduction of ester **IV-5i**, and the ester can be readily obtained while the bromide **IV-4i** was subjected to hydrogenation.

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Scheme 4.2 Retrosynthetic Analysis

Bromide **IV-4i** can be formed from the Prins product **IV-3i**. The Prins product can be attained from nitron using our methodology. This nitron can be readily obtained by a simple condensation of an aldehyde and a hydroxylamine. The hydroxylamine can be obtained from an aldehyde, again, using our methodology.

4.5. Total Synthesis of (–)-indolizidines 209B

The total synthesis (–)-indolizidine 209B was shown in the following (Scheme 4.3).

Scheme 4.3 Total synthesis of (–)-indolizidine 209B

Our total synthesis started with an aza-Prins cyclization of nitron **IV-2i**,⁴¹ providing the piperidine-core **IV-3i** in 55% yield with more than 98% enantiomeric excess.

41 Readily obtained *via* our methodology. Cheng, H. S.; Seow, A. H.; Loh, T. P. *Org. Lett.* **2008**, *10*, 2805.

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The absolute stereochemistry was preserved.⁴² In one single step, all relative stereochemistries of (–)-indolizidine 209B were established.

Piperidine **IV-3i** was then converted to **IV-4i**, *via* oxonolysis followed by *in situ* Wittig reaction. **IV-4i** was then converted to ester **IV-5i** *via* reduction with formate in the presence of Palladium catalyst. Further reduction of ester **IV-5i** to alcohol with LiAlH₄, followed by bromination and *in situ* ring cyclization, finally provided (–)-indolizidine 209B in 55% yield.

4.6 Conclusion

Using aza-Prins cyclization developed in our group as key reaction, the total synthesis of (–)-indolizidine 209B was accomplished in seven steps with an overall yield of 8.5%.

42 For leakage in Prins cyclization of pyran, see (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2001**, *4*, 3407-3410. (b) (c) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919-3922. (c) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9936-9945.

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(–)-PERHYROHISTRIONICOTOXIN

5.1. Isolation and bioactivity of histrionicotoxins

In 1971, Witkop *et al.* isolated histrionicotoxins from the skin extracts of Colombian poison arrow frogs *Dendrobates Histrionicus*.⁴³ From the 200 mg mixture of six alkaloids isolated from the skin extracts of 1110 frogs, two major fractions were identified as histrionicotoxin (HTX-283A) and isodihydrohistrionicotoxin (HTX-285A). Since then, other members of this alkaloid family have also been identified.⁴⁴ This family of compounds has been found to exhibit remarkable biological activities with unusual effects as selective non-competitive inhibitors of the neuromuscular, ganglionic and central neuronal nicotinic acetylcholine receptors.⁴⁵

However, histrionicotoxins have a very low natural abundance, with less than 180µg of histrionicotoxins in a frog. Frogs bred in captivity also do not secrete these toxins, which suggest that these toxins are accumulated via dietary sources from nature.⁴⁶ Moreover, the frogs are currently protected under the Convention on International Trade in Endangered Species (CITES).⁴⁷

43 (a) Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1870.(b) Karle, I. L. *J. Am. Chem. Soc.* **1973**, *95*, 4036.

44 (a) Tokuyama, T.; Uenoyama, K.; Brown, G.; Daly, J. W.; Witkop, B. *Helv. Chim. Acta.* **1974**, *57*, 2597; (b) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta.* **1977**, *60*, 1128.(c) Tokuyama, T.; Yamamoto, J.; Daly, J. W.; Highet, R. J. *Tetrahedron*, **1983**, *39*, 49.(d) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron*, **1986**, *42*, 3453.(e) Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Takuyama, T.; Shimada, A. *Tetrahedron*, **1992**, *48*, 1823.

45 (a) Lapa, A. J.; Albuquerque, J.; Sarvey, J.; Daly, J. W.; Witkop, B. *Exp. Neurol.* **1975**, *47*, 558.(b) Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta.* **1982**, *65*, 252.(c) Spivak, C. E.; Maleque, M. A.; Oliveria, A. C.; Maasukawa, M.; Tokuyama, J.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *21*, 351.(d) Takahashi, K.; Jacobson, A. E.; Mak, C. P.; Witkop, B.; Brossi, A.; Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Bavoso, A.; Silverton, J. V. *J. Med. Chem.* **1982**, *25*, 919.(e) Gessner, W.; Takahashi, K.; Witkop, B.; Brossi, A.; Albuquerque, E. X.; *Hel. Chim. Acta.* **1985**, *69*, 49.(f) Daly, J. W.; Nishizawa, Y.; Edwards, J. A.; Waters, J. A.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 489.

46 (a) Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 9.(b) Daly, J. W.; Garaffo, H. M.; Myers C. W. *Pharm. News.* **1997**, *4*, 9.(c) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.(d) Daly, J. W.; Garraffo, H. M.; Jain, P.; Spande, T. F.; Snelling, R. R.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **2000**, *26*, 73.

47 <http://www.cites.org/>

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Due to the extreme scarcity in nature, interesting and potent bioactivity as well as unique spirocyclic structures of histrionicotoxins, there have been many reports on their partial, formal, and total syntheses since they were isolated in 1971. These syntheses are targeted predominantly at histrionicotoxin (HTX-283A) --- the fully unsaturated parent alkaloid and perhydrohistrionicotoxin (pHTX) --- the fully hydrogenated synthetic derivative of histrionicotoxin.⁴⁸

5.2. Syntheses of Perhydrohistrionicotoxin (pHTX)

Among the many attempts to synthesize pHTX,⁴⁸ there are three reports on the total synthesis of (–)-pHTX and four reports on that of (±)-pHTX. In comparison, there are

⁴⁸ For review on synthesis of histrionicotoxins, see: Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298.

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five reports on the formal synthesis of (–)-pHTX and thirteen reports on that of (±)-pHTX. Given the small molecular weight of (–)-pHTX, the high proportion of formal syntheses and other less successful attempts only serve to highlight the challenge of constructing the seemingly simple spirocyclic core.

All reports on the total syntheses and formal syntheses of pHTX are summarised below.

5.2.1. Asymmetric total synthesis of (–)-pHTX

All the three total synthesis of (–)-pHTX reported are summarized below.

5.2.1.1. By Winkler

In 1989, Winkler's group completed the first total synthesis of (–)-pHTX,^{49a} using the [2 + 2] cycloaddition strategy established in their previous study^{49b}. The asymmetric synthesis employed a chiral starting material whose chiral center controlled the stereochemistry in the key step, a diastereoselective intramolecular [2 + 2] cycloaddition, which constructed the spirocyclic core.

49 (a) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.(b) Winkler, J. D.; Hershberger; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177.

In 1998, Comin *et al.* achieved the total synthesis of (-)-pHTX.⁵⁰ A chiral auxiliary provided the chirality in this asymmetric synthesis. The spirocyclic core was also established *via* an intramolecular [2 + 2] cycloaddition. The facial selectivity of this reaction was controlled with another chiral auxiliary.

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5.2.2. Total synthesis of (±)-pHTX

Four years after the isolation of histrionicotoxins, Corey *et al.* and Kishi *et al.* reported the total synthesis of pHTX.

5.2.2.1. By Corey

In 1975, Corey *et al.* achieved the total synthesis of (±)-pHTX by using the Beckmann rearrangement in the key step.^{52a}

52 (a) Corey, E. J.; Arnett, J. F.; Widiger, G. N. *J. Am. Chem. Soc.* **1975**, 97, 430. (b) Corey, E. J.; Balanson, R. D. *Heterocycles*, **1976**, 5, 445

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In 1976, the same group reported another total synthesis of (±)-pHTX via the Michael addition reaction strategy.^{52b}

5.2.2.2. By Kishi

In 1975, there was another report of a total synthesis of (±)-pHTX from the Harvard campus, by Kishi's group.⁵³ The spirocyclic core was obtained *via* an intramolecular reductive amide formation.

5.2.2.3. By Duhamel

In 1989, Duhamel *et al.* reported a total synthesis of (±)-pHTX,^{65b} using the strategy developed earlier in their formal synthesis of (±)-pHTX.^{65a}

53 Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009.

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5.2.2.4. By Stockman

In 2004, Stockman provided a total synthesis of (±)-pHTX *via* symmetrical starting materials.⁵⁴

5.2.3. Formal asymmetric synthesis of (–)-pHTX

There are five formal asymmetric syntheses of (–)-pHTX, all of which are summarized in chronological order as follows.

⁵⁴ Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1598.

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5.2.3.1. By Duhamel

In 1991, Duhamel *et al.* provided the formal synthesis of (–)-pHTX,^{65c} based on the same synthetic route used in their previous formal synthesis of (±)-pHTX^{65a}.

5.2.3.2. By Luzzio

In 1999, Luzzio *et al.* provided the formal synthesis of both (–)-pHX and unnatural (+)-pHTX.⁵⁵ The symmetrical spirocyclic structure was constructed *via* an intramolecular amide formation, after which a kinetic resolution catalyzed by pig liver esterase provided the required stereochemistry.

55 (a) Fitch, R. W.; Luzzio, F. A. *Ultrason. Sonochem.* **1997**, *4*, 99. (b) Luzzio, F. A.; Fitch, R. W. *J. Org. Chem.* **1999**, *64*, 5485.

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5.2.3.3. By Westermann

In 2002, Westermann *et al.* provided a formal synthesis.⁵⁶ The skeleton of pHTX was constructed via a Beckmann rearrangement to form the piperidine core, followed by a Dieckmann condensation.

5.2.3.4. By Wardrop

In 2004, the following formal synthesis was reported by Wardrop.⁵⁷ The spirocyclic core was obtained *via* an intramolecular cyclization under oxidative condition.

5.2.3.5. By Kim

In 2005, Kim *et al.* synthesized the tertiary amine *via* a Claisen rearrangement and obtained the spirocyclic core employing Grubbs' ring-closing metathesis, in their formal synthesis of (–)-pHTX.⁵⁸

56 Diedrichs, N.; Krelaus, R.; Gedrath, I.; Westermann, B. *Can. J. Chem.* **2002**, *80*, 686.

57 Wardrop, D. J.; Zhang, W.; Landrie, C. L. *Tetrahedron Lett.* **2004**, *45*, 4229.

58 Kim, S.; Ko, H.; Lee, T.; Kim, D. J. *Org. Chem.* **2005**, *70*, 5756.

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5.2.4. Formal synthesis of (±)-pHTX

The thirteen formal syntheses of (±)-pHTX since 1979 are chronologically summarized as follows.

5.2.4.1. By Evans and Speckamp

In 1979, the groups of Evans and Speckamp independently reported the formal synthesis of (±)-pHTX.⁵⁹ Coincidentally, both groups employed the Mannich reaction, in the key step, to construct the spirocyclic core, using the same starting material.

59 (a) Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 4841. (b) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.* **1979**, 411. (c) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, 104, 3695.

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5.2.4.2. By Ibuka

In 1982, Ibuka *et al.* provided a formal synthesis of Corey's⁵² lactam.^{60b} The spirocyclic core was attained *via* a Bechmann rearrangement, which was also the strategy used in Corey's original synthesis.⁵²

5.2.4.3. By Keck

In 1982, Keck *et al.* reported a formal synthesis of (±)-pHTX *via* an intramolecular ene reaction.⁶¹ This formal synthesis was concluded with Corey's lactam.⁵²

60 (a) Ibuka, T.; Minakata, H.; Mitsui, Y.; Tabushi, E.; Taga, T.; Inubushi, Y. *Chem. Lett.* **1981**, 1409. (b) Ibuka, T.; Minakata, H.; Mitsui, Y.; Hayashi, K.; Taga, T. Inubushi, Y. *Chem. Pharm. Bull.* **1982**, 30, 2840.

61 Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, 47, 3591.

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5.2.4.4. By Winterfeldt

In 1982, a symmetrical starting material was used in Winterfeldt's formal synthesis of pHTX.⁶² A Michael addition provided the spirocyclic amine, which was later converted to Kishi's⁵³ imine.

5.2.4.5. By Smith

In 1984, Smith *et al.* provided a formal synthesis of pHTX *via* an intramolecular [2 + 2] cycloaddition.⁶³

5.2.4.6. By Holme

In 1984, Holmes *et al.* reported a formal synthesis of pHTX *via* intramolecular condensations.⁶⁴

62 Glanzmann, M.; Karalai, C.; Ostersehl, B.; Schon, U.; Frese, C.; Winterfeldt, E. *Tetrahedron*, **1982**, 38, 2805.

63 Koft, E. R.; Smith, A. B.; *J. Org. Chem.* **1984**, 49, 832.

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5.2.4.7. By Duhamel

In 1986, a formal synthesis of (±)-pHTX was reported by Duhamel's group.^{65a} The piperidine ring was attained *via* ring contraction of the enamino aldehyde. The group subsequently completed the formal synthesis of (–)-pHTX and total synthesis of (±)-pHTX using this strategy.^{65b, 65c}

5.2.4.8. By Tanis

In 1987, Tanis's group achieved the formal synthesis of (±)-pHTX.⁶⁶ The spirocyclic skeleton was constructed using an intramolecular Mannich reaction.

64 Holmes, A. B.; Russell, K.; Stern, E. S.; Stubbs M. E.; Wellard, N. K. *Tetrahedron Lett.* **1984**, 25, 4163.

65 (a) Duhamel, P.; Kotera, M.; Monteil, T. *Bull. Chem. Soc. Jpn.* **1986**, 59, 2353.(b) Duhamel, P.; Kotera, M.; Monteil, T.; Marabout, B. *J. Org. Chem.* **1989**, 54, 4419.(c) Duhamel, P.; Kotera, M.; Marabout, B. *Tetrahedron: Asymmetry*, **1991**, 2, 203.

66 Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, 28, 2495.

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5.2.4.9. By Tanner

In 1999, Tanner's group employed Grubbs' ring-closing metathesis in the formation of the piperidine ring and provided the formal synthesis of (±)-pHTX.⁶⁷

2.1.10. By Vatele

In 1996, intramolecular aza-Prins cyclization was used to construct the piperidine ring in Vatele's formal synthesis of (±)-pHTX.⁶⁸

67 Tanner, D.; Hagburg, L.; Poulsen, A. *Tetrahedron*, **1999**, 55, 1427.

68 (a) Compain, P.; Gore, J.; Vatele, J. M. *Tetrahedron*, **1996**, 52, 6647. (b) Compain, P. *Actual. Chim.* **2000**, 62.

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5.2.4.11. By Kim

In 1997, Kim *et al.* used a series of tandem pinacol rearrangement to provide the ring skeleton, which was later converted to Corey's lactam⁵² in the formal synthesis of (±)-pHTX.⁶⁹

5.2.4.12. By Harrity

In 2006, Harrity's group attained Tanner's spirocycle in the formal synthesis of (±)-pHTX.⁷⁰ The spirocycle skeleton was constructed *via* a stepwise [3 + 3] annelation strategy.

69 (a) Kim, D.; Hong S. W.; Park, C. W. *Chem. Commun.* **1997**, 2263. (b) Kim, D.; Shim, P. J.; Lee, J.; Park, C. W.; Hong, S. W.; Kim, S. J. *Org. Chem.* **2000**, 65, 4864.

70 Provoost, O. Y.; Hedley, S. J.; Hazelwood, A. J.; Harrity, J. P. *Tetrahedron Lett.* **2006**, 47, 331.

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5.3. Our strategy

Despite the many reported syntheses of pHTX, an effective and practical synthesis remains to be developed. Therefore, one of the strategies is to develop cascade reactions which allow fast and effective construction of the molecules.

In this chapter, we focus on the cascade reaction involving 1,3-dipolar cycloaddition to construct the spirocyclic core in histrionicotoxins. The 1,3-dipolar cycloaddition is particularly attractive as compared to other methods, as it establishes not only the spirocyclic core, but also the three chiral centers in the desired diastereoselectivity.

Hence, this strategy has been attempted towards the total synthesis of histrionicotoxins in as early as 1974. Tufariello *et al.* reported an unsuccessful attempt at using intramolecular 1,3-dipolar cycloaddition in the construction of the spirocyclic core, which resulted in the undesired regioselectivity being obtained as the sole product.⁷¹ This was ascribed to the steric interactions between the methyl ester with the methylene groups in the transition state.

⁷¹ Tufariello, J. J.; Trybulski, E. J. *J. Org. Chem.* **1974**, *39*, 3378.

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In 1975, another attempt was reported by Gossinger *et al.*⁷² The model of undesired intramolecular 1,3-dipolar cycloaddition was successful, where product (kinetic product) was converted to desired product (thermodynamic product). However, this 1,3-dipolar cycloaddition failed again to provide the desired spirocyclic core in another model.

In 1999, Holmes' group reported a total synthesis of (–)-Histrionicotoxin ((–)-HTX 283A).^{73a} In their report, they demonstrated the first successful usage of intramolecular 1,3-dipolar cycloaddition to obtain the spirocyclic core and a sterically-strained tertiary amine, as well as to establish three new chiral centres with the desired stereochemistry in one single step.

72 Gossinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta.* **1975**, *58*, 96.

73 (a) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900. (b) Stockman, A. B. *Tetrahedron Lett.* **2000**, *41*, 9163. (c) Smith, C. J.; Holmes, A. B.; Press, N. *J. Chem. Commun.* **2002**, 1214. (d) Stockman, R. A.; Sinclair, A.; Arini, L. G.; Szeto, P.; Hughes, D. L.; *J. Org. Chem.* **2004**, *69*, 1598. (e) Karatholuvhu, M. S.; Sinclair, A.; Newton, A.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656.

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Since then, this strategy was used in some of the total syntheses of histrionicotoxins.^{73b-e}

5.4. Retrosynthetic analysis

With the establishment of a rapid access to the total synthesis of histrinicotoxins using intramolecular 1,3-dipolar cycloaddition, a quick access to its nitrone starting material with high optical purity is important (Scheme 5.1). Unfortunately, there is so far no efficient and convenient method of obtaining the nitrone in high optical purity.

Scheme 5.1 Quick access to hydroxylamine with high enantioselectivity

Therefore, we would like to apply our newly established method, which affords a convenient access to hydroxyamine in good yield and high enantioselectivity, to the total synthesis of (–)-pHTX.

The Product **V-1** could readily be obtained from nitrone **V-3** *via* 1,3 dipolar cycloaddition and FGIs (Scheme 5.2).⁷³

5.5. Total Synthesis of (–)-pHTX

5.5.1. Synthesis of Nitrile **V-4**

Scheme 5.3 Preparation of nitrile **V-4**

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When the freshly prepared Grignard reagent was added into a THF solution of aldehyde **V-7** at 0 °C, alcohol **V-6** was obtained. The crude alcohol **V-6** was then oxidized with IBX in DMSO solution,⁷⁴ affording ketone **V-5** in 76% overall yield over 2 steps. The ketone **V-5** was treated with acrylonitrile using Hoveyda Grubbs 2nd generation catalyst in refluxing THF,^{73e} to afford nitrile **V-4** in 81% convergent yield (40% isolated yield) as a mixture of *E/Z* isomer (23:77).

5.5.2 Synthesis of nitrile **V-2**

With the acetal **V-4** obtained, we proceeded with the one-pot synthesis of nitron **V-3** (Scheme 5.4).

Scheme 5.4 Synthesis of spirocyclic nitrile **V-2**

Initial attempt of subjecting acetal **V-4** directly to our original reaction conditions¹⁵ did not afford any desired product. Only starting material (acetal **V-4**) was recovered. This is probably due to the neutral reaction conditions.⁷⁵ Subsequently, we found that the acetic

74 Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, 35, 8019.

75 Catalytic acidic CSA was quenched by excess hydroxylamine.

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acid/water mixture is an ideal condition for these series of reactions. It is important to note that acetic acid catalyzed the hydrolysis of acetal **V-4** as well as the [3,3]-sigmatropic rearrangement. The resulting nitron **V-3** was found to slowly convert nitrile **V-2'**, the kinetic product of intramolecular 1,3-dipolar cycloaddition. Hence, the mixture of **V-2'** and **V-3** was refluxed to 180 °C in sealed tube for 2.5 h using Holmes' condition, resulted to the formation of the desired thermodynamic product.^{73a-c} The spirocyclic nitrile, **V-2**, was obtained in 53% yield as a single isomer after purification. The product was found to be optically pure, as confirmed by condensation of the aldehyde **V-8** (Scheme 5.5) with an optically pure hydroxylamine.⁷⁶

5.5.3 Synthesis of perhydrohistrionicotoxin **V-1**

With the spirocyclic structure established, nitrile **V-2** was then converted to dialdehyde **V-9** in 80% yield, *via* DIBALH reduction of nitrile followed by ozonolysis of olefin.

Scheme 5.5 Synthesis of perhydrohistrionicotoxin **V-1**

Wittig reaction of dialdehyde **V-9** followed by hydrogenation afforded the product **V-1** in 54% yield over two steps.

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5.5 Conclusion

In conclusion, an quick access to the spirocyclic core of histrionicotoxin was established based 2-aza-[3,3]-sigmatropic rearrangement and dipolar cycloaddition. The total synthesis of (–)-perhydrohistrionicotoxin was established in 14% overall yield.

CHAPTER 6

EXPERIMENTAL SECTION

6.1 General Information

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in flame-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhyd THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 °C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under "Chromatography"). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 °C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 °C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego⁷⁷. Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhyd tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen. Acrolein and crotonaldehyde were freshly distilled prior to usage.

⁷⁷ Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

Triethylamine, toluene and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. DMF was distilled over Linde type 4A molecular sieve prior to usage. 1*N* and 4*N* hydrochloric acid was diluted from concentrated 37% solution using deionised water. 3*M* sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F₂₅₄ pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, potassium permanganate solution or ceric molybdate solution followed by heating on a hot plate.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 nm) and freshly distilled solvents. Columns were packed as slurry of silica gel in hexane/CH₂Cl₂ and equilibrated with the appropriate solvent/solvent mixture prior to use. The solute was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between NaCl salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm. Concentration is denoted as c and was calculated as grams per milliliters (g / 100 mL) whereas the solvent was indicated in parentheses (c , solvent).

Mass Spectroscopy

Mass spectrometry was performed by the staffs in the Division of Chemistry and Biological Chemistry of the Nanyang Technological University. MS (EI) spectra were recorded on a Thermo Finnigan Polaris Q GCMS. MS (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. HRMS (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and HRMS were reported in units of mass of charge ratio (m/z).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and 500 NMR spectrometers. Boron (^{11}B) nuclear magnetic resonance and fluorine (^{19}F) nuclear magnetic resonance were performed on a Bruker Avance 300 NMR spectrometer.

Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.00), using the residual solvent signal as an internal standard: deuteriochloroform- d , CDCl_3 (^1H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet).

Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplets), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and ddt (doublet of doublet of triplets). Coupling constants (J) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by $n\text{H}$.

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 11 software.

6.2 Branch homoallylic Hydroxylamines

Standard reaction condition (for racemic via Barbier allylation):

A solution of DCC (1.0 mmol, 1.0 equiv) in 2 mL CH_2Cl_2 was added dropwise into a stirring solution of benzaldehyde oxime (1.0 mmol, 1.0 equiv) and AcOH (1.05 mmol, 1.05 equiv) in CH_2Cl_2 at 0°C , the solution was allowed to warm up to room temperature. After 1 h. the Urea precipitate was removed by filtration over celite, and the filtrate was concentrated *in vacuo*. The crude product was used directly in Zinc allylation in the following step.

The crude product was mixed with THF (1 mL) and Zinc power (1.5 mmol, 1.5 equiv) with vigorous stirring at 0°C , the saturated NH_4Cl (1 mL) was then added, followed by crotyl bromide (1.2 mmol, 1.2 equiv). The reaction was monitored with TLC. After 20 min, the reaction mixture was extracted with Et_2O (20 mL), sat aq NH_4Cl (15 mL) solution and H_2O (5 mL). (*Note: prolong reaction time will result in lower yield*) The aqueous layer was separated and extracted with Et_2O (20 mL) twice. The combined organic layer was washed with sat aq NaCl (15 mL) and dried over anhyd MgSO_4 . The product was purified with silica gel chromatography.

The purified product was then dissolved in 3 mL MeOH, CSA (1.2 mmol, 1.2 equiv) was then added. The solution was stirred for 12 h (monitored by TLC). The solution was then concentrated *in vacuo*, and dissolved in 30 mL Et_2O , and extracted with sat aq NaHCO_3 (20 mL, to removed CSA). The aqueous layer was further extracted with Et_2O twice (20 mL x2). The combined organic layer was washed with sat aq NaCl and dried over anhyd MgSO_4 . Product is purified with silica gel column chromatography.

***N*-(2-methyl-1-phenylbut-3-enyl)hydroxylamine**

R_f = (*anti* isomer) 0.60, (*syn* isomer) 0.54 (1:1 hexane/diethyl ether)

^1H NMR (300 MHz, CDCl_3): δ (*anti* isomer) 7.38-7.28 (m, 5H, ArH), 5.69 (dt, J = 17.0, 9.0 Hz, 1H, $-\text{CH}=\text{CH}_2$), 5.12 (d, J = 17.0 Hz, 1H, $-\text{CH}=\text{CH}'\text{H}''$), 5.09 (dd, J = 10.3, 1.5 Hz, 1H, $-\text{CH}=\text{CH}'\text{H}''$), 3.63 (d, J = 9.3 Hz, 1H, NHCH), 2.39 (sextet, J = 8.8, 2 Hz, 1H, $-\text{CH}(\text{CH}_3)=\text{CH}_2$), 0.76 (d, J = 7.0 Hz, 3H, $-\text{CH}(\text{CH}_3)=\text{CH}_2$) ppm (*syn* isomer) 7.37-7.25 (m, 5H, ArH), 5.65 (ddd, J = 16.8, 10.6, 7.5 Hz, 1H, $-\text{CH}=\text{CH}_2$), 5.01 (br d, J = 8.8 Hz, 1H, $-\text{CH}=\text{CH}'\text{H}''$), 5.00 (br d, J = 18.6 Hz, 1H, $-\text{CH}=\text{CH}'\text{H}''$), 3.90 (d, J = 5.8 Hz, 1H, NHCH), 2.79 (sextet, J = 6.8 Hz, 1H, $-\text{CH}(\text{CH}_3)=\text{CH}_2$), 1.00 (d, J = 6.8 Hz, 3H, $-\text{CH}(\text{CH}_3)=\text{CH}_2$) ppm.

^{13}C NMR (75 MHz, CDCl_3) δ . (*anti* isomer) 141.3, 140.4, 128.3, 128.2, 127.4, 116.2, 70.9, 41.6, 17.7 ppm (*syn* isomer) 139.8, 139.2, 128.2, 128.0, 127.4, 115.4, 70.6, 40.1, 16.3 ppm.

FTIR (film) (*anti* isomer) 3265, 3078, 3030, 2960, 2928, 2870, 1637, 1497, 1454, 1415, 1069 cm^{-1} (*syn* isomer) 3265, 3109, 3064, 2960, 2910, 1638, 1454, 1373, 1352, 1022, 921 cm^{-1} .

HRMS Calcd for $[\text{M} - \text{H}]^+$: 176.1070. Found: 176.1067.

Standard reaction condition (asymmetric, *via* stannane allylation)

AcBr (24mmol, 1.2 equiv) was added dropwise into a solution of nitron⁷⁸ (20 mmol, 1 equiv) and crotyltributylstannane (80 mmol, 4 EquivE/Z = 66:33) in 100 mL anhyd CH_2Cl_2 at -78°C . The reaction was stirred at -78°C for 12h. The reaction was quenched by adding saturated NaHCO_3 (150 mL). The reaction mixture was then extracted with 200 mL Et_2O three times. The combined organic layer was then washed with sat aq NaCl and dried over anhyd MgSO_4 . The product in mixture of isomers was obtained after purification with silica gel chromatography at Hexane/EA = 10/1. It was obtained in 95% yield (8.81g, 19.09 mmol)

⁷⁸ Nitron was obtained according to literature's procedure. Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J.D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103.

This isomers of products was obtained in the ratio of (1.7 : 10.2 : 7.6 : **80.5**) as determined by HPLC.

The practically optically pure product was obtained after repeated recrystallization using heptane, in 4.18g (9.06 mmol, 45%). (alternatively, the optically pure product can be obtained by careful separation using silica gel chromatography at solvent system $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O} = 15/1$, at 76% isolated yield).

LiOH (1.5 equiv) was then added into the a mixture of the purified product (4.18g, 9.06 mmol) in 20 mL MeOH . The reaction was monitored with TLC. After all the starting material was reacted (~ 3 h), 6 mL of H_2O was added, followed by $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.5 equiv) the reaction was then monitored with TLC. The solvent was removed *in vacuo* after the reaction was completed. The crude product was purified with silica gel chromatography. The product was obtained in 96% yield (1.54 g, 8.70 mmol) as colorless oil.

The absolute stereochemistry of **(R,S)-II-2** was confirmed by X-ray Crystallography.

6.3 Linear homoallylic hydroxylamine

Standard reaction condition:

CSA (23 mg, 0.1 mmol, 0.2 equiv) was added in portion into a solution of hydrocinnamaldehyde (67mg, 0.5 mmol, 1.0 equiv) and hydroxylamine **(R,S)-II-2** (97 mg, 0.55 mmol, 1.1 equiv) in 2 mL of isopropanol at room temperature with stirring. The

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reaction was monitored with TLC. After 7 h, the reaction was quenched by adding sodium bicarbonate powder (53 mg, 0.5 mmol, 1 equiv), and the reaction mixture was concentrated *in vacuo* and it was purified with silica gel column chromatography with mix solvent of hexane and ethyl acetate at ratio of 10 : 1. The product was obtained (117 mg, 80%, 99% ee) as colorless solid.

II-3a, (S,5E,NZ)-N-benzylidene-1-phenylhept-5-en-3-amine oxide

$R_f = 0.51$ (2:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 8.29 (dd, $J = 7.8, 2.5$ Hz, 2H, ArH), 7.47-7.44 (m, 3H, ArH), 7.33-7.18 (m, 6H, ArH, N=CH), 5.57 (dq, $J = 15.0, 6.3$ Hz, 1H, =CHCH₃), 5.35 (dtq, $J = 15.1, 7.1, 1.5$ Hz, 1H, CH=CHCH₃), 3.77-3.68 (m, 1H, ON-CH), 2.83-2.69 (m, 2H, PhCH₂-), 2.62-2.40 (m, 2H, PhCH₂CH₂-), 2.32 (br dt, $J = 14.2, 6.3$ Hz, 1H, -CH'H''CH=), 1.96-1.86 (m, 1H, -CH'H''CH=), 1.6 (dd, $J = 6.3, 1.2$ Hz, 3H, CH=CHCH₃) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 140.9, 134.2, 130.4, 130.2, 129.0, 128.6, 128.5, 128.4, 128.4, 126.1, 125.8, 76.3, 36.4, 33.2, 32.0, 17.9 ppm.

FTIR (film): 3026, 2959, 2931, 2918, 1734, 1578, 1497, 1454, 1333, 1146, 968, 806 cm^{-1} .

HRMS Calcd for $\text{C}_{20}\text{H}_{23}\text{NO}$ $[\text{M}]^+$: 293.1780. Found: 293.1770.

$[\alpha]_D = -6.2$ ($c = 1.3$, *i*PrOH)

Chiral HPLC Analysis: Daicel Chiracel ADH column, Hexane: *i*PrOH 95:5, 1.0 mL/min, 25.0 °C

Racemic, retention time : 18.50 min, 22.9 min.

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Asymmetric, 99% *e. e.*

II-3b, (*R,3E,NZ*)-*N*-benzylidene-1-cyclohexylpent-3-en-1-amine oxide

$R_f = 0.76$ (2:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 8.26-8.23 (m, 2H, ArH), 7.44-7.39 (m, 3H, ArH), 7.26 (s, 1H, N=CH), 5.55 (dq, $J = 15.1, 6.3$ Hz, 1H, CH=CH-CH₃), 5.35 (dtq, $J = 13.8, 7.1, 1.4$ Hz, 1H, CH=CH-CH₃), 3.39 (td, $J = 10.6, 3.3$ Hz, 1H, ON-CH), 2.73-2.63 (m, 1H, -CH'H''CH=CH), 2.42-2.31 (m, 1H, -CH'H''CH=CH), 1.97-1.60 (m, 7H, *c*-(CH₂)₂-), 1.56 (d, $J = 6.3$ Hz, 3H, CH=CH-CH₃), 1.35-1.21 (m, 4H, *c*-(CH₂)₂-) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 134.3, 130.4, 130.0, 128.5, 128.4, 128.4, 126.4, 83.1, 39.4, 32.8, 29.8, 29.3, 26.2, 26.0, 25.7, 17.9 ppm.

FTIR (film): 3022, 2930, 2853, 1578, 1560, 1452, 1321, 1148, 968, 920 cm^{-1} .

HRMS Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}$ [M]⁺: 271.1936. Found: 271.1923.

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$[\alpha]_D = +26.8$ ($c = 1.1$, $i\text{PrOH}$)

Chiral HPLC Analysis: Daicel Chiracel ADH column, Hexane: $i\text{PrOH}$ 95:5, 1.0 mL/min, 25.0 °C

Racemic, retention time: 18.0 min, 27.7 min.

Asymmetric, 98% *e.e.*

II-3c, (*R*,5*E*,*NZ*)-*N*-benzylidene-2,2-dimethylhept-5-en-3-amine oxide

$R_f = 0.67$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 8.26-8.22 (m, 2H, ArH), 7.42-7.38 (m, 3H, ArH), 7.28 (s, 1H, N=CH), 5.56 (br dq, $J = 15.1, 6.3$ Hz, 1H, =CHCH₃), 5.34 (dtq, $J = 16.5, 6.9, 1.5$ Hz, 1H, -CH=CHCH₃), 3.42 (dd, $J = 11.3, 2.3$ Hz, 1H, ON-CH), 2.94-2.83 (m, 1H, -CH'H''CH=), 2.23 (br dd, $J = 14.3, 7.3$ Hz, 1H, -CH'H''CH=), 1.56 (dd, $J = 6.3, 1.1$ Hz, 3H, =CHCH₃), 1.08 (s, 9H, -C(CH₃)₃) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 134.5, 130.6, 129.9, 128.5, 128.4, 128.2, 126.9, 85.6, 34.3, 30.2, 27.2, 17.9 ppm.

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FTIR (film): 2964, 2938, 1578, 1560, 1466, 1366, 1321, 1150, 968 cm^{-1} .

HRMS Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}$ $[\text{M}]^+$: 245.1780. Found: 245.1773.

$[\alpha]_{\text{D}} = +31.7$ ($c = 0.5$, $i\text{PrOH}$)

Chiral HPLC Analysis: Daicel Chiracel ADH column, hexane: $i\text{PrOH}$ 99:1, 1.0 mL/min, 25.0 $^{\circ}\text{C}$

Racemic, retention time: 14.7 min 18.7 min.

Asymmetric, 94% *e. e.*

II-3e, (*R*,4*E*,*NZ*)-*N*-benzylidene-1-(benzyloxy)hex-4-en-2-amine oxide

$R_f = 0.55$ (2:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 8.31-8.27 (m, 2H, ArH), 7.48-7.43 (m, 3H, ArH), 7.42 (s, 1H, N=CH-), 7.30-7.28 (m, 5H, ArH), 5.59 (dq, $J = 15.1, 6.4$ Hz, 1H, -CH=CHCH₃), 5.38 (dtq, $J = 15.2, 6.7, 1.5$ Hz, 1H, CH₂CH=CHCH₃), 4.59 & 4.50 (ABq, $J = 12.0$ Hz, 2H, PhCH₂O), 4.06-4.02 (m, 2H, BnOCH₂, -CH₂CH(NO)CH₂-), 3.61 (dd, $J = 14.6, 7.8$ Hz, 1H, BnOCH₂),

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2.67 (br dt, $J = 13.8, 8.0$ Hz, 1H, CH(NO)-CH₂CH=), 2.31 (br dt, $J = 13.2, 5.4$ Hz, 1H, CH(NO)-CH₂CH=), 1.62 (dd, $J = 6.3, 1.0$ Hz, 3H, CH=CHCH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 137.9, 134.9, 130.5, 130.2, 129.3, 128.8, 128.4, 128.3, 127.7, 127.7, 125.2, 76.9, 73.5, 69.7, 32.4, 17.9 ppm.

FTIR (film): 2918, 2862, 1701, 1579, 1452, 1335, 1148, 1105, 1094, 968, 737 cm⁻¹.

HRMS Calcd for C₂₀H₂₃NO₂ [M]⁺: 309.1729. Found: 309.1723.

$[\alpha]_D = +2.0$ ($c = 0.8$, *i*PrOH)

Chiral HPLC Analysis: Daicel Chiracel ADH column, hexane: *i*-propanol 95:5, 1.0 mL/min, 25.0 °C.

Racemic, retention time: 29.3 min, 58.5 min.

Asymmetric, 97% *e. e.*

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II-3f, (*S*,6*E*,*NZ*)-*N*-benzylidene-1-(benzyloxy)oct-6-en-4-amine oxide

$R_f = 0.51$ (2:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 8.25-8.22 (m, 2H, ArH), 7.43-7.21 (m, 9H, 8 ArH, 1 N=CH), 5.58 (dq, $J = 15.1, 6.3$ Hz, 1H, CH=CHCH₃), 5.37 (br dt, $J = 15.1, 6.9$ Hz, 1H, CH=CHCH₃), 4.52 & 4.47 (ABq, $J = 12.0$ Hz, 2H, PhCH₂O-), 3.86-3.76 (m, 1H, -CH₂CH(NO)CH₂-), 3.58-3.44 (m, 2H, BnOCH₂-), 2.71 (br td, $J = 7.8, 6.7$ Hz, 1H, -CH₂CH=CHCH₃), 2.76-2.66 (m, 1H, -CH₂CH=CHCH₃), 2.20-2.06 (m, 1H, BnOCH₂CH₂-), 1.80-1.63 (m, 3H, BnOCH₂CH₂CH₂-), 1.62 (d, $J = 6.3$ Hz, 3H, CH=CHCH₃) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 138.4, 134.0, 130.4, 130.1, 128.9, 128.6, 128.4, 128.4, 127.7, 127.6, 126.0, 77.3, 73.0, 69.9, 36.4, 29.3, 26.3, 17.9 ppm.

FTIR (film): 3030, 2936, 2857, 1578, 1454, 1360, 1333, 1148, 1099, 1028, 968 cm^{-1} .

HRMS Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_2$ $[\text{M}]^+$: 337.2042. Found: 337.2036.

$[\alpha]_D = +9.2$ ($c = 1.2$, *i*PrOH)

Chiral HPLC Analysis: Daicel Chiracel ADH column, hexane: *i*PrOH 95:5, 1.0 mL/min, 25.0 °C.

Racemic, retention time: 26.8 min, 29.1 min.

Asymmetric, 98% e.e.

II-3g, (*S*,2*E*,*NZ*)-*N*-benzylidene-9-(benzyloxy)non-2-en-5-amine oxide

$R_f = 0.52$ (2:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 8.26-8.22 (m, 2H, ArH), 7.42-7.38 (m, 3H, ArH), 7.31-7.24 (m, 6H, ArH, N=CH), 5.55 (dq, $J = 15.1, 6.4$ Hz, 1H, =CHCH₃), 5.34 (br dt, $J = 15.1, 6.9$ Hz, 1H, -CH₂CH=CH), 4.45 (s, 2H, Ph-CH₂O-), 3.72-3.72 (m, 1H, ON-CH), 3.49-3.37 (m, 2H, BnOCH₂-), 2.68 (dt, $J = 14.3, 7.5$ Hz, 1H, -CH'H''CH=), 2.32-2.23 (m, 1H, -CH'H''CH=), 2.14-2.01 (m, 1H, -CH₂CH'H''CH₂-), 1.66-1.58 (m, 6H, =CHCH₃ and -CH₂-), 1.53-1.37 (m, 2H, -CH₂-) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 138.4, 133.8, 130.4, 130.0, 128.8, 128.6, 128.4, 128.3, 127.6, 127.4, 126.0, 77.6, 72.8, 69.9, 36.3, 32.0, 29.3, 22.9, 17.9 ppm.

FTIR (film): 2936, 2860, 1578, 1560, 1454, 1363, 1333, 1148, 1101, 968 cm^{-1} .

HRMS Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_2$ $[\text{M}]^+$: 351.2198. Found: 351.2186.

$[\alpha]_D = +13.4$ ($c = 1.9$, *i*PrOH)

Chiral HPLC Analysis: Daicel Chiracel ADH column, hexane: *i*PrOH 95:5, 1.0 mL/min, 25.0 °C.

Racemic, retention time: 26.9 min, 47.2 min.

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Asymmetric, 97% e.e.

II-3d, (*R*,3*E*,*NZ*)-*N*-benzylidene-1-phenylpent-3-en-1-amine oxide

$R_f = 0.57$ (2:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 8.26-8.24 (m, 2H, ArH), 7.42-7.22 (m, 9H, ArH), 5.66 (dq, $J = 15.1, 6.4$ Hz, 1H, $-\text{CH}=\text{CHCH}_3$), 5.42 (br dtq, $J = 15.1, 6.8, 1.6$ Hz, 1H, $-\text{CH}=\text{CHCH}_3$),

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4.92 (dd, $J = 9.0, 5.9$ Hz, 1H, PhCH(NO)CH₂-), 3.29 (br dt, $J = 14.3, 8.0$ Hz, 1H, -CH'H''CH=), 2.72 (dtq, $J = 14.3, 7.2, 1.0$ Hz, 1H, -CH'H''CH=), 1.63 (dd, $J = 6.3, 1.4$ Hz, 3H, =CHCH₃) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 137.5, 133.3, 130.5, 130.1, 129.1, 128.7, 128.6, 128.6, 128.4, 127.7, 125.9, 80.3, 35.8, 17.9 ppm.

FTIR (film): 3028, 2965, 2916, 1560, 1493, 1454, 1321, 1142, 1076, 1028, 966 cm⁻¹.

HRMS Calcd for C₁₈H₁₉NO [M⁺]: 265.1467. Found: 265.1466.

$[\alpha]_D = -7.6$ ($c = 1.5$, *i*PrOH)

Chiral HPLC Analysis: Daicel Chiracel ADH column, hexane: *i*PrOH 95:5, 1.0 mL/min, 25°C.

Racemic, retention time: 38.7 min, 49.0 min.

Asymmetric, 92% *e. e.*

Applications of Nitrones

Reaction Condition:

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NaOAc (1.5mmol, 1.5 equiv) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.5 mmol, 1.5 equiv) was added into a solution of **3a** (1.0 mmol, 1.0 equiv) in 2 mL of MeOH/ H_2O (3:1) solution. The reaction was monitored with TLC. After reaction was completed (~ 2 h) the solvent was removed *in vacuo*. The crude product was purified with silica gel chromatography, yielding product in 195 mg (0.95 mmol), 95% yield.

(Note :The product should be used immediately. It can be stored at -20°C for a week.)

$R_f = 0.31$ (2:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.33-7.20 (m, 5H, ArH), 5.60 (dq, $J = 15.3, 6.5$ Hz, 1H, $=\text{CHCH}_3$), 5.40 (dtq, $J = 15.3, 6.2, 1.5$ Hz, 1H, $-\text{CH}_2\text{CH}=\text{}$), 2.95 (qn, $J = 6$ Hz, 1H, $-\text{CH}(\text{NHOH})-$), 2.70 (t, $J = 8.0$ Hz, 2H, PhCH_2-), 2.33-2.21 (m, 2H, $-\text{CH}_2\text{CH}=\text{}$), 2.02-1.93 (m, 1H, $\text{PhCH}_2\text{CH}_2-$), 1.78-1.70 (m, 1H, $\text{PhCH}_2\text{CH}_2-$), 1.71 (d, $J = 5.5$ Hz, 3H, $=\text{CH}_2\text{CH}_3$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 141.7, 129.5, 128.4, 128.3, 126.2, 126.0, 60.4, 33.8, 32.3, 32.2, 21.4, 18.0 ppm.

FTIR (film) 3063, 3026, 2936, 2920, 2857, 1709, 1602, 1497, 1454, 1416, 1273, 970, 739, 700 cm^{-1} .

HRMS Calcd for $[\text{M} - \text{H}]^+$: 204.1383. Found: 204.1383.

The freshly purified hydroxylamine (0.5 mmol, 1.0 equiv) and hydrocinnamaldehyde (0.55 mmol, 1.1 equiv) was dissolved in CH_2Cl_2 . The progress of the reaction was monitored with TLC. The reaction mixture was concentrated under reduced pressure. The crude

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product was purified with silica gel chromatography. The product was obtained in 137 mg (85% yield).

$R_f = 0.21$ (1:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.18 (m, 9H, ArH), 7.08 (d, $J = 7.0$ Hz, 2H, ArH), 6.59-6.55 (m, 1H, N=CH-), 5.52 (dq, $J = 15, 6.5$ Hz, 1H, =CHCH₃), 5.23 (dtq, $J = 15.3, 7, 1.8$ Hz, 1H, -CH₂CH=), 3.48 (tt, $J = 9.8, 4.8$ Hz, 1H, -CH(NO)-), 3.00-2.87 (m, 4H, PhCH₂-), 2.69-2.57 (m, 2H, -CH₂CH(NO)-), 2.45-2.32 (m, 2H, -CH₂CH=), 2.20 (qn, $J = 7.8$ Hz, -CH₂CH(NO)-), 1.81-1.62 (m, 1H, -CH₂CH(NO)-), 1.62 (dd, $J = 6.3, 1.3$ Hz, =CHCH₃) ppm.

^{13}C NMR (100 MHz, CDCl_3) δ 140.8, 140.4, 139.2, 129.0, 128.6, 128.4, 128.3, 126.4, 126.0, 125.8, 74.8, 35.9, 32.8, 31.9, 31.3, 27.3, 17.9 ppm.

FTIR (film) 3026, 2930, 2857, 1719, 1603, 1497, 1454, 1325, 1140, 1030, 1013, 968, 910 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 321.2087. Found: 321.2087.

Zinc powder (4.0 mmol, 4 equiv) was added in portions over 2 h into a solution of **II-3a** (1.0 mmol, 1 equiv) in 2 mL of AcOH/H₂O (3:1) with vigorous stirring at room temperature. The reaction was monitored with TLC. The reaction mixture was then concentrated under reduced pressure, followed by azeotropic removal of H₂O in the crude

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product with 2 mL of THF twice. 2 mL of CH₂Cl₂ was then added into reaction mixture, followed by Ac₂O (0.5 mL). The reaction mixture was then vigorously stirred for 1 h at room temperature. A few drops of Et₃N was added dropwise until the solution turned clear. The mixture was then stirred for another 1 h. The reaction mixture was then concentrated *in vacuo*. The crude product was then purified with silica gel chromatography.

R_f = 0.36 (1:1 hexane/ethyl acetate)

¹H NMR (300 MHz, CDCl₃): δ 7.32-7.28 (m, 2H, ArH), 7.22-7.18 (m, 3H, ArH), 5.52 (dq, *J* = 15, 6.3 Hz, 1H, =CHCH₃), 5.40 (br dt, *J* = 16.3, 8.3 Hz, 1H, -CH₂CH=), 4.05 (tq, *J* = 8.6, 5.8 Hz, 1H, -CH(NHAc)-), 2.67 (t, *J* = 8.0 Hz, 2H, PhCH₂-), 2.27-2.14 (m, 2H, -CH₂CH=), 1.97 (s, 3H, -NHCOCH₃), 1.88-1.80 (m, 1H, PhCH₂CH₂-), 1.75-1.68 (m, 1H, PhCH₂CH₂-), 1.69 (d, *J* = 5.3 Hz, 3H, =CHCH₃) ppm.

¹³C NMR (75 MHz, CDCl₃) δ 169.6, 141.9, 128.7, 128.4, 128.3, 126.3, 125.9, 49.0, 37.9, 36.1, 32.5, 23.5, 18.1 ppm.

FTIR (film) 3427, 3321, 2937, 2920, 1664, 1514, 1371, 970 cm⁻¹.

HRMS Calcd for [M]⁺: 231.1618. Found: 231.1618.

Stereochemistry of **II-3d**

(The *N*-Acyl homoallylic amine, **II-6d**, was obtained from **II-3d** using the method described above.)

A mixture of **II-6d** and Pd/C (~ 0.2 equiv) in Ethyl Acetate with rigorous stirring was subjected to hydrogen atmosphere for 3 h. The reaction mixture was filtered through celite and the organic solvent was removed under reduced pressure.

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$R_f = 0.36$ (1:1 hexane/ethyl acetate)

All Physical Data matched the literature values (Ref: Aggarwal, V. K.; Guang, Y. F.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, 127, 1642.)

Chiral HPLC Analysis: Daicel Chiracel OD column, hexane: *i*PrOH 95:5, 1.0 mL/min, 20.0 °C.

The HPCL retention time of product obtained matched well with the value of *R* isomer in the literature.

Racemic, retention time: 16.6 min, 20.0 min. (*Lit. Value.* 17.1 min for *R* isomer, 22.6 for *S* isomer).

Asymmetric.

6.4 Prins cyclization product

Typical reaction condition:

To a rigorously stirred solution of nitrones **III-2a** (140 mg, 0.5 mmol, 1equiv) in 2 mL anhyd CH_2Cl_2 at room temperature under N_2 atmosphere, AcBr (0.055 mL, 0.75 mmol, 1.5 equiv) was added dropwise. After 15 min, the reaction mixture was cooled with ice-bath, followed by quenched with 15 mL of saturated NaHCO_3 . (*Caution: CO_2 gas evolved.*) The reaction mixture was then extract with 30 mL of Et_2O three times. The combined organic layer was washed with sat aq NaCl and was dried over anhyd MgSO_4 . The organic solution was concentrated under reduced pressure and purified with Silica gel flash chromatography using solvent hexane/ Et_2O at 25/1. The product **III-3a** was obtained as colourless oil at 55% yield (111 mg, 0.276 mmol; **III-3a_{eq}**/**III-3a_{ax}** = 9/91).

III-3a_{ax}, 4-bromo-2-phenethyl-6-phenylpiperidin-1-yl acetate

$R_f = 0.44$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.42-7.17 (m, 10H, ArH), 4.67 (br t, $J = 2.6$ Hz, 1H, $-\text{CHBr}-$), 4.35 (dd, $J = 11.7, 2.7$ Hz, 1H, $\text{PhCH}(-\text{N})-$), 3.49 (tq, $J = 8.1, 3.2$ Hz, 1H, $\text{PhCH}_2\text{CH}_2\text{CH}(-\text{N})-$), 2.82 (ddd, $J = 13.4, 10.6, 5.3$ Hz, 1H, $\text{PhCH}'\text{H}''-$), 2.61-2.36 (m, 3H, $-\text{CH}_2-$), 2.31-2.22 (m, 2H, $-\text{CH}_2-$), 2.01-1.79 (m, 2H, $\text{PhCH}_2\text{CH}_2-$), 1.61 (s, 3H, $\text{CH}_3\text{CO}-$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 169.4, 141.7, 140.2, 128.4, 128.3, 128.2, 128.0, 127.8, 125.9, 67.1, 61.4, 48.9, 42.5, 39.0, 34.1, 31.7, 18.7 ppm.

FTIR (film): 3063, 3028, 2957, 2868, 1767, 1603, 1495, 1364, 1206 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 401.0985. Found: (EI) 401.0998.

III-3a_{eq}, 4-bromo-2-phenethyl-6-phenylpiperidin-1-yl acetate

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$R_f = 0.56$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.16 (m, 10H, ArH), 4.17-4.07 (m, 1H, -CHBr-), 3.75-3.71 (m, 1H, PhCH(-N)-), 2.93-2.82 (m, 2H, PhCH₂-), 2.62-2.27 (m, 5H, -CH₂- and -CH₂CH(-N)CH₂-), 1.99-1.81 (m, 2H, PhCH₂CH₂-), 1.59 (s, 3H, CH₃CO) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 169.2, 141.5, 139.7, 128.5, 128.3, 128.2, 128.0, 127.7, 126.0, 72.6, 66.7, 44.9, 44.8, 41.4, 34.4, 31.4, 18.7 ppm.

FTIR (film): 3028, 2957, 2866, 1767, 1602, 1495, 1454, 1364, 1200, 760 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 401.0985. Found: (EI) 401.1003.

III-3b_{ax}, 4-bromo-2-cyclohexyl-6-phenylpiperidin-1-yl acetate

$R_f = 0.47$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.42-7.25 (m, 5H, ArH), 4.68 (t, $J = 2.7$ Hz, 1H, -CHBr-), 4.31 (dd, $J = 11.5, 2.7$ Hz, 1H, PhCH(N-)-), 3.32-3.26 (m, 1H, -CH-CH(N-)-), 2.35 (ddd, $J = 14.8, 11.5, 3.3$ Hz, 1H, PhCH(N-)CH'H"-, {axial ^1H }), 2.24-2.21 (m, 4H), 1.82-1.52 (m, 5H), 1.62 (s, 3H, CH₃CO), 1.31-1.05 (m, 5H) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 168.8, 140.6, 128.1, 128.1, 127.7, 67.4, 66.2, 49.6, 42.6, 38.8, 34.5, 30.3, 27.1, 27.1, 26.8, 26.6, 18.7 ppm.

FTIR (film): 2930, 2855, 1765, 1455, 1209 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 379.1141. Found: (EI) 379.1146.

III-3b_{eq}, 4-bromo-2-cyclohexyl-6-phenylpiperidin-1-yl acetate

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$R_f = 0.62$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, $J = 7.1$ Hz, 2H, ArH), 7.41-7.26 (m, 3H, ArH), 4.66 (d, $J = 5.2$ Hz, 1H, PhCH(N-)-), 4.46-4.32 (m, 1H, -CHBr-), 2.84-2.77 (m, 1H), 2.56-2.68 (m, 1H), 2.50-2.39 (m, 1H), 2.25-2.04 (m, 5H), 1.75-1.59 (m, 4H), 1.57 (s, 3H, CH_3CO), 1.23-1.05 (m, 4H) ppm.

FTIR (film): 2928, 2855, 1765, 1453, 1366, 1209 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 379.1141. Found: (EI) 379.1151.

III-3c_{ax}, 4-bromo-2-tert-butyl-6-phenylpiperidin-1-yl acetate

$R_f = 0.47$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.36-7.25 (m, 5H, ArH), 5.05 (t, $J = 5.8$ Hz, -CHBr-), 4.57 (dd, $J = 12.3, 2.7$ Hz, 1H, PhCH(N-)-), 3.34 (dd, $J = 12.0, 2.2$ Hz, 1H, $\text{Me}_3\text{CCH(N-)-}$), 2.85 (br t, $J = 12.5$ Hz, 1H), 2.38 (br t, $J = 12.7$ Hz, 1H), 2.10-1.94 (m, 2H), 1.64 (s, 3H, CH_3CO), 0.97 (s, 9H, $(\text{CH}_3)_3\text{C-}$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 168.7, 138.7, 128.6, 128.0, 127.8, 68.6, 64.2, 53.0, 33.9, 31.2, 28.1, 27.8, 19.4 ppm.

FTIR (film): 2960, 2926, 1763, 1368, 1202 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 353.0985. Found: (EI) 353.0986.

III-3d_{ax}, 4-bromo-2,6-diphenylpiperidin-1-yl acetate

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$R_f = 0.44$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.51 (d, $J = 7.3$ Hz, 4H, ArH), 7.34–7.26 (m, 6H, ArH), 4.72 (br qn, $J = 2.6$ Hz, 1H, -CHBr-), 4.51 (br d, $J = 11.4$ Hz, 2H, PhCH-), 2.59 (ddd, $J = 14.9, 11.8, 3.1$ Hz, 2H, Ph(-CH)CH'H''- {axial ^1H }), 2.34 (dd, $J = 15.1, 2.1$, 2H, Ph(-CH)CH'H''- {equatorial ^1H }), 1.27 (s, 3H, CH_3CO) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 172.2, 139.8, 128.3, 128.1, 127.9, 67.3, 48.9, 42.7, 18.3 ppm.

FTIR (film): 1767, 1643, 1632, 1364, 1206, 1180, 1049 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 373.0672. Found: (EI) 373.0678.

III-3d_{eq}, 4-bromo-2,6-diphenylpiperidin-1-yl acetate

$R_f = 0.50$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.45–7.42 (m, 4H, ArH), 7.33–7.25 (m, 6H, ArH), 4.22 (tt, $J = 11.0, 5.4$ Hz, 1H, -CHBr-), 3.87 (dd, $J = 10.5, 3.4$ Hz, 2H, PhCH-), 2.64–2.49 (m, 4H, Ph(CH-) CH_2 -), 1.23 (s, 3H, CH_3CO -) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 167.8, 139.4, 128.2, 128.0, 128.0, 72.7, 45.1, 44.4, 18.3 ppm.

FTIR (film): 1764, 1643, 1632, 1204, 1180, 1049, 910, 831 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 373.0672. Found: (EI) 373.0658.

III-3e_{ax}, 4-bromo-2-(naphthalen-2-yl)-6-phenylpiperidin-1-yl acetate

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$R_f = 0.56$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.93-7.26 (m, 12H, ArH), 4.74-4.67 (m, 2H, $-\text{CHBr}-$ and $\text{C}_{10}\text{H}_7-\text{CH}(\text{N}-)$), 4.57 (dd, $J = 11.5, 1.8$ Hz, 1H, $\text{PhCH}(\text{N}-)$), 2.72-2.58 (m, 2H), 2.38 (br d, $J = 15.0$ Hz, 2H), 1.21 (s, 3H, CH_3CO) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 167.9, 139.7, 137.5, 133.1, 133.1, 128.3, 128.1, 127.9, 127.9, 127.8, 127.6, 127.1, 126.0, 125.9, 125.9, 67.4, 67.3, 48.9, 42.9, 42.6, 18.3 ppm.

FTIR (film): 3431, 1767, 1631, 1364, 1206 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 423.0828. Found: (EI) 423.0818.

III-3e_{eq}, 4-bromo-2-(naphthalen-2-yl)-6-phenylpiperidin-1-yl acetate

$R_f = 0.44$ (4:1 hexane/ethyl acetate)

^1H NMR (500 MHz, CDCl_3): δ 7.85-7.79 (m 4H, ArH), 7.66 (d, $J = 8.5$ Hz, 1H, ArH), 7.48-7.45 (m, 4H, ArH), 7.33-7.25 (m, 3H, ArH), 4.28 (tt, $J = 11.8, 4.5$ Hz, 1H, $-\text{CHBr}-$), 4.05 (d, $J = 10.5$ Hz, 1H, $\text{C}_{10}\text{H}_7\text{CH}(\text{N}-)$), 3.92 (d, $J = 10.0$ Hz, 1H, $\text{PhCH}(\text{N}-)$), 2.70-2.53 (m, 4H), 1.17 (s, 3H, CH_3CO) ppm.

^{13}C NMR (125 MHz, CDCl_3): δ 172.0, 139.4, 137.1, 133.2, 133.0, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.7, 126.9, 126.0, 126.0, 125.7, 72.8, 72.8, 45.2, 45.0, 44.4, 18.4 ppm.

FTIR (film): 3414, 1767, 1655, 1638, 1364, 1206 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 423.0828. Found: (EI) 423.0821.

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III-3f_{ax}, 3-(1-acetoxy-4-bromo-6-phenylpiperidin-2-yl)propyl benzoate

R_f = 0.29 (4:1 hexane/ethyl acetate)

¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, *J* = 7.2 Hz, 2H, ArH), 7.58-7.52 (m, 1H, ArH), 7.46-7.25 (m, 7H, ArH), 4.66 (br s, 1H, -CHBr-), 4.37-4.30 (m, 3H, BzOCH₂- and PhCH(N-)-), 3.52-3.45 (m, 1H, -CH₂CH(N-)-), 2.47-2.17 (m, 4H), 2.05-1.91 (m, 1H), 1.83-1.63 (m, 3H), 1.58 (s, 3H, CH₃CO) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 169.3, 166.5, 140.1, 132.9, 130.3, 129.5, 128.3, 128.2, 127.9, 127.8, 67.0, 64.7, 61.3, 48.7, 42.4, 39.0, 28.9, 24.7, 18.6 ppm.

FTIR (film): 2959, 1765, 1717, 1452, 1364, 1314, 1277, 1205, 1176, 1114, 910 cm⁻¹.

HRMS Calcd for [M]⁺: 459.1040. Found: (EI) 459.1039.

3f_{eq}, 3-(1-acetoxy-4-bromo-6-phenylpiperidin-2-yl)propyl benzoate

III-3g, 4-(1-acetoxy-4-bromo-6-phenylpiperidin-2-yl)butyl benzoate

R_f = 0.29 (4:1 hexane/ethyl acetate)

¹H NMR (400 MHz, CDCl₃): δ 8.06 (d, *J* = 8.5 Hz, 2H, ArH), 7.57 (t, *J* = 7.4 Hz, 1H, ArH), 7.48-7.25 (m, 7H, ArH), 4.65 (br s, 1H, -CHBr-), 4.35-4.31 (m, 3H, BzOCH₂- and PhCH(N-)-), 3.46-3.39 (m, 1H, -CH₂CH(N-)CH₂-), 2.48-2.12 (m, 4H), 1.84-1.66 (m, 4H), 1.61 (s, 3H, CH₃CO) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 169.5, 166.6, 140.2, 132.8, 130.4, 129.5, 128.3, 128.2, 127.9, 127.8, 67.0, 64.7, 61.6, 48.9, 42.4, 39.0, 32.0, 28.8, 22.1, 18.7 ppm.

FTIR (film): 2959, 2870, 1765, 1717, 1277, 1206, 1177, 1115, 910 cm⁻¹.

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HRMS Calcd for $[M]^+$: 473.1196. Found: (EI) 473.1191.

III-3h, 4-bromo-2-cyclohexyl-6-phenethylpiperidin-1-yl acetate

R_f = 0.21 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3) {mixture of 2 isomers}: δ 7.31-7.16 (m, 5H, ArH), {4.85; 4.64 (br s, 1H, -CHBr-)}, 3.48-3.28 (m, 1H, -CH(N-)-), 3.15-3.07 (m, 1H, -CH(N-)-), {2.96 (ddd, J = 15.2, 10.2, 5.5 Hz) and 2.81-2.47 (m): total 2H, PhCH_2 -}, 2.45-2.25 (m, 1H), 2.18-1.92 (m, 4H), {2.08; 2.06 (s, CH_3CO , 3H)}, 1.88-1.42 (m, 6H), 1.35-0.87 (m, 4H) ppm.

^{13}C NMR (100 MHz, CDCl_3) {mixture of 2 isomers}: δ 169.4, {142.2; 141.8}, {128.6; 128.4}, 128.3, {125.9; 125.7}, {65.9; 64.9}, {61.5; 59.9}, {52.5; 49.7}, {39.6; 39.1}, {39.0; 35.6}, {34.4; 33.5}, {34.4; 32.5}, {31.7; 31.0}, {30.5; 30.2}, {29.6; 27.1}, {26.9; 26.5}, {26.8; 26.2}, {26.7; 26.0}, {19.3; 19.1} ppm.

FTIR (film): 3026, 2926, 2853, 1761, 1452, 1364, 1202, 999, 937, 822, 700 cm^{-1} .

HRMS Calcd for $[M]^+$: 407.1454. Found: 407.1469.

III-3i, 4-bromo-2,6-diphenethylpiperidin-1-yl acetate

R_f = 0.59 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3) {mixture of 2 isomers}: δ 7.33-7.19 (m, 10H, ArH), {4.83 and 4.65 (br s, 1H, -CHBr-)}, 3.51-3.30 (m, 2H, -CH(N-)-), 3.49-3.02 (m, 4H), 2.33-2.10 (m, 3H), 2.08 (s, 3H, CH_3CO), 1.94-1.80 (m, 4H), 1.62-.147 (m, 1H) ppm.

^{13}C NMR (100 MHz, CDCl_3) {mixture of 2 isomers}: δ {170.2; 169.7}, {142.0; 141.7}, 128.5, 128.3, 125.8, {61.0; 59.5}, {51.7; 48.9}, {38.8; 35.3}, {34.2; 33.4}, {32.5; 31.5}, 19.2 ppm.

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FTIR (film): 3053, 1761, 1643, 1634, 1604, 1265, 1205 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 429.1298. Found: (EI) 429.1281.

III-3j_{ax}, 4-bromo-3-methyl-2,6-diphenylpiperidin-1-yl acetate

R_f = 0.34 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, J = 7.54 Hz, ArH), 7.49 (d, J = 6.9 Hz, ArH), 7.39-7.17 (m, 7H, ArH), 4.60 (q, J = 5.7 Hz, 1H, $-\text{CHBr}-$), 4.52 (dd, J = 11.7, 1.4 Hz, 1H, $\text{PhCH}(\text{N}-)\text{CH}_2-$), 4.02 (d, J = 10.4 Hz, 1H, $\text{PhCH}(\text{N}-)\text{CH}(\text{CH}_3)-$), 2.69 (ddd, J = 14.9, 11.8, 3.1 Hz, 1H, $-\text{CH}_{\text{ax}}\text{H}_{\text{eq}}-$: axial ^1H), 2.43 (dt, J = 15.0, 2.8 Hz, 1H, $-\text{CH}_{\text{ax}}\text{H}_{\text{eq}}-$: equatorial ^1H), 2.32 (dq, J = 9.9, 6.6, 3.0 Hz, 1H, $-\text{CH}(\text{CH}_3)-$), 1.22 (s, 3H, $\text{CHCO}-$), 0.80 (d, J = 6.6 Hz, 3H, $-\text{CH}(\text{CH}_3)-$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 167.7, 140.0, 138.3, 130.5, 128.6, 128.2, 128.1, 127.8, 127.8, 127.7, 127.3, 66.7, 58.7, 42.5, 41.8, 18.4, 18.3 ppm.

FTIR (film): 1766 1643, 1631, 1204 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 387.0828. Found: (EI) 387.0834.

III-3j_{eq}, 4-bromo-3-methyl-6-phenethyl-2-phenylpiperidin-1-yl acetate

R_f = 0.44 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.45-7.24 (m, 10H, ArH), 3.94 (td, J = 11.1, 4.7 Hz, 1H, $-\text{CHBr}-$), 3.88 (dd, J = 11.7, 1.7 Hz, 1H, $\text{PhCH}(\text{N}-)\text{CH}_2-$), 3.52 (d, J = 10.4 Hz, 1H, $\text{PhCH}(\text{N}-)\text{CH}(\text{CH}_3)-$), 2.71 (dt, J = 13.5, 11.9 Hz, 1H, $-\text{CH}_{\text{ax}}\text{H}_{\text{eq}}-$: axial ^1H), 2.60 (ddd, J = 13.6, 4.5, 2.9 Hz, 1H, $-\text{CH}_{\text{ax}}\text{H}_{\text{eq}}-$: equatorial ^1H), 2.46 (tq, J = 10.6, 6.5 Hz, 1H, $-\text{CH}(\text{CH}_3)-$), 1.19 (s, 3H, CH_3CO), 0.94 (d, J = 6.5 Hz, 3H, $-\text{CH}(\text{CH}_3)-$) ppm.

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^{13}C NMR (100 MHz, CDCl_3): δ 167.3, 139.5, 138.7, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 78.5, 72.5, 54.6, 45.9, 44.7, 18.2, 18.1 ppm.

FTIR (film): 1764, 1644, 1632, 1205 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 387.0828. Found: (EI) 387.0839.

III-3k_{ax}, 4-bromo-3-methyl-6-phenethyl-2-phenylpiperidin-1-yl acetate

R_f = 0.48 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, J = 7.4 Hz, 1H, ArH), 7.37-7.14 (m, 9H, ArH), 4.56 (q, J = 2.9 Hz, 1H, -CHBr-), 3.87 (d, J = 10.5 Hz, 1H, PhCH(N)-), 3.53-3.48 (m, 1H, -CH₂CH(N-)(CH₂-), 2.83 (ddd, J = 13.6, 10.6, 5.4 Hz, 1H, PhCH'H''-), 2.57 (ddd, J = 13.6, 10.4, 6.5 Hz, 1H, PhCH'CH''-), 2.51 (dt, J = 14.9, 2.8 Hz, 1H, -CH_{ax}H_{eq}CHBr-), 2.38 (ddd, J = 14.7, 11.4, 3.1 Hz, -CH_{ax}H_{eq}CHBr-), 2.18 (dq, J = 10.4, 6.6, 3.0 Hz, 1H -CH(CH₃)-), 1.97-1.81 (m, 2H, PhCH₂CH₂-), 1.55 (s, 3H, CH₃CO), 0.75 (d, J = 6.6 Hz, 3H, -CH(CH₃)-) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 169.3, 141.7, 138.7, 130.4, 128.6, 128.4, 128.3, 127.8, 127.3, 127.1, 125.9, 72.6, 60.9, 58.6, 41.5, 38.9, 34.1, 31.6, 18.6, 18.4 ppm.

FTIR (film): 3047, 1761, 1620, 1495, 1364, 1210 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 415.1141. Found: (EI) 415.1135.

III-3k_{eq}, 4-bromo-3-methyl-2-phenethyl-6-phenylpiperidin-1-yl acetate

R_f = 0.66 (4:1 hexane/ethyl acetate)

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^1H NMR (400 MHz, CDCl_3): δ 7.32-7.16 (m, 10H, ArH), 3.81 (td, J = 12.0, 4.4 Hz, $-\text{CHBr}-$, 3.36 (d, J = 10.5 Hz, $\text{PhCH}(\text{N}-)$), 2.89-2.82 (m, 2H, PhCH_2-), 2.65 (ddd, J = 13.5, 7.1, 4.4 Hz, 1H), 2.57 (ddd, J = 13.8, 10.4, 6.8 Hz, 1H), 2.45-2.31 (m, 2H), 1.97-1.78 (m, 2H, $\text{PhCH}_2\text{CH}_2-$), 1.53 (s, 3H, CH_3CO), 0.88 (d, J = 6.5 Hz, $-\text{CH}(\text{CH}_3)-$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 169.0, 141.5, 139.1, 128.5, 128.5, 128.3, 128.2, 128.0, 126.0, 78.4, 66.5, 54.9, 45.7, 41.1, 34.4, 31.5, 18.6, 18.0 ppm.

FTIR (film): 3021, 2950, 1765, 1608, 1455, 1366 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 415.1141. Found: (EI) 415.1136.

6.5 Total Synthesis of (–)indolizidine 209 B

IV-2i, (*R*,2*E*,*NZ*)-*N*-((*E*)-but-2-enylidene)dec-2-en-5-amine oxide

To a mixture of (*R,E*)-*N*-(dec-2-en-5-yl)hydroxylamine⁷⁹ (3.42 g, 20 mmol, 1 equiv) and crotonaldehyde (1.75 g, 25 mmol, 1.25 equiv) in 20 mL CH_2Cl_2 were added 4Å MS (1.0 g). The reaction mixture was stirred for 24 h at rt and it was filtered through celite. The filtrate

79 For synthesis, see: Cheng, H. S.; Seow, A. H.; Loh, T. P. *Org. Lett.* **2008**, *10*, 2805.

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was then concentrated *in vacuo* and purify with flash chromatography (hexane/EA = 15/1).

The product was obtained in 96% yield (4.29 g, 1.92 mmol).

R_f = 0.39 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 6.98 (d, J = 9.4 Hz, 1H, $-\text{N}^+(\text{O}^-)=\text{CH}-$), 6.79 (ddq, J = 15.8, 9.5, 1.7 Hz, 1H, $-\text{N}^+(\text{O}^-)=\text{CH}-\text{CH}=\text{CH}-$), 6.24 (dq, J = 15.7, 6.9 Hz, 1H, $-\text{N}^+(\text{O}^-)=\text{CH}-\text{CH}=\text{CH}(\text{CH}_3)$), 5.53 (dq, J = 15.1, 6.4 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCH}_3$), 5.31 (dtq, J = 15.2, 7.1, 1.5 Hz, 1H, $-\text{CH}_2\text{CH}=\text{CHCH}_3$), 3.49 (tt, J = 9.2, 4.6 Hz, 1H, $-\text{CH}(\text{N}^+\text{O}^-)-$), 2.60 (dt, J = 14.9, 8.2 Hz, $-\text{CH}(\text{N}^-)\text{CH}'\text{H}''\text{CH}=\text{CH}-$), 2.21 (dt, J = 14.0, 6.8 Hz, 1H, $-\text{CH}(\text{N}^-)\text{CH}'\text{H}''\text{CH}=\text{CH}-$), 2.00-1.91 (m, 1H), 1.89 (dd, J = 6.9, 1.5 Hz, 3H, $-\text{N}^+(\text{O}^-)=\text{CH}-\text{CH}=\text{CH}(\text{CH}_3)$), 1.63 (dd, J = 6.3, 0.8 Hz, 3H, $-\text{CH}_2\text{CH}=\text{CHCH}_3$), 1.52-1.46 (m, 1H), 1.30-1.15 (m, 6H, $-\text{CH}_2-$), 0.86 (t, J = 6.7 Hz, 3H, $-\text{CH}_2\text{CH}_3$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 135.9, 130.8, 129.1, 128.8, 125.7, 75.2, 36.0, 31.9, 31.3, 25.7, 22.4, 18.9, 17.9, 13.9 ppm.

FTIR (film): 3026, 2965, 1325, 965 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 223.1931. Found: (EI) 223.1945.

IV-3i, (2S,3S,4S,6R)-4-bromo-3-methyl-6-pentyl-2-((E)-prop-1-enyl)piperidin-1-yl acetate

To a mixture of nitron, **2i** (0.446 g, 2.0 mmol, 1equiv) and Magnesium Bromide (0.55 g, 3.0 mmol, 1.5 equiv) in 5 mL CH_2Cl_2 under vigorously stirring, were added AcBr (0.37 g, 3.0 mmol, 1.5 equiv) dropwise. The reaction mixture was stirred for 30 min at rt before it was cooled with ice-bath and quenched by adding 40 mL saturated NaHCO_3 . The reaction mixture was extracted with Et_2O (30 mL x 3) thrice. The combined organic solvent was washed with sat aq NaCl and dried over anhyd MgSO_4 . The product was purified with Silica

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gel flash chromatography (hexane/EA = 20/1). Product **IV-3i** was obtained in 55% yield (0.381 g, 1.10 mmol).

R_f = 0.55 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 5.54 (dq, J = 15.2, 6.5 Hz, 1H, $-\text{CH}=\text{CHCH}_3$), 5.30 (ddq, J = 15.1, 10.2, 1.2 Hz, 1H, $-\text{CH}=\text{CHCH}_3$), 3.63 (td, J = 11.9, 3.8 Hz, 1H, $-\text{CHBr}-$), 2.72 (t, J = 9.69 Hz, 1H, $=\text{CHCH}(\text{N-})\text{CH}(\text{CH}_3)-$), 2.63 (ddt, J = 11.6, 8.5, 2.9 Hz, $-\text{CH}_2\text{CH}(\text{N-})\text{CH}_2-$), 2.41 (ddd, J = 13.4, 4.2, 2.8 Hz, 1H, $-\text{CH}'\text{H}''\text{CHBr}-$), 2.15-1.95 (m, 2H, $-\text{CH}'\text{CH}''\text{CHBr}-$ & $-\text{CH}(\text{CH}_3)-$), 1.92 (s, 3H, $-\text{COCH}_3$), 1.65 (dd, J = 6.4, 1.5 Hz, 3H, $=\text{CHCH}_3$), 1.55-1.13 (m, 8H, $-\text{CH}_2-$), 1.03 (d, J = 6.6 Hz, 3H, $-\text{CH}(\text{CH}_3)-$), 0.85 (t, J = 7.13 Hz, $-\text{CH}_2\text{CH}_3$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 170.7, 128.6, 126.6, 76.5, 66.0, 55.1, 43.7, 41.0, 32.9, 31.9, 31.5, 24.9, 22.5, 18.3, 17.5, 13.9 ppm.

FTIR (film): 3024, 1760, 1205, 934 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 345.1298. Found: (EI) 345.1310.

IV-4i, (E)-methyl 3-((2S,3S,4S,6R)-1-acetoxy-4-bromo-3-methyl-6-pentylpiperidin-2-yl)acrylate

A solution of **3i** (0.346 g, 1.0 mmol, 1 equiv) in CH_2Cl_2 at -78°C was repeatedly bubbled with ozone for 10 second followed by checking of the progress of reaction with TLC. (*Note: Yield decreased significantly if reaction was over ozonized*). At the completion of reaction as indicated by TLC, the reaction mixture was purged with N_2 gas for 1 min and PPh_3 (1.31 g, 5.0 mmol, 5 equiv) was added at -78°C , followed by ylide, $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ (1.67 g, 5.0 mmol, 5 equiv). The reaction mixture was then stirred at -78°C for another 2 h, at 0°C for 5 h and at room temperature for 48 h. The reaction mixture was then concentrated and

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purified with Silica gel chromatography (Hex/EA = 15/1). The product **IV-4i** was obtained in 40% yield (0.156 g , 0.40 mmol).

R_f = 0.43 (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 6.71 (dd, J = 15.7, 9.3 Hz, 1H, $-\text{CH}=\text{CHCO}_2\text{Me}$), 5.88 (d, J = 15.7 Hz, 1H, $-\text{CH}=\text{CHCO}_2\text{Me}$), 3.70 (s, 3H, $-\text{CO}_2\text{CH}_3$), 3.63 (td, J = 11.7, 3.8 Hz, 1H, $-\text{CHBr}-$), 2.99 (t, J = 9.8 Hz, 1H, $-\text{CH}(\text{N})\text{CH}=\text{}$), 2.70-2.65 (m, 1H, $-\text{CH}_2\text{CH}(\text{N})\text{CH}_2-$), 2.44 (br dt, J = 13.1, 3.0 Hz, 1H, $-\text{CH}(\text{N})\text{CH}'\text{H}''\text{CH}(\text{Br})-$), 2.16-1.99 (m, 2H, $-\text{CH}(\text{N})\text{CH}'\text{H}''\text{CH}(\text{Br})-$ & $-\text{CH}(\text{N})\text{CH}(\text{Me})\text{CH}(\text{Br})-$), 1.91 (s, 3H, $-\text{COCH}_3$), 1.39-1.13 (m, 8H, $-\text{CH}_2-$), 1.04 (d, J = 6.6 Hz, 3H, $-\text{CH}(\text{CH}_3)\text{CBr}-$), 0.85 (t, J = 7.2 Hz, CH_2CH_3) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 169.4, 165.8, 145.6, 125.0, 74.8, 66.3, 53.8, 51.8, 43.2, 40.8, 32.6, 31.8, 24.8, 22.4, 19.0, 18.0, 13.9 ppm.

FTIR (film): 3022, 1761, 1680, 1195, 1179 cm^{-1} .

HRMS Calcd for $[\text{M}]^+$: 389.1196. Found: (EI) 389.1185.

Chiral HPLC Analysis: Daicel Chiracel ODH column, hexane: *i*PrOH 99:1, 0.5

mL/min, 25.0 $^\circ\text{C}$

Racemic, retention time: 23.6 min 26.6 min.

Asymmetric >98% ee

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IV-5i, methyl 3-((2S,3R,6R)-3-methyl-6-pentylpiperidin-2-yl)propanoate

To a mixture of bromide **4i** (0.156 g, 0.40 mmol, 1 equiv), Pd/C (0.16 mmol, 0.4 equiv) in 5 mL MeOH were added a solution of Et₃N (0.40 g, 4.0 mmol, 10.0 equiv) and HCOOH (0.18 g, 4.0 mmol, 10 equiv) in 4 mL MeOH. The reaction mixture was then refluxed for 2 h. MeOH was removed *in vacuo* and the reaction mixture was then filtered through celite (using CH₂Cl₂). The filtrate was concentrated *in vacuo* and purified with Silica gel column chromatography (CH₂Cl₂/MeOH = 20/1). Product was obtained in 83% yield (0.084 mg, 0.33 mmol).

R_f = 0.14 (95:5 CH₂Cl₂/MeOH)

¹H NMR (400 MHz, CDCl₃): δ 3.70 (s, 3H, -CO₂CH₃), 2.65-2.56 (m, 1H, -CH(N-)-), 2.54-2.45 (m, 2H, -CH₂CO₂Me), 2.42-2.37 (ddd, *J* = 10.6, 8.2, 3.0 Hz, 1H, -CH(N-)-), 2.13-2.05 (dtd, *J* = 17.5, 7.9, 3.0 Hz, 1H), 1.84-1.73 (m, 3H), 1.61-1.53 (m, 1H), 1.49-1.40 (m, 2H), 1.33-1.23 (m, 7H), 1.18-1.08 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H, -CH(CH₃)-), 0.90 (t, *J* = 7.0 Hz, 3H, -CH₂CH₃) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 174.4, 62.2, 57.4, 51.7, 35.4, 34.9, 33.5, 31.8, 31.0, 30.1, 27.4, 25.4, 22.6, 18.4, 14.0 ppm.

FTIR (film): 2915, 1724, 1451, 1173 cm⁻¹.

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HRMS Calcd for $[M]^+$: 255.2193. Found: (EI) 255.2193.

$[\alpha]_D = -28.17$ (c 1.27, iPrOH)

IV-6i (–)-indolizidine 209B

To a solution of ester **5i** (77 mg, 0.30 mmol, 1 equiv) in 3 mL THF at 0 °C were added LiAlH_4 (23 mg, 0.60 mmol, 2.0 equiv) in 4 portion over 2 h. The reaction mixture was then refluxed for 2 h. The reaction was cooled to 0 °C and quenched by adding 23 μL water, followed by 23 μL 15% NaOH. The reaction was then stirred at rt for 30 min and 69 μL water was added. Excess Na_2SO_4 was then added after 1 h. The reaction mixture was then filtered through celite and concentrated.

To a solution of the crude product in 1 mL CH_2Cl_2 were added Ph_3P (0.12 g, 0.45 mmol, 1.5 equiv) and CBr_4 (0.12 g, 0.36 mmol, 1.2 equiv). After 30 min, Et_3N (0.6 mL) was added and the mixture was stirred at 0 °C for 20 min. The reaction mixture was warmed up to rt and was concentrated *in vacuo*. It was purified with Silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 95/5$) to afford **IV-6i** as a colorless oil in 55% yield (34.4 mg, 0.164 mmol)

$R_f = 0.43$ (95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$)

^1H NMR (400 MHz, CDCl_3): δ 3.26 (td, $J = 8.7, 2.1$ Hz, 1H, $\text{CH}_2\text{CH}(\text{N-})\text{CH}(\text{CH}_3)\text{-}$), 1.98-1.80 (m, 3H), 1.78-1.58 (m, 5 H), 1.51-1.16 (m, 11H), 1.00-0.92 (m, 1H), 0.88 (t, $J = 6.9$ Hz, 3H, $-\text{CH}_2\text{CH}_3$), 0.86 (d, $J = 6.5$ Hz, 3H, $-\text{CH}(\text{CH}_3)\text{-}$) ppm.

^{13}C NMR (100 MHz, CDCl_3): δ 71.4, 63.7, 51.8, 36.4, 34.4, 33.6, 32.3, 31.1, 29.0, 25.6, 22.7, 20.3, 18.9, 14.1 ppm.

FTIR (film): 2957, 2930, 1458, 1377, 1333, 1242, 1220, 1167 cm^{-1} .

HRMS Calcd for $[M]^+$: 209.2138. Found: (EI) 209.2140.

$[\alpha]_D = -88.3$ ($c = 0.34$, MeOH); lit.⁸⁰ $= -87.7$ ($c = 0.6$, MeOH)

6.6 Total Synthesis of (–)-Perhydrohistrionicotoxin

V-7, 5,5-dimethoxypentanal

(Based on Schreiber's procedures, Claus, R. E.; Schreiber, S. L. *Org. Syn.*, **1990**, 7, 168)

A solution of cyclopentene (11.05 mL, 125 mmol, 1 equiv) in 250 mL of dichloromethane and 50 mL of methanol was cooled to -78°C (acetone–dry ice). Ozone was bubbled through the solution with stirring until the solution turned blue. Nitrogen was passed through the solution until the blue color was discharged and the cold bath was removed. 1.62 g of p-toluenesulfonic acid was added. The solution was allowed to warm to rt as it stirred for 90 min. Anhyd NaHCO_3 (2.86 g) was added to the flask and the mixture was stirred for 15 min, and then 16 mL of DMS was added. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure. Et_2O (200 mL) was added and the mixture was washed with a mixture of 50 mL of water and 50 mL of sat aq NaCl. The organic layer was dried over anhyd MgSO_4 , filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel flash chromatography (1:1 ether: hexane) afforded product as colourless oil in 30% yield 5.48 g.

$R_f = 0.28$ (4:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 9.77 (t, $J = 1.5$ Hz, 1H, $-\text{CHO}$), 4.36 (t, $J = 5.5$, 1H, $-\text{CH}(\text{OMe})_2$), 3.32 (s, 6H, $-\text{CH}(\text{OMe})_2$), 2.47 (td, $J = 7.0$ Hz, 2H, $-\text{CH}_2\text{CHO}$), 1.74–1.60 (m, 4H, $-\text{CH}_2\text{CH}_2-$) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 202.2, 104.2, 52.9, 43.5, 31.8, 17.2 ppm.

80 Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, 65, 4543.

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FTIR (neat) : 1724, 1454, 1387, 1127 cm^{-1} .

HRMS (EI) Calcd for $\text{C}_7\text{H}_{14}\text{O}_3$ $[\text{M}]^+$: 146.0937. Found: 146.0919.

V-5, 1,1-dimethoxydec-9-en-5-one

To stirring THF solution (10 mL) of freshly prepared Grignard Reagent pent-4-enylmagnesium bromide (12 mmol, 1.2 equiv) at 0°C , a solution of aldehyde (10 mmol, 1.0 equiv) in 5 mL THF was added drop-wise. The solution was stirred for 4 h at 0°C before it was quenched with 10 mL NH_4Cl solution. The organic layer was concentrated under reduced pressure. The aqueous layer was extracted with diethylether three times (50 mL each), the combined organic solvent was washed with saturated NaHCO_3 and with sat aq NaCl , and it was dried over anhyd MgSO_4 . The solution was concentrated under reduced pressure.

The resulting crude product was then added into a solution of IBX (15 mmol, 1.5 equiv) in 15 mL DMSO and it was stirred for 4 h at r.t. The reaction was monitored with TLC. 15 mL Water was added into the reaction mixture and the white precipitate was filtered. The filtrate was extracted with diethylether (50 mL x 3). the combined organic solvent was washed with saturated NaHCO_3 solution and sat aq NaCl . It was dried over anhyd MgSO_4 . The organic layer was concentrated under reduced pressure and the resulting crude product was purified by silica gel flash chromatography (1: 20 EA: hexane) afforded product as colourless oil in 76 % yield 1.63 g.

R_f = 0.57 (2:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 5.75 (ddt, J = 17.1, 10.3, 6.7 Hz, 1H, $-\text{CH}=\text{CH}_2$), 5.02-4.94 (m, 2H, $-\text{CH}=\text{CH}_2$), 4.33 (t, J = 5.4 Hz, 1H, $-\text{CH}(\text{OCH}_3)_2$), 3.29 (s, 6H, $-\text{CH}(\text{OCH}_3)_2$), 2.41 (t, J =

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6.9 Hz, 2H, $-\text{CH}_2\text{CO}-$), 2.39 (t, $J = 7.5$ Hz, 2H, $-\text{COCH}_2-$), 2.04 (br qt, $J = 7.2, 1.2$ Hz, 2H, $-\text{CH}_2\text{CH}=\text{CH}_2$), 1.70-1.53 (m, 6H, $-\text{CH}_2-$ x3) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 210.6, 138.0, 115.2, 104.3, 52.7, 42.3, 41.9, 33.1, 31.9, 22.8, 18.8 ppm.

FTIR (neat) : 3076, 2941, 2830, 1713, 1639, 1450, 1371, 1192, 1128, 1070, 914 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_3\text{Na}_1$ $[\text{M} + \text{Na}]^+$: 237.1461. Found: 237.1309.

V-4, (Z)-11,11-dimethoxy-7-oxoundec-2-enenitrile

contain 23% *E* isomer

To a solution of 1,1-dimethoxydec-9-en-5-one (257mg, 1.2 mmol, 1 equiv) in THF (10 mL) under Ar, was added acrylonitrile (48 mg, 0.90 mmol, 1.5 equiv) and Hoveyda-Grubbs 2nd Generation catalyst (38 mg, 0.060 mmol, 5 mol%). The solution was refluxed for 14 days, adding further portion of catalyst at 2 days intervals. The solution was concentrated, redissolved in neat acrylonitrile and concentrated again. The product was purified with silica gel chromatography (hex/EA = 8/1). The product was obtained as pale yellow oil in 40 % isolated yield or 81% convergent yield (116 mg, 0.485 mmol, 23% in *E* isomer), while starting material 1,1-dimethoxydec-9-en-5-one was recovered in 129 mg (0.602 mmol).

$R_f = 0.28$ (2:1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 6.43 (dtd, $J = 10.8, 7.7, 1.1$ Hz, 1H, $-\text{CH}=\text{CHCN}$), 5.31 (dd, $J = 10.9, 1.3$ Hz, 1H, $-\text{CH}=\text{CHCN}$), 4.31 (t, $J = 5.4$ Hz, 1H, $-\text{CH}(\text{OCH}_3)$), 3.27 (s, 6H, $-\text{CH}(\text{OCH}_3)_2$), 2.44-2.36 (m, 6H, $-\text{CH}_2\text{COCH}_2-$ and $-\text{CH}_2\text{CH}=\text{CHCN}$), 1.76-1.67 (m, 2H, $-\text{CH}_2-$), 1.63-1.50 (m, 4H, $-\text{CH}_2-$ x2) ppm.

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^{13}C NMR (75 MHz, CDCl_3): δ 209.5, 154.1, 115.8, 104.2, 100.1, 52.7, 42.3, 41.4, 31.8, 31.2, 21.9, 18.7 ppm.

FTIR (neat) : 2941, 2831, 2220, 1712, 1634, 1622, 1448, 1412, 1375, 1190, 1126, 1070, 745 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{21}\text{O}_3\text{N}_1\text{Na}_1$ $[\text{M} + \text{Na}]^+$: 262.1414. Found: 262.1447.

V-2, Nitrile Spirocyclic core

A mixture of 11,11-dimethoxy-7-oxoundec-2-enenitrile (239mg, 1.0 mmol, 1 equiv), N -((1R,2S)-1-(4-methoxyphenyl)-2-methylbut-3-enyl)hydroxylamine (269mg, 1.3 mmol, 1.3 equiv), AcOH (2 mL) and water (0.5 mL) was stirred for 12 h at rt. The solvent was then removed under reduced pressure. It was dissolved with 2 mL of CH_2Cl_2 and 1 mL of H_2O . $\text{NH}_2\text{OH}\cdot\text{HCl}$ (2.6 mmol, 2 equiv) and NaOAc (2.6 mmol, 2equiv) was then added, and the mixture was stirred vigorously for 24 h at rt. The reaction mixture was then concentrated under reduced pressure and it was partitioned between CH_2Cl_2 (20 mL) and 1.0 M NaOH (5 mL). The aqueous layer was further extracted 3 times with CH_2Cl_2 (20 mL each) and the combined organic layer was washed with sat aq NaCl and dried over anhyd MgSO_4 . The solvent was then removed *in vacuo* and the product was dissolved in 20 mL toluene and refluxed to 180°C for 2.5 h in a sealed tube. The reaction mixture was then concentrated under reduced pressure and purified with silica gel column chromatography (eluent = 20:1 hexane/EA). The product was obtained in 53% yield (131 mg, 0.53 mmol) as colourless oil.

R_f = 0.55 (4:1 hexane/EA) and 0.48 (100% CH_2Cl_2)

^1H NMR (400 MHz, CDCl_3): δ 5.47 (dqt, J = 15.2, 6.3, 1.1 Hz, 1H, $-\text{CH}=\text{CHCH}_3$), 5.38 (dtq, J = 15.2, 7.6, 1.5 Hz, 1H, $-\text{CH}=\text{CHCH}_3$), 4.71 (dt, J = 6.5, 2.5 Hz, 1H, $-\text{CH}(\text{O}-)-$), 3.43 (dd, J =

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6.4, 1.7 Hz, 1H, -CH(-)CN), 2.61-2.56 (m, 1H), 2.39 (ddt, $J = 12.0, 9.0, 3.1$ Hz, 1H, -CH(N-)-), 2.18 (ddt, $J = 14.7, 3.9, 2.6$ Hz, 1H), 2.02-1.92 (m, 2H), 1.88-1.75 (m, 4H), 1.69-1.53 (m, 8H), 1.29 (qt, $J = 13.5, 3.6$ Hz, 1H), 1.14-1.05 (m, 1H) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 127.8, 127.4, 117.9, 75.7, 65.5, 65.5, 38.1, 37.5, 36.1, 32.4, 29.4, 27.2, 19.2, 18.0, 17.6 ppm.

FTIR (neat) : 2938, 2855, 2239, 1441, 1375, 1356, 1250, 1238, 1084, 968, 932 cm^{-1} .

HRMS EI Calcd for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}$ $[\text{M}]^+$:246.1727 . Found: 246.1725 .

$[\alpha]_{\text{D}} = -120.6$ ($c = 0.9$, EtOH)

V-9, dialdehyde spirocyclic core

To a solution of nitrile (120 mg, 0.50 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) at -78°C with vigorous stirring, was added DIBAL-H (1.0M in heptane, 0.60 mL, 0.60 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred for 2 h at -78°C and it was quenched by adding MeOH (0.5 mL) at -78°C . Saturated potassium sodium tartrate (10 mL) was then added and the reaction mixture was stirred at rt for 30 min. The reaction mixture was extracted with diethylether 3 times (20 mL each) and the combined organic layer was washed with sat aq NaCl and dried over anhyd MgSO_4 .

The organic layer was then concentrated under reduced pressure and it was redissolved in CH_2Cl_2 (5 mL) and cooled to -78°C . The reaction mixture was ozonized while the progress of the reaction was monitored with TLC. When the reaction was completed, reaction mixture was purged with N_2 gas for 1 min and dimethylsulphite (1 mL) was added. The reaction mixture was stirred at -78°C for another 12 h, at 0°C for 24 h. The reaction mixture was then concentrated under reduced pressure and purified with silica gel

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chromatography (4:1 hexane/EA). The product was obtained in 80% yield (95 mg, 0.40 mmol) as colourless oil.

R_f = 0.38 (1: 1 hexane/ethyl acetate)

^1H NMR (400 MHz, CDCl_3): δ 10.01 (d, J = 2.6 Hz, 1H, -CHCHO), 9.82 (t, J = 2.0 Hz, 1H, -CH₂CHO), 4.77 (t, J = 5.6 Hz, 1H, -CH(O-)-), 3.33-3.31 (m, 1H, -CH(-)CHO), 3.15 (br dtd, J = 14.8, 6.2, 3.3 Hz, 1H, -CH(N-)-), 2.86 (ddd, J = 16.3, 5.1, 2.4 Hz, 1H, -CH₂CHO), 2.50 (ddd, J = 16.3, 6.3, 1.8 Hz), 2.13 (br dq, J = 14.4, 2.7 Hz, 1H), 2.08-1.97 (m, 1H), 1.81-.124 (m, 10H) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 202.1, 200.8, 76.0, 65.6, 60.7, 56.4, 49.3, 35.9, 32.3, 30.9, 26.6, 19.1 and 18.1 ppm.

FTIR (neat) : 2940, 2868, 2731, 1715, 1449, 1304, 1269, 1107, 922, 735 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{13}\text{H}_{19}\text{O}_3\text{N}_1\text{Na}$ $[\text{M}+\text{Na}]^+$: 260.1257. Found: 260.1277.

$[\alpha]_D = -192.5$ (c = 0.80, EtOH)

V-1, (-)-perhydrohistrionicotoxin

To a solution of phosphonium salt (0.307g, 0.8 mmol, 8 equiv) in 2 mL of THF under vigorously stirring at -78°C , were added *n*-BuLi (1.6 M, 0.5 mL, 0.8 mmol, 8 equiv) dropwise. The reaction mixture was stirred at -78°C for 2 h, stirred at 0°C for 1h, and it was cooled to -78°C . A solution of dialdehyde, (24 mg, 0.1 mmol, 1 equiv) in 2 mL of THF was then added dropwise. The reaction mixture was stirred at -78°C for 2 h and 0°C for 2h. It was then quenched by adding 10 mL sat aq NH_4Cl solution and extracted with Et_2O (20 mL x 3) three times. The combine organic solvent was washed with saturated NaHCO_3 solution and Brine.

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It was dried over anhyd MgSO_4 . The product concentrated and purified with silica gel column chromatography (eluent: hex/EA = 20/1) . (R_f = 0.53 at EA/Hexane = 1/4)

A mixture of the purified product, Pd/C (0.04 mmol, 0.4 equiv), and MeOH (3 mL) were stirred under H_2 for 12 h. The reaction mixture was then concentrated under reduce pressure and it was filter over celite using 20 mL CH_2Cl_2 as solvent. The filtrate was washed with 20 mL of pH 7 buffer and dried over anhyd Na_2SO_4 . The solvent was then removed *in vacuo* and the product was obtained in 54% yield (16 mg, 0.054 mmol) as a colourless oil.

R_f = 0.12 (95/5 CH_2Cl_2 / MeOH)

^1H NMR (500 MHz, CDCl_3): δ 3.94 (d, J = 2.2 Hz, 1H, -CH(OH)-), 2.95-2.92 (m, 1H, -CH(NH)-), 2.21 (d, J = 9.7 Hz, 1H), 2.04 (qt, J = 13.8, 4.2 Hz, 1H), 1.81 (dt, J = 14.0, 2.6 Hz, 1H), 1.75 (dq, J = 13.1, 2.9 Hz, 1H), 1.68-1.46 (m, 6H), 1.41-1.20 (m, 15H), 1.12-.1.05 (m, 1H), 0.90 (t, J = 6.8 Hz, 3H), 0.87 (J = 7.2 Hz, 3H), 0.84-0.73 (m, 1H) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 69.9, 55.5, 50.2, 38.1, 38.1, 37.3, 37.2, 33.7, 32.1, 30.3, 27.7, 27.6, 25.6, 23.1, 22.5, 19.5, 15.2, 14.1, 14.1 ppm.

FTIR (neat) : 3415, 2933, 1466, 1196, 1177 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{38}\text{NO}$ $[\text{M}+1]^+$: 296.2948. Found: 296.3023.

$[\alpha]_D = -82.9$ (c = 0.12 , CH_2Cl_2)

APPENDIX

List of Publication

International Publications- Scientific Journals

1. General and practical approach to the syntheses of linear homoallylic alcohols.
Cheng, H. S.; Loh, T. P. *Pure and Applied Chemistry* **2005**, 77, 1199-1206.
2. Diastereoselective allylation of planar chiral substituted ferrocenecarboxaldehyde: an efficient entry to chiral ferrocenyl ligands. Li, H.; Cheng, H. S.; Seow, A. H. *Tetrahedron Lett.*, **2007**, 48, 2209-2211.
3. Homoallylic nitron isomerization: Convenient enantioselective synthesis of homoallylic nitrones and homoallylic hydroxylamines. Cheng, H. S., Seow, A. H., Loh, T. P. *Org. Lett.* **2008**, 10, 2805-2807.
4. Aza-Prins cyclization and total synthesis of (–)-indolizidines 209 B: Cheng, H. S.; Seow, A. H.; Loh, T. P. Manuscript in preparation.
5. Total synthesis of (–)-Perhyrohistronicotoxin: Cheng, H. S.; Loh, T. P. Manuscript in preparation.

International Conference

6. Singapore International Chemical Conference 4. Synthetic Studies Towards Total Synthesis of Calvine. **Hin-Soon Cheng**. Teck-Peng Loh, Singapore 2005
7. 5. Singapore International Chemical Conference 4. Stereochemical studies using ferrocene-based chiral carbocation. Ai-Hua Seow, **Hin-Soon Cheng**, Hao Li, Teck-Peng Loh, Singapore 2005
8. Singapore International Symposium (SIS2006) *Advances in Materials & Chemicals* Asymmetric synthesis of amine derivatives using ferrocene-based chiral carbocation. Ai-Hua Seow, **Hin-Soon Cheng**, Hao Li, Teck-Peng Loh, Singapore 2006.
9. 40th National Organic Chemistry Symposium. Total Synthesis of (–)-indolizidine 209B via aza-Prins Cyclization. **Hin-Soon Cheng**, Hao Li, Teck-Peng Loh, Durham USA, 2007.