PART I : DEVELOPMENT OF NOVEL METHODS FOR THE SYNTHESIS OF HOMOALLYLIC ALCOHOLS

PART II : MULTIGRAM SYNTHESIS OF (–)-EPIBATIDINE

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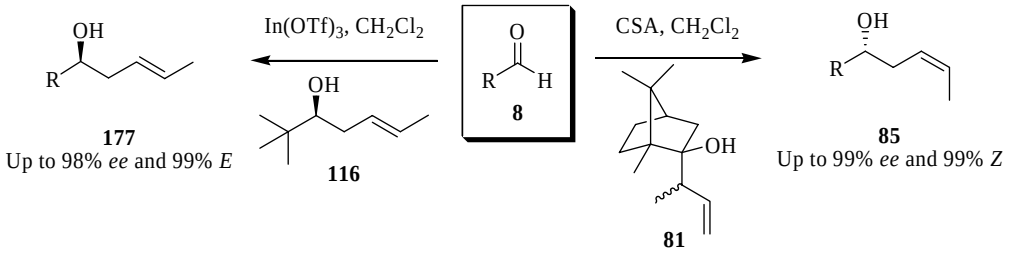
SUMMARY

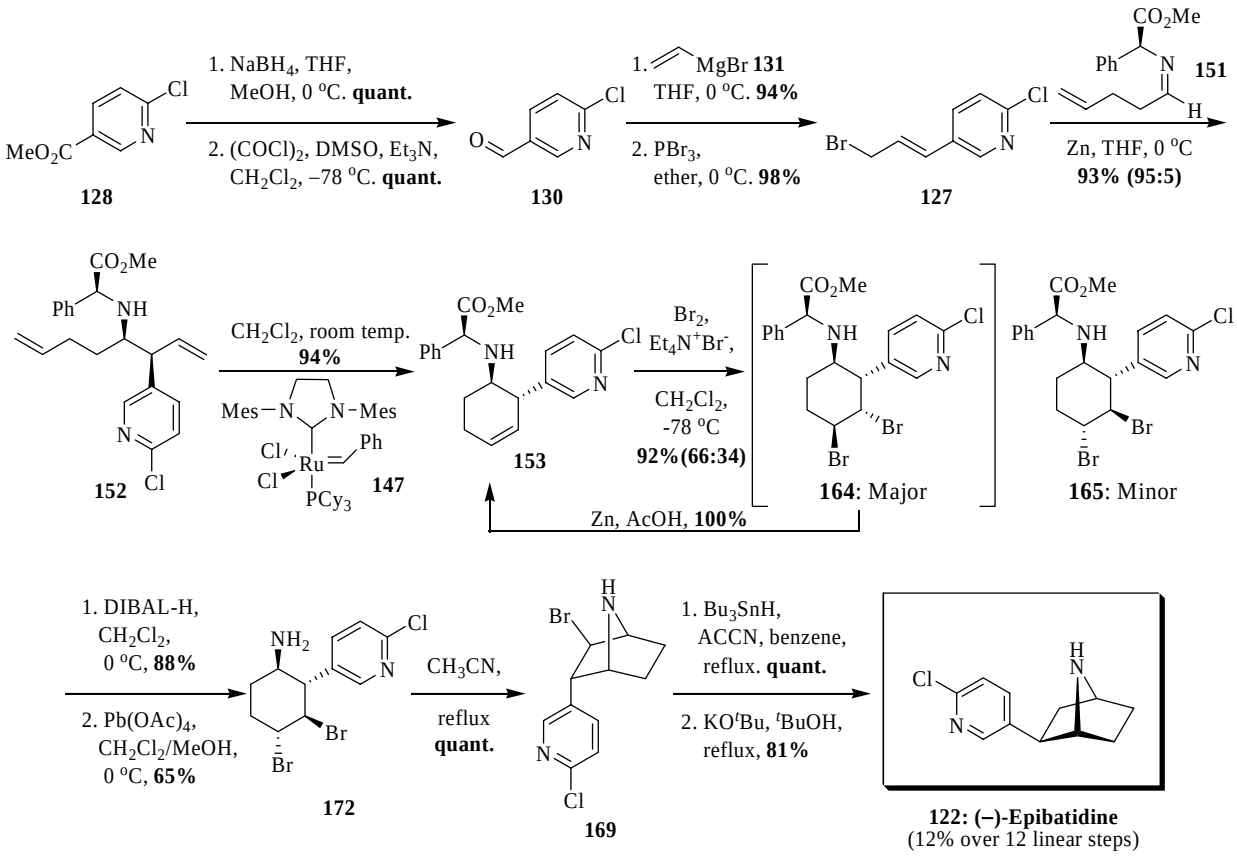
PART I: Development of Novel Methods for the Synthesis of Homoallylic Alcohols

In the development of novel methods for the synthesis of homoallylic alcohols, two conceptual strategies to access *cis*- and *trans*-linear homoallylic alcohols will be revealed. The first methodology reveals a conceptually different strategy to access *cis*-linear homoallylic alcohols with moderate to high yields. This approach features the following highlights: (1) First efficient method that controls, in situ, both the enantioselectivity (up to 99% *ee*) and the olefinic geometry (up to 99% *Z*) of *cis*-linear homoallylic alcohols; (2) The chemoselective crotyl transfer is highly feasible for aliphatic substrates; (3) Excess chiral camphor-derived branched homoallylic alcohol (89% recovery) and the camphor (83% recovery) generated from the reaction can be recovered and reused, thus, making this method attractive for scale-up preparation. We anticipate that this new Brönsted acid catalyzed allyl transfer reaction will be an indispensable tool in the synthesis of complex natural products, thereby allowing this methodology to undergo an exciting renaissance as a synthetic method.



The second methodology describes a novel Lewis acid-catalyzed enantioselective linear homoallylic alcohol transfer reaction, from sterically hindered starting material to its sterically less hindered analogue *via* a branched-adduct intermediate. In all cases, the whole rearrangement is thermodynamically favorable and a steric effect is the driving force of this reaction. The preservation of the stereocenter and olefin geometry together with the isolation of the branched-adduct homoallylic alcohols in one isomeric form have warranted the proposed mechanism.

PART II: Multigram Synthesis of (–)-Epibatidine



In the next chapter, a short and multigram scale process has been developed for the synthesis of (–)-epibatidine from commercially available starting materials using mild

and easily controlled reactions. There are several significant features in this synthetic route: (1) the synthesis of (–)-epibatidine requires only a total of 12 steps and delivers the alkaloid with a 12% yield over the longest linear sequence; (2) both enantiomers of epibatidine can be obtained by simply switching the chiral auxiliary; (3) the facile method of obtaining enantiomerically pure cyclohexenylamines and the first RCM of unprotected amines have been achieved; (4) the bottleneck of the synthesis, the bromination procedure, was overcame by recycling the undesired **164** to **153** through a reductive elimination of the former; (5) the entire synthetic route is straightforward and convenient for gram scale synthesis.

LIST OF ABBREVIATIONS

Ac	acetyl
ACCN	1,1'Azobis(cyclohexanecarbonitrile)
AIBN	2,2'-Azobisisobutyronitrile
aq	aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	butoxycarbonyl
Br-CSA	(1*S*)-(+)-3-bromocamphor-10-sulfonic acid hydrate
brs	broad singlet
c	concentration (100mg/1mL)
calcd	calculated
CH_3CN	acetonitrile
CITES	Convention on International Trade in Endangered Species
CSA	(1*R*)-(-)-10-camphorsulfonic acid
d	density
d	doublet
dd	doublet of a doublet
ddd	doublet of a doublet of a doublet
dddd	doublet of a doublet of a doublet of a doublet
de	diastereoselectivity excess
DIBAL-H	dissiobutylaluminium hydride
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of a triplet
ee	enantioselectivity excess
EI	electron ionisation

equiv.	equivalents
Et	ethyl
FTIR	fourier transform infrared spectroscopy
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
LDA	lithium dissopropylamide
M	molar
m	multiplet
m/z	mass to charge ratio
Me	methyl
MHz	megahertz
min	minute
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
$OAcCF_3$	trifluoro-acetyl acetonate
OTf	triflate (trifluoromethanesulfonate)
Ph	phenyl
ppm	part per million
pTSA	*para*-toluenesulfonic acid
q	quartet
RCM	ring closing metathesis
R_f	retardation factor
s	singlet
SAR	structure activity relationship
t	triplet
^{t}Bu	*tert*-but(yl)
tert	tertiary

Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoromethanesulfonyl acid
THF	tetrahydrofuran
TIPS	triisoproplysilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet

PART I

Enantioselective Allyl Transfer

1.1 INTRODUCTION

Over the last few decades, homoallylic alcohols have become an indispensable moiety for the construction of complex organic molecules, securing their widespread involvement in both natural products and medicinal agent synthesis.[1] Being important building blocks and versatile synthons, homoallylic alcohols are featured in many medicinal agents such as prostaglandin E_3,[2] prostaglandin F_{3a},[2] (+)-amphidinolide K,[3] and leukotriene B_4,[4] etc (Figure 1).

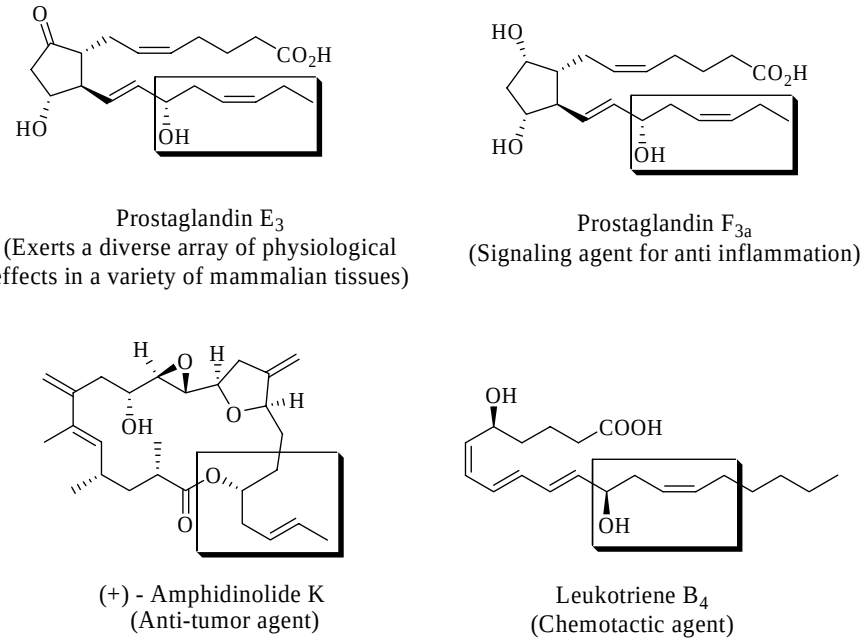


Figure 1. Importance of homoallylic alcohols.

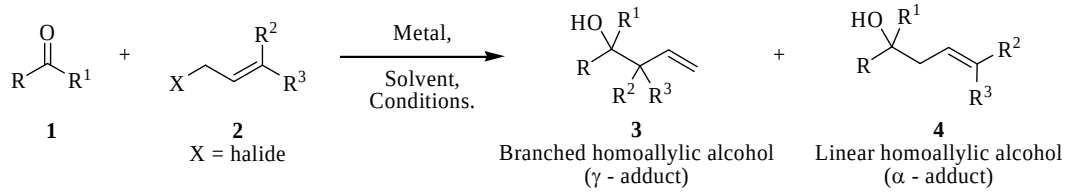
[1] (a) Nicolaou, K. C.; Kim, D. W.; Baati. R. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701. (b) Hornberger, K. R.; Hamblet, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. (c) Felpin, F. X.; Lebreton. J. *J. Org. Chem.* **2002**, *67*, 9192.

[2] (a) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490. (b) Corey, E. J.; Albonico, S. M.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491. (c) Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc.* **1984**, *106*, 3875.

[3] William, D. R.; Meyer, K. G. J. Am. Chem. Soc. **2001**, *123*, 765.

[4] For the first total synthesis, see: (a) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984. For a recent stereocontrolled total synthesis, see: (b) Kerdesky, F.; Schmidt, S. P.; Brooks, D. W. *J. Org. Chem.* **1993**, *58*, 3516.

Among the many methods for the synthesis of homoallylic alcohols, the most frequently employed methodology is the allylation of aldehydes and ketones with allylic metals (Scheme 1).[5] The use of organometallic reagents is today so common that hardly any synthesis is now completed without the inclusion of at least one step involving an organometallic reagent. Beginning in the late 1970s, considerable synthetic interest began to surface in the control of the stereochemistry of C – C bond formation in the reactions of allylmetals with aldehydes and ketones. This widespread use of allylic organometallics in stereocontrolled organic synthesis appears to have been triggered by three papers: Heathcock's breakthrough that the Hiyama (*E*)-crotylchromium reagent undergoes highly anti-selective addition to aldehydes (Scheme 2);[6a] Hoffmann's discovery that (*Z*)-crotylboronates produce *syn*-homoallylic alcohols stereoselectively;[6b] and Yamamoto's innovation that the Lewis acid mediated reaction of crotyltins with aldehydes produces *syn*-homoallylic alcohols regardless of the initial geometry of the double bond of the allylic tins (Scheme 3).[6c]

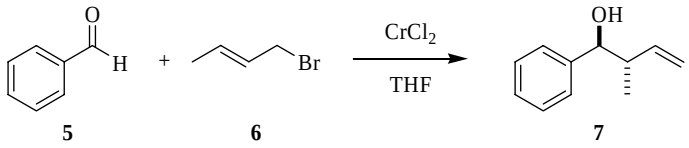


1 **2** X = halide **3** Branched homoallylic alcohol (γ - adduct) **4** Linear homoallylic alcohol (α - adduct)

Scheme 1. Metal mediated allylation of aldehydes and ketones.

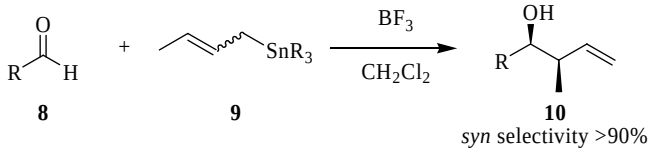
[5] (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1 – 53. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

[6] (a) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (b) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306. (c) Yamamoto, Y.; Yatagi, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc*. **1980**, *102*, 7107.



5 **6** **7**

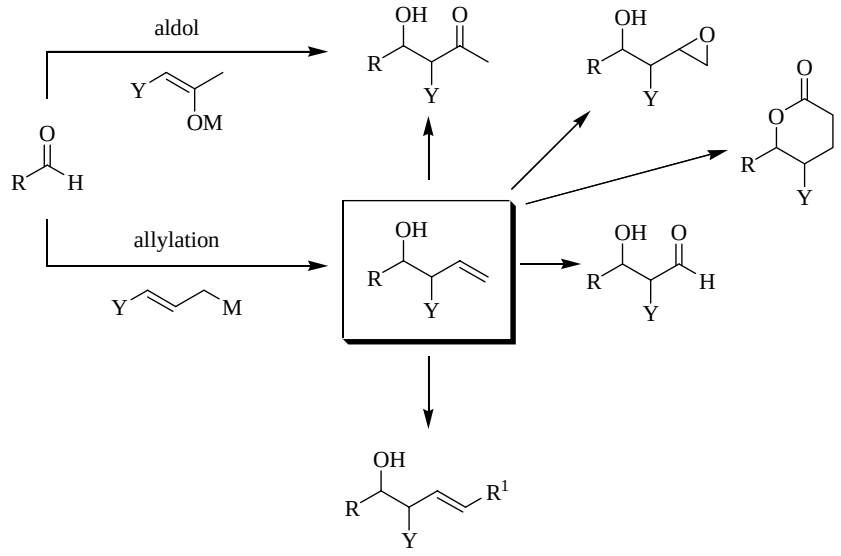
Scheme 2. Heathcock's discovery of *anti*-selective addition to aldehydes.



8 **9** **10**
syn selectivity >90%

Scheme 3. Yamamoto's report on addition of crotyltrialkyltins to aldehydes.

From a synthetic point of view, the ready formation of homoallylic alcohols into the corresponding aldols renders the addition of organometallic allylic reagents to carbonyls complementary to the aldol additions of metal enolates. Furthermore, the great versatility of the alkene functionality, which is capable of the conversion to aldehydes *via* ozonolysis, the facile one-carbon homologation to δ-lactones *via* hydroformylation, the selective epoxidation for introduction of a third stereogenic center, or the cross olefin metathesis to various linear homoallylic alcohol fragments, offers the additions of allylic metals a considerable advantage over the aldol counterpart (Scheme 4).

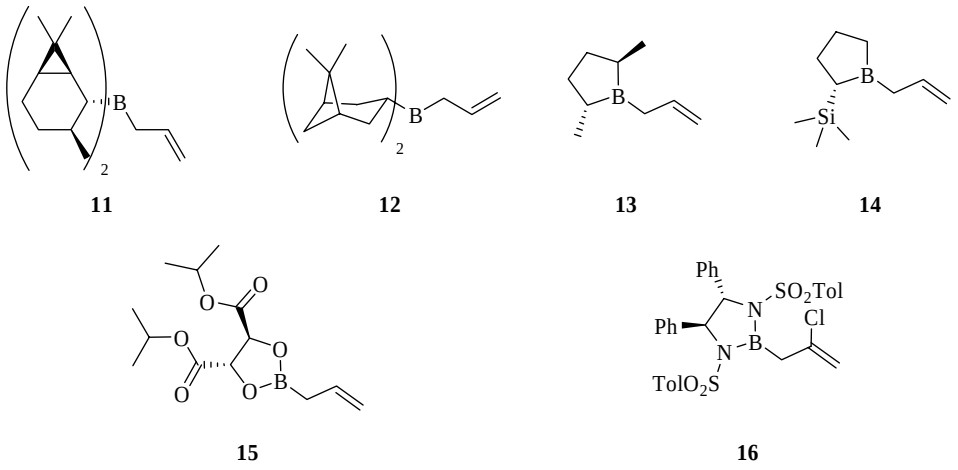


Scheme 4. Versatile building block – homoallylic alcohol.

The development of new highly enantioselective C – C bond formation methods is therefore an utmost task to organic chemists.[7] In this aspect, extensive efforts have been devoted to the exploration of chiral reagents and catalysts for the carbonyl-allylation and carbonyl-ene reactions, since the resulting homoallylic alcohols are versatile building blocks in the synthesis of many natural products and pharmaceuticals.[5,8] In the past two decades, several asymmetric allylation methods have been developed based on either chiral allylation reagents or chiral catalysts.

[7] Ojima, I. In *Catalytic Asymmetric Synthesis*; 2nd Ed.; Wiley-VCH, 2000; pp 465 – 498.
[8] Mikami, K.; Shimuzu, M. *Chem. Rev.* **1992**, *92*, 1021.

The most well studied and widely used chiral allylation reagents are allylboranes.[9] A series of chiral *B*-allylborolanes have been successfully developed (Figure 2). These chiral reagents have been frequently utilized in several natural product syntheses (Scheme 5).

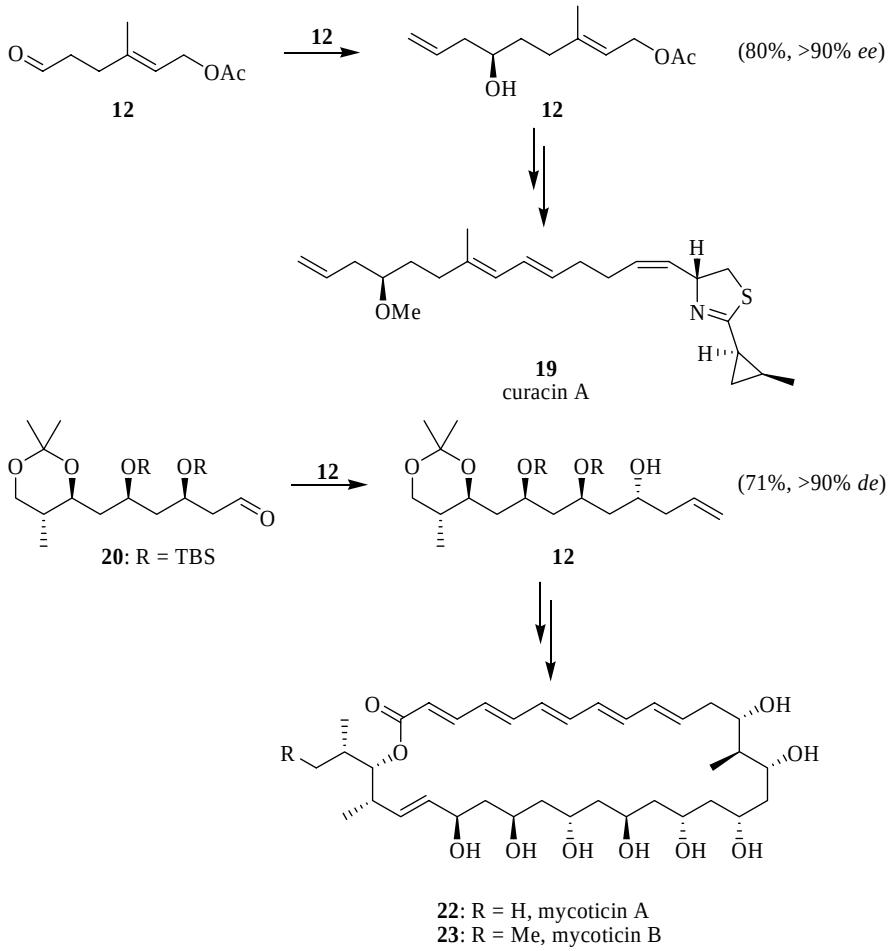


11 **12** **13** **14**

15 **16**

Figure 2. Representative chiral *B*-allylborolanes.

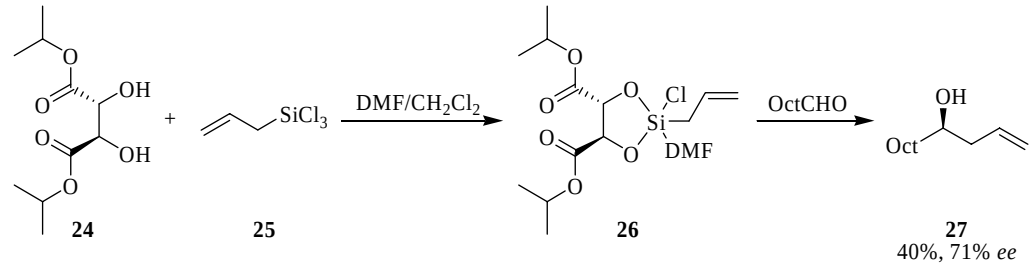
[9] (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. (c) Ito, H.; Tanikawa, S.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 1795. (d) Schreiber, S.; Groulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (e) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (f) Roush, W. R.; Hoong, L. K.; Palmer, M. A. G.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109.



Scheme 5. Application of chiral *B*-allylborolanes in natural product synthesis.

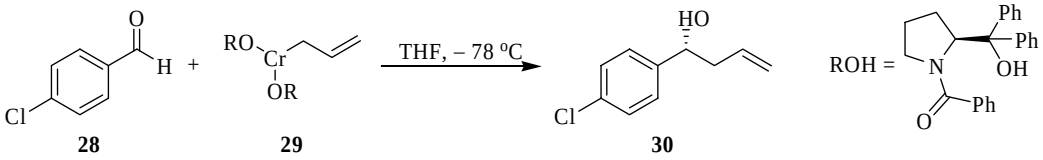
Besides the extensively studied allylborane reagents, many other chiral allylation reagents have also attracted substantial attention, and been well-developed. For instance, allyltrichlorosilane, pretreated with (+)-diisopropyl tartrate, has been used to react with aldehydes, and affords optically active alcohols with up to 71% *ee* (Scheme 6).[10]

[10] Wang, Z.; Wang, D.; Sui, X. J. *J. Chem, Soc., Chem. Commun.* **1996**, 2261.



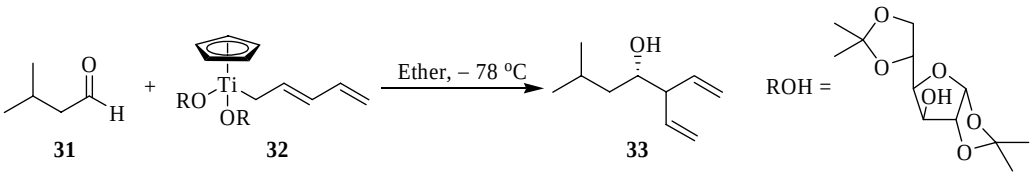
Scheme 6. Chiral allylsilane reagent for allylation.

A dialkoxyallylchromium complex possessing *N*-benzoyl-*L*-proline gave excellent stereoselectivity in the allylation reaction with aldehydes (Scheme 7).[11]



Scheme 7. Chiral allylchromium reagent for allylation.

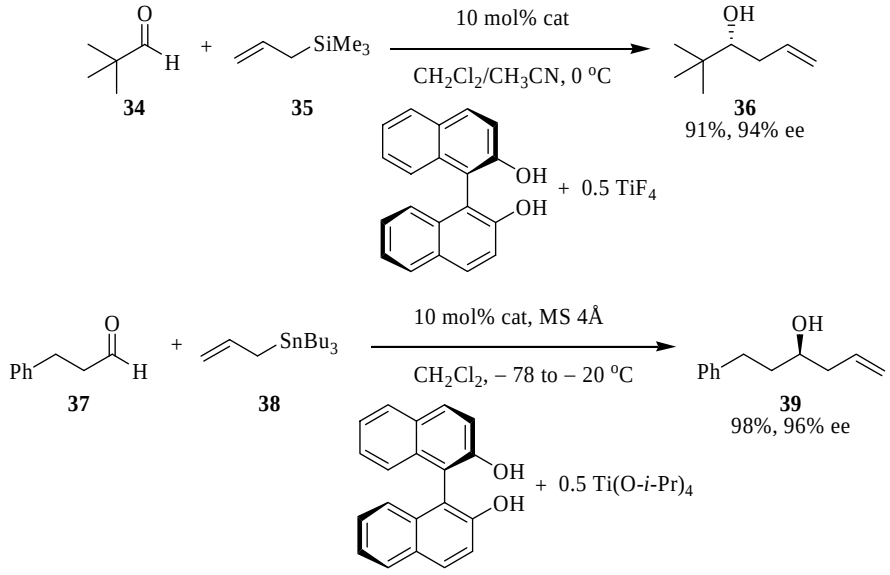
Organotitanates modified with a carbohydrate auxiliary were also successfully applied to the enantioselective allylations of aldehydes (Scheme 8).[12]



Scheme 8. Chiral allyltitanium reagent for allylation.

[11] Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322.
[12] Riediker, M.; Duthaler, R. O. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 494.

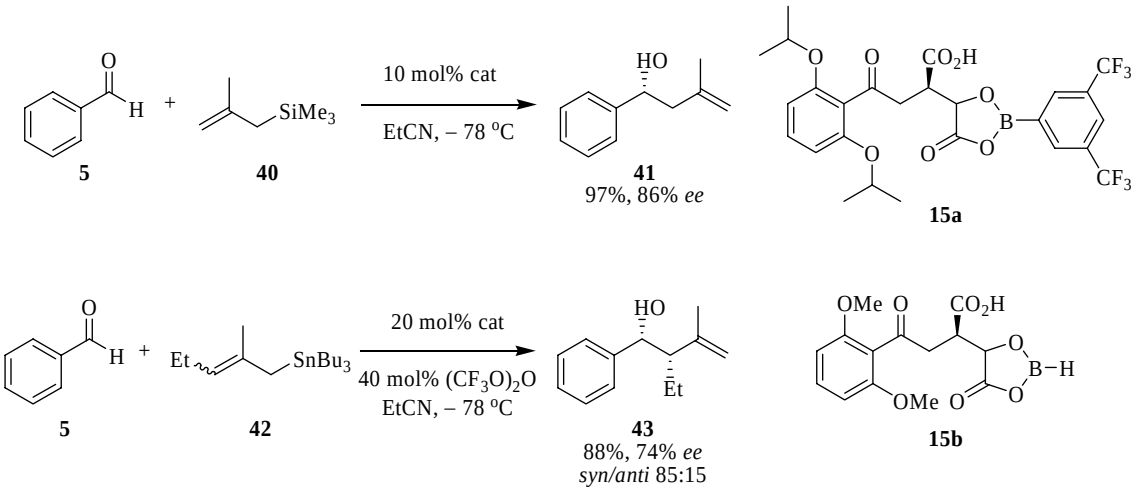
On the other hand, several enantioselective catalytic allylation methods have been developed. Various BINOL-based titanium complexes have been demonstrated to catalyze the enantioselective addition of aldehydes with allylstannanes or allylic silanes (Scheme 9).[13]



Scheme 9. Allylation catalyzed by BINOL-based titanium complexes.

In the presence of a chiral (Acyloxy)borane (CAB) complex, derived from tartaric acid, allylic silanes or allylic stannanes can react with aldehydes to produce the corresponding homoallylic alcohols in good yield and high enantioselectivity (Scheme 10).[14]

[13] (a) Gauthier, D. R. Jr.; Carreira, E. M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2363. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am Chem. Soc.* **1993**, *115*, 8467.
[14] (a) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. (b) Marchall, J. A.; Tang, Y. *Synlett* **1992**, 653.

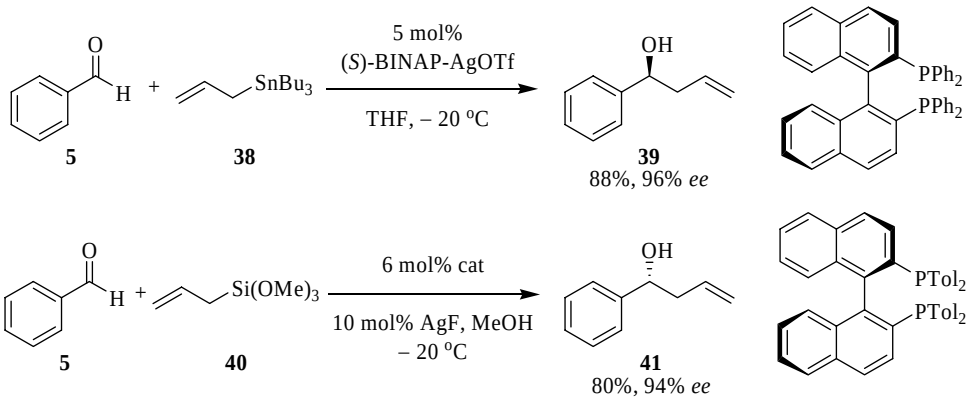


5 **40** **41** 97%, 86% *ee* **15a**

5 **42** **43** 88%, 74% *ee* *syn/anti* 85:15 **15b**

Scheme 10. Allylation catalyzed by CAB complexes.

Recently, Yamamoto *et al.* reported that BINAP-Ag complexes are efficient chiral catalysts for enantioselective allylation reactions (Scheme 11).[15] Our group found out that this complex can catalyze enantioselective allylation in aqueous medium ($EtOH/H_2O$, v/v 9:1).[16] This represents the first report of a catalytic enantioselective allylation in aqueous medium.



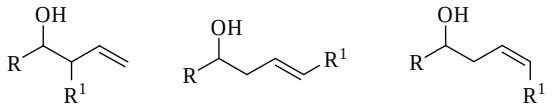
5 **38** **39** 88%, 96% *ee*

5 **40** **41** 80%, 94% *ee*

Scheme 11. Allylation catalyzed by BINAP-Ag complexes.

[15] (a) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (b) Yanagisawa, A.; Kageyama, H.; Ishiba, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 3701.
[16] Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *41*, 5261.

Our group has always been very interested in the development of enantioselective synthesis of homoallylic alcohols, especially the linear adducts. In fact, we are very much concerned with the stereocontrol of the C – OH bond and the olefinic geometry. Even though extensive efforts have been devoted to the exploration of chiral reagents and catalysts for the carbonyl-allylation and carbonyl-ene reactions to produce homoallylic alcohols, almost all current methods produce branched (γ-adducts) homoallylic alcohols **42** exclusively,[17] except for a few special cases, hence limiting access to the linear (α-adducts) homoallylic alcohols **43** and **44** (Figure 3).[18]



42 **43** **44**

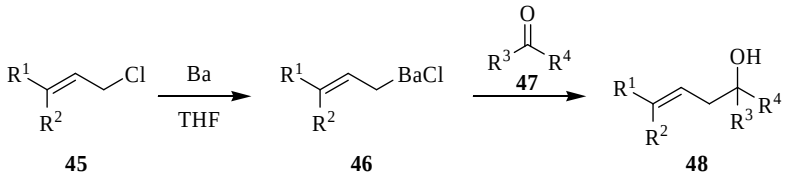
Figure 3. Various regioisomers of homoallylic alcohols.

[17] For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Helmchen, G.; Hoffmann, R.; Mulzer, J.; Schaumann, E. Eds. In Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Werl), 21st ed; Thieme Stuttgart: New York, 1996; Vol. 3, pp 1357-1602. (c) Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, *103*, 2763.

[18] For some examples, see: (a) Nokami, J.; Yoshizane, K.; Matsuura H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Tan, K. T.; Cheng, H. S.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (c) Loh, T. P.; Lee, C. L. K.; Tan, K. T. *Org. Lett.* **2002**, *17*, 2985. (d) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 4990. (e) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, A. *Chem. Commun*. **2001**, 387. (f) Okuma, K.; Tanaka, Y.; Ohta, H.; Matsuyama, H. *Heterocycles*, **1993**, *1*, 37.

In general, four common strategies are employed for the synthesis of linear homoallylic alcohols, namely, barium-mediated allylation (Scheme 12),[19] Lewis acid catalyzed ene-reactions of chiral glyoxylates (Scheme 13),[20] transmetallation (Scheme 14)[21] and thermodynamic conversion from the corresponding kinetic branched homoallylic alcohol adduct (Scheme 15).[22]

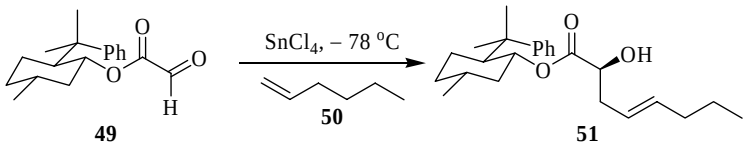
The strict anhydrous procedure of barium-mediated allylation limits its application, and moreover, the reaction is difficult to handle due to its sensitivity towards moisture. More importantly, there is no asymmetric version for this labor intensive methodology.



Scheme 12. Barium-mediated allylation.

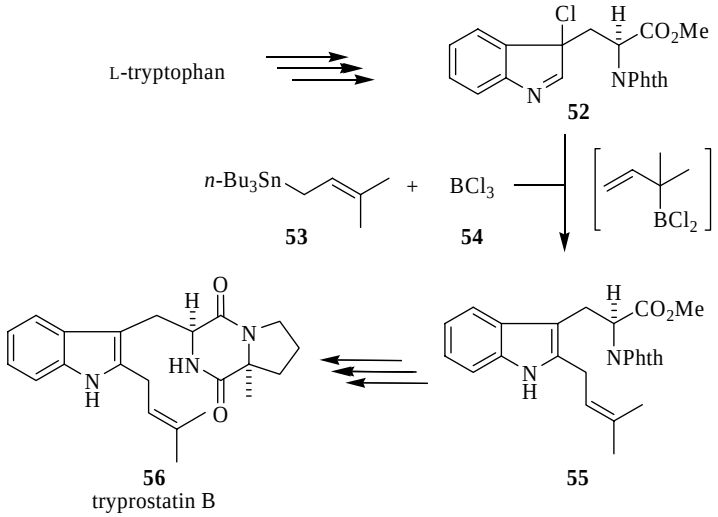
As for the ene-reaction, the limitation in substrates confines this method to a limited scope of homoallylic alcohols. The high specificity to substrate associated with transmetallation method also reduces the application of this strategy.

[19] Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.
[20] (a) Whitesell, J. K.; Lawrence, R. M.; Chen, H.-H. *J. Org. Chem.* **1986**, *57*, 4779. (b) Whitesell, J. K. *Acc. Chem. Res.* **1985**, *18*, 280, and references cited therein.
[21] (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152. (b) Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463.
[22] Hong, B.-C.; Hong, J.-H.; Tsai, Y.-C. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 468.



49 **50** **51**

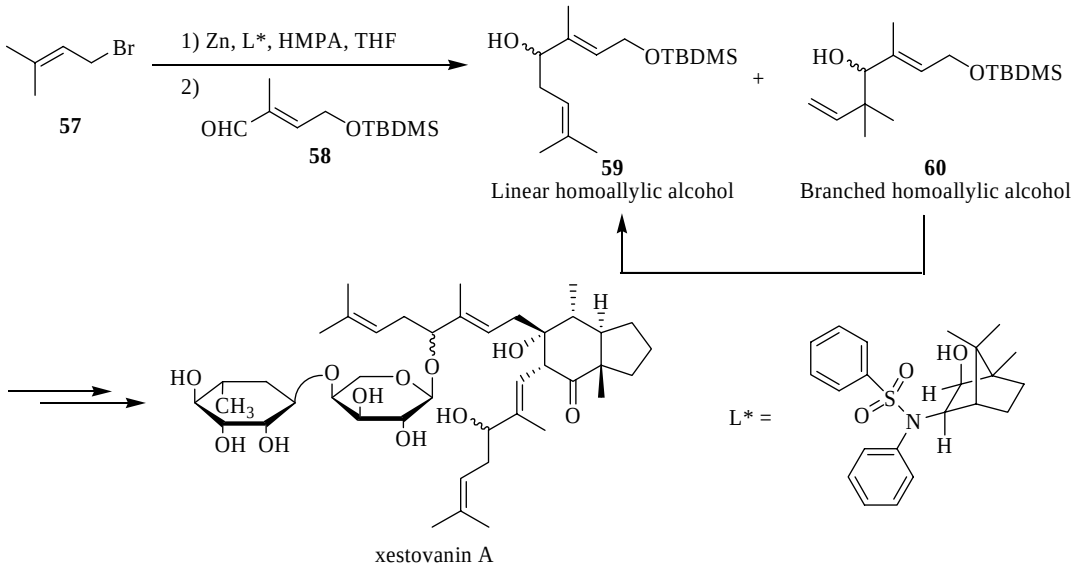
Scheme 13. Asymmetric ene-reaction of chiral glyoxylates.



52 **53** **54** **56** tryprostatin B **55**

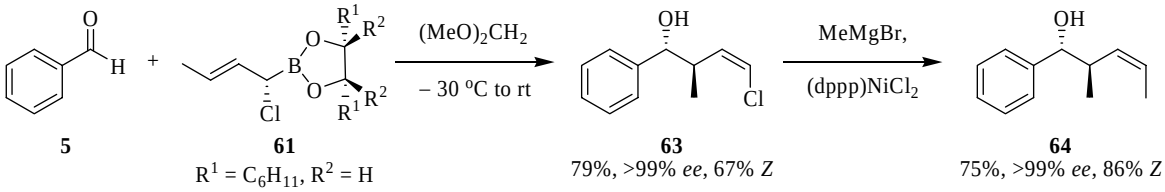
Scheme 14. Transmetallation method in the synthesis of tryprostatin B.

Therefore, the thermodynamically-controlled conversion of a branched homoallylic alcohol to its corresponding linear homoallylic alcohol appears to be an appealing complementary approach. For example, Hong *et al*. demonstrated such an example in their synthesis of xestovanin A (Scheme 15).



Scheme 15. Thermodynamic conversion in the synthesis of rosiridol A.

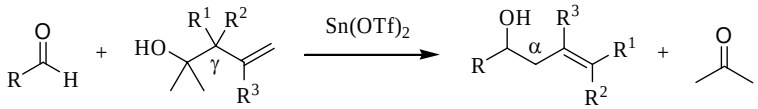
Despite tremendous advances achieved in the past two decades, there are no general and yet efficient methods developed that exhibit α-regioselectivity. Hoffmann *et al.* had demonstrated that *cis*-linear homoallylic alcohols could be obtained in a two-step pathway: an allylboration reaction with α-substituted allylboronates followed by a coupling reaction catalyzed by nickel (Scheme 16).[23]



Scheme 16. Hoffmann's two-step methodology to prepare *cis*-linear homoallylic alcohol.

[23] (a) Hoffmann, R. W.; Giesen, V.; Fuest, M. *Liebigs Ann. Chem.* **1933**, 629. (b) Stürmer, R.; Hoffmann, R. W. *Synlett* **1990**, 759.

Recently, Nokami *et al.* disclosed a novel concept in the α-regiospecific allylation of aldehydes *via* a $Sn(OTf)_2$-catalyzed allyl transfer reaction from the corresponding branched (γ-adducts) homoallylic alcohols **X** derived from acetone (Scheme 17).[24] Other branched homoallylic alcohol donors derived from 2-butanone, cyclohexanone and cyclopentanone were found to exert a similar effect as that derived from acetone **67**, but a drop in reactivity was observed as steric encumbrance of the γ-adduct increases.

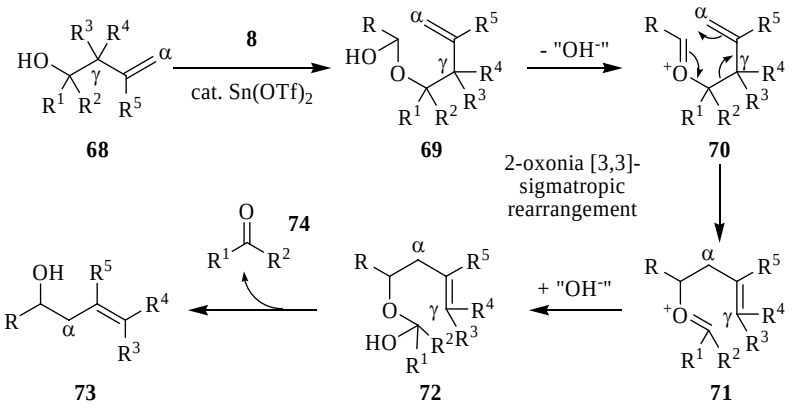


8 **65** **66** **67**

Scheme 17. $Sn(OTf)_2$ catalyzed allyl transfer by Nokami *et al.*

Subsequently, Nokami *et al.* further developed the method into a strategy for the $Sn(OTf)_2$-catalyzed conversion of the kinetic branched homoallylic alcohol **65** to the corresponding thermodynamic linear homoallylic alcohol **66**, in the presence of a catalytic amount of the parent aldehyde **8**.[25] The mechanism for this allyl transfer reaction was postulated to proceed *via* an oxycarbenium ion intermediate **70** that undergoes a 2-oxonia [3,3]-sigmatropic rearrangement[26] as shown in Scheme 18.

[24] (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. I. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Nokami, J.; Nomiyama, K.; Shafi, S. M.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261.
[25] Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310.
[26] (a) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748. (b) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.



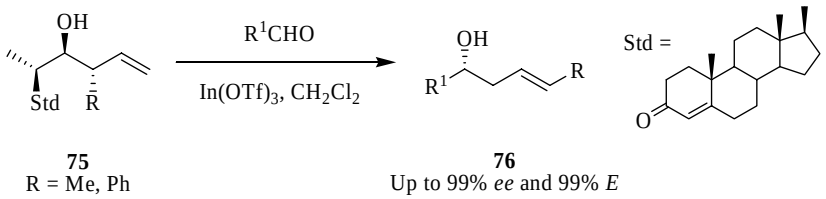
In the case where $R^1 = R = R^2 = H$, the sequence degenerates to conversion of the γ–adduct of homoallylic alcohol to the corresponding α–adduct

Scheme 18. Proposed mechanism for the allyl transfer reaction.

It was also suggested that the reaction could be driven toward products derived from the most stable cations or those containing sterically less hindered homoallylic alcohols and/or thermodynamically more stable olefins. These findings supplied new opportunities for the development of linear homoallylic alcohols.

In our laboratory, chiral branched homoallylic sterols successfully transferred their chirality and allyl species to other aldehydes for the preparation of optically active linear homoallylic alcohols as depicted in Scheme 19.[27] Allyl transfer reactions using these chiral branched homoallylic sterols afforded desired linear homoallylic alcohols in both excellent enantioselectivities and olefinic geometry (*trans*).

[27] Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett.* **2001**, *42*, 9277.



75
R = Me, Ph

76
Up to 99% *ee* and 99% *E*

Scheme 19. Allyl transfer from γ-adduct 22β-sterol to various aldehydes.

While the enantioselective crotyl transfer reactions developed by Nokami[28] and our group have been shown to be useful for the synthesis of *trans*-linear homoallylic alcohols, there are no reported examples for a one-pot synthesis of enantiomerically *cis*-linear homoallylic alcohols.

Based on Scheme 19, it can be concluded that if another chiral auxiliary[29] can be judiciously chosen to effectively present an asymmetric steric environment, in which the formation of the branched homoallylic alcohols precursor is highly diastereometrically preferred, stereoselective access to the linear homoallylic alcohols would be achieved. It is hence conceivable that this crotyl transfer reaction would provide a valuable platform for the development of a new highly stereoselective homoallylic alcohol protocol.

[28] Nokami, J.; Nomiyana, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 1273, and references therein.
[29] For an extensive list of chiral auxiliaries, see: (a) Rahmen, A. U.; Shah, A. *Stereoselective Synthesis in Organic Chemistry*, Springer, Berlin, 1993. (b) I. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**. (c) Ager, D. J.; Prakash, J.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

In the next section, a new methodology to prepare enantiomerically enriched *cis*-linear homoallylic alcohols will be discussed first. A range of catalysts, aldehydes, and solvents were investigated to obtain the optimum yield, enantioselectivity, and *cis* olefinic geometry. Following that, the first enantioselective linear homoallylic alcohol transfer reaction will be revealed. Both methodologies are derived from a mechanism based on the 2-oxonia-[3,3]-sigmatropic rearrangement.

1.2 SYNTHESIS OF ENANTIOMERICALLY CIS-LINEAR HOMOALLYLIC ALCOHOLS BASED ON THE STERIC INTERACTION MECHANISM OF CAMPHOR SCAFFOLD[30]

The abundance, crystallinity and manifold transformations of (+)-camphor **77** have attracted considerable interest throughout the history of organic chemistry.[31] By means of various rearrangements and functionalizations at C(3), C(5), C(8), C(9), and C(10), as well as the cleavage of the C(1)/C(2) and C(2)/C(3) bonds, camphor has served as a fascinating versatile starting material for the synthesis of enantiomerically pure natural products (Figure 4). This chemistry, which entails incorporation of the camphor topicity into the target molecule, has been reviewed.[32]

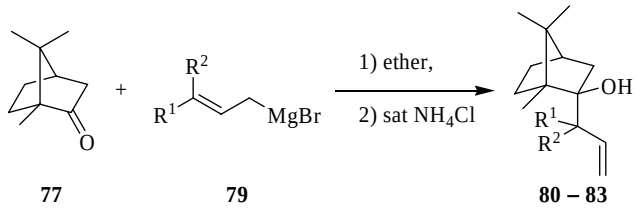
77 1*R*-(+)-Camphor **78** 1*S*-(-)-Camphor

Figure 4. The two enantiomeric forms of camphor.

[30] Chi-Lik Ken Lee, Cheng-Hsia Angeline Lee, Kui-Thong Tan, Teck-Peng Loh. **An Unusual Approach Towards the Synthesis of Enantiomerically Cis-Linear Homoallylic Alcohols Based on the Steric Interaction Mechanism of Camphor Scaffold.** *Organic Letters* **2004**, *6*, 1281.
[31] For a review on camphor-based chiral auxiliaries, see: Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.
[32] Money, T. *Natural Prod. Reports* **1985**, 253.

Our initial efforts were focused on synthesizing a series of chiral auxiliaries based on the camphor scaffold. The Grignard procedure allows the reaction of the allylmetal species with the camphor **77** to be performed at low temperatures, but only **80** and **81** were successfully synthesized in this way (Table 1, entries 1 and 2).[33] The reason for the lack of formation of **82** and **83**[34] may be due to the bulky nature in phenyl and ester group, that might hinder allyl attack on the carbonyl group of camphor. Notably, **3b** was isolated as an inseparable mixture of diastereomers with a *syn*/*anti* ratio of 70/30, based on ^{1}H NMR and ^{13}C NMR determination.

Table 1. Synthesis of chiral auxiliaries based on the camphor scaffold.



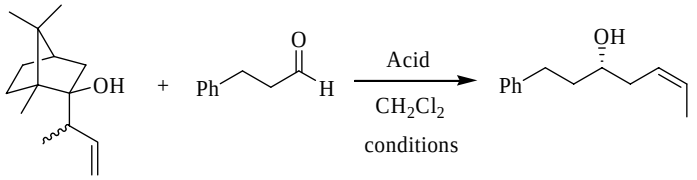
77 **79** **80 – 83**

Entry	R^1	R^2	Temp (^{o} C)	Time (h)	Product	Yield (%)
1	H	H	0	1.5	**80**	82
2	CH_3	H	0	2.0	**81**	87
3	Ph	H	0	12.0	**82**	-
4	CO_2Et	H	– 78	12.0	**83**	-

[33] Dimitrov, V.; Simova, S.; Kostova, K. *Tetrahedron.* **1996**, *52*, 1699.
[34] Method used for the preparation of **83**: Alkylation of **77** (10 mmol, 1 equiv) with ethyl crotonate (20 mmol, 2 equiv) using lithium diisopropylamide (LDA) (40 mmol, 4 equiv) in anhy THF (40 mL) stirring at – 78 ^{o}C.

Our initial studies of the crotyl transfer reaction entailed stirring a diastereomeric mixture (*syn*/*anti* = 70/30) of the camphor branched homoallylic alcohol **81** (0.5 mmol, 1 equiv.) with 3-phenylpropanal **37** (0.75 mmol, 1.5 equiv.) in dichloromethane (2 mL) at room temperature, under the catalysis of indium(III) triflate. In accordance with the recent surge in interest in metal triflates, indium(III) triflate has emerged as a promising choice particularly in our research group.[35] However, no desired product was obtained for this crotyl transfer reaction when $In(OTf)_3$ was employed as the acid catalyst (Table 2, entry 1). This prompted us to explore the use of other acids, for instance Brönsted acids.

Table 2 Crotyl transfer reaction from 81 to 37 with various acids.



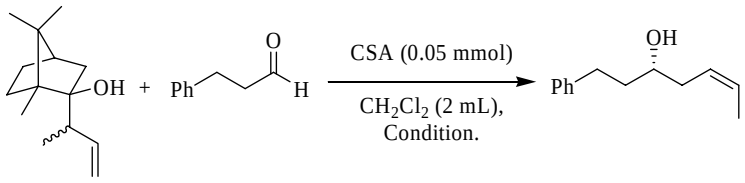
81 **37** **84**

Entry	Acid	Temp (^oC)	Time (h)	Yield (%)	% *ee* (*Z:E*)
1	$In(OTf)_3$	25	18	-	--
2	pTsOH	25	18	<7	96 (95:5)
3	TFA	25	18	<7	94 (94:6)
4	CSA	25	18	25	93 (94:6)
5	Br-CSA	25	18	15	95 (99:1)

[35] (a) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am Chem. Soc.* **2001**, *123*, 2450. (b) Loh, T. P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett.* **2001**, *3*, 2669. (c) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 2921. (d) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 4990.

When *p*-toluene sulfonic acid (pTsOH) and trifluoroacetic acid (TFA) were employed, the crotyl transfer reactions were successfully catalyzed (Table 2, entries 2 and 3). Although the yield for pTsOH was rather low, the desired linear homoallylic alcohol obtained showed high *cis*-olefinic geometry (*Z:E* = 95:5) and enantioselectivity (96% *ee*). A similar observation was made when TFA was used (*Z:E* = 95:5; 94% *ee*). Remarkably, 1*R*-(+)-camphor sulfonic acid (CSA) proved to be the acid catalyst of choice when it gave a moderate yield of 25% with significant *cis*-olefinic geometry (*Z:E* = 96:4) and enantiomeric excess (93% *ee*). This superior catalytic efficiency exhibited by CSA prompted us to select this Brönsted acid for further exploration.

Table 3. Crotyl transfer reaction from 81 to 37 under various temperature conditions.



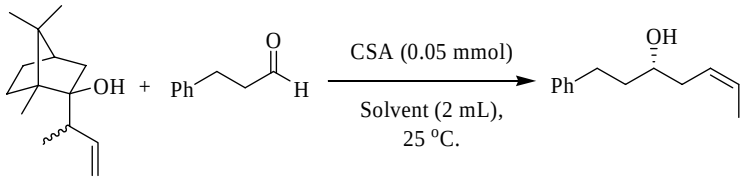
81 (0.5 mmol) **37** (0.75 mmol) **84**

Entry	Conditions	Time (h)	Yield (%)	% *ee* (*Z:E*)
1	- 78 ^{o}C	24	15	93 (97:3)
2	0 ^{o}C	24	20	93 (97:3)
3	25 ^{o}C	24	25	93 (94:6)
4	reflux	24	11	93 (96:4)

We next focused on optimization of the reaction conditions by investigating on the temperature (Table 3) and solvent (Table 4) effects. It is evident from Table 3 that the crotyl transfer reaction performed at 25 ^{o}C remained the preeminent condition, giving the product in the highest yield (25%). In all cases, the olefinic geometries and

enantioselectivities did not fluctuate to any great extent. As shown in Table 4, the best yield was significantly improved when the crotyl transfer reaction was carried out in dichloromethane (Table 4, entries 2 and 3). The reactions employing toluene and chloroform were unimpressive, providing rather low yields of 8% and <7% respectively (Table 4, entries 1 and 3). It is important to note that the polarity of solvents had no direct relationship with the crotyl transfer reaction due to the observations obtained using toluene and chloroform.

Table 4. Crotyl transfer reaction from 81 to 37 using various solvents.

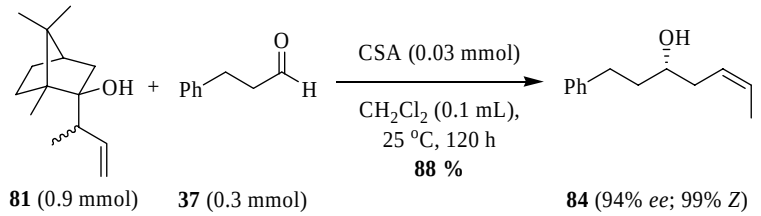


81 (0.5 mmol) **37** (0.75 mmol) **84**

Entry	Solvent	Polarity index	Time (h)	Yield (%)	% *ee* (*Z*:*E*)
1	Toluene	2.4	24	8	93 (98:2)
2	CH_2Cl_2	3.1	24	25	93 (94:6)
3	CH_2Cl_2	3.1	120	56	92 (98:2)
4	$CHCl_3$	4.1	24	<7	94 (98:2)
5	THF	4.0	24	-	-
6	Diethyl ether	2.8	24	-	-
7	CH_3CH_2OH	5.2	24	-	-

When the reaction was carried out using an excess of camphor homoallylic alcohol **81** and it took a time of 120 h for the disappearance of **37** on the TLC to afford the desired product **84** with an improved yield of 56%. Optimal results were obtained when the reaction was carried out at ambient temperature and at a higher concentration (6.0 molar solution) with 3 equivalents of the branched homoallylic alcohol **81** being added slowly

to a stirred solution of 1 equivalent of 3-phenylpropanal **37** and 0.1 equivalent of CSA for 120 h (Scheme 20).



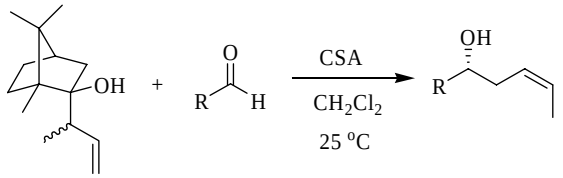
Scheme 20. Optimized reaction conditions for the crotyl transfer reaction of 81.

With these optimized conditions, we carried out the crotyl transfer reactions on various aldehydes. While the slightly bulkier substrate (Table 5, entry 4) gave a moderate yield, the linear ones offered excellent yields (Table 5, entries 2 and 3). Reactions of the dioxygenated substrates (Table 5, entries 5, 6 and 7) afforded the desired products with *ee* up to 99% and *cis*-olefinic geometries almost predominantly. It is worthwhile to mention that reactions of the (1*S*)-(-)-camphor branched homoallylic alcohol with **4** furnished the other enantiomer of **84** (60% yield; 93% *ee*; 99% *Z*).

This reaction can also tolerate other functional groups. Using *cis*-hept-4-enal, fine yields were obtained with comparable *ee* and *cis* olefinic geometry (>99% *ee*, 84% *Z*) (Table 5, entry 8) while the α,β-unsaturated ethyl ester type aldehyde needed a longer time before moderate yields were achieved with excellent *ee* and *cis*-olefinic geometry (>99% *ee*, 97% *Z*) (Table 5, entry 9). Based on the sluggish reactivity of aromatic aldehydes (Table 5, entries 10 and 11), a chemoselective study revealed that the transfer

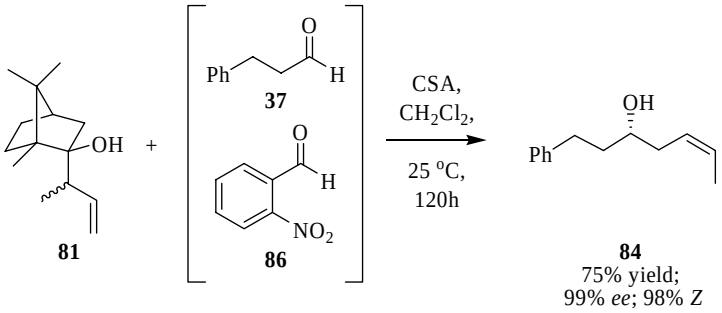
selectively react with the aliphatic substrate even in the presence of a more reactive aldehyde (Scheme 21).

Table 5. Enantioselective crotyl transfer reaction of 81 with different aldehydes.



81 **8** **85a – 85k**

Entry	R	Time (h)	**85**	Yield (%)	% *ee* (% *Z*)
1	$PhCH_2CH_2$	120	**85a**	88	94 (99)
2	n-C_5H_{11}	144	**85b**	68	97 (>99)
3	n-C_8H_{17}	144	**85c**	95	90 (94)
4	c-C_6H_{11}	144	**85d**	40	92 (96)
5	$BnO(CH_2)_2$	120	**85e**	74	97 (>99)
6	$BnO(CH_2)_3$	96	**85f**	94	99 (>99)
7	$BnO(CH_2)_4$	96	**85g**	80	98 (98)
8	$CH_3CH_2CH=CH(CH_2)_2$	96	**85h**	83	>99 (84)
9	$EtO_2CCH=CH(CH_2)_3$	240	**85i**	66	98 (99)
10	Ph	240	**85j**	<10	-
11	*o*-NO_2Ph	240	**85k**	<10	-



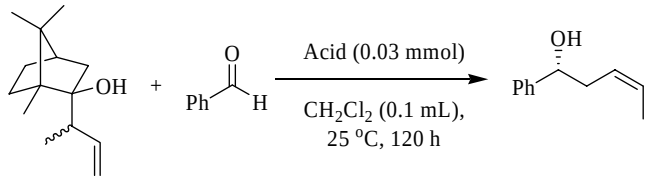
81 **84** 75% yield; 99% *ee*; 98% *Z*

Scheme 21. Chemoselective study.

In order to broaden the scope and overcome of this methodology on aromatic substrates, intense attempts were made trying to obtain the desired product 8**5j** when

benzaldehyde was used as the starting material aldehyde. As depicted in Table 6, the crotyl transfer reaction is indeed bound by the steric limitation of the aldehyde as none of the acid catalyst was able to afford the desired product in a useful yield.

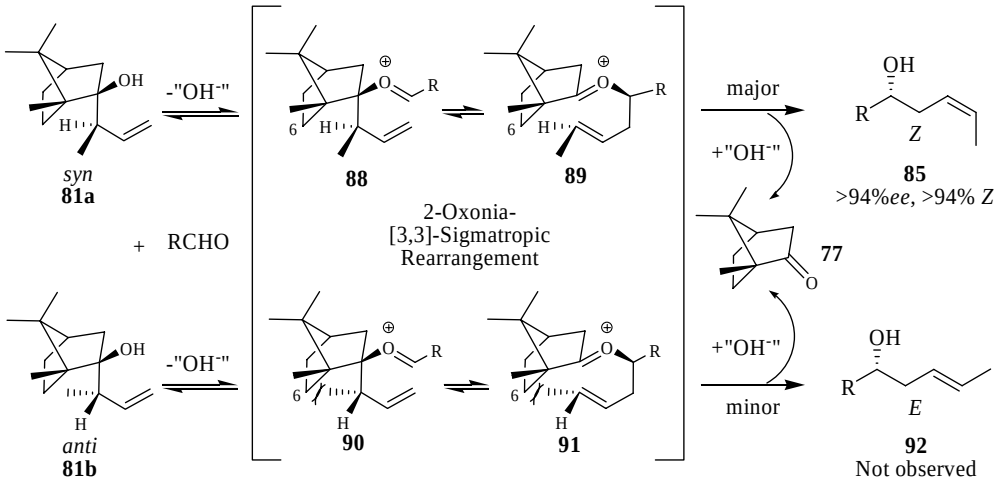
Table 6. Crotyl transfer reaction from 81 to 5 catalyzed by different acids.



81 (0.9 mmol) **5** (0.3 mmol) **85j**

Acid catalyst	Yield (%)	% *ee* (% *Z*)	Acid catalyst	Yield (%)	% *ee* (% *Z*)
HCl	-	-	$Yb(OTf)_3$	-	-
TMS(OTf)	Trace	-	$Lu(OTf)_3$	-	-
TIPS(OTf)	Trace	-	$Ho(OTf)_3$	-	-
InF_3	-	-	$Tm(OTf)_3$	-	-
$InCl_3$	Trace	-	$Er(OTf)_3$	-	-
$InBr_3$	Trace	-	$Dy(OTf)_3$	-	-
$In(OAcCF_3)_3$	-	-	$Tb(OTf)_3$	-	-
TfOH	-	-	$Nd(OTf)_3$	-	-
$Sn(OTf)_3$	-	-	$Pr(OTf)_3$	-	-
$Cu(OTf)_2$	-	-	$Gd(OTf)_3$	-	-
$Zn(OTf)_2$	-	-	$Eu(OTf)_3$	-	-
Ag(OTf)	-	-	$Y(OTf)_3$	-	-
$La(OTf)_3$	-	-	$Ce(OTf)_4$	-	-
$Sc(OTf)_3$	Trace	-	$Sm(OTf)_3$	-	-

Of mechanistic interest is the recovery of the excess chiral camphor homoallylic alcohol **81**, which is enriched as its *anti* isomer **81b** (*syn/anti* = 40/60) from an original diastereomeric ratio of *syn/anti* = 70/30. From the molecular model for the transition state of the corresponding camphor branched homoallylic alcohol **81** depicted in Scheme 22, we realized that only one isomer, the *syn*-branched homoallylic alcohol **81a**, was allowed to transfer using this camphor auxiliary.[36]



Scheme 22. Proposed transition state of crotyl transfer reaction.

[36] Another reaction was performed with **only** the pure *syn*-branched homoallylic alcohol **81a** (0.36 mmol; 1.2 equiv), 3-phenylpropanal (0.3 mmol; 1 equiv), and CSA (0.03 mmol; 0.1 equiv) in CH_2Cl_2 (0.1 mL; 3.0 M), furnished the desired linear homoallylic alcohol (**81%** yield; **98%** ***ee*** and **99%** ***Z***). The *syn* isomer was prepared by a slow elution on the flash column chromatography. On numerous occasions before the complete elution of the *syn* isomer, the *anti* isomer eluted and hence the latter was not successfully purified.

The branched homoallylic alcohol **81** probably formed oxonium-type ions with the aldehyde catalyzed by the acid catalyst, revealing two possible transition states. The *anti* branched homoallylic alcohol **81b** would most likely adopt a transition state similar to that of **90**. Based on a Zimmerman-Traxler six-membered transition state,[37] it is evident that the methyl groups from the *anti* isomer **81b** will develop severe steric repulsion with the C-6 of the camphor scaffold, which explains why the *trans*-linear isomer **92** was not observed at all.

On the contrary, the transition state **88** shows that the *syn* isomer's methyl group is fixed in a manner where it avoids any close contacts with the camphor's methylene protons before undergoing the rearrangement to furnish the thermodynamically preferred linear regioisomer **85**.

[37] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

1.3 THE FIRST EXAMPLE OF ENANTIOSELECTIVE ALLYL TRANSFER FROM A LINEAR HOMOALLYLIC ALCOHOL TO AN ALDEHYDE[38]

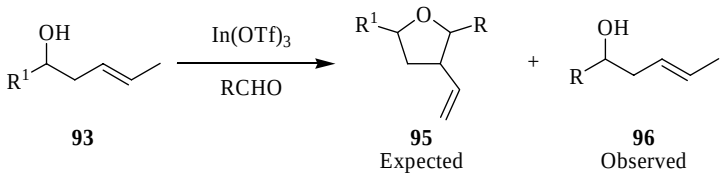
In the past few years, indium complexes have found widespread application in organic synthesis including their application for the catalysis of various C–C bond formation reactions in aqueous media.[39] Besides our interest in indium chemistry,[40] our group has also exploited the special characteristics of indium complexes to catalyze a wide variety of organic transformations.[41]

In a recent paper, our group reported a novel $In(OTf)_3$ catalyzed (3,5) oxonium-ene type cyclization for the facile construction of various multisubstituted tetrahydrofurans and tetrahydropyrans.[42] It was noted that a disubstituted double bond of a homoallylic alcohol is essential for this oxonium-ene type cyclization. During the course of our studies on the scope and limitations of this oxonium-ene reaction, we carried out the reaction of the homoallylic alcohol **93** with a different aldehydes in the presence of catalytic amount of $In(OTf)_3$.

---

[38] Teck-Peng Loh, Chi-Lik Ken Lee, Kui-Thong Tan. **The First Example of Enantioselective Allyl Transfer from a Linear Homoallylic Alcohol to an Aldehyde**. *Organic Letters* **2002,** *4*, 2985.
[39] Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.
[40] (a) Wang, R. B.; Lim, C. M.; Tan, C. H.; Lim, B. K.; Sim, K. Y.; Loh, T. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825. (b) Loh, T. P.; Li, X. R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 980. (c) Loh, T. P.; Chua, G. L.; Vittal, J. J.; Wong, M. W. *Chem. Commun*. **1998**, 861.
[41] (a) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc*. **2001**, *123*, 2450. (b) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 2921.
[42] Loh, T. P.; Hu, Q. Y.; Tan, K. T.; Cheng, H. S. *Org. Lett*. **2001**, *3*, 2669.

To our surprise, the homoallylic alcohol **93** gave no desired tetrahydrofuran product **95** but instead another linear homoallylic alcohol **96** was obtained as shown in Scheme 23. Herein, an unprecedented pathway leading to this linear homoallylic alcohol and the optimization of this reaction to make it synthetically useful will be reported.



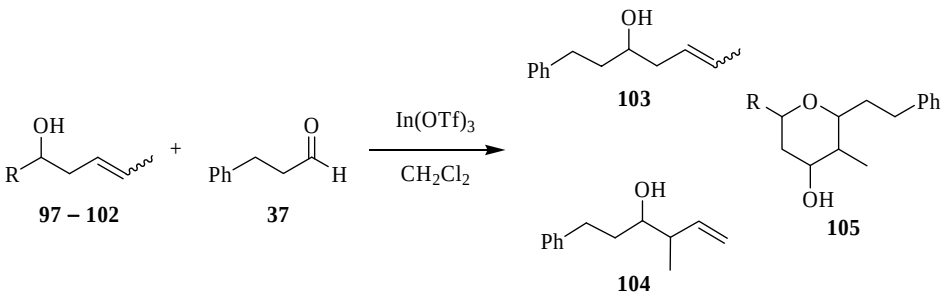
Scheme 23. Unexpected observation.

We chose to examine the most effective protocol for the crotyl transfer reaction by employing substrates that were easily obtained via indium mediated allylation (Table 6).[43] Treatment of the linear homoallylic alcohol (1.25 mmol, 2.5 equiv) and 3-phenylpropanal **37** (0.5 mmol, 1 equiv)) with 10 mol% of $In(OTf)_3$ in CH_2Cl_2 (3 mL) at room temperature was initially examined to test the feasibility of the crotyl transfer reaction. The reactions were heated reflux when TLC showed no desired product after stirring for 18 h at room temperature (Table 7, entries 2 and 3). This preliminary study not only produced the desired linear homoallylic alcohol **103**, but also a small amount (between 5 – 10 %) of the Prins cyclization product **105** was formed.[44]

[43] (a) Loh, T. P.; Tan, K. T.; Yang, Y. J.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701. For some examples of α-allylation, see: (b) Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem*. **2000**, *65*, 494. (c) Yamamoto, Y.; Maeda, N.; Maruyama, K. *Chem. Commun*. **1983**, *48*, 1564. (d) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc*. **1991**, *113*, 8955.

[44] (a) For some examples of Lewis acid catalyzed Prins cyclizations, see: Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc*. **1999**, *121*, 1092. (b) Nishizawa, M.; Shigaraki, T.; Takao, H.; Imagawa, H.; Sugihara, T. *Tetrahedron Lett*. **1999**, *40*, 1153. (c) Yang, X. F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739.

Table 7. Crotyl transfer reaction from various linear homoallylic alcohols to 37 catalyzed by $In(OTf)_3$.



Entry	Reactants	R	Temp (^oC)[a]	Time (h)	Yield %[b] (**103**:**104**) (*E*/*Z*)[c]	**105**
1	**97**	*c*-C_6H_{11}	25	2.0	25 (100:0) (80/20)	**105a**
2	**98**	$(CH_3)_2CH$	40	5.0	23 (100:0) (80/20)	**105b**
3	**99**	*n*-C_8H_{17}	40	6.0	25 (76:24) (80/20)	**105c**
4	**100**	Ph	25	1.5	45 (100:0) (80/20)	**105d**
5	**101**	*c*-C_6H_{11}	25	5.0	49 (100:0) (80/20)	**105e**
6	**102**	^{t}Bu	25	2.0	69 (100:0) (80/20)	**105f**

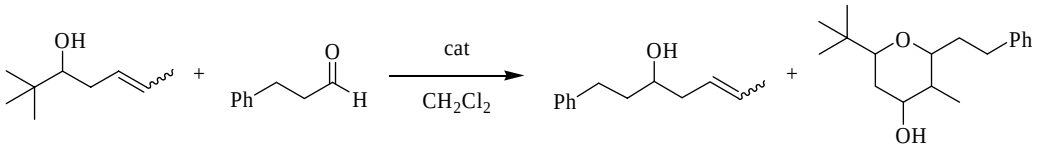
[a]The reactions were heated to reflux when TLC shows no desired product after stirring for 18 h at room temperature. [b]Combined yield based on **9a**. [c]Determined by ^{1}H NMR and ^{13}C NMR.

Using a more sterically congested substrate (Table 7, entry 6), an improved yield of the product **103** was obtained. It was found that this crotyl transfer reaction was largely dependent on the steric effect of the substituents on the allylic alcohol and aldehyde. In many cases, improved yields of the desired linear homoallylic alcohol arose because the amount of the Prins product decreased. Switching the substrate to the nonyl fragment (Table 7, entry 3) proved interesting as a substantial amount of the branched homoallylic adduct **104** was isolated.

Given the success of the development of a standard substrate for the crotyl transfer, Table 8 demonstrates a broad scope of the effect of catalysts on this allylation. The failure of the initial attempts with several catalysts was quite puzzling (Table 8, entries 1 to 5). Perhaps the Lewis/Brönsted acidities of these catalysts were not suitable enough for

this demanding crotyl transfer reaction. However, it is noteworthy to mention that trace amount **105f** was isolated.

Table 8. Crotyl transfer reaction from 102 to 37 catalyzed by various acids.



102 **37** **103** **105f**

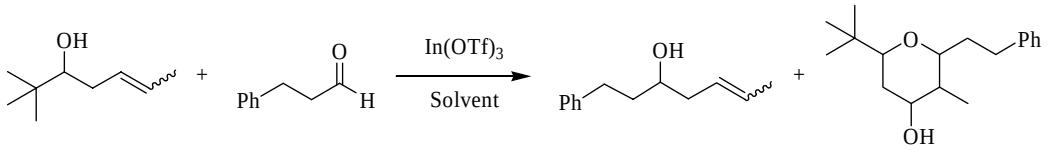
Entry	Catalyst	Temp (°C)	Time (h)	Yield **9a** (%) (α:γ) (*E/Z*)	Yield **11f** (%)
1	$InBr_3$	40	48	-	2
2	Ag(OTf)	40	48	-	-
3	$La(OTf)_3$	40	48	-	7
4	$Lu(OTf)_3$	40	48	-	5
5	CSA	40	48	-	13
6	$Yb(OTf)_3$	25	48	15 (75:25) (100/0)	5
7	$Cu(OTf)_2$	25	5	22 (23:77) (80/20)	3
8	$Sc(OTf)_3$	40	18	40 (99:1) (82/18)	28
9	$Sn(OTf)_2$	25	4	55 (100:0) (80/20)	23
10	$In(OTf)_3$	25	3	69 (100:0) (80/20)	10

The investigations on the effects of solvent showed intriguing results (Table 9). Although water, tetrahydrofuran and dimethylformamide all showed negative results for the crotyl transfer reaction, the reaction in hexane yielded more Prins product than the desired linear homoallylic alcohol product. Further studies on this phenomenon revealed that the selectivity towards getting the Prins product can be increased by carrying out the reaction in hexane and 4Å molecular sieves.

In fact, when this condition was carried out, formation of the linear homoallylic alcohol was almost totally suppressed (< 7% yield) and afforded 62% yield of the Prins

product. Nonetheless, dichloromethane became the solvent of choice for the crotyl transfer reaction when it gave the desired product in good yield.

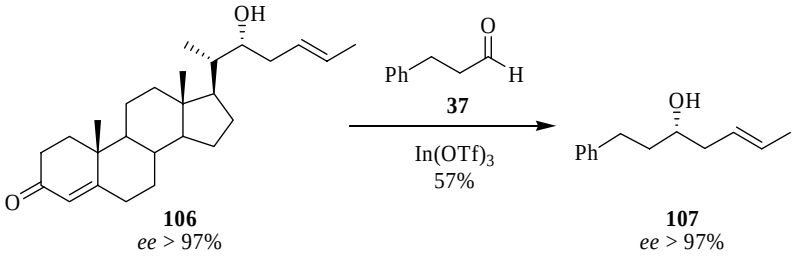
Table 9. Crotyl transfer reaction from 102 to 37 using various solvents.



102 **37** **103** **105f**

Entry	Solvent	Temp (°C)	Time (h)	Yield **102** (%) (α:γ) (*E/Z*)	Yield **105f** (%)
1	H_2O	40	48	-	-
2	THF	40	48	-	-
3	DMF	40	48	-	-
4	Hexane	40	48	15 (100:0) (80/20)	37
5	$CHCl_3$	40	48	30 (100:0) (80/20)	10
6	CH_2Cl_2	25	3	69 (100:0) (80/20)	10

In order to understand the mechanism of this crotyl transfer reaction, optically active steroid linear homoallylic alcohol (*ee* > 97%) was used to study the stereochemistry of this reaction (Scheme 24). The enantiomeric excess of the product was determined. It was found that the chirality of the alcohol, *ee* and regiochemistry were preserved. Furthermore, a trace amount of the branched homoallylic alcohol in one isomeric form was obtained in the reaction. Notably, the Prins product was suppressed in this reaction.

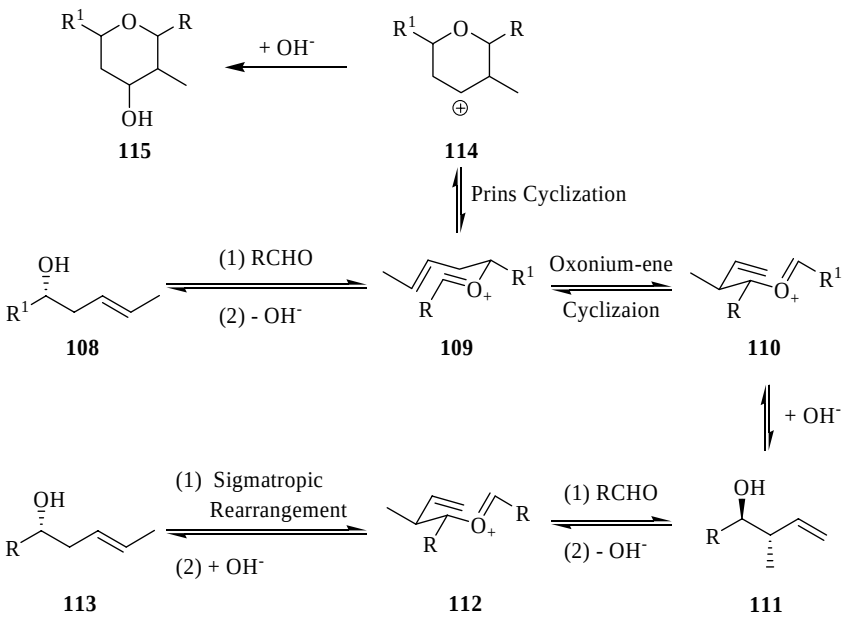


106
ee > 97%

107
ee > 97%

Scheme 24. Stereochemical study of the linear to linear crotyl transfer reaction.

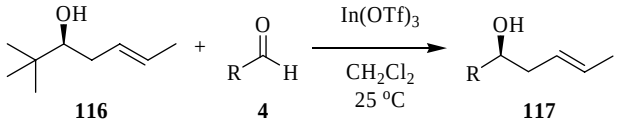
From the reactions and results illustrated by Scheme 24, Table 7, 8 and 9, a plausible mechanism can be proposed. Scheme 25 outlines a mechanistic rationale based upon (i) the branched γ-adduct homoallylic alcohol **111** was generated from the $In(OTf)_3$ promoted crotyll transfer reaction from the linear homoallylic alcohol **108**, perhaps through a 2-oxonia [3,3]-sigmatropic rearrangement. Following that, **111** underwent a thermodynamic conversion to the preferred linear regioisomer **113**, plausibly by the similar concerted rearrangement as mentioned previously.[28] (ii) The stereochemistry was retained after the crotyl transfer reaction from steroid homoallylic alcohol. (iii) Steric effects are very important, and the whole rearrangement was driven by the difference in steric bulk of the two substrates, with the less bulkier substrate being more stable. (iv) The Prins product was derived from the oxonium ions **109** which can cyclize to give a stable cation **114**, which reacts with a hydroxyl equivalent generated in situ to give **115**.



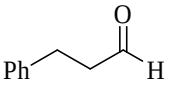
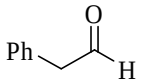
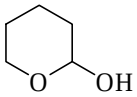
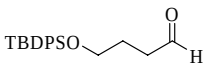
Scheme 25. Mechanistic Rationale for the linear to linear crotyl transfer reaction and Prins cyclization reaction.

With such understanding of the mechanism, this crotyl transfer reaction was then carried out with 4 different aldehydes. Starting material **116** with *e*e > 97 % and *E*/*Z* ratio 100/0 was used to perform this reaction. As shown from Table 10, the regio and stereochemistry remained unchanged after the reaction. It is interesting to point out that this crotyl transfer reaction can also work well with the lactol substrate **119** (Table 10, entry 3). Especially noteworthy, the stereoselective crotyl transfer reaction of **116** with aldehyde **120** in entry 4, demonstrated the assembly of the C15 - C22 fragment of (+)-amphidinolide K (Figure 1).[45]

Table 10. Enantioselective crotyl transfer reaction of 116 with different aldehydes.



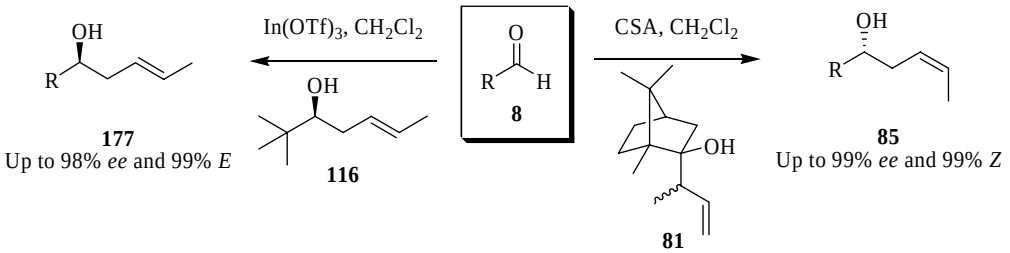
116 >97% *ee;* >95% *E* — **4** — **117**

Entry		**4**	Time (h)	Yield (%) (*E*/*Z*)	*ee* (%)
1	**37**		2	69 (100/0)	> 97[b]
2	**118**		3	41 (100/0)	> 97[b]
3	**119**		6	52 (100/0)	> 97[c]
4	**120**		2	35 (100/0)	> 97[c]

[45] (a) William, D. R.; Meyer, K. G. *J. Am. Chem. Soc*. **2001**, *123*, 765. (b) Loh, T. P.; Hu, Q. Y.; Chok, Y. K.; Tan, K. T. *Tetrahedron Lett*. **2001**, *42*, 9277.

1.4 CONCLUSION

In conclusion, two novel methods have been developed for the enantioselective synthesis of linear homoallylic alcohols. In the first section, a conceptually different strategy to prepare *cis*-linear homoallylic alcohols, with moderate to high yields, has been developed in this laboratory. To the best of our knowledge, this is the first efficient method[24b] that controls, in situ, both the enantioselectivity (up to 99% *ee*) and the olefinic geometry (up to 99% *Z*) of *cis*-linear homoallylic alcohols. Our investigations have also shown that this chemoselective crotyl transfer reaction is highly feasible for aliphatic substrates. Moreover, excess chiral camphor-derived branched homoallylic alcohol (89% recovery) and the camphor (83% recovery) generated from the reaction can be recovered and reused, thus, making this method attractive for scale-up preparation of *cis*-linear homoallylic alcohols with high enantioselectivities. We anticipate that this new Brönsted acid catalyzed crotyl transfer reaction will be an indispensable tool in the synthesis of complex natural products, thereby allowing this methodology to undergo an exciting renaissance as a synthetic method.



Scheme 26. New protocols to prepare enantiomerically enriched linear homoallylic alcohols.

The second methodology describes the Lewis acid catalyzed enantioselective linear homoallylic alcohol transfer reaction, from a sterically hindered starting material to its sterically less hindered analogue *via* its branched-adduct intermediate, has been developed. In all cases, the whole rearrangement is thermodynamically favorable and steric effects drive the reaction. The preservation of the stereocenter and the olefin geometry together with the isolation of the branched-adduct homoallylic alcohols in one isomeric form have warranted the proposed mechanism.

PART II

Multigram Synthesis of (–)-Epibatidine

2.1 HISTORY AND THE DISCOVERY OF EPIBATIDINE

In the mid-1970s, a novel class of amphibian alkaloid epibatidine **13** was first isolated by Daly *et al.* at the National Institute of Health in trace amount from the skin of the Ecuadorian poison frog, *Epipedobates tricolor* of the family Dendrobatidae.[25] Its structure was elucidated by this research group in 1992,[26] revealing the relative stereochemistry and an unprecedented structure with a strained nitrogen-bridged six-membered carbon ring system (7-azabicyclo[2.2.1]heptane) with an exo-orientated 3-(6-chloropyridyl) substituent. Because of the very small quantities of the natural product (*ca.* 1 mg isolated from 750 frogs), the assignment of the absolute stereochemistry was determined by Fletcher *et al.*[27] in 1994, establishing as 1*R*,2*R*,4*S* for **122** (Figure 5).

121: (+)-Epibatidine **122**: (-)-Epibatidine

Figure 5. Structures of (+)-epibatidine and (–)-epibatidine.

[25] Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.
[26] Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannel, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.
[27] (a) Fletcher, S. R.; Baker, R. B.; Chambers, M. S.; Hobbs, S. C.; Mitchell, P. J. *J. Chem. Soc. Chem. Commun.* **1993**, 1216. (b) Fletcher, S. R.; Baker, R. B.; Chambers, M. S.; Herbert, R. H. Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *3*, 1771.

The discovery of epibatidine's pharmacological properties and the travails surrounding its chemical isolation and characterization is a fascinating story – one that holds a lesson about our environment. As related by Daly *et al.*, the initial skin extracts collected from *Epipedobates tricolor* in 1974 yielded a small amount of an alkaloid that when injected into mice produced the Straub-tail effect characteristic of opioids.[28]

Subsequent extractions of the additional frog skins collected two years later yielded *ca.* one milligram of active material, which was shown to have potent analgesic activity that contained at least eleven carbons, two nitrogens and a chlorine atom, but elucidation of its structure would have to await for more complete purification and sensitive methods for structural scrutiny.[29] Therefore, the small amount of relatively pure extract that remained was stored for future study.

In 1984, the Convention on International Trade in Endangered Species (CITES) put all the dendrobatid frogs on their Appendix II listing. From a scientist's standpoint, such a CITES listing means that no investigator will ever be able to obtain permits to collect the requisite hundreds or more specimens required for structure elucidation of minor and trace compounds found in dendrobatid frogs, even though such frogs are often incredibly abundant.

[28] (a) Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445. (b) Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162. (c) Badio, B.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Med. Chem. Res.* **1994**, *4*, 440.
[29] Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023.

To complicate matters further, the skin extracts that could be collected contained very little of the active alkaloid (possibly due to the changes in their native habitat). Worse still, it was soon realized that the skin extracts from frogs raised in captivity in Daly's labs did not contain the analgesic material, reinforcing speculation that the active compound itself, or an essential precursor, is derived from a dietary source (perhaps insects) indigenous to the frog's Ecuadorian habitat and then sequestered in the frog's skin.[30]

In 1990 the small amount of extract that had been stored by Daly and his colleagues a decade earlier was essentially the only remaining supply of the potent analgesic material remaining. The power and sensitivity of NMR advanced remarkably and so Daly and his colleagues gambled the remaining material on gas chromatography-infrared spectroscopy and NMR analyses after its conversion to the *N*-acetyl derivative. This strategy worked and the structure of epibatidine was published in 1992.[26] However, the *N*-acetyl derivative proved to be biologically inactive and efforts to recover epibatidine from the derivative were unsuccessful. Thus further work on the pharmacological properties of epibatidine would have to await *de novo* synthesis. Interestingly, the (+)- and (–)-enantiomers of epibatidine are nearly equipotent in tests of analgesic activity.[31-33]

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[30] (a) Daly, J. W.; Secunde, S. I.; Garraffo, H. M.; Spande, T. F.; Wisnieski, A.; Cover, J. F. *Toxicon* **1994**, *32*, 657. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **1994**, *20*, 943.
[31] Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563.
[32] Damaj, M. I.; Creasy, K. R.; Grove, A. D.; Rosecrans, J. A.; Martin, B. R. *Brain Res.* **1994**, *664*, 34.
[33] Li, T.; Qian, C.; Eckman, J.; Huang, D. F.; Shen, T. Y. *Bioorg. Med. Chem. Lett.* **1994**, *3*, 2759.

2.2 BIOLOGICAL ACTIVITY OF EPIBATIDINE

Historically, amphibian skin has provided many biologically active compounds. Vasoactive, analgetic, and antibiotic peptides, such as physalaemin, caerulein, sauvagine, dermorphin, and magainin,[34,35] biogenic amines, including serotonins, tryptamines, histamines, and tyramines,[34] cardioactive steroidal bufadienolides,[36] tetrodotoxins,[37] and one novel structural class of steroidal alkaloids, the smandarines,[38] have been found in amphibian skin. Over the years, a rich harvest of unique alkaloids have been isolated, some of which have had a major impact on biomedical research where radiolabeled probes are being developed to investigate the sites of action (Figure 6).

[34] Erspamer, V.; *Basic Appl. Histochem.* **1981,** *25*, 3.
[35] Berkowitz, B. A.; Bevins, C. L.; Zasloff, M. A. *Biochem. Pharmocol.* **1990**, *39*, 625.
[36] Meyer, K.; Lindle, H.; Bücherl, W.; Buckley, E. E. *Eds.; Academic Press:* New York, **1971**; Chapter 40, pp 521.
[37] Kim, Y. H.; Brown, G. H.; Mosher, H. S.; Fuhrman, F. A. *Science* **1975**, *189*, 151.
[38] Habermehl, G.; Manske, R. H. F. *Ed.; Academic Press:* New York, **1967***; Vol 9*, pp 427.

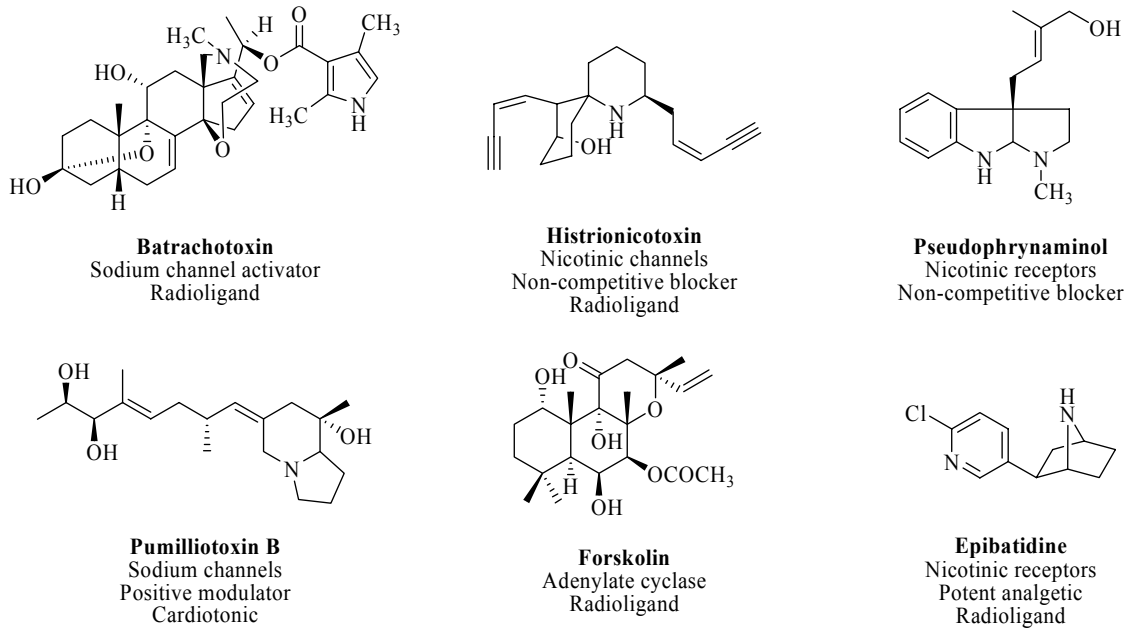
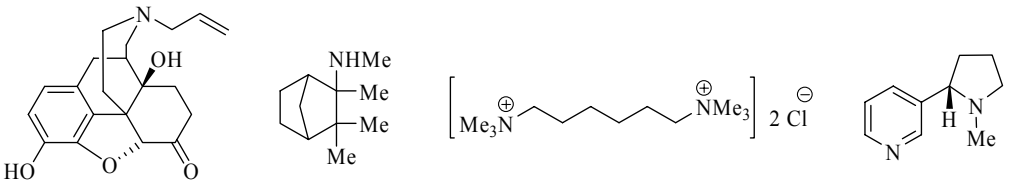


Figure 6. Natural products as pharmacodynamic probes: structures and targets. Development of radioligands is indicated.

Epibatidine has been shown to possess potent analgesic activity.[39] The analgesic effects were not blocked by administration of the potent opiate receptor antagonist naloxone **123** (Figure 7).[26,28(c),31,40–42] However, the analgesic activity was antagonized by the neuronal nicotinic acetylcholine receptor channel blocker, mecamylamine **124** but was not affected by the nicotinic acetylcholine receptor antagonist, hexamethonium **125**. Since hexamethonium has been shown to be incapable of crossing the blood–brain barrier, it is believed that the primary mechanism of action of epibatidine is mediated through occupation of nicotinic acetylcholine receptors in the brain.[31,32,40]

[39] Heard, N. E.; Turner, J. *J. Org. Chem.* **1995**, *60*, 4302.
[40] Qian, C.; Li, T.; shen, T. Y. *Eur. J. Pharm.* **1993**, *150*, R13.
[41] Li, T.; Eckman, J.; Huang, D. F.; Shen, T. Y. *Bio-Org. Med. Chem. Lett.* **1993**, *3*, 2759.
[42] Dukat, M.; Damaj, M. I.; Glassco, W.; Dumas, D.; May, E. L.; Martin, B. R.; Glennon, R. A. *Med. Chem. Res.* **1994**, *4*, 131.



123 **124** **125** **126**

Figure 7. Structures of receptor antagonists, blocker and nicotine.

Limited structure activity relationships (SAR) studies have demonstrated that both the (+) and (–) enantiomers of epibatidine exhibit equipotent analgesic activity. Both enantiomers also equally displaced bound [^{3}H]nicotine **126** from rat brain, making epibatidine one of the most potent nicotinic acetylcholine receptor ligands known to date.[31,32,42] In addition, it was found that removal of the chlorine atom has little effect on the binding affinity.[43] A decade ago, it has been shown that (±)-[^{3}H]epibatidine binds to two sites in rat brain with affinities of 15 and 360 pM (IC_{50}).[44] Epibatidine was also found to bind to two sites in human brain with affinities less than 1 pM (IC_{50}).

[43] Corey, E. J.; Loh, T.-P.; Achyutha Rao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600.
[44] (a) Houghtling, R. A.; Dávila-García, M. I.; Hurt, S.; Kellar, K. J. *Med. Chem. Res.* **1994**, *4*, 538. (b) Houghtling, R. A.; Dávila-García, M. I.; Kellar, K. J. *Mol. Pharmacol.* **1995**, *48*, 280.

Studies with (–)-epibatidine *in vivo* have further demonstrated that the pharmacological activity of this novel alkaloid is mediated by nicotinic acetylcholine receptors in the central and autonomic nervous systems.[31,32,42,44–46] On top of the analgesic activity, (–)-epibatidine brought forth similar effects to those of other nicotinic acetylcholine receptor ligands, albeit with much greater potency. Moreover, epibatidine has been shown to be an extremely potent toxin producing convulsions and death at doses of 40 – 86 μg/kg in mice.[47]

With the availability of synthetic (±), (+), and (–)-epibatidine, a number of useful nicotinic acetylcholine receptor probes have been developed. [^{3}H]Epibatidine has been employed as chemical probe for the study of nicotinic receptors in chick retina and in rodent and human brains.[44,48] Besides this, the 4'-substituted ^{18}F and ^{123}I analogues have also being investigated as useful imaging agents for emission tomography (PET).[49] More importantly, a number of nicotinic acetylcholine receptor ligands have been reported that are selective for neuronal nicotinic acetylcholine receptor subtypes and may have potential in the treatment of Alzheimer's disease and Parkinson's disease.[50]

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[45] Fisher, M.; Huangfu, D.; Shen, T. Y.; Guynet, G. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 702.
[46] Sullican, J. P.; Briggs, C. A.; Donnelly-Roberts, D.; Brioni, J. D.; Radek, R. J.; McKenna, D. G.; Campbell, J. E.; Arneric, S. P.; Decker, M. W.; Bannon, A. W. *Med. Chem. Res.* **1994**, *4*, 502.
[47] Bonhaus, D. W.; Bley, K. R.; Broka, C. A.; Fontana, D. J.; Leong, L.; Lewis, R.; Sheih, A.; Wong, E. H. F. *J. Pharmacol. Exp, Ther.* **1995**, *272*, 1199.
[48] Lehn, J. M. *Chem. Forsch.* **1970**, *15*, 311.
[49] London, E. D.; Scheffel, U.; Kimes, A. A.; Kellar, K. J. *Eur. J. Pharmacol.* **1995**, *278*, R1.
[50] Decker, M. W.; Bannnon, A. W.; Curzon, P.; Gunther, K. L.; Brioni, J. d.; Holladay, M. W.; Lin, N.-H.; Li, Y.; Daanen, J. F.; Buccafusuco, J. J.; Prendergast, M. A.; Jackson, W. J.; Arneric, S. P. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 247; and references cited therein.

The introduction of epibatidine as a nicotinic agonist and analgesic provided the impetus for major synthetic efforts to obtain an analogue that would retain analgesic activity while being much less toxic. One such analogue, ABT 594, underwent phase I and II clinical trials as an analgetic.[51] Undoubtedly other analogues are still under investigation. The relative activity of (–)-epibatidine at four major subtypes of nicotinic receptors, some analogues, and other natural nicotinic agonists are illustrated in Figure 8.

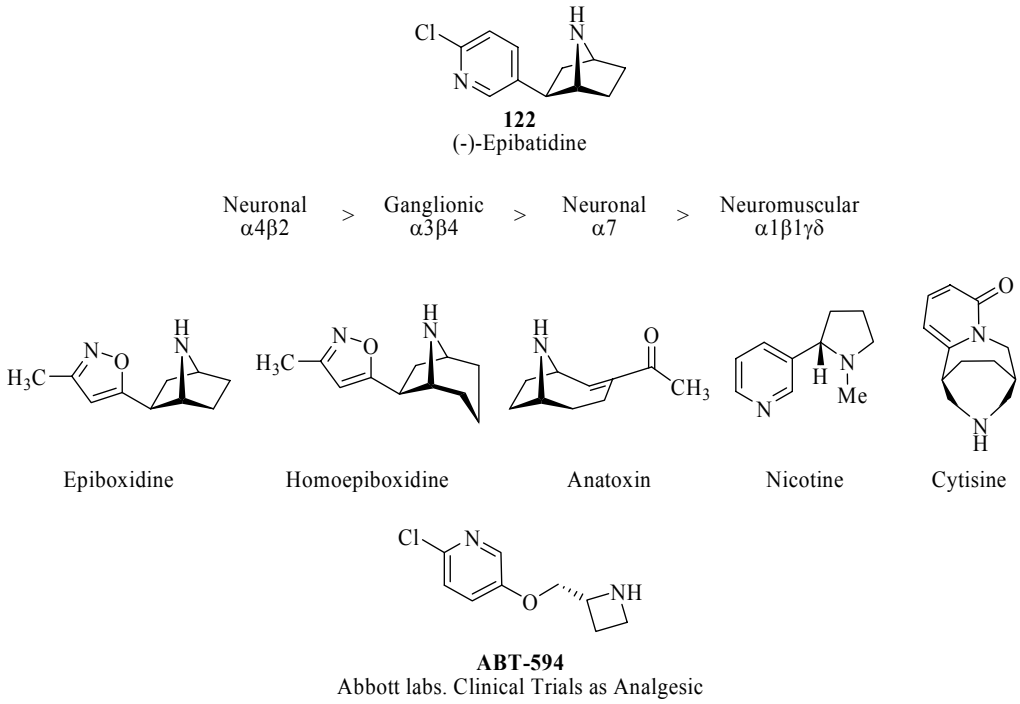


Figure 8. Nicotinic agents: epibatidine (relative activity indicated) and analogues and other natural nicotinic agonists.

[51] Daly, J. W.; Garraffo, H. M.; Spande, T. F. Decker, M. W.; Sullivan, J. P.; Williams, M. *Nat. Prod. Rep.* **2000**, *17*, 131.

2.3 RELEVANT STUDIES ON THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF EPIBATIDINE

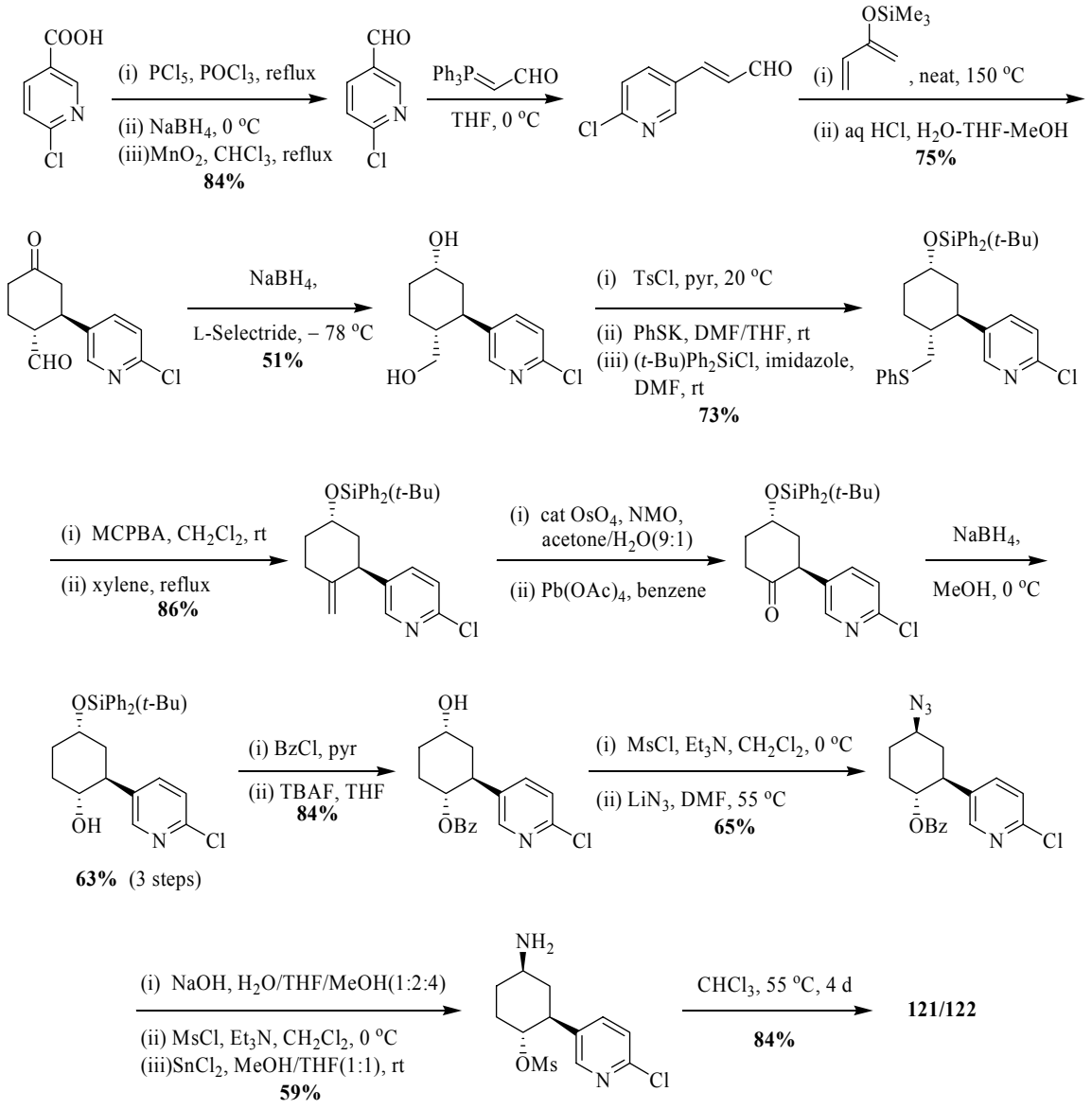
The exciting biological properties of epibatidine, unique structure, combined with its scarcity in nature (*ca.* 1 mg of the alkaloid was isolated from the skin extract of some 750 frogs) have aroused the interest of synthetic chemists around the world. In a relatively short time after its intriguing structure has been elucidated back in 1992, a vast number of synthetic approaches were published. Surprisingly, while approximately 50 total[27,52] and formal[53] syntheses have been reported, few full syntheses are enantioselective. It is useful to note that in some cases, epibatidine's availability in enantiomeric pure forms have only occurred through resolution at some point in the synthesis of the final product. The fact that the collection of dendrobatid frogs has been prevented by an international treaty enacted in 1984 for the protection of endangered species has also spurred synthetic efforts to prepare needed material for further critically important biological investigation.

[52] For the first total synthesis of epibatidine, see: (a) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251. For subsequent total synthesis of epibatidine, see: (b) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477. (c) Corey, E. J.; Loh, T.-P.; Achyutha Rao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600. (d) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493. (e) Senokuchi, K.; Nakai, H.; Kawamura, M.; Katsube, N.; Nonaka, S.; Sawaragi, H.; Hamanaka, N. *Synlett* **1994**, 343. (f) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C., Jr.; Temesvári-Major, E.; Blaskó, G. *Tetrahedron Lett.* **1994**, *35*, 3171. (g) Sestani, K.; Melenski, E.; Jirkovsky, I. *Tetrahedron Lett.* **1994**, *35*, 5417. (h) Pandey, G.; Bagul, T. D.; Lakshmaiah, G. *Tetrahedron Lett.* **1994**, *35*, 7439. (i) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9297. (j) Ko, S. Y.; Lerpiniere, J.; Linney, I. D.; Wriddlesworth, R. *J. Chem. Soc., Chem.. Commun.* **1994**, 1775. (k) Okabe, K.; Natsume, M. *Chem. Phar. Bull. Jpn.* **1994**, *42*, 1432. (l) Kotian, P. L.; Carroll, F. I. *Synth. Commun.* **1995**, *25*, 63. (m) Xu, R.; Chu, G.; Bai, D. *Tetrahedron Lett.* **1996**, *37*, 1463. (n) Bai, D.; Xu, R.; Chu, G.; Zhu, X. *J. Org. Chem.* **1996**, *61*, 4600. (o) Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189. (p) Giblin, G. M.; Jones, C. D.; Simkins, N. S. *Synlett* **1997**, 589. (q) Pavri, N. P.; Trudell, M. L. *Tetrahedron Lett.* **1997**, *38*, 7993. (r) Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760. (s) Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059. (t) Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans, 1* **1999**, 1253. (u) Olivo, H. F.; Hemenway, M. S. *J. Org. Chem.* **1999**, *64*, 8969. (v) Roy, B.; Watanabe, H.; Kitahara, T. *Heterocycles* **2001**, *55*, 861.

Epibatidine is one of the few natural products known which contains the unique 7-azabicyclo[2.2.1]heptane ring system as a structural element.[54] Furthermore in the first synthesis of epibatidine described by Broka in 1993, this desired ring system was invoked from an intramolecular displacement strategy (Scheme 27).[52a] While this synthetic route portrayed a non-enantioselective pathway, it would seem that by incorporating a suitable chiral auxiliary into the dienophile might have a good chance of rendering the synthesis enantioselective.

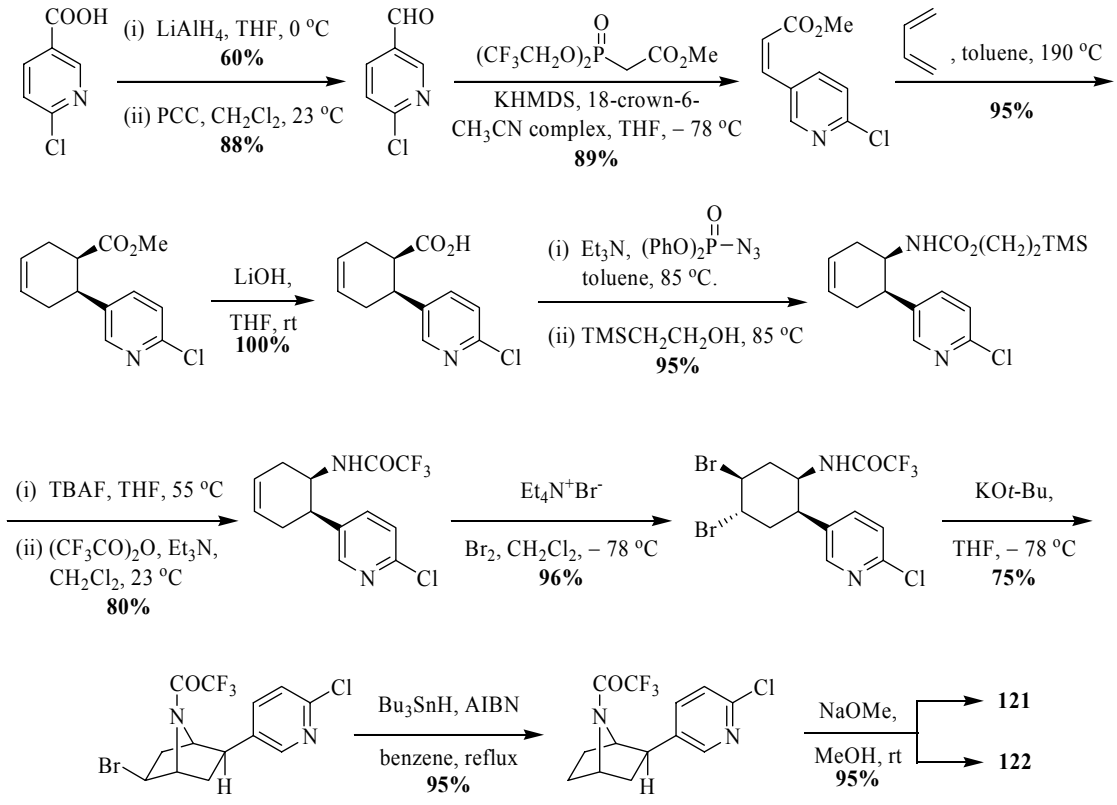
[53] For some examples of formal total synthesis of epibatidine, see: (a) Hernández, A.; Marcos, M.; Rapport, H. *J. Org. Chem.* **1995**, *60*, 2683. (b) Davis, C. R.; Johnson, R. A.; Ciadella, J. I.; Liggett, W. F.; Mizsak, S. A.; Marshall, V. P. *J. Org. Chem.* **1997**, *62*, 2244. (c) Singh, S.; Basmaddjian, G. P. *Tetrahedron Lett.* **1997**, *38*, 6829. (d) Ikeda, M.; Kugo, Y.; Kondo, Y.; Yamazaki, T.; Sato, T. *J. Chem. Soc., Perkin Trans, 1* **1997**, 3339. (e) albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *tetrahedron* **1997**, *53*, 17177. (f) Clive, D. L.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789.

[54] For a review on 7-azabicyclo[2.2.1]heptane ring system, see: Chen, Z.-M.; Trudell, M. L. *Chem. Review* **1996**, *96*, 1179.



Scheme 27. First total synthesis of (±)-epibatidine by Broka.

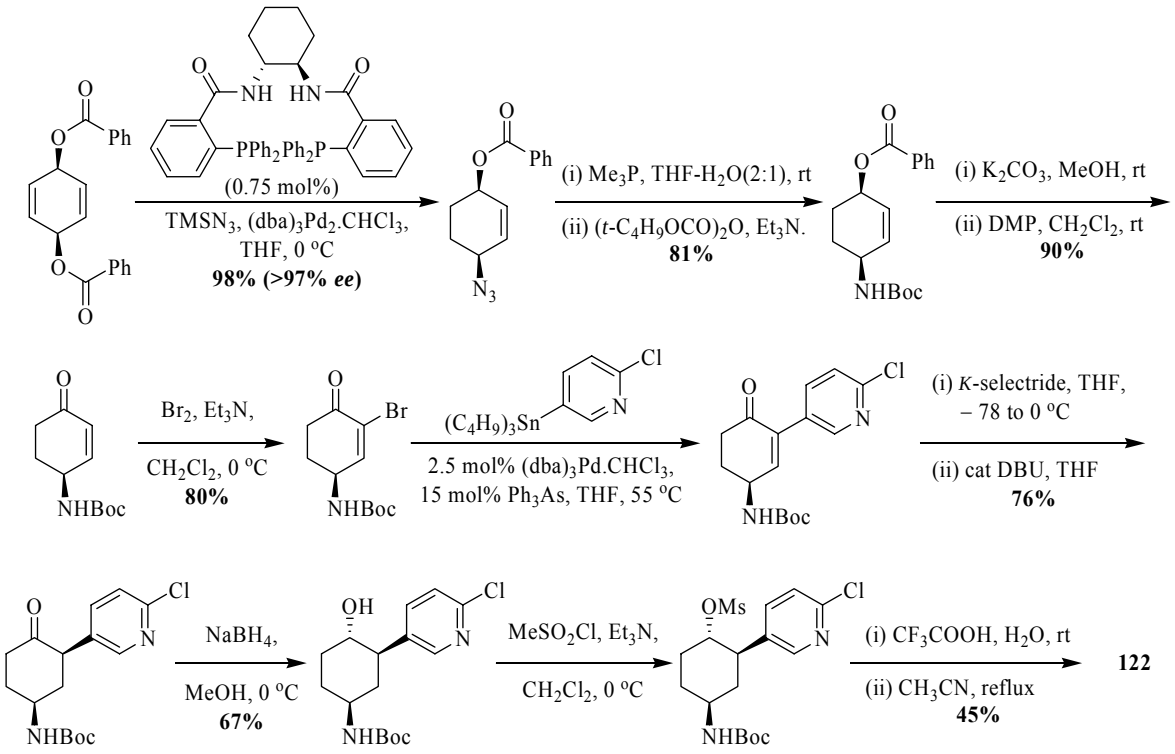
In 1993, Corey *et al.* reported a simple, efficient, and stereocontrolled synthesis of epibatidine (Scheme 28).[52c] As the absolute configuration of epibatidine was unknown at that time, this synthesis was developed to provide both possible enantiomers of epibatidine.



Scheme 28. Stereocontrolled total synthesis of (+) and (-)-epibatidine by Corey *et al.*

Trost and Cook demonstrated the first enantioselective synthesis of (–)-epibatidine in 1996 by employing a Pd catalyzed desymmetrization of *cis*-3,6-dibenzoyloxy-2-cyclohexene and a Pd catalyzed cross-coupling as key reactions (Scheme 29).[55] This synthetic route revealed the possibility to provide entry into either enantiomer of epibatidine which proceeds through the Boc derivative of enantiomerically pure 4-aminocyclohex-2-enone, a potentially versatile intermediate. In addition, it also represents a useful entry to enantiomerically pure 7-azabicyclo[2.2.1]heptanes without the need to effect resolutions.

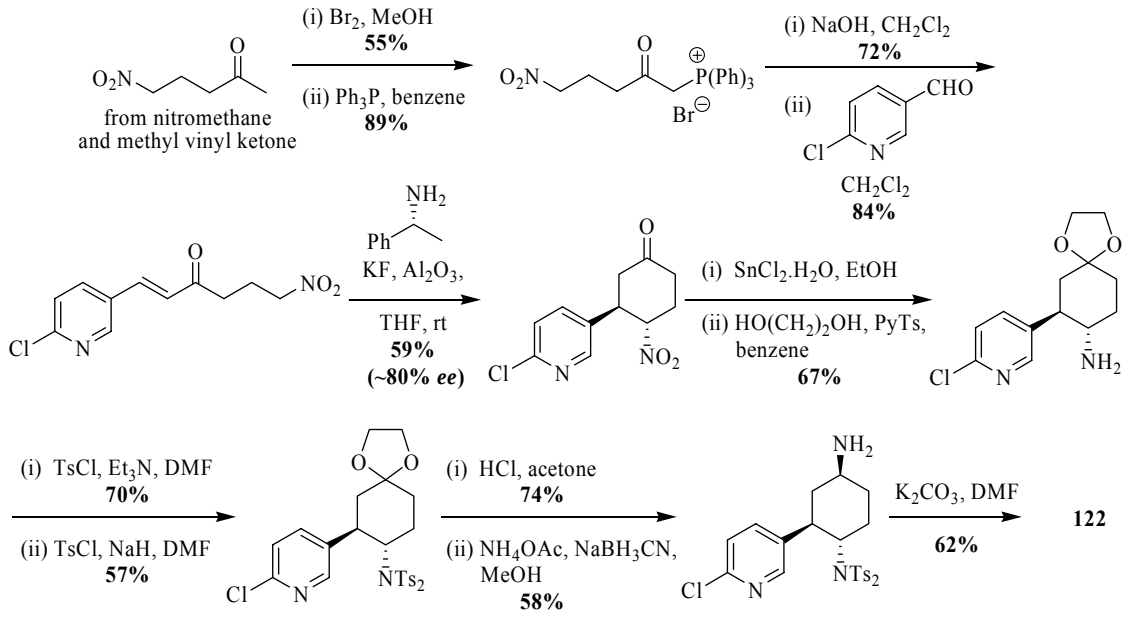
[55] Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485.



Scheme 29. Asymmetric synthesis of (-)-epibatidine by Trost *et al.* in 1996.

Szántay *et al.* designed two different syntheses of (–)-epibatidine in 1996 (Scheme 30).[56] While this synthesis was carried out using easily accessible reagents and convenient reaction conditions, the key step involved the ring closure of the prochiral *trans*-chloropyridinenitrohexenone catalyzed by optically active α-phenylethylamine to afford the chloropyridinenitrocyclohexanone in over 80% *ee*.

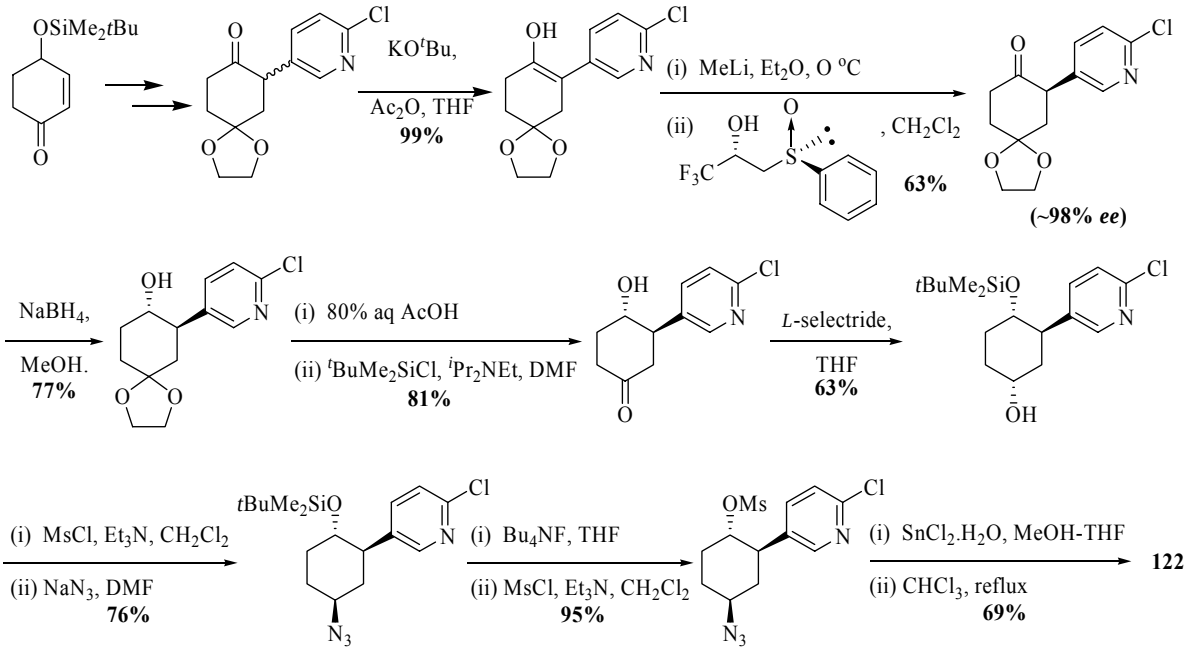
[56] Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C., Jr.; Temesvári-Major, E.; Blaskó, G. *Tetrahedron* **1996**, *52*, 11053.



Scheme 30. Enantioselective synthesis of (-)-epibatidine by Szántay *et al.*

In 1997, Kosugi *et al.* reported the asymmetric synthesis of (–)-epibatidine by employing the enantioselective protonation of the achiral lithium enolate of cyclohexanone derivative with chiral β-hydroxylsulfoxide (Scheme 31).[57]

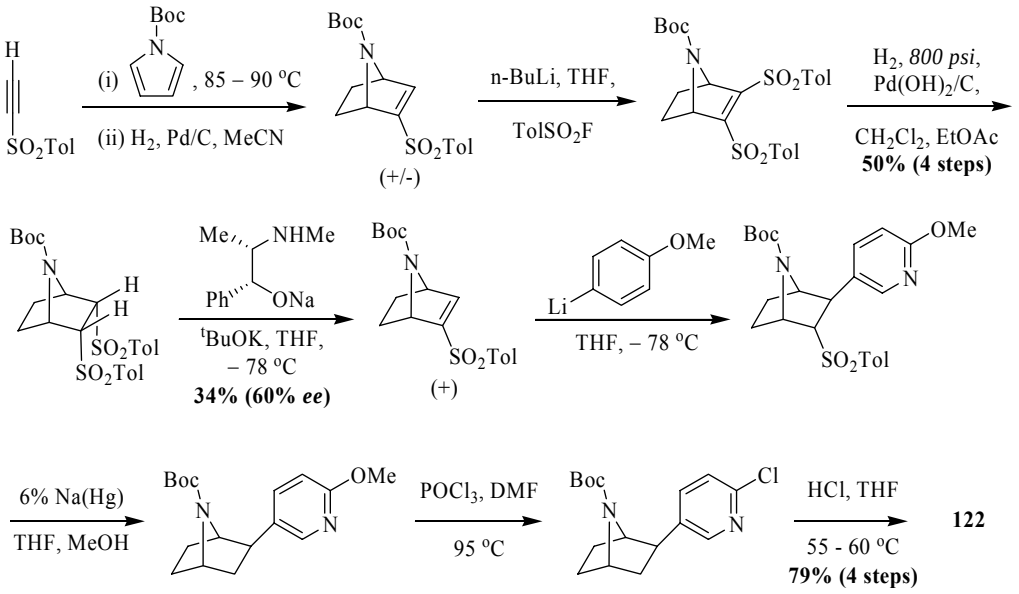
[57] Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997,** 1857.



Scheme 31. Asymmetric synthesis of (-)-epibatidine by Kosugi *et al.*

A year later in 1998, Jones and Simpkins revealed the asymmetric synthesis of (–)-epibatidine by the use of a novel enantioselective sulfinate elimination reaction (Scheme 32).[58] A vicinal bis-sulfone having the 7-azabicyclo[2.2.1]heptane skeleton underwent a novel type of asymmetric elimination on treatment with the sodium alkoxide derivative of (1*R*, 2*S*)-ephedrine, to give an alkenyl sulfone product, which is a key intermediate in this synthesis.

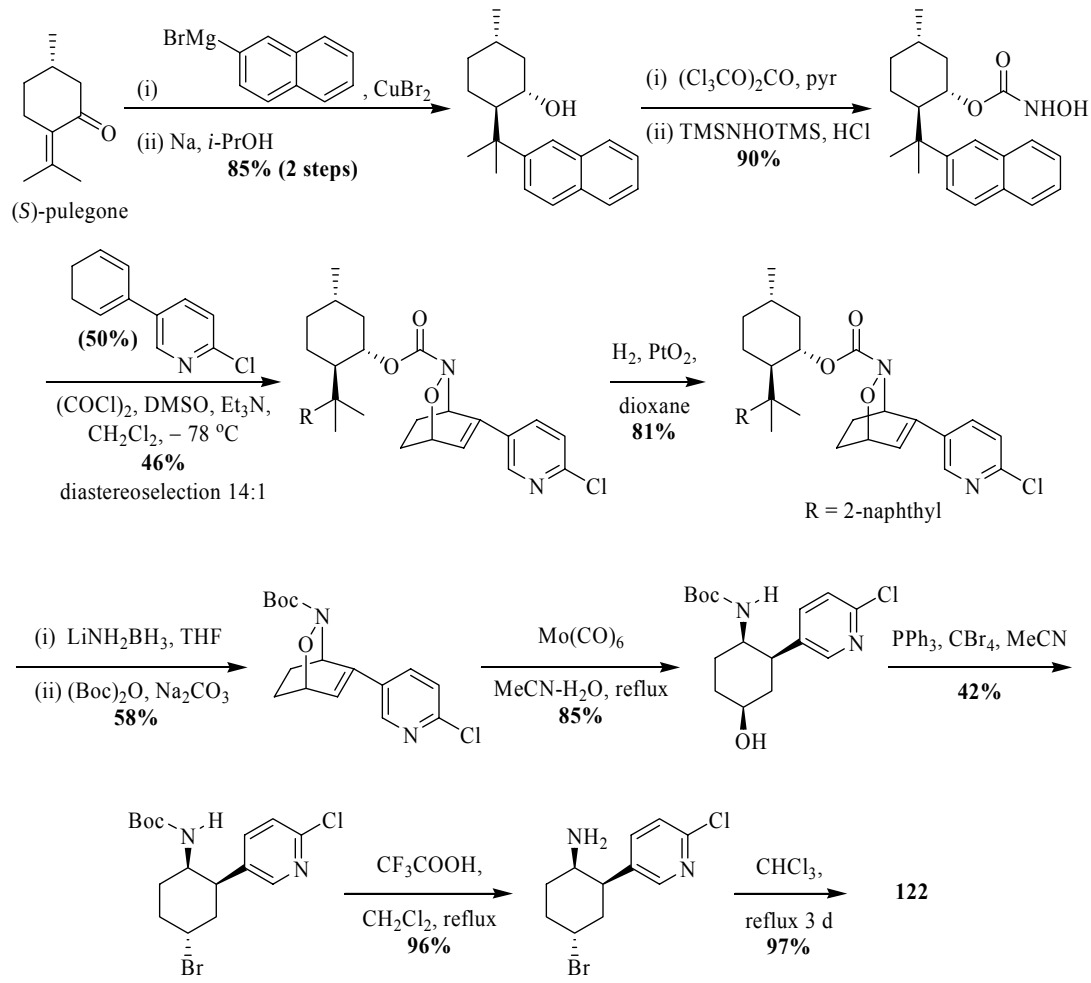
[58] Jones, C. D.; Simpkins, N. S.; Giblin, G. M. P. *Tetrahedron Lett.* **1998**, *39*, 1023.



Scheme 32. Asymmetric synthesis of (-)-epibatidine by Jones and Simpkins.

In the same year, Kibayashi *et al.* reported an interesting enantioselective synthesis of (–)-epibatidine based on an asymmetric hetero Diels-Alder cycloaddition with an N-acylnitroso dienophile bearing 8-(2-naphthy)menthol as the chiral auxiliary (Scheme 33).[59] It was postulated that π – π stacking interaction between the naphthyl and nitrosocarbonyl groups may have contributed to the facial control.

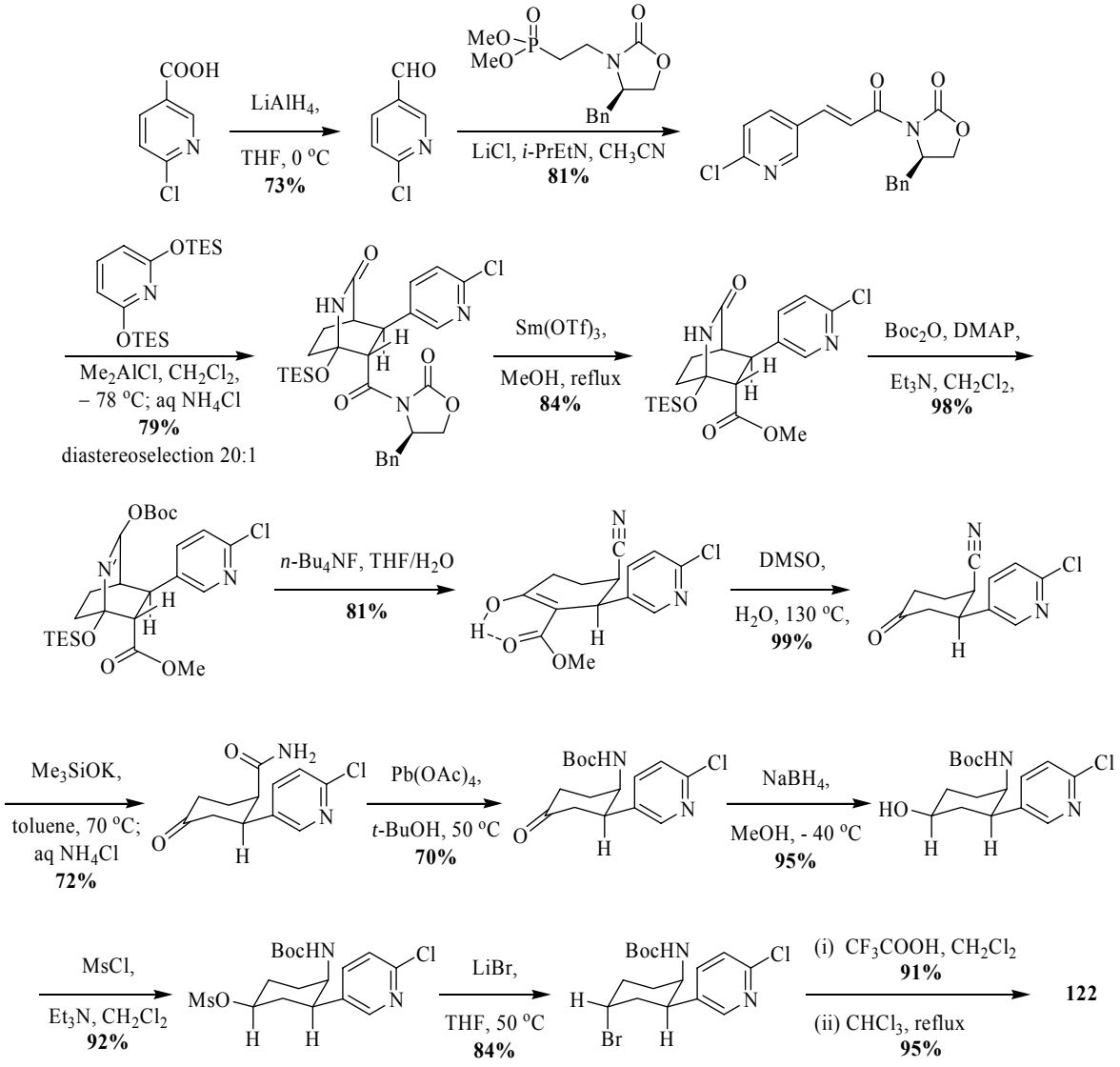
[59] (a) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 4513. (b) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397.



Scheme 33. Asymmetric total synthesis of (-)-epibatidine by Kibayashi *et al.*

The latest report on the enantioselective synthesis of (–)-epibatidine was accomplished by Evans *et al.* utilizing a highly *exo*-selective asymmetric hetero Diels-Alder reaction (Scheme 34).[60] The key steps employed to transform the resulting bicycle into the natural product includes a fluoride-promoted fragmentation and a Hofmann rearrangement.

[60] Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009.



Scheme 34. Synthesis of (-)-epibatidine by Evans *et al.*

2.4 OUR STRATEGY

In our approach towards the total synthesis of (–)-epibatidine, we had several goals in mind. First, we would like to make use of the metal mediated allylation reactions developed in our group to perform some of the carbon-carbon bond formation reactions for the molecule.[61] The principle behind our synthetic scheme is to provide the core structure (7-azabicyclo[2.2.1]heptane ring) in the shortest number of steps, making provision for a simple and efficient multigram scale synthesis that could be applicable in the drug industry. The synthetic route must also be versatile, allowing easy access to different analogues.

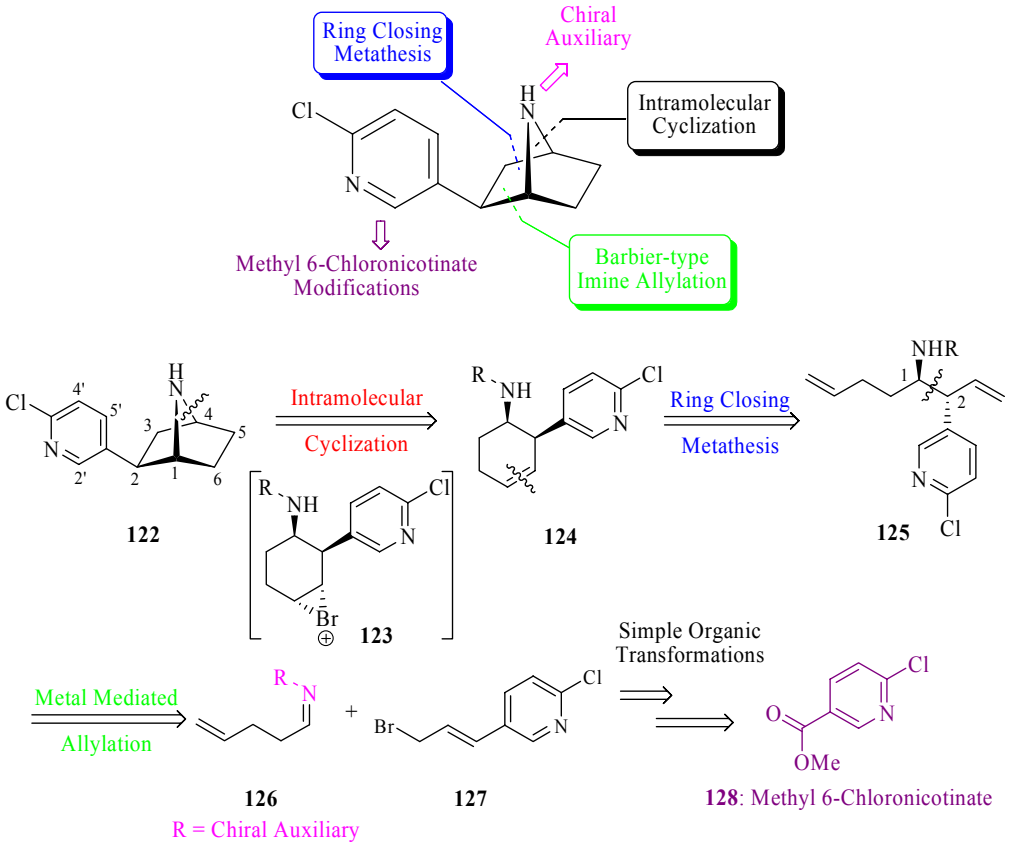
Our retrosynthetic analysis for (–)-epibatidine is shown in Scheme 35. The 7-azabicyclo[2.2.1]heptane ring of **122** was envisioned to arise by an intramolecular nucleophilic cyclization between the amine and the electrophilic brominium-bearing carbon of the intermediate precursor **123**.[62] The latter could have come from the bromination reaction involving N-bromosuccinimide (NBS) and the cyclohexenylamine **124**. We planned to utilize ring-closing metathesis (RCM) on the chiral homoallylic amine precursor **125** using the established ruthenium (Ru) type catalysts. The homoallylic amine may be prepared by an In-mediated Barbier type allylation between chiral imine **126** and 5-((*E*)-3-bromoprop-1-enyl)-2-chloropyridine **127**.[63]

---

[61] For some representative ezamples, see: (a) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042. (b) Tan, K.-T; Chng, S.-S; Cheng, H.-S; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (c) Loh, T.-P; Lin, M.-J; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507. (d) Loh, T.-P; Tan, K.-T; Hu, Q.-Y. *Tetrahedron Lett.* **2001**, *42*, 8705. (e) Loh, T.-P; Zhou, J.-R; Yin, Z. *Org. Lett.* **1999**, *1*, 1855. (f) Loh, T.-P; Zhou, J.-R. *Tetrahedron Lett.* **1999**, *40*, 9115.

[62] Chen, Z.-M.; Trudell, M. L. *Chem. Review* **1996**, *96*, 1179.

Our experience with imine allylation suggested that the ability to control the stereochemistry at C1 and C2 may be related to the judicious choice of chiral auxiliary used.[64] The chiral imine can be easily prepared through condensation from commercially available reagents. We see the commercially cheap methyl-6-chloronicotinate **128** as the precursor for 5-((*E*)-3-bromoprop-1-enyl)-2-chloropyridine **127**.



Scheme 35. Our general synthetic strategy.

[63] For a discussion of the mechanism, see: (a) Molle, B. *J. Am. Chem. Soc.* **1982**, *104*, 348175. For some representative examples, see: (b) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18. (c) Einhorn, C.; Einhorn, J.; Luche, J.-L. *Synthesis* **1989**, 787. (d) Molander, G. *Chem. Rev.* **1992**, *92*, 29. (e) Cintas, P. *Synthesis* **1992**, 248. (f) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943. (g) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023.

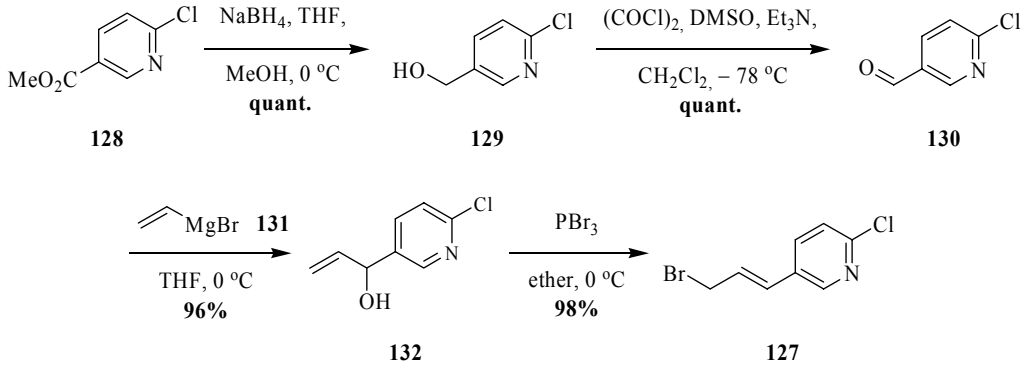
[64] (a) Huang, J.-M; Xu, K.-C; Loh, T.-P. *Synthesis-Stuttgart* **2003,** *5*, 755. (b) Loh, T.-P; Huang, J.-M; Xu, K.-C; Goh, S.-H; Vittal, J. J. *Tetrahedron Lett.* **2000**, *41*, 6511. (c) Loh, T.-P; Wang, R.-B; Tan, K.-L; Sim, K.-Y. *Main Group Met. Chem.* **1997**, *20*, 237. (d) Loh, T.-P; Ho, D. S. C; Xu, K.-C; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865.

The next section describes our progress towards the multigram scale total synthesis of (–)-epibatidine **122**. The synthesis commences from the commercially available methyl chloro-nicotinate **128**, by way of the homoallylic amine key intermediate **152**, to give the advanced intermediate **153**. Like most investigations in organic synthesis, we encountered several surprises and interesting results in our synthesis of (–)-epibatidine. Even though some changes were made in our synthetic strategy, subsequent manipulations were geared towards the synthesis of (–)-epibatidine.

2.5 RESULTS AND DISCUSSION I

Retrosynthetic analysis (Scheme 35) identified the commercially available methyl 6-chloronicotinate **128** as the starting material, which undergoes reduction with $NaBH_4$ in THF and MeOH (4:1) at 0 ^oC to provide the primary alcohol **129** in quantitative yield. The conversion of **129** to aldehyde **130** can be simply achieved by means of Swern oxidation.[65] Indeed, when the primary alcohol was introduced into a stirred solution of oxalyl chloride, dimethyl sulfoxide and CH_2Cl_2 at – 78 ^oC, a quantitative yield of the desired aldehyde was obtained when the reaction mixture was further stirred in triethylamine.[66] Aldehyde **130** then underwent a Grignard addition with vinylmagnesium bromide **131** in THF at 0 ^oC to provide the allylic alcohol **132** in 96% yield. The initial reaction conditions for the bromination procedure of the allylic alcohol **132** proved difficult in view of its rather low yield, leading to the adoption of a revised course of action to circumvent this problem. In the modified method, more solvent was used (from 0.3M to 0.1M) and this adaptation furnished the desired allylic bromide **127** with up to 98% yield (Scheme 36). With a practical synthesis of 5-((*E*)-3-bromoprop-1-enyl)-2-chloropyridine **127** realized (four steps, 97% yield from methyl 6-chloronicotinate **128**), our studies entered into the next synthetic phase.

[65] Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
[66] Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760.

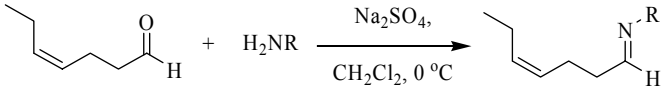


Scheme 36. Preparation of 5-((*E*)-3-bromoprop-1-enyl)-2-chloropyridine 127.

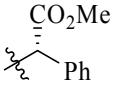
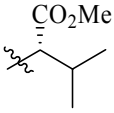
It is well documented that amino acid methyl esters are cheap and efficient chiral auxiliaries for the formation of chiral imines.[67] For that reason, a number of chiral auxiliaries, including a non-amino acid methyl ester type, were put to the test (Table 10). The optically pure amino acid methyl esters (**134** and **135**) were easily obtained by dissolving their hydrochloride salt form in saturated Na_2CO_3 and followed by extraction with diethyl ether. After drying and removal of solvent, the crude amines were used for subsequent reactions without any purification.

[67] For an excellent review, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. For a list of representative examples, see: (a) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc*. **1986**, *108*, 7778. (b) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (c) Neumann, W.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett*. **1991**, *32*, 5865. (d) Beuchet, P.; Le Martec, N.; Mosset, P. *Tetrahedron Lett*. **1992**, *33*, 5959. (d) Wu, M.-J.; Pridgen, L. N. *Synlett* **1990**, 636. (e) We, M.-J.; Pridgen, L. N. *J. Org. Chem*. **1991**, *56*, 1340. (f) Dembélé, Y. A.; Belaud, C.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511. (g) Tanaka, H.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett*. **1990**, *31*, 3023. (h) Dembélé, Y. A.; Belaud, C.; Hitchcock, P.; Villiéras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351. (i) Giammaruco, M.; Taddei, M.; Ulivi, P. *Tetrahedron Lett*. **1993**, *34*, 3635. (j) Bhuyan, P. J.; Prajapati, D.; Sandhu, J. *Tetrahedron Lett*. **1993**, *34*, 7975. (k) Laschat, S.; Kunz, H. *Synlett* **1990**, 51. (l) Laschat, S.; Kunz, H. *J. Org. Chem*. **1991**, *56*, 5883. (m) Alvaro, G.; Martelli, G.; Savoia, D. *J. Chem. Soc. Perkins Trans.* **1998**, *1*, 777. (n) Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem Commun*. **1993**, 1542. (o) Razavi, H.; Polt, R. *J. Org. Chem*. **2000**, *65*, 5693.

Table 11. Imine formation using different chiral amines.[a]



133 **134 - 136** **137 - 139**

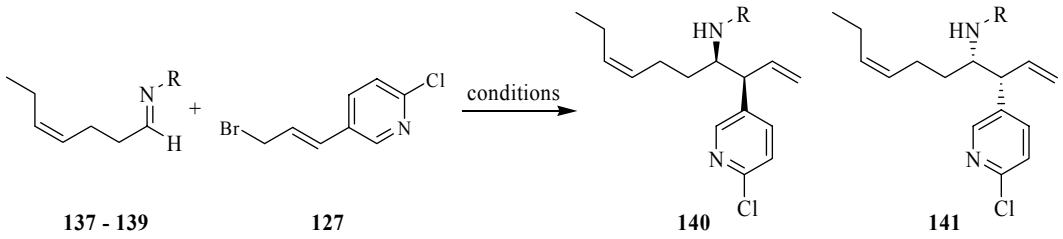
Entry	Amine	R	Imine	Time (h)	Yield (%)[b]
1	**134**		**137**	5	~ 100
2	**135**		**138**	6	98
3	**136**		**139**	4	87

[a]1.0 equivalent of aldehyde was allowed to condense with 1.0 equivalent of chiral amine. [b]Crude yield; which was determined by ^{1}H NMR.

The chiral imines were formed by stirring a mixture of the commercially available aldehyde **133**[68] and the amine in CH_2Cl_2 at 0 ^oC for up to 6 h. The crude imines were used for subsequent reactions without any purification. We next evaluated a number of substrates in the imine allylation pathway. Imines formed from (*S*)-phenylglycine methyl ester **134**, (*S*)-valine methyl ester **135** and (*S*)-methylbenzylamine **139** were assessed. As revealed in Table 12, various allylation conditions on imine **139** were not successful (Table 12, entries 9, 10, 11 and 12). Despite the failure to attain the desired product using In mediated conditions (using DMF and MeOH as the solvent medium), the reactions using Zn/THF on the imine **138** did furnish the desired homoallylic amine product (Table 12, entry 8). (*S*)-Phenylglycine methyl ester **134** appears to be the better chiral auxiliary in this case, providing a satisfactory 59% yield and a diastereoselectivity ratio (*dr*) of 70:30 (Table 12, entry 4).[69]

[68] *cis*-Hept-4-enal **133** was used initially in this study as pent-4-enal **150** was not available at that point of research.
[69] The absolute configuration was determined by X-ray crystallographic analysis of an intermediate at a later stage.

Table 12. Allylation of imines 137 – 139 using different conditions.

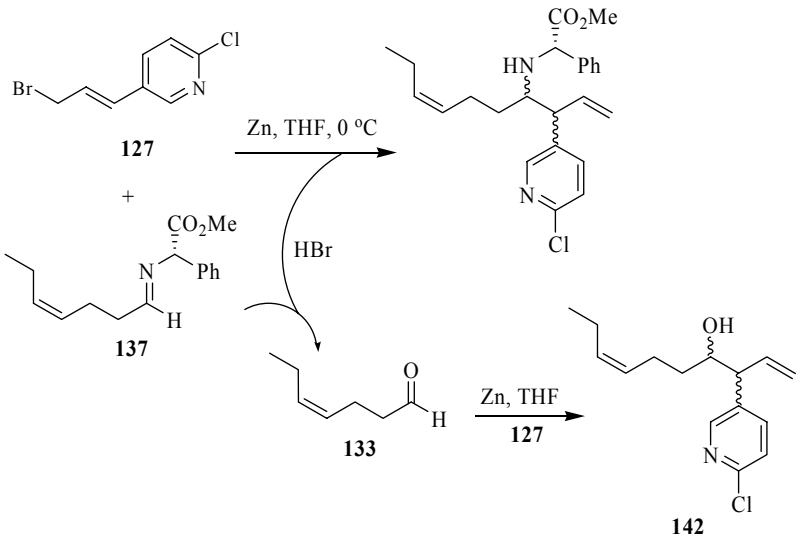


137 - 139 **127** **140** **141**

Entry	Imines (R)	Conditions	Yield (**140:141**)[a]
1	**137**	In, DMF, 0 °C	-
2		In, MeOH, 0 °C	-
3		In, $InCl_3$, MeOH, 0 °C	-
4		Zn, THF, 0 °C	59% (70:30)
5	**138**	In, DMF, 0 °C	-
6		In, MeOH, 0 °C	-
7		Mg, THF, 0 °C	-
8		Zn, THF, 0 °C	29% (65:35)
9	**139**	In, DMF, 0 °C	-
10		In, MeOH, 0 °C	-
11		Mg, THF, 0 °C	-
12		Zn, THF, 0 °C	-

[a]Diastereoselectivity ratio (*dr*) based on the only 2 isomers obtained from the reaction, determined by ^{1}H NMR and ^{13}C NMR.

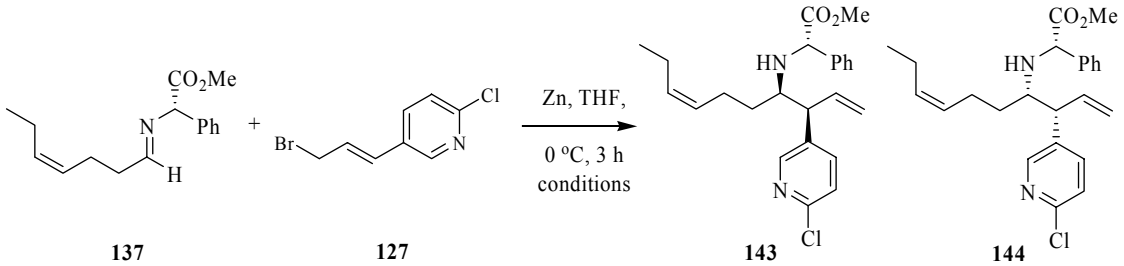
With (*S*)-phenylglycine methyl ester **134** being the chosen chiral auxiliary, we went on to investigate the allylation procedure in detail. It is noteworthy to point out that several side products were formed during the course of the Zn mediated allylation of imine **137** in THF (Scheme 38). One of them, the aldehyde side product **142**, is believed to arise from the allylation of the aldehyde, which had probably been "cleaved off" from the imine. Even though detailed mechanistic studies were not performed, we postulate that the source of the protons needed for this kind of hydrolysis reaction would come from the HBr produced by the allylation reaction with the allylic bromide **127**.



Scheme 38. Plausible explanation of the formation of 142.

In order to circumvent this problem, the chiral amine **134** was added in excess for the formation of the imine **137**. We postulated that the excess amine would serve as a base to neutralize the undesired acidic protons in the reaction. As revealed in Table 13, the excess chiral amine added proved to be the key factor in the reconsumption of the undesired aldehyde. Optimum conditions were obtained when a 0.5 M solution of the allylic bromide **127** in THF was slowly added a stirred suspension of Zn, imine **137** (formed from 1.0 equivalent of aldehyde with 1.5 equivalent of chiral amine **134**) and THF at 0 ^{o}C (Table 13, entry 3).

Table 13. Imine allylation under selected conditions.



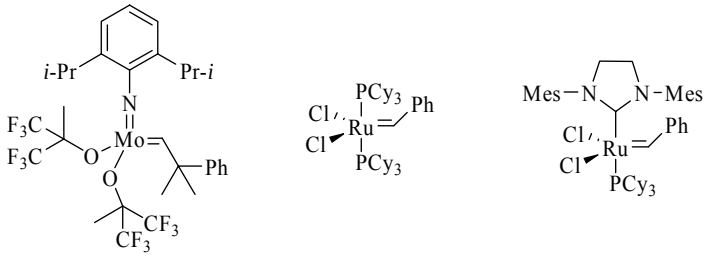
137 **127** **143** **144**

Entry	Imine **137**		**127**	Yield (**143**:**144**)[a]
	Aldehyde (equiv)	Amine (equiv)		
1	1.0	1.0	Neat (solid)	59% (70:30)
2	1.0	1.2	0.5 M solution[b]	20% (95:5)
3	1.0	1.5	0.5 M solution[b]	75% (87:13)

[a]Diastereoselectivity ratios were based on the 2 isomers isolated from the reaction. [b]**127** was prepared as a 0.5 M solution in THF.

Because of the availability of efficient ruthenium and molybdenum catalysts, the olefin metathesis reaction has emerged as a new and powerful method in organic chemistry.[70] More importantly, ring-closing metathesis (RCM) is widely recognized as a powerful method for creating heterocycles, constrained peptides, and complex natural products.[71] Schrock's molybdenum based catalyst **145** is characterized by its very high activity, however, its sensitivity towards air and moisture requires handling under rigorously dried solvents, under an inert atmosphere.[72] In contrast, the Grubbs' ruthenium catalysts **146**[73] and **147**[74] have been used most extensively in RCM because of their high reactivity, air-stability, and remarkable functional group tolerance (Figure 9).

[70] For a general review, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012-3043.
[71] For excellent reviews on the RCM with nitrogen-containing compounds, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (b) Pandit, U. K.; Overkleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959. (c) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.
[72] For some examples, see: (a) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2114. (b) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036.
[73] Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9858.
[74] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.



145 **146** **147**

Figure 9. Schrock's molybdenum and Grubbs' ruthenium catalysts.

While amino acids and amide type functional groups have enjoyed much success,[75] alkylated amines are typically incompatible with RCM owing to catalyst inhibition by the basic nitrogen.[76] In our case, the scenario is made worse with the presence of another pyridine-type functional group. Since it was considered desirable to avoid the use of protecting group strategies during the assembly of the 7-azabicyclo[2.2.1]heptane ring, we first examined the cyclization of the homoallylic amine **148** without the presence of other addictives.

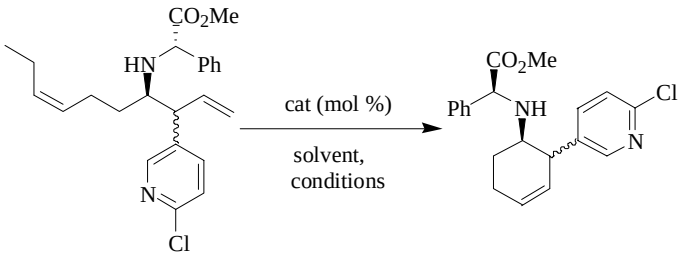
[75] For selective examples employing RCM for total synthesis of natural products, see: (a) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (b) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chemie. Int. Ed.* **2004**, *43*, 2020. (c) Kim, S.; Lee, T.; Lee, E.; Tan, G.-J.; Lee, S. K.; Kim, D. *J. Org. Chem.* **2004**, *69*, 3144. (d) Davis, A. S.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2004**, *69*, 3139. (e) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (f) Felpin, F. X.; Boubekeur, K.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *23*, 4518. (g) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87. (h) Wang, X.; Porco, Jr. J. A. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (i) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042. (j) Schaudt, M.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 2913. (k) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774. (l) Humphrey, J. M.; Liao, Y.-S.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (m) Fellows, I. M.; Kaelin, Jr. D. E.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781. (n) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738. (o) Cook, G. R.; Shanker, P. S.; Peterson, S. L. *Org. Lett.* **1999**, *1*, 615. (p) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 2027. (q) Voigtmann, U.; Blerchet, S. *Org. Lett.* **2000**, *2*, 3971. (r) Maldaner, A. O.; Pilli, A. A. *Tetrahedron Lett.* **2000**, *41*, 7843.
[76] (a) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (b) Wright, D. L.; Schulte II, J. P.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847.

The branched homoallylic amine **148** was submitted to RCM using Grubbs' catalysts **145** and **146** in various amounts and different reaction conditions. Based on classical RCM conditions, two reaction solvents for the reaction were chosen, CH_2Cl_2 and toluene. The results are presented in Table 14.

RCM using catalyst **145** yielded no desired product (Table 14, entry 1). Exposure to catalyst **146** under reflux conditions when employing either toluene or CH_2Cl_2 as reaction solvent provided unsatisfactory results (Table 14, entries 1 and 2). Even though it has been demonstrated that ammonium salts can tolerate the ruthenium catalyst **146**, the introduction of Brönsted and Lewis acids such as *p*TsOH and $TiCl_4$ respectively, complicated the results further (Table 14, entries 3 and 5). Nevertheless, the desired cyclohexenylamine product **149** was isolated in 54% yield when the much robust catalyst 146 was used (Table 13, entry 7). The homoallylic amine was cyclized productively (69% yield) when the reaction was carried out under more dilute conditions (0.01M).[77]

[77] For an example on the effects of concentration in some RCM reactions, see: Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297.

Table 14. Reaction conditions for the RCM of homoallylic amine 148.[a]



148 **149**

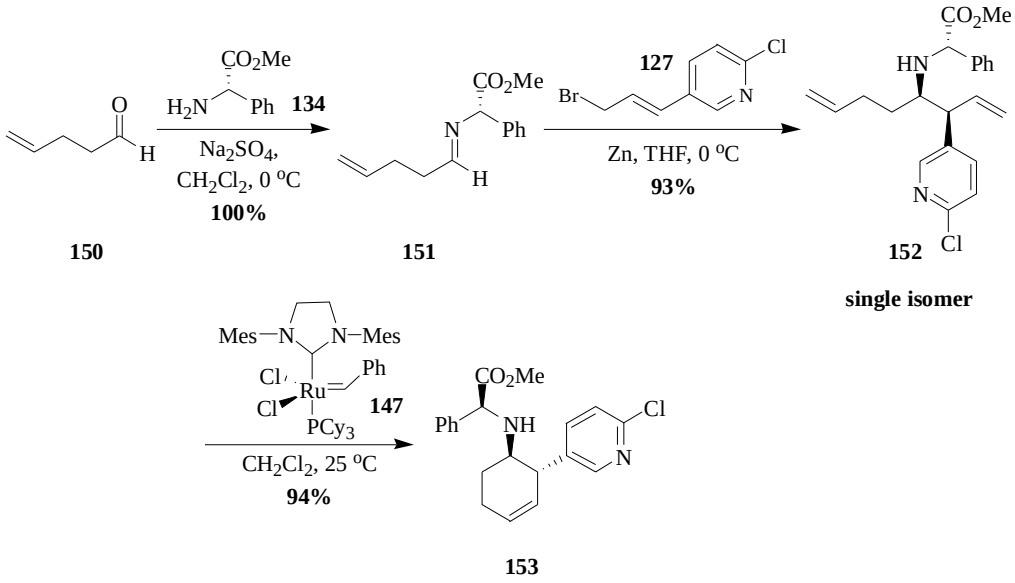
Entry	Cat. (mol %)	Solvent	Temp. (^{o}C)	Conditions	Time (h)	Yield (%)
1	**145** (10)	CH_2Cl_2	25	-	>24	-
2	**146** (20)	CH_2Cl_2	40	-	>24	15
3	**146** (20)	CH_2Cl_2	25	*p*TSA[b]	>24	-[c]
4	**146** (20)	CH_2Cl_2	25	Sonicate	1	Trace
5	**146** (20)	CH_2Cl_2	25	$TiCl_4$[d]	>24	-
6	**146** (10)	Toluene	110	-	>24	<10
7	**147** (20)	CH_2Cl_2	25	-	7	54[e] (69)[f]
8	**147** (10)	CH_2Cl_2	25	-	6	88[g]

[a]A mixture of 2 isomers were used for RCM and the *dr* was maintained based on ^{1}H NMR and ^{13}C NMR of the products obtained. [b]1.0 equivalent of *p*TsOH added. [c]No product was observed even when 2.0 equivalent of *p*TSA was added. [d]0.2 equivalent of $TiCL_4$ added. [e]Solvent concentration at 0.1 M. [f]Solvent concentration at 0.01 M. [g]Reaction was carried out using 2 sequential loadings of **147**.

The yield was greatly improved (88%) when the catalyst was loaded on two separate occasions at about 0.5 h apart and with only a total loading of 10 mol % (Table 14, entry 8). It was observed that the RCM could be effected without blocking the secondary nitrogen although these transformations would ultimately involve higher catalyst loading and longer reaction times than typical metathesis reactions.

It is well documented that monosubstituted alkenes readily give the desired RCM product in excellent yields.[70] To test this theory, the aldehyde **150** was used for the synthesis of the homoallylic amine **152** (Scheme 39). The desired homoallylic amine **152** was isolated in excellent yields as a single isomer (93% yield). Even though mechanistic data was not available, we postulate that this improved selectivity, compared to chiral

imine **137** (Table 13, entry 3), was due to the excess chiral amine (0.5 equiv more) in the reaction mixture. The subsequent RCM went very smoothly to afford the desired cyclohexenylamine **153** with an improved yield of 94% and 10 mol % catalyst loading.



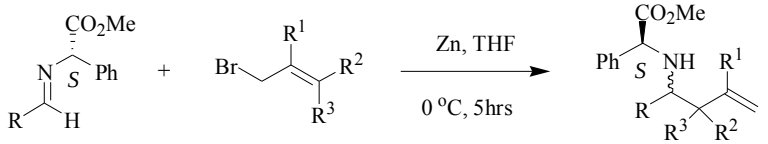
Scheme 39. Improved synthesis of 153.

2.5.1 ASYMMETRIC SYNTHESIS OF *C*-ALIPHATIC HOMOALLYLIC AMINES AND BIOLOGICALLY IMPORTANT CYCLOHEXENYLAMINE ANALOGS

Given the success of the asymmetric synthesis of the homoallylic amine **152** and the cyclohexenylamine **153**, we next explored their generality in order to test the viability of this strategy.[78] Our initial studies on the Barbier tyope allylation revealed that a relatively high asymmetric induction can be accomplished using a variety of allylic bromides (Table 15). When cyclohexanecarbaldehyde was used as the corresponding aldehyde moiety for the construction of the chiral imine **37**, the reactions with allylic bromides generally provide satisfactory yields. In fact, crotylation and prenylation of the chiral imine **154** provided excellent yields with good selectivities and *syn*/*anti* ratios (Table 15, entries 2 and 3). As expected, this Zn mediated allylation using THF as the solvent of choice gave the desired homoallylic amines derived from 3-phenylpropanal, although in modest yields (for allyl and metallyl bromides) except when prenyl and cinnamyl bromides were used (Table 14, entries 7 and 8). Nonetheless, good diastereoselectivities and *syn*/*anti* ratios were achieved in all cases.

[78] (a) Maier, M. E.; Lapeva, T. *Synlett* **1998**, 891. (b) Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 2323.

Table 15. Allylation of Chiral Imines Using Different Allylic Bromides.[a]



R = *c*-C_6H_5 (**154**)
$PhCH_2CH_2$ (**155**)
CH_2=$CHCH_2CH_2$ (**151**)
CH_3CH_2CH=$CHCH_2CH_2$ (**137**)

Entry	R	R^1	R^2	R^3	Yield	*dr* (*S,R*:*S,S*)[b]	*syn*:*anti*[c]
1	*c*-C_6H_{11}	H	H	H	60	12:88	-
2	*c*-C_6H_{11}	H	CH_3	H	94	80:20	75:25[e]
3	*c*-C_6H_{11}	H	CH_3	CH_3	92	89:11	-
4	*c*-C_6H_{11}	H	Ph	H	65	88:12	82:18[d]
5	*c*-C_6H_{11}	CH_3	H	H	65	11:89	-
6	$PhCH_2CH_2$	H	H	H	20	18:82	-
7	$PhCH_2CH_2$	H	CH_3	H	39	78:22	79:21[e]
8	$PhCH_2CH_2$	H	CH_3	CH_3	63	89:11	-
9	$PhCH_2CH_2$	H	Ph	H	50	88:12	90:10[d]
10	$PhCH_2CH_2$	CH_3	H	H	20	10:90	-
11	CH_2=$CHCH_2CH_2$	H	H	H	26	15:85	-
12	CH_2=$CHCH_2CH_2$	H	CH_3	H	52	75:25	86:14[e]
13	CH_2=$CHCH_2CH_2$	H	CH_3	CH_3	63	89:11	-
14	CH_2=$CHCH_2CH_2$	H	Ph	H	55	10:90	95:5[d]
15	CH_2=$CHCH_2CH_2$	CH_3	H	H	25	35:65	-
16	CH_3CH_2CH=$CHCH_2CH_2$	H	H	H	25	13:87	-
17	CH_3CH_2CH=$CHCH_2CH_2$	H	CH_3	H	45	80:20	81:19[d]
18	CH_3CH_2CH=$CHCH_2CH_2$	H	CH_3	CH_3	92	90:10	-
19	CH_3CH_2CH=$CHCH_2CH_2$	H	Ph	H	59	10:90	88:12[f]
20	CH_3CH_2CH=$CHCH_2CH_2$	CH_3	H	H	15	27:73	-

[a]Allylic bromides used (crotyl and cinnamyl) were predominantly *trans*. [b]Determined by ^{1}H NMR and ^{13}C NMR; unless in some cases where the diastereomers can be well separated by flash column chromatography. [c]Determined by ^{1}H NMR and ^{13}C NMR; *syn*/*anti* ratios refer to only the 2 major diastereomers. [d]Traces of linear homoallylic amines were isolated. [e]No linear homoallylic amine was observed.

The allylation of chiral imine **151** with pent-4-enal as the aldehyde, proceeded smoothly and afforded some of the desired homoallylic amines with relatively good yields, high diastereoselectivities and excellent *syn*/*anti* ratios. Prenyl bromide proved again to be the allylic bromide of choice when it gave the desired chiral homoallylic amine with 72% yield and 78% *de* (Table 15, entry 13). Though the reactions with crotyl

and cinnamyl bromides both gave slightly lower yields, fine *syn*/*anti* ratios were obtained (Table 15, entries 12 and 14). We next examined the ability of this methodology to *cis*-hept-4-enal. Considerable variation of allylic bromides is possible without any significant loss in efficiency of diastereocontrol (up to 92% yield and 80% *de*). Besides, a relatively high ratio of *syn* adducts were obtained in all cases. It is interesting to note that the reactions of cinnamyl bromide with chiral imines **154** and **155** resulted in trace amount of the linear homoallylic amine adducts, but however, when the same bromide was injected into either chiral imines **137** or **151**, no such side products were observed.

The homoallylic amines synthesized from **151** in Table 15 were then converted to the corresponding cyclohexenylamines using the RCM approach.[78] These chiral cyclohexenylamines are important building blocks for several alkaloids such as sarain A,[79] aphanorphine,[80] hetisine,[81] and some of the *Securinega* group.[82] More interestingly, some of these cyclohexenylamines, in the presence of inorganic pyrophosphate, have been reported to show strong cooperative inhibition with trichodiene synthase.[83]

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[79] (a) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem*. **1998**, *63*, 9616. (b) Irie, O.; Samizu, K.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem*. **1999**, *64*, 587. (c) Downham, R.; Ng, F.-W.; Overman, L. E.; *J. Org. Chem*. **1998**, *63*, 8096. (d) Sung, M. J.; Lee. H. I.; Chong, Y.; Cha, J. K. *Org. Lett*. **1999**, *1*, 2017.

[80] (a) Tamura, O.; Yanagimachi, T.; Kobayashi, T.; Ishibashi, H. *Org. Lett*. **2001**, *3*, 2427, and references cited therein.

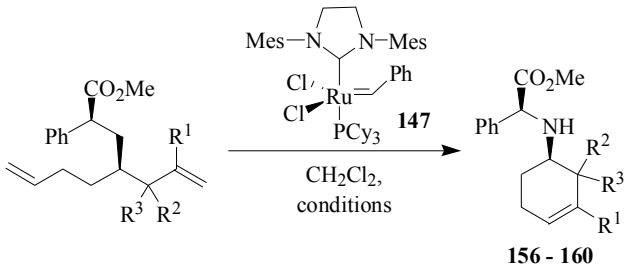
[81] Kwak, Y.-S.; Winkler, J. D. *J. Am. Chem. Soc*. **2001**, *123*, 7429.

[82] Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett*. **2001**, *3*, 703, and references cited therein

[83] (a) Mcgready, P.; Pyun, H.-J.; Coates, R. M.; Croteau, R. *Arch. Biochem. Biophys*. **1992**, *299*, 63. (b) Cane, D. E.; Yang, G.-Y.; Coates, R. M. Pyun, H.-J.; Hohm, T. M. *J. Org. Chem*. **1992**, *57*, 3454.

As revealed in Table 16, the homoallylic amines underwent ring-closing metathesis in excellent yields. These ring-closing reactions were performed by stirring a dichloromethane solution of the homoallylic amines in the presence of 10 mol % of the catalyst **147** for up to 12 hours. In all cases, the cyclohexenylamines derivatives can be obtained in very good yields.[76] It is important to note that most of the homoallylic amines needed reflux conditions to allow full depletion. However, the cyclohexenylamine product **158** was obtained in excellent yield (92 %) with 10 mol% of the catalyst stirring at ambient temperature (Table 16, entry 3).

Table 16. RCM of Homoallylic Amines Derived from Chiral Imine 151.[a]



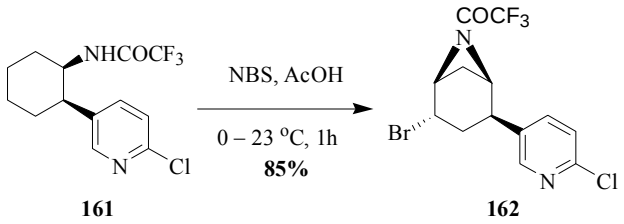
156 - 160

Entry	R^1	R^2	R^3	Temp. (^{o} C)	Time (h)	Product	Yield (%)
1	H	H	H	40	6	**156**	88
2	H	CH_3	H	40	6	**157**	84
3	H	CH_3	CH_3	25	12	**158**	92
4	H	H	H	40	6	**159**	86
5	CH_3	H	H	40	6	**160**	78[b]

[a]Only the major (*S*,*R*)-diastereomer was allowed to undergo ring-closing metathesis. [b]15 mol % of the catalyst was used.

2.6 RESULTS AND DISCUSSION II

With relatively large quantities of cyclohexenylamine **153** in hand, attention was turned to the synthesis of the 3-membered ring brominium intermediate **123** which will most probably undergo in situ intramolecular cyclization with the presence of the amine nucleophile. As reported by Corey *et al.*, the unsaturated amide **161** could serve as a useful intermediate for the synthesis of azabicyclo[3.3.1]heptane analogues of epibatidine (Scheme 40).[52c] Reaction of **161** with *N*-bromosuccinimide in acetic acid at 0 – 23 ^{o}C for 1 h afforded the azabicyclo[3.1.1]heptane derivative **162**.



161 **162**

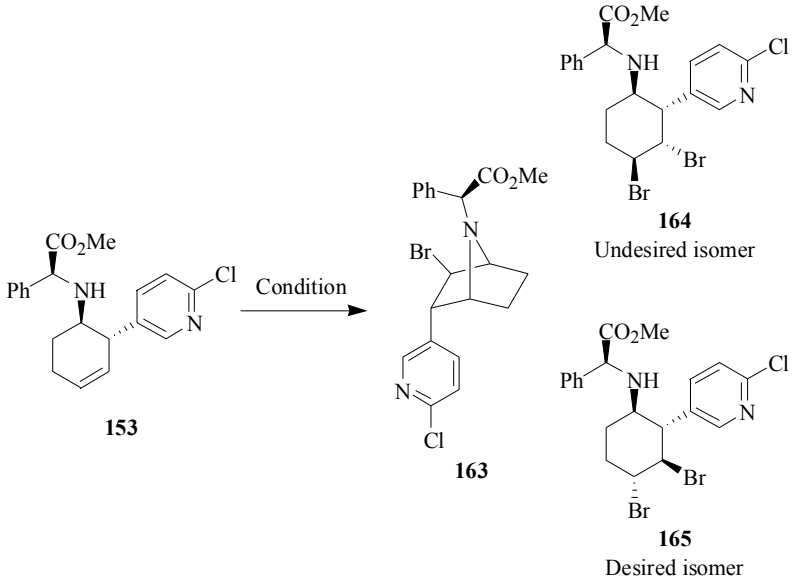
Scheme 40. Novel intramolecular cyclization reported by Corey *et al.* in 1993.

Upon attempting to brominate the cyclohexenylamine **153** under similar conditions described above, we observed no desired product **163** and instead, trace amount of dibrominated product **164** was isolated. As revealed in Table 17, bromination of **153** in other commonly known solvents proved futile, despite formation of trace amounts of **164** in chlorinated solvents (entries 2 and 3).

Our revised plan towards the construction of the 7-azabicyclo[2.2.1]heptane ring then turned to traditional bromination. We envisioned that with the desired dibromo isomer

formed, where the amino group and bromide atom are *trans* with respect to each other, intramolecular cyclization could arise. Bromination of **153** under various selected conditions is revealed in Table 17.

Table 17. Bromination of 153 under various conditions.[a]



Entry	Conditions	T (^{o}C)	Cyclized Product Yield (%)	Dibrominated Product Yield (%) (**164**:**165**)
1	NBS, AcOH[c]	0	-	-[b]
2	NBS, CH_2Cl_2	− 78	-	<10 (-)
3	NBS, $Et_4N^+Br^-$, CH_2Cl_2	− 78	-	53 (85:15)
4	Br_2, CH_2Cl_2	− 78	-	65 (>99:<1)
5	Br_2, $Et_4N^+Br^-$, CH_2Cl_2	0	-	78 (93:7)
6	Br_2, $Et_4N^+Br^-$, CH_2Cl_2[c]	− 78	-	92 (66:34)

[a]For NBS reactions: they were performed in AcOH (10 mL) where NBS (2.4 mmol) was added into **153** (2 mmol) at the 0 ^{o}C temperature. [b]**153** was almost fully recovered. [c]The reaction was carried out in more dilute conditions.

A single-crystal X-ray structure of **164** confirmed that the bromination had occurred in the undesired fashion for further intramolecular cyclization, with the amino group and bromide atom being *cis* with respect to each other (Figure 10). Based on this

crystallographic analysis and simple retrosynthetic study, the absolute configurations of all the preceding intermediates were established.

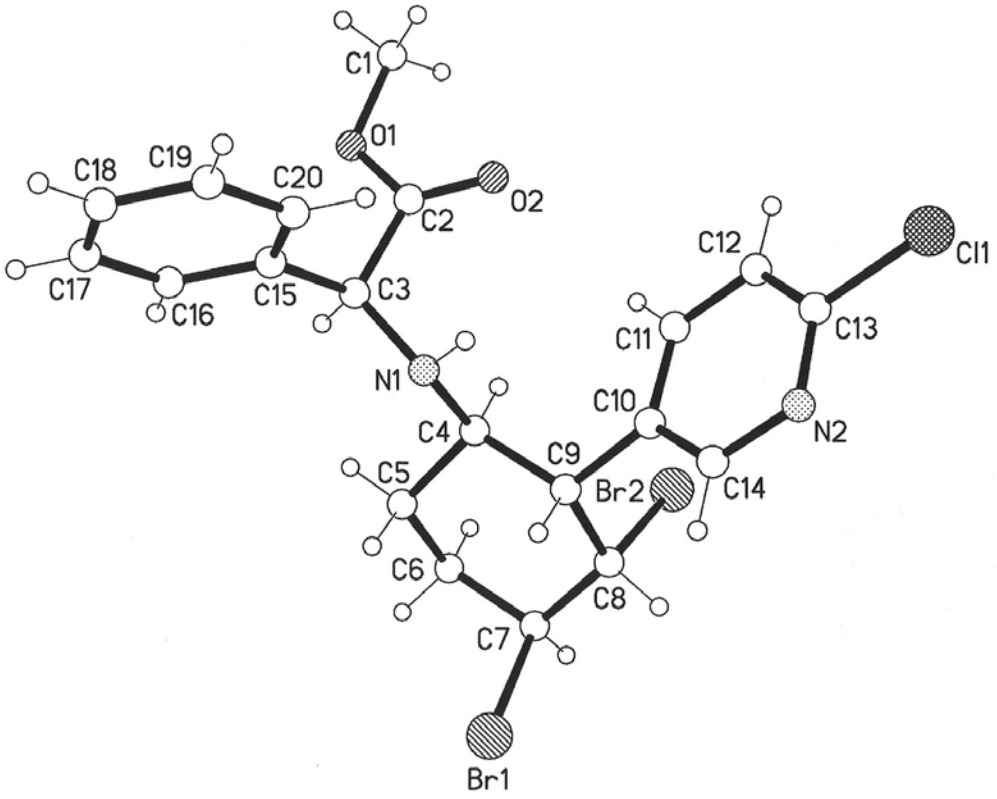
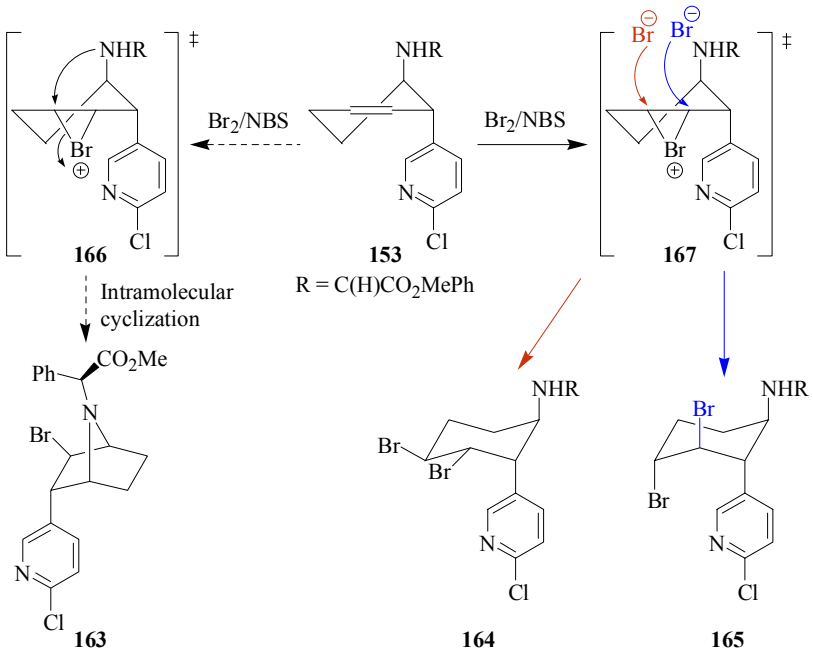


Figure 10. Single-crystal X-ray structure of 164.

Although definitive mechanistic data has not been obtained, one possibility, outlined in Scheme 41, appears to be reasonable. The unsuccessful attempt using NBS in chlorinated solvents concluded that no nucleophilic attack of the amino group on the electrophilic carbon had taken place, that will eventually lead to the 7-azabicyclo[2.2.1]heptane ring of **163**. The formation of the 2 dibromo diastereomers **164** and **165** suggested that the 3-membered brominium ion did formed, probably in the state

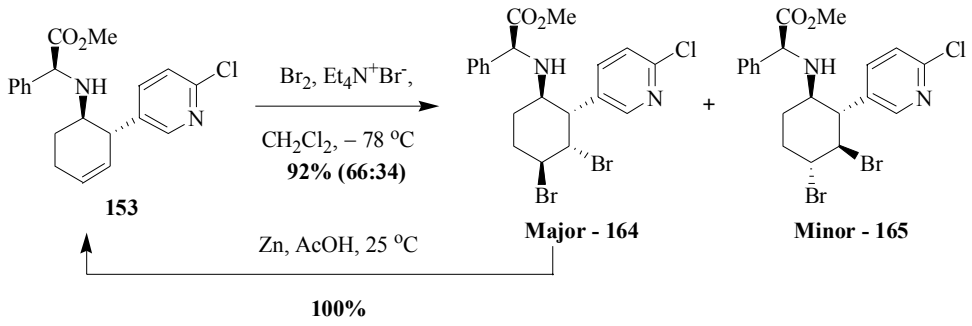
of intermediate **167**. Subsequent ring opening by the bromide nucleophile (from $Et_4N^+Br^-$) then furnished the 2 epimers.



Scheme 41. Proposed mechanism for the bromination (Br_2/NBS) of Cyclohexenylamine 153.

Through systematic investigations, the optimum conditions to afford the dibromo isomer with the desired *trans* stereochemistry required more dilute conditions to be added and in addition, the Br_2 (further diluted with CH_2Cl_2) had to be introduced very slowly into the stirred mixture of **153** at – 78 ^oC (Table 17, entry 6). Under these optimized reaction conditions, the bromination could be efficiently carried out in excellent yield (92 %) and moderate selectivity. The 66:34 mixture of diastereomers obtained was easily separable by flash column chromatography, and the undesired epimer was recycled in quantitative yield through a reductive elimination procedure.[84] According to Scheme 42,

the reductive elimination of the undesired epimer **164** successfully afforded the cyclohexenylamine **153** in quantitative yield.

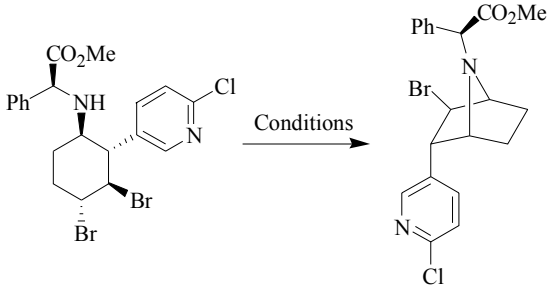


Scheme 42. Bromination and reductive elimination pathways.

With the appropriate stereochemistry of the dibromo isomer in hand, completion of the 7-azabicyclo[2.2.1]heptane ring has now possible and began with intramolecular cyclization of **165**. As revealed in Table 18, treatment of **165** with ^{t}BuOK did not afford the desired product (entry 1), although a somewhat similar substrate had been reported to undergo cyclization before.[52c] Nevertheless, refluxing **165** in toluene provided the desired product in good yields (72%) with trace amount of starting material being recovered (conventional yield = 80%; Table 18, entry 3).[54]

[84] Martin J. D.; Pérez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 516.

Table 18. Intramolecular cyclization of 165 under various conditions.



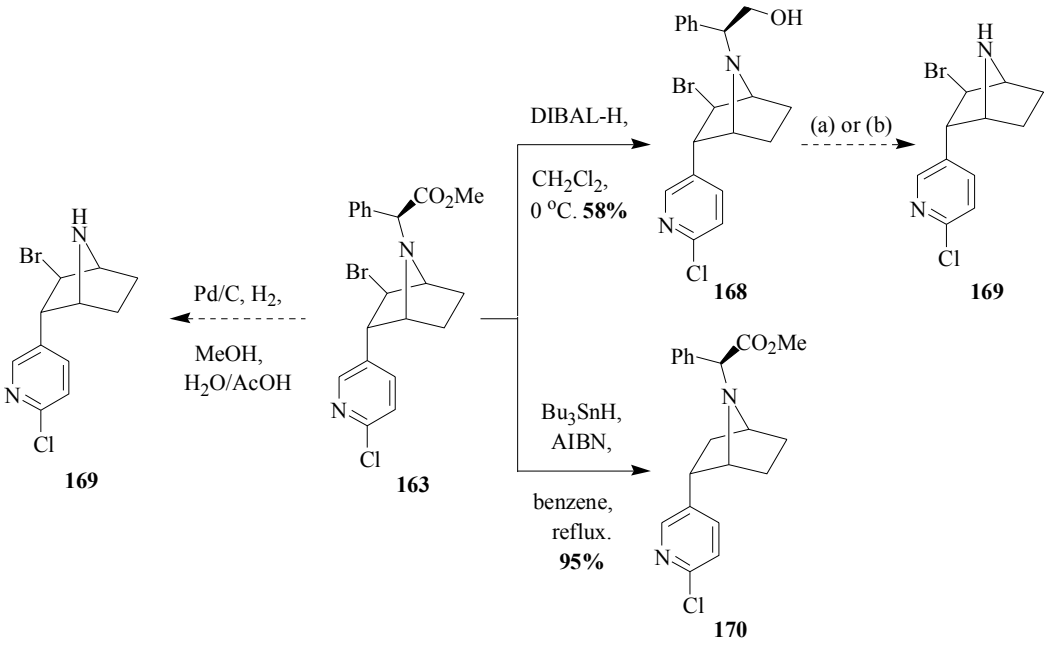
165 **163**

Entry	Conditions	Yield (%)
1	^{t}BuOK, THF, - 78 ^{o}C, 16 h.	-[a]
2	$CHCl_3$, 60 ^{o}C, 40 h.	32[b]
3	Toluene, 110 ^{o}C, 45h.	72 (80)[b,c]

[a]Intractable mixtures were formed. [b]Starting material **165** was recovered. [c]Conventional yield in parentheses.

Further efforts towards *endo*-epibatidine required the nitrogen-bridged intermediate **163** to be stirred in catalytic amount of Pd/C and excess H_2 (*200psi*) in MeOH/H_2O/AcOH to effect deprotection of the tertiary amine.[85] However, no desired product was formed (Scheme 43). Another alternative was to make use of a two-step reduction-oxidative cleavage sequence on the chiral auxiliary.[86] Reduction of **163** was carried out and the desired primary alcohol **168** was obtained in 58% yield, with its X-ray crystal structure being depicted in Figure 11. Even after experimenting with various reagents for oxidative cleavage, no desired product **169** was generated. Nonetheless, the radical dehalogenation of **163** did provide the *N*-protected-*endo*-epibatidine **170** product in excellent yield (95%).

[85] For some representative examples, see: (a) Gray, B. D.; Jeffs, P. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1329. (b) ElAmin, B.; Anantharamaiah, G. G.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1996**, *44*, 3442.
[86] For oxidative cleavage employing $Pb(OAc)_4$, see: (a) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1341. (b) Leonard, N. J.; Rebenstorf, M. A. *J. Am. Chem. Soc.* **1945**, *67*, 49. For oxidative cleavage employing H_5IO_6, see: (c) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475.



(a) $Pb(OAc)_4$, CH_2Cl_2/MeOH, 0 °C; (b) H_5IO_6, $EtNH_2$, MeOH/H_2O, 25 °C

Scheme 43. Attempts towards the synthesis of *endo*-epibatidine.

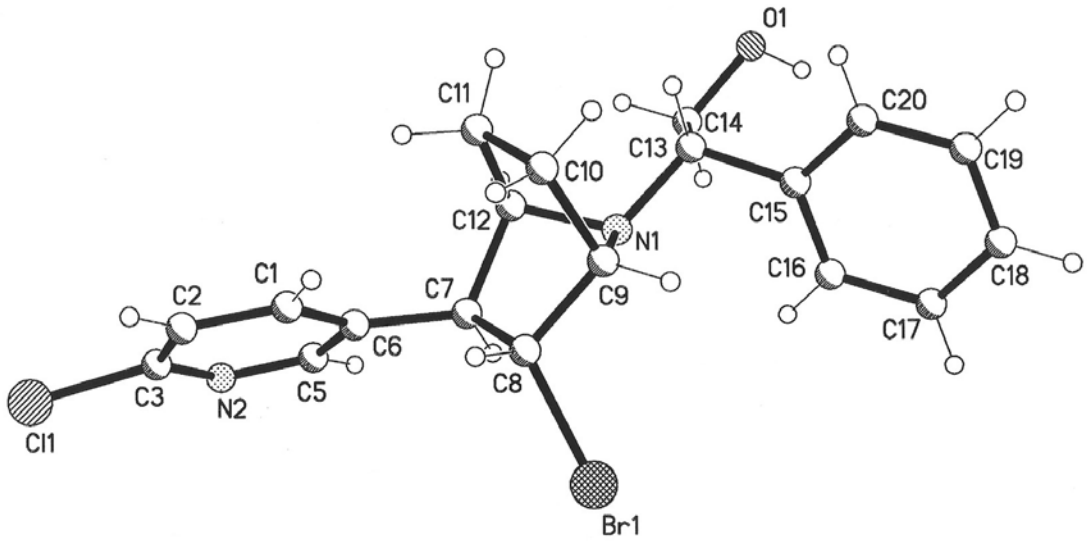
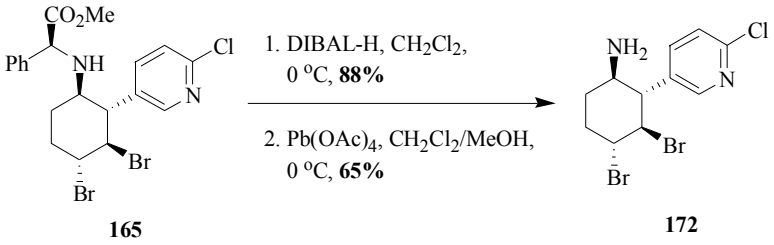


Figure 10. Single-crystal X-ray structure of 168.

The inability to remove the *N*-protecting group prompted investigation of an alternative. We took one step back to the dibromo **165** where it was envisioned that the deprotection might be feasible. Indeed, **165** was converted into the primary amine **172** by the two-step deprotection sequence with an overall yield of 57% (Scheme 44).

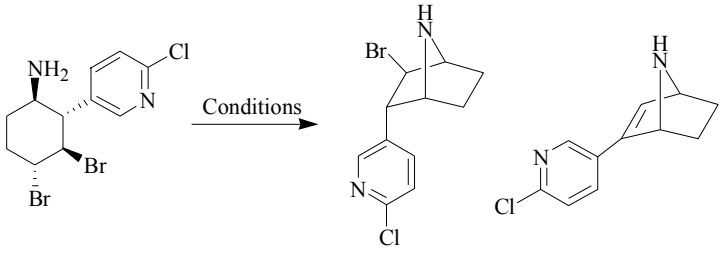


165 **172**

Scheme 44. A two-step deprotection sequence of 165.

Conversion of the primary amine **172** to the nitrogen-bridged intermediate **169** was probed in great detail. As revealed in Table 19, treatment of **172** with ^{t}BuOK resulted in intractable mixtures, regardless of the solvents used (entries 1 and 2). Although toluene served as an ideal solvent for reflux pertaining to intramolecular cyclization of the *N*-protected **165** (Table 18, entry 3), only trace amounts of desired **169** was formed when the same conditions were applied for the free amine **172** (Table 19, entry 3).

Table 19. Intramolecular cyclization of 172 under various conditions.



172 **169** **173**

Entry	Conditions	Time (day)	Yield **169**:**173**:**172**[a] (%)
1	^{t}BuOK, THF, – 78 ^{o}C.-	0.6	-[b]
2	^{t}BuOK, DMF, benzene, 25 ^{o}C	1	-[b]
3	Toluene, 110 ^{o}C	2	<10:0:65
4	$CHCl_3$, 60 ^{o}C	5	42:5:40
5	$CHCl_3$, 90 ^{o}C	5	15:32:43
6	$CHCl_3$, Et_3N, 60 ^{o}C	4.5	28:10:35
7	$CH_2(Cl)CH_2Cl$, 80 ^{o}C	5	-[c]
8	CH_3CN, 80 ^{o}C	2	85:5:5
9	CH_3CH_2CN, 95 ^{o}C	2	45:10:30

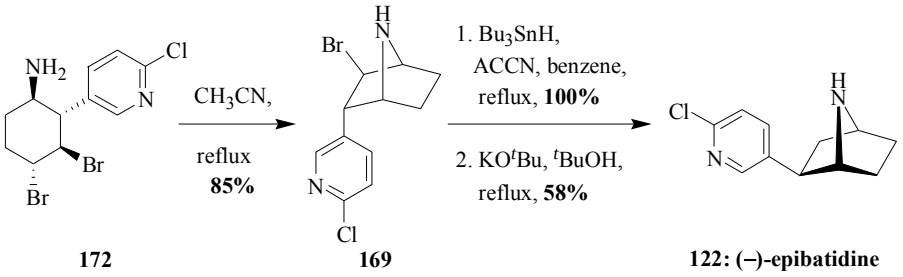
[a]Recovered starting material **172**. [b]Intractable mixtures. [c]No desired product where **172** was quantitatively recovered.

It is important to note that the dehydrobrominated product **173** was isolated when chlorinated solvents were used, and its yield was more prominent when the temperature of the reaction increased (Table 19, entries 4, 5 and 6). CH_3CN became the solvent of choice which managed to afford **169** in an impressive yield (85% isolated) together with trace amounts of **173** and starting material **172** (Table 19, entry 8). Although the success of this intramolecular cyclization was extremely sensitive toward temperature and reaction time, careful monitoring by TLC allowed us to prepare the desired nitrogen-bridged intermediate **169** in >98% yield based on recovery.

With the complete 7-azabicyclo[2.2.1]heptane carbon skeleton of epibatidine now assembled, the task of radical dehalogenation and the final epimerization step could now

be addressed. Treatment of **169** with excess Bu_3SnH, catalytic amount of 1,1'–αzobis(cyclohexanecarbonitrile) [ACCN] in benzene under reflux conditions afford the desired *endo*-epibatidine **174** in quantitative yield.[87,88]

Our synthesis had now arrived at a late-stage intermediate similar to those featured in published syntheses of (–)-epibatidine and consequently, it was hoped that similar reaction conditions would provide success.[52f,52t,56] All that remained was epimerization of the α-pyridyl proton of **174** to give the thermodynamically more stable *exo*-isomer of epibatidine **122**. While following very closely to Professor Szántay's patented work on the epimerization procedure, we managed to obtain **122** in only 35% yield after refluxing the reaction mixture in ^{t}BuOK/ ^{t}BuOH for about 8 days.[89] However, when ^{t}BuOK was added systematically over 4 days, the yield went up to 58% with 30% of the *endo* isomer being recovered (Scheme 45).



172 **169** **122: (–)-epibatidine**

Scheme 45. Synthesis of *exo*-epibatidine.

[87] 1,1'-azobis(cyclohexanecarbonitrile) [ACCN], a more efficient radical initiator than AIBN, see: Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958.
[88] Another rationale for the replacement was that AIBN was not allowed to be shipped outside America/Europe/Japan anymore for security reasons.
[89] Szántay, C. U.S. Patent 5 545 741, **1996**; *Tetrahedron* **1996**, *52*, 11053.

The structure determination of **122** was accomplished by NMR studies and the ^{1}H and ^{13}C NMR data are essentially identical to that documented by Evans *et al*.[60] With the successful preparation of **122**, a total synthesis of (–)-epibatidine was completed.

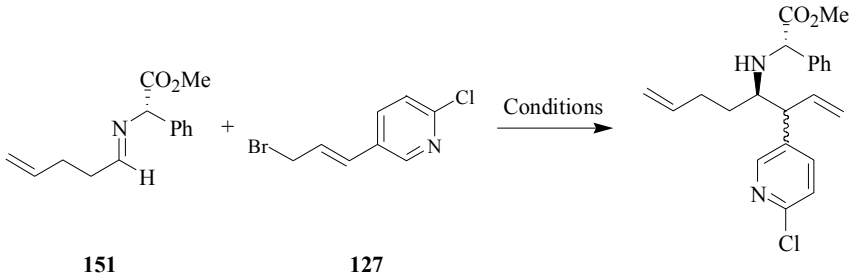
2.7 ATTEMPTS TO REFINE SYNTHETIC ROUTE

To base our design on an epimerization as the last step in the synthesis was initially not on the agenda. Even though the Zn mediated allylation of the chiral imine **151** managed to afford the homoallylic amine **152** with the desired absolute stereochemistry at C1, its *syn*-selectivity was not preferred. It is evident that with the *trans* relative stereochemistry, the late stage epimerization procedure would be omitted.

This plan was probed by allowing the chiral imine **151**, to react with the allylic bromide **127** under different reaction conditions. As revealed in Table 20, the introduction of several Lewis acids to "scramble" the selectivity did not provide satisfactory results (entries 1, 4 and 5), except for entry 6, where Et_2AlCl seems to work with In metal. However, the moderate selectivity towards the *anti* isomer and the relatively low yield of the reaction makes this method unattractive for further investigation.

Apparently, temperature is not a critical factor in controlling the relative stereochemistry of this allylation procedure (Table 20, entries 2 and 3). When gallium (Ga) was employed, no desired product was seen by TLC (Table 20, entries 7 and 8).

Table 20. Allylation of chiral imine 151 under various conditions.

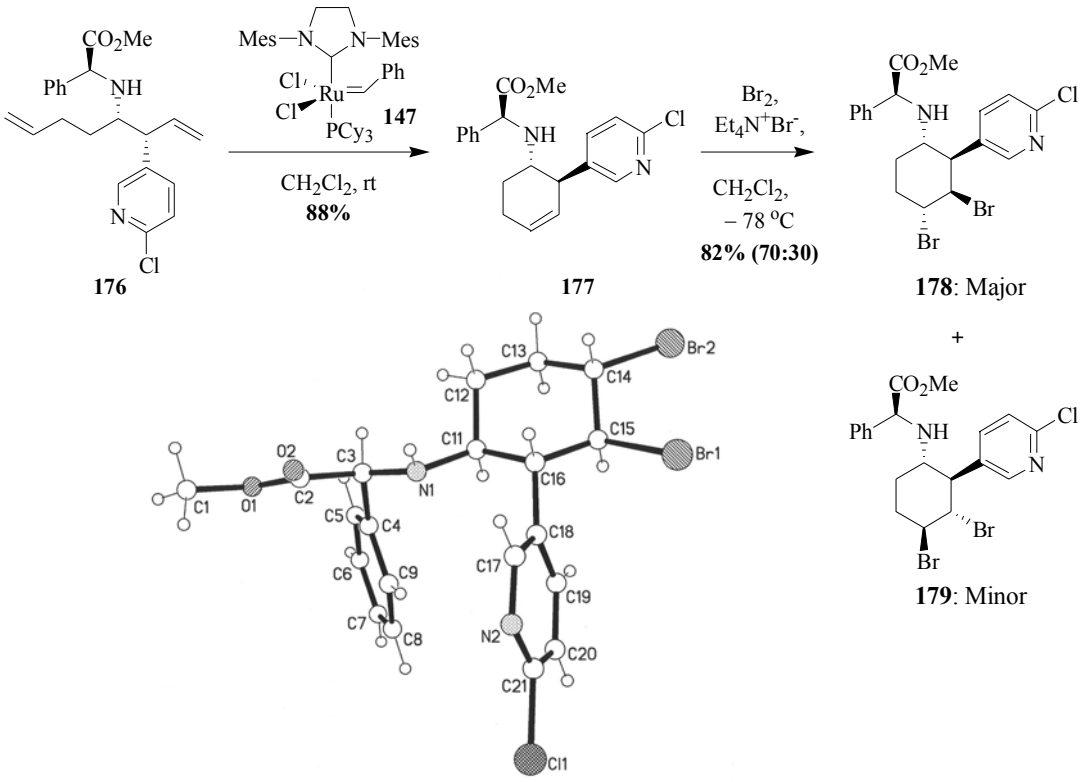


151 **127**

Entry	Conditions	Yield (*syn:anti*)
1	Zn, THF, AgOTf,[a] 0 °C	Trace (-)
2	Zn, THF, reflux	64% (88:12)
3	Zn, THF, – 78 °C	62% (>99:<1)
4	In, DMF, $La(OTf)_3$[a], – 78 °C	-
5	In, DMF, $In(OTf)_3$[a], – 78 °C	-
6	In, DMF, Et_2AlCl,[a] – 78 °C	33% (83:17)
7	Ga, THF, 0 °C	-
8	Ga, MeOH, 0 °C	-

[a]0.1 equivalent was employed.

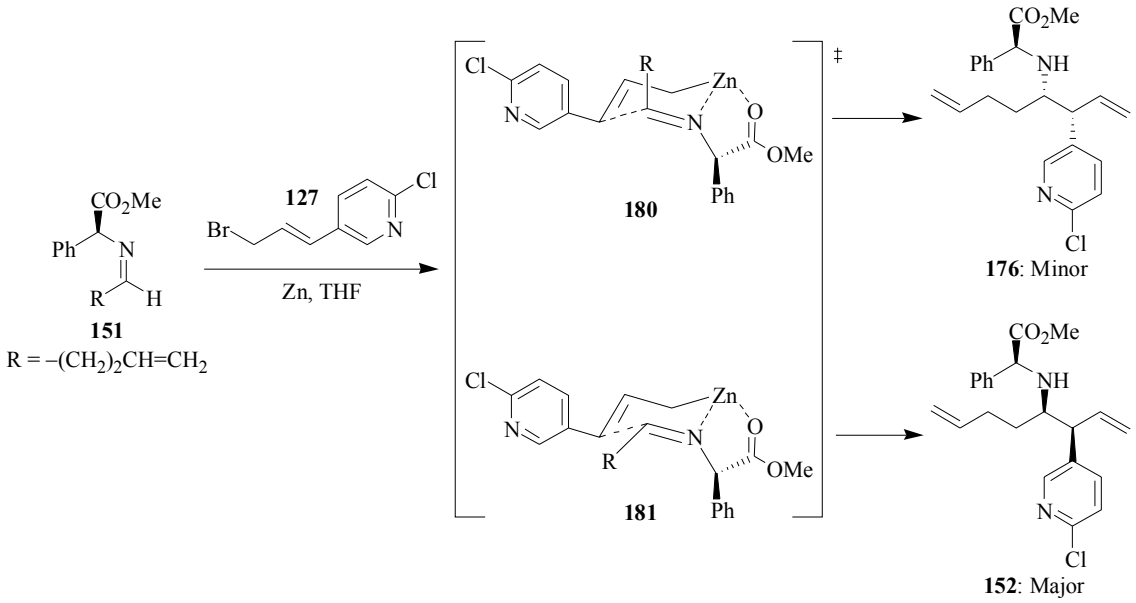
Nevertheless, the minor product **176**, initially assumed as the *anti* isomer, was brought forward to the bromination procedure after the RCM. To our dismay, the X-ray crystal structure of the minor brominated product **179** showed through retrosynthetic analysis that this minor product **176** possesses a *syn* stereochemistry (Scheme 46).



Scheme 46. Synthesis and X-ray crystal structure of 179.

A common feature of the α-amino acid esters as auxiliaries is the presence of a second heteroatom that is capable of rigidifying the transition state of the 1,2-addtion through chelation.[92] This is also referred to as "chelation control".[93] Based on the absolute stereochemistry of **152** obtained, we postulate that the two heteroatoms of the (*S*)-phenylglycine methyl ester chelate with the zinc atom of the allylzinc reagent to form a five-membered ring. Simultaneously, a six-membered chair-like transition state is formed from the allylic system and the C=N double bond of the imine. The 1,2-addition proceeds in a concerted fashion by an allylic rearrangement (Scheme 47).

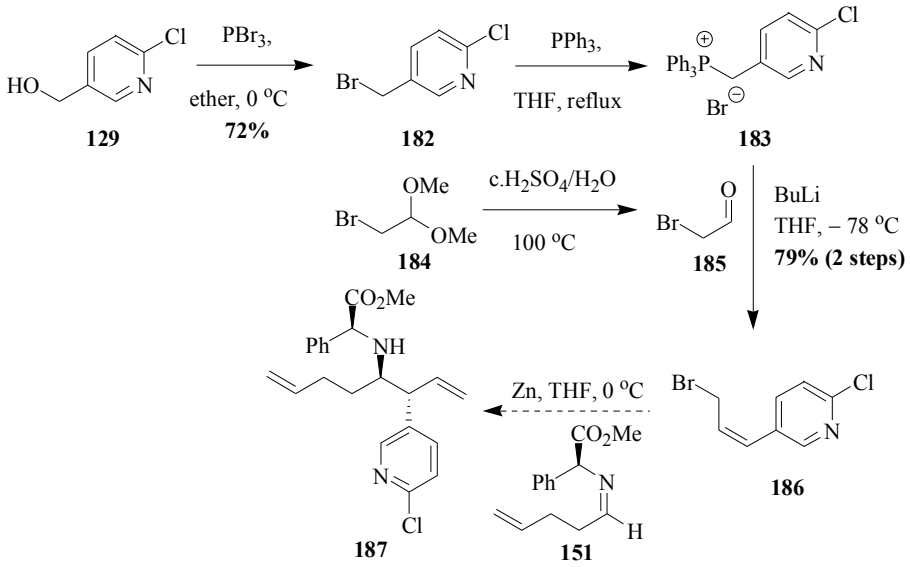
[92] Juaristi, E.; Leon-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.
[93] Neuman, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865.



Scheme 47. Chelation-controlled addition of the allylic bromide 127 to chiral imine 151.

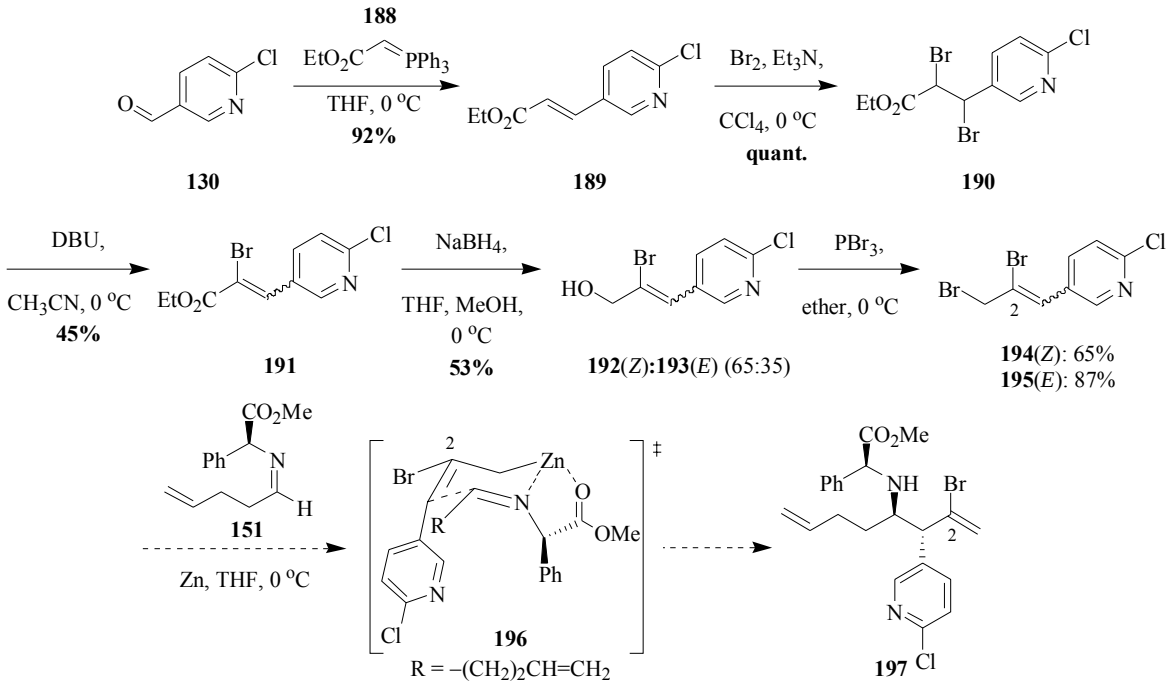
The major homoallylic amine (mostly obtained as only a single isomer) probably formed from transition state **181** where the *si*-face 1,2-addition is preferred. With the pseudo-axial conformation of the R group, the less preferred transition state **180** will result in the minor isomer **176**. It is evident from these transition states that having the chloronicotinyl group at the pseudo-axial position, instead of the pseudo-equatorial one as shown in Scheme 47, would probably give rise to the desired *anti* isomer.

Efforts were then directed towards the synthesis of the corresponding 5-((*Z*)-3-bromoprop-1-enyl)-2-chloropyridine **186**. As revealed in Scheme 48, 5-((*Z*)-3-bromoprop-1-enyl)-2-chloropyridine **186** was synthesized through a short 3 steps sequence. To our disappointment, no desired homoallylic amine was formed when **186** was subjected to our optimized Zn mediated allylation conditions.



Scheme 48. Synthesis of 5-((*Z*)-3-bromoprop-1-enyl)-2-chloropyridine **186 and subsequent allylation.**

Taking a closer look at the transition state **181**, we realized that if a bulky substituent like Br was to be placed at C2, the chloronicotinyl group perhaps will be forced to adopt a pseudo-axial position whereby the desired *anti* isomer **187** might preferentially formed. This plan was then probed by a 5 steps synthesis of allylic bromide **194**/**195**, from the available starting material **130** (Scheme 49).



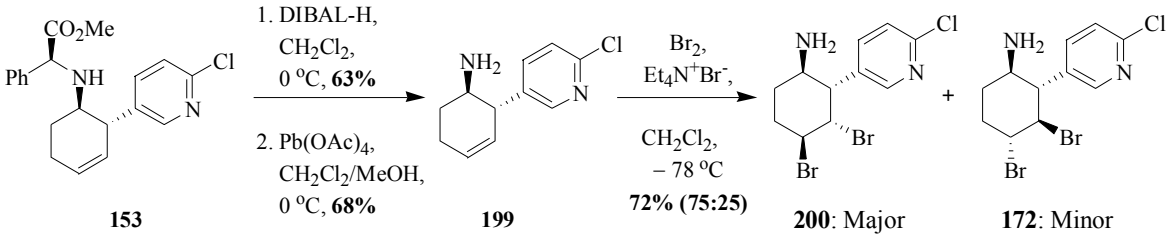
Scheme 51. Unsuccessful attempt towards the synthesis of 197.

The allylation of the chiral imine **151** with the two geometric dibromo allylic bromides **194** and **195** did not give any desired product, even when the reactions conditions were altered.[94] Even though mechanistic data is not available, we believe that the dibromo allylic bromide is too bulky for the chelation to occur.

We turned our attention to the bromination sequence. With the bromination occurring in an undesired fashion, whereby the major isomer is stereochemically not suitable for further intramolecular cyclization, we postulated that if the chiral auxiliary was removed before this procedure, then the selectivity might be reversed. Hence, the cyclohexenyl amine **153** underwent a two-step deprotection sequence to afford the primary amine **199** with an overall yield of 43%.

[94] Reflux condition, sonication and addition of Lewis acids [$La(OTf)_3$] were in vain.

Unfortunately, bromination of **199** seemed rather complicated (Scheme 50). The reaction produced some intractable mixtures with traces of starting material **199** recovered. Nevertheless, the bromination proceeded with a yield of 72% and a selectivity of 75:25 for the major but undesired stereoisomer.

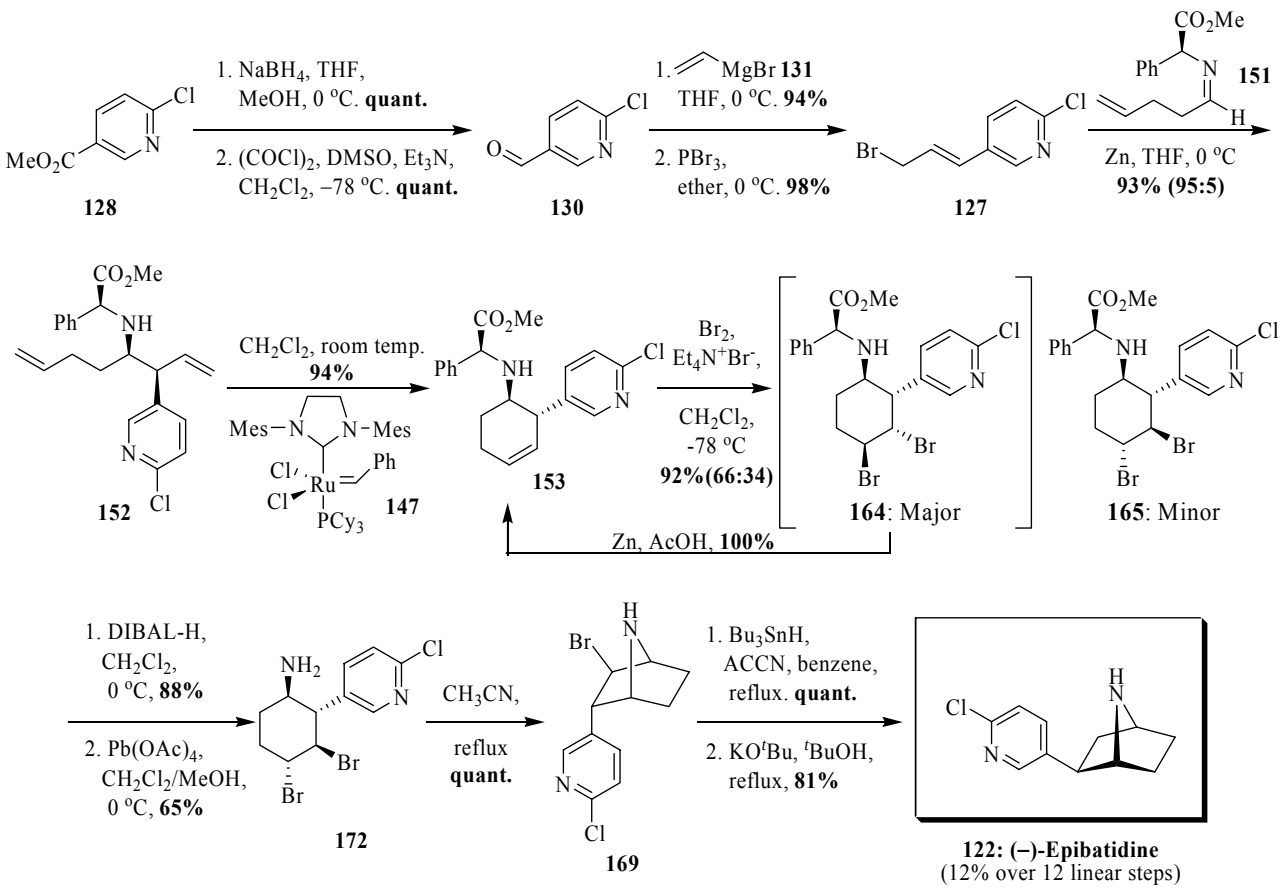


Scheme 50. Revised bromination sequence.

2.8 CONCLUSION

In summary, a short, practical and large scale process has been developed for the synthesis of (–)-epibatidine **122** from commercially available starting materials using mild and easily controlled reactions (Scheme 51).[90] There are several significant features in this synthetic route: (1) the synthesis of (–)-epibatidine requires only a total of 12 steps and delivers the alkaloid with a 12% yield over the longest linear sequence; (2) both enantiomers of epibatidine can be obtained by simply switching the chiral auxiliary **134**; (3) the facile method of obtaining enantiomerically pure cyclohexenylamines and the first RCM of unprotected amines have been achieved; (4) the bottleneck of the synthesis, the bromination procedure, was overcame by recycling the undesired **164** to **153** through a reductive elimination of **164**; (5) the entire synthetic route is straightforward and convenient for gram scale synthesis.

[90] Lee, C. L. K.; Loh, T. P. **Gram Scale Synthesis of (−)-Epibatidine.** *Submitted for publication.*

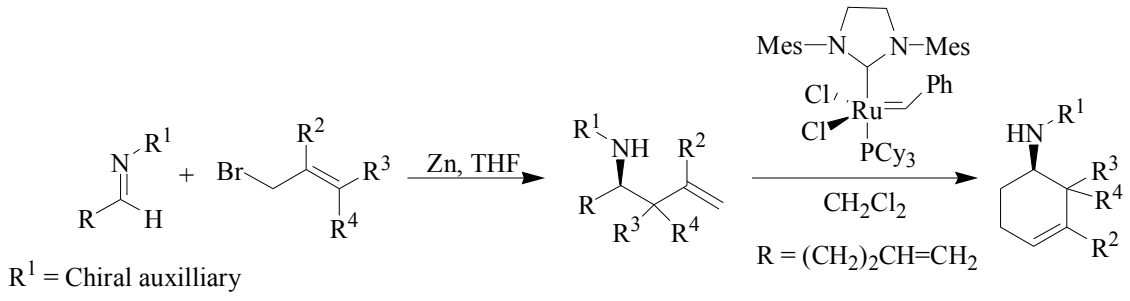


Scheme 51. Total synthesis of (–)-epibatidine.

Continuing efforts in our laboratory have the goal of further refining our synthetic route such that we may attain multigram quantities of epibatidine analogs, thereby aiding meaningful in vivo studies with this intriguing alkaloid.

Preliminary investigations of several nitrogen-bridged intermediates (**163**, **168**, **169**, **170** and **173**), *endo*-(–)-epibatidine and (–)-epibatidine itself have all shown exciting biological activities on zebra fish embryos. More interesting results on the phenotype activities of these compounds are forthcoming.

Moreover, we have successfully described an efficient allylation of chiral *C*-aliphatic imines, affording the desired aliphatic homoallylic amines in high diastereoselectivities (up to 80% *de*).[91] This methodology has enabled the preparation of a larger variety of chiral *C*-aliphatic homoallylic amines, including those inaccessible by conventional means. The simple synthesis of biologically important cyclohexenylamines by ring-closing metathesis reaction has also been demonstrated. This course offers a valuable option to the Diels-Alder strategy to cyclohexenes with an electon donating substituent in the homoallylic position. The combination of the ring-closing metathesis reaction with transannular cyclization should also provide access to interesting natural products.



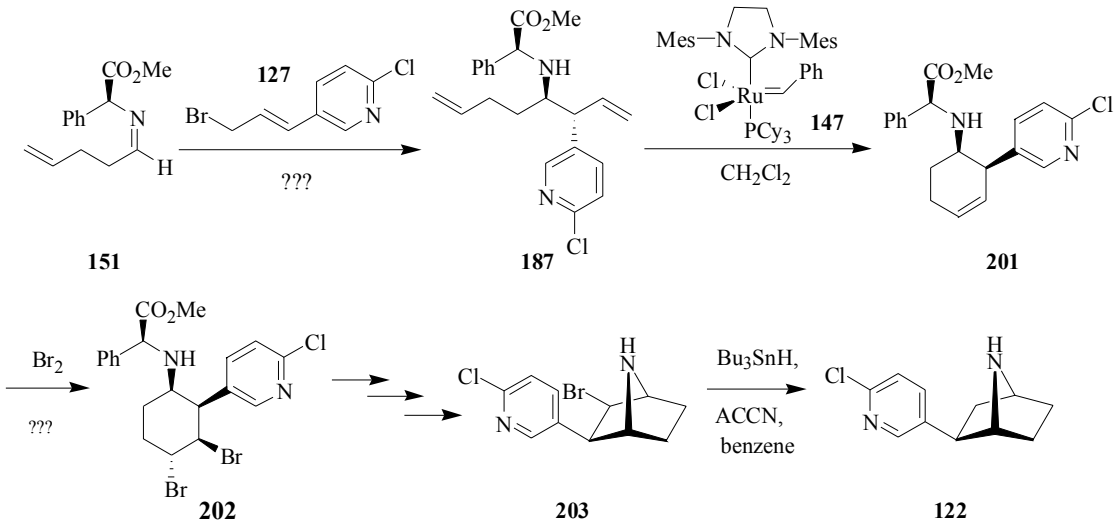
Up to 94% yield; 80% *de*

Scheme 52. Asymmetric synthesis of *C*-aliphatic homoallylic alcohols and biologically important cyclohexenylamine analogs.

[91] Lee, C. L. K.; Ling, H. Y.; Loh, T. P. **Asymmetric Synthesis of *C*-Aliphatic Homoallylic alcohols and Biologically Important Cyclohexenylamine Analogs.** *J. Org. Chem.* **2004**, *69*, **7787.**

2.9 FUTURE WORK

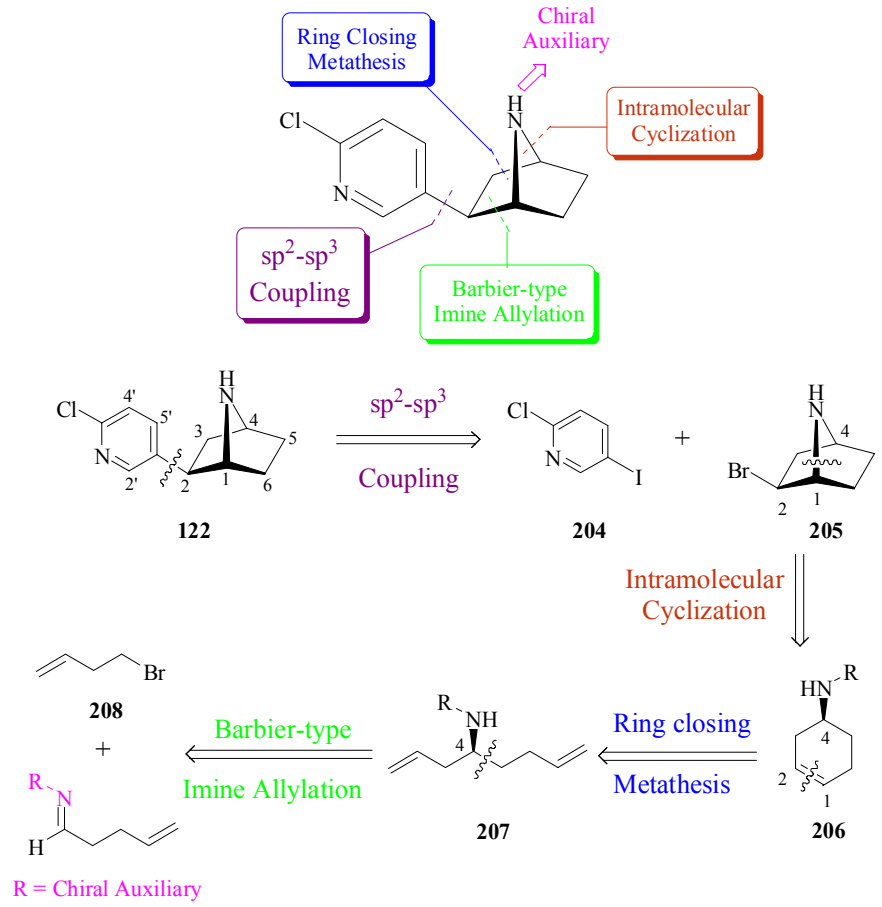
Having achieved the total synthesis of (–)-epibatidine on a multigram scale, the next immediate target in our synthetic exploration currently focuses on the optimization of certain reaction conditions and overcoming certain inherent limitations. In the Zn-mediated allylation of the chiral imine **151**, the resultant *syn*-homoallylic amine **152** (Scheme 39) was isolated as a single isomer. Undoubtedly, having the *anti*-homoallylic amine **187** will avoid the final epimerization procedure (Scheme 53). Moreover, we strongly believe that with the *cis*-cyclohexenylamine **187** would probably afford the desired **202** as the major diastereomer. Besides reducing the overall synthetic route by one step, more importantly, the overall yield would probably increase tremendously.



Scheme 53. Proposed strategy to shorten the overall synthetic route.

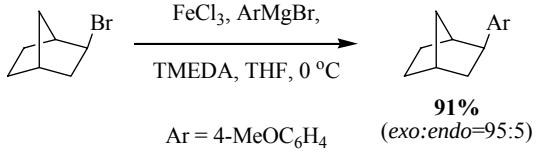
Last of all, we have another much shorter and elegant synthetic strategy in mind. As shown in Scheme 54, the key towards the proposed synthetic route relies on the

intramolecular cyclization and the sp^2 – sp^3 coupling pathways since similar substrates of the homoallylic amine **207** and the cyclohexenylamine **206** had been mentioned before in the preceding chapters.



Scheme 54. A much shorter and elegant strategy towards (–)-epibatidine.

The recent communication by Nakamura *et al.* on the iron-catalyzed cross coupling of secondary alkyl halides with aryl Grignard reagents has revealed promising insights into our proposed sp^2 – sp^3 coupling strategy (Scheme 55).[95] It is important to note that reports on the use of secondary alkyl halides under cobalt[96] or nickel catalysis[97] also suggested a high potential for transition metal catalysis in this approach.[98]



Scheme 55. Iron-catalyzed cross-coupling reported by Nakamura *et al.*

[95] Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.
[96] Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137.
[97] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.
[98] For a recent review, see: Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.

Experimental Section

3.1 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 anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 ^{o}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 ^{o}C using a Büchi rotary evaporator cooled with running water at 0 ^{o}C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[99] 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.

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

Both triethylamine and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. Activated Zn powder was obtained by "washing" commercial Zn powder using glacial acetic acid and subsequently filtered and washed with diethyl ether. Cyclohexanecarbaldehyde and 3-phenylpropanal were distilled over 4Å molecular sieve under nitrogen atmosphere. Concentrated NH_4OH are used directly from the bottle stating 28% NH_3 in water. Hydrochloric acid was diluted from concentrated 37% solution. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate, sodium thiosulphate, potassium sodium tartrate, potassium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F_{254} pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, $KMnO_4$ 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/CH_2Cl_2 and equilibrated with the appropriate solvent/solvent mixture prior to use. The analyte 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 Bio-RAD FTS 165 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between KBr salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotations were measured using a JASCO DIP-1000 Digital Polarimeter equipped with a sodium vapour 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 spectrometries were performed by the staff from the Chemical and Molecular Analysis Center of the National University of Singapore (http://www.chemistry.nus.edu.sg/cmac/ms/MS_Instrument.html). MS (EI) spectra were recorded on a Hewlett-Packard 5890A chromatogram, and HRMS (EI) spectra were recorded on a V>G> Micromass 7035. MS and HRMS (ESI) spectra were recorded on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. HRMS (FAB) spectra were recorded on a Finnigan MAT 95XL-T. MS and HRMS were reported in units of mass of charge ratio (*m/z*).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a 300 MHz Bruker ACF 300, 300 MHz Bruker DPX 300 and 500 MHz Bruker AMX 500 NMR spectrometer.

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

Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), qn (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 is indicated by nH.

Nomenclature

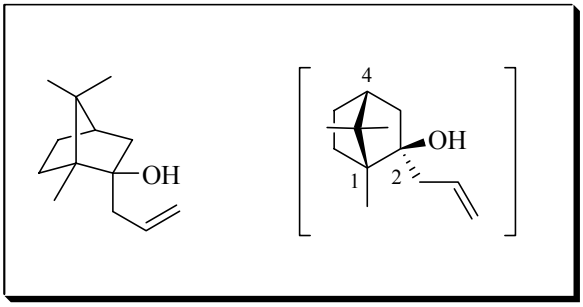
Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named using the CS Chemdraw Ultra 8.0 software.

3.2 AN UNUSUAL APPROACH TOWARDS THE SYNTHESIS OF ENANTIOMERICALLY CIS-LINEAR HOMOALLYLIC ALCOHOLS BASED ON THE STERIC INTERACTION MECHANISM OF CAMPHOR SCAFFOLD[30]

General procedures for camphor-derived branched homoallylic alcohols

To a cooled (0 ^{o}C) solution of (1*R*)-(+)-camphor (7.61 g, 50 mmol) in diethyl ether (100 mL) under nitrogen was added freshly prepared allyl/crotylmagnesium bromide (150 mmol) dropwise. The reaction mixture was allowed to warm up to room temperature slowly and stir for another 3 hours. The reaction mixture was quenched using 40 mL saturated NH_4Cl solution and was extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with water, and then with brine, before drying over $MgSO_4$. The crude mixture was then filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography (hexane/Et_2O = 60:1).

80: (1*R*,2*R*,4*R*)-2-allyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol



Colorless oil (7,95 g, 82%);

$[\alpha]_D^{25}$ = + 6.7 ^{o} (1.0, CH_2Cl_2)

R_f = 0.78 (2:1 hexane/ethyl acetate);

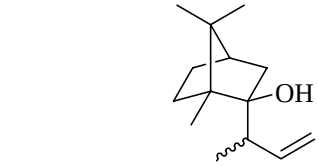
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94-5.90 (m, 1H), 5.18-5.13 (m, 2H), 2.29-2.16 (m, 2H), 1.90 (dt, *J* = 12.9, 3.5 Hz, 1H), 1.65-1.32 (m, 6H), 1.03 (s, 3H), 0.78 (s, 6H);

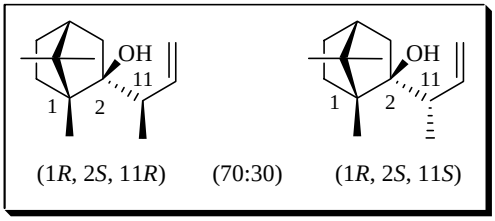
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 135.0, 118.8, 79.6, 52.1, 49.4, 46.0, 45.0, 44.5, 30.5, 27.0, 21.4, 20.9, 10.9;

FTIR (neat): 3487, 2949, 1638, 1456, 1390, 911 cm^{-1};

HRMS (EI) Calcd for $C_{13}H_{22}0$ [M^+]: 194.1671. Found: 194.1666.

81: 2-(but-3-en-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol[33]





Colourless oil (9.06 g, 87 %)

1*R*, 2*S*, 11*R* – **81a**/1*R*, 2*S*, 11*S* – **81b** = 70/30 by ^{1}H and ^{13}C NMR:

^{1}H NMR: By integrating the peaks at δ 2.31 (**81a**) and δ 2.35 (**81b**), ^{13}C NMR: By integrating the peaks at δ 80.9 (**81a**) and δ 82.1 (**81b**). Both sets of integrals approximately show a ratio of 70:30;

R_f = 0.70 (2:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 2.7 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): (**81a**) δ 6.04 – 5.87 (m, 1H), 5.06 (dd, *J* = 15.2, 2.8 Hz, 1H), 4.95 (dd, *J* = 10.6, 1.2 Hz, 1H), 2.31 (dq, *J* = 7.6, 7.2 Hz, 1H), 1.90 – 1.73 (m, 1H), 1.67 – 1.30 (m, 6H), 0.99 (d, *J* = 4.0 Hz, 3H), 0.95 (s, 3H), 0.79 (s, 3H), 0.76 (s, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): (2 isomers) δ 141.4, 115.9, 114.2, 82.1, 80.9, 52.8, 52.4, 50.4, 50.1, 47.3, 47.0, 46.3, 46.0, 44.7, 44.5, 29.7, 29.3, 27.6, 27.5, 21.4, 21.0, 15.5, 14.7, 12.2, 12.0;

FTIR (neat): 3479, 3075, 2963, 2881, 1634, 1459, 1381, 1268, 1081, 1001, 913 cm^{-1};

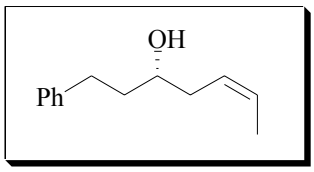
HRMS (EI) Calcd for $C_{14}H_{24}O$ [M^+]: 208.1827, found 208.1803.

[33] Dimitrov, V.; Simova, S.; Kostova, K. *Tetrahedron.* **1996**, *52*, 1699.

General procedures for crotyl transfer reaction from camphor homoallylic alcohol.

To a solution of (1*R*)-(-)-10-camphorsulfonic acid (7 mg, 0.03 mmol) and aldehyde (0.3 mmol) in dichloromethane (0.05 mL) under nitrogen at room temperature was added 2-(but-3-en-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (as a mixture of isomers 70:30; 187 mg, 0.9 mmol). The reaction mixture was allowed to stir for 5-6 days. The reaction mixture was diluted with 20 mL diethyl ether, washed with saturated $NaHCO_3$ solution and followed by brine, before drying over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified *via* column chromatography.

84: (*R*,*Z*)-1-phenylhept-5-en-3-ol[25]



(94 % *ee*, 99% *Z*)

Colorless oil (50 mg, 88 %);

R_f = 0.35 (4:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 21.2 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.09 (m, 5H), 5.59 (ddq, *J* = 10.8, 7.2, 0.8 Hz, 1H), 5.36 (dtq, *J* = 10.8, 7.6, 1.6 Hz, 1H), 3.65 – 3.55 (m, 1H), 2.75 – 2.62 (m, 2H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.73 (dq, *J* = 13.5, 7.2 Hz, 2H), 1.58 (dd, *J* = 7.2, 0.8 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.1, 128.4, 128.3, 127.5, 125.9, 125.8, 70.8, 38.4, 35.1, 32.1, 13.0;

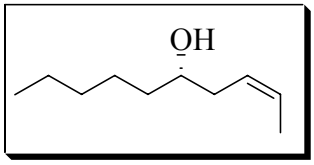
FTIR (neat): 3376, 3062, 3022, 2929, 2862, 1661, 1602, 1494, 1447, 1407, 1373, 1361, 1049, 395, 861, 744, 701, 580, 506 cm^{-1};

HRMS (EI) Calcd for $C_{13}H_{18}0$ [M^+]: 190.1358, found: 190.1357.

The enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane: i-propanol 99:1, 1.0 mL/min): t_1 = 11.13, t_2 = 13.21 and t_3 = 21.80 min.

[25] Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310.

85b: (*R*,*Z*)-dec-2-en-5-ol[100]



(97 % *ee*, >99% *Z*)

Colorless oil (32 mg, 68 %);

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

$[\alpha]_D^{25}$ = + 1.3 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.70 – 5.59 (m, 1H), 5.48 - 5.39 (m, 1H), 3.62 (q, *J* = 5.9 Hz, 1H); 2.22 (t, *J* = 6.97 Hz, 2H), 1.64 (dd, *J* = 7.0, 0.7 Hz, 3H); 1.46 (bs, 2H), 1.30 (m, 4H), 0.89 (t, *J* = 6.0 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 127.2, 126.3, 71.6, 36.9, 35.0, 31.9, 25.5, 22.7, 14.1, 13.0;

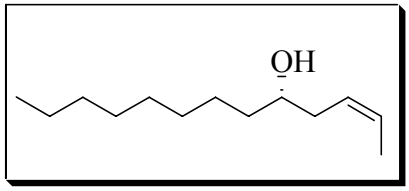
FTIR (neat): 3400, 3019, 2957, 2957, 2930, 2858, 2370, 2345, 1656, 1639, 1459, 1378, 1124, 1030, 968 cm^{-1};

HRMS (EI) Calcd for $C_{10}H_{10}0$ [M^+]: 156.1514, found: 156.1521.

Product was derivatized with *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mösher acid) before the enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel AD column (Hexane: i-propanol 99.5:0.5, 0.5 mL/min): t_1 = 7.77 and t_2 = 9.95 min.

[100] Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.

85c: (*R*,*Z*)-tridec-2-en-5-ol



(90 % *ee*, 94% *Z*)

Light yellow oil (24 mg, 95 %);

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

$[\alpha]_D^{25}$ = – 4.5 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.58 (ddq, *J* = 10.9, 6.8, 1.6 Hz, 1H), 5.37 (dtq, *J* = 10.9, 7.2, 0.8 Hz, 1H), 3.58 – 3.54 (m, 1H), 2.15 (dt, *J* = 6.8 Hz, 2H), 1.57 (dd, *J* = 6.8, 0.8 Hz, 3H), 1.40 (m, 2H), 1.26 (m, 12H) 0.81 (t, *J* = 6.4 Hz, 3H);

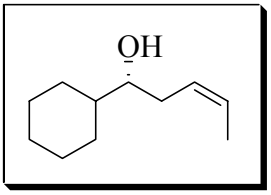
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 127.2, 127.1, 71.5, 36.9, 35.0, 31.9, 29.7, 29.6, 29.3, 25.8, 22.6, 14.1, 13.0;

FTIR (neat): 3361, 3018, 2925, 2858, 1658, 1457, 1373, 1124, 1029, 859, 706 cm^{-1};

HRMS (EI) Calcd for $C_{13}H_{26}0$ [M^+]: 198.1984, found: 198.1984.

Product was derivatized with *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mösher acid) before the enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel AD column (Hexane: i-propanol 99.5:0.5, 1 mL/min): t_1 = 5.86, t_2 = 5.89 and t_3 = 6.94 min.

85d: (*Z*)-1-cyclohexylpent-3-en-1-ol



(92 % *ee*, 96% *Z*)

Colorless oil (20 mg, 40 %);

R_f = 0.51 (4:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 2.5 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.69 – 5.61 (m, 1H), 5.49 – 5.41 (m, 1H), 3.38 (dt, *J* = 6.6, 5.6 Hz, 1H), 2.28 – 2.23 (m, 2H), 1.64 (d, *J* = 6.3 Hz, 3H), 1.32 – 1.27 (m, 1H), 1.13 – 1.09 (m, 5H), 1.05 – 0.91 (m, 5H);

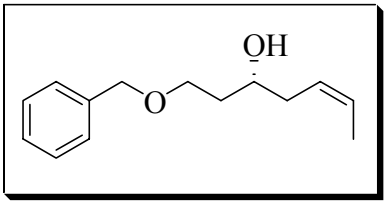
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 127.3, 126.7, 75.6, 43.2, 31.8, 29.3, 28.2, 26.6, 26.4, 26.2, 13.0;

FTIR (neat): 3591, 3020, 2925, 2854, 1625, 1448, 1261, 1086, 1065, 1030, 968, 892 cm^{-1};

HRMS (EI) Calcd for $C_{11}H_{20}0$ [M^+]: 168.1514 , found: 168.1520.

Product was derivatized with 3,5-dinitrobenzoyl chloride before the enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel OD followed by a Daicel Chiracel ODH column (Hexane: i-propanol 99:1, 0.3 mL/min): t_1 = 68.86, t_2 = 70.16 and t_3 = 78.78 min.

85e: (*S*,*Z*)-1-(benzyloxy)hept-5-en-3-ol



(97 % *ee*, >99% *Z*)

Light yellow oil (27 mg, 40 %);

R_f = 0.44 (2:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 72.8 ^{o} (1.0, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 - 7.26 (m, 5H), 5.66 - 5.55 (m, 2H), 5.55 - 5.29 (m, 2H), 4.52 (s, 2H), 3.89 - 3.81 (m, 1H), 3.73 (t, J = 6.42 Hz, 2H), 2.34-2.15 (m, 2H), 1.79 - 1.74 (m, 2H), 1.63 (d, J = 6.6 Hz, 3H);

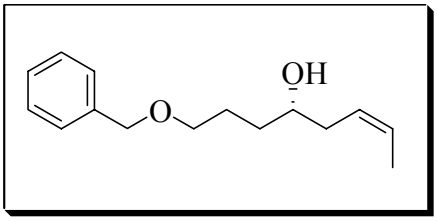
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.0, 128.5, 127.7, 126.7, 126.2, 73.4, 71.1, 69.1, 35.9, 34.9, 13.0;

FTIR (neat): 3429, 3031, 2939, 2858, 1638, 1453, 1095, 969, 697 cm^{-1};

HRMS (EI) Calcd for $C_{14}H_{20}O_2$ [M^+]: 220.1463, found 220.1459.

The enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel OB x 2 (Hexane 100%; 3.0 mL/min): t_1 = 33.01, t_2 = 46.03 and t_3 = 52.52 min.

85f: (*R*,*Z*)-1-(benzyloxy)oct-6-en-4-ol



(>99 % *ee*, >99% *Z*)

Light yellow oil (66 mg, 94 %);

R_f = 0.33 (4:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 1.7 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 5H), 5.69 – 5.59 (m, 1H), 5.51 – 5.42 (m, 1H), 4.53 (s, 2H), 3.72 – 3.62 (m, 1H), 3.53 (t, *J* = 5.9 Hz, 2H), 2.33 – 2.24 (m, 2H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.53 (q, *J* = 7.3 Hz, 2H), 1.31 – 1.25 (m, 2H);

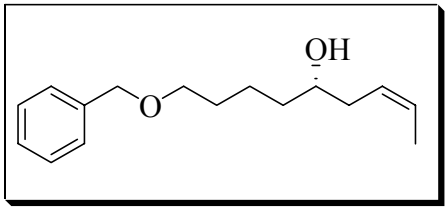
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.3, 128.4, 127.7, 127.6, 126.8, 126.4, 73.0, 71.3, 70.5, 35.0, 34.0, 26.4, 13.0;

FTIR (neat): 3393, 3067, 2926, 1717, 1602, 1584, 1452, 1278, 1114, 1071, 1027, 859, 801, 715 cm^{-1};

HRMS (EI) Calcd for $C_{15}H_{22}O_2$ [M^+]: 234.1620, found 234.1617.

The enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel OD followed by a Daicel Chiracel ODH column (Hexane: i-propanol 99:1, 1.0 mL/min): t_1 = 23.592 min.

85g: (*R*,*Z*)-9-(benzyloxy)non-2-en-5-ol



(98 % *ee*, 98% *Z*)

Light yellow oil (74 mg, 80 %);

R_f = 0.35 (4:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 2.0 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 5H), 5.71 – 5.61 (m, 1H), 5.49 – 5.41 (m, 1H), 4.52 (s, 2H), 3.66 – 3.63 (m, 1H), 3.50 (d, *J* = 6.3 Hz, 2H), 2.26 – 2.21 (m, 2H), 1.65 (d, *J* = 6.6 Hz, 3H), 1.57 – 1.44 (m, 4H), 1.31 – 1.25 (m, 2H);

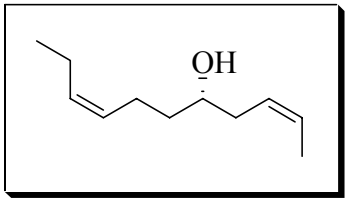
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.6, 128.4, 127.6, 127.5, 127.2, 126.2, 72.9, 71.4, 70.3, 36.6, 35.0, 29.7, 22.4, 13.0;

FTIR (neat): 3414, 3026, 2932, 2858, 1720, 1452, 1364, 1101, 1028, 939, 735, 698 cm^{-1};

HRMS (EI) Calcd for $C_{16}H_{24}O_2$ [M^+]: 248.1776, found 248.1770.

The enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel OD followed by a Daicel Chiracel ODH column (Hexane: i-propanol 99:1, 1.0 mL/min): t_1 = 20.80, t_2 = 21.68 and t_3 = 22.31 min.

85h: (*R*,2*Z*,8*Z*)-undeca-2,8-dien-5-ol



(>99 % *ee*, 84% *Z*)

Colorless oil (42 mg, 83 %);

R_f = 0.35 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 7.4 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67 – 5.59 (m, 1H), 5.47 – 5.33 (m, 3H), 3.67 – 3.61 (m, 1H), 2.24 (dd, *J* = 6.6, 6.2 Hz, 2H), 2.16 (m, 2H), 2.06 (m, 2H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.52 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H);

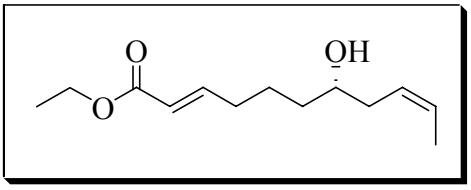
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 132.3, 128.6, 127.2, 126.1, 71.2, 36.7, 35.0, 23.6, 20.5, 14.3, 13.0;

FTIR (neat): 3399, 3007, 2963, 2930, 1653, 1449, 1373, 1305, 1163, 968, 866, 706 cm^{-1};

HRMS (EI) Calcd for $C_{11}H_{20}O$ [M^+]: 168.1517, found 168.1507.

Product was derivatized with *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mösher acid) before the enantiomeric excess and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel AD column (Hexane: i-propanol 99.5:0.5, 0.5 mL/min): t_1 = 8.00 and t_2 = 10.99 min.

85i: (*R*,2*E*,9*Z*)-ethyl 7-hydroxyundeca-2,9-dienoate



(98 % *ee*, 99% *Z*)

Light yellow oil (42 mg, 66 %);

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

$[\alpha]_D^{25}$ = – 1.3 ^{o} (1.0, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (dt, J = 15.7, 7.0 Hz, 1H), 5.82 (dt, , J = 15.7, 1.7 Hz, 1H), 5.66 (ddq, J = 10.8, 7.0, 1.4 Hz, 1H), 5.43 (dtq, J = 10.8, 7.3, 1.7 Hz, 1H), 4.18 (q, J = 7.3 Hz, 2H), 3.68 – 3.60 (m, 1H), 2.24 – 2.20 (m, 4H), 1.64 (dd, , J = 6.9, 0.7 Hz, 3H), 1.53 – 1.45 (m, 4H), 1.28 (t, J = 7.3 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 149.0, 127.7, 125.9, 121.6, 71.2, 60.2, 36.2, 35.1, 32.2, 24.3, 14.3, 13.1;

FTIR (neat): 3431, 2980, 2934, 2863, 1718, 1653, 1446, 1369, 1270, 1189, 1042, 984, 859, 706 cm^{-1};

HRMS (EI) Calcd for $C_{13}H_{22}O_3$ [M^+]: 226.1569, found 226.1568.

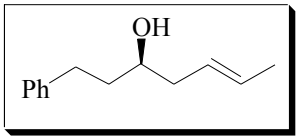
Product was derivatized with Mösher acid before the *ee* and the *E*/*Z* selectivity were determined by HPLC analysis employing a Daicel Chiracel ODH column (Hexane: i-propanol 99:1, 0.5 mL/min): t_1 = 13.58, t_2 = 15.01 and t_3 = 18.55 min.

3.3 THE FIRST EXAMPLE OF ENANTIOSELECTIVE ALLYL TRANSFER FROM A LINEAR HOMOALLYLIC ALCOHOL TO AN ALDEHYDE

General procedure for crotyl transfer reactions from 2,2-dimethyl-5-hepten-3-ol 102

A mixture of 2,2-dimethyl-5-hepten-3-ol **102** (0.18 g, 1.25 mmol) in 1 mL of CH_2Cl_2 was added to a round bottom flask containing $In(OTf)_3$ (0.028 g, 0.05 mmol) and 1 mL of CH_2Cl_2. Following that, the aldehyde (0.056 g, 0.5 mmol) in 1 mL of CH_2Cl_2 was slowly added to the reaction mixture in 10 to 15 minutes at room temperature. The reaction mixture was stirred for 2 hours at ambient temperature. Ether was added to dilute the reaction mixture followed by 1 M HCl to quench the reaction. The reaction mixture was extracted with ether. The combined organic layer was washed with brine, and dried over anhydrous magnesium sulphate, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography to afford the desired linear homoallylic alcohol product.

117a: (*R*,*E*)-1-phenylhept-5-en-3-ol[101]



(97% *ee*, 100% *E*)

Colourless oil (60 mg, 67%);

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

$[\alpha]_D^{25}$ = + 6.4 °, (1.8, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$) *E* isomer: δ 7.31 – 7.16 (m, 5H), 5.57 (dq, *J* = 15.3, 6.3 Hz, 1H), 5.47 – 5.37 (m, 1H), 3.61 (br m, 1H), 2.86 – 2.63 (m, 2H), 2.29 – 2.05 (m, 2H), 1.81 – 1.58 (m, 2H), 1.69 (d, *J* = 5.94 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) *E* isomer: δ 142.2, 129.2, 128.5, 128.4, 126.9, 125.8, 70.2, 40.9, 38.4, 32.1, 18.1;

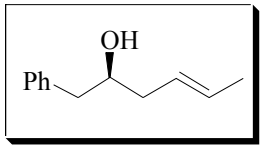
FTIR (neat): 3568, 3412, 3083, 3064, 3028, 3001, 2963, 2932, 2868, 1640, 1545, 1000, 914, 748, 700 cm^{-1};

HRMS (EI) Calcd for $C_{13}H_{16}$ $[M - H_2O]^+$: 172.1252, found 172.1259.

HPLC analysis employing a Daicel Chiralcel OD column (*n*hexane : *i*-propanol 99: 1; 1.0 ml/min): t_1 = 19.97 min and t_2 = 13.21 min.

[101] Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

117b: (*S*,*E*)-1-phenylhex-4-en-2-ol



(97% *ee*, 100% *E*)

Light yellow oil (36 mg, 41%);

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

$[\alpha]_D^{25}$ = + 5.3 ^{o}, (1.6, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$) *E* isomer: δ 7.36 – 7.23 (m, 5H), 5.60 (ddd, *J* = 15.3, 6.3, 5.6 Hz, 1H), 5.51 (dq, *J* = 15.3, 7.7 Hz, 1H), 3.86 (dddd, *J* = 7.7, 6.90, 5.6, 4.9 Hz, 1H), 2.82 (dd, *J* =13.9, 4.9 Hz, 1H), 2.75 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.29 (dt, *J* = 13.9, 6.9 Hz, 1H), 2.16 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.73 (d, *J* = 6.9 Hz, 3H);

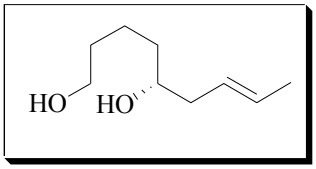
^{13}C NMR (75.4 MHz, $CDCl_3$) *E* isomer: δ 138.6, 129.4, 129.0, 128.5, 127.0, 126.4, 72.0, 43.3, 40.0, 18.1;

FTIR (neat):ν 3562, 3407, 3027, 2933, 2917, 2732, 1602, 1496, 1454, 1080, 1031, 742 cm^{-1};

HRMS (EI) Calcd for $[C_{12}H_{16}O]^+$: 176.1201, found 176.1206.

HPLC analysis employing a Daicel Chiralcel OD column (*n*hexane : *i*-propanol 99: 1; 1.0 ml/min): t_1 = 8.90 min and t_2 = 11.34 min.

117c: (*R*,*E*)-non-7-ene-1,5-diol



(97% *ee*, 100% *E*)

Colourless oil (41 mg, 52%);

R_f = 0.14 (1:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 13.0 ^{o}, (0.4, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$) *E* isomer: δ 5.55 (dt, *J* = 14.6, 6.3, 1H), 5.42 (ddq, *J* = 14.6, 6.3, 1.4, 1H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.62-3.56 (m, 1H), 2.23 (dddd, *J* = 11.1, 7.7, 6.3, 1.4 Hz, 1H), 2.06 (ddd, *J* = 11.1, 7.7, 6.9 Hz, 1H), 1.70 (d, *J* = 6.3 Hz, 3H), 1.60 – 1.40 (m, 6H);

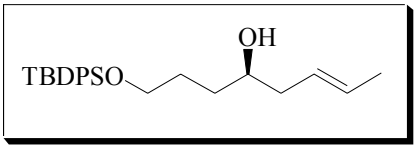
^{13}C NMR (75.4 MHz, $CDCl_3$) *E* isomer: δ 129.0, 127.0, 70.7, 62.7, 40.6, 36.2, 32.5, 21.7, 17.9;

Product was derivatized with *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mösher acid) before the enantiomeric excess and the *E*/*Z* selectivity were determined by ^{19}F NMR.

^{19}F NMR (282.2 MHz, $CDCl_3$) *E* isomer: δ 4.27 (integration = 1), 3.92 (integration = 0.015);

FTIR (neat): ν 3345, 3026, 2934, 2863, 1695, 1646, 1449, 1373, 1340, 1256, 1063, 1026, 963 917 cm^{-1};

117d: 1-(*tert*-Butyl-diphenyl-silanyloxy)-(*R*,*E*)-oct-6-en-4-ol



(97% *ee*, 100% *E*)

Light yellow oil (71 mg, 35%);

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

$[\alpha]_D^{25}$ = – 7.7 °, (0.7, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$) *E* isomer: δ 7.69 – 7.67 (m, 4H), 7.46 – 7.36 (m, 6H), 5.62 – 5.39 (m, 2H), 3.71 (t, *J* = 6.3 Hz, 2H), 3.66 – 3.58 (m, 1H), 2.29-2.06 (m, 3H), 1.80-1.40 (m, 4H), 1.70 (dd, *J* = 5.91, 1.05 Hz, 3H), 1.07 (s, 9H);

^{13}C NMR (75.4 MHz, $CDCl_3$) *E* isomer: δ 135.6, 133.9, 129.6, 128.7, 127.6, 127.2, 70.9, 64.1, 40.7, 33.4, 28.8, 26.9, 19.2, 18.1;

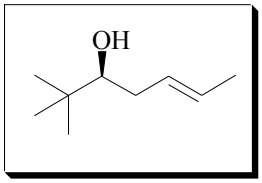
Product was derivatized with *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mösher acid) before the enantiomeric excess and the *E*/*Z* selectivity were determined by ^{19}F NMR.

^{19}F NMR (282.2 MHz, $CDCl_3$) *E* isomer: δ 4.16 (integration = 1), 3.68 (integration = 0.015);

FTIR (neat): ν 3427, 2960, 2932, 2858, 2636, 1428, 1112, 969, 823, 740, 701 cm^{-1};

HRMS (ESI) Calcd for $[C_{24}H_{34}O_2SiNa]^+$: 404.2148, found 404.2152.

116: (S,*E*)-2,2-dimethylhept-5-en-3-ol[102]



(97% *ee*, 95% *E*)

Light yellow oil;

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

$[\alpha]_D^{25}$ = + 11.4 °, (5.2, MeOH);

^{1}H NMR (300 MHz, $CDCl_3$) *E* isomer: δ 5.69 – 5.31 (m, 2H), 3.17 (dd, *J* = 10.4, 2.0, 1H), 2.36 – 2.19 (m, 2H), 1.70 (d, *J* = 6.4, 3H), 0.90 (s, 9H);

^{13}C NMR (75.4 MHz, $CDCl_3$) *E* isomer: δ 128.8, 128.3, 78.3, 35.2, 34.4, 25.7, 17.9;

Product was derivatized with *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mösher acid) before the enantiomeric excess and the *E*/*Z* selectivity were determined by ^{19}F NMR.

^{19}F NMR (282.2 MHz, $CDCl_3$) *E* isomer: δ 4.33 (integration = 1), 3.12 (integration = 0.015);

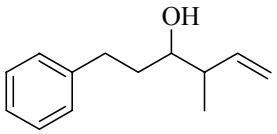
FTIR (neat): ν 3406.4, 3081.2, 2974.0, 2246.3, 1637.6, 1453.9, 1021.3, 912.8, 701.3;

HRMS (EI) Calcd for $C_9H_{17}O$ $[M - H]^+$: 141.1279, found 141.1279.

[102] Hayashi, T.; Iwamura, H.; Uozumi, Y. *Tet. Lett.* **1994**, *35*, 4813.

Partial characterization for branched homoallylic alcohol side product.

104: 4-Methyl–1-phenyl-hex-5-en-3-ol



Light yellow oil;

R_f = 0.38 (4:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$) *anti* isomer: δ 7.30 – 7.17 (m, 5H), 5.82–5.68 (m, 1H), 5.14 – 5.05 (m, 2H), 3.42 (ddd, *J* = 9.1, 6.0, 3.2 Hz, 1H), 2.86 (ddd, *J* = 13.9, 10.0, 5.1 Hz, 1H), 2.67 (ddd, *J* = 13.9, 10.0, 6.0 Hz, 1H), 2.23 (ddq, *J* = 8.3, 7.0, 6.0 Hz, 1H), 1.89 – 1.63 (m, 2H), 1.02 (d, *J* = 6.9 Hz, 3H); *syn* isomer: δ 7.30 – 7.17 (m, 5H), 5.77 (m, 1H), 5.15 – 5.08 (m, 2H), 3.53 (ddd, *J* = 8.9, 4.9, 3.1 Hz, 1H), 2.86 (ddd, *J* = 14.2, 10.0, 5.1 Hz, 1H), 2.65 (ddd, *J* = 14.2, 9.9, 6.5 Hz, 1H), 2.31 (ddq, *J* = 7.5, 6.7, 4.9 Hz, 1H), 1.82 – 1.68 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H);

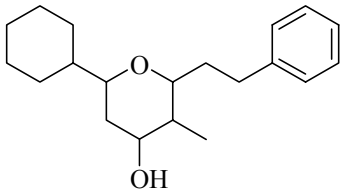
^{13}C NMR (75.4 MHz, $CDCl_3$) *anti* isomer: δ 142.1, 140.1, 128.3, 125.7, 116.4, 74.0, 44.3, 36.0, 32.1, 16.2; syn isomer: δ 142.2, 140.7, 125.7, 128.4, 115.4, 73.9, 44.3, 35.7, 32.4, 14.2;

FTIR (neat) 3429, 3084, 3012, 2968, 2930, 2870, 1640, 1603, 1496, 1454, 1218, 1038, 918, 767, 700 cm^{-1};

HRMS (EI) Calcd for $C_{13}H_{18}O$ [M^+]: 190.1357, found 190.1365.

Partial characterization for Prins-type side products.

105a: 6-Cyclohexyl-3-methyl-2-phenethyl-tetrahydro-pyran-4-ol



Light yellow oil;

R_f = 0.38 (4:1 hexane/ethyl acetate);

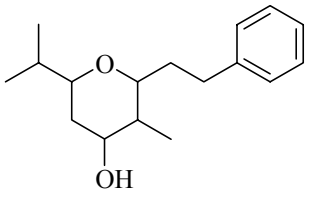
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 – 7.15 (m, 5H), 3.27 (dt, *J* = 10.3, 4.6 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.93-2.80 (m, 2H), 2.78 – 2.59 (m, 1H), 2.12-1.88 (m, 3H), 1.79 – 1.62 (m, 8H), 1.27-1.18 (m, 5H), 1.03 – 0.99 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.6, 128.6, 128.3, 125.7, 125.7, 79.7, 79.5, 74.2, 44.3, 42.9, 38.6, 34.9, 31.8, 29.4, 29.0, 26.6, 26.2, 26.1, 12.8;

FTIR (neat) 3649, 3589, 3530, 3455, 3427, 1631, 455, 430 cm^{-1};

HRMS (EI) Calcd for $C_{20}H_{30}O_2$ [M^+]: 302.2246, found 302.2239.

105b: 6-Isopropyl-3-methyl-2-phenethyl-tetrahydro-pyran-4-ol



Light yellow oil;

R_f = 0.30 (4:1 hexane/ethyl acetate);

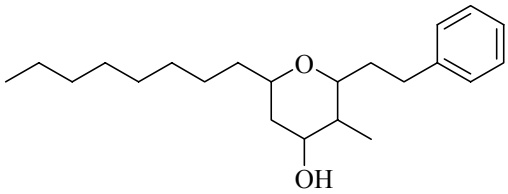
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.15 (m, 5H), 3.28 (dt, *J* = 10.5, 4.5 Hz, 1H), 2.99 – 2.92 (m, 2H), 2.87 (dt, *J* = 2.6, 9.6 Hz, 1H), 2.72 – 2.59 (m, 1H), 2.05 – 1.88 (m, 2H), 1.82 – 1.65(m, 2H), 1.39 – 1.16 (m, 2H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.7, 128.6, 128.3, 125.7, 80.5, 79.5, 74.2, 44.2, 38.5, 34.9, 33.3, 31.8, 19.0, 18.8, 12.8, 5.1;

FTIR (neat) 3630, 3568, 3475, 3423, 2958, 2874, 1456, 1152, 1008, 747, 699 cm^{-1};

HRMS (EI) Calcd for $C_{17}H_{26}O_2$ [M^+]: 262.1933, found 262.1963.

105c: 3-Methyl-6-octyl-2-phenethyl-tetrahydro-pyran-4-ol



Light yellow oil;

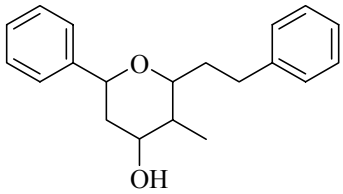
R_f = 0.33 (4:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.15 (m, 5H), 3.30 – 3.22 (m, 2H), 2.87 (dt, *J* = 2.8, 9.8 Hz, 1H), 2.82 – 2.59 (m, 2H), 2.03 – 1.88 (m, 12H), 1.83 – 1.28 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.6, 128.6, 128.4, 125.8, 79.6, 75.3, 73.9, 44.2, 41.6, 36.2, 35.6, 34.8, 31.9, 31.8, 29.7, 29.4, 25.8, 22.7, 14.3, 5.1;

FTIR (neat) 3566, 2930, 2089, 1684, 1606, 1496, 1374, 735, 699, 429.

105d: 3-Methyl-2-phenethyl-6-phenyl-tetrahydro-pyran-4-ol



Light yellow oil;

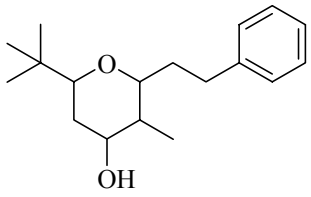
R_f = 0.33 (4:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.16 (m, 10H), 4.41 (dd, *J* = 1.7, 11.5 Hz, 1H), 3.52 – 3.46 (m, 1H), 3.14 (dt, *J* = 2.8, 9.4 Hz, 1H), 2.95 – 2.70 (m, 3H), 2.27 (ddd, *J* = 2.1, 4.5, 12.5 Hz, 1H), 2.09 – 1.98 (m, 2H), 1.46-1.37 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (75.4 MHz, CDCl3): δ 142.6, 142.4, 128.6, 128.4, 127.4, 125.9, 125.8, 125.7, 80.2, 76.9, 74.0, 43.7, 43.0, 34.8, 31.6, 12.9;

FTIR (neat) 3657, 3630, 1685, 1638, 1497, 1453, 699, 414 cm^{-1};

105f: 6-*tert*-Butyl-3-methyl-2-phenethyl-tetrahydro-pyran-4-ol



Light yellow oil;

R_f = 0.24 (4:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.15 (m, 5H), 3.33-3.24 (m, 1H), 2.94 – 2.87 (m, 2H), 2.86 (dt, *J* = 3.3, 9.6 Hz, 1H), 2.66 (dt, *J* = 1.7, 7.4 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.76 – 1.64 (m, 1H), 1.32 – 1.13 (m, 2H), 0.95 (s, 9H), 0.92 (d, *J* = 6.6 Hz, 3H);

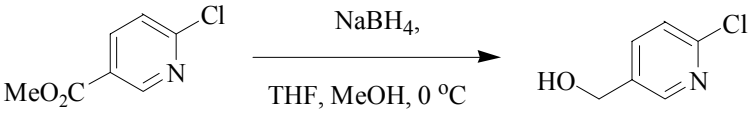
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.9, 128.6, 128.3, 125.7, 82.7, 79.6, 74.7, 44.1, 35.6, 35.0, 34.2, 26.2, 12.9;

FTIR (neat) 3648, 3629, 3477, 3383, 2954, 698, 458, 431 cm^{-1};

HRMS (EI) Calcd for $C_{18}H_{28}O_2$ [M^+]: 276.2089, found 276.2081.

3.4 MULTIGRAM TOTAL SYNTHESIS OF (–)-EPIBATIDINE

129: (6-Chloropyridin-3-yl)methanol[66]



128 **129**

A solution of the commercially available ester **128** (1.80 g, 10.50 mmol) in THF (20 mL) was stirred at 0 °C for 30 minutes, followed by the addition of $NaBH_4$ (1.58 g, 42.00 mmol) and the resulting mixture was allowed to stir for another 30 minutes. MeOH (5 mL) was then added dropwise into the mixture and stirred at 0 °C for a further 2 hours. When TLC had shown the full depletion of the starting material **128**, 1 M HCl (10 mL) was then added to the resultant mixture. The mixture was filtered and the filtrate was then concentrated *in vacuo*. CH_2Cl_2 (5 x 15 mL) was used to extract the resultant mixture and the combined extracts were washed with brine (20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residual oil was purified *via* flash column chromatography (8:1 hexane/ethyl acetate), yielding 1.50 g (10.47 mmol, ~100%) of the primary alcohol **129** as a yellow oil.

R_f = 0.28 (1:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 1.74 Hz, 1H), 7.67 (dd, *J* = 8.36, 2.44 Hz, 1H), 7.29 (d, *J* = 8.02 Hz, 1H), 4.68 (d, *J* = 4.53 Hz, 2H), 3.24 (s, 1H);

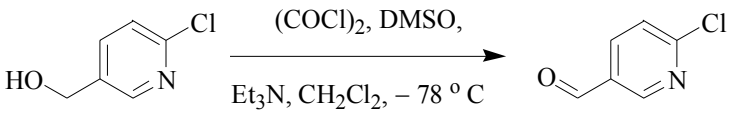
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.1, 147.9, 137.9, 135.7, 124.2, 61.3;

FTIR (neat): 3387, 1647, 1570, 1458, 1384, 1284, 1203, 1105, 1022, 822, 736 cm^{-1};

HRMS (EI) Calcd for C_6H_6ClNO [M^+]: 143.0138, found: 143.0141.

[66] Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760.

130: 6-Chloropyridine-3-carbaldehyde[66]



129 **130**

A solution of oxalyl chloride (2.57 mL, 29.46 mmol) in CH_2Cl_2 (25 mL) was stirred at – 78 ^oC for 30 minutes, followed by the dropwise addition of dimethyl sulfoxide (4.18 mL, 58.92 mmol) and the resulting mixture was allowed to stir at the same temperature for another 30 minutes. **129** (1.41 g, 9.82 mmol) in CH_2Cl_2 (20 mL) was then introduced into the mixture and the latter was allowed to stir for 30 minutes before triethylamine (12.32 mL, 88.38 mmol) was added. Water (15 mL) was added into the reaction mixture before CH_2Cl_2 (5 x 20 mL) was used to extract the aqueous layer. The combined organic extracts were dried in Na_2SO_4 and evaporated *in vacuo*. The crude solid was purified *via* flash column chromatography (20:1 hexane/ethyl acetate), yielding 1.39 g (9.81 mmol, ~100%) of the aldehyde **130** as a light yellow solid.

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

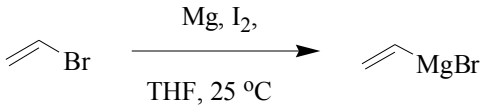
^1H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.86 (dd, *J* = 0.72, 2.46 Hz, 1H), 8.13 (dd, *J* = 2.46, 8.37 Hz, 1H), 7.51 (d, *J* = 8.37 Hz, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 189.2, 157.0, 152.4, 137.9, 130.2, 125.2;

FTIR (KBr): 2873, 1701, 1586, 1106 cm^{-1};

HRMS (EI) Calcd for C_6H_4ClNO [M^+]: 140.9981, found: 140.9969.

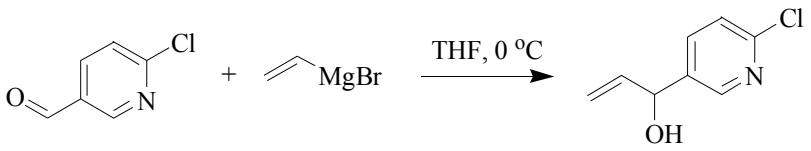
131: Vinylmagnesium Bromide



131

1M in THF solution of vinyl bromide (3.00 mL, 3.00 mmol) was added into a round bottom flask containing Mg turnings (5.00 g, 205.68 mmol) and a small crystal of iodine. The resultant mixture was stirred at 25 ^{o}C before vinyl bromide (213.00 mL, 213.00 mmol) was added dropwise when the yellow coloration of iodine has decolorized. After the bromide has depleted, the reaction mixture was allowed to stir for a further 1 hour. The vinylmagnesium bromide solution **131** was removed from the reaction flask and was used immdediately for the next step.

132: 1-(6-Chloropyridin-3-yl)prop-2-en-1-ol



130 **131** **132**

A solution of vinyl magnesium bromide **131** (100.00 mL, 100.00 mmol) in THF was added dropwise into another solution of **130** (5.66 g, 39.98 mmol) in THF (300 mL) at 0 °C and the resulting mixture was allowed to stir for 2 hours. When TLC had shown the full depletion of the starting material **130**, saturated ammonium chloride (100 mL) was then used to quench the reaction. The mixture was filtered and the filtrate was then concentrated *in vacuo* where ethyl acetate (5 x 100 mL) was used to extract the aqueous layer. The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was purified *via* flash column chromatography (10:1 hexane/ethyl acetate), yielding 6.51 g (38.38 mmol, 96%) of the allylic alcohol **132** as a dark yellow oil.

R_f = 0.43 (2:1 hexane/ethyl acetate);

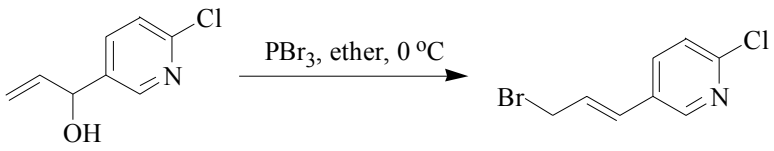
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, *J* = 2.07 Hz, 1H), 7.68 (dd, *J* = 2.46, 8.37 Hz, 1H), 7.30 (d, *J* = 8.37 Hz, 1H), 5.99 (ddd, *J* = 3.83, 10.10, 17.07 Hz, 1H), 5.42 – 5.26 (m, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.6, 147.9, 139.1, 137.0, 136.9, 124.1, 116.7, 72.5;

FTIR (neat): 1648, 1583, 1459, 1377, 1106, 1025, 932, 825, 746 cm^{-1};

HRMS (ESI) Calcd for C_8H_8ClNO [M^+]: 169.0294, found: 170.0373 (M + 1).

127: 5-((*E*)-3-Bromoprop-1-enyl)-2-chloropyridine



132 **127**

Phosphorous tribromide (3.95 mL, 42.03 mmol) was introduced dropwise into a stirred solution of **132** (5.94 g, 35.02 mmol) in diethyl ether (350 mL) at 0 °C and the resulting mixture was allowed to stir for 5 hours. When TLC had shown the full depletion of the starting material **132**, saturated sodium bicarbonate (50 mL) was then used to quench the reaction. Diethyl ether (5 x 80 mL) was used to extract the aqueous layer and the combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude solid was purified *via* flash column chromatography (15:1 hexane/ethyl acetate), yielding 7.98 g (34.32 mmol, 98%) of the allylic bromide **127** as a white solid, where it was then stored as 0.5 M solution in anhydrous THF.

R_f = 0.38 (8:1 hexane/ethyl acetate);

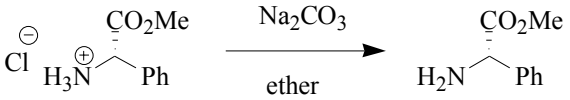
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, *J* = 2.44 Hz, 1H), 7.66 (dd, *J* = 8.36, 1.44 Hz, 1H), 7.27 (d, *J* = 8.36 Hz, 1H), 6.58 (d, *J* = 16.02 Hz, 1H), 6.42 (m, 1H), 4.11 (dd, *J* = 0.70, 7.32 Hz, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.8, 148.2, 135.7, 130.5, 129.3, 128.2, 124.2, 32.0;

FTIR (KBr): 1650, 1615, 1501, 1459, 1199, 1098, 970, 816, 580 cm^{-1};

HRMS (EI) Calcd for C_8H_7BrClN [M^+]: 230.9450, found: 230.9448.

134: (*S*)-Phenylglycine methyl ester

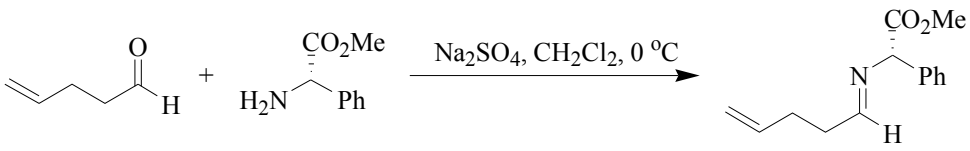


134

The commercially available optically pure (*S*)-Phenylglycine methyl ester hydrochloride salt (100.00 g, 495.91 mmol) was dissolved in saturated Na_2CO_3 (150 mL) and was extracted with diethyl ether (5 x 100 mL). The combined organic phases were washed with brine, before drying over $MgSO_4$. The crude mixture was then filtered and concentrated *in vacuo*. The crude amine **134** was obtained as light yellow oil (79.66 g, 482.21 mmol) and was used for subsequent reaction without any purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 5H), 4.61 (s, 1H), 3.69 (s, 3H), 1.88 (bs, 2H).

151: (*S*,*E*)-Methyl 2-(pent-4-enylideneamino)-2-phenylacetate

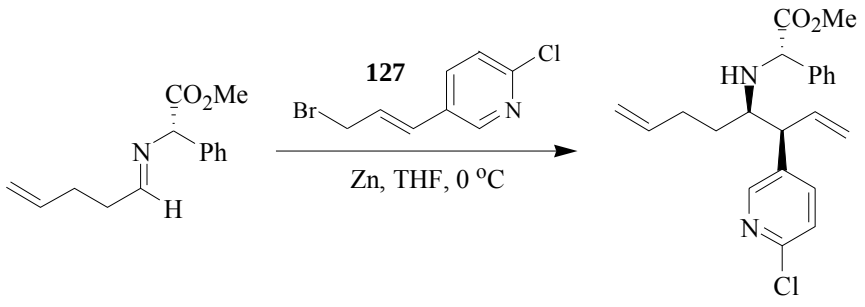


150 **134** **151**

A single-necked round bottom flask with Na_2SO_4 (2.00 g) and a magnetic stirring bar were septum and flame dried. After the apparatus had cooled down to room temperature, (*S*)-phenylglycine methyl ester **134** (6.62 g, 40.08 mmol) and CH_2Cl_2 (66 mL) were introduced and the reaction mixture was further cooled to 0 ^oC. The commercially available aldehyde **150** (1.98 mL, 20.04 mmol) was added slowly into the reaction mixture and the contents were allowed to stir for up to 5 hours. The reaction mixture was then filtered, concentrated *in vacuo* and was dried azeotropically using anhydrous THF (3 x 5 mL). The crude imine **151** (4.63 g, 20.01 mmol) was obtained as a yellow oil and was used for subsequent reaction without any purification.

^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (t, J = 4.69 Hz, 1H), 7.43 – 7.32 (m, 5H), 5.89 – 5.76 (m, 1H), 5.06 – 4.95 (m, 2H), 4.62 (s, 1H), 3.72 (s, 3H), 2.48 – 2.36 (m, 2H), 2.34 – 2.29 (m, 2H);
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 168.1, 137.1, 128.8, 128.7, 128.0, 127.7, 126.8, 115.4, 58.8, 52.4, 35.1, 29.9.

152: (*S*)-Methyl 2-((3*S*,4*R*)-3-(6-chloropyridin-3-yl)octa-1,7-dien-4-ylamino)-2-phenylacetate



151 **152**

127 (36.58 mL, 18.29 mmol) in THF was added slowly a stirred solution of **151** (2.35 g, 10.16 mmol), activated Zn powder (1.33 g, 20.32 mmol) and THF (50 mL) at 0 °C and the reaction mixture was allowed to stir for up to 3 hours. 1M HCl (30 mL) was then slowly added the reaction mixture and the entire contents were evaporated *in vacuo*. CH_2Cl_2 (5 x 60 mL) was used to extract the aqueous layer and the combined organic extracts were washed with water (2 x 15 mL) before drying in Na_2SO_4. The contents were then filtered and concentrated in vacuo. The crude solid was purified *via* flash column chromatography (24:1 hexane/ethyl acetate), yielding 3.75 g (9.75 mmol, 96%) of the homoallylic amine **152** as a yellow oil.

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

$[\alpha]_D^{25}$ = + 21.3 ° (0.5, CH_2Cl_2);

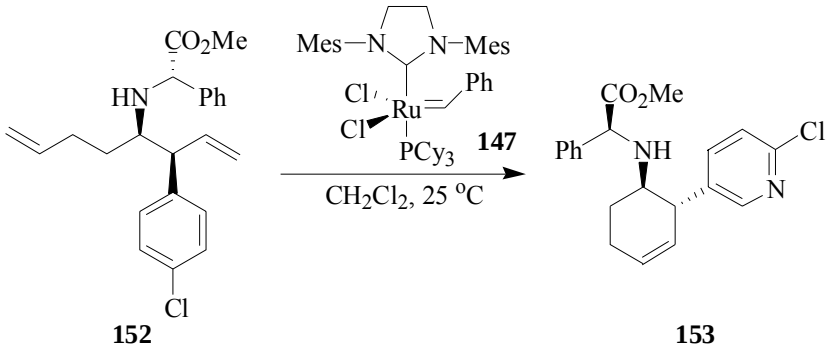
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.78 Hz, 1H), 7.54 (dd, *J* = 8.32, 2.78 Hz, 1H), 7.35 – 7.29 (m, 5H), 7.25 (d, *J* = 8.32 Hz, 1H), 6.04 (ddd, *J* = 1.85, 10.18, 17.10 Hz, 1H), 5.59 (ddt, *J* = 6.94, 10.18, 17.11 Hz, 1H), 5.25 (d, *J* = 10.63 Hz, 2H), 5.13 (d, *J* = 17.11 Hz, 1H), 4.87 – 4.82 (m, 2H), 4.45 (s, 1H), 3.66 (s, 3H), 3.52 (t, *J* = 6.94 Hz, 1H), 2.80 (q, *J* = 6.01 Hz, 1H), 2.13 – 2.07 (m, 1H), 1.96 – 1.88 (m, 1H), 1.43 – 1.39 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.1, 149.9, 149.6, 138.7, 138.0, 136.7, 136.0, 128.7, 128.2, 127.7, 123.9, 118.5, 114.9, 62.9, 58.1, 52.3, 49.9, 30.2, 29.4;

FTIR (neat): 3448, 3074, 2945, 1736, 1637, 1458, 1383, 1311, 1207, 1172, 1104, 1018, 996, 919, 740, 699, 632 cm^{-1};

HRMS (ESI) Calcd for $C_{22}H_{25}ClN_2O_2$ [M^+]: 384.1605, found: 385.1675 (M + 1).

153: (*S*)-Methyl 2-((1*R*,2*S*)-2-(6-chloropyridin-3-yl)cyclohex-3-enylamino)-2-phenylacetate



152 **153**

Grubbs' 2nd generation catalyst **147** (0.28 g, 0.33 mmol) was added in one portion a solution of **152** (2.53 g, 6.57 mmol) in CH_2Cl_2 (651 mL) at room temperature and the resultant solution was allowed to stir for 30 minutes. Another portion of the catalyst (0.28 g, 0.33 mmol) was then added the reaction mixture. When TLC had shown the full depletion of the starting material **152**, the reaction mixture was then filtered through a pad of celite and the resultant solution was then evaporated *in vacuo*. The crude product was purified *via* flash column chromatography (12:1 hexane/ethyl acetate), yielding 2.20 g (6.18 mmol, 94%) of the cyclohexenylamine **153** as a dark brown oil.

R_f = 0.23 (4:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 11.4 ^{o} (1.3, CH_2Cl_2);

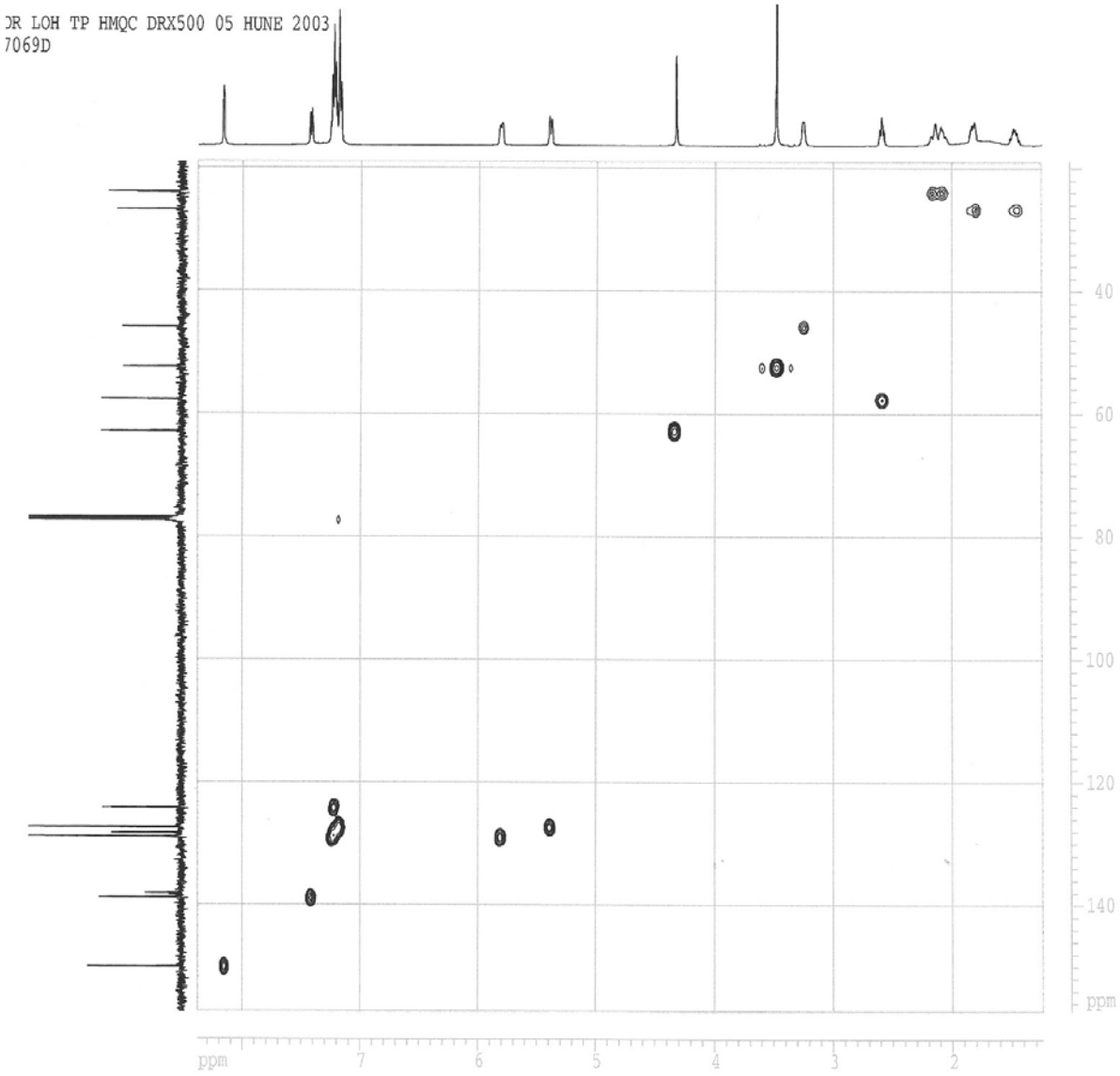
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 2.09 Hz, 1H), 7.49 (dd, *J* = 2.44, 8.01 Hz, 1H), 7.32 – 7.23 (m, 6H), 5.92 – 5.86 (m, 1H), 5.47 (dq, *J* = 2.43, 9.76 Hz, 1H), 4.40 (s, 1H), 3.55 (s, 3H), 3.34 – 3.31 (m, 1H), 2.66 (dt, *J* = 3.14, 9.76 Hz, 1H), 2.22 – 2.12 (m, 2H), 1.93 – 1.85 (m, 2H), 1.60 – 1.47 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.3, 150.1, 139.1, 138.4, 128.9, 128.2, 127.5, 124.2, 62.7, 57.1, 52.3, 45.8, 26.5, 23.8;

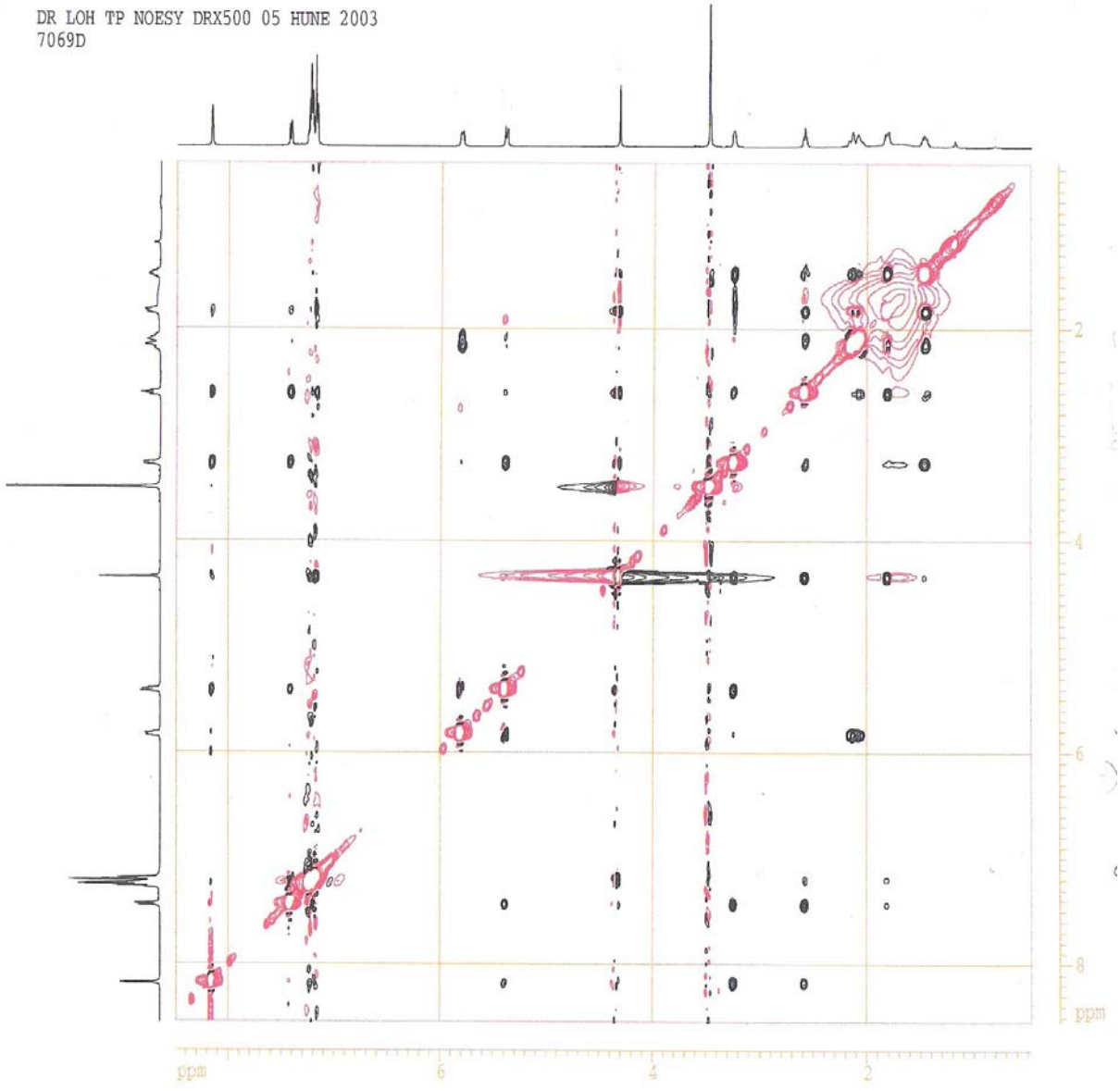
FTIR (neat): 3433, 3027, 2947, 1735, 1643, 1455, 1207, 1170, 1103, 1024, 829, 731, 699, 654 cm^{-1};

HRMS (EI) Calcd for $C_{20}H_{21}ClN_2O_2$ [M^+]: 356.1292, found: 357.1366 (M + 1) .

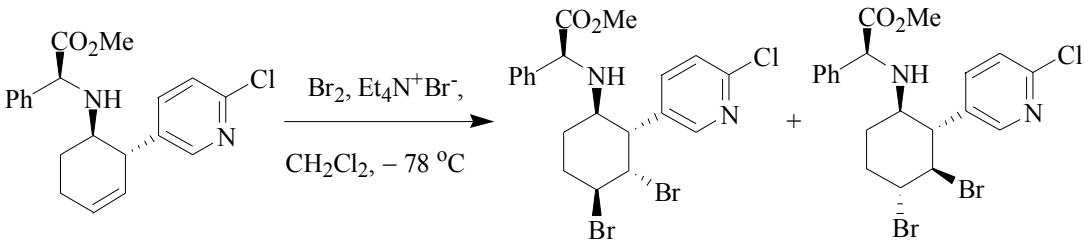
HMQC Spectrum of **153**:



NOESY Spectrum of **153**:



(S)-Methyl 2-((1*R*,2*S*)-3,4-dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylacetate



153 **164**: Major **165**: Minor

Tetraethylammonium bromide (21.49 g, 102.30 mmol) was added into a stirred solution of **1533** (3.65 g, 10.23 mmol) in CH_2Cl_2 (180 mL) and the solution was cooled to – 78 ^oC. After the reaction mixture had stirred for 45 minutes, bromine (1.58 mL, 30.69 mmol), which was diluted with CH_2Cl_2 (20 mL), was introduced slowly into the former at the same temperature. The resultant solution was allowed to stir for a further 2 hours. When TLC had shown the full depletion of the starting material **153**, the reaction mixture was washed with saturated $NaHSO_3$ (2 x 20 mL) and water (2 x 20 mL). After drying in Na_2SO_4, the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (12:1 hexane/ethyl acetate), yielding 3.31 g (6.41 mmol) of the major isomer **164** as a white solid and 1.71 g (3.30 mmol) of the minor isomer **165** as a viscous light brown oil (95% yield, 66:34 ratio).

Major diastereomer 164: (*S*)-Methyl 2-((1*R*,2*S*,3*S*,4*S*)-3,4-dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylacetate

R_f = 0.48 (3:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 14.7 ^{o} (1.4, CH_2Cl_2);

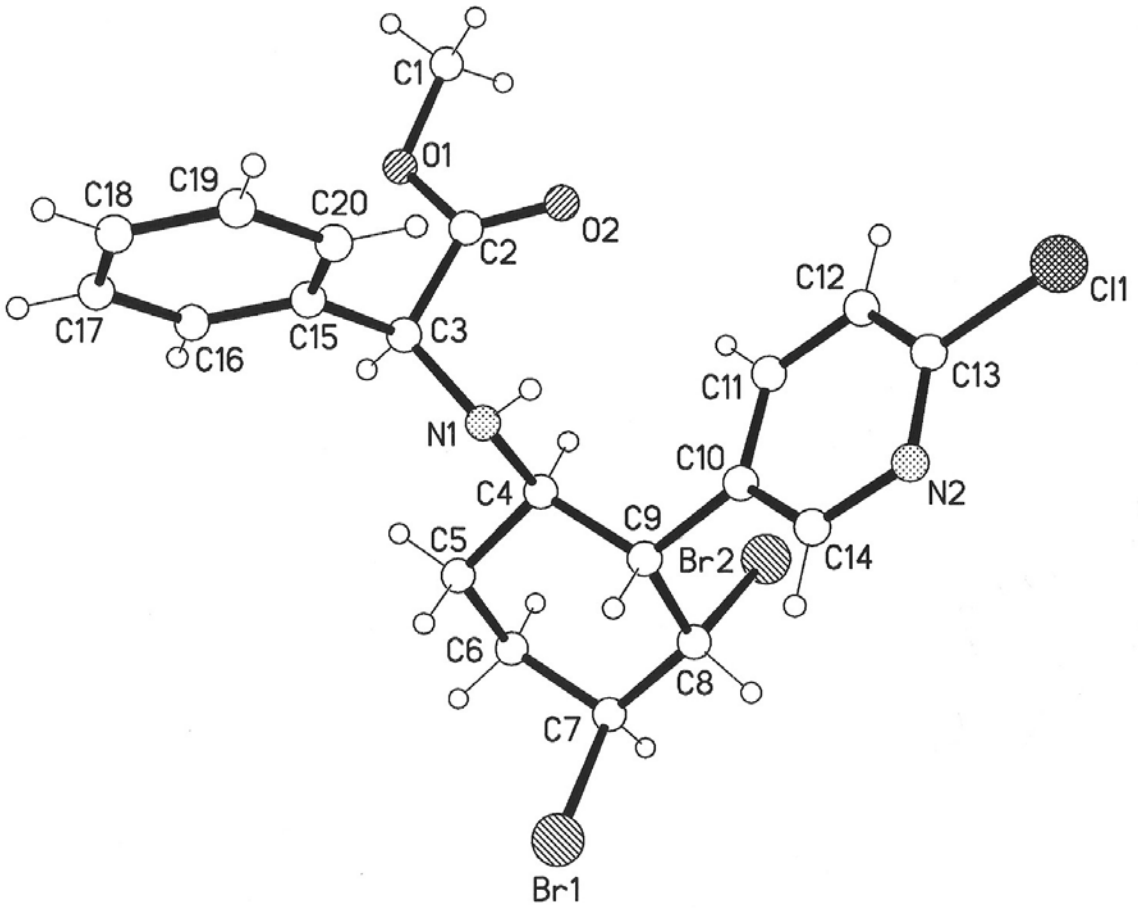
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 2.46 Hz, 1H), 7.79 (dd, *J* = 2.43, 8.37 Hz, 1H), 7.36 (d, *J* = 8.34 Hz, 1H), 7.37 – 7.15 (m, 5H), 4.78 (d, *J* = 2.43 Hz, 1H), 4.52 (s, 1H), 4.39 (d, *J* = 1.38 Hz, 1H), 3.68 (s, 3H), 3.61 (dd, *J* = 2.79, 10.80 Hz, 1H), 3.45 (dt, *J* = 4.18, 10.80 Hz, 1H), 2.65 – 2.52 (m, 1H), 2.11 – 2.07 (m, 2H), 2.01 – 1.90 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 173.1, 150.6, 150.5, 139.8, 138.0, 133.0, 128.6, 128.1, 127.0, 123.6, 61.4, 60.4, 52.5, 52.2, 51.0, 44.9, 27.2, 26.5;

FTIR (KBr): 2949, 1738, 1456, 1433, 1311, 1204, 1173, 1103, 731, 698, 545 cm^{-1};

HRMS (FAB) Calcd for $C_{20}H_{21}Br_2ClN_2O_2$ [M^+]: 516.9658, found: 516.9716.

Crystal data and structure refinement for **164**:



Crystal growing solvent	Dichloromethane and hexane	
Empirical formula	C20 H21 Br2 Cl N2 O2	
Formula weight	516.66	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.4496(5) Å	α = 97.8950(10)°.
	b = 9.7695(5) Å	β = 100.5530(10)°.
	c = 12.1143(7) Å	γ = 108.2840(10)°.
Volume	1020.95(10) $Å^3$	
Z	2	
Density (calculated)	1.681 Mg/m^3	
Absorption coefficient	4.119 mm^{-1}	
F(000)	516	
Crystal size	0.40 x 0.30 x 0.14 mm^3	
Theta range for data collection	1.75 to 27.50°.	
Index ranges	-12<=h<=12, -12<=k<=12, -15<=l<=15	
Reflections collected	13486	
Independent reflections	4690 [R(int) = 0.0298]	
Completeness to theta = 27.50°	99.9 %	
Absorption correction	Sadabs, (Sheldrick 2001)	
Max. and min. transmission	0.5963 and 0.2896	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4690 / 1 / 249	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0323, wR2 = 0.0766	
R indices (all data)	R1 = 0.0447, wR2 = 0.0809	
Largest diff. peak and hole	0.760 and -0.279 $e.Å^{-3}$	

In depth discussion with Professor Koh Lip Lin revealed that this stereoisomer could still be optically active even though a P-1 space group was revealed. The minor isomer could have crystallized with an equal portion of major and desired isomer.

Minor diastereomer 165: (*S*)-Methyl 2-((1*R*,2*S*,3*R*,4*R*)-3,4-dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylacetate

R_f = 0.38 (3:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 9.1 ^{o} (0.3, CH_2Cl_2);

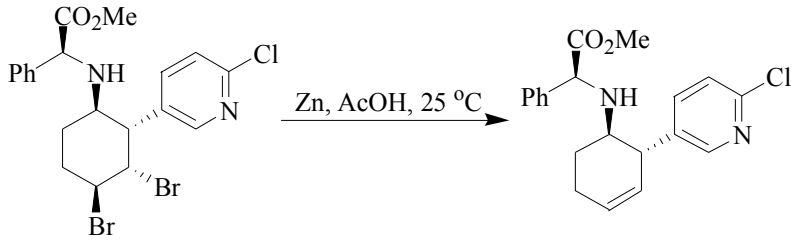
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 2.43 Hz, 1H), 7.54 (dd, *J* = 2.43, 8.34 Hz, 1H), 7.38 (d, *J* = 8.34 Hz, 1H), 7.25 – 7.22 (m, 3H), 7.09 – 7.06 (m, 2H), 4.18 – 4.02 (m, 3H), 3.54 (s, 3H), 2.92 (t, *J* = 10.44 Hz, 1H), 2.77 (dt, *J* = 3.84, 10.44 Hz, 1H), 2.56 – 2.47 (m, 1H), 2.10 – 2.03 (m, 1H), 1.99 – 1.93 (m, 1H), 1.46 – 1.37 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.2, 150.4, 149.7, 137.6, 137.4, 134.4, 128.4, 127.8, 126.6, 123.9, 61.9, 60.7, 57.7, 56.9, 5.3, 51.8, 35.2, 32.0;

FTIR (neat): 3423, 3402, 2952, 2864, 2417, 1736, 1583, 1458, 1394, 1315, 1265, 1209, 1173, 1104, 1022, 827, 735, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{20}H_{21}Br_2ClN_2O_2$ [M^+]: 516.9658, found: 516.9711.

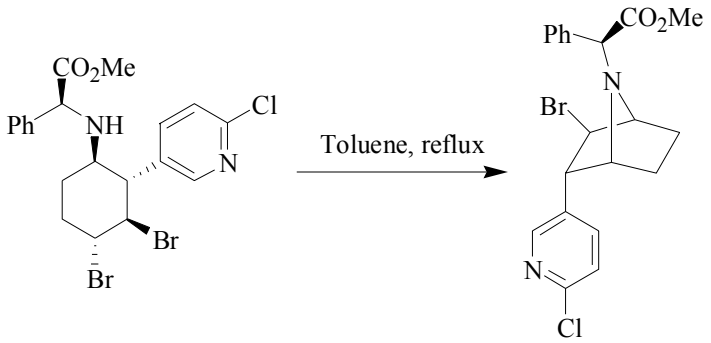
153: (*S*)-Methyl 2-((1*R*,2*S*)-2-(6-chloropyridin-3-yl)cyclohex-3-enylamino)-2-phenylacetate



164 **153**

Zinc powder (0.91 g, 13.99 mmol) was added a stirred solution of **164** (5.16 g, 9.99 mmol) and glacial acetic acid (100 mL) at room temperature. The resultant mixture was allowed to stir for up to 4 hours. When TLC had shown the full depletion of the starting material **164**, the reaction mixture was concentrated *in vacuo*. The resultant mixture was then diluted with ethyl acetate (120 mL), washed with saturated $NaHCO_3$ (3 x 20 mL) and brine (3 x 20 mL). After adding $MgSO_4$, the reaction mixture was filtered and concentrated *in vacuo*. The crude product **153** (3.56 g, 9.97 mmol, ~100%) was obtained as a yellow oil and was used for subsequent reaction without any purification.

163: (*S*)-Methyl 2-(2-bromo-3-(6-chloropyridin-3-yl)-7-aza-bicyclo[2.2.1]heptan-7-yl)-2-phenylacetate



165 **163**

A solution of **165** (1.03 g, 2.00 mmol) in dry toluene (40 mL) was refluxed for up to 45 hours. When TLC had shown the full depletion of the starting material **165**, the reaction mixture was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (4/1 hexane/ethyl acetate), yielding 0.69 g (1.60 mmol, 80%) of the bicyclo-product **163** as a light brown oil.

R_f = 0.68 (1:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 33.6^o (3.52, CH_2Cl_2);

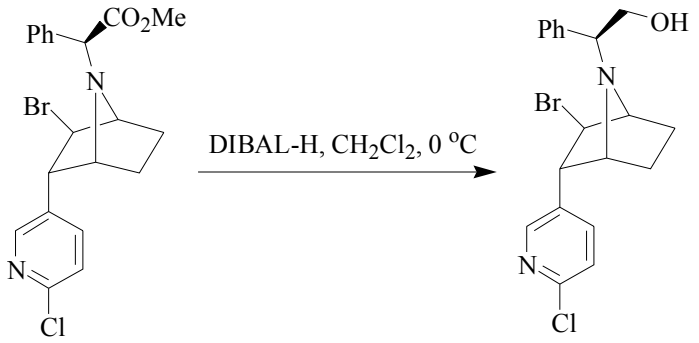
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 2.44 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.45 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.30 (d, *J* = 8.36 Hz, 1H), 4.34 (s, 1H), 4.04 (t, *J* = 4.52 Hz, 1H), 3.91 (d, *J* = 4.53 Hz, 1H), 3.75 (t, *J* = 4.52 Hz, 1H), 3.68 (s, 3H), 3.40 (dd, *J* = 1.05, 5.48 Hz, 1H), 1.91 – 1.88 (m, 1H), 1.78 – 1.73 (m, 1H), 1.37 – 1.31 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 171.7, 150.1, 148.8, 137.9, 136.9, 132.5, 128.7, 128.6, 128.3, 124.1, 67.2, 64.2, 64.0, 57.2, 52.5, 52.3, 26.7, 20.0;

FTIR (neat): 2953, 2884, 1745, 1583, 1561, 1259, 1209, 1168, 1131, 1106, 1023, 814, 731 698 cm^{-1};

HRMS (ESI) Calcd for $C_{20}H_{20}BrClN_2O_2$ [M^+]: 435.0397, found: 459.0267 (M + 23).

168: (*S*)-2-(2-Bromo-3-(6-chloropyridin-3-yl)-7-aza-bicyclo[2.2.1]heptan-7-yl)-2-phenylethanol



163 **168**

DIBAL–H (4.18 mL, 4.18 mmol) was added slowly into a stirred solution of **163** (0.88 g, 2.01 mmol) and CH_2Cl_2 (20.10 mL) at 0 °C. The reaction mixture was allowed to stir for up to 30 minutes. When TLC had shown the full depletion of the starting material **163**, MeOH was added dropwise at 0 °C till the disappearance of effervescence was observed. Potassium sodium tartrate (3 mL) was then added and the reaction mixture was allowed to stir for up to 5 hours. Ethyl acetate (5 x 10 mL) was used to extract the aqueous layer and the combined organic extracts were washed with brine (3 x 7 mL) before drying with $MgSO_4$. The contents were then filtered and concentrated *in vacuo.* The crude product was purified *via* flash column chromatography (4/1 hexane/ethyl acetate), yielding 0.67 g (1.65 mmol, 82%) of the alcohol **168** as a white crystalline solid.

R_f = 0.60 (1:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 41.2° (0.05, CH_2Cl_2);

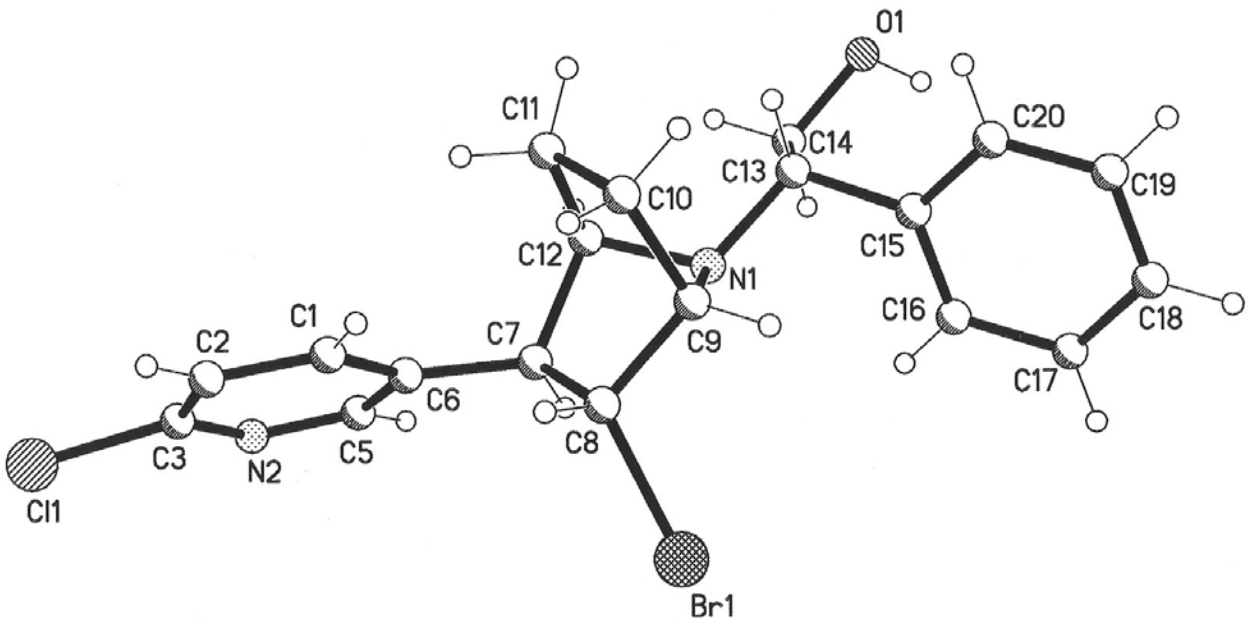
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 2.31 Hz, 1H), 7.51 (d, *J* = 7.40 Hz, 2H), 7.45 (dd, *J* = 2.77, 8.33 Hz, 1H), 7.39 – 7.30 (m, 4H), 3.93 – 3.89 (m, 4H), 3.85 (brs, 1H), 3.68 (brs, 1H), 3.47 – 3.44 (m, 1H), 1.86 – 1.84 (m, 1H), 1.81 – 1.78 (m, 1H), 1.37 – 1.25 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.1, 149.3, 148.8, 137.9, 128.6, 128.1, 128.0, 124.1, 67.7, 66.4, 63.1, 61.6, 57.7, 52.9, 26.6, 19.9;

FTIR (neat): 2953, 2361, 1561, 1459, 1370, 1106, 1026, 700 cm^{-1};

HRMS (ESI) Calcd for $C_{19}H_{20}BrClN_2O$ [M^+]: 406.0448, found: 407.0524 (M + 1).

Crystal data and structure refinement for **168**

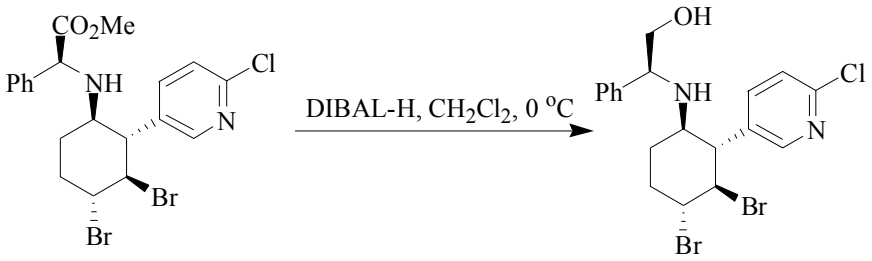


Crystal growing solvent	Dichloromethane and hexane	
Empirical formula	C20 H21 Br Cl N2 O	
Formula weight	527.10	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 14.602(4) Å	$\alpha = 90^{o}$.
	b = 10.005(3) Å	$\beta = 95.789(7)^{o}$.
	c = 15.505(5) Å	$\gamma = 90^{o}$.
Volume	2253.6(12) $Å^3$	
Z	4	
Density (calculated)	1.554 Mg/m^3	
Absorption coefficient	2.312 mm^{-1}	
F(000)	1064	
Crystal size	0.60 x 0.50 x 0.50 mm^3	
Theta range for data collection	1.83 to 25.00°.	
Index ranges	-12<=h<=17, -10<=k<=11, -18<=l<=18	

Reflections collected	12220
Independent reflections	3947 [R(int) = 0.0621]
Completeness to theta = 27.50^{o}	99.6 %
Absorption correction	Sadabs, (Sheldrick 2001)
Max. and min. transmission	0.3910 and 0.3376
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3947 / 0 / 254
Goodness-of-fit on F^2	1.015
Final R indices [I>2sigma(I)]	R1 = 0.0746, wR2 = 0.2125
R indices (all data)	R1 = 0.1043, wR2 = 0.2329
Largest diff. peak and hole	1.287 and -0.876 e.Å^{-3}

In depth discussion with Professor Koh Lip Lin revealed that this stereoisomer could still be optically active even though a P2(1)/n space group (that includes both hands) was revealed. The minor isomer could have crystallized with an equal portion of major and desired isomer.

171: (*S*)-2-((1*R*,2*S*,3*R*,4*R*)-3,4-Dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylethanol



165 **171**

DIBAL–H (4.18 mL, 4.18 mmol) was added slowly into a stirred solution of **165** (1.80 g, 3.48 mmol) and CH_2Cl_2 (23.20 mL) at 0 ^oC. The reaction mixture was allowed to stir for up to 30 minutes. When TLC had shown the full depletion of the starting material **165**, MeOH was added dropwise at 0 ^oC till the disappearance of effervescence was observed. Potassium sodium tartrate (7 mL) was then added and the reaction mixture was allowed to stir for up to 5 hours. Ethyl acetate (5 x 20 mL) was used to extract the aqueous layer and the combined organic extracts were washed with brine (3 x 10 mL) before drying with $MgSO_4$. The contents were then filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (3:1 hexane/ethyl acetate), yielding 1.49 g (3.06 mmol, 88%) of the primary alcohol **171** as a viscous light brown oil.

R_f = 0.33 (2:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 8.3 ^{o} (0.1, CH_2Cl_2);

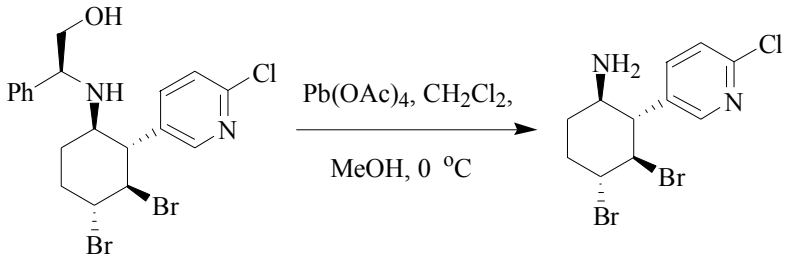
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, *J* = 2.43 Hz, 1H), 7.51 (dd, *J* = 2.43, 8.34 Hz, 1H), 7.36 (d, *J* = 8.01 Hz, 1H), 7.30 – 7.27 (m, 3H), 7.11 (d, *J* = 7.65 Hz, 1H), 4.11 – 4.01 (m, 2H), 3.35 – 3.33 (m, 1H), 3.24 – 3.18 (m, 1H), 3.18 – 3.16 (m, 1H), 2.88 (t, *J* = 10.80 Hz, 1H), 2.73 (dt, *J* = 4.17, 11.13, 1H), 2.44 – 2.39 (m, 1H), 2.25 (brs, 1H), 1.93 (dd, *J* = 3.48 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.27 – 1.22 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.4, 148.7, 140.3, 137.9, 135.6, 128.6, 128.5, 128.0, 127.8, 127.1, 124.2, 66.0, 64.1, 60.9, 59.9, 57.5, 55.3, 35.8, 34.1

FTIR (neat): 2954, 1641, 1460, 1265, 1106, 1026, 737, 702 cm^{-1};

HRMS (ESI) Calcd for $C_{19}H_{21}Br_2ClN_2O$ [M^+]: 485.9709, found: 486.9781 (M + 1).

172: (1*R*,2*S*,3*R*,4*R*)-3,4-Dibromo-2-(6-chloropyridin-3-yl)cyclohexanamine



171 **172**

Lead(IV) acetate (4.02 g, 9.06 mmol) was added into a stirred solution of **171** (4.43 g, 9.06 mmol) in CH_2Cl_2 (200 mL) and MeOH (100 mL) at 0 ^oC. When TLC had shown the full depletion of the starting material **39**, 10% NaOH (50 mL) was added slowly into the reaction mixture. The contents were evaporated *in vacuo* and subsequently extracted with CH_2Cl_2 (5 x 30 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (100:2 CH_2Cl_2/MeOH), yielding 2.17 g (5.89 mmol, 65%) of the primary amine **172** as a viscous brown oil.

R_f = 0.58 (8:1 ethyl acetate/MeOH);

$[\alpha]_D^{25} = -63.0^o$ (1.7, CH_2Cl_2);

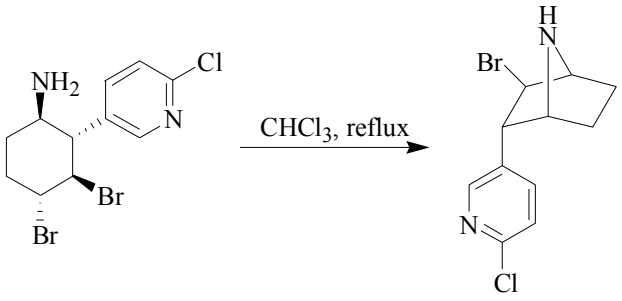
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 2.09 Hz, 1H), 7.49 (dd, *J* = 2.43, 8.36 Hz, 1H), 7.30 (d, *J* = 8.36 Hz, 1H), 4.18 – 4.03 (m, 2H), 2.95 (dt, *J* = 3.83, 10.80 Hz, 1H), 2.72 (t, *J* = 10.45 Hz, 1H), 2.51 (ddd. *J* = 3.83, 3.83, 13.59 Hz, 1H), 2.14 – 1.95 (m, 2H), 1.44 (dd, *J* = 3.48, 11.15 Hz, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.5, 149.6, 137.6, 135.3, 124.4, 60.5, 59.2, 55.6, 54.3, 35.9, 34.8;

FTIR (neat): 3403, 2947, 2835, 2609, 2129, ,1643, 1458, 1400, 1107, 1025 cm^{-1};

HRMS (ESI) Calcd for $C_{11}H_{13}Br_2ClN_2$ [M^+]: 365.9134, found: 366.9215 (M + 1).

164: *exo*-3-Bromo-*endo*-2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]-heptane



172 **169**

172 (1.88 g, 5.10 mmol) in dry acetonitrile (500 mL) were heated to reflux where the temperature oil bath was strictly kept below 83 ^{o}C. The reaction mixture was allowed to stir for up to 2 days. When TLC had shown the near depletion of the starting material **172**, the reaction mixture was cooled to room temperature and 10% NaOH solution (20 mL) was added. The resultant solution was stirred for a further 15 minutes and concentrated *in vacuo*. CH_2Cl_2 (5 x 50 mL) was used to extract the aqueous layer before the combined organic extracts were dried in anhydrous K_2CO_3. The mixture was then filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (100:2:1 CH_2Cl_2/MeOH/c.NH_4OH), yielding 1.33 g [4.65 mmol, 85%(isolated yield); 100%(convergent yield)] of the product **169** as a light brown oil. The starting material **172** was usually recovered (0.24 g, 0.85 mmol, 10%) with the dehalogenated side product **173** isolated as well (<5%).

R_f = 0.50 (9:1 CH_2Cl_2/MeOH);

$[\alpha]_D^{25}$ = + 26.2^{o} (0.6, CH_2Cl_2);

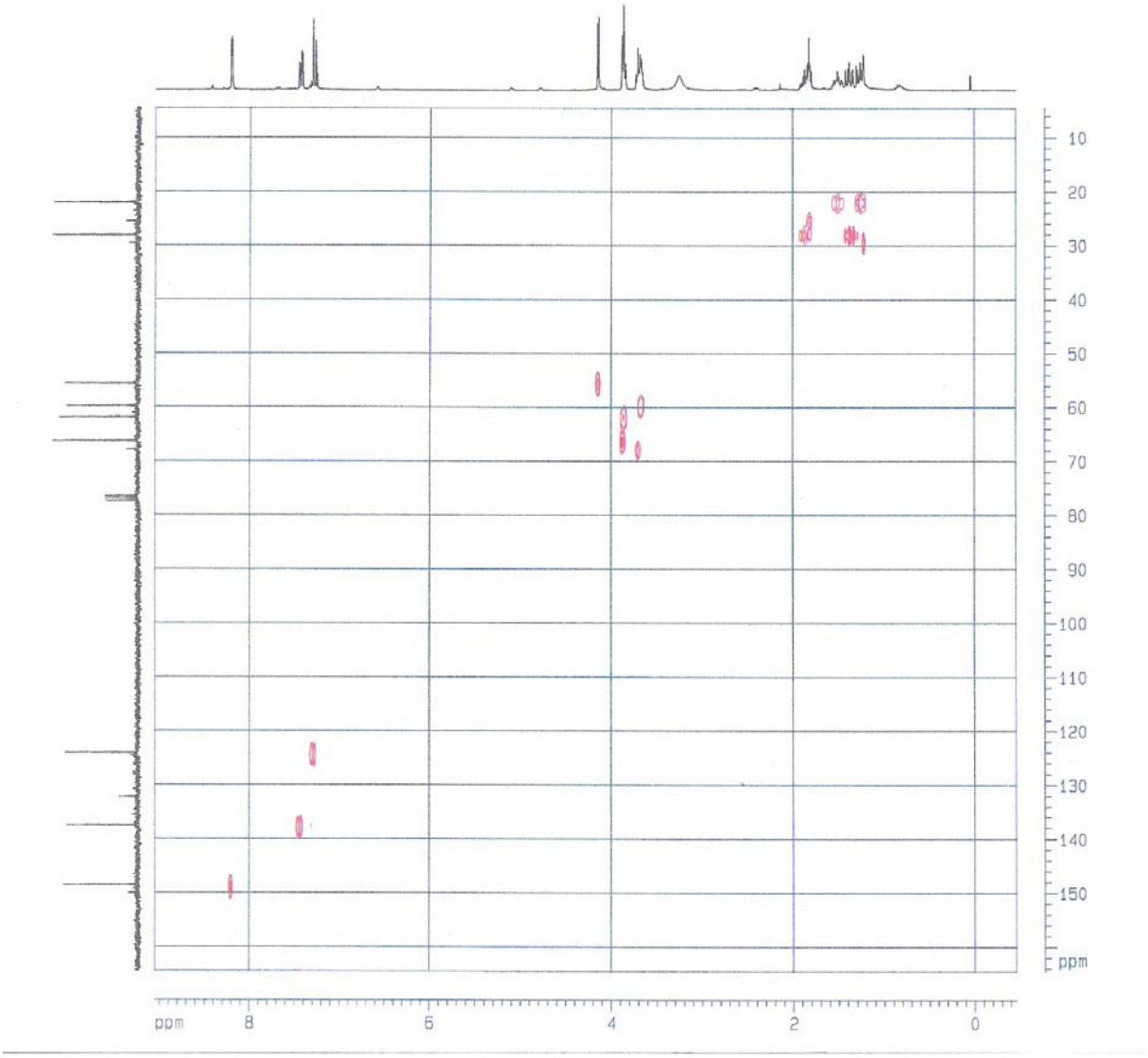
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 1.38 Hz, 1H), 7.44 (dd, *J* = 1.41, 4.98 Hz, 1H), 7.29 (d, *J* = 4.98 Hz, 1H), 4.15 (d, *J* = 2.49 Hz, 1H), 3.88 – 3.85 (m, 2H), 3.68 – 3.66 (m, 1H), 1.90 – 1.84 (m, 1H),

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.0, 148.6, 137.6, 132.3, 124.1, 69.3, 61.9, 59.9, 55.6, 28.2, 22.1;

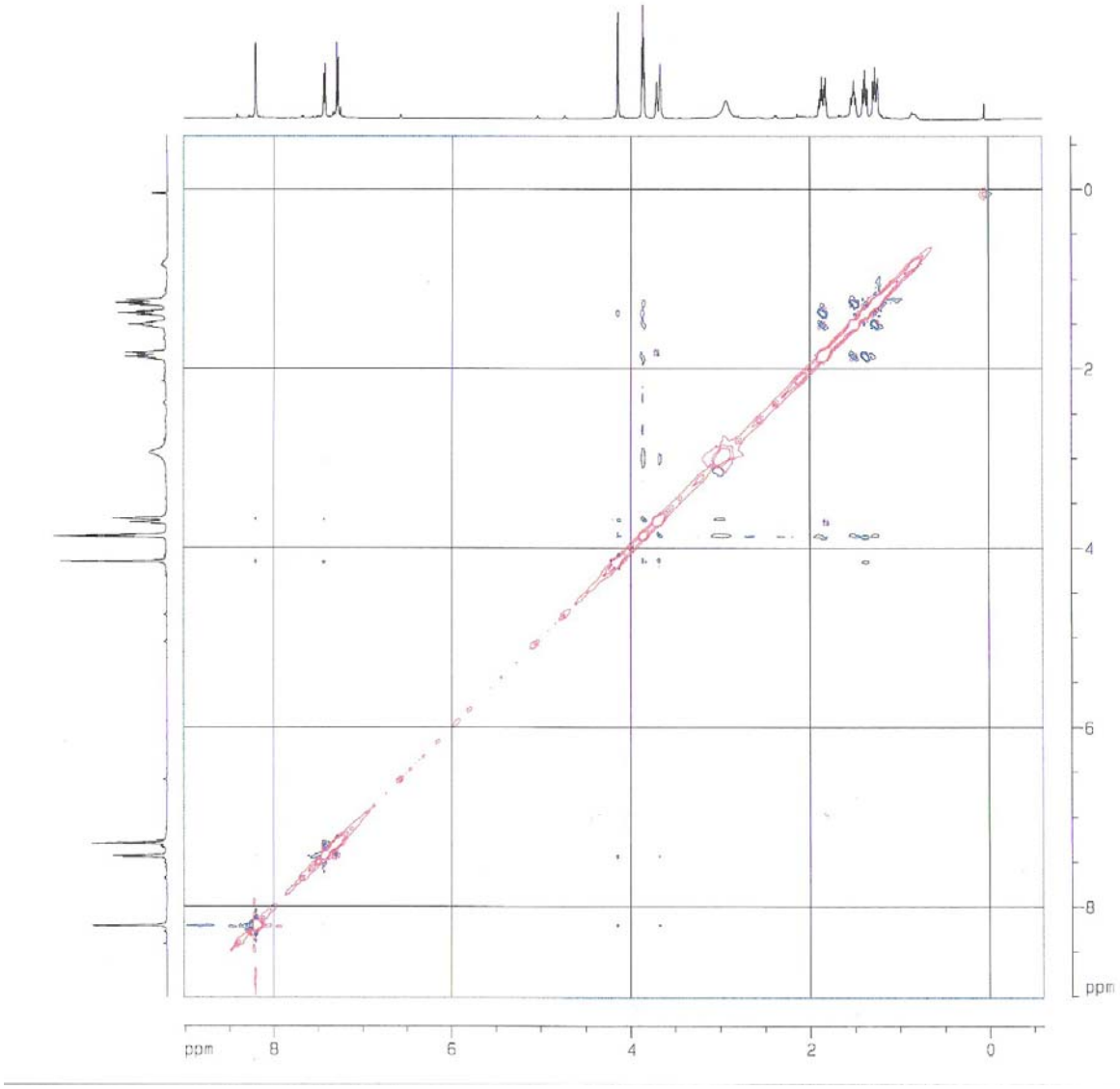
FTIR (neat): 2955, 2930, 1724, 1642, 1461, 1286, 1107, 808, 733 cm^{-1};

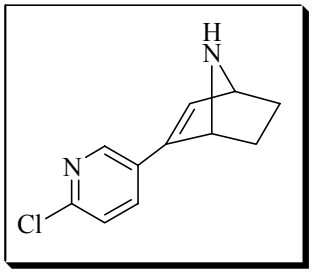
HRMS (ESI) Calcd for $C_{11}H_{12}BrClN_2$ [M^+]: 285.9872, found: 286.9944 (M + 1).

HMQC spectrum of **169**:



NOESY spectrum of **169**:





R_f = 0.30 (9:1 CH_2Cl_2/MeOH);

$[\alpha]_D^{25}$ = + 28.7° (0.9, CH_2Cl_2);

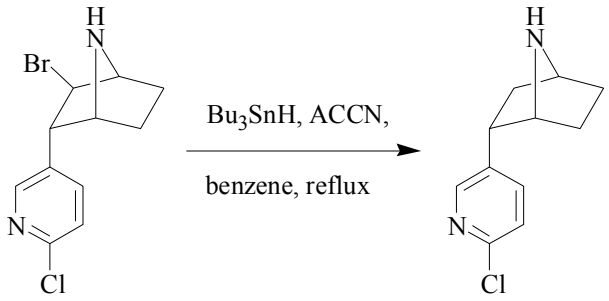
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, *J* = 2.09 Hz, 1H), 7.61 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.27 (d, *J* = 8.36 Hz, 1H), 6.56 (d, *J* = 2.09 Hz, 1H), 4.65 (d, *J* = 2.79 Hz, 1H), 4.41 (s, 1H), 2.06 – 2.03 (m, 2H), 1.33 – 1.18 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.2, 146.3, 144.7, 135.2, 1332.1, 127.9, 124.2, 61.2, 60.7, 25.0, 23.4;

FTIR (neat): 3419, 2954, 2545, 2421, 2243, 2136, 1651, 1580, 1462, 1366, 1267, 1209, 1140, 1028, 956, 919, 875, 819, 735 cm^{-1};

HRMS (ESI) Calcd for $C_{11}H_{11}ClN_2$ [M^+]: 206.0611, found: 207.0682 (M + 1).

174: *endo*-2-(6-Chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane



169 **174**

ACCN (0.48 g, 1.96 mmol) was added into a stirred solution of **169** (2.05 g, 9.81 mmol), Bu_3SnH (26.38 mL, 98.1 mmol) and benzene (800 mL) and the resultant reaction mixture was heated to reflux at 81 ^oC for up to 2 hours. When TLC had shown the full depletion of the starting material **169**, the reaction mixture was concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (100:3:1 CH_2Cl_2/MeOH/c.NH_3), yielding 2.04 g (9.78 mmol, 100%) of the *endo* adduct **174** as a light brown oil.

R_f = 0.18 (6:1 CH_2Cl_2/MeOH);

$[\alpha]_D^{25} = -6.3^o$ (0.7, CH_2Cl_2);

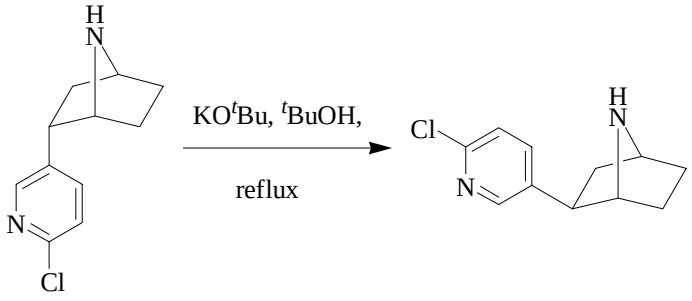
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24 (d, *J* = 2.79 Hz, 1H), 7.46 (dd, *J* = 2.46, 8.37 Hz, 1H), 7.27 (d, *J* = 7.32 Hz, 1H), 3.75 – 3.80 (m, 2H), 3.30 (ddd, *J* = Hz, 1H), 2.11 (dddd, *J* = Hz, 1H), 1.70 – 1.52 (m, 1H), 1.50 (dd, *J* = 5.57, 12.54 Hz, 1H), 1.45 – 1.32 (m, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.6, 149.2, 138.4, 135.9, 123.7, 61.1, 57.5, 44.9, 34.9, 31.0, 24.1;

FTIR (neat): 2963, 2876, 1582, 1561, 1459, 1366, 1197, 1105, 1025, 934, 870, 799, 740 cm^{-1};

HRMS (ESI) Calcd for $C_{11}H_{13}ClN_2$ [M^+]: 208.0767, found: 209.0842 (M + 1).

122: *exo*-2-(6-Chloropyridin-3-yl)-7-azabicyclo[2.2.1]-heptane[60]



174 **122**

KO^{t}Bu (3.14 g, 28.02 mmol) was added into a stirred solution of **174** (1.95 g, 9.34 mmol) in ^{t}BuOH (300 mL) at room temperature. The reaction mixture was then heated to reflux at 85 ^{o}C for 3 hours before the same amount of KO^{t}Bu was added again after the reaction mixture had cooled down. The sequential addition of the base was continued for up to 4 days. The reaction mixture was then concentrated *in vacuo* (Another workup method involved dissolving the reaction mixture in 10% K_2CO_3 solution before extracting it with CH_2Cl_2). The crude product was then purified by flash column chromatography (100:4:1 CH_2Cl_2/MeOH/c.NH_3), yielding 1.13 g [5.41 mmol, 58% (isolated yield); 81%(convergent yield)] of the *exo* adduct **122** as a faint yellow oil. The starting material **174** was recovered (0.078 g, 0.37 mmol, 30%).

R_f = 0.51 (9:1:0.1 CH_2Cl_2/MeOH/c.NH_4OH);

$[\alpha]_D^{25}$ = – 5.1^o (0.6, $CHCl_3$);[103]

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, *J* = 2.43 Hz, 1H), 7.76 (dd, *J* = 2.43, 8.34 Hz, 1H), 7.23 (d, *J* = 8.34 Hz, 1H), 3.79 (t, *J* = 4.20 Hz, 1H), 3.55 (s, 1H), 2.76 (dd, *J* = 5.22, 9.03 Hz, 1H), 1.90 (dd, *J* = 9.03, 12.18 Hz, 1H), 1.63 – 1.56 (m, 5H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 148.8, 148.6, 141.0, 137.7, 123.9, 62.8, 56.5, 44.6, 40.3, 31.4, 30.2;

FTIR (neat): 3257, 2965, 2873, 1658, 1563, 1459, 1103, 1056, 1024, 820, 736 cm^{-1};

HRMS (ESI) Calcd for $C_{11}H_{13}ClN_2$ [M^+]: 208.0767, found: 209.0842 (M + 1).

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[60] Evans, D. A.; Scheidt, K. A.; Downey, C. W. *Org. Lett.* **2001**, *3*, 3009.

[103] Reported literature optical rotation value for (–)-epibatidine: $[\alpha]_D^{25}$ = –6.2^o (*c* 0.42, CH_2Cl_2), see ref. 55.

^{1}H and ^{13}C NMR Spectral Comparison of Synthetic Epibatidine

Lee and Loh (–)-epibatidine	Evans *et al.* *Org. Lett.* **2001**, *3*, 3009 (–)-epibatidine	Kibayashi *et al.* *J. Org. Chem.* **1998**, *63*, **8397** (–)-epibatidine
^{1}H NMR		
8.27 (d, *J* = 2.43 Hz, 1H)	8.27 (d, *J* = 2.4 Hz, 1H)	8.27 (d, *J* = 2.5 Hz, 1H)
7.76 (dd, *J* = 2.43, 8.34 Hz, 1H)	7.77 (dd, *J* = 2.4, 8.3 Hz, 1H)	7.76 (dd, *J* = 2.5, 8.3 Hz, 1H)
7.23 (d, *J* = 8.34 Hz, 1H)	7.23 (d, *J* = 8.3 Hz, 1H)	7.23 (d, *J* = 8.3 Hz, 1H)
3.79 (t, *J* = 4.20 Hz, 1H)	3.80 (dd, *J* = 4.4, 4.4 Hz, 1H)	3.80 (t, *J* = 4.0 Hz, 1H)
3.55 (s, 1H)	3.57 (d, *J* = 2.4 Hz, 1H)	6.60 (d, *J* = 2.0 Hz, 1H)
2.76 (dd, *J* = 5.22, 9.03 Hz, 1H)	2.76 (dd, *J* = 4.9, 9.3 Hz, 1H)	2.77 (dd, *J* = 4.9, 9.0 Hz, 1H)
1.90 (dd, *J* = 9.03, 12.18 Hz, 1H)	1.91 (dd, *J* = 9.3, 12.2 Hz, 1H)	1.91 not reported (?)
1.63 – 1.56 (m, 5H);	1.65 – 1.50 (m, 5H)	1.65 – 1.48 (m, 5H)
^{13}C NMR		
148.8	148.9	149.0
148.6	148.8	148.9
141.0	141.1	141.1
137.7	137.7	137.7
123.9	123.9	124.0
62.8	62.8	62.8
56.5	56.4	56.5
44.6	44.5	44.6
40.3	40.4	40.4
31.4	31.4	31.4
30.2	30.2	30.2

3.5 ASYMMETRIC SYNTHESIS OF *C*-ALIPHATIC HOMOALLYLIC ALCOHOLS AND BIOLOGICALLY IMPORTANT CYCLOHEXENYLAMINE ANALOGS

Preparation of (*S*)-Phenylglycine methyl ester for imine formation.

(*S*)-Phenylglycine methyl ester (10 g, 60 mmol) was dissolved in saturated Na_2CO_3 (150 mL) and was extracted with diethyl ether (5 x 100 mL). The combined organic phases were washed with brine, before drying over $MgSO_4$. The crude mixture was then filtered and concentrated *in vacuo*. The crude product was obtained as light yellow oil and was used for subsequent reaction without any purification.

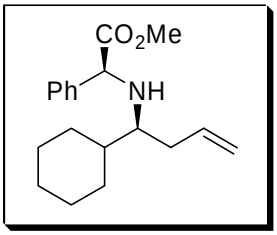
General procedure for the preparation of imines.

To a stirred solution of aldehyde (1mmol, 1 equiv) and Na_2SO_4 (0.5 g) in dichloromethane (3 mL, 0.33M) under nitrogen at 0 ^{o} C was added (*S*)-phenylglycine methyl ester (1.5 – 2.0 mmol, 1.5 to 2.0 equiv). The reaction mixture was allowed to stir for 5 hrs. The resulting reaction mixture was then filtered and concentrated *in vacuo*. The crude product obtained was used without purification for subsequent steps.

General reaction procedure for the Zn mediated allylation of chiral imines.

To a stirred suspension of the chiral imine (1 mmol) in THF (5 mL) and "activated" Zn powder (3.2 mmol), was added the allylic bromide (3.0 mmol) at 0 ^{o}C and the reaction mixture was stirred for up to 7 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ (10 mL) before being extracted with CH_2Cl_2 (3 x 10 mL). The mixture was then washed with water (2 x 10mL), before being dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

(*S*)-Methyl 2-((*S*)-1-cyclohexylbut-3-enylamino)-2-phenylacetate



(76 % *de*)

Light yellow oil (181 mg, 60 %);

R_f = 0.65 (10:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 29.2 ^{o} (0.4, CH_2Cl_2);

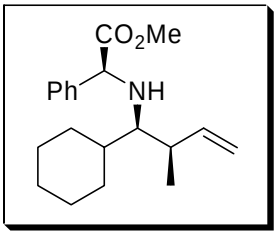
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.28 (m, 5H), 5.87 – 5.73 (m, 1H), 5.13 – 5.03 (m, 2H), 4.51 (s, 1H), 3.67 (s, 3H), 2.34 – 2.22 (m, 2H), 2.18 – 2.08 (m, 1H), 1.73 – 1.61 (m, 5H), 1.44 – 1.35 (m, 1H), 1.18 – 0.97 (m, 5H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 138.8, 136.4, 136.1, 128.5, 127.9, 127.8, 127.6, 117.1, 116.9, 63.2, 59.2, 52.1, 40.6, 35.1, 29.1, 28.6, 26.7, 26.6, 26.5;

FTIR (neat): 3332, 3064, 3028, 2925, 2852, 2668, 1739, 1638, 1450, 1313, 1204, 1170, 993, 914, 783, 736, 698, 519 cm^{-1};

HRMS (ESI) Calcd for $C_{19}H_{27}NO_2$ [M^+]: 301.2042, found 302.2118 (M + 1).

(*S*)-Methyl 2-((1*R*,2*R*)-1-cyclohexyl-2-methylbut-3-enylamino)-2-phenylacetate



(60 % *de*; *syn* : *anti* = 75 : 25)

Light yellow oil (296 mg, 94 %);

R_f = 0.58 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 26.4 ^{o} (0.4, CH_2Cl_2);

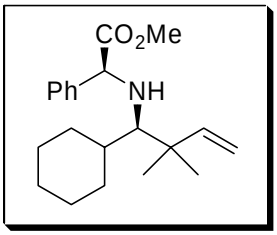
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 5H), 5.93 – 5.80 (m, 1H), 5.07 – 4.98 (m, 2H), 4.48 (s, 1H), 3.66 (s, 3H), 2.45 – 2.39 (m, 1H), 2.19 – 2.11 (m, 1H), 1.64 – 1.46 (m, 5H), 1.44 – 1.33 (m, 1H), 1.21 – 1.04 (m, 8H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 173.8, 143.3, 142.2, 128.3, 128.3, 127.9, 127.7, 114.4, 113.4, 65.2, 64.8, 64.1, 51.9, 51.8, 41.0, 40.7, 40.5, 39.7, 31.3, 31.1, 28.8, 28.6, 26.8, 26.7, 26.6, 26.6, 26.5, 17.8, 15.0;

FTIR (neat): 3839, 3064, 2925, 2851, 1738, 1491, 1451, 1169, 1001, 912, 730, 699 cm^{-1};

HRMS (EI) Calcd for $C_{20}H_{29}NO_2$ [M^+]: 315.2198, found 316.2273 (M + 1).

(*S*)-Methyl 2-((*R*)-1-cyclohexyl-2,2-dimethylbut-3-enylamino)-2-phenylacetate



(78 % *de*)

Light yellow oil (303 mg, 92 %);

R_f = 0.69 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 17.5 ^{o} (0.4, CH_2Cl_2);

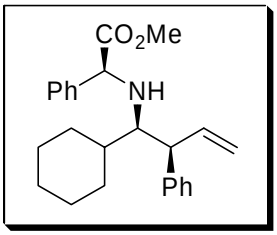
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H), 5.90 (dd, *J* = 17.1, 11.2 Hz, 1H), 5.02 – 4.96 (m, 2H), 4.50 (s, 1H), 3.68 (s, 3H), 2.06 (d, *J* = 1.7 Hz, 1H), 1.74 – 1.62 (m, 5H), 1.32 – 1.24 (m, 1H), 1.09 – 0.99 (m, 11H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 147.1, 139.5, 128.4, 127.8, 127.6, 111.6, 68.6, 66.2, 51.8, 43.0, 39.2, 35.6, 29.1, 27.4, 26.8, 26.5, 24.6, 23.6;

FTIR (neat): 3038, 3061, 2851, 2525, 1939, 1491, 1450, 1167, 1005, 912, 698, 575 cm^{-1};

HRMS (EI) Calcd for $C_{21}H_{31}NO_2$ [M^+]: 329.2355, found 328.2271 (M - 1).

(*S*)-Methyl 2-((1*R*,2*S*)-1-cyclohexyl-2-phenylbut-3-enylamino)-2-phenylacetate



(76 % *de*; *syn* : *anti* = 82 : 18)

Yellow oil (245 mg, 65 %);

R_f = 0.59 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 36.7 ^{o} (0.5, CH_2Cl_2);

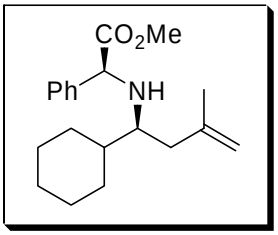
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 8H), 7.20 – 7.17 (m, 2H), 6.06 (dt, *J* = 17.7, 9.4 Hz, 1H), 5.08 – 5.02 (m, 1H), 3.80 (s, 1H), 3.48 (s, 3H), 2.61 (dd, *J* = 8.7, 2.8 Hz, 1H), 1.82 (brs, 2H), 1.73 (brs, 4H), 1.50 – 1.44 (m, 1H), 1.21 – 1.11 (m, 5H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.4, 140.1, 139.2, 128.6, 128.4, 128.2, 128.1, 127.7, 126.5, 115.4, 64.2, 63.9, 55.0, 52.0, 40.4, 31.4, 31.5, 26.8, 26.6, 26.5;

FTIR (neat): 3700, 3356, 3062, 3029, 2926, 2851, 2665, 1948, 1871, 1805, 1737, 1635, 1599, 1491, 1305, 1247, 1173, 996, 915, 847, 760, 734, 517 cm^{-1};

HRMS (EI) Calcd for $C_{25}H_{31}NO_2$ [M^+]: 377.2355, found 376.2274 (M - 1).

(*S*)-Methyl 2-((*S*)-1-cyclohexyl-3-methylbut-3-enylamino)-2-phenylacetate



(78 % *de*)

Light yellow oil (205 mg, 65 %);

R_f = 0.59 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = – 1.3 ^{o} (0.4, CH_2Cl_2);

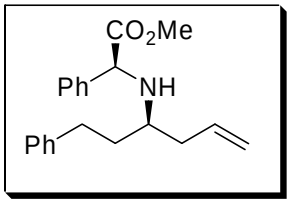
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H), 4.89 – 4.78 (m, 2H), 4.51 (s, 1H), 3.68 (s, 3H), 2.52 – 2.47 (m, 1H), 2.14 – 2.05 (m, 2H), 1.76 – 1.52 (m, 8H), 1.46 – 1.40 (m, 1H), 1.27 – 1.01 (m, 5H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 143.6, 143.3, 138.9, 128.5, 127.8, 127.4, 113.4, 113.1, 72.4, 63.0, 57.1, 52.0, 43.4, 42.9, 40.2, 39.6, 39.0, 28.8, 28.2, 27.8, 26.9, 26.8, 26.7, 26.6, 26.3, 26.2, 22.2, 20.0;

FTIR (neat): 3028, 2926, 2852, 1740, 1645, 1581, 1450, 1311, 1240, 1168, 892, 735, 698, 627, 516 cm^{-1};

HRMS (EI) Calcd for $C_{20}H_{29}NO_2$ [M^+]: 315.2198, found 314.2111 (M - 1).

(*S*)-Methyl 2-((*R*)-1-phenylhex-5-en-3-ylamino)-2-phenylacetate



(64 % *de*)

Yellow oil (65 mg, 20 %);

R_f = 0.44 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 4.3 ^{o} (0.2, CH_2Cl_2);

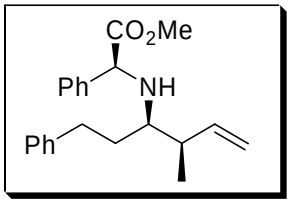
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.08 (m, 10H), 5.88 – 5.74 (m, 1H), 5.15 – 5.10 (m, 1H), 4.51 (s, 1H), 3.67 (s, 3H), 2.67 – 2.54 (m, 3H), 2.36 – 2.16 (m, 3H), 1.72 (dt, *J* = 8.0, 2.1 Hz, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 142.4, 138.7, 135.1, 128.8, 128.7, 128.6, 128.3, 128.3, 128.2, 128.0, 127.6, 125.7, 117.7, 62.8, 54.1, 52.2, 38.4, 35.9, 31.7;

FTIR (neat): 3063, 2927, 2587, 1949, 1737, 1638, 1600, 1452, 1367, 1206, 1170, 1072, 996, 914, 744, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{21}H_{25}NO_2$ [M^+]: 323.1885, found 324.1963 (M + 1).

(*S*)-Methyl 2-((3*R*,4*R*)-4-methyl-1-phenylhex-5-en-3-ylamino)-2-phenylacetate



(56 % *de*; *syn* : *anti* = 79 : 21)

Yellow oil (132 mg, 39 %);

R_f = 0.58 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 22.7 ^{o} (0.4, CH_2Cl_2);

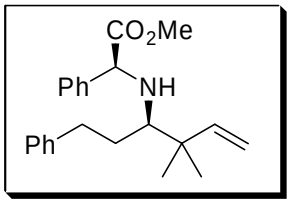
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.05 (m, 10H), 5.75 – 5.58 (m, 1H), 5.10 – 5.04 (m, 1H), 4.16 (s, 1H), 3.61 (s, 3H), 2.74 – 2.68 (m, 3H), 2.58 – 2.51 (m, 2H), 2.17 – 2.05 (m, 1H), 0.8 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.4, 142.0, 141.9, 141.8, 141.7, 140.2, 138.6, 137.1, 131.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.5, 127.2, 127.0, 125.8, 125.7, 125.6, 116.0, 114.2, 68.4, 65.0, 62.2, 51.7, 42.2, 36.1, 34.9, 33.3, 30.6, 18.2, 13.6;

FTIR (neat): 3062, 3027, 2952, 1737, 1599, 1453, 1300, 1204, 1170, 997, 917, 733, 699, 551 cm^{-1};

HRMS (ESI) Calcd for $C_{22}H_{27}NO_2$ [M^+]: 337.2042, found 338.2113 (M + 1).

(*S*)-Methyl 2-((*R*)-4,4-dimethyl-1-phenylhex-5-en-3-ylamino)-2-phenylacetate



(78 % *de*)

Yellow oil (253 mg, 72 %);

R_f = 0.70 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 32.8 ^{o} (0.6, CH_2Cl_2);

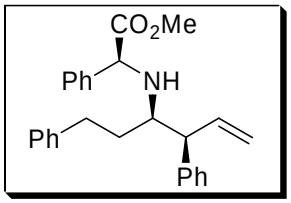
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.09 (m, 10H), 5.88 (dd, *J* = 17.1, 11.5 Hz, 2H), 5.04 – 4.98 (m, 2H), 4.47 (s, 1H), 3.67 (s, 3H), 2.53 (dt, *J* = 5.6, 5.3 Hz, 1H), 2.28 – 2.17 (m, 2H), 1.86 – 1.74 (m, 1H), 1.49 – 1.37 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 146.9, 142.7, 139.7, 128.9, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.1, 125.6, 112.1, 65.2, 63.9, 52.1, 42.4, 34.3, 34.1, 24.1, 23.2;

FTIR (neat): 3027, 2954, 2868, 1737, 1600, 1454, 1361, 1307, 1253, 1201, 1169, 1004, 914, 738, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{23}H_{29}NO_2$ [M^+]: 351.2198, found 352.2281 (M + 1).

(*S*)-Methyl 2-((3*R*,4*S*)-1,4-diphenylhex-5-en-3-ylamino)-2-phenylacetate



(76 % *de*; *syn* : *anti* = 90 : 10)

Dark Yellow oil (231 mg, 58 %);

R_f = 0.48 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 29.7 ^{o} (0.8, CH_2Cl_2);

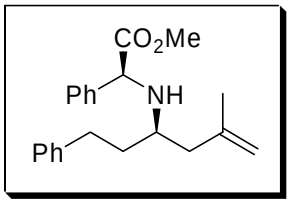
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 6.95 (m, 15H), 6.08 (dt, *J* = 10.5, 9.4 Hz, 1H), 5.21 – 5.15 (m, 2H), 4.40 (s, 1H), 3.61 (3H), 3.57 – 3.48 (m, 1H), 2.86 (dt, *J* = 10.5, 3.8 Hz, 1H), 2.71 (ddd, *J* = 10.5, 5.6, 5.2 Hz, 1H), 2.44 (ddd, *J* = 10.5, 6.3, 5.6 Hz, 1H), 1.80 – 1.63 (m, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.4, 142.6, 141.8, 138.9, 138.0, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 126.6, 125.6, 117.2, 63.0, 58.6, 53.4, 52.2, 32.8, 31.0;

FTIR (neat): 3027, 2949, 1737, 1601, 1491, 1452, 1305, 1171, 996, 920, 737, 700 cm^{-1};

HRMS (ESI) Calcd for $C_{27}H_{29}NO_2$ [M^+]: 399.2198, found 400.2270 (M + 1).

(*S*)-Methyl 2-((*R*)-5-methyl-1-phenylhex-5-en-3-ylamino)-2-phenylacetate



(80 % *de*)

Yellow oil (67 mg, 20 %);

R_f = 0.68 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 23.0 ^{o} (0.7, CH_2Cl_2);

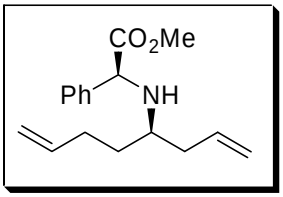
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 – 7.13 (m, 10H), 4.91 (brs, 1H), 4.85 (brs, 1H), 4.30 (s, 1H), 3.59 (s, 3H), 3.25 – 3.20 (m, 1H), 2.81 – 2.76 (m, 2H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.13 – 2.05 (m, 1H), 1.95 (brs, 1H), 1.79 (s, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.1, 142.8, 141.8, 140.0, 138.7, 138.6, 129.2, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 127.5, 127.0, 125.8, 125.7, 113.6, 61.8, 58.8, 51.6, 44.9, 35.9, 33.6, 30.2, 21.5;

FTIR (neat): 3062, 3027, 2927, 2854, 1737, 1641, 1600, 1492, 1452, 1309, 1205, 1170, 986, 895, 735, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{22}H_{27}NO_2$ [M^+]: 337.2042, found 338.2641 (M + 1).

(*S*)-Methyl 2-((*R*)-octa-1,7-dien-4-ylamino)-2-phenylacetate



(80 % *de*)

Yellow oil (71 mg, 26 %);

R_f = 0.41 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 37.9 ^{o} (0.5, CH_2Cl_2);

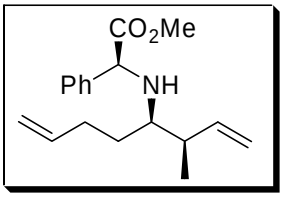
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H), 5.83 – 5.67 (m, 2H), 5.13 – 5.07 (m, 2H), 4.98 – 4.86 (m, 2H), 4.50 (s, 1H), 3.68 (s, 3H), 2.52 (qn, *J* = 5.9 Hz, 1H), 2.25 – 2.15 (m, 2H), 2.10 – 2.02 (m, 2H), 1.52 – 1.45 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 138.6, 135.1, 128.6, 127.9, 127.5, 117.6, 114.5, 62.7, 53.8, 52.2, 38.3, 33.3, 29.7;

FTIR (neat): 3072, 2926, 2855, 1819, 1740, 1640, 1452, 1364, 1311, 1208, 1122, 1028, 995, 914, 736, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{17}H_{23}NO_2$ [M^+]: 273.1729, found 274.1796 (M + 1).

(*S*)-methyl 2-((3*R*,4*R*)-3-methylocta-1,7-dien-4-ylamino)-2-phenylacetate



(50 % *de*; *syn* : *anti* = 86 : 14)

Yellow oil (169 mg, 59 %);

R_f = 0.66 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 31.2 ^{o} (0.2, CH_2Cl_2);

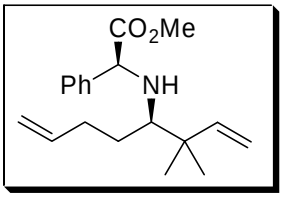
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 5.88 – 5.63 (m, 2H), 5.10 – 5.02 (m, 2H), 4.91 – 4.85 (m, 2H), 4.51 (s, 1H), 3.67 (s, 3H), 2.47 – 2.41 (m, 1H), 2.39 – 2.32 (m, 1H), 2.19 – 2.09 (m, 1H), 1.99 – 1.86 (m, 1H), 1.49 – 1.41 (m, 1H), 1.38 – 1.29 (m, 1H), 0.98 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.6, 141.7, 140.7, 138.9, 138.8, 138.7, 128.4, 127.8, 127.7, 127.5, 114.9, 114.4, 63.0, 62.8, 58.4, 52.1, 39.9, 39.3, 30.3, 30.1, 29.5, 15.4, 14.8;

FTIR (neat): 3072, 3029, 2958, 1739, 1600, 1639, 1452, 1373, 1315, 1252, 1203, 1171, 1132, 998, 912, 785, 733, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{18}H_{25}NO_2$ [M^+]: 287.1885, found 288.1961 (M + 1).

(*S*)-Methyl 2-((*R*)-3,3-dimethylocta-1,7-dien-4-ylamino)-2-phenylacetate



(78 % *de*)

Yellow oil (197 mg, 72 %);

R_f = 0.64 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 40.6 ^{o} (0.5, CH_2Cl_2);

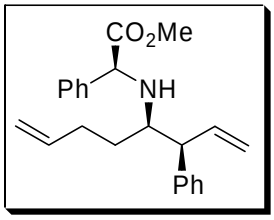
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.28 (m, 5H), 5.88 (dd, *J* = 17.1, 11.5 Hz, 1H), 5.62 (ddt, *J* = 13.9, 10.5, 6.6 Hz, 1H), 5.13 – 5.07 (m, 2H), 4.98 – 4.86 (m, 2H), 4.50 (s, 1H), 3.68 (s, 3H), 2.56 – 2.48 (m, 1H), 2.25 – 2.15 (m, 2H), 2.10 – 2.02 (m, 2H), 1.52 – 1.45 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 138.6, 135.1, 128.6, 127.9, 127.5, 117.6, 114.5, 62.7, 53.8, 52.2, 38.3, 33.3, 29.7;

FTIR (neat): 3072, 2926, 2855, 1819, 1740, 1640, 1452, 1364, 1311, 1208, 1122, 1028, 995, 914, 736, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{17}H_{23}NO_2$ [M^+]: 273.1729, found 274.1796 (M + 1).

(*S*)-Methyl 2-((3*S*,4*R*)-3-phenylocta-1,7-dien-4-ylamino)-2-phenylacetate



(80 % *de*; *syn* : *anti* = 95 : 5)

Dark Yellow oil (216 mg, 62 %);

R_f = 0.55 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 33.8 ^{o} (0.6, CH_2Cl_2);

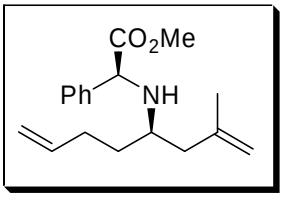
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 – 7.17 (m, 10H), 6.08 (dt, *J* = 16.7, 9.8 Hz, 1H), 5.64 (ddt, *J* = 13.9, 9.8, 6.6 Hz, 1H), 5.19 – 5.12 (m, 2H), 4.86 – 4.82 (m, 2H), 4.39 (s, 1H), 3.62 (s, 3H), 3.53 – 3.48 (m, 1H), 2.80 (q, *J* = 3.8 Hz, 1H), 2.21 – 2.11 (m, 1H), 2.09 – 1.93 (m, 1H), 1.49 – 1.43 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.2, 141.8, 138.6, 137.9, 128.4, 128.4, 128.1, 127.8, 127.6, 126.4, 117.0, 114.3, 62.7, 58.3, 23.3, 21.9, 29.9, 29.1;

FTIR (neat): 3063, 3028, 2947, 2405, 1738, 1639, 1600, 1492, 1450, 1309, 1207, 1172, 996, 915, 732, 700 cm^{-1};

HRMS (ESI) Calcd for $C_{23}H_{27}NO_2$ [M^+]: 349.2042, found 350.2119 (M + 1).

(*S*)-Methyl 2-((*R*)-2-methylocta-1,7-dien-4-ylamino)-2-phenylacetate



(30 % *de*)

Yellow oil (72 mg, 25 %);

R_f = 0.48 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 4.1 ^{o} (0.4, CH_2Cl_2);

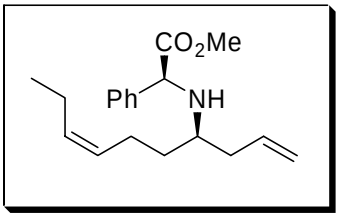
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 5H), 5.74 (ddt, *J* = 14.3, 10.5, 6.6 Hz, 1H), 4.98 – 4.85 (m, 4H), 4.50 (s, 1H), 3.68 (s, 3H), 2.63 (q, *J* = 5.9 Hz, 1H), 2.15 (d, *J* = 6.6 Hz, 2H), 2.11 – 2.03 (m, 2H), 1.70 (s, 3H), 1.51 – 1.44 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 143.0, 138.6, 128.7, 127.9, 127.5, 127.4, 114.5, 113.4, 62.6, 52.1, 52.0, 43.4, 33.2, 29.5, 22.1;

FTIR (neat): 3072, 2929, 2854, 1740, 1641, 1313, 1204, 1170, 996, 895, 736, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{18}H_{25}NO_2$ [M^+]: 287.1885, found 288.1964 (M + 1).

(*S*)-Methyl 2-((*R*,*Z*)-deca-1,7-dien-4-ylamino)-2-phenylacetate



(74 % *de*)

Yellow oil (75 mg, 25 %);

R_f = 0.55 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 26.4 ^{o} (0.4, CH_2Cl_2);

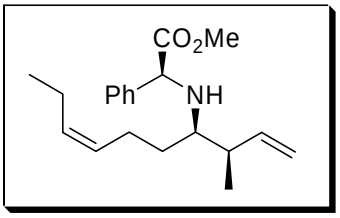
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 5H), 5.84 – 5.76 (m, 1H), 5.36 – 5.31 (m, 1H), 5.27 – 5.22 (m, 1H), 5.15 – 5.09 (m, 2H), 4.50 (s, 1H), 3.68 (s, 3H), 2.53 (qn, *J* = 6.0 Hz, 1H), 2.29 – 2.24 (m, 1H), 2.18 – 2.13 (m, 2H), 2.09 – 1.97 (m, 3H), 1.48 – 1.43 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 138.6, 135.2, 132.2, 131.9, 128.6, 128.6, 128.5, 127.9, 127.5, 117.9, 117.5, 62.8, 54.2, 52.1, 41.9, 38.4, 367, 34.1, 23.4, 23.1, 20.5, 14.3;

FTIR (neat): 3004, 2960, 2929, 1740, 1639, 1454, 1309, 1255, 1205, 1170, 996, 915, 735, 698 cm^{-1};

HRMS (ESI) Calcd for $C_{19}H_{27}NO_2$ [M^+]: 301.2042, found 302.2119 (M + 1).

(*S*)-Methyl 2-((*Z*,3*R*,4*R*)-3-methyldeca-1,7-dien-4-ylamino)-2-phenylacetate



(60 % *de*; *syn* : *anti* = 81 : 19)

Yellow oil (167 mg, 53 %);

R_f = 0.60 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 43.7 ^{o} (0.5, CH_2Cl_2);

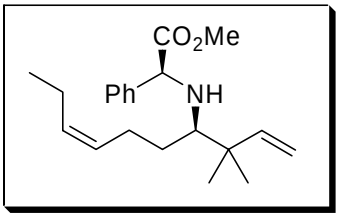
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.28 (m, 5H), 5.83 (ddd, *J* = 13.6, 10.5, 6.9 Hz, 1H), 5.36 – 5.17 (m, 2H), 5.09 – 5.02 (m, 2H), 4.51 (s, 1H), 3.68 (s, 3H), 2.46 – 2.29 (m, 2H), 2.17 – 1.84 (m, 4H), 1.49 – 1.23 (m, 2H), 1.99 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 141.0, 138.9, 131.8, 128.8, 128.6, 128.5, 127.9, 127.7, 127.5, 114.9, 62.9, 58.9, 52.2, 39.5, 31.1, 23.8, 20.5, 15.4, 14.3;

FTIR (neat): 3003, 2962, 1873, 1740, 1638, 1454, 1374, 1204, 1170, 999, 914, 731, 698 cm^{-1};

HRMS (ESI) Calcd for $C_{20}H_{29}NO_2$ [M^+]: 315.2198, found 316.2277 (M + 1).

(*S*)-Methyl 2-((*R*,*Z*)-3,3-dimethyldeca-1,7-dien-4-ylamino)-2-phenylacetate



(80 % *de*)

Yellow oil (303 mg, 92 %);

R_f = 0.71 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 43.7 ^{o} (0.4, CH_2Cl_2);

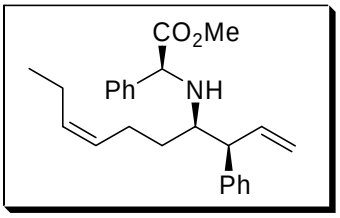
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.28 (m, 5H), 5.92 (dd, *J* = 11.9, 10.4 Hz, 1H), 5.39 – 5.15 (m, 2H), 5.07 – 5.07 (m, 2H), 4.50 (s, 1H), 3.68 (s, 3H), 2.23 (dd, *J* = 6.9, 3.5 Hz, 1H), 2.06 (brs, 1H), 1.98 – 1.88 (m, 2H), 1.78 – 1.67 (m, 1H), 1.63 – 1.51 (m, 1H), 1.27 – 1.17 (m, 1H), 1.06 (s, 3H), 0.96 (s, 3H), 0.93 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 146.9, 139.4, 131.6, 128.8, 128.4, 127.8, 127.6, 111.8, 64.9, 63.8, 51.9, 42.1, 32.0, 25.8, 24.0, 22.9, 20.4, 14.3;

FTIR (neat): 3004, 2963, 2872, 1740, 1690, 1637, 1434, 1454, 1363, 1257, 1199, 1166, 1130, 1071, 913, 865, 728, 699 cm^{-1};

HRMS (ESI) Calcd for $C_{21}H_{31}NO_2$ [M^+]: 329.2355, found 330.2441 (M + 1).

(*S*)-Methyl 2-((*Z*,3*S*,4*R*)-3-phenyldeca-1,7-dien-4-ylamino)-2-phenylacetate



(80 % *de*; *syn* : *anti* = 88 : 12)

Dark Yellow oil (253 mg, 67 %);

R_f = 0.55 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 39.2 ^{o} (0.3, CH_2Cl_2);

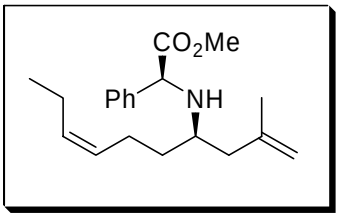
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.22 (m, 10H), 6.12 (ddd, *J* = 16.4, 15.3, 9.4 Hz, 1H), 5.37 – 5.15 (m, 4H), 4.42 (s, 1H), 3.63 (s, 3H), 3.52 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.89 – 2.83 (m, 1H), 2.20 – 2.10 (m, 2H), 2.09 – 1.93 (m, 2H), 1.59 – 1.39 (m, 2H), 0.93 (t, *J* = 7.7 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.3, 141.8, 138.6, 138.2, 131.7, 128.8, 128.6, 128.4, 128.1, 127.9, 127.8, 127.5, 126.5, 116.8, 62.8, 58.6, 53.6, 51.9, 30.8, 22.5, 20.4, 14.3;

FTIR (neat): 3063, 3028, 3004, 2960, 2932, 2872, 1738, 1600, 1492, 1453, 1306, 1204, 1170, 995, 919, 731, 700 cm^{-1};

HRMS (ESI) Calcd for $C_{25}H_{31}NO_2$ [M^+]: 377.2355, found 378.2436 (M + 1).

(*S*)-Methyl 2-((*R*,*Z*)-2-methyldeca-1,7-dien-4-ylamino)-2-phenylacetate



(46 % *de*)

Yellow oil (66 mg, 21 %);

R_f = 0.51 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 20.3 ^{o} (0.3, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.26 (m, 5H), 5.38 – 5.32 (m, 1H), 5.29 – 5.23 (m, 1H), 4.87– 4.79 (m, 2H), 4.51 (s, 1H), 3.68 (s, 3H), 2.67 – 2.62 (m, 1H), 2.17 – 2.07 (m, 2H), 2.06 – 1.98 (m, 5H), 1.72 (s, 3H), 1.53 – 1.39 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 143.0, 138.6, 131.9, 128.7, 128.7, 127.9, 127.4, 113.4, 62.7, 52.3, 52.1, 43.4, 34.0, 22.9, 22.1, 20.5, 14.3;

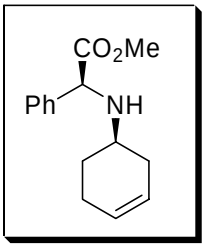
FTIR (neat): 3004, 2960, 1720, 1646, 1452, 1204, 1168, 892, 731, 698 cm^{-1};

HRMS (ESI) Calcd for $C_{20}H_{29}NO_2$ [M^+]: 315.2198, found 316.2281 (M + 1).

General reaction procedure for the ring-closing metathesis of homoallylic amines.

To a stirred suspension of the chiral homoallylic amine (1 mmol) in CH_2Cl_2 (100 mL) was added the Grubbs' 2nd generation catalyst (0.1 mmol) at two portions (interval of 30 minutes) at 25 ^oC and the reaction mixture was stirred for up to 12 hours. Reactions were heated to reflux at 40 ^oC if the TLC showed starting material after 12 hours of stirring at room temperature The reaction mixture was then filtered through a pad of celite before being concentrated *in vacuo*. The crude product was purified by flash column chromatography.

(*S*)-Methyl 2-((*R*)-cyclohex-3-enylamino)-2-phenylacetate



Dark brown oil (216 mg, 88 %);

R_f = 0.29 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 76.8 ^{o} (0.3, CH_2Cl_2);

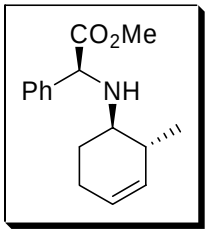
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.29 (m, 5H), 5.64 – 5.54 (m, 2H), 4.55 (s, 1H), 3.69 (s, 3H), 2.71 – 2.61 (m, 1H), 2.29 – 2.24 (m, 1H), 2.09 – 1.79 (m, 3H), 1.52 – 1.39 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.9, 138.4, 128.8, 128.1, 128.0, 127.4, 126.9, 124.7, 62.6, 52.3, 50.8, 32.1, 29.2, 24.4;

FTIR (neat): 3025, 2920, 2839, 1752, 1295, 1246, 1203, 1170, 929, 783, 698 cm^{-1};

HRMS (ESI) Calcd for $C_{15}H_{19}NO_2$ [M^+]: 245.1416, found 246.1496 (M + 1).

(*S*)-Methyl 2-((1*R*,2*R*)-2-methylcyclohex-3-enylamino)-2-phenylacetate



Dark brown oil (218 mg, 84 %);

R_f = 0.51 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 1.8 ^{o} (0.4, CH_2Cl_2);

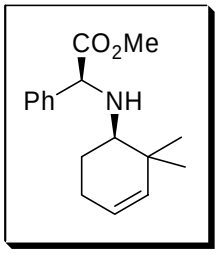
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 5H), 5.63 – 5.59 (m, 1H), 5.45 (ddd, *J* = 10.2, 2.3, 1.8 Hz, 1H), 4.55 (s, 1H), 3.69 (s, 3H), 2.35 (dt, *J* = 9.7, 2.8 Hz, 1H), 2.14 – 1.93 (m, 3H), 1.87 – 1.82 (m, 1H), 1.45 – 1.38 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.0, 138.9, 131.6, 128.6, 128.5, 127.9, 127.5, 127.3, 125.8, 125.6, 62.9, 58.2, 52.1, 36.4, 26.8, 23.8, 19.4;

FTIR (neat): 3018, 2953, 2926, 2870, 1737, 1453, 1250, 1205, 1168, 1137, 1016, 729, 698 cm^{-1};

HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ [M^+]: 259.1572, found 259.1574.

(*S*)-Methyl 2-((*R*)-2,2-dimethylcyclohex-3-enylamino)-2-phenylacetate



Dark brown oil (251 mg, 92 %);

R_f = 0.61 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 25.1 ^{o} (0.5, CH_2Cl_2);

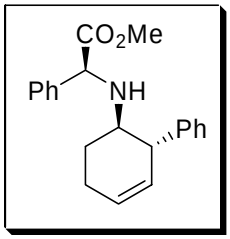
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.28 (m, 5H), 5.50 (ddd, *J* = 10.2, 2.8, 1.8 Hz, 1H), 5.36 (dt, *J* = 10.2, 1.9 Hz, 1H), 5.54 (s, 1H), 3.69 (s, 3H), 2.43 (dd, *J* = 11.1, 2.8 Hz, 1H), 2.06 – 1.93 (m, 3H), 1.75 – 1.71 (m, 1H), 1.49 – 1.42 (m, 1H), 1.13 (s, 3H), 1.00 (s, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.0, 139.1, 137.6, 128.5, 127.9, 127.3, 123.7, 63.7, 61.0, 51.9, 36.2, 28.4, 24.7, 24.4, 22.9;

FTIR (neat): 3013, 2954, 1738, 1454, 1363, 1298, 1204, 1168, 916, 737, 698 cm^{-1};

HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ [M^+]: 273.1729, found 273.1731.

(*S*)-Methyl 2-((1*R*,2*S*)-2-phenylcyclohex-3-enylamino)-2-phenylacetate



Dark brown oil (276 mg, 86 %);

R_f = 0.40 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 44.1 ^{o} (0.4, CH_2Cl_2);

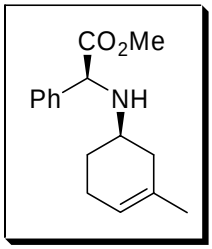
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.25 (m, 10H), 5.86 – 5.82 (m, 1H), 5.59 (ddd, *J* = 10.2, 2.3, 1.9 Hz, 1H), 4.40 (s, 1H), 3.50 (s, 3H), 3.36 – 3.33 (m, 1H), 2.72 (dt, *J* = 10.6, 2.8 Hz, 1H), 2.33 – 2.16 (m, 4H), 1.97 – 1.92 (m, 1H), 1.60 – 1.53 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.3, 143.4, 138.5, 129.0, 128.5, 128.4, 127.8, 127.3, 127.2, 126.7, 62.8, 58.1, 51.9, 49.2, 27.0, 24.0;

FTIR (neat): 3025, 2947, 2925, 2860, 1737, 1491, 1453, 1290, 1248, 1207, 1169, 1135, 1029, 787, 760, 733,701 cm^{-1};

HRMS (EI) Calcd for $C_{21}H_{23}NO_2$ [M^+]: 321.1729, found 321.1730.

(*S*)-Methyl 2-((*R*)-3-methylcyclohex-3-enylamino)-2-phenylacetate



Dark brown oil (202 mg, 78 %);

R_f = 0.38 (8:1 hexane/ethyl acetate);

$[\alpha]_D^{25}$ = + 12.6 ^{o} (0.2, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.27 (m, 5H), 5.32 (brs, 1H), 4.56 (s, 1H), 3.69 (s, 3H), 2.70 – 2.64 (m, 1H), 2.14 – 2.04 (m, 3H), 1.98 – 1.77 (m, 3H), 1.63 (s, 3H), 1.42 – 1.34 (m, 1H);

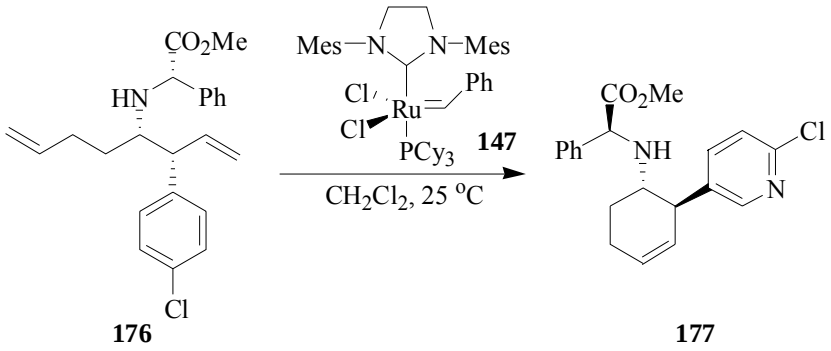
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.8, 138.5, 131.8, 128.7, 128.0, 127.4, 120.7, 62.5, 52.2, 51.3, 37.0, 28.8, 24.2, 23.5;

FTIR (neat): 3029, 2920, 2839, 1738, 1492, 1450, 1435, 1377, 1314, 1203, 1171, 1008, 925, 787, 730, 699 cm^{-1};

HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ [M^+]: 259.1572, found 259.1573.

3.6 ATTEMPTS TO REFINE SYNTHETIC ROUTE

177: (*S*)-Methyl 2-((1*S*,2*R*)-2-(6-chloropyridin-3-yl)cyclohex-3-enylamino)-2-phenylacetate



Grubbs' 2nd generation catalyst **147** (0.11 g, 0.13 mmol) was added in one portion into a solution of **176** (1.01 g, 2.63 mmol) in CH_2Cl_2 (260 mL) at room temperature and the resultant solution was allowed to stir for 30 minutes. Another portion of the catalyst (0.11 g, 0.13 mmol) was then added into the reaction mixture. When TLC had shown the full depletion of the starting material **176**, the reaction mixture was then filtered through a pad of celite and the resultant solution was then evaporated *in vacuo*. The crude product was purified *via* flash column chromatography (12:1 hexane/ethyl acetate), yielding 0.82 g (2.31 mmol, 88%) of the cyclohexenylamine **177** as a dark brown oil.

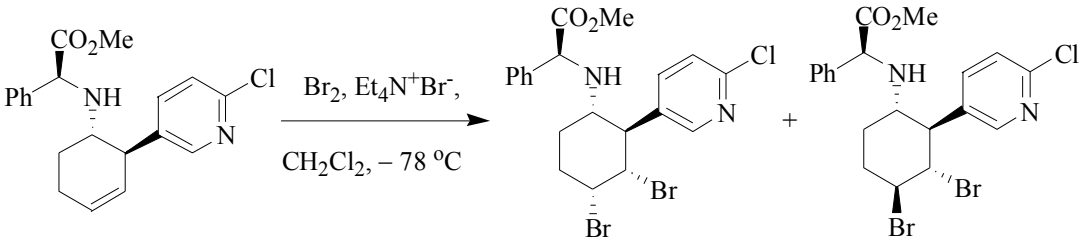
R_f = 0.19 (4:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 2.32 Hz, 1H), 7.28 (d, *J* = 2.31, 8.32 Hz, 1H), 7.20 – 7.13 (m, 5H), 6.94 (d, *J* = 8.32 Hz, 1H), 5.83 – 5.79 (m, 1H), 5.41, (dd, *J* = 1.85, 9.71 Hz, 1H), 4.33 (s, 1H), 3.60 (s, 3H), 3.23 – 3.20 (m, 1H), 2.38 – 2.34 (m, 1H), 2.12 – 2.05 (m, 2H), 2.02 – 1.98 (m, 1H), 1.55 – 1.47 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.8, 149.7, 149.3, 138.3, 137.9, 137.4, 128.4, 128.3, 127.7, 127.4, 127.1, 123.6, 62.3, 56.6, 52.0, 46.2, 26.8, 24.1;

HRMS (ESI) Calcd for $C_{20}H_{21}ClN_2O_2$ [M^+]: 356.1292, found: 357.1366 (M+1).

(*S*)-Methyl 2-((1*S*,2*R*)-3,4-dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylacetate



177 **178**: Major **179**: Minor

Tetraethylammonium bromide (4.30 g, 20.46 mmol) was added into a stirred solution of **177** (0.73 g, 2.05 mmol) in CH_2Cl_2 (36 mL) and the solution was cooled to – 78 ^oC. After the reaction mixture had stirred for 45 minutes, bromine (0.32 mL, 6.14 mmol), which was diluted with CH_2Cl_2 (4 mL), was introduced slowly at the same temperature. The resultant solution was allowed to stir for a further 2 hours. When TLC had shown the full depletion of the starting material **177**, the reaction mixture was washed with saturated $NaHSO_3$ (2 x 10 mL) and water (2 x 10 mL). After drying in Na_2SO_4, the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (12:1 hexane/ethyl acetate), yielding 0.65 g (1.26mmol) of the major isomer **178** as a light yellow oil and 0.22 g (0.42 mmol) of the minor isomer **179** as a dark yellow paste (82% yield, 75:25 ratio).

Major diastereomer 178: (*S*)-Methyl 2-((1*S*,2*R*,3*S*,4*R*)-3,4-dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylacetate

R_f = 0.32 (3:1 hexane/ethyl acetate);

^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, *J* = 1.74 Hz, 1H), 7.38 – 7.36 (m, 3H), 7.19 – 7.15 (m, 4H), 4.76 (d, *J* = 2.79 Hz, 1H), 4.47 (s, 1H), 4.39 (d, *J* = 2.09, 1H), 3.65 – 3.60 (m, 4H), 3.09 (dt, *J* = 4.18, 10.80 Hz, 1H), 2.33 – 2.31 (m, 1H), 2.20 – 2.15 (m, 1H), 1.94 – 1.81 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.9, 150.5, 150.3, 139.7, 137.4, 133.4, 128.7, 128.4, 127.6, 123.4, 61.8,60.5, 52.6, 52.4, 49.9, 44.9, 27.4, 26.7;

HRMS (ESI) Calcd for $C_{20}H_{21}Br_2ClN_2O_2$ [M^+]: 516.9658, found: 516.9712.

Major diastereomer 179: (*S*)-Methyl 2-((1*S*,2*R*,3*S*,4*S*)-3,4-dibromo-2-(6-chloropyridin-3-yl)cyclohexylamino)-2-phenylacetate

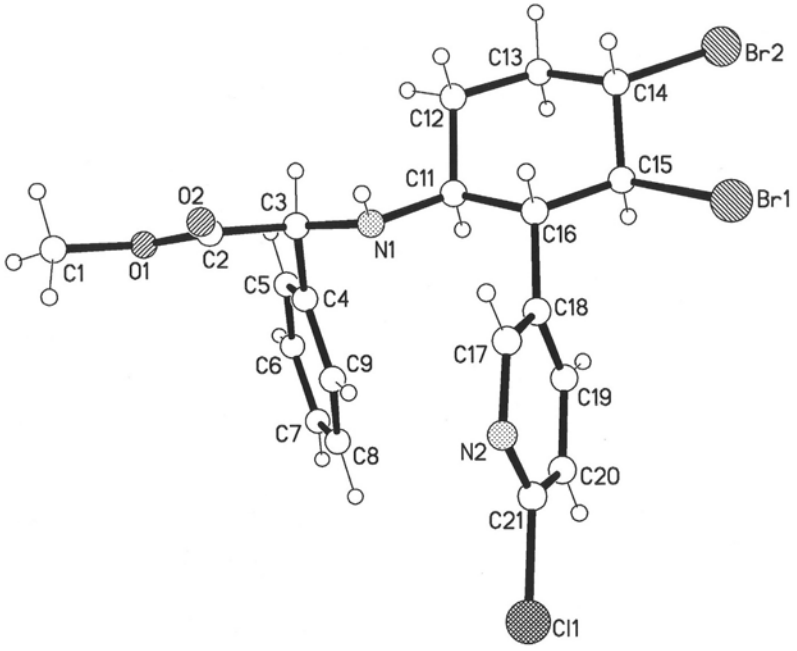
R_f = 0.25 (3:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.29 – 7.22 (m, 5H), 6.85 – 6.82 (m, 2H), 4.16 (s, 1H), 4.12 (dd, *J* = 4.53, 12.19 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.59 (s, 3H), 2.93 (t, *J* = 10.80 Hz, 1H), 2.59 – 2.42 (m, 1H), 2.24 – 2.17 (m, 1H), 2.00 – 1.86 (m, 2H), 1.51 – 1.37 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 172.4, 150.7, 149.7, 137.9, 136.6, 134.9, 128.8, 128.5, 127.2, 124.2, 62.3, 60.6, 57.2, 55.3, 52.5, 35.6, 31.9, 29.7;

HRMS (ESI) Calcd for $C_{20}H_{21}Br_2ClN_2O_2$ [M^+]: 516.9658, found: 516.9709.

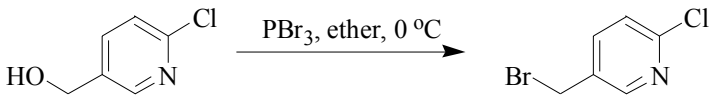
Crystal data and structure refinement for **179**:



Crystal growing solvent	Dichloromethane and hexane	
Empirical formula	C20 H21 Br2 Cl N2 O2	
Formula weight	516.66	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.5571(7) Å	$\alpha = 90^{o}$.
	b = 20.2210(17) Å	$\beta = 111.691(2)^{o}$.
	c = 11.8903(10) Å	$\gamma = 90^{o}$.
Volume	2135.1(3) $Å^3$	
Z	4	
Density (calculated)	1.607 Mg/m^3	
Absorption coefficient	3.939 mm^{-1}	
F(000)	1032	
Crystal size	0.34 x 0.26 x 0.10 mm^3	
Theta range for data collection	2.01 to 27.50^{o}.	
Index ranges	-9<=h<=12, -19<=k<=26, -15<=l<=15	
Reflections collected	14583	
Independent reflections	4690 [R(int) = 0.0434]	
Completeness to theta = 27.50^{o}	99.9 %	
Absorption correction	Sadabs, (Sheldrick 2001)	
Max. and min. transmission	0.6941 and 0.3477	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4690 / 1 / 249	
Goodness-of-fit on F^2	1.019	
Final R indices [I>2sigma(I)]	R1 = 0.0585, wR2 = 0.1366	
R indices (all data)	R1 = 0.1097, wR2 = 0.1555	
Largest diff. peak and hole	1.036 and -0.632 $e.Å^{-3}$	

In depth discussion with Professor Koh Lip Lin revealed that this stereoisomer could still be optically active even though a P2(1)/n space group (that includes both hands) was revealed. The minor isomer could have crystallized with an equal portion of major and desired isomer.

182: 5-(Bromomethyl)-2-chloropyridine



129 **182**

Phosphorous tribromide (2.00 mL, 21.50 mmol) was introduced dropwise into a stirred solution of **129** (2.57 g, 17.80 mmol) in diethyl ether (150 mL) at 0 °C and the resulting mixture was allowed to stir for 5 hours. When TLC had shown the full depletion of the starting material **129**, sodium bicarbonate (20 mL) was then used to quench the reaction. Diethyl ether (5 x 40 mL) was used to extract the aqueous layer and the combined extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude solid was purified *via* flash column chromatography (20:1 hexane/ethyl acetate), yielding 2.57 g (12.43 mmol, 72%) of the allylic bromide **182** as a white solid.

R_f = 0.60 (4:1 hexane/ethyl acetate);

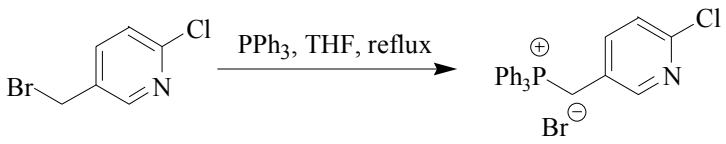
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (d, *J* = 2.44 Hz, 1H), 7.70 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.33 (d, *J* = 8.36 Hz, 1H), 4.44 (s, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.3, 149.5, 139.4, 132.6, 124.5, 28.4;

FTIR (neat): 3679, 3047, 3031, 2857, 2662, 1583, 1460, 1381, 1099, 399, 835, 741, 692 cm^{-1};

HRMS (ESI) Calcd for C_6H_5BrClN [M^+]: 204.9294, found: 205.9381 (M + 1).

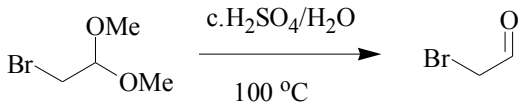
183: Triphenylphosphino-5-methyl-2-chloropyridine bromide



182 **183**

Triphenylphosphine (0.74 g, 2.80 mmol) was added into a stirred solution of **182** (0.58 g, 2.80 mmol) in THF (28 mL) at room temperature and the resulting mixture was heated to reflux. When TLC had shown the full depletion of the starting material **182**, the reaction mixture was concentrated *in vacuo*. Hexane/Diethyl ether (9:1) was used to dilute the solid and the resultant suspension was filtered. The residual white solid was used immediately for the subsequent step without further purification.

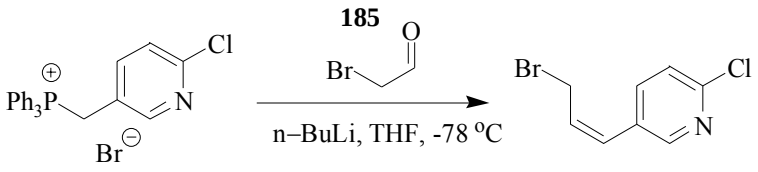
185: 2-Bromoacetaldehyde



184 **185**

A mixture of **184** (5.00 mL, 42.00 mmol), concentrated H_2SO_4 (0.15 mL) in water (11.50 mL) was heated at 100 ^oC for 2 hours. The reaction mixture was cooled and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by blowing N_2 over the solution. The yellow liquid **185** obtained was used immediately for the next reaction without further purification.

186: 5-((*Z*)-3-Bromoprop-1-enyl)-2-chloropyridine



183 **186**

Butyl lithium (1.6 M in hexane solution) (1.75 mL, 2.80 mmol) was introduced dropwise into a stirred solution of **183** (2.571.31 g, 2.80 mmol) in THF (20.70 mL) at – 78 ^{o}C and the resulting mixture was allowed to stir for 30 minutes. **185** (0.68 mL, 5.60 mmol) was then added slowly into the stirred solution at the same temperature and the resultant reaction mixture was allowed to stir for a further 2 hours. Sodium bicarbonate (15 mL) was used to quench the reaction and diethyl ether (5 x 20 mL) was used to extract the aqueous layer. The combined extracts were washed with brine (2 x 15 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude solid was purified *via* flash column chromatography (30:1 hexane/ethyl acetate), yielding 0.51 g with *E*/*Z* = 45/55 (2.21 mmol, 79%) of the allylic bromide **186** as a clear oil.

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

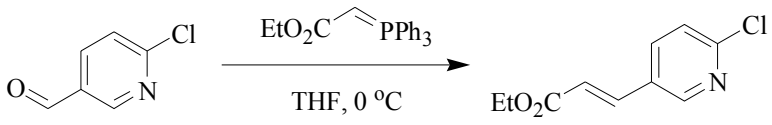
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 2.44 Hz, 1H), 7.60 (dd, *J* = 2.44, 8.01 Hz, 1H), 7.30 (d, *J* = 8.01 Hz, 1H), 6.45 (d, *J* = 11.49 Hz, 1H), 6.13 – 6.04 (m, 1H), 4.01 (dd, *J* = 0.70, 8.71 Hz, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.6, 149.3, 138.3, 129.7, 129.6, 128.2, 123.9, 27.1;

FTIR (neat): 1650, 1615, 1501, 1459, 1199, 1098, 970, 816, 580 cm^{-1};

HRMS (ESI) Calcd for C_8H_7BrClN [M^+]: 231.9533, found: 232.5049 (M + 1).

189: (*E*)-Ethyl 3-(6-chloropyridin-3-yl)acrylate



130 **189**

A solution of **130** (1.42 g, 10.00 mmol) in THF (10L) was added into a stirred solution of the ylide (4.18 g, 12.00 mmol) in THF (23 mL) at 0 °C and the resultant solution was allowed to stir for up to 30 minutes. When TLC had shown the full depletion of the starting material **130**, the reaction mixture was then concentrated *in vacuo*. The residual oil was purified *via* flash column chromatography (8:1 hexane/ethyl acetate), yielding 1.95 g (9.21 mmol, 92%) of the ester **189** as a white solid.

R_f = 0.58 (2:1 hexane/ethyl acetate);

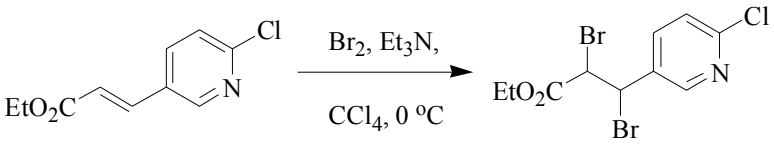
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, *J* = 2.44 Hz, 1H), 7.79 (dd, *J* = 2.78, 8.36 Hz, 1H), 7.63 (d, *J* = 16.38 Hz, 1H), 7.36 (d, *J* = 8.36 Hz, 1H), 6.48 (d, *J* = 16.03 Hz, 1H), 4.28 (q, *J* = 7.32 Hz, 2H), 1.34 (t, *J* = 7.32 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.0, 152.6, 149.5, 139.3, 136.6, 129.2, 124.6, 121.1, 60.9, 14.2;

FTIR (neat): 1711, 1465, 1379, 1296, 1266, 1205, 1103, 984, 831 cm^{-1};

HRMS (ESI) Calcd for $C_{10}H_{10}ClNO$ [M^+]: 211.0400, found: 212.0469 (M + 1).

190: Ethyl 2,3-dibromo-3-(6-chloropyridin-3-yl)propanoate



189 **190**

Br_2 (0.52 mL, 10.00 mmol) was added slowly into a stirred solution of **189** (1.76 g, 8.33 mmol) in CCl_4 (39.6 mL) at 0 ^oC and the resultant solution was allowed to stir for 15 minutes. Triethylamine (0.27 mL, 1.92 mmol) was then added into the stirred reaction mixture at 0 ^oC and the resultant reaction mixture was allowed to stir for a further 18 hours. When TLC had shown the full depletion of the starting material **189**, water (15 mL) was then added to quench the reaction. CH_2Cl_2 (3 x 20 mL) was used to extract the aqueous layer and the combined organic extracts were washed thoroughly with $NaHCO_3$ (2 x 10 mL) and brine (2 x 15 mL). The mixture was further dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residual oil was purified *via* flash column chromatography (8:1 hexane/ethyl acetate), yielding 3.09 g (8.33 mmol, ~100%) of the dibromo **190** as a yellow solid.

R_f = 0.68 (2:1 hexane/ethyl acetate);

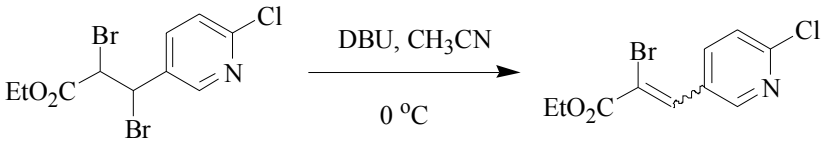
^1H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, *J* = 2.44 Hz, 1H), 7.70 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.38 (d, *J* = 8.02 Hz, 1H), 5.33 (d, *J* = 11.49 Hz, 1H), 4.72 (d, *J* = 11.85 Hz, 1H), 4.36 (q, *J* = 7.32 Hz, 2H), 1.37 (t, *J* = 7.32 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.2, 152.2, 149.2, 138.0, 132.9, 124.7, 62.9, 46.3, 46.1, 13.9;

FTIR (KBr): 2984, 1736, 1567, 1470, 1149, 1113, 1027, 836, 589 cm^{-1};

HRMS (ESI) Calcd for $C_{10}H_{10}Br_2ClNO$ [M^+]: 368.8767, found: 369.8840 (M + 1).

191: Ethyl 2-bromo-3-(6-chloropyridin-3-yl)acrylate



190 **191**

DBU (1.21 mL, 8.13 mmol) was added slowly into a stirred solution of **190** (3.02 g, 8.13 mmol) in CH_3CN (40 mL) at 0 ^oC and the resultant solution was allowed to stir for 12 hours. When TLC had shown the full depletion of the starting material **190**, water (20 mL) was then added to quench the reaction. The reaction mixture was concentrated *in vacuo* before ethyl acetate (3 x 30 mL) was used to extract the aqueous layer. The combined organic extracts were washed thoroughly with brine (2 x 15 mL) and dried over $MgSO_4$. The crude solution was then filtered and concentrated in vacuo. The residual oil was purified *via* flash column chromatography (10:1 hexane/ethyl acetate), yielding 1.06 g (3.66 mmol, 45%) of the bromo-alkene **191** as a dark yellow oil.

R_f = 0.53 (4:1 hexane/ethyl acetate);

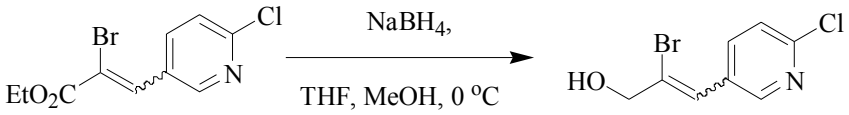
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, *J* = 2.44 Hz, 1H), 8.30 (dd, *J* = 2.44, 8.36 Hz, 1H), 8.14 (s, 1H), 7.40 (d, *J* = 8.71 Hz, 1H), 4.36 (q, *J* = 6.97 Hz, 2H), 1.39 (t, *J* = 6.97 Hz, 3H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 162.5, 152.4, 151.5, 138.7, 135.9, 128.8, 124.0, 116.6, 63.2, 14.1;

FTIR (neat): 2093, 1641, 1580, 1460, 1373, 1242, 1106, 1037, 825 cm^{-1};

HRMS (ESI) Calcd for $C_{10}H_9BrClNO$ [M^+]: 288.9505, found: 289.9586 (M + 1).

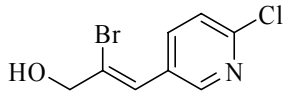
2-Bromo-3-(6-chloropyridin-3-yl)prop-2-en-1-ol



191 **192 + 193**

$NaBH_4$ (0.44 g, 11.60 mmol) was added slowly into a stirred solution of **191** (0.84 g, 2.90 mmol) in THF (5.25 mL) and MeOH (1.75 mL) at 0 ^oC and the resultant solution was allowed to stir for up to 30 mins. When TLC had shown the full depletion of the starting material **191**, 1M HCl (15 mL) was then added to quench the reaction. The reaction mixture was concentrated before dichloromethane (3 x 20 mL) was used to extract the aqueous layer. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residual oil was purified *via* flash column chromatography (7:1 hexane/ethyl acetate), yielding 0.38 g (1.54 mmol, 53%; *E*/*Z* = 35/65) of the primary alcohol as a yellow oil.

Major diastereomer 192: (*Z*)-2-Bromo-3-(6-chloropyridin-3-yl)prop-2-en-1-ol



R_f = 0.38 (2:1 hexane/ethyl acetate);

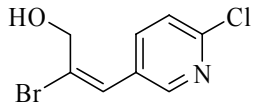
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, *J* = 2.44 Hz, 1H), 8.02 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.33 (d, *J* = 8.36 Hz, 1H), 7.08 (s, 1H), 4.43 (s, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.4, 150.0, 138.3, 130.2, 129.9, 123.8, 122.4, 68.6;

FTIR (neat): 2907, 1645, 1365, 1110,1086, 1030, 817, 733 cm^{-1};

HRMS (ESI) Calcd for $C_8H_7BrClNO$ [M^+]: 246.9400, found: 247.9479 (M + 1).

Minor diastereomer 193: (*E*)-2-Bromo-3-(6-chloropyridin-3-yl)prop-2-en-1-ol



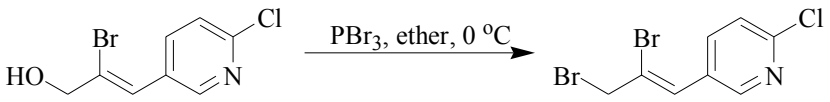
R_f = 0.53 (2:1 hexane/ethyl acetate);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 2.43 Hz, 1H), 7.58 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.34 (d, *J* = 8.36 Hz, 1H), 7.05 (s, 1H), 4.41 (s, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.6, 148.9, 138.3, 130.4, 130.3, 129.9, 124.2, 63.6;

HRMS (ESI) Calcd for $C_8H_7BrClNO$ [M^+]: 246.9400, found: 247.9484 (M + 1).

194: 5-((*Z*)-2,3-Dibromoprop-1-enyl)-2-chloropyridine



192 **194**

PBr_3 (0.60 mL, 6.20 mmol) was added slowly into a stirred solution of **192** (1.28 g, 5.16 mmol) in ether (51.6 mL) at 0 °C and the resultant solution was allowed to stir for up to 5 hours. When TLC had shown the full depletion of the starting material **192**, saturated $NaHCO_3$ (10 mL) was then added slowly to quench the reaction. Ether (3 x 20 mL) was used to extract the aqueous layer and the combined organic extracts were washed with brine (2 x 15 mL) before drying over $MgSO_4$. The resultant mixture was then filtered and concentrated *in vacuo*. The crude solid was purified *via* flash column chromatography (10:1 hexane/ethyl acetate), yielding g (mmol, 65%) of the allylic bromide **194** as a light brown solid.

R_f = 0.45 (4:1 hexane/ethyl acetate);

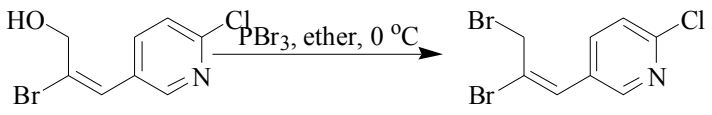
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, *J* = 2.43 Hz, 1H), 8.06 (dd, *J* = 2.43, 8.36 Hz, 1H), 7.34 (d, *J* = 8.36 Hz, 1H), 7.09 (s, 1H), 4.42 (s, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): 150.2, 138.1, 129.6, 127.6, 127.4, 124.2, 123.8, 39.3;

FTIR (neat): 2960, 1570, 1453, 1369, 1215, 1107,1074, 619 cm^{-1};

HRMS (ESI) Calcd for $C_8H_6Br_2ClN$ [M^+]: 308.8556, found: 309.8620 (M + 1).

195: 5-((*E*)-2,3-Dibromoprop-1-enyl)-2-chloropyridine



193 **195**

PBr_3 (0.34 mL, 3.60 mmol) was added slowly into a stirred solution of **193** (0.74 g, 3.00 mmol) in ether (30 mL) at 0 °C and the resultant solution was allowed to stir for up to 5 hours. When TLC had shown the full depletion of the starting material **193**, saturated $NaHCO_3$ (10 mL) was then added slowly to quench the reaction. Ether (3 x 20 mL) was used to extract the aqueous layer and the combined organic extracts were washed with brine (2 x 15 mL) before drying over $MgSO_4$. The resultant mixture was then filtered and concentrated *in vacuo*. The crude solid was purified *via* flash column chromatography (10:1 hexane/ethyl acetate), yielding g (mmol, 87%) of the allylic bromide **195** as a light brown solid.

R_f = 0.60 (4:1 hexane/ethyl acetate);

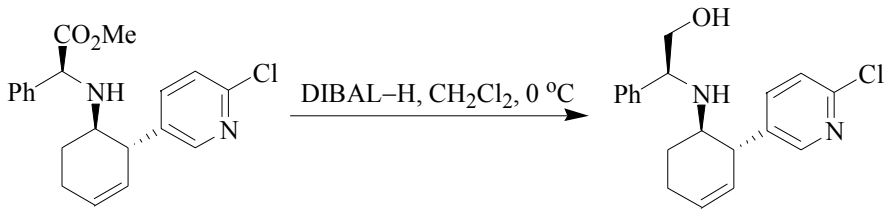
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.44 Hz, 1H), 7.66 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.38 (d, *J* = 8.36 Hz, 1H), 7.02 (s, 1H), 4.30 (s, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.2, 148.8, 137.6, 131.6, 130.0, 125.3, 124.5, 33.7;

FTIR (neat): 2361, 1577, 1454, 1105, 1026, 646 cm^{-1};

HRMS (ESI) Calcd for $C_8H_6Br_2ClN$ [M^+]: 308.8556, found: 309.8615 (M + 1).

198: (*S*)-2-((1*R*,2*S*)-2-(6-Chloropyridin-3-yl)cyclohex-3-enylamino)-2-phenylethanol



153 **198**

DIBAL–H (9.81 mL, 9.81 mmol) was added slowly into a stirred solution of **153** (1.00 g, 2.80 mmol) and CH_2Cl_2 (14.00 mL) at 0 °C. The reaction mixture was allowed to stir for up to 30 minutes. When TLC had shown the full depletion of the starting material **153**, MeOH was added dropwise at 0 °C till the disappearance of effervescence was observed. Potassium sodium tartrate (3 mL) was then added and the reaction mixture allowed to stir for up to 5 hours. Ethyl acetate (5 x 10 mL) was used to extract the aqueous layer and the combined organic extracts were washed with brine (3 x 5 mL) before drying with $MgSO_4$. The contents were then filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (3:1 hexane/ethyl acetate), yielding 0.58 g (1.76 mmol, 63%) of the primary alcohol **198** as a viscous light brown oil.

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

$[\alpha]_D^{25}$ = – 30.9 ° (1.4, CH_2Cl_2);

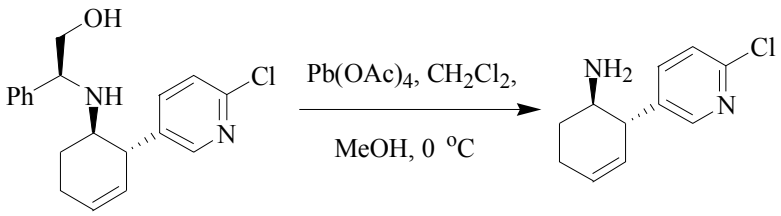
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 2.44 Hz, 1H), 7.38 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.29 – 7.17 (m, 6H), 5.86 (dd, *J* = 2.09, 9.75 Hz, 1H), 5.45 (dd, *J* = 2.79, 10.10 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.53 – 3.48 (m, 1H), 3.35 – 3.32 (m, 1H), 2.65 – 2.59 (m, 1H), 2.08 – 2.06 (m, 2H), 1.67 – 1.57 (m, 1H), 1.44 – 1.32 (m, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.6, 149.0, 141.3, 138.6, 138.5, 129.0, 128.3, 127.3, 127.1, 127.0, 126.4, 123.7, 66.3, 62.6, 57.4, 44.6, 26.8, 23.0;

FTIR (neat): 3799, 3026, 1864, 2666, 2326, 2124, 1951, 1673, 1563, 1457, 1271, 1265, 1194, 1079, 904, 836, 737, 543 cm^{-1};

HRMS (ESI) Calcd for $C_{19}H_{21}ClN_2O$ [M^+]: 328.1342, found: 329.1405 (M + 1).

199: (1*R*,2*S*)-2-(6-Chloropyridin-3-yl)cyclohex-3-enamine



198 **199**

Lead(IV) acetate (0.78 g, 1.75 mmol) was added into a stirred solution of **198** (0.56 g, 1.75 mmol) in CH_2Cl_2 (20 mL) and MeOH (10 mL) at 0 ^oC. The reaction mixture was allowed to stir up to 20 minutes. When TLC had shown the full depletion of the starting material **1988**, 10% NaOH (15 mL) was added slowly into the reaction mixture. The contents were evaporated *in vacuo* and subsequently extracted with CH_2Cl_2 (5 x 10 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (40:1 CH_2Cl_2/MeOH), yielding 0.25 g (1.19 mmol, 68%) of the primary amine **199** as a viscous brown oil.

R_f = 0.48 (5:1 CH_2Cl_2/MeOH);

$[\alpha]_D^{25}$ = – 42.9 ^{o} (0.6, CH_2Cl_2);

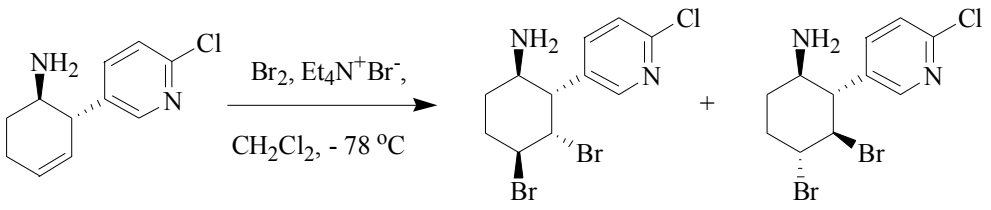
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, *J* = 2.09 Hz, 1H), 7.52 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.29 (d, *J* = 8.37 Hz, 1H), 5.94 – 5.87 (m, 1H), 5.49 (dd, *J* = 2.09, 9.75 Hz, 1H), 3.21 – 3.18 (m, 1H), 2.94 – 2.87 (m, 1H), 1.96 – 1.89 (m, 1H), 1.71 – 1.58 (m, 1H), 0.87 – 0.82 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.9, 149.8, 138.6, 138.0, 128.9, 127.2, 124.3, 53.9, 48.2, 30.1, 29.7, 24.5;

FTIR (neat): 3648, 3048, 2967, 2857, 2666, 2383, 2127, 1562, 1457, 1264, 1139, 1101, 923, 824, 738, 587 cm^{-1};

HRMS (ESI) Calcd for $C_{11}H_{13}ClN_2$ [M^+]: 208.0767, found: 209.0847 (M + 1).

(1*R*,2*S*)-3,4-Dibromo-2-(6-chloropyridin-3-yl)cyclohexanamine



199 **200**: Major **172**: Minor

Tetraethylammonium bromide (1.74 g, 8.27 mmol) was added into a stirred solution of **199** (0.17 g, 0.83 mmol) in CH_2Cl_2 (17 mL) and the solution was cooled to – 78 ^oC. After the reaction mixture had stirred for 45 minutes, bromine (0.13 mL, 2.48 mmol) was introduced slowly at the same temperature. The resultant solution was allowed to stir for a further 2 hours. When TLC had shown the full depletion of the starting material **199**, the reaction mixture was washed with saturated $NaHSO_3$ (2 x 10 mL) and water (2 x 10 mL). After drying in Na_2SO_4, the reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (40:1 CH_2Cl_2/MeOH), yielding 0.16 g (0.45 mmol) of the major isomer **200** as a viscous yellow oil and 0.05 g (0.15 mmol) of the minor isomer **172** as a viscous light brown oil (72% yield, 75:25 ratio).

Major diastereomer 200: (1*R*,2*S*,3*S*,4*S*)-3,4-Dibromo-2-(6-chloropyridin-3-yl)cyclohexanamine

R_f = 0.53 (5:1 CH_2Cl_2/MeOH);

$[\alpha]_D^{25}$ = + 24.9 ^{o} (1.3, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, *J* = 2.09 Hz, 1H), 7.52 (dd, *J* = 2.44, 8.36 Hz, 1H), 7.30 (d, *J* = 8.36 Hz, 1H), 4.78 – 4.77 (m, 1H), 4.40 (q, *J* = 2.44 Hz, 1H), 3.54 (dt, *J* = 4.53, 10.46 Hz, 1H), 3.46 – 3.42 (m, 1H), 2.70 – 2.59 (m, 1H), 2.58 – 2.07 (m, 2H), 1.86 – 1.79 (m, 2H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.9, 150.4, 139.5, 133.7, 123.9, 59.9, 52.7, 46.9, 46.8, 30.0, 27.7;

FTIR (neat): 3420, 3050, 2926, 2850, 2083, 1638, 1586, 1460, 1394, 1265, 1139, 1104,1024, 957, 833, 734, 689 cm^{-1};

HRMS (ESI) Calcd for $C_{11}H_{13}Br_2ClN_2$ [M^+]: 365.9134, found: 366.9210 (M + 1).

Minor diastereomer 172: (1*R*,2*S*,3*R*,4*R*)-3,4-Dibromo-2-(6-chloropyridin-3-yl)cyclohexanamine

R_f = 0.35 (5:1 CH_2Cl_2/MeOH);

$[\alpha]_D^{25}$ = – 63.0° (1.7, CH_2Cl_2);

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 2.09 Hz, 1H), 7.49 (dd, *J* = 2.43, 8.36 Hz, 1H), 7.30 (d, *J* = 8.36 Hz, 1H), 4.18 – 4.03 (m, 2H), 2.95 (dt, *J* = 3.83, 10.80 Hz, 1H), 2.72 (t, *J* = 10.45 Hz, 1H), 2.51 (ddd. *J* = 3.83, 3.83, 13.59 Hz, 1H), 2.14 – 1.95 (m, 2H), 1.44 (dd, *J* = 3.48, 11.15 Hz, 1H);

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.5, 149.6, 137.6, 135.3, 124.4, 60.5, 59.2, 55.6, 54.3, 35.9, 34.8;

HRMS (ESI) Calcd for $C_{11}H_{13}Br_2ClN_2$ [M^+]: 365.9134, found: 366.9215 (M + 1).