NANYANG TECHNOLOGICAL UNIVERSITY

DEVELOPMENT OF NEW SYNTHETIC METHODS TOWARDS PRINS CYCLIZATION

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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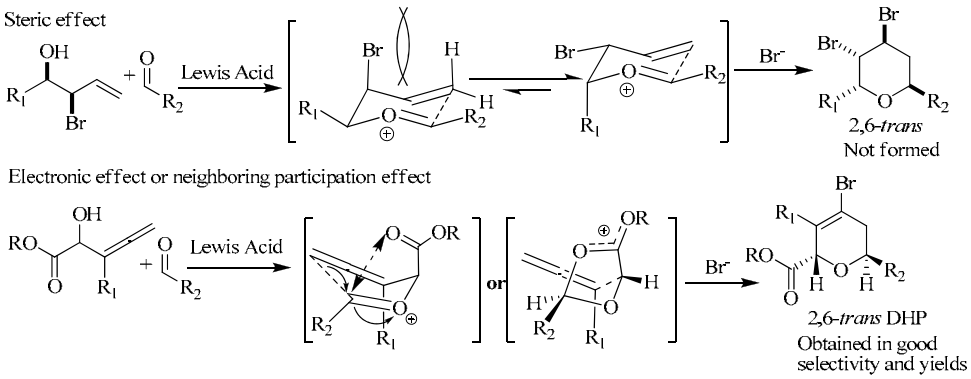
SUMMARY

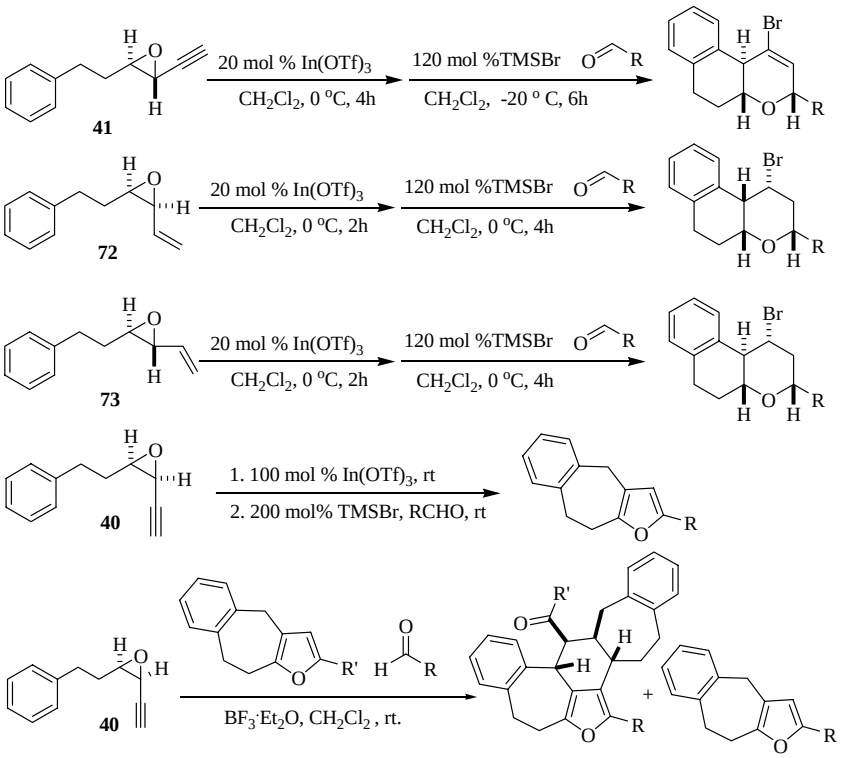
Prins cyclization is now one of the most versatile methods for the synthesis of 2,6-*cis*-disubstituted tetrahydropyrans from homoallylic alcohols and aldehydes after its rapid methodology development in the past decades. A brief introductory description towards the major aspects of the Prins cyclization is presented in chapter 1, including the prevailing strategies of substrate design, suppression of the racemization of homoallylic alcohols, utilization of the trapping nucleophiles, and Prins cascade reactions.

It still remains a challenge to devise a novel *trans* Prins cyclization from readily prepared substrates for thermodynamic reasons. In Chapter 2, two strategies were employed to attempt to develop a novel *trans* Prins cyclization *via* exploitation of steric and electronic effects. The first strategy utilizing the steric effect (based on A value) failed to form 2,6-*trans*-THP rings. However, the second strategy using the electronic effect (static electronic interaction between the lone pair on carbonyl oxygen atom and partially positively charged carbonyl carbon, as depicted in the oxocarbenium intermediate) or neighboring participation effect succeeded in providing us with a novel and efficient *trans* Prins cyclization in good chemical yields and with good diastereoselectivity.

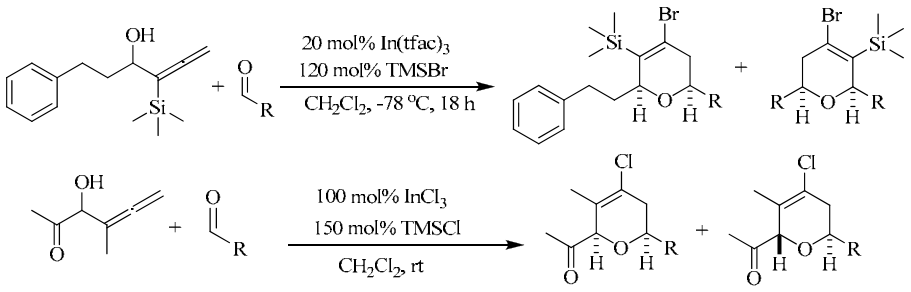


With properly tailored starting substrates, Prins cascade reactions are effective

in generating novel complex structures with multiple bonds and stereogenic centers formed in a one-pot manner through a combination of the Prins cyclization with other reactions. In Chapter 3 & 4, a convergent and stereoselective Friedel-Crafts-Prins cascade condensation reaction was devised to construct polycyclic THP/DHP rings or furans from propargylic and allylic epoxides. Upon treatment with Lewis acids, cyclic homopropargylic and homoallylic alcohols were formed diastereoselectively *via* Friedel-Crafts cyclization. For *trans* propargylic epoxide and allylic epoxides, subsequent Prins cyclization afforded the desired polycyclic THP/DHP rings in an efficient and diastereoselective manner. However, complicated situation was encountered when *cis* propargylic epoxide was subjected to the cascade reaction conditions. Polycyclic furans rather than the polycyclic pyrans were obtained in satisfactory yields, and a novel [3+3] annulation reaction of substituted furans was also disclosed in this study.



In Chapter 5, a novel *cis* Prins cyclization reaction of TMS-substituted allenic alcohols with aldehydes was developed through suppression of undesirable oxonia-Cope rearrangement by tuning the reaction temperature and Lewis acidity. For Me-substituted allenic alcohols, however, it is necessary to incorporate a carbonyl function adjacent to the hydroxyallenyl moiety to suppress the oxonia-Cope rearrangement, and the target DHP rings could only be obtained in moderate yields and with moderate *cis*/*trans* stereoselectivities. By far, the application of this methodology to the synthesis of (+)-Sambutoxin was unsuccessful due to the low reactivity of the starting pyridinone aldehyde.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
ºC	degree centrigrade
Ac	acetyl
acac	acetoacetonate
ACCN	*azo-bis*-cyclohexylcarbonitrile
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	*azo-bis*-isobutyronitrile
aq.	aqueous
Bn	benzyl
BOC	tert-butoxycarbonyl
br s	broad singlet
BuLi	butyl lithium
Bz	benzoyl
Cacld	calculated
Cat.	catalytic
$CDCl_3$	deuterated chloroform
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexane; cyclohexanyl
d	doublet
dd	doublets of doublet
ddd	doublets of doublets of doublet
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide

DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dq	doublets of quartet
dt	doublets of triplet
ee	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electronspray ionization
Et	ethyl
ether	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
H	hydrogen
HDA	hetero Diels-Alder
hept	heptet
Hex	hexane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
J	coupling constants
kg	kilogram
L.A.	Lewis acid
LDA	lithium diisopropylamide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile

MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
N	concentration (normality)
n-Bu	*n*-butyl
nmr	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
N.R.	no reaction
obs.	observed
OTf	trifluoromethanesulfonate
PBr_3	phophorus tribromide
PCC	pyridinium chlorochromate
Pd / C	palladium on carbon
Ph	phenyl
PhH	benzene
PhMe	toluene
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
q	quartet
qd	quartets on doublet
quint.	quintet
rt.	room temperature
RBF	round bottom flask
R_f	retention factor
s	singlet
sat	saturated
s-Bu	*sec*-Butyl
t	triplet

TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenyl silyl
TBS	*tert*-butyldimethyl silyl
t-Bu	*tert*-butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TFA	trifluoroacetic acid
TfOH	triflate acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Ts	*p*-toluenesulfonyl
T.S.	transition state
vol	volume

CHAPTER 1

Prins Cyclization in Modern Organic Synthesis

1.1 NATURAL PRODUCTS WITH TETRAHYDROPYRAN AND DIHYDROPYRAN BACKBONES

Tetrahydropyran (THP) and dihydropyran (DHP) rings constitute the fundamental structural features in numerous natural products.[1] Over the past few decades, there has been a continuous stream of novel natural products with THP/DHP ring backbones isolated from marine sponges and microorganisms. Some examples are illustrated in Figure 1.1. These naturally occurring compounds usually exhibit interesting and important biological activities, such as the antibiotic,[1] antibacterial,[2] antifungal[3] and cytotoxic[4] activities. These properties make these natural products interesting synthetic targets for the organic synthetic community, and also serve as attractive drug candidates for pharmaceutical purposes.

With the justifications evidenced by both academic importance and potential therapeutic values, synthetic interests and efforts remained continually strong towards the development of novel methods for the efficient synthesis of these natural products with THP/DHP rings.[5] Many elegant methodologies have been devised in the past decade for the stereoselective synthesis of functionalized THP/DHP rings in either racemic or enantioenriched manner. These methods include radical cyclization,[6]

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[1] (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis* Wiley-VCH **1996**. (b) Nicolaou, K. C.; Synder, S. A. *Classics in Total Synthesis II* Wiley-VCH **2003**. (c) Bycroft, B. W. *Dictionary of Antibiotics and Related Substances*; Chapman and Hall: London, 1988. (d) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. (e) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (f) Class, Y. J. Deshong, P. *Chem. Rev.* **1995**, *95*, 1843. (g) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

[2] Wesley, J. W. *Polyether Antibiotics: Naturally Occuring Acid Ionophores*. Marcel Dekker: New York, **1982**, Vol. I and II.

[3] Cybulska, B.; Borowski, E.; Gary-Bobo, C. M. *Biochem. Pharmacol.* **1989**, *38*, 1755.

[4] (a) Hioki, H.; Yoshio, S.; Motosue, M.; Oshita, Y.; Nakamura, Y.; Mishima, D.; Fukuyama, Y.; Kodama, M.; Ueda, K.; Katsu, T. *Org. Lett.* **2004**, *6*, 961. (b) Rutten, M. J.; Cogburn, J. N.; Schasteen, C. S.; Solomon, T. *Pharmacology* **1991**, *42*, 156. (c) Norcross, R. D.; Patterson, I. *Chem. Rev.* **1995**, *95*, 2041. (d) Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* **1988**, *53*, 3644.

[5] For reviews see (a) Borvin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (c) Kang, E. J. ; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (d) Nakata, T. *Chem. Rev*. **2005**, *105*, 4314.

[6] (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831. (b) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017. (c) Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.***1991**, *113*, 2335. (d) Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619.

hetero-Diels-Aldar cycloaddition,[7] hydroxyl-epoxide cylization,[8] oxy-Michael addition,[9] dioxanone Claisen rearrangement,[10] Petasis-Ferrier rearrangement,[11] oxidative carbon-hydrogen bond activation,[12] Maitland-Japp reaction[13] and ring closing metathesis[14] and so on.

Besides all these methods mentioned above, Prins cyclization emerged as one of the most versatile and powerful tools for the diastereoselective synthesis of THP/DHP backbones after the rapid advancement accompanied by various novel methodology studies in the past decades. In the following section, a brief introduction to the Prins cyclization will be presented, focusing on novel methodology development and synthetic applications of towards the total synthesis of natural products.

[7] (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chime. Int. Ed.* **1999**, *38*, 2398. (b) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772. (c) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chime. Int. Ed.* **2002**, *41*, 3059.
[8] Nicolaou, K. C.; Prasad, C. V. C.; Somers, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.
[9] (a) Jung, H. H.; Floreancig, P. E. *Org. Lett.* **2006**, *8*, 1949. (b) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 4055.
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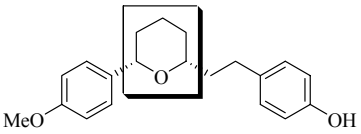
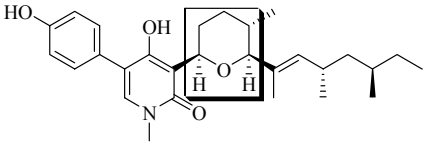
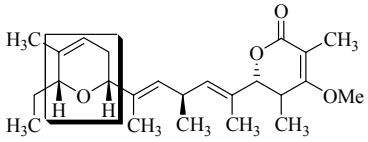
[11] (a) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhass, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (b) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948. (c) Smith, A. B., III; Saffonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426. (d) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (e) Smith, A. B., III; Fox, R. J; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675.
[12] Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4184.
[13] (a) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Chem. Commun*. **2005**, *8*, 1061-1063. (b) Clarke, P. A.; Martin, W. H. C.; Hargreaves, J. M.; Wilson, C.; Blake, A. J. *Org. Biomol.Chem.* **2005**, *3*, 3551.
[14] (a) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33; (b) Crimmins, M. T.; Vanier, G. S. *Org. Lett.* **2006**, *8*, 2887.



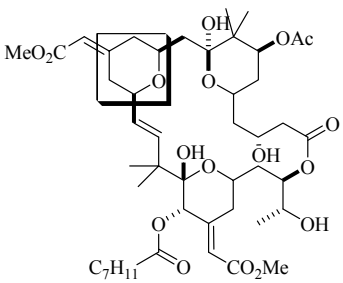
(-)-Centrolobine: Isolated from the heartwood of Centrolobium robustum and from the stem of Brosinum potabile. Exhibit antimicrobial activity and anti-leishmanial effects.



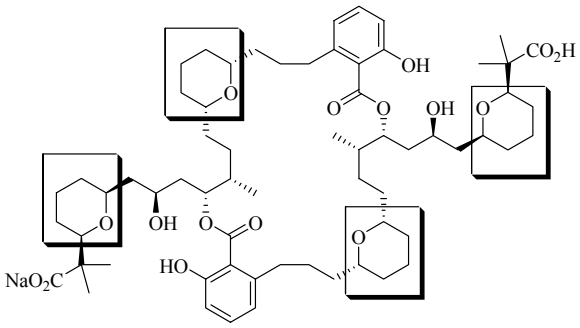
(+)-Sambutoxin: Isolated from wheat cultures of *Fusarium sambucinum* PZF-4. Exhibit antibiotic, antiinsecticidal, antifugal, and antitumor activity.



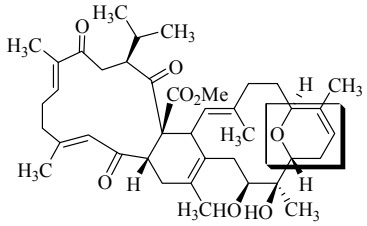
Jerangolid D:a secondary metabolite procedured by *Sorangium cellulosun.* Exhibit potential antifugal, antiproliferation activity.



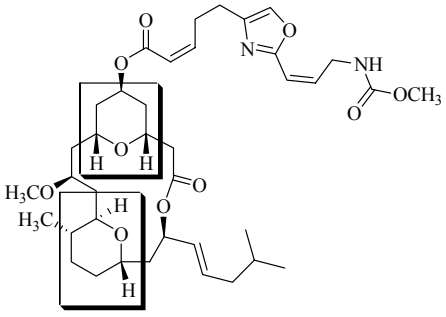
Bryostatin 1: Exhibit anticancer properties and has been shown to synergize the effects of other antineoplastic agents, promote apoptosis, reverse multidrug resistance, and stimulate the immune system



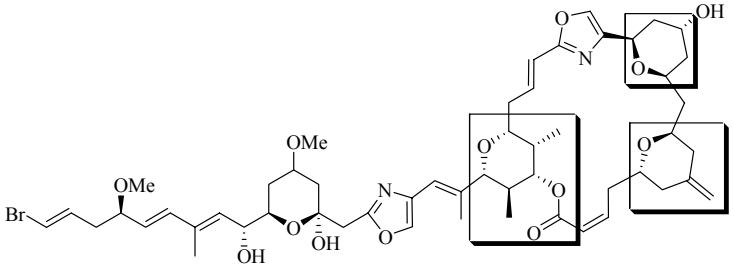
(+)-SCH 351448, a novel activator of low-dentsity lipoprotein receptor promoter with an IC_{50} of 25 μM.



Methyl Sarcophytoate: Isolated from *Sarcophyton glaucum*. Exhibit cytotoxicity.



Leucascandrolide A: Isolated from thecalcareous sponge *Leucascandra caveolata*. Exhibit high cytotoxicity against human KB tumor cell lines and potent antifungal activity.



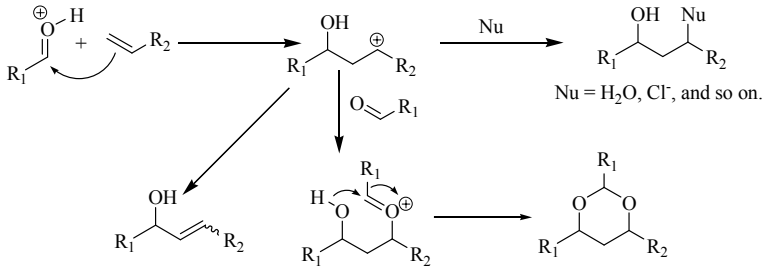
Phorboxazole A: Macrolactone with anti-tumour activity

Figure 1.1 Natural products containing tetrahydropyran (THP) and dihydropyran (DHP) backbones.

1.2 GENERAL DISCUSSION ON PRINS CYCLIZATION

1.2.1 Prins Reaction

From a historical perspective, the concept of Prins cyclization comes from the Prins reaction. Since the pioneering systematic studies by H. J. Prins, the Prins reaction has come to become an important carbon-carbon bond formation tool *via* the condensation of alkenes with aldehydes catalyzed by mineral acids.[15] It is well-established that from a mechanistic point of view, the Prins reaction is of cationic nature proceeding in a step-wise manner.[16] The resultant carbocation formed in the Prins reaction can undergo elimination, nucleophilic trapping or acetalization with excess aldehydes to form different products. The final outcome of this reaction depends on the substrates and reaction conditions, and various condensation products could be obtained, including 1,3-diols, 1,3-dioxanes and unsaturated alcohols (Scheme 1.1). Extensive studies revealed its uncontrollable nature in terms of the chemo- and regio-selectivity, which severely limited its applications in organic synthesis.



Scheme 1.1 Prins reaction of olefins with aldehydes.

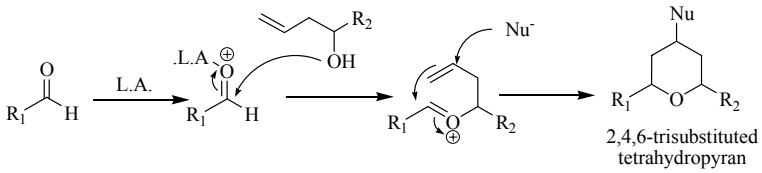
[15] (a) Prins, H. J.; *Chem. Weekblad*. **1917**, *14*, 932. (b) Prins, H. J.; *Chem. Weekblad*. **1919**, *16*, 1072. (c) Prins, H. J.; *Chem. Weekblad*. **1919**, *16*, 1510. (d) Prins, H. J.; *Proc. Acad. Sci. Amsterdam* **1919**, *22*, 51. (e) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505. (f) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, *10*, 661.

[16] (a) Schowen, K. B.; Smissman, E. E.; Schowen, R. L. *J. Org. Chem.* **1968**, *33*, 1873. (b) Smissman, E. E.; Schnettler, R. A.; Portoghese, P. S. *J. Org. Chem.* **1970**, *35*, 797. (c) Wilkins, C. L.; Marianelli, R. S. Pickett, C. S. *Tetrahedron* **1958**, *14*, 5109. (d) Wilkins, C. L.; Marianelli, R. S. *Tetrahedron* **1970**, *26*, 4131. (e) Dolby, L. J. *J. Org. Chem.* **1963**, *28*, 1456. (f) Dolby, L. J. *J. Am. Soc. Chem.* **1963**, *85*, 47. (g) Dolby, L. J.; Schwarz, M. J. *J. Org. Chem.* **1965**, *30*, 3581. (h) Dolby, L. J. Meneghini, F. A.; Koizumi, T. *J. Org. Chem.* **1968**, *33*, 3060. (i) Dolby, L. J. *J. Org. Chem.* **1971**, *27*, 2971. (j) Yang, N. C.; Yang, D. D. H.; Ross, C. B. J. *J. Am. Soc. Chem.* **1959**, *81*, 133. (k) Meresz, O.; Leung, P.; Denes, A. S. *Tetrahedron* **1972**. *28*, 2797.

1.2.2 Prins Cyclization

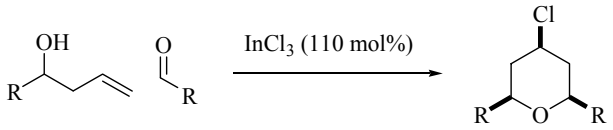
In contrast to the uncontrollable Prins reaction, its advanced version, the Prins cyclization, emerges as one highly valuable, efficient, versatile and superior tool for diastereoselective synthesis of tetrahydropyran and dihydropyran rings as a result of intensive research and rapid advancement in the past decades.

One general strategy for carrying out the Prins cyclization is to append the allylic moiety of a molecule (e.g. a homoallylic alcohol) onto an oxocarbenium cation, which is generated *in situ* from an aldehyde in the presence of a Lewis or Br□nsted acid, followed by trapping with a nucleophile to yield 2,4,6-trisubstituted tetrahydropyran (Scheme 1.2).



Scheme 1.2 Prins cyclizatoin of homoallylic alcohols with aldehydes.

Li[17] reported a $InCl_3$-mediated Prins cyclization of homoallylic alcohols with aldehydes, where a stoichiometric amount of $InCl_3$ was used as both the promoter and the halogen counterion source to afford *meso*-4-chloro-THP rings (Scheme 1.3). Despite of the good yields and stereoselectivity, only the *meso*-products were obtained, which severely limited its synthetic applications.

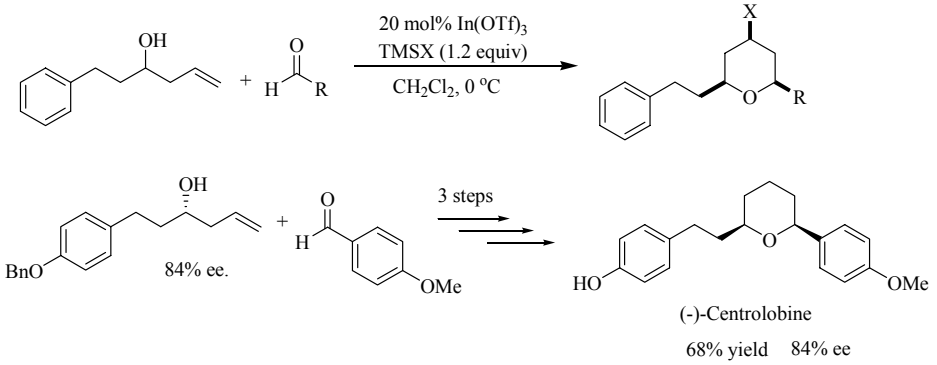


Scheme 1.3 Prins cyclization mediated by stoichoimetric $InCl_3$ forming *meso*-THP rings.

For synthetic purposes, our group devised a novel and efficient In(III) complex-catalyzed asymmetrical Prins cyclization by using silyl halides as the

[17] (a) Yang, J.; Viswanthan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. (b) Yang, X. –F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739.

counterion source to construct 2,6-*cis*-disubstitued-4-halo-tetrahydropyran rings in excellent yields and diastereoselectivity (Scheme 1.4).[18] In addition, the synthetic value of this method was elegantly demonstrated in the total synthesis of (-)-Centrolobine. Epimerization originating from a undesirable allyl-transfer process (oxonia-Cope rearrangement) was successfully suppressed with complete retention of chirality of the starting homoallylic alcohol by tuning the Lewis acidity and the reaction temperature (Scheme 1.4). Importantly, this methodology offers an effective solution to the racemization problem frequently encountered in Prins cyclization which is caused by a symmetric oxonia-Cope rearrangement (Scheme 1.5).[19] Still on this topic, Willis proposed a mechanism for the formation of *meso*-THP side products in his study of BF_3·OEt_2-mediated Prins cyclization (Scheme 1.5).[19]

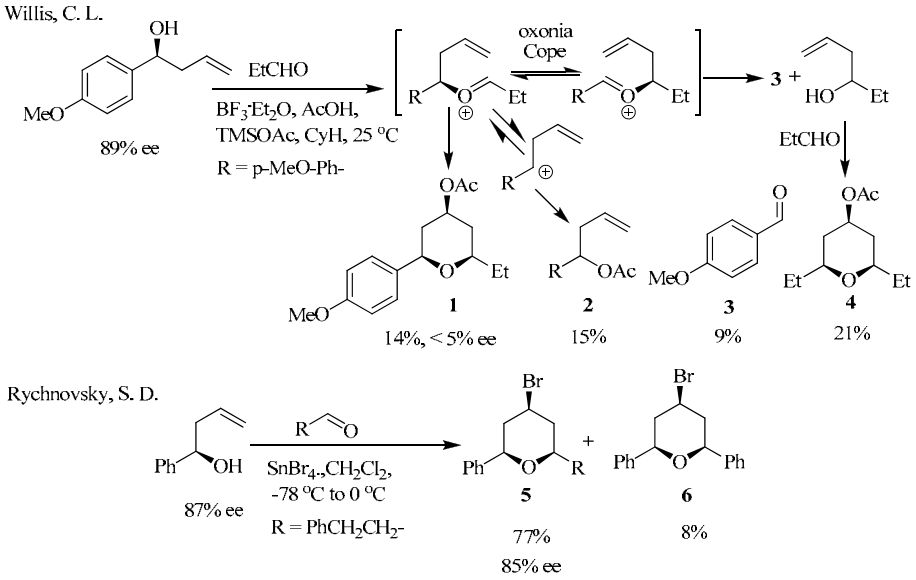


Scheme 1.4 In(III) complex catalyed Prins cyclization using silyl halides to 2,4,6-trisubstituted THP rings and its application to the total synthesis of (-)-Centrolobine.

Prior to our findings in suppressing epimerization, Rychnovsky disclosed an effective method to overcome this problem by using the $SnBr_4$ instead of BF_3·OEt_2/AcOH to promote the cyclization, where it was rationalized that $SnBr_4$

[18] Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491.
[19] (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577. (b) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (c) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; Simpson, T. J.; Smith, R. W.; King, C. D.; Willis, C. L. *Chem. Commun.* **2001**, *5*, 835.

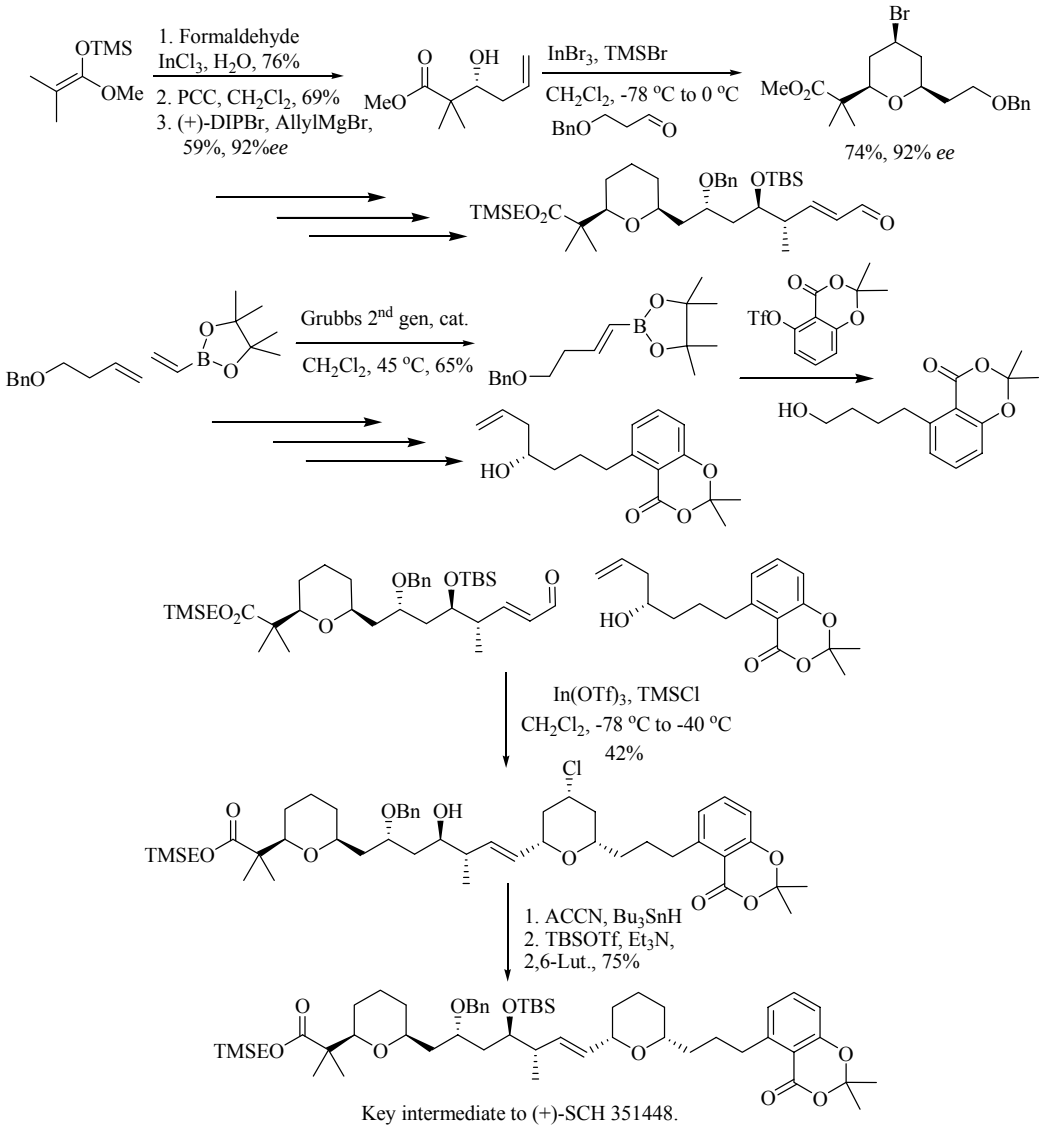
promotes cyclization much faster than $BF_3 \cdot OEt_2$/AcOH, resulting in the suppression of the competing symmetric oxonia-Cope rearrangement (Scheme 1.5) .[5b, 20]



Scheme 1.5 Racemization caused by oxonia-Cope rearrangement in Prins cyclization and Rychnovsky's suppression with $SnBr_4$.

Besides (-)-Centrolobine, the versatility and synthetic value of our asymmetrical catalytic Prins cyclization methodology was further demonstrated as the key strategy in the elegant formal synthesis of (+)-SCH 351448 (Scheme 1.6).[21] It also featured adoption of several other strategies for the preparation of the major precursors, including aqueous Mukaiyama aldol, Suzuki-Miyaura coupling, and Brown's allylation/crotylation. The key step in the synthesis of the monomeric unit is successfully achieved through catalytic Prins cyclization in moderate yield without significant racemization.

[20] Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.
[21] (a) Chan, K. P.; Ling, H. Y.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939. (b) Chan, K. P. dissertation, 2006.

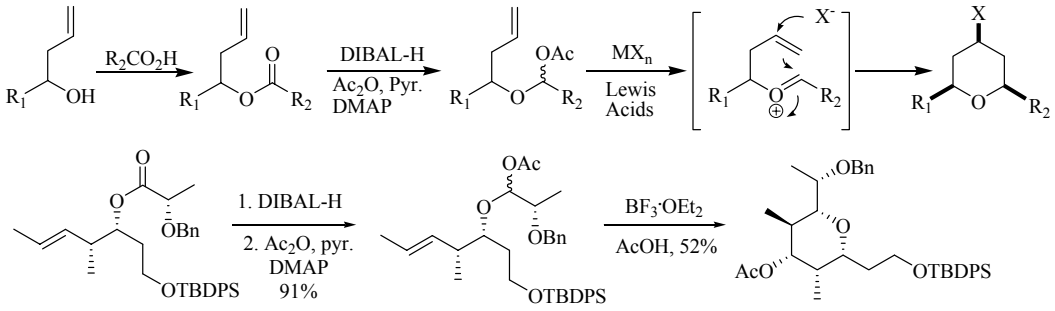


Scheme 1.6 Formal synthesis of (+)-SCH 351448 with catalytic Prins cyclization strategy.

Formation of the oxocarbenium cation is one of the central topics in Prins cyclization. Rychnovsky has reported an elegant THP formation method *via* the segment-coupling Prins cyclization strategy (Scheme 1.7).[22] The starting α-acetoxy ethers could be readily prepared from the corresponding homoallylic alcohols over three steps: coupling to the homoallylic ester; DIBAL-H reduction of the homoallylic ester, and acetate protection of the resulting hemiacetal. Upon treatment with a Lewis

[22] (a) Rychnovsky, S. D.; Hu, Y. Q.; Ellsworth, B.; *Tetrahedron, Lett.* **1998**, *39*, 7271. (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (c) Jaber, J. J. Mutsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.

acid, the oxocarbenium cation intermediate is spontaneously generated through the solvolysis of the α-acetoxy ether precursor, which then cyclizes to form asymmetrical THP rings in the presence of counterion. The elegance of this strategy was illustrated in the extremely concise construction of the key precursor for phorboxazole synthesis.

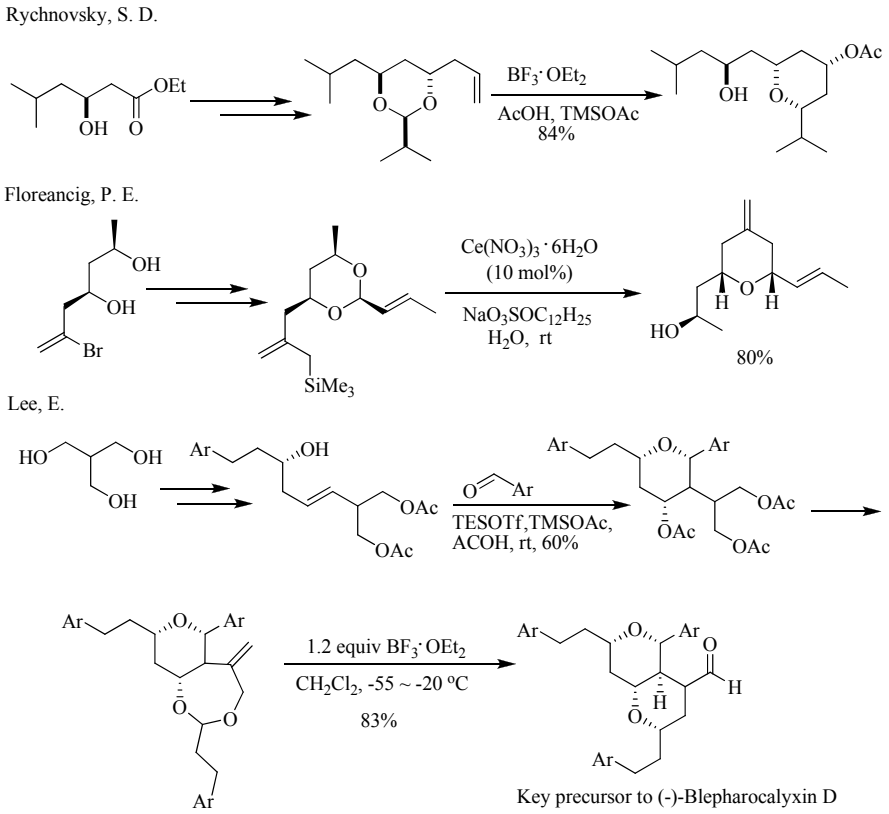


Key precursor to phorboxazole A

Scheme 1.7 Rychnovsky's segment-coupling Prins cyclization strategy for THP ring synthesis.

In addition, allylic 1,3-dioxanes are also ideal precursors to generate the oxocarbenium cation intermediates in the Prins cyclization because the acetal function can be cleaved regioselectively upon treatment with a Lewis acid (Scheme 1.8).[23] Tetrahydropyrans are formed diastereoselectively after cyclization of the allylic moiety onto the oxocarbenium cation intermediates generated *in situ*. This strategy also found its application as the key step in the elegant total synthesis of (-)-Blepharocalyxin D.[24]

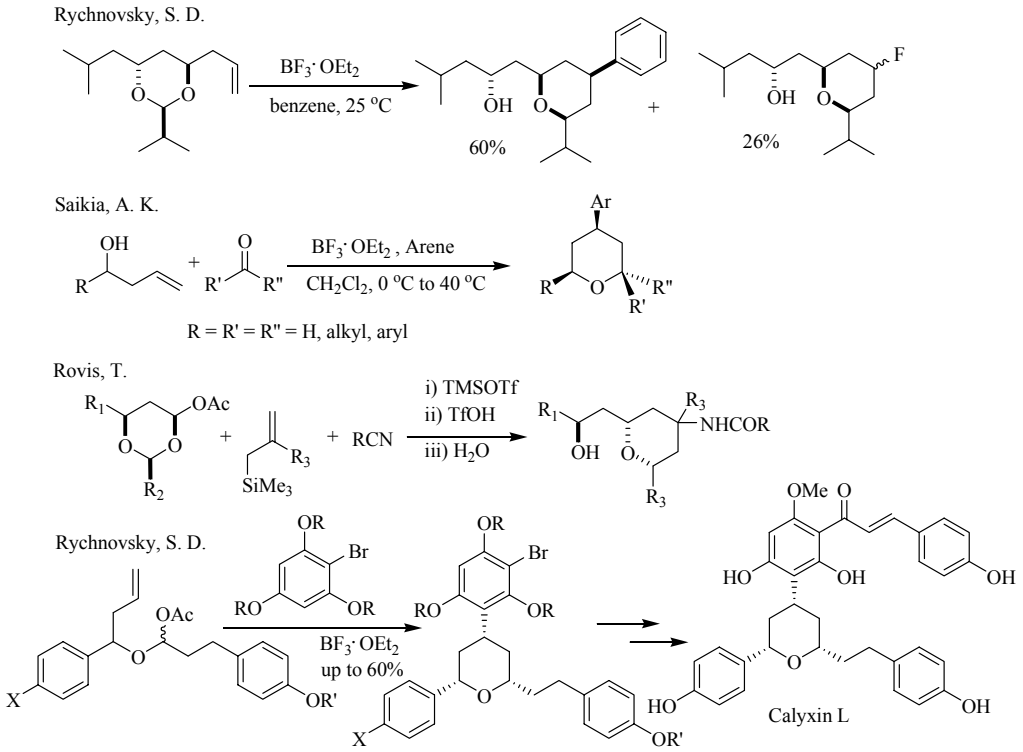
[23] (a) Hu, Y. Q.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron, Lett.* **1996**, *37*, 8679. (b) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 4521.
[24] Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Org. Lett.* **2009**, *11*, 141.



Scheme 1.8 Dioxane strategy for THP ring synthesis *via* Prins cyclization.

Besides the common counterions, such as halides (Cl^-, Br^-, I^-),[18] F^-,[25] OTs^-, OH^-,[26] and OAc^-,[19] cationoic reaction intermediates were also observed to trap nuleophilic solvents during the cyclization, such as arenes *via* a Friedel-Crafts type alkylation,[23a, 27] alkyl nitriles *via* a Sakurai-Prins-Ritter sequence[28] (Scheme 1.9). Rychnovsky disclosed a sophisticated utilization of the nucleophile for trapping the oxocarbenium cation intermediate in the synthetic studies towards the calyxins.[29]

[25] Kishi, Y.; Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun.* **2008**, 3876.
[26] Kataoka, K.; Ode, Y.; Matsumoto, M.; Nakami, J. *Tetrahedron Lett.* **2006**, *62*, 2471.
[27] (a) Reddy, U. C.; Bondalapti, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605. (b) Reddy, U. C.; Bondalapti, S.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, 1625.
[28] Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480.
[29] Tian, X.; Jaber, J. J.; Rychnovsky, S. D.*J. Org. Chem.* **2006**, *71*, 3176.



Scheme 1.9 Trapping of solvents during Prins cyclization for novel THP rings synthesis.

The regioselectivity of the Prins cyclization depends on the structure of the allylic/propargylic fragment and reaction conditions. Normally, Prins cyclization proceeds *via* two possible pathways: the conventional 6-*endo* cyclization (pathway **I**) to THP/DHP rings, and the 5-*exo* cyclization (pathway **II**) to THF rings (Scheme 1.10).[30] In this area, our group has demonstrated an $In(OTf)_3$-catalyzed Prins-type cyclization of homoallylic alcohols with aldehydes to afford tetrahydrofuran rings in good yields and selectivity.[31] In addition, for the Prins-type cyclization of propargylic alcohols, the divergent formation of dihydropyrans[32] and tetrahydrofurans[33] had also

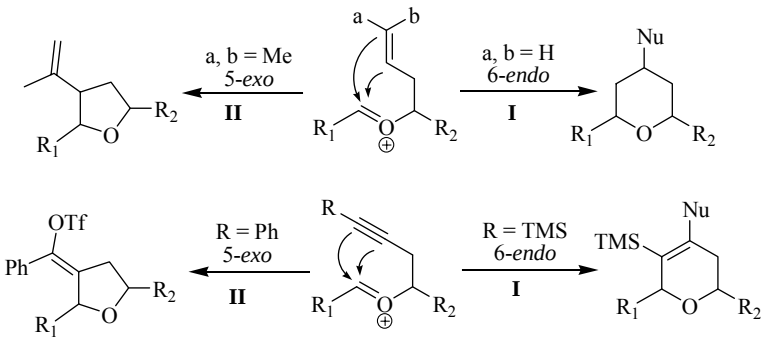
[30] (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, *18*, 734. (b) Baldwin, J. E.; Thomas, X.; Kruse, X.; Silberman, X. *J. Org. Chem.* **1977**, *42*, 3846. (c) Baldwin, J. E.; Lusch, X. *Tetrahedron* **1982, *38,*** 2939.

[31] 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.

[32] (a) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Pardón, J. I. *Chem. Eur. J.* **2008**, *14*, 6260. (b) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Pardón, J. I. *Org. Lett.* **2006**, *8*, 1633.

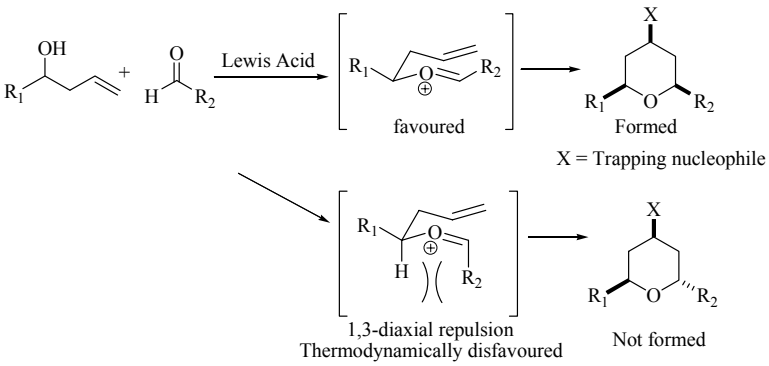
[33] a) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett.* **2006**, *8*, 3617. (b) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *J. Org. Chem.* **2008**, *73*, 7467.

been documented with good stereoselectivity and chemical yields, where the regioselectivity was also substrate and reaction conditions dependent.



Scheme 1.10 Divergent formation of tetrahydrofuran and tetrahydropyran rings in Prins cyclization.

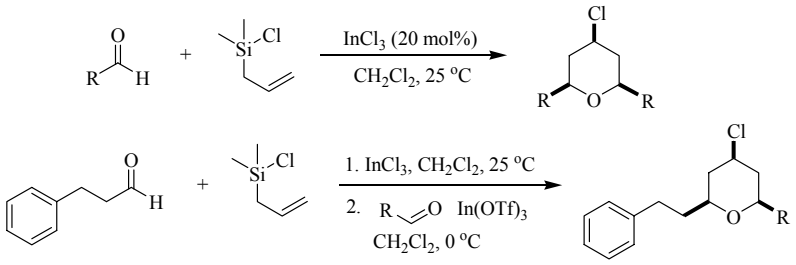
Under most circumstances, high 2,6-*cis*-diasteroselectivity is observed for the Prins cyclization. Formation of the chair-like oxocarbenium transition state is thermodynamically favored so as to avoid severe 1,3-diaxial interaction, resulting in predominant generation of the 2,6-*cis*-THP rings (Scheme 1.11).



Scheme 1.11 Mechanistic basis of Prins cyclization to 2,6-*cis*-tetrahydropyran.

Despite these elegant Prins cyclization methods described above, Prins cascade reactions become more and more appealing to synthetic chemists because of the intrinsic advantages and efficiency in forming multiple bonds and stereogenic centers in an one-pot manner through a combination of the Prins cyclization with

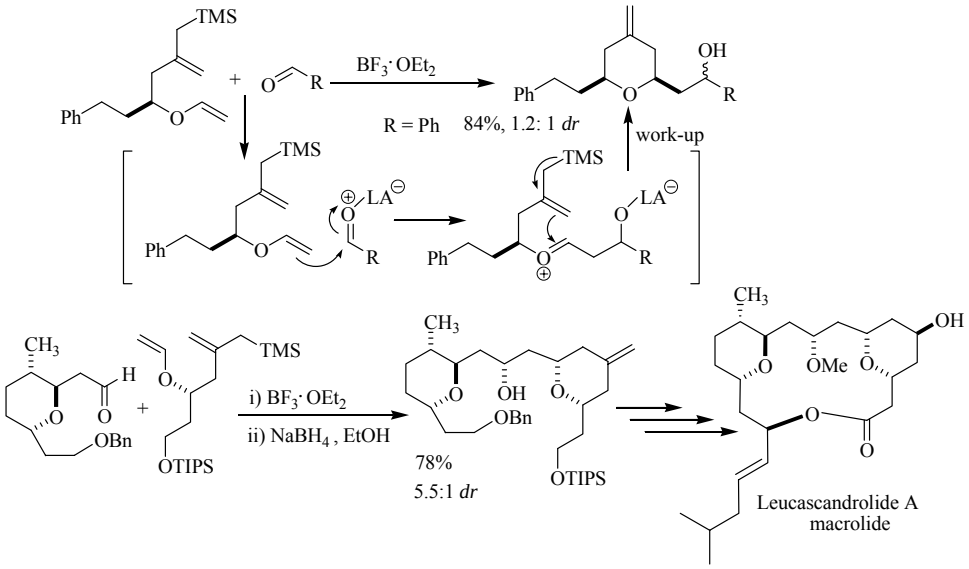
other reactions. Our group devised a In(III) complex-catalyzed one-pot Prins cyclization by using allylchlorosilane as the allylating reagent and also the counterion source to afford 2,6-*cis*-disubstituted tetrahydropyrans in good yields and diasteroselectivity (Scheme 1.12).[34] The usage of catalytic amount of Lewis acids and the one-pot operation for facile access to THP rings make this methodology valuable and attractive for synthetic purposes.



Scheme 1.12 One-pot Prins cyclization using allylchlorosilane as allylating agent.

In this respect, Rychnovsky devised an elegant and powerful Mukaiyama Adol-Prins cyclization cascade reaction to form a novel tetrahydropyran ring with concurrent generation of an alcohol function (Scheme 1.13).[35] Enol ether underwent a Mukaiyama adol condensation with Lewis acid activated aldehydes to form the oxocabenium cation intermediate *in situ*, followed with a Prins cyclization of the allylic moiety to afford a THP ring. The utility of this strategy was demonstrated in its concise application in the formal total synthesis of Leucascandrolide A macrolide.

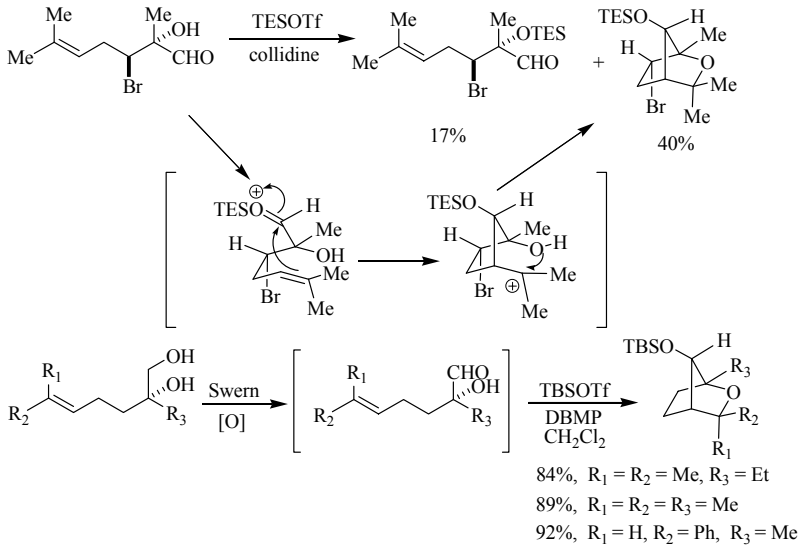
[34] Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387.
[35] (a) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (b) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163. (c) Orden, L. J. V.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784.



Scheme 1.13 Mukaiyama Adol-Prins cyclization cascade reaction and formal synthesis of Leucascandrolide A.

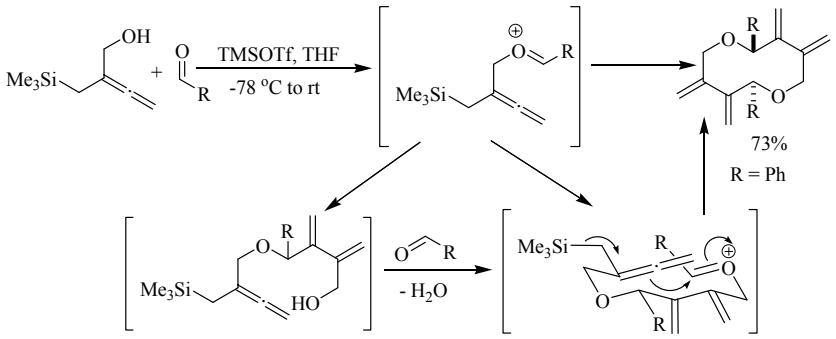
In addition to the formation of THP rings, Prins cascade reactions are also capable of generating novel complex structures by exploiting properly tailored starting substrates. For instance, bicyclic annulation products (7-(silyloxy)-2-oxabicyclo[2.2.1] heptanes) could be constructed in one operation *via* an intramolecular double Prins cyclization cascade reaction triggered by Lewis acid from α-hydroxy aldehydes with an electron-rich double bond (Scheme 1.14).[36] More importantly, the chemical yields were further improved to 84-92% by carrying out this cascade reaction from the corresponding diols through a Swern oxidation and the subsequent activation sequence.

[36] Jung, M. E.; Angelica, S.; D'Amico, D. C. *J. Org. Chem.* **1997**, *62*, 9182.



Scheme 1.14 Intramolecular double Prins cyclization to novel bicyclic heptane rings.

Interestingly, intermolecular double Prins cyclization cascade reaction has also been documented to afford novel complex oxygenated heterocycles. In a recent account, Cho reported an efficient and facile method to make 1,6-dioxecanes *via* an intermolecular double Prins-type cyclization of allenylsilanes with aromatic aldehydes (Scheme 1.15).[37] This cascade sequence offers an effective approach to make entropically disfavored medium-sized oxygenated heterocycles *via* Prins cyclizations.



Scheme 1.15 Intermolecular double Prins cyclization to novel oxygenated heterocycles.

[37] Ullapu, P. R.; Min, S. J.; Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Chang, M. H.; Cho, Y. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 2196.

1.3 DEVELOPMENT OF NOVEL PRINS CYCLIZATION REACTIONS

After a general discussion of some of the available methods used to construct THP rings, it is notable that some methods are confined to small molecule synthesis and the construction of small fragments in a stepwise manner to build up the structural cores in the application to natural product synthesis. Importantly, it still remains a challenge for synthetic chemists to devise a novel Prins cyclization to access 2,6-*trans*-substituted THP/DHP rings from readily prepared substrates.

Although a variety of substrates and strategies have been devised for construction of 2,6-*cis*-substituted THP/DHP rings *via* Prins cyclization, there exists an undying demand for novel, milder, straightforward and convergent methods to make THP/DHP rings, especially in an efficient cascade reaction manner. Sophisticated design of substrates and careful screening of reaction conditions are essential for the discovery of novel Prins cascade reactions.

CHAPTER 2

Development of Novel trans Prins Cyclization Reaction

2.1 INTRODUCTION

Although the 2,6-*cis*-tetrahydropyran (THP) motif is commonly encountered in various biologically active marine natural products, however, there are also a large number of natural products containing the 2,6-*trans*-tetrahydropyran framework (Figure 2.1). These compounds exhibit important biological activities, including anti-tumor, anti-fungal and anti-bacterial properties, which makes them highly valuable screening candidates for discovery of new pharmaceuticals. Thus, strong interest has been long directed towards the development of novel methods to synthesize these 2,6-*trans*-tetrahydropyrans.

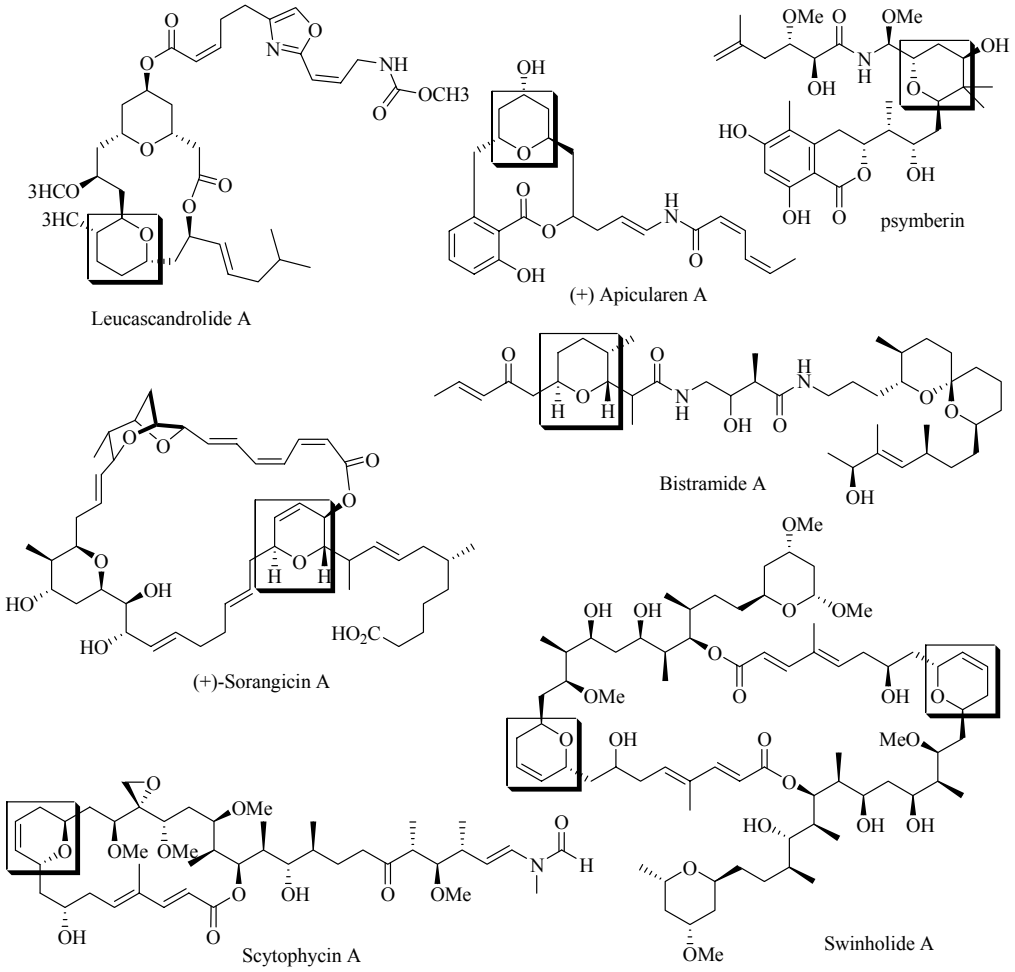
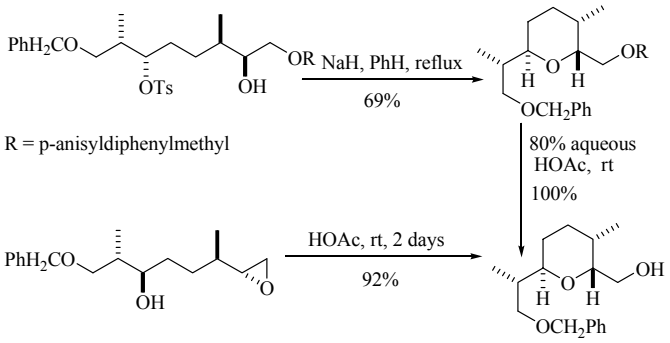


Figure 2.1 Natural products with 2,6-*trans*-tetrahydropyran frameworks.

2.2 GENERAL METHODS FOR CONSTRUCTION OF 2,6-TRANS TETRAHYDROPYRANS

2.2.1 Substrate-Controlled Stereospecific Cyclization

Several methods have been developed to make 2,6-*trans*-disubstituted tetrahydropyran rings. Ho reported a general and stereospecific method for the preparation of 2,6-*trans*-disubstituted tetrahydropyrans with excellent diastereoselectivity (Scheme 2.1).[1] The linear substrate was prepared over several chemical transformations with the complete carbon skeleton and functionalities assembled. The 2,6-*trans*-disubstituted tetrahydropyran was smoothly formed *via* intramolecular S_N2 type displacement under basic condition or *via* an alternative hydroxyl addition to epoxy functionality when treated with acetic acid.

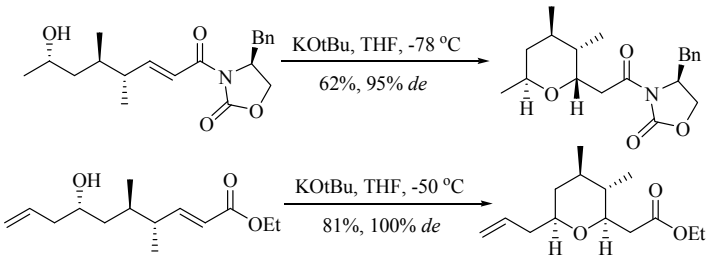


Scheme 2.1 Stereospicific S_N2 type cyclization to 2,6-*trans*-tetrahydropyran.

In addition to the hydroxy-displacement or hydroxy-epoxide cyclization strategy, intramolecular oxy-Michael type cyclization of 7-hydroxy-2-enimide upon treatment with base offers an alternative approach to generate the *trans*-isomer with excellent diastereoselectivity as demonstrated by Schneider (Scheme 2.2).[2] It was revealed that the stereoselectivity of the cyclization is substrate-dependent and the chiral auxiliary only plays a supporting role. Interestingly, reversal of selectivity

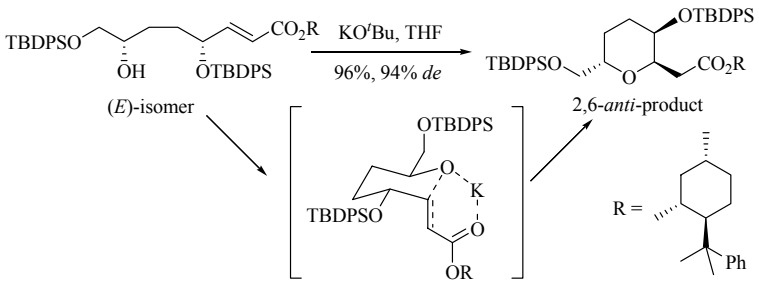
[1] Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90.
[2] Schineider, C.; Schuffenhauer, A. *Eur. .J. Org. Chem.* **2000**, 73.

could be achieved by using hydroxyenoate instead of the enimide, and molecular orbital interaction between the lone pair of the oxygen and the anti-bonding π* orbital of the conjugate double bond was proposed to account for this stereoselectivity.



Scheme 2.2 oxy-Michael type cyclization of hydroxy-enimide.

Rein also reported a base mediated oxy-Michael type cyclization of (*E*)-hydroxy-acrylate to afford the 2,6-*trans*-tetrahydropyrans with excellent diastereoselectivity (Scheme 2.3).[3] The acrylate group is forced to reside on an axial position in order to form the favorable chair-like transition state, which simultaneously maximizes overall chelating with K^+ ion.



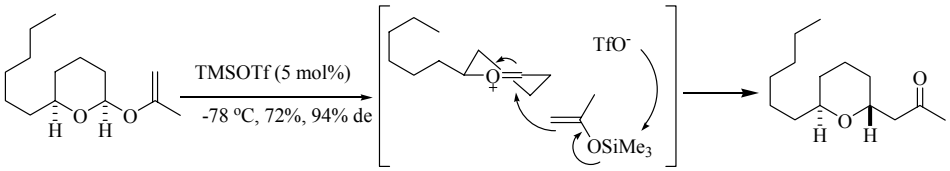
Scheme 2.3 oxy-Michael type cyclization of (*E*)-hydroxy-acrylate.

2.2.2 Anomeric Oxygen to Carbon Rearrangement

Ley [4] reported an elegant method through anomeric oxygen to carbon rearrangement to prepare 2,6-*trans*-tetrahydropyrans, by treating 2,6-*cis*-tetrahydropyrans enol ether with Lewis acid at low temperature, in satisfactory yields

[3] Vares, L. ; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226.
[4] (a) Dixon, D. J. ; Ley, S. V. ; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2665. (b) Buffet, M. F. ; Dixon, D. J. ; Edwards, G. L. ; Ley, S. V. ; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1815. (c) Dixon, D. J. ; Ley, S. V. ; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385.

and excellent diastereoselectivity (Scheme 2.4). Catalytic amount of TMSOTf activates the leaving group leading to the formation of oxonium ion and silyl enol ether *in situ*. These components recombine kinetically to afford the *trans*-pyranyl-ketone products.



Scheme 2.4 Anomeric oxygen to carbon rearrangement of 2,6-*cis*-tretrahydropyranyl enol ether.

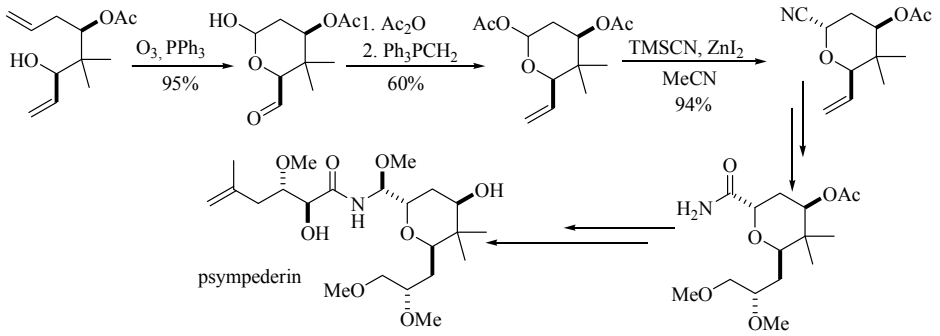
2.2.3 Nucleophilic Addition

It is well established that carbohydrate derivatives undergo nucleophilic displacement easily with preferential formation of the axial isomer in the presence of a Lewis acid and a soft nucleophilie.[5] Recently, Branbander[6] demonstrated a facile introduction of an axial nitrile onto pyranyl motif by ZnI_2-mediated acetate displacement with trimethyl cyanide in the synthesis of psymberin analogues (Scheme 2.5).[7]

[5] (a) Isobe, M. ; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, *24*, 2665. (b) Lewis, M. D. ; Cha, J. K. ; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (c) Patterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847. (d) Tabacco, S. A. ; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168. (e) Greer, P. B. ; Donaldson, W. A. *Tetrahedron* **2002**, *58*, 6009. (e) Hinkle, R. J.; Lain, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, 11679.

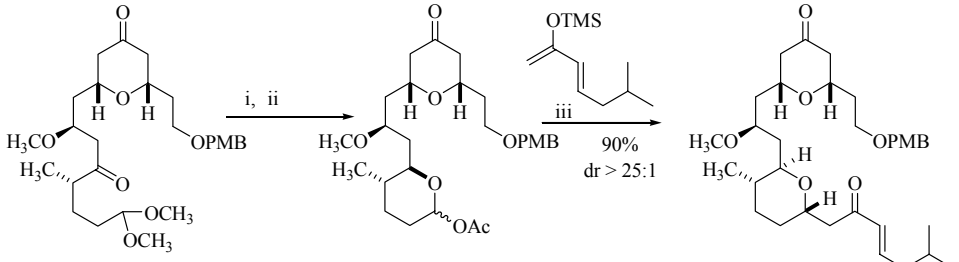
[6] Jiang, X.; Williams, N.; Brabander, J. K. De. *Org. Lett.* **2007**, *9*, 227.

[7] For other examples of synthesis of Psymberin and its anologues see (a) Narquizian, R.; Kocienski, P. J. The Pederin Family of Antitumor Agents: Structures, Synthesis and Biological Activity. In *The Role of Natural products in Drug Disco*Very; Mulzer, J., Bohlmann, R., Eds.; Ernst Schering Research Foundation Workshop 32; Springer: New York, 2000; pp 25-56. (b) Kocienski, P. J.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 2357. (c) Kocienski, P.; Jarowicki, K.; Marczak, S. *Synthesis* **1991**, 1191. (d) Takemura, T.; Nishii, Y.; Takahashi, S.; Kobayashi, J.; Nakata, T. *Tetrahedron* **2002**, *58*, 6359.



Scheme 2.5 Functionalization of pyranyl acetate in synthesis of pesympederin.

In addition, Williams[8] disclosed an elegant Mukaiyama-aldol transformation of pyranyl acetate with enol ether in high yield and excellent diastereoselectivity in a second generation formal synthesis of leucascandrolide A.[9]



i. excess $LiAlH_4$ / (+)-N-methylephedrine / N-ethylaniline (1:1:2), Et_2O, -78 °C, 96%
ii. H_3PO_4, THF/H_2O (3:2), then add Ac_2O, py., DMAP, CH_2Cl_2 to crude lactol, 85%
iii. $ZnCl_2$, (1M in Et_2O), CH_2Cl_2, -78 °C to rt, 90%

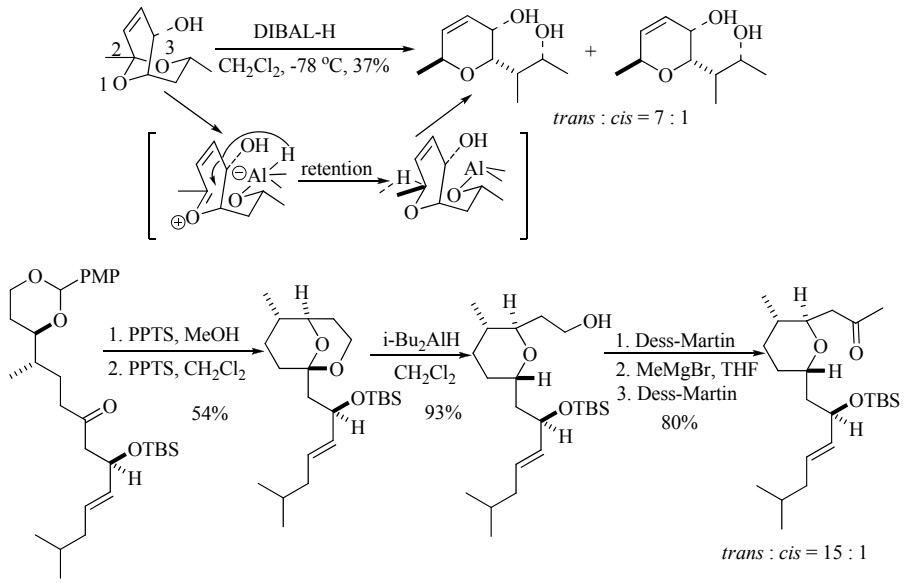
Scheme 2.6 Mukaiyama-aldol process of pyranyl acetate in synthesis of leucascandrolide A.

2.2.4 Diastereoselective Reductive Opening of Bicyclic Ketal

DeShong recently developed a novel reductive opening of bicyclic ketal to form 2,6-*trans*-pyran derivatives in a highly regio- and stereoselective manner.[10] It was proposed that a pyran-oxonium ion is formed when the aluminum reagent coordinates to the O(3)-ketal oxygen under nonpolar conditions in the DIBALH

[8] Williams, D. R.; Patnaik, S.; Plummer, S. V. *Org. Lett.* **2003**, *5*, 5035.
[9] For other examples of synthesis of leucascandrolide A see (a) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641. (b) Williams, D. R.; Plummer, S. V.; Patnaik, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3934. (c) Paterson, I.; Tudge, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 343. Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833. (d) Fettes, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4098. (e) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. (f) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (g) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (h) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894.
[10] Bogaczyk, S.; Brescia, M. R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 4352.

reduction. Hydride attack occurs preferentially from the same direction as a result of the rapid intramolecular capture of the oxonium ion, leading to the *trans* stereoselectivity (Scheme 2.7). The power of this method was elegantly demonstrated in the enantioselective total synthesis of (+)-Leucascandrolide A macrolactone.[9a] The bicyclic ketal could be derived from a Homer-Wadsworth-Emmons reaction between the corresponding aldehydes and ketone phosphonate, which makes this strategy highly attractive from a synthetic point of view.

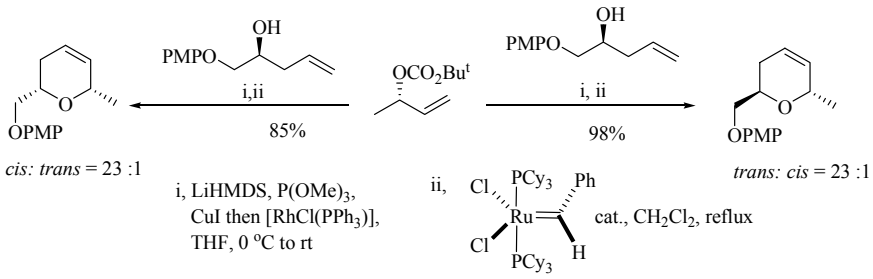


Scheme 2.7 Diastereoselective reductive opening of bicyclic ketal.

2.2.5 Etherization and Ring Closing Metathesis

Rhodium(I)-catalyzed etherification of an allylic carbonate with optically pure homoallylic alcohols, followed by ring-closing metathesis proceeded with excellent diastereoselectivity to afford 2,6-*cis*- and 2,6-*trans*-dihydropyrans in high yields (Scheme 2.8).[11]

[11] Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uraguchi, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 3459.

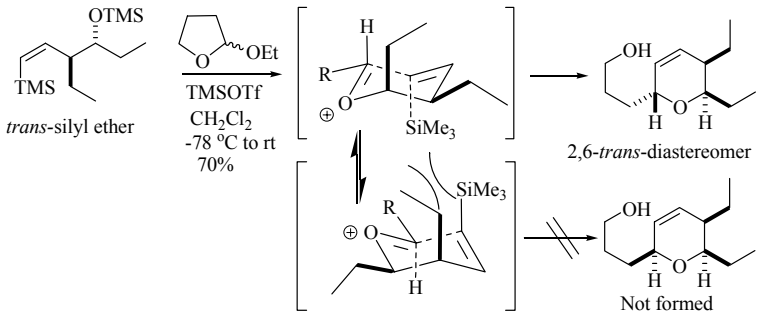


Scheme 2.8 Etherization of allylic carbonate with alkenyl alcohol followed with RCM.

2.3 PRINS CYCLIZATION TO 2,6-TRANS-TETRAHYDROPYRAN

2.3.1 Substrate-Controlled 2,6-*trans*-Prins Cyclization: Steric Effect.

In the synthetic study of Okadaic acid, Markó[12] reported a steric compression strategy to construct 2,6-*trans* dihydropyran in an effective manner. When *anti*-silyl ether was subjected to the intramolecular Silyl-Modified Sakurai (ISMS) reaction, it could react *via* two possible transition states (Scheme 2.9). Nevertheless, severe 1,3-diaxial interaction between the $SiMe_3$ substituent and the ethyl group should strongly disfavor formation of the 2,6-*cis*-isomer. Thus, only 2,6-*trans*-dihyropyran was formed as the single diastereoisomer in satisfactory yield.

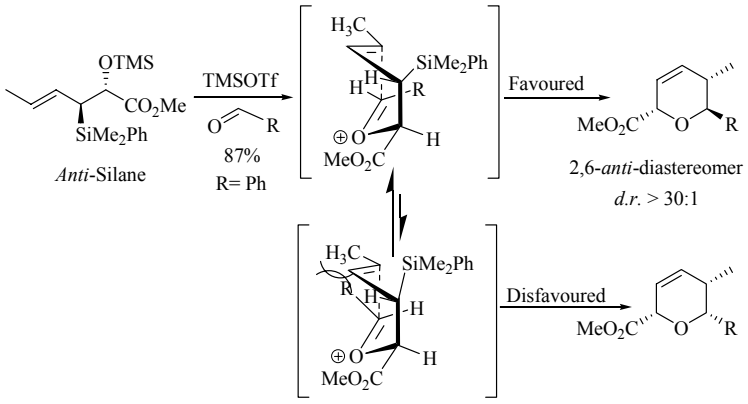


Scheme 2.9 Steric compression strategy to generate 2,6-*trans*-dihydropyran in ISMS reaction.

[12] Markó, E. I.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899.

However, only the 2,6-*cis*-isomers could be obtained in those cases without the essential substituent that is *trans* to the OTMS group both in ISMS reaction[12] and in Prins-type cyclizations.[13]

Later, Panek[14] reported a more sophisticated stereoselective [4+2] annulation of chiral *anti*-hydroxycrotylsilane to afford 2,6-*trans*-pyran ring (Scheme 2.10). A pseudo-axial orientation for the silyl group has been proposed for effective σ-π overlap in a boat-like transition state. This conformation determines the *trans* cyclization stereo-outcome, which is rationalized through an *anti*-S_E' mode of addition. From the viewpoint of both steric and electronic considerations, the bulky silyl group will be placed in an *anti* orientation to the neighboring ester group in the oxocarbenium intermediate, resulting in the desired *trans*-isomer upon cyclization. The efficiency of this strategy has been elegantly demostrated in the synthetic studies of many natural products, such as Leucascandrolide A,[14b] Callipeltoside A,[14c] Kendomycin,[14d] and Bistramide A.[14e, 15]



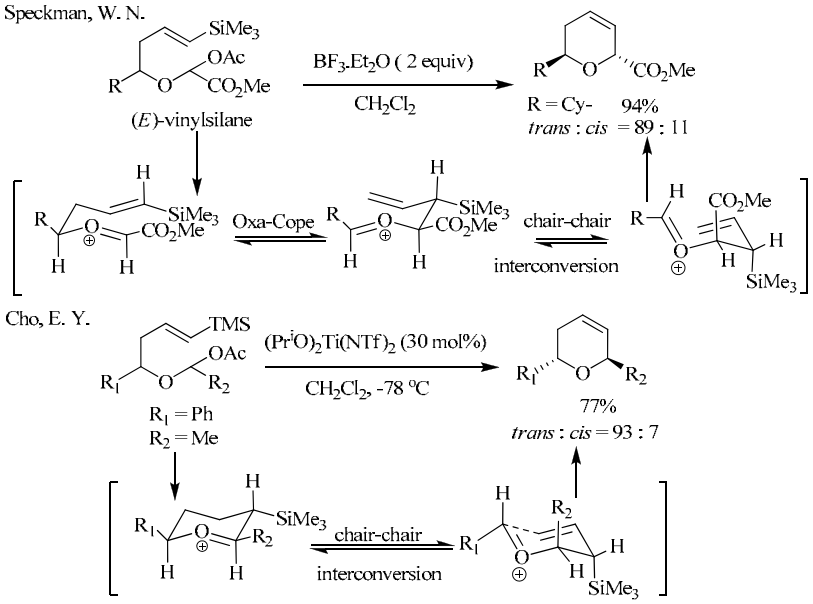
Scheme 2.10 *trans*-Prins cyclization of chiral *anti*-hydroxycrotylsilane.

[13] (a) Dobbs, A. P; Martinović, S. *Tetrahedron Lett.* **2002**, *43*, 7055. (b) Dobbs, A. P; Guesné, S. J. J.; Martinović, S. Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880.

[14] (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836. For applications on total synthesis, see (b) Dakin, L. A.; Panek, J. S. *Org.Lett.* **2003**, *5*, 3995. (c) Huang, H.; Panek, J. S. *Org.Lett.* **2004**, *6*, 4383. (d) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529. (e) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231.

[15] For other synthesis of Bistramide A, see (a) Crimmins, M. T.; BeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936. (b) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546.

Speckman devised an intramolecular Prins cyclization of (*E*)-vinylsilanes to form 2,6-*trans*-dihydropyran rings.[16] The *trans* selectivity was rationalized as originating from the most preferred cyclization conformation featuring an axial silyl function, which comes from reorganization of the reaction intermediates *via* a cationic oxonia-Cope rearrangement and a subsequent chair-chair interconversion (Scheme 2.11).[16] In the case of the (*Z*)-vinylsilanes, only *cis* cyclization was observed, where the oxocarbenium cation has an equatorial ester substituent with the TMS function axially oriented because of the (*Z*)-double bond geometry. Yu[17] also disclosed a similar strategy to construct 2,6-*trans*-dihydropyrans in good yields and stereoselectivity using a titanium-based catalyst.



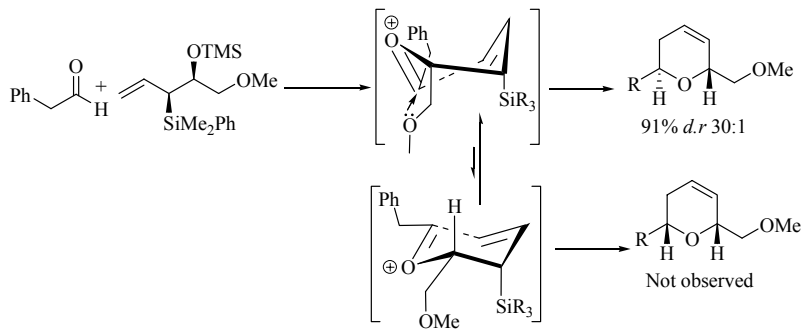
Scheme 2.11 Intramolecular Prins type cyclization of vinyl silane.

[16] (a) Semeyn, C.; Blaauw, R. H.; Heimstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (b) Lolkema, L. D. M; Semeyn, C.; Ashek, L.; Heimstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *50*, 7129.

[17] Yu, C. M.; Shim, M.S; *Bull. Korean Chem. Soc.* **2004**, *25*, 1627.

2.3.2 Substrate-Controlled 2,6-*trans*-Prins Cyclization: Electronic Effect.

In the synthetic study of (-)-Apicularen A,[18] Panek observed that a *syn*-organosilane with methyl ether as the terminal substitutent can be used to afford 2,6-*trans*-dihydropyran in excellent diastereselectivity.[19] A twist boat-like transition state was proposed to account for this stereochemical outcome. The electrostatic attraction between the nonbonding lone pair of electrons on the methoxy group and the positively-charged oxocarbenium cation, which resides on the carbon atom, can stabilize the twist boat conformer and accelerates the annulation (Scheme 2.12).

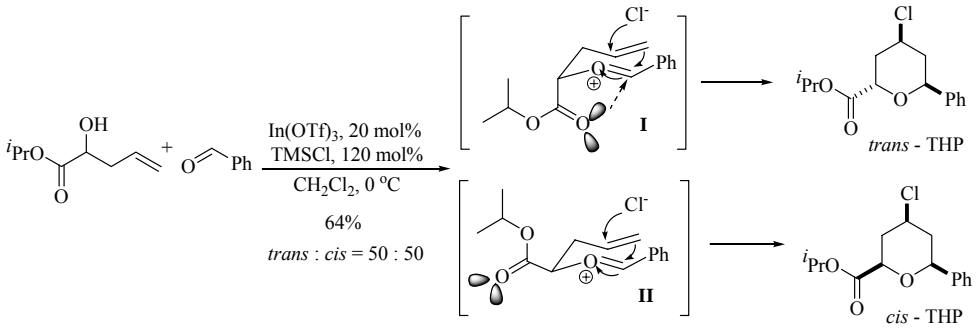


Scheme 2.12 *trans*-Prins Cyclization of *syn*-methyl ether crotyl silane.

Chan,[20] a senior member in our group, also devised a *trans* cyclization channel which utilizes the lone pair directing effects for stabilizing the oxocarbenium cation in Prins cyclization. By incorporating ester functionality onto the homoallylic alcohol, spatial electrostatic interaction overcame 1,3-diaxial steric repulsion in the chair-like transition state **I**, thus resulting in the formation of the *trans*-isomer (Scheme 2.13) in moderate selectivity and yields. However, the cyclization also proceeded quite well

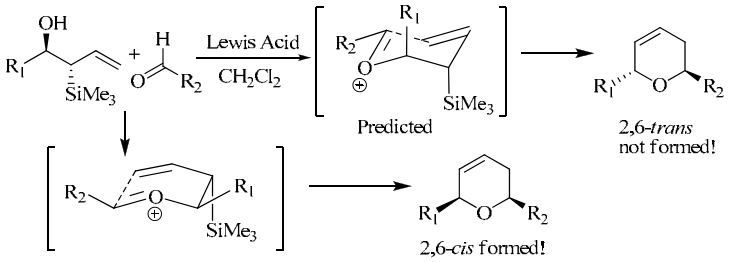
[18] For other synthesis of (-)-Apicularen A, see (a) Petri, A. F.; Bayer, A.; Maier, M. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821. (b) Hilli, F.; White, J. M.; Rizzacasa, M. A. *Org. Lett.* **2004**, *6*, 1289. (c) Graetz, B. R.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3357. (d) Nicolaou, K. C.; David, W.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701. (e) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549. (f) Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahderon Lett.* **2001**, *42*, 1217. (g) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407.
[19] Su, Q.; Panek, J. S. *I. Am. Chem. Soc.* **2004**, *126*, 2425.
[20] Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, *48*, 37.

when the electron rich moiety (isopropyl ester) adopts the equatorial position (transition state **II**), thus lowering the overall *trans* selectivity.



Scheme 2.13 Competing steric and electronic effects in substrate-controlled Prins cyclization.

During the total synthesis of scytophycin C, Roush devised a strategy to access 2,6-*trans*-dihydropyrans *via* Prins cyclization of β-hydroxyallylsilane with aldehydes (Scheme 2.14).[21] The *trans* selectivity was expected to originate from a chair transition state with axial R_1 and TMS, where the axially oriented TMS is preferred for stereoelectronic reasons when forming the carbocationic structure at the β–position.[22] However, 2,6-*cis*-cyclization was found to predominate. It was finally revealed that all the reaction processes involved in this study proceeded *via* a boat-like conformation with high stereochemical retention after a careful examination of the absolute C-O stereochemistry.



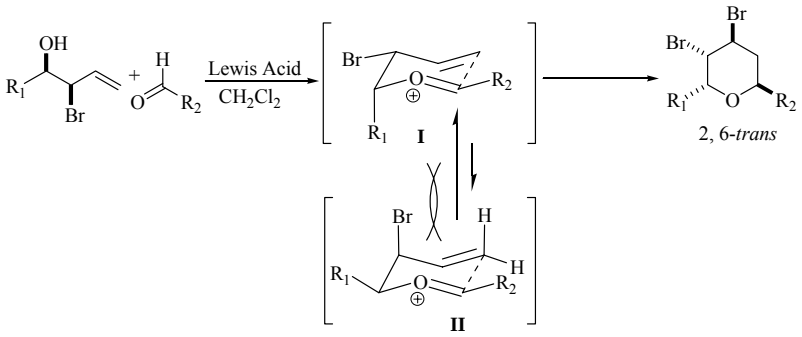
Scheme 2.14 Dehydrative Prins cyclization of vinyl β-hydroxysilane.

[21] Roush, W. R.; Dilley, G. J. *Synlett* **2001** *S1*, 955.
[22] (a) Lambert, J. B.; Wang, G. T. *J. Phys. Org. Chem.* **1988**, *1*, 169. (b) Lambert, J. B.; Finzel, R. B. *J. Am. Chem.Soc.* **1982**, *104*, 2020.

2.4 DEVELOPMENT OF NOVEL TRANS PRINS CYCLIZATION

2.3.1 From Steric Effect

It is established after the general discussions described above that both steric and electronic effects could be utilized to devise novel *trans* Prins cyclization. Here, we conceived a strategy by utilizing the **A value** [23] to develop a novel *trans* Prins cyclization reaction, where *syn* vinyl bromohydrin was selected as the candidate substrate to form 2,6-*trans*-THP rings (Scheme 2.15). The *trans* selectivity is based on the hypothesis that R_1 should be forced to assume an axial position by the bulky bromo-substituent, which prefers to occupy an equatorial position in order to avoid strong 1,3-diaxial repulsive interaction. Based on this assumption, if the cyclization does proceed through transition state **I**, 2,6-*trans*-THP rings will be obtained with all bromo-substituents residing at equatorial positions.



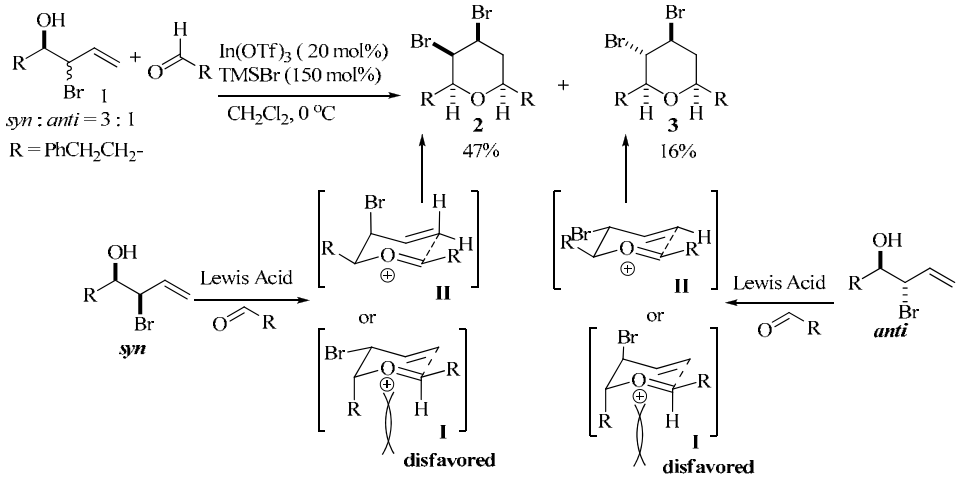
Scheme 2.15 Hypothesized *trans* Prins cyclization of *syn* vinyl bromohydrin based on A value.

A mixture of **1** (*syn* : *anti* = 3 : 1) was subjected to the standard Prins cyclization condition[24] developed in our group, and the two Prins cyclized products **2** and **3** were obtained in 47% and 16% yields respectively (Scheme 2.16). The relative stereochemistry was determined by NOESY experiments. For both *syn* and *anti*

[23] A value denotes the 1,3-diaxial interaction on six membered rings, see: Corey, E. J.; Feiner, N. F. *J.Org. Chem.* **1980**, *45*, 765.

[24] (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387. (b) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491. (c) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939. (d) Liu F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063.

bromohydrins, Prins cyclization reaction may proceed *via* two possible transition states I and II, however, transition state I is actually disfavored because of the severe 1,3-diaxial repulsion between the alkyl chain and the aldehydic proton, as depicted below. In contrast to our initial envision, bromine substituent was found to be capable to reside on axial position because of its relative small A value, which makes transition state II favorable during the cyclization of the *syn* bromohydrin. For this reason, only 2,6-cis-THPs were formed in this case. Thus, our strategy exploiting **A value** failed to form the desired 2,6-*trans*-THP rings from *syn* vinyl bromohydrins.

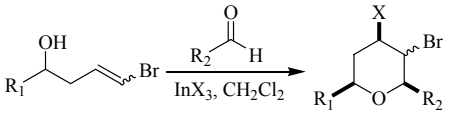


Scheme 2.16 Prins cyclization of *syn* and *anti* bromohydrin with aldehydes.

Although we failed to obtain the desired 2,6-*trans*-THP rings, we envisage that 2,6-*cis*-dibromo-THP rings could serve as potentially important precursors to form other THP-containing compounds *via* further elaborations, such as debromination to form a double bond selectively. Interestingly, Blepharocalyxins D & E are believed to be synthesized from a precursor with a double bond on the pyran ring from a biogenetic point of view.[25]

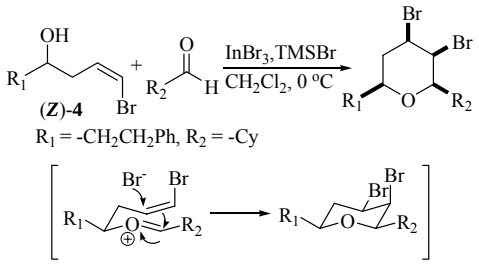
[25] Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491.

Because of the difficulties in preparing and purifying **1**, we devised an alternative approach to make the 2,6-*cis*-dibromo-tetrasubstituted THP rings by using *(Z)* and *(E)*-γ-brominated homoallylic alcohols in the presence of indium-based Lewis acids, which will offer an opportunity to further confirm the stereochemistry involved in the *cis* Prins cyclization of *syn* vinyl bromohydrins with aldehydes (Scheme 2.17).[26, 27]



Scheme 2.17 Prins cyclization of γ-brominated homoallylic alcohol with aldehydes.

γ-Brominated homoallylic alcohol (*Z*)-**4** and cyclohexanecarboxaldehyde were selected for the optimization of reaction conditions (Scheme 2.18). Indium-based Lewis acids, such as $InCl_3$, $In(OTf)_3$ and $InBr_3$ were employed to mediate the Prins cyclization at 0 ^oC in CH_2Cl_2. No Prins product was formed when $InCl_3$ was utilized to promote this cyclization and no desired crossed product could be obtained when using $In(OTf)_3$.



Scheme 2.18 Prins cyclization of *(Z)*-**4** with cyclohexanecarboxaldehyde.

[26] (a) Mallaiah, K.; Satyanarayana, J.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*, 3145-3148. (b) Hoffmann, R. W.; Landmann, B. *Tetrahedron Lett.* **1983**, *24*, 3209-3212. (c) Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042-13043. (d) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899-2902. (e) Björkling, F.; Norin, T.; Unelius, C. R.; Miller, R. B. *J. Org. Chem.* **1987**, *52*, 292-294. (f) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424-4431.

[27] (*Z*)-**4** was prepared in 62% yield by using hydrocinnamaldehyde to trap allylic anion generated from allyl bromide in the presence of LDA and zinc bromide.[26a] (*E*)-**5** was prepared in three steps: (1) propargylation of trialkylsilyl propargyl bromide with hydrocinnamaldehyde mediated with indium and indium bromide (60%),[26c] (2) DIBAL-H reduction converting the triple bond into the *cis* double bond (64%),[26d] (3) bromination (90%). [26e,f]

However, $InBr_3$ was discovered to be a highly efficient Lewis acid to promote this Prins cyclization and the yields were dependent on the amount of $InBr_3$ employed (Table 2.1, entries 1, 2 and 3), with the best condition being 1.0 equiv. of $InBr_3$ with 1.2 equiv. of TMSBr[28] in CH_2Cl_2 at 0 °C to afford **5** in 95% yield as a single isomer (Table 2.1, entry 3). This cyclization proceeded smoothly with high stereoselectivity and introduced four stereogenic centers into the product in one step. 2,4,6-*cis*-5-*trans* THP ring **5** was expected to be constructed with an axial bromine substituent at 5 position and all other three substituents occupying equatorial positions. This was confirmed by the X-ray crystal structure of **5** (Figure 2.1).[29]

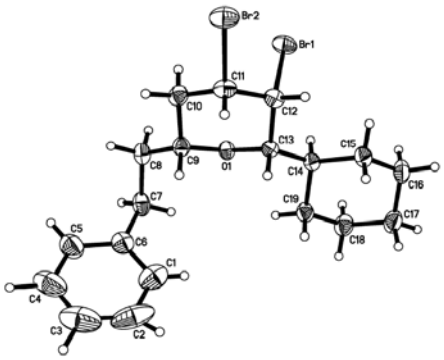


Figure 2.1 Crystal structure of **5**, showing an axial bromine at 5 position and all equatorial substituents at 2,4,6 positions.

Using the above optimized reaction conditions (Table 1, entry 3),[30] a variety of aldehydes were selected to construct the 2,6-*cis*-4,5-dibromo-THP rings with both

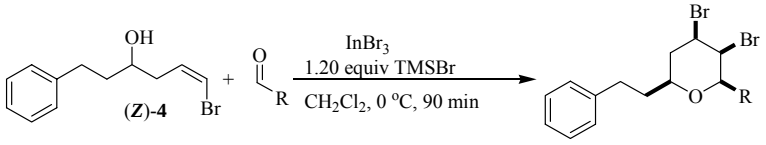
[28] Our initial investigations revealed that TMSBr serves as a bromide source. No reaction occurred when only TMSBr was used as promoter. With stoichiometric amount of $InBr_3$ as the sole promoter, only trace amount of the product could be observed when (***Z***)-**4** was reacted with cyclohexanecarboxaldehyde; for (***E***)-**11** only 21% yield was obtained.

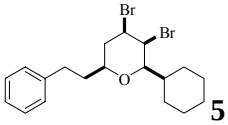
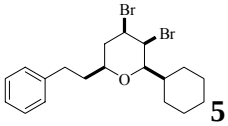
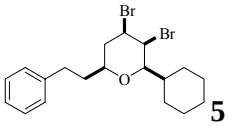
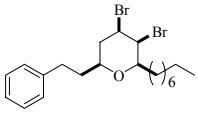
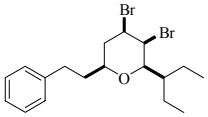
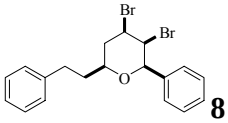
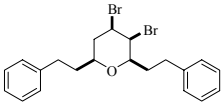
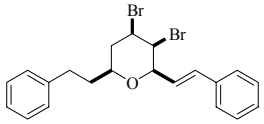
[29] Crystal data for **5** see Appendix.

[30] Typical experimental procedures for our Prins cyclization to 2,6-*cis*-4,5-dibromo-THP rings: to an oven-dried round-bottom flask with a magnetic stirrer was added indium bromide 106.0 mg (0.30 mmol, 1.0 equiv.) and anhydrous dichloromethane 1.5 mL. The mixture was vigorously stired at 0 °C. *(Z)*-**4** 91.8 mg (0.36 mmol, 1.2 equiv.) dissolved in 1 mL anhydrous CH_2Cl_2 was introduced into the suspension, and 5 minutes later bromotrimethylsilane TMSBr 0.05 mL (0.36 mmol, 1.2 equiv.) was added. Cyclohexanecarboxaldehyde 33.7 mg (0.30 mmol, 1.0 equiv.) dissolved in 1 mL anhydrous CH_2Cl_2 was slowly introduced over 10 minutes. The reaction was allowed to proceed at 0 °C for 90 minutes before quenching with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residual crude product was purified via flash chromatography (0.5% diethyl ether in hexane) to afford **5** as a white solid in 95 % yield.

(Z)-**4** and *(E)*-**11**, and moderate to good yields with excellent stereoselectivities were obtained. The results are summarized in Table 2.1 and Table 2.2.

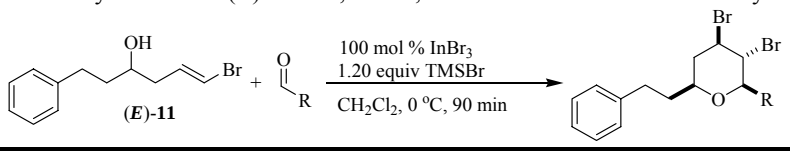
Table 2.1 Prins cyclization of (**Z**)-**4** to 2,6-*cis*-4,5-dibromo-tetrasubstituted tetrahydropyrans.

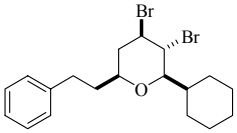
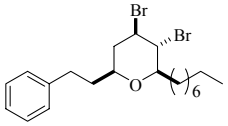
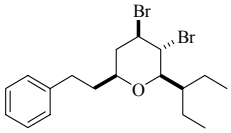
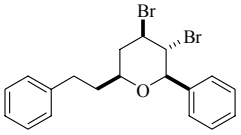
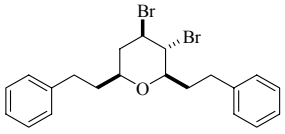
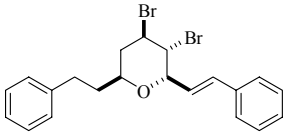


Entry	R	Time (h)	Product	Yield (%)[a]
1	-Cy	1.5	 **5**	32[b]
2	-Cy	1.5	 **5**	63[c]
3	-Cy	1.5	 **5**	95[d]
4	$-(CH_2)_7CH_3$	1.5	 **6**	87[d]
5	$-CH(CH_2CH_3)_2$	1.5	 **7**	68[d]
6	-Ph	25	 **8**	71[d]
7	$-CH_2CH_2Ph$	1.5	 **9**	91[d]
8	-CHCHPh	25	 **10**	N.R.[e]

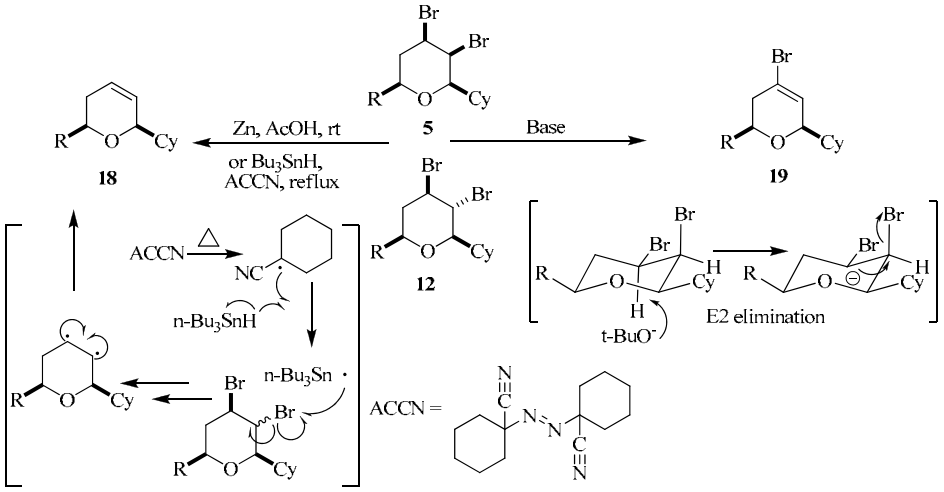
[a] isolated yield. [b] 0.2 equiv. $InBr_3$ employed, and an X-ray crystal structure was obtained and shown in Figure 2.1. [c] 0.5 equiv. $InBr_3$ employed. [d] 1.0 equiv. $InBr_3$ employed. [e] N.R. denotes no reaction with the recovery of starting materials.

Table 2.2 Prins cyclization of (***E***)-**11** to 2,6-*cis*-4,5-dibromo-tetrasubstituted tetrahydropyrans.



Entry	R	Time (h)	Product	Yield (%)[a]
1	-Cy	1.5	 **12**	92
2	$-(CH_2)_7CH_3$	1.5	 **13**	82
3	$-CH(CH_2CH_3)_2$	1.5	 **14**	90
4	-Ph	1.5	 **15**	77
5	$-CH_2CH_2Ph$	1.5	 **16**	90
6	-CHCHPh	25	 **17**	N.R.[b]

[a] isolated yield. [b] N.R. denotes no reaction with the recovery of starting materials.



Scheme 2.19 Chemical transformations of 2,6-*cis*-4,5-dibromo-THP rings.

THP products **5** and **12** were selected to perform a series of chemical transformations to explore the synthetic versatilities of our dibromo-THP rings (Scheme 2.19). As expected, **18** was readily obtained with a selective double bond *via* direct debromination using activated zinc in acetic acid at room temperature,[31a] and an unexpected alternative approach was also discovered to create such selective double bond under radical reaction conditions (Table 2.3, entries 3 and 4).[31b]

The presence of axial bromine makes **5** more reactive compared to **12** (all bromine equatorial). The double bond of **18** allows further functionalizations, such as epoxidation[32] and hydroxylation.[33] In addition, elimination product **19** was formed when **5** and **12** were treated with potassium *tert*-butoxide. **5** was again found to be more reactive than **12**. Results are summarized in Table 2.3. Vinyl bromide **19** is also a versatile intermediate which can be converted into 2,6-alkyl-3-hydroxy-tetrahydro-pyran-4-one *via* osmium-catalyzed *cis*-dihydroxlation or into 2,6-disubstituted-THP ring upon catalytic hydrogenation using Pd/C.[34]

Table 2.3 Chemical transformations of 2,6-cis-4,5-dibromo-THP rings.

Entry	Substrate	Conditions	Product	Yield (%)[a]
1	**5**	Zn, AcOH, rt, 24 h.	**18**	70
2	**12**	Zn, AcOH, rt, 24 h.	**18**	58
3	**5**	Bu_3SnH, ABCCN, $PhCH_3$, reflux, 24 h.	**18**	71
4	**12**	Bu_3SnH, ABCCN, $PhCH_3$, reflux, 24 h.	**18**	56
5	**5**	t-BuOK, EtOH, rt, 24 h.	**19**	69
6	**12**	t-BuOK, $PhCH_3$, reflux, 24 h.	**19**	59

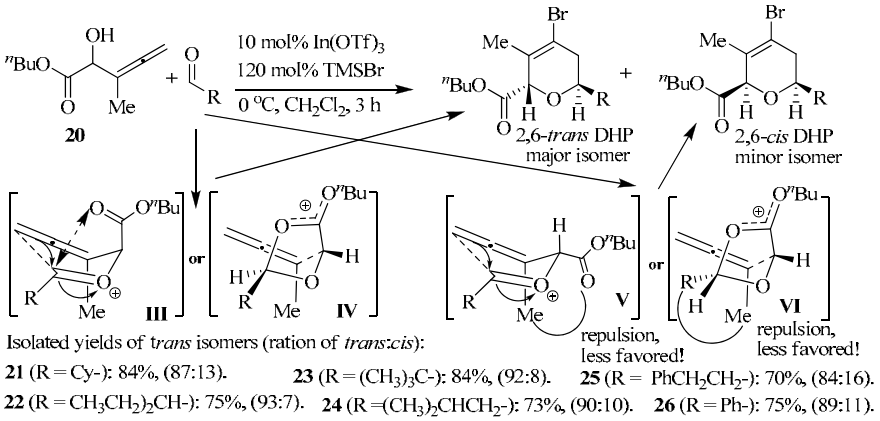
[a] isolated yield.

[31] (a) Sato, F.; Akiyama, T.; Iida, K.; Sato, M. *Synthesis*, **1982**, *12*, 1025. (b) RajanBabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*: Paquette, L.; Ed.: Wiley: New York, **1995**, *7*, 5016.
[32] Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem.* **2000**, *18*, 3145.
[33] Dobbs, A. P.; Guesné, S. J. J.; Martinović, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880.
[34] Miranda, P. O.; Díaz, D. D.; Pardón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979.

2.4.2 From Electronic Effect

As mentioned above, our group's *trans* Prins cyclization utilized the electronic directing effect leading to a moderate *trans* selectivity.[20] Here, we progress further in our studies towards this topic to achieve a higher *trans*/*cis* selectivity by using this electronic directing effect. In our group's reported method, the moderate *trans* diasteroselectivity originated from the spatial electrostatic interaction that overcame steric repulsion (1,3-diaxial interaction) in the chair-like transition state **I** (Scheme 2.13). We wonder whether a higher *trans* diasteroselectivity could be achieved if we remove the 1,3-diaxial interaction by changing the allyl group to a linear allenyl functionality. Bearing this thinking in mind, we devised another *trans* cycliztation by subjecting allenyl alcohol with carbonyl functionality to Prins cyclization conditions.

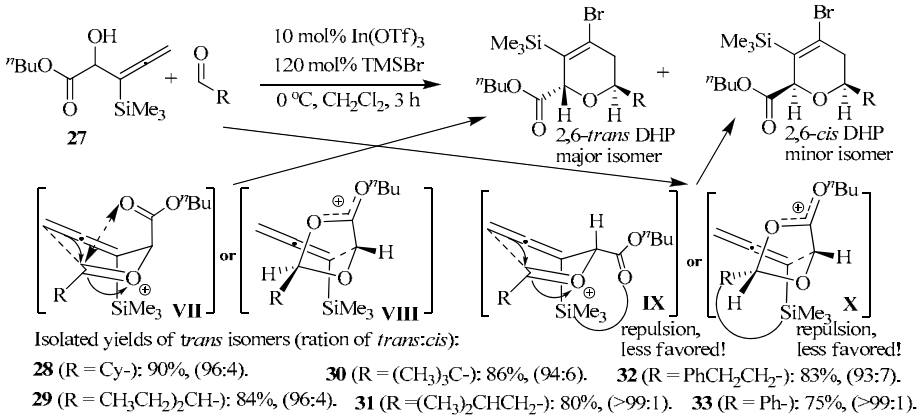
By subjecting allenyl alcohol bearing α-alkoxycarbonyl group **20** to Prins cyclization conditions (10 mol % $In(OTf)_3$, 1.2 equiv. of TMSBr, 0 ^oC, in CH_2Cl_2) developed in previous studies),[24a] the desired 2,6-*trans*-disubstituted-4-bromo-3,4-dihydropyrans were formed smoothly in good yields with high *trans* diastereoselcetivity (Scheme 2.20).[35]



Scheme 2.20 Prins cyclization of Me-substituted allenyl alcohol bearing α-alkoxycarbonyl group.

[35] This part of work was done in collaboration with a group member, see: Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009**, *11*, 1741.

Interestingly, the *trans* diastereoselectivity was further enhanced to a higher level of up to > 99:1 when TMS substituted allenyl alcohol bearing α-alkoxycarbonyl group **27** was utilized for this Prins cyclization (Scheme 2.21), where the TMS group strongly prefers to adopt an axial position for stereoelectronic reasons in reactions that develop carbocationic character at the β-position.[21, 22] Thus, an enhancement of the repulsive effect in transition state IX and X probably further suppressed the formation of the undesired 2,6-*cis* DHP isomers.



Scheme 2.21 Prins cyclization of TMS-substituted allenyl alcohol bearing α-alkoxycarbonyl group.

The alkoxycarbonyl function adjacent to the allenic alcohol motif played a central role for this 2,6-*trans* diastereoselectivity: firstly, it serves to suppress the undesired oxonia-Cope rearrangement, because the electron-withdrawing alkoxycarbonyl function disfavours the oxonia-Cope rearrangement product in which the alkoxycarbonyl function is directly attached to the oxonium carbon;[21] secondly, the stereoelectronic interaction between the lone pair on the carbonyl oxygen and the partially positive-charged oxonium carbon directs the alkoxycarbonyl group to adopt an axial orientation, resulting in the 2,6-*trans* diastereoselectivity. Alternatively, the trans selectivity originates from the 1,2-neighboring participation effect that leads to the formation of 5-membered transiton states IV, VIII, however, transition states VI, X are less favored due to the intrinsic steric repulsions.

2.5 CONCLUSION

From the point of view of steric effect, our **A value** strategy failed to provide us with a novel *trans* Prins cyclization reaction. It is established that the *syn* vinyl bromohydrins underwent *cis* Prins cyclization *via* chair-like transition states affording only 2,6-*cis*-THP products as evidenced by the crystal strucute of **5** (Figure 2.1). To our delight, we have developed an efficient Prins cyclization reaction to construct 2,6-*cis*-4,5-dibromo-tetrasubstituted THP rings with excellent diastereoselectivity in good yields. Effective control of the stereochemistry of the bromo-substituent at C(5) position was achieved by manipulating the geometric configuration of the γ-brominated homoallylic alcohols. This method offers a stereoselective approach to make dibromo-THP rings *via* Prins cyclization that results in a *cis* configuration of bromine atoms. Other approaches to dibromo-THP rings were realized *via* bromination of dihydropyrans, and only *trans* addition products were obtained.[36] Our dibromo-THP products serve to provide versatile intermediates that allow further functionalization to various substituted pyran-containing compounds.

Our second strategy succeeded in disclosing a novel, highly efficient *trans* Prins cyclization by utilizing allenyl alcohol bearing α-alkoxycarbonyl group. The high *trans* diastereoselectivity probably originates from the spatial electrostatic directing effect between the lone pair of electrons on carbonyl oxygen atom and the positively charged oxonium carbon, or from the 1,2-neighboring participation effect that leads to the formation of 5-membered transiton states IV, VIII. Importantly, the ester function allows further elaborations to other interesting functions for synthetic applications.

[36] (a) Woods, G. F.; Temin, S. C. *J. Am. Chem. Soc.* **1950**, *72*, 139. (b) Dale, W. J.; Sisti, A. J. *J. Am. Chem. Soc.* **1954**, *76*, 81. (c) Brown, R. K.; Srivastava, R. M.; Sweet, F.; Murry, T. P. *J. Org. Chem.* **1971**, *36*, 3633. (d) Brown, R. K.; Srivastava, R. M.; Sweet, F. *J. Org. Chem.* **1972**, *37*, 190.

CHAPTER 3

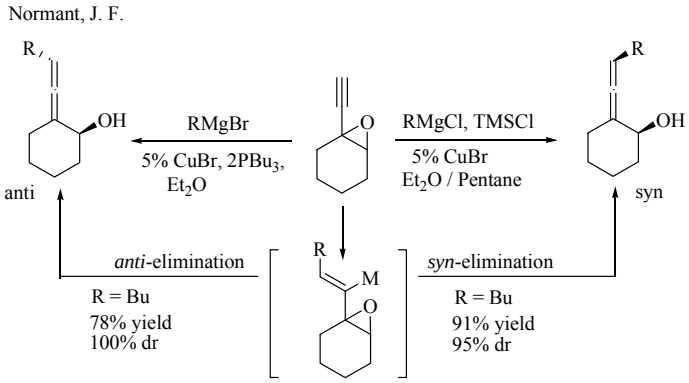
Friedel-Crafts-Prins Cascade Condensation of Propargylic Epoxides with Aldehydes

3.1 INTRODUCTION

3.1.1 Propargylic Epoxide in Organic Synthesis

Propargylic epoxides are versatile synthons for the preparations of important intermediates in modern organic synthesis. The coexistence of the triple bond and the epoxy functionality guarantees its versatilities in undergoing various chemical transformations.

Propargylic epoxides react readily with organometallic reagents to afford allenic alcohols. Normant disclosed a stereospecific method to synthesize *syn* and *anti* α-allenic alcohols from the corresponding propargylic epoxides and Grignard reagents in the presence of a Cu(I) catalyst, using the "halogen effect" to achieve the selectivity through an addition-elimination mechanism (Scheme 3.1). [1] This methodology is also applicable to linear substrates with moderate to good selectivities using either Grignard or organolithium reagents.[1]



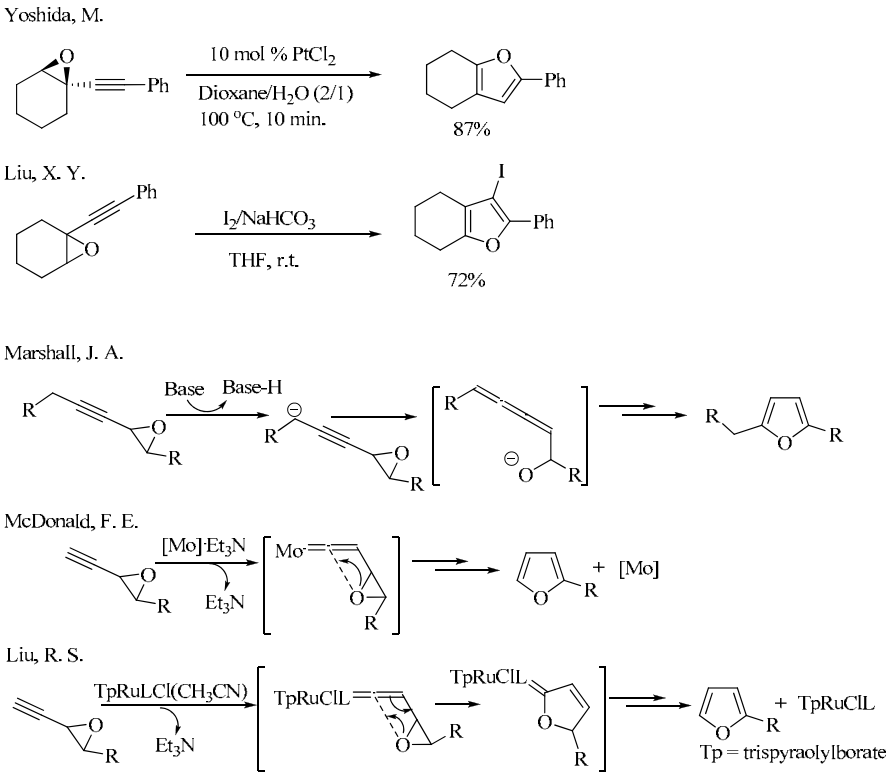
Scheme 3.1 A stereospecific synthesis of α–allenic alcohol from propargyllic epoxide.

In addition, Normant also developed a stereospecific approach to prepare bromoallenic alcohols using hydrobromic acid and cuprous bromide with

[1] (a) Alexis, A.; Marek, I.; Mangeney P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387. (b) Alexis, A.; Marek, I.; Mangeney P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677. The "halogen effect" denotes that the halogen atom X in RMgX plays a crucial role affecting the overall stereochemical outcome. Detailed explanations see (c) Alexis, A.; Marek, I.; Mangeney P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

ammounium bromide as additive in aqueous media.[2] 1,2-Disubstituted homopropargylic alcohols can also be readily obtained in a highly diastereoselective manner by reacting propargylic epoxides with Grignard or organolithium reagents in the presence of catalytic trifluoroborate etherate.[3]

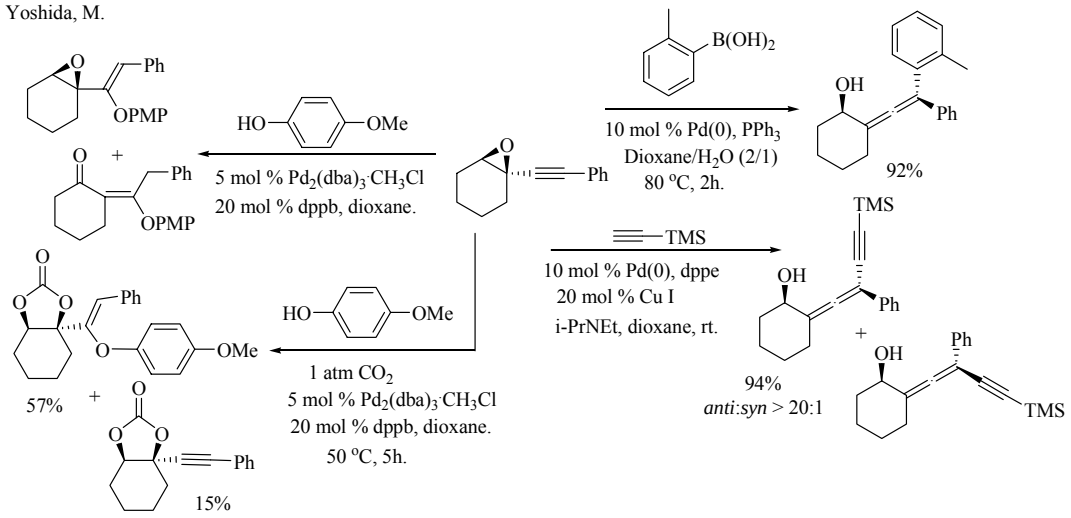
Cycloisomerization of propargylic epoxides constitutes one of the most useful methods to construct substituted furans, in which a variety of reagents activate this reaction (Scheme 3.2). When treated with catalyst $PtCl_2$,[4] iodine,[5] base,[6] molybdenum, and ruthenium complexes,[7] substituted furans could be obtained from propargyllic epoxides in an efficient manner.



Scheme 3.2 Cyclization of propargylic epoxides to furans.

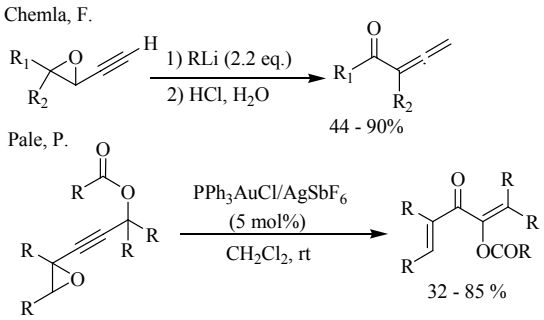
[2] Bernard, N.; Chemla, F.; Normant, J. F. *Tetrahedron Lett.* **1998**, *39*, 8837.
[3] Chemla, F.; Bernard, N.; Normant, J. F. *Eur. J. Org. Chem.* **1999**, 2067.
[4] Yoshida, M.; Al-Amin, M.; Matsuda, K.; Shishido, K. *Tetrahedron Lett.* **2008**, 49, 5021.
[5] Xie, Y. X.; Liu, X. Y.; Wu, L. Y.; Han, Y.; Zhao, L. B.; Fan, M. J.; Liang, Y. M. *Eur. J. Org. Chem.* **2008**, 1013.
[6] (a) Marshall, J. A.; DuBay, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1450. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1991**, *56*, 1685.
[7] (a) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363. (b) Lo, C. Y.; Guo, H.; Lian, J. J.; Shen, F. M.; Liu, R. S. *J. Org. Chem.* **2002**, *67*, 3930.

Yoshida also developed novel palladium-catalyzed regio- and diastereoselective coupling reactions of propargylic epoxides with phenols,[8] arylboronic acids,[9] carbon dioxide together with phenols,[10] and terminal alkynes (Scheme 3.3).[11]



Scheme 3.3 Palladium-catalyzed coupling reactions of propargyllic epoxides.

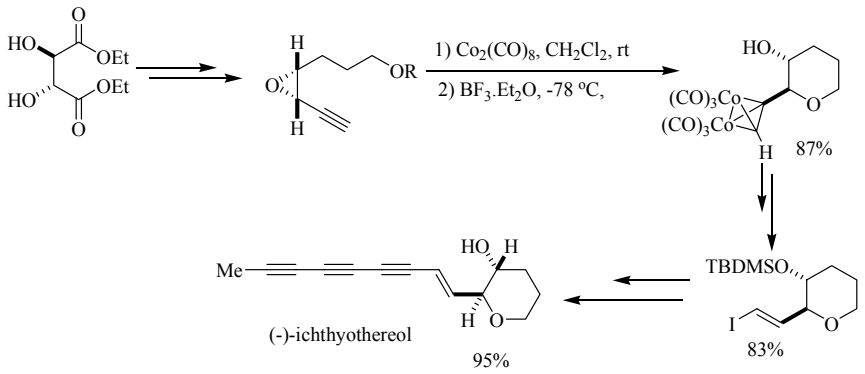
Allenic ketones[12] can also be easily prepared through dilithio ynenolates by the double deprotonation of propargylic epoxides. By using gold (I) catalyst, Pale disclosed a facile approach to divinyl ketones *via* a rearrangement of the starting propargylic epoxides.[13]



Scheme 3.4 Rearrangement of propargyllic epoxides to allenic ketones.

[8] Yoshida, M.; Morishita, Y.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 3669.
[9] Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705.
[10] Yoshida, M.; Murao, T.; Sugimoto, K.; Ihara, M. *SynLett.* **2007**, 4, 575.
[11] Yoshida, M.; Maiko, H.; Shishido, K. *Org. Lett.* **2007**, *9*, 1643.
[12] Denichoux, A.; Ferreira, F.; Chemla, F. *Org. Lett.* **2004**, *6*, 3509.
[13] Cordonnier, M. C.; Blanc, A.; Pale, P. *Org. Lett.* **2008**, *10*, 1569.

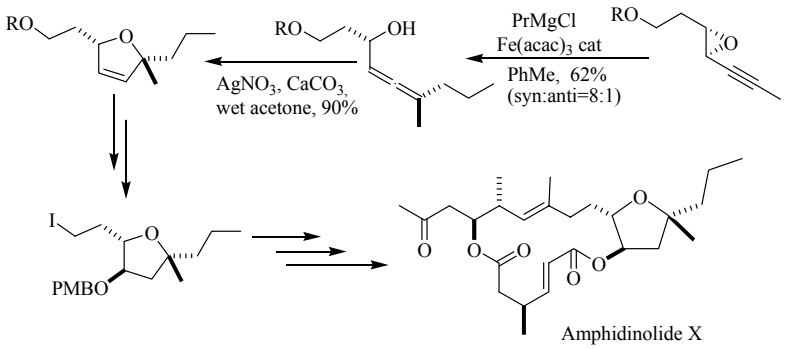
Propargylic epoxide also found its applications in the total synthesis of natural products. Hanaoka[14] completed the first total synthesis of the highly toxic fish poison (-)-ichthyothereol and its acetate analogue with its core structure prepared through a dicobalt octacarbonyl [$Co_2(CO)_8$]-mediated *endo* mode cyclization of the propargylic epoxide intermediate, which was readily generated from the commercially available material, diethyl L-tartrate. This [$Co_2(CO)_8$]-mediated *endo* mode cyclization of propargylic epoxides could also be applied to the construction of tetrahydrofuran, tetrahydropyran, and oxepane frameworks containing a 2-ethynyl-3-hydroxy substituents as a common feature.[15]



Scheme 3.5 [$Co_2(CO)_8$]-mediated *endo* mode cyclization of propargylic epoxide.

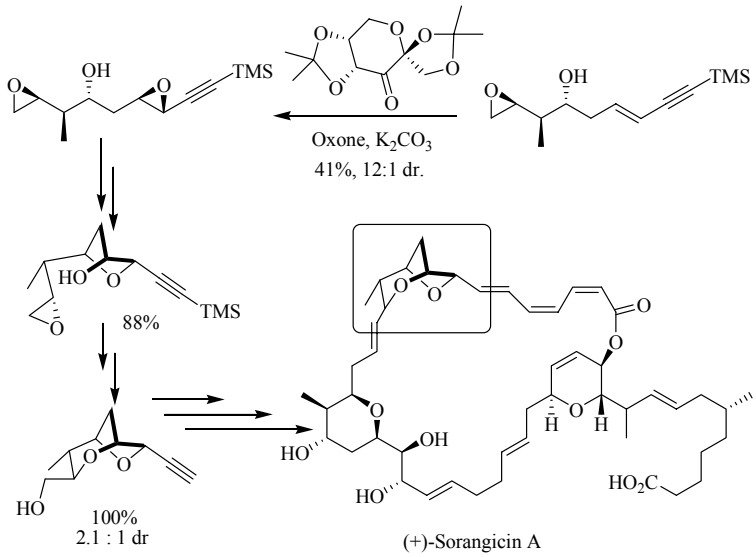
In the total syntheses of Amphilinolide X[16] and Y[17], propargylic epoxide prepared from allylic alcohol *via* Sharpless epoxidation, was converted to the target tetrahydrofuran motif after further elaborations to the allenic alcohol and subsequently dihydrofuran (Scheme 3.6).

[14] Mukai, C.; Miyakoshi, N.; Hanaoka, M. *J. Org. Chem.* **2001**, *66*, 5875.
[15] (a) Mukai, C.; Yamaguchi, S.; Sugimoto, Y.; Miyakoshi, N.; Kasamatsu, E.; Hanaoka, M. *J. Org. Chem.* **2000**, *65*, 6761. (b) Mukai, C.; Ikeda, Y.; Sugimoto, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2179. (c) Mukai, C.; Sugimoto, Y.; Ikeda, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2183. (d) Mukai, C.; Sugimoto, Y.; Ikeda, Y.; Hanaoka, M. *J. Chem. Soc. Chem. Commun.*, **1994**, 1161. (e) Mukai, C.; Sugimoto, Y.; Ikeda, Y.; Hanaoka, M. *Tetrahedron* **1998**, *54*, 823.
[16] Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970.
[17] Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2004**, *126*, 9194.



Scheme 3.6 Functionalized furan motif synthesized from propargylic epoxide.

The versatility of propargylic epoxide in construction of novel structures was also elegantly demonstrated in Smith's synthetic studies towards (+)-sorangicin A (Scheme 3.7).[18] The novel dioxabicyclo[3.2.1]octane motif, one of the key structural features of the potent antibiotic (+)-sorangicin A, was assembled *via* a series of Lewis acid-catalyzed epoxide-opening cyclizations, and a higher yield and regioselectivity of the desired 6-*exo*-*tet* cyclization product was achieved by reducing the alkyne steric bulkiness, at the same time accelerating the reaction rate.

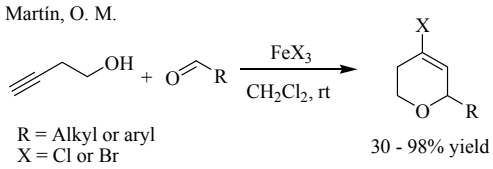


Scheme 3.7 Novel dioxabicyclo[3.2.1]octane assembled from propargylic epoxide.

[18] (a) Smith, A. B., III; Fox, R. *Org. Lett.* **2004**, *6*, 1477. (b) Smith, A. B., III; Fox, R.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099.

3.1.2 Prins Cyclization of Homopropargylic Acohols

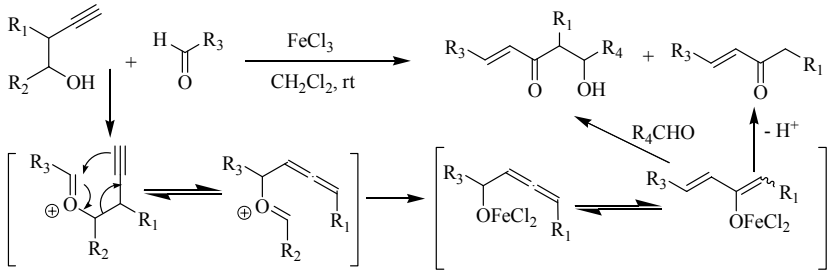
Besides homoallylic alcohols, homopropargylic alcohols are also useful substrates to undergo Prins cyclization with various aldehydes to afford substituted dihydropyrans in a highly stereoselective manner. Martín and Padrón developed an efficient and facile ferric halides mediated method to make 1-alkyl-4-halo-5,6-dihydropyrans *via* Prins cyclization of primary homopropargylic alcohols (Scheme 3.8).[19] An aza-Prins cyclization was also disclosed by Martín to synthesize the six-membered aza-heterocycles from the propargyl tosylamines and aldehydes in excellent yields.[20]



Scheme 3.8 Ferric halides mediated Prins cycliation of primary homopropargylic alcohol.

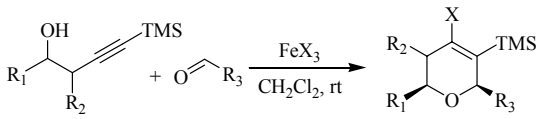
However, when secondary homopropargylic alcohol was subjected to this cyclization conditions, it suffered from undesired oxonia-Cope rearrangement and a 1,3-*O*-transposition process to afford unexpected coupling reaction products, including unsaturated β-hydroxyketone and α,β-unsaturated ketones, instead of generating the target Prins cyclization products(Scheme 3.9).[21]

[19] Miranda, P. O.; Díaz, D. D.; Pardón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *5*, 1979.
[20] (a) Rubén, M. C.; Ramírez, M. A.; Rodríguez, M. L.; Bermejo, J.; Martín, V. S.; Pardón, J. I. *Org. Lett.* **2006**, *8*, 3837. (b) Miranda, P. O.; Rubén, M. C.; Martín, V. S.; Pardón, J. I. *Org. Lett.* **2009**, *11*, 357.
[21] (a) Miranda, P. O.; Ramírez, M. A.; Pardón, J. I.; Martín, V. S. *Tetrahedron. Lett.* **2006**, *47*, 283. (b) Miranda, P. O.; Díaz, D. D.; Pardón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57.



Scheme 3.9 Reaction mechanism of secondary homopropargylic alcohols with aldehydes

This problem could be effectively solved by modifying the propargylic alcohol with substituents installed either at the end of the triple bond or α to the hydroxy functionality, which serve to suppress the undesired oxonia-Cope rearrangement either by stabilizing the vinyl carbocation intermediate or destabilizing the allenic species (after rearrangement in theory).[22] Subsequently, an efficient approach was developed to generate Prins products from TMS-substituted secondary homopropargylic alcohols in excellent yields and stereoselctivity (Scheme 3.10).



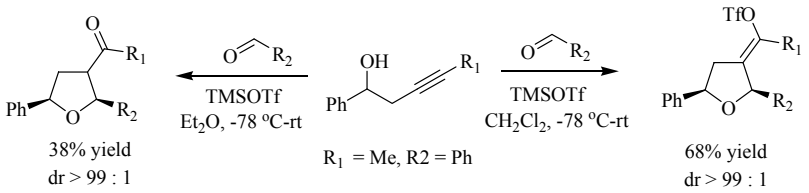
R1 , R2 , R3 = Alkyl or aryl
X = Cl or Br

55 - 82% yields
dr > 99 : 1

Scheme 3.10 Prins cyclization of silyl-homopropargylic alcohols with aldehydes.

Interestingly, when the homopropargylic alcohol was terminated with alkyl or aryl substituents on its triple bond, the regioselectivity in the Prins cyclization was switched from the normally preferred 6-*endo* type to an exclusive 5-*exo* cyclization mode, offering a novel approach to construct substituted tetrahydrofurans.[23]

[22] (a) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Pardón, J. I. *Chem. Eur. J.* **2008**, *14*, 6260. (b) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Pardón, J. I. *Org. Lett.* **2006**, *8*, 1633.
[23] (a) Chavre, S. N.; Choo, H.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S. *Org. Lett.* **2006**, *8*, 3617. (b) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *J. Org. Chem.* **2008**, *73*, 7467.



Scheme 3.11 5-*exo*-Prins cyclization of homopropargylic alcohols to tetrahydrofurans

3.2 CASCADE REACTION TO MAKE POLYCYCLIC FRAMEWORKS

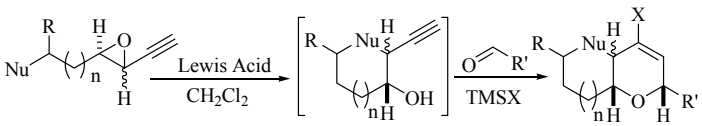
Cascade reactions become more and more appealing to synthetic chemists due to their intrinsic efficiency and elegance in building up molecular complexities, where the concurrent formation of multiple bonds and installation of multiple stereogenic centers usually occur in a highly chemo-, regio- and stereoselective manner from simple linear precursors, exhibiting numerous other impressive advantages, including atom, labor and time economy as well as less waste generation.[24] It still remains a challenge for synthetic chemists to design and tailor substrates properly in order to enable them to undergo various chemical transformations to afford polycyclic frameworks in a diastereoselective cascade manner. Importantly, sophisticated substrate design is essential to discover new cascade reactions, and the successful executions of these cascade reactions have been elegantly demonstrated in the total synthesis of numerous natural products, such as (-)-FR-182877 and dihydroprotodaphniphyline.[25]

To our knowledge, we found that Prins cascade reactions prove to be highly efficient in generating important intermediates in a highly regio- and stereoselective

[24] (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (b)Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

[25] (a) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (b) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393. (c) Heathcock, C. H. Proc. *Natl. Acad. Sci. USA* **1996**, *93*, 14323. (d) Vilotijevic, I.; Jamison, T. F. *Science* **2007** *317* 1189.

way, which are of great importance in synthetic practice.[26] With our understanding towards Prins cyclization,[27a, b] we envisioned that cyclic propargylic alcohols would be viable substrates for Prins cyclization, which could be generated *in situ* from linear propargylic epoxide *via* an intramolecular epoxide-opening-addition reaction (Scheme 3.12).[27c,d, 30b] We also felt that by tuning the chain and the terminal nucleophile, this cascade Prins reaction would serve as a potentially useful methodology in the synthetic study towards polycyclic ethers, which are frequently occurring structural elements found in numerous marine natural products having important biological activities.[28]



Scheme 3.12 Proposed Prins cascade reaction to polycyclic substituted dihydropyrans.

In our preliminary investigation towards this Prins cascade reaction, a bezene ring was selected as the terminal nucleophile for ease of handling. In this chapter, we report our newly developed Friedel-Crafts-Prins (**FCP**) cascade reaction as a convergent and efficient approach to generate complex polycyclic substituted dihydropyrans and furans by condensation of the linear propargylic epoxides with various aldehydes in the presence of Lewis acids.

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[26] For Prins cascade processes see, (a) Kopechy, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (b) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163. (c) Bolla, M. L.; Patterson, B.; Rychnovshy, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 16044. (d) Epstein, O. L.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 16480. (e) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143. (f) Li, H; Loh, T-P. *J. Am. Chem. Soc.* **2008**, *130*, 7194.

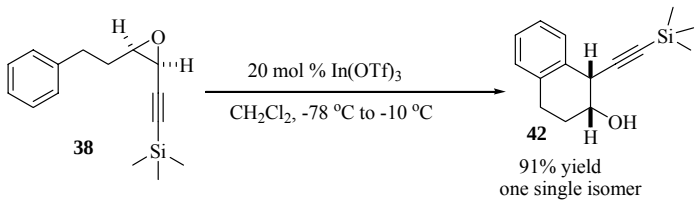
[27] (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387. (b) Liu F.; Loh, T. P. *Org. Lett.* **2007**, *9*, 2063. (c) Restorp, P.; Somfai, P. *Eur.J.Org. Chem.* **2005**, 3946. (d) Taylor, S. K.; Bischoff, D. S.; Blankespoor, C. L.; Deck, P. A.; Harvey, S. M.; Johnson, P. L.; Marolewski, A. E.; Mork, S. W.; Motry, D. H.; Eenenaam, R. V. *J. Org. Chem.* **1990**, *55*, 4202.

[28] (a) Nakata, T. *Chem. Rev*. **2005**, *105*, 4314. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis* Wiley-VCH **1996**. (c) Nicolaou, K. C.; Synder, S. A. *Classics in Total Synthesis II* Wiley-VCH **2003**. (d) Bycroft, B. W. *Dictionary of Antibiotics and Related Substances; Chapman and Hall: London*, **1988**. (e) Faul, M. M.; Huff, B. E. *Chem. Rev*. **2000**, *100*, 2407. (f) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (g) Hirata, Y. *Pure & Appl. Chem.* **1989** *61* 293.

3.3 RESULTS AND DISCUSSION

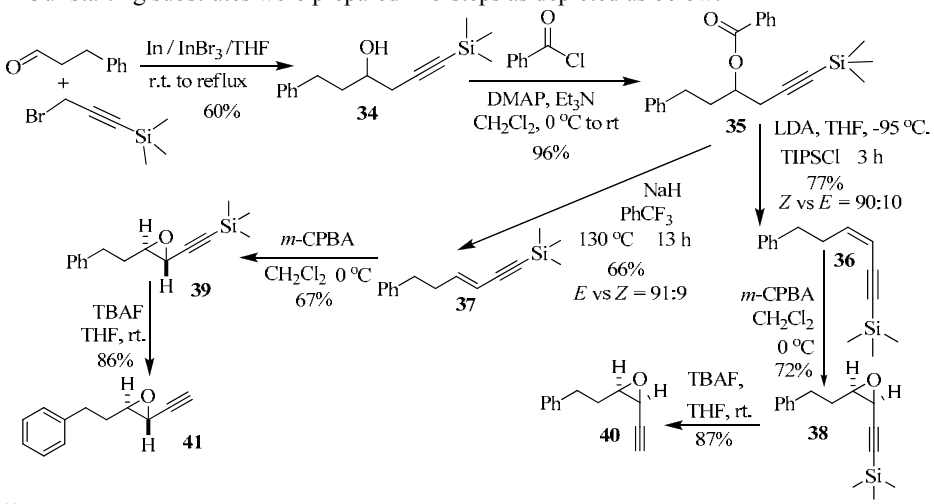
3.3.1 Fiedel-Crafts-Prins Cascade Condensation of *cis*-Propargylic Epoxide

Firstly, the regio- and stereoselectivity was established in the epoxide-opening Friedel-Crafts cyclization for the *cis*-propargylic epoxide **38** (Scheme 3.13).[29] When **38** was treated with indium triflate catalyst, it underwent a regio- and stereoselective Friedel-Crafts cyclization to afford cyclic homopropargylic alcohol **42** in 91% as a single isomer (X-ray structure illustrated in Figure 3.1).[30] The presence of the triple bond dictates this regioselectivity because it facilitates the delocalization of the positive charge during the epoxide-opening cyclization process.[31]



Scheme 3.13 Friedel-Crafts cyclization of *cis* propargylic epoxide.

[29] Our starting substrates were prepared in 5 steps as depicted as below:



[30] (a) Mühlthau, F.; Bach, T. *Synthesis* **2005**, *19*, 3428. (b) Restorp, P.; Somfai, P. *Chem. Commun.* **2004**, 2086.

[31] Nicolaou, K. C.; Prasad, C. V. C.; Somers, R. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

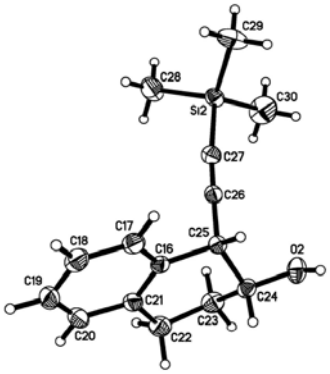


Figure 3.1 X-ray structure of **42**.

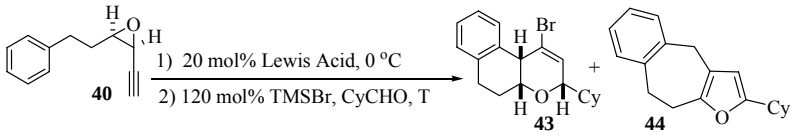
In our initial efforts focused on making the target Prins cyclization products, *cis*-propargylic epoxide **40** was subjected to the stirred suspension of indium triflate catalyst to undergo a Fridel-Crafts cyclization, followed a standard Prins cyclization procedure in the presence of aldehydes using TMSBr as a counterion (Br^-) source.

It turned out rather sluggish for **40** to undergo the planned Friedel-Crafts-Prins cascade condensation with cyclohexanecarboxaldehyde (Table 3.1, entry 1). Target polycyclic dihydropyran **43** was obtained in low yield with unexpected furan **44**. Furan **44** was probably due to the undesirable rearrangement of the cyclic vinyl carbocation **I**,[32] forming the benzylic-allylic-type carbocation **II**, which underwent subsequent hydride shifts and elimination steps to afford the polycyclic furan (Scheme 3.14). We proceeded to optimizing the reaction conditions such as by lowering reaction temperatures in the Prins cyclization step with prolonged reaction time, tuning acidity by changing Lewis acids from robust indium triflate to relatively milder ones (such as indium trifluoroacetate, indium bromide and so on) and even employing the so-called "β-effect" to stabilize the cyclic vinyl carbocation **I** using

[32] For information about rearrangement of cyclic vinyl carbocations see: (a) Pellicciari, R.; Natalini, B.; Sadeghpour, B. M.; Marinozzi, M.; Snyder, J. P.; Williamson, B. L.; Kuethe, J. T.; Padwa, A. *J. Am. Chem. Soc.* **1996**, *118*, 1. (b) Johnson, T. O.; Overman, L. E. *Tetrahedron Lett.* **1991**, *32*, 7361. (c) Chandy, M. J.; Hanack, M. *Tetrahedron Lett.* **1977**, *50*, 4377. (d) Stang, P. J.; Deuber, T. E. *Tetrahedron Lett.* **1977**, *6*, 563.

TMS-terminated epoxide **38**.[33] However, no substantial improvements could be made either in increasing the yields or the selectivity. Only low selectivity and low conversions to the target Prins product could be achieved in spite of our efforts (Table 3.1, entries 2 to 12).

Table 3.1 Lewis acids catalyzed **FCP** cascade condensation of *cis* propargylic epoxide with aldehydes.[a]



Entry	Aicds	Temp (°C)	Product	Yield [b]	Ratio: (43 : 44) [c]
1	$In(OTf)_3$	25	**43**	21%	85:15
2	$In(OTf)_3$	0	**43**	22%	86:14
3	$In(OTf)_3$	-10	**43**	25%	69:31
4	$In(OTf)_3$	-20	**43**	31%	51:49
5	$In(OTf)_3$	-40	**43** [d]	22%	72:28
6	$In(OTf)_3$	-80	**43** [d]	13%	71:29
7	$In(O_2CCF_3)_3$	-20	**43**	15%	76:24
8	$InBr_3$	-20	**43**	25%	34:66
9	TMSOTf	-20	**43**	21%	35:65
10	$TMSNTf_2$	-20	**43**	9%	31:69
11	$BF_3{\cdot}Et_2O$	-20	**43**	16%	53:47
12	$In(OTf)_3$	-20	**43'** [e]	33%	52:48

[a] Epoxide **40** (0.1 mmol) was subjected to stirred suspension of $In(OTf)_3$ (0.02 mmol) in 2 mL CH_2Cl_2 at 0 °C for 4 hours, followed by addition of TMSBr (0.12 mmol) and corresponding aldehyde (0.1 mmol, in 1 mL CH_2Cl_2), and stirred for 6 hours. [b] Isolated yield. [c] Determined by ^{1}H nmr. [d] Reaction time 12 hours for the Prins cyclization step. [e] Structure see X-ray of **43'**, **43'** was obtained when **38** was subjected to the **FCP** reaction conditions.

[33] (a) Sommer, L. H.; Whitemore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 485. (b) Sommer, L. H.; Dofjman, E.; Golberg, G. M.; Whitmore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 488. (c) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83. (d) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. (e) Nguyen, K. A.; Gordon, M. S.; Wang, G.; Lambert, J. B. *Organometallics* **1991**, *10*, 2798.

As illustrated in the X-ray structure of **43'**, ring strain could probably be imposed on the cyclic vinyl carbocation **I**, which makes it unstable and short-lived, thus difficult for trapping with bromide. In contrast, the rearrangement of the cyclic vinyl carbocation **I** into much more stabilized benzylic- allylic-type carbocation **II** becomes a competitive reaction channel. The exact reasons for low yields are not clear. Other factors, such as decomposition, oligomerization and so on, may contribute to the low yields of the target polycyclic dihydropyrans.

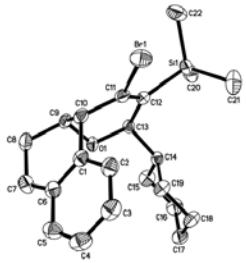
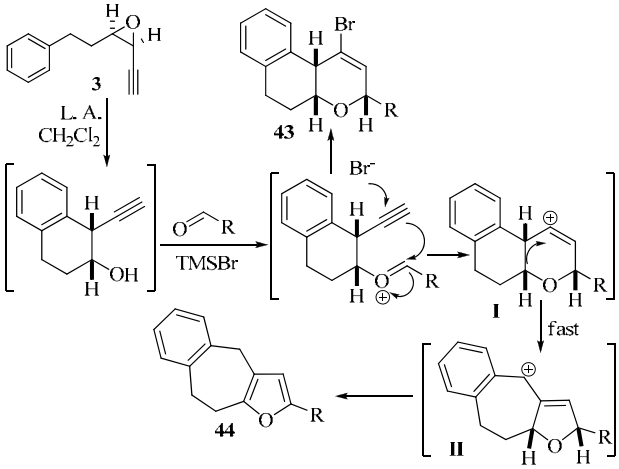


Figure 3.2 X-ray structure of **43'**.

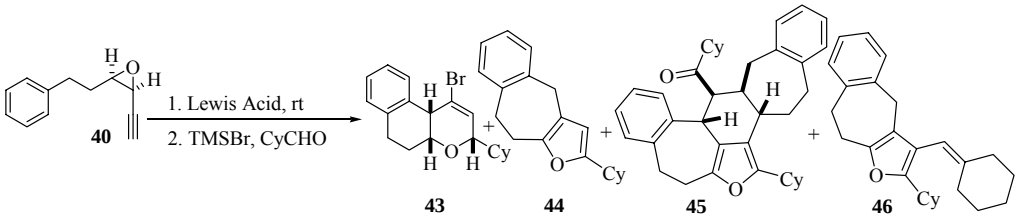


Scheme 3.14 Proposed reaction mechanism of *cis* propargylic epoxide in FCP cascade condensation.

Because substituted furans are also frequently occurring structural moieties in numerous natural products having important biological activities, and also in bulk

commodity chemicals and commercially important pharmaceuticals.[34] We furthered reaction condition screening aiming to develop an efficient method to make polycyclic furans. Various Lewis acids were screened to mediate this condensation. Results are tabulated in Table 3.2.

Table 3.2 Lewis acids mediated **FCP** cascade condensation of *cis* propargylic epoxide with aldehydes.[a]



43 44 45 46

Entry	Aicds	Product	Yield[b]	Ratio: (43:44:45:46)[c]
1	$In(OTf)_3$[d, e]	**44**	7%	0:100:0:0
2	$In(OTf)_3$[e, f]	**44**	28%	0:54:33:13
3	TMSOTf[e, f]	**44**	19%	0:45:0:55
4	$BF_3{\cdot}Et_2O$[e, f]	**44**	31%	0:58:42:0
5	$In(OTf)_3$[g, h]	**44**	21%	37:29:34:0
6	$In(OTf)_3$[f, h]	**44**	63%	<1:99:0:0
7	$In(OTf)_3$[f, i]	**44**	81%	<1:99:0:0

[a] Epoxide **40** (0.1 mmol, in 1 mL CH_2Cl_2) was added to stirred solution of Lewis acid in 1 mL CH_2Cl_2 at room temperature, stirred for 1 hour, followed by addition of corresponding aldehyde (0.1 mmol, in 1 mL CH_2Cl_2) for 2 hours. [b] Isolated yield. [c] Determined ^{1}H NMR. [d] 20 mol % acid used. [e] without using TMSBr. [f] 100 mol % aicd used. [g] 50 mol % acid used. [h] 120 mol % TMSBr used. [i] 200 mol % TMSBr used.

Interestingly, trifluoroborate etherate ($BF_3{\cdot}Et_2O$), TMSOTf and $In(OTf)_3$ were not efficient enough to generate the desired polycyclic furan **44** in high yields (Table 3.2 entries 1 to 4), while a combination of stoichiometric amount of indium triflate

[34] (a) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7. (c) Keay, B. A.; Hopkins, J. M.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Oxford, **2007**; Vol. 3, p 571.

with excess TMSBr was found to efficiently generate the target furans in good yields at room temperature (Table 3.2, entry 7). Satisfactory results from condensation of **40** with various aldehydes are tabulated in Table 3.3. This condensation fails to afford the corresponding furans when using benzaldehyde and cinnamaldehyde. By installing a strong electron-withdrawing substituent on the phenyl ring, we did manage to obtain the corresponding furan in moderate yield (Table 3.3 entry 8). When hydrocinnamadehyde was subjected to this **FCP** reaction, a mixture of novel polycyclic tetrahydrofurans **50** was isolated in 70% yield, as illustrated in Figure 3.5. The reaction could be rationalized as a 5-*exo* type cyclization of the triple bond onto the oxocarbenium followed by a second intramolecular Friedel-Crafts addition to the vinyl carbocation which was generated *in situ* (Scheme 3. 15).

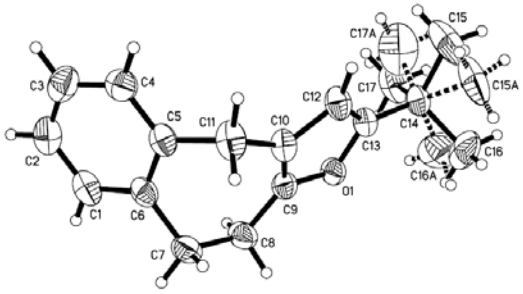


Figure 3.3 X-ray structure of **49**.

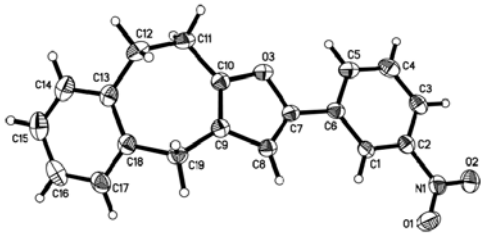


Figure 3.4 X-ray structure of **53**.

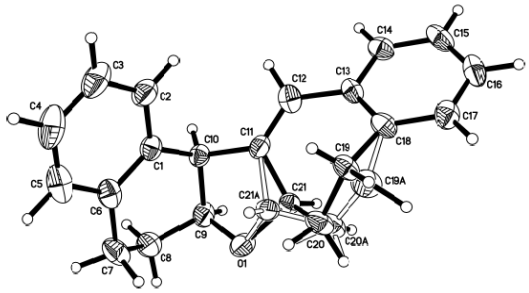
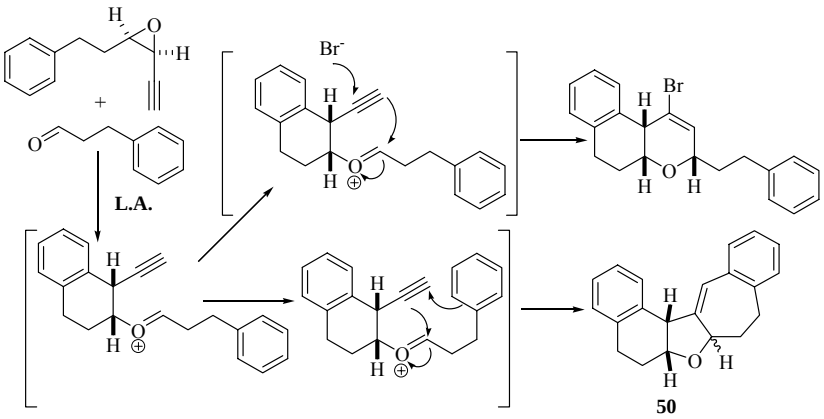
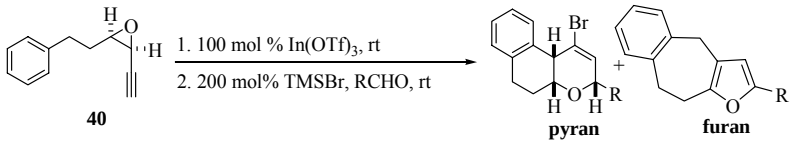


Figure 3.5 X-ray structure of **50**.



Scheme 3.15 Proposed formation mechanism of **50** *via* **FCP** cascade reaction.

Table 3.3 $In(OTf)_3$-mediated **FCP** cascade condensation of *cis* propargylic epoxide with aldehydes.



Entry	R	Product	Yield[a]	Ratio: (pyran:furan)[b]
1	Cy-	**44**[c]	81%	<1:99
2	$CH_3(CH_2)_7$-	**47**	73%	3:97
3	$(CH_3CH_2)_2CH$-	**48**	91%	<1:99
4	$(CH_3)_3C$-	**49**[d]	64%	10:90
5	$PhCH_2CH_2$-	**50**[d]	70%	16:84
6	$PhCH_2$-	**51**	55%	30:70
7	Ph-	**52**	-	-
8	*m*-NO_2-Ph-	**53**[d]	63%	<1:99
9	PhCHCH-	**54**	-	-
10	*m*-NO_2- PhCHCH-	**55**	-	-

[a] Isolated yield. [b] Determined ^1H NMR. [c] Epoxide **40** (0.1 mmol) was subjected to stirred suspension of $In(OTf)_3$ (0.1 mmol) in 2 mL CH_2Cl_2 at rt for 1 hour, followed by addition of TMSBr (0.2 mmol) and corresponding aldehyde (0.1 mmol, in 1 mL CH_2Cl_2) for 2 hours. [d] X-ray structure obtained.

Interestingly, in our screening of Lewis acids to generate polycyclic furans, a [3+3]-type annulation product **45** was isolated as a single isomer with amazing molecular complexity when using stoichiometirc amount of trifluoroborate etherate ($BF_3{\cdot}Et_2O$). A certain amount of **45** could also be observed when excess indium triflate was used to mediate this condensation (Table 3.2, entries 2 and 5). The structure of **45** was established form the X-ray structure of **56** (isolated in 18% yield as a single isomer) when 2-ethylbutyraldehyde was used to run this annulation reaction.

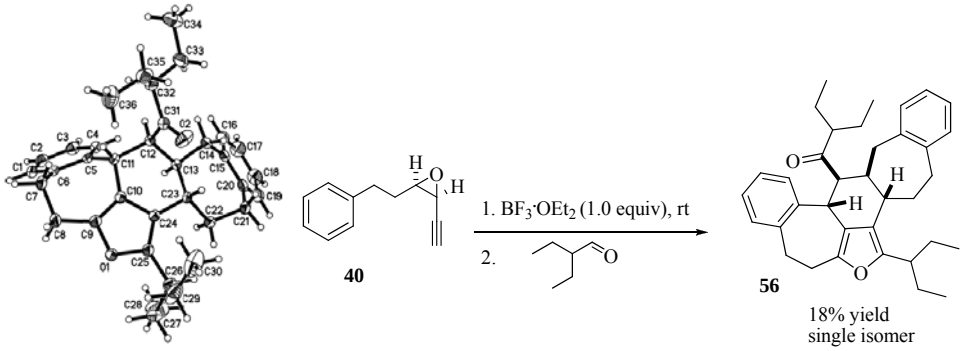
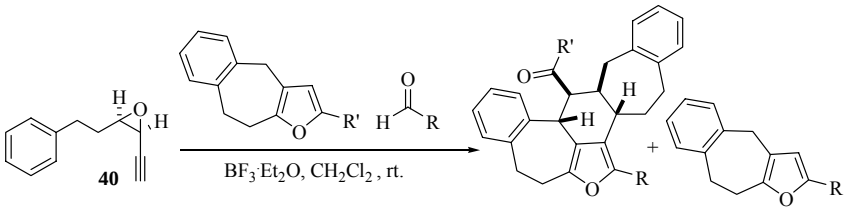


Figure 3.6 X-ray structure of **56**.

Upon closer examination, we infer that **45** could have originated from **44** because the lower part of **45** shared the same structural features. This structural feature prompted us to conceive the reaction mechanism and led us to believe that transient cyclic vinyl carbocation **I** and the benzylic-allylic type carbocation **II** played a central role in the whole cascade process (Scheme 3.14).

We envisage that at a certain threshold after initial generation of **44**, reaction intermediate **II** (Scheme 3.14) was trapped by **44** and finally converted to **45** after subsequent transformations, such as multiple hydride shift and aromatization process. In order to confirm our hypothesis, we designed a reaction approach to make crossed

[3+3] annulation products with different terminal substituents (Scheme 3.16). In this design, we planned to use the parent polycyclic furan that was preformed from a different aldehyde (R'CHO), to trap the reaction intermediate **II** generated *in situ* from the condensation of starting *cis*-epoxide **40** with aldehyde RCHO. If the desired crossed [3+3] annulation product could be formed as expected, we would then be able to give a plausible interpretation towards our **FCP** cascade reaction at a mechanistic level, which is quite important to obtain a thorough understanding towards this **FCP** cascade reaction.



Scheme 3.16 Designed crossed [3+3] annulation *via* Friedel-Crafts-Prins cascade approach.

Gratifyingly, our daring interpretation was verified by our success to make desired crossed [3+3] annulation products **57-60**. Results are shown in Table 3.4.

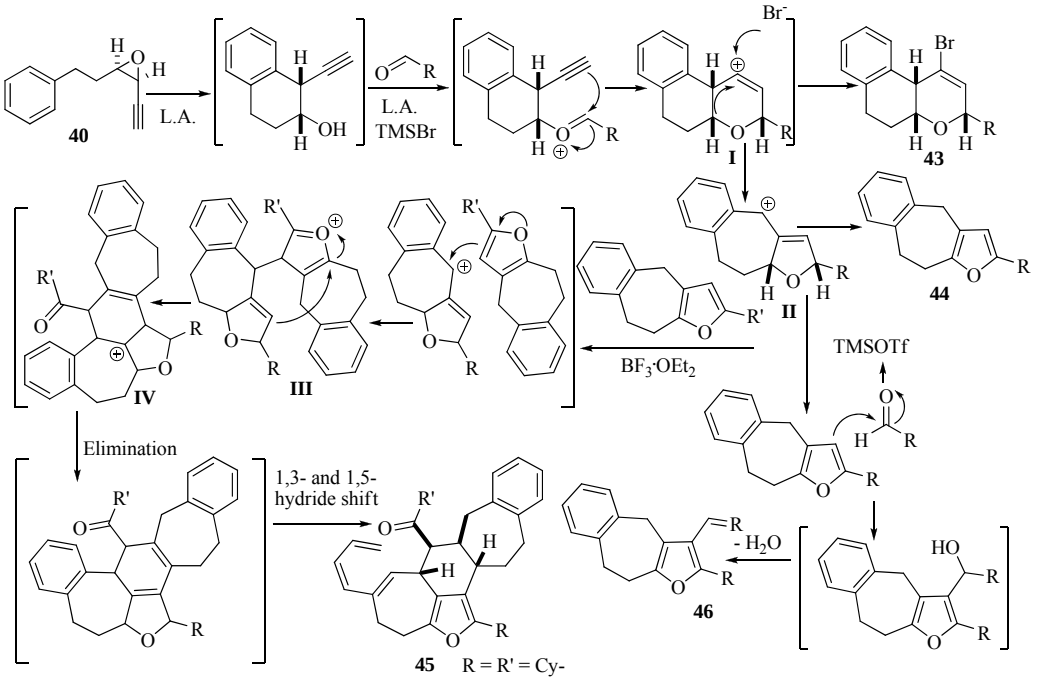
Table 3.4 $BF_3{\cdot}Et_2O$-mediated **FCP** cascade condensation to crossed [3+3] annulated furans.

Entry	R	R'	Product	Yield[a]
1	$CH_3(CH_2)_7$-	$(CH_3CH_2)_2CH$-	**57**	47%
2	$(CH_3CH_2)_2CH$-	Cy-	**58**	40%
3	*Cy*-	$(CH_3CH_2)_2CH$-	**59**	42%
4	$(CH_3CH_2)_2CH$-	$(CH_3)_3C$-	**60**	35%

[a] Isolated yield. [b] Epoxide **40** (0.1 mmol) was treated with $BF_3{\cdot}Et_2O$ (0.1 mmol) in CH_2Cl_2 at room temperature for 1 hour followed by adding the preformed polycyclic pyran (0.1 mmol), and the aldehyde was added slowly over 15 minutes, reaction was allowed to proceed at room temperature for 3 hours before quenching with saturated $NaHCO_3$ solution.

Crossed [3+3] type annulation reveals the reaction mechanism of this Friedel-Crafts-Prins cascade condensation (Scheme 3.17). Cyclic homopropargylic alcohol is

smoothly generated *in situ* as reaction intermediate. In the following Prins cyclization, the distorted configuration of **I** imposes ring strain on **I** that diminishes its stability and its lifespan, thus the difficulty in generating the desired polycyclic dihydropyrans. Instead, rearrangement of **I** to **II** predominates, affording polycyclic furan **44**. At a certain concentration threshold, **44** undergoes an electrophilic addition onto the 3-position of intermediate **II** to afford **III**, followed by a furan ring opening[7] and a Michael-type nucleophilic addition to intermediate **IV**. A highly complicated [3+3] type annulation product **45** was finally generated from intermediate **IV** after undergoing elimination and subsequent 1,3-and 1,5- hydride shifts. Another novel strucutre **46** is believed to be generated from the further Fridel-Crafts addition of **44** to the cyclohexanecarboxaldehyde followed with a dehydration step in the presence of robust TMOTf acid.



Scheme 3.17 Reaction mechansim of **FCP** cascade condensation of *cis* propargylic epoxide.

3.3.2 Friedel-Crafts-Prins Cascade Condensation of *trans*-Propargylic Epoxide

In sharp contrast to the complicated situation of **FCP** cascade condensation of **40**, *trans* propargylic epoxide **41**[29] proves to be a straightforward substrate for this **FCP** cascade condensation to afford target polycyclic pyrans in good yields with excellent stereocontrol. Results are summarized in Table 3.5. Rearrangement of cyclic vinyl carbocation intermediate to furans could be effectively suppressed by running Prins cyclization at -20 ^{o}C (Table 1, entries 1 and 2). This condensation also failed to afford the desired polycylclic pyrans from benzaldehyde and cinnamaldehyde. We managed to make the polycyclic pyran by using *m*-nitro benzaldehyde in good yield (X-ray structure shown in Figure 3.7), where the strongly electron-withdrawing substituent activates the aldehydic functionality (Table 3.5, entry 9). However, no reaction was observed for conjugate aldehydes, including cinnamaldehyde and *p*-nitro-cinnamaldehyde.

We infer that it is probably due to the stability of the intermediate **V,** which allows efficient trapping by bromide anion rather than rearranging to benzylic-allylic type carbocation **II** (Scheme 3.18). In contrast to **I**, rearrangement of **V** to the polycyclic furans could be effectively suppressed by lowering the reaction temperatures (Table 3.5 entry 2).

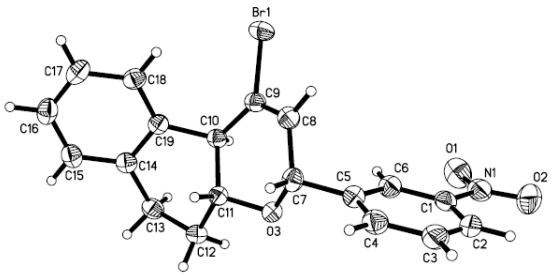
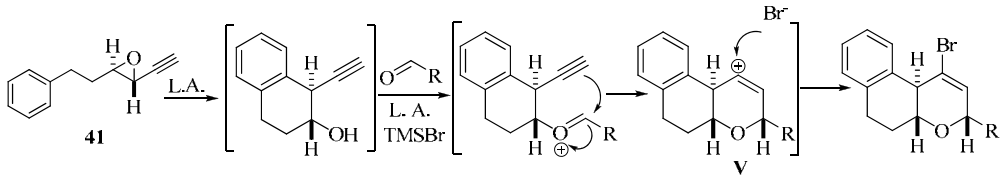
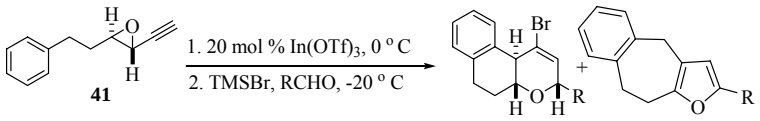


Figure 3.7 X-ray structure of **69**.



Scheme 3.18 Reaction mechansim of **FCP** cascade condensation of *trans* propargylic epoxide.

Table 3.5 $In(OTf)_3$-catalyzed **FCP** cascade condensation of *trans* propargylic epoxide with aldehydes.



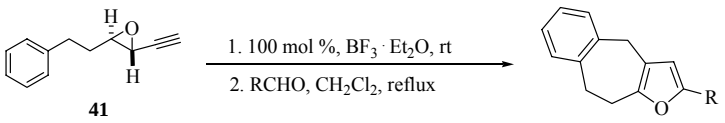
Entry	R	Product	Yield[a]	Ratio: (pyran: furan)[b]
1	Cy-	**61**[c]	83%	96:4
2	Cy-	**62**[d]	87%	> 99:1
3	$CH_3(CH_2)_7$-	**63**	77%	> 99:1
4	$(CH_3CH_2)_2CH$-	**64**	80%	96:4
5	$(CH_3)_3C$-	**65**	89%	97:3
6	$PhCH_2CH_2$-	**66**	83%	> 99:1
7	$PhCH_2$-	**67**	69%	> 99:1
8	Ph-	**68**	-	-
9	*m*-NO_2-Ph-	**69**[e]	75%	> 99:1
10	PhCHCH-	**70**	-	-
11	*m*-NO_2-PhCHCH-	**71**	-	-

[a] Isolated yield. [b] Determined ^1H NMR. [c] Reaction performed all at 0 °C. [d] Epoxide **41** (0.1 mmol) was subjected to stirred suspension of $In(OTf)_3$ (0.02 mmol) in 2 mL CH_2Cl_2 at 0 °C for 4 hour, cooled to -20 °C, followed by addition of TMSBr (0.12 mmol) and corresponding aldehyde (0.1 mmol, in 1 mL CH_2Cl_2) for 6 hours. [e] X-ray structure obtained.

Interestingly, polycyclic furans could also be generated from the *trans*-propargylic epoxide **41** by subjecting **41** to harsh reaction conditions, such as higher

reaction temperatures with stoichiometric amount of strong Lewis acid, as illustrated in Table 3.6.

Table 3.6 $BF_3{\cdot}Et_2O$-mediated **FCP** cascade condensation of *trans* propargylic epoxide with aldehydes.



41

Entry	R	Product	Yield[a]
1	Cy-	**44**[b]	47%
2	$(CH_3CH_2)_2CH$-	**48**	77%
3	$(CH_3)_3C$-	**49**	91%
4	$PhCH_2CH_2$-	**50**	-
5	Ph-	**52**	-

[a] Isolated yield. [b] Epoxide **41** (0.1 mmol) was subjected to stirred solution of $BF_3{\cdot}Et_2O$ (0.1mmol) in 2 mL CH_2Cl_2 at rt for 1 hour, followed by addition of the corresponding aldehyde (0.1 mmol, in 1 mL CH_2Cl_2), reflux for 2 hours.

3.4 CONCLUSION

In conclusion, a novel Lewis acid catalyzed (mediated) Friedel-Crafts-Prins cascade condensation reaction of propargylic epoxides with various aldehydes has been developed which allows us to make a series of complex polycyclic dihydropyrans and polycyclic furans in a convergent and efficient manner. This Friedel-Crafts-Prins cascade condensation shows the following main features: (1) the π-orbital on the triple bond assists the regioselective epoxide-opening Friedel-Crafts cyclization reaction, (2) relative stereochemistry of the propargylic epoxide controls the stereochemical outcome of the intermediate cyclic homopropargylic alcohol; (3) Prins cyclization affords the desired polycyclic substituted dihydropyrans as a single

diastereoisomer from *trans*-propargylic epoxide. However, cyclic vinyl carbocation rearrangement predominated and afforded polycyclic substituted furans as major products from the *cis*-propargylic epoxide.

In addition, this Friedel-Crafts-Prins cascade reaction also provides an excellent occasion for probing reaction mechanisms by controlling reaction conditions. It also offers a clear vision towards the importance of substrates design in discovering new cascade reactions.

CHAPTER 4

Friedel-Crafts-Prins Cascade Condensation of Allylic Epoxides with Aldehydes

4.1 INTRODUCTION

4.1.1 Allylic Epoxide in Organic Synthesis

Allylic epoxide is an important structural moiety observed in many natural products having remarkable biological activities (Figure 4.1). Examples include algal pheromones lamoxirene, caudoxirene, biosynthetic precursor to leukotriene, and macrocyclic lactones.[1]

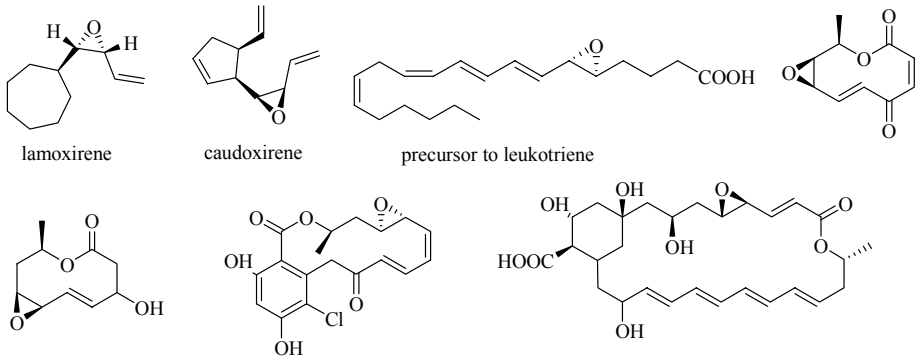
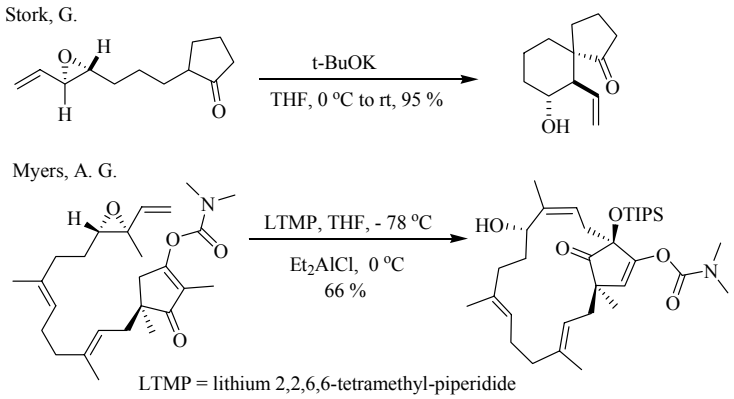


Figure 4.1 Natural products possessing allylic epoxide moiety.

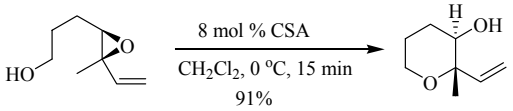
Allylic epoxides are also important intermediates in modern organic synthesis. It is well established that allylic epoxide could be utilized as electrophile in intramolecular carbocyclization reactions with enolate derivatives. The Stork cyclization is a typical demonstration of this strategy to form cyclohexane systems with complete control of regiochemistry and stereochemistry *via* the intramolecular cyclization of allylic epoxide.[2] In addition, this stereocontrolled enolate alkylation reaction found its application in the total synthesis of (-)-terpestacin and (-)-fusaproliferin, although with undesirable stereochemical outcome in terms of the double geometry (Scheme 4.1).[3]

[1] Hertweck, C.; Boland, W. Eur. J. Org. Chem. 1998, 2143 and references cited therein.
[2] Stork, G.; Kobayashi, Y.; Suzuki, T.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *112*, 1661.
[3] Myers, A. G.; Siu, M. *Tetrahedron* **2002**, *58*, 6397.



Scheme 4.1 Regio- and diasteroselective intramolecular carbocyclization of allylic epoxide.

In the synthetic studies towards the total synthesis of Brevetoxin A, Nicolaou[4] developed a novel strategy to construct medium-sized cyclic ether *via* a regio- and diastereoselective intramolecular hydroxy-epoxide-opening cyclization of allylic epoxide (Scheme 4.2). The incorporation of a double bond adjacent to the epoxide function determines the 6-*endo* cyclization mode due to its facilitation of the delocalization of partial positive charge generated *in situ* during the cyclization process. This type of cyclization was also observed by Nakata[5] under acidic or basic conditions, and by Somfai[6] for an internal Friedel-Crafts type addition catalyzed by Lewis acid.

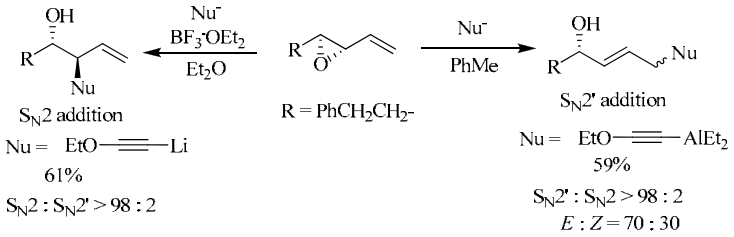


Scheme 4.2 Regio- and diasteroselective intramolecular hydroxy-epoxide-opening cyclization.

On the other hand, the intermolecular version of the nucleophilic addition occurred in a divergent manner, and both S_N2 and S_N2' type adducts could be observed during epoxide-opening. For electronic stabilization reasons, epoxide is

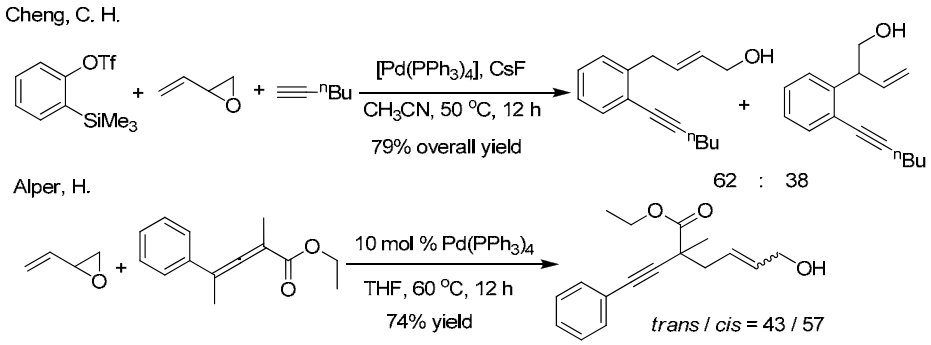
[4] (a) Nicolaou, K. C. Prasad, C. V. C.; Hwang, C. K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Nicolaou, K. C. Prasad, C. V. C.; Somers, P. K.; Hwang, C. K.; *J. Am. Chem. Soc.* **1989**, *111*, 5330.
[5] Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.
[6] (a) Restorp, P.; Somfai, P. *Chem. Commun.* **2004**, 2086 and references cited therein. (b) Restorp, P.; Somfai, P. *Eur. J. Org. Chem.* **2005**, 3946. (c) Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109.

normally cleaved at the allylic position and attacked by hard nucleophiles to afford S_N2 type adduct, while for bulky soft nucleophiles, S_N2' attack is preferred.[6] Regioselective addition could be realized by controlling the reaction conditions, for instance, a combination of lithium ethoxyacetylides and $BF_3{\cdot}OEt_2$ afforded S_N2 displacement, whereas S_N2'addition predominated when alkynylalanes was utilized (Scheme 4.3).[6]



Scheme 4.3 Regio-selective and divergent epoxide-opening of allylic epoxide with nucleophiles.

Allylic epoxides also serve as excellent electrophiles in transition metal-catalyzed carbon-carbon coupling reactions, such as palladium-catalyzed alkylation and arylation of allylic epxides with various nucleophiles (Scheme 4.4).[7]

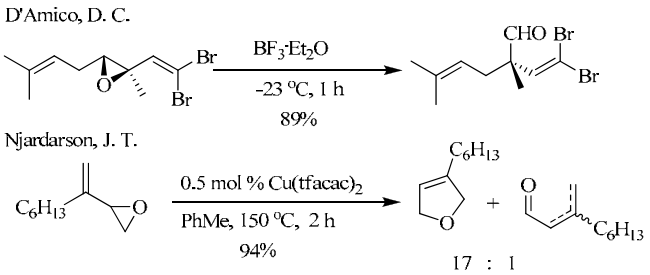


Scheme 4.4 Palladium-catalyzed coupling reaction of allylic epoxide with nucleophiles.

In addition, Lewis acid-catalyzed stereospecific rearrangement of optically pure tertiary allylic epoxides offers a rapid access to chiral quaternary aldehydes, which are important precursors for the synthesis of biologically active compounds,

[7] (a) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 391. (b) Nanayakkara, P.; Alper, H. *J. Org. Chem.* **2004**, *69*, 4686.

such as α-alkyl amino aldehydes and acids (Scheme 4.5).[8] Recently, Njardarson[9] described a novel method to synthesize a series of 3,4-dihydrofurans *via* copper(II) complex-catalyzed rearrangement of allylic epoxides, which is elegant and appealing due to the low catalyst loading, broad tolerance of substitution patterns and solvent-free manner.



Scheme 4.5 Rearrangement of allylic epoxides to novel structures.

4.1.2 Fused Bicyclic and Polycyclic Tetrahydropryan Systems

Substituted tetrahydropyran rings are ubiquitous structural features frequently encountered in numerous natural products possessing potent biological activities.[10] Both *cis*- and *trans*-fused bicyclic or polycyclic tetrahydropyran ring systems are also frequently occurring in a wide range of biologically active natural products, such as (3*Z*)-dactomelyne, (3*E*)-dactomelyne,[11] thyrsiferol,[12] okadaic acid,[13] and so on[14]

[8] Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379.
[9] Batory, L. A.; Mclnnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 16054.
[10] (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis* Wiley-VCH **1996**. (b) Nicolaou, K. C.; Synder, S. A. *Classics in Total Synthesis II* Wiley-VCH **2003**. (c) Bycroft, B. W. *Dictionary of Antibiotics and Related Substrates*; Chapman and Hall: London, 1988.
[11] Isolation of (3*Z*)-dactomelyne, (3*E*)-dactomelyne see: Gopichand, Y.; Schmitz, F. J.; Shelly, J.; Rahman, A.; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 5192. synthetic stydies towards (3*Z*)-dactomelyne, (3*E*)-dactomelyne see: (a) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017. (b) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863. (c) Hoffmann, R. W.; Münster, I. *Tetrahedron. Lett.* **1995**, *36*, 1431.
[12] Isolation of thyrsiferol see: Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C. *Tetrahedron. Lett.* **1978**, 69. synthetic stydies towards thyrsiferol see: (a) González, I. C.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 319. (b) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099. (c) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088. (d) Broka, C. A.; Lin, Y. T. *J. Org. Chem.* **1988**, *53*, 5876. (e) Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H.; Matsumoto, T.; Kanagawa, H. *Tetrahedron. Lett.* **1987**, *28*, 5665.
[13] Markó, E. I.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899 and references cited therein.

(Figure 4.2). Considerable efforts have been stimulated in the synthetic community, and many elegant methods have been devised towards synthesis of these challenging structures.[11-14] However, most of these syntheses rely on iterative or reiterative strategies in which one cyclic tetrahydropyran ring is constructed over a series of chemical transformations in a stepwise manner. [11-14, 15]

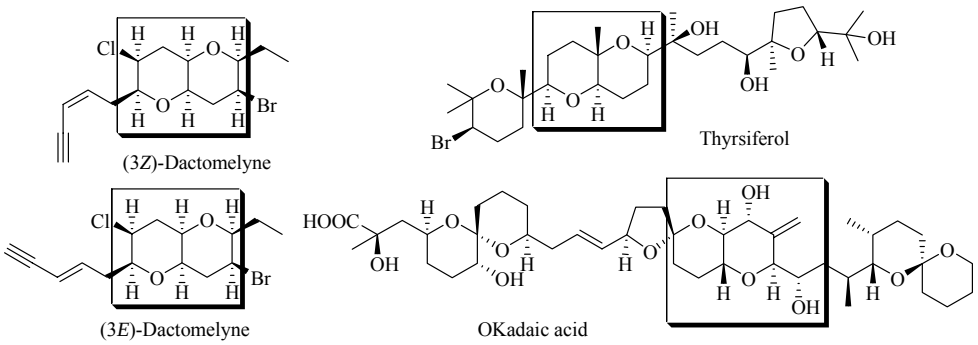
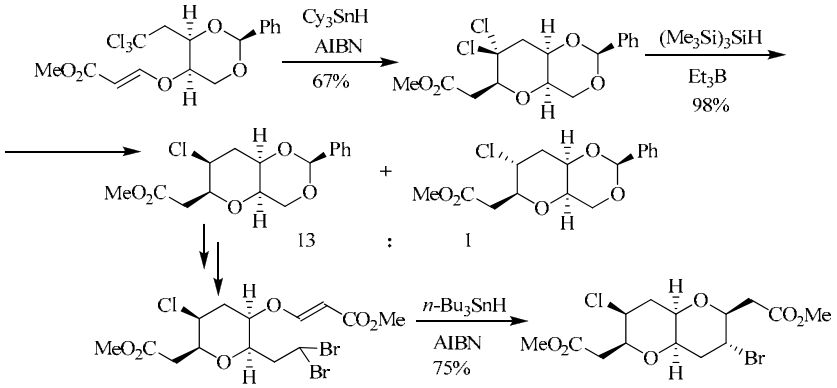


Figure 4.2 Natural products possessing bicyclic tetrahydropyran rings.

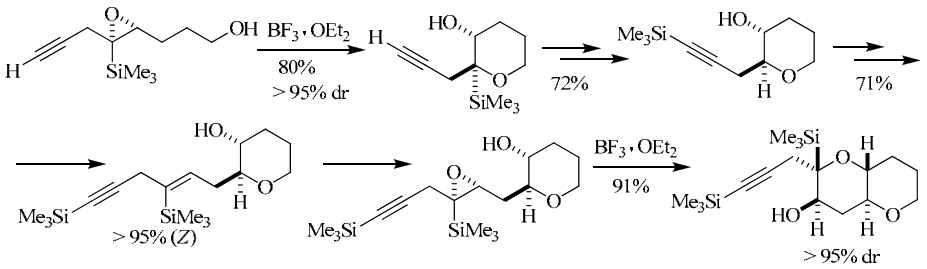
An iterative radical cyclization strategy was adopted to form the *cis*-fused bicyclic tetrahydronpyran ring skeleton in the total synthesis of marine natural prouduct, (3*Z*) and (3*E*)-dactomelyne.[16] Lee[11] developed a highly stereoselective radical cyclization using the β-alkoxyacrylates twice as radical acceptors for the introduction of alkyl and halogen substituents onto the pyranopyran ring system (Scheme 4.6).



Scheme 4.6 Double radical cyclization of β-alkoxycarylates to *cis*-fused bicyclic THP ring skeleton.

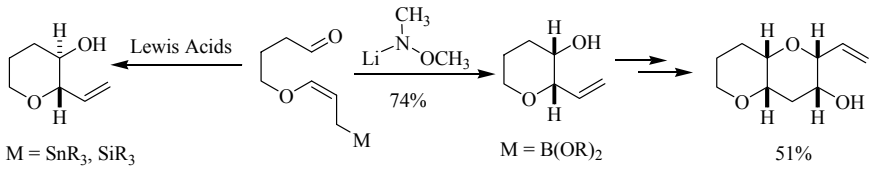
[14] Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
[15] Nakata, T. *Chem. Rev*. **2005**, *105*, 4314. (b)
[16] Koert, U. *Angew. Chem. Int. Ed.* **1996**, *35*, 405.

Similarly, bicyclic and polycyclic tetrahdropyran ring systems could also be generated through iterative 6-*endo*-mode hydroxy-epoxide-opening cyclization with the assistance of π-orbital (Scheme 4.3)[4] or TMS substituent (Scheme 4.7).[17] Such strategy proves to be quite effective for formation of the bicyclic THP skeleton in the total synthesis of thyrisferol and its anologues.[18]



Scheme 4.7 TMS assisted homologation-epoxidation-cyclization to ladder THP ring skeleton.

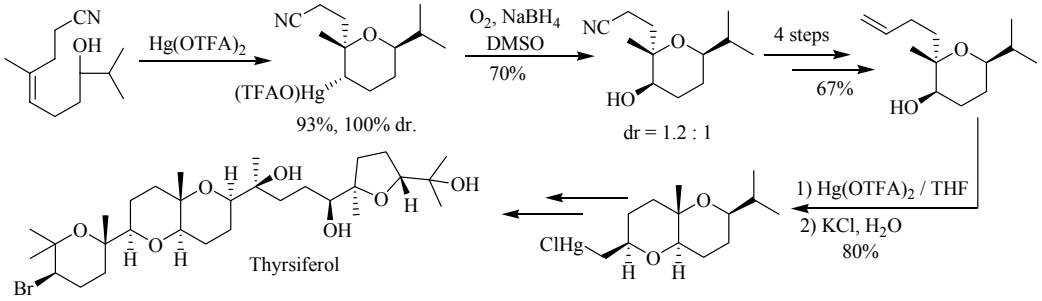
By controlling the reaction conditions, the intramolecular allylation of internal aldehyde with allylstannanes, [19] allylsilanes, [20] and alkoxyallylboranates [21] also constitute one effective approach to selectively form both *cis*- and *trans*-linked bicyclic- and tricyclic- tetrahydropyran rings (Scheme 4.8).



Scheme 4.8 Intramolecular allylation of internal aldhyde with allylmetals.

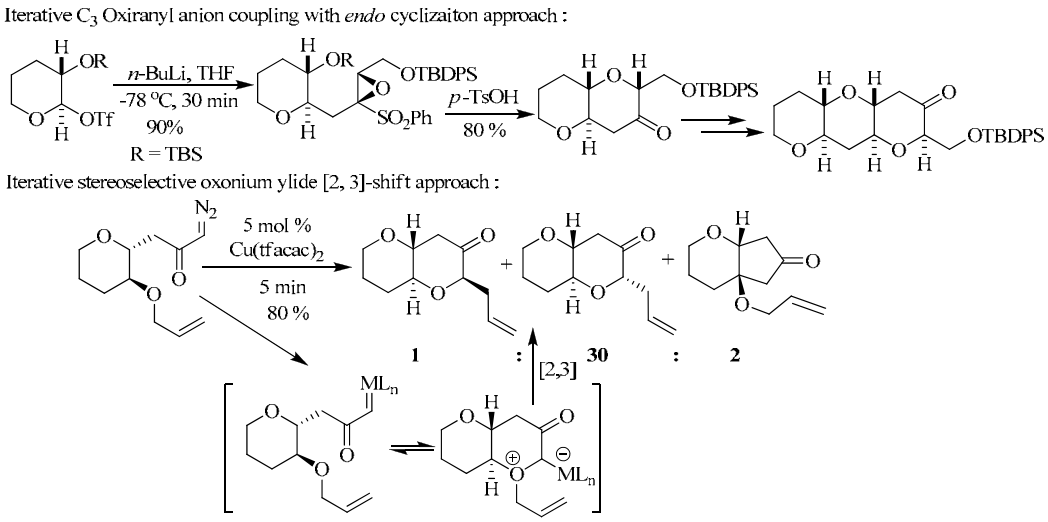
[17] Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339.
[18] Gonzaléz, I. C.; F. G.; Forsyth, *J. Am. Chem. Soc.* **2000**, *122*, 9099. (b)
[19] (a) Yamada, J.; Asano, T.; Kadota, M.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 6066. (b) Gevorgyan, V.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett*. **1993**, *34*, 1313.
[20] (a) Suzi, T.; Sato, O.; Hirama, M.; Yamamoto, Y.; Murata, M.; Yamamoto, T.; Harada, N. *Tetrahedron Lett*. **1991**, *32*, 4505. (b) Kadota, I.; Gevorgyan, V.; Yamada, J.; Yamamoto, Y. *SynLett* **1991**, 823. (c) Yamamoto, Y.; Yamada, J.; Kadota, I. *Tetrahedron Lett*. **1991**, *32*, 7069. (d) Ravelo, J. L.; Regueiro. A.; Martín, J. D. *Tetrahedron Lett*. **1992**, *33*, 3389. (e) Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848.
[21] Hoffmann, R. W.; Münster, I. *Tetrahedron Lett*. **1995**, *36*, 1431.

Another approach is the intramolecular Michael-addition of an alcohol to an internal α,β-unsaturated ester[22] or stereoselective mercuricyclization of hydroxyl group onto an internal double bond (Scheme 4.9).[23]



Scheme 4.9 Double iterative intramolecular stereoselective mercuricyclization.

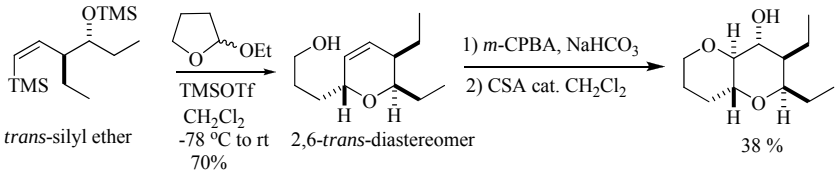
Some other type iterative approaches to *trans*-fused THP ring systems have also been reported, including the reiterative coupling reaction of C_3 oxiranyl anion followed with a 6-*endo* cyclization,[24] or through stereoselective generation and rearrangement of cyclic oxonium ylide [2,3]-shift in an iterative manner (Scheme 4.10).[25]



Scheme 4.10 Iterative oxiranyl anion coupling-cyclization and oxonium ylide [2,3]-shift approaches.

[22] (a) Cooper, A. J.; Salomon, R. G. *Tetrahedron Lett.* **1990**, *31*, 3813. (b) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1459. (C) Martín, V. S.; Palazón, J. M. *Tetrahedron Lett.* **1992**, *33*, 2399. (d) Gung, B. W.; Francis, M. B. *J. Org. Chem.* **1993**, *58*, 6177. (e) Kozikiwski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863.
[23] Broka, C. A.; Lin, Y. T. *J. Org. Chem.* **1988**, *53*, 5876.
[24] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158.
[25] Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144.

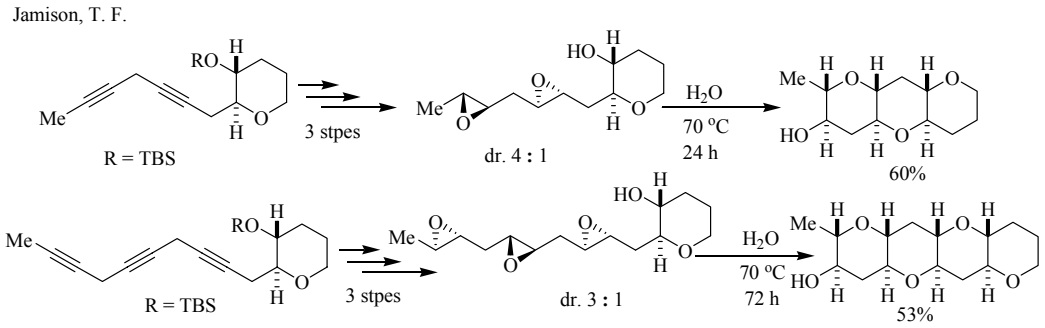
Importantly, *trans*-fused bicyclic THP ring skeleton could also be formed *via* the intramolecular sily-modified Sakurai condensation (ISMS) of vinylsilanes followed with further elaborations (epoxidation and cyclization) in a stepwise manner (Scheme 4.11).[26]



Scheme 4.11 Iterative intramolecular silyl-modified Sakurai condensation of vinylsilane.

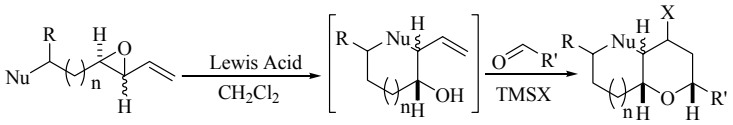
Despite the effectiveness and elegance of these iterative approaches to such bicyclic and polycyclic *cis*- or *trans*-fused tetrahydropyran ring systems, interest and demand for novel and facile methods for rapid access to these motifs remain unabated.[27] Cascade epoxide-opening cyclization reaction is of great superiority as compared to those iterative approaches because of its intrinsic efficiency and elegance in rapidly building up the polycyclic tetrahydropyran frameworks with high regio- and stereoselectivities. Jamison described a highly elegant biomimic synthesis of ladder ether ring skeleton *via* an epoxide-opening cyclization cascade using water as both the solvent and promoter (Scheme 4.12).[26b]

[26] Markó, E. I.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899.
[27] (a) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. (b) Vilotijevic, I.; Jamison, T. F. *Science*, *2007*, 317, 1189. (c) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. (d) Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050.



Scheme 4.12 Regio- and stereoselective cascade epoxide-opening cyclization approach to *trans*-fused polycyclic THP ring frameworks.

It is self-evident that cascade reaction exhibits appealing advantages for construction of polycyclic tetrahydropyrans, which is highly impressive to synthetic chemists. In our group a long-lasting interest has been ongoing towards the development of novel methodologies for the synthesis of various THP-containing compounds. Our previous studies revealed that linear homoallylic alcohols are excellent substrates to undergo Prins cyclization with various aldehydes to afford 2,6-*cis*-4-halo-trisubstituted tetrahydropyrans in a highly stereoselective manner.[28] We envisaged that cyclic homoallylic alcohols should also be excellent substrates to undergo Prins cylization with aldehydes. We also felt that it would be a facile and rapid approach to make bicyclic THP ring system in one-pot manner: Lewis acid catalyzed epoxide-opening cyclization to generate the cyclic homoallylic alcohol *in situ*, followed with a Prins cyclization operation to construct the second THP (Scheme 4.13).



Scheme 4.13 Proposed Prins cascade reaction to bicyclic THP rings.

[28] (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387-8390. (b) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491-4494. (c) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939-941. (d) Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, *48*, 37.

In this chapter, we report our novel, efficient and convergent indium triflate catalyzed Friedel-Crafts-Prins (**FCP**) cascade condensation of allylic epoxides with aldehydes to construct complex polycyclic tetrahydropyran rings in a rigio- and stereoselective manner. Both *cis*- and *trans*-allylic epoxides terminated with phenyl ring were prepared as our starting materials for this **FCP** cascade reaction.[29]

4.2 RESULTS AND DISCUSSION

4.2.1 Friedel-Crafts-Prins Cascade Condensation of *cis*-Allylic Epoxide

In the beginning, *cis*-allylic epoxide **72** was first selected to test our designed **FCP** cascade reaction. Epoxide **72** was subjected to the vigorously stirred suspension of indium triflate catalyst in dichloromethane at 0 ^{o}C for 2 hours to generate the reaction intermediate (cyclic homoallylic alcohol) *in situ* through a epoxide-opening Friedel-Crafts cyclization, followed with addition of the additive TMSBr and the corresponding aldehydes to undergo the Prins cyclization reaction. To our delight, this **FCP** cascade reaction proceeded smoothly in a highly efficient and stereoselective manner to afford our desired polycyclic tetrahydropyran in good yield as a single diastereoisomer. Results are tabulated in Table 4.1. The stereochemistry was determined and further confirmed by the X-ray crystal structure of **80** (Figure 4.3), with all stereogenic centers installed as expected.

[29] Our starting materials, *cis*- and *trans*-allylic epoxides were prepared from the corresponding propargylic epoxides, respectively.

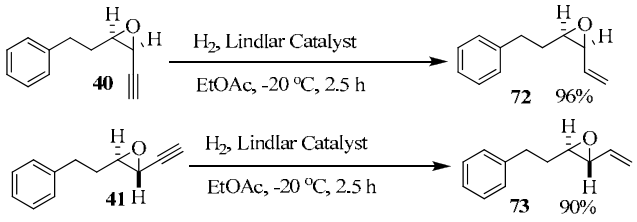
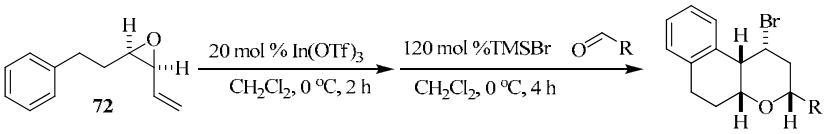
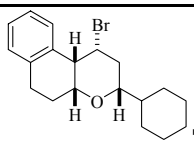
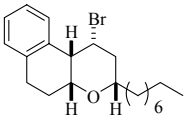
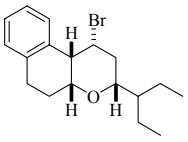
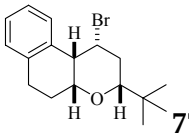
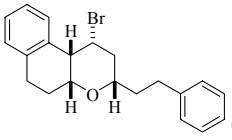
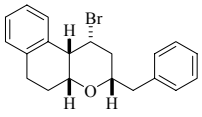
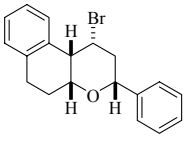
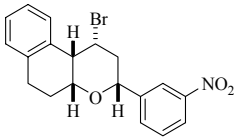


Table 4.1 $In(OTf)_3$-catalyzed Friedel-Crafts-Prins cyclization of *cis* allylic epoixde with aldehydes.



72

Entry	RCHO	product	yield (%)[a]
1	-Cy	 **74**	91
2	$-(CH2)_7CH_3$	 **75**	84
3	$-CH(CH_2CH_3)_2$	 **76**	85
4	$-C(CH_3)_3$	 **77**	72
5	$-CH_2CH_2Ph$	 **78**	80
6	$-CH_2Ph$	 **79**	63
7	-Ph	 **80**	70[b]
8	-*m*-NO_2-Ph	 **81**	84

[a] isolated yield. [b] X-ray structure obtained.

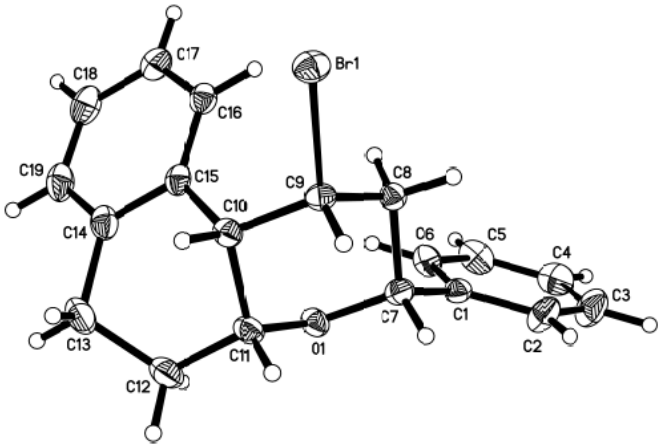
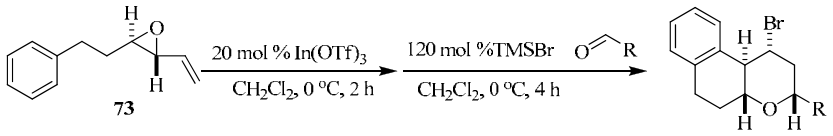


Figure 4.3 X-ray structure of **80**.

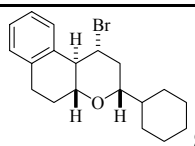
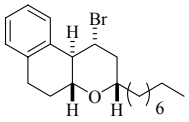
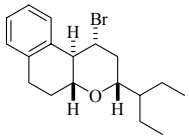
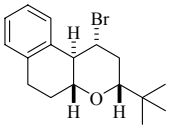
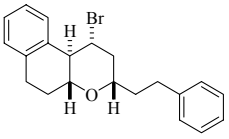
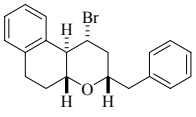
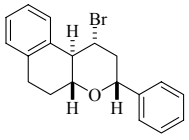
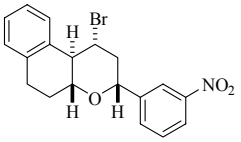
4.2.2 Friedel-Crafts-Prins Cascade Condensation of *trans*-Allylic Epoxide

With the exciting results obtained from our **FCP** cascade condensation of *cis*-allylic epoxide **72** with various aldehydes, we moved to run this condensation using *trans*-isomer **73** under the same sequential reaction conditions. Epoxide **73** was converted to the *trans* cyclic homoallylic alchol upon treatment with indium triflate catalyst, and the target condensation products were formed smoothly after the subsequent Prins cyclization reaction in the presence of slightly excess TMSBr as counterion (Br^-) source. As expected, *trans*-isomer **73** proved to be an excellent substrate for this **FCP** cascade condensation. Desired polycyclic tetrahydropyrans could be synthesized through this cascade condensation in good yields as a single isomer, whose stereochemistry was clearly illustrated in the X-ray crystal structure of **85** (Figure 4.4). Results are summarized in Table 4.2.

Table 4.2 $In(OTf)_3$-catalyzed Friedel-Crafts-Prins cyclization of *trans* allylic epoixde with aldehydes.



73

Entry	RCHO	product	yield (%)[a]
1	-Cy	 **82**	83
2	$-(CH2)_7CH_3$	 **83**	81
3	$-CH(CH_2CH_3)_2$	 **84**	85
4	$-C(CH_3)_3$	 **85**	75 [b]
5	$-CH_2CH_2Ph$	 **86**	76
6	$-CH_2Ph$	 **87**	70
7	-Ph	 **88**	70
8	$-m-NO_2-Ph$	 **89**	86

[a] isolated yield. [b] X-ray structure obtained.

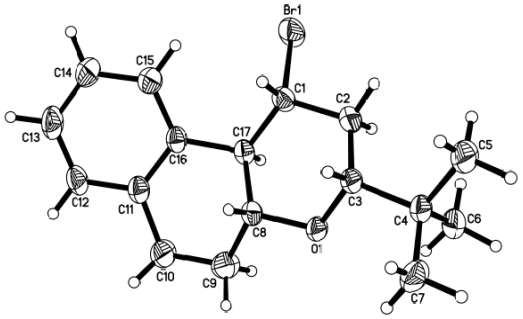
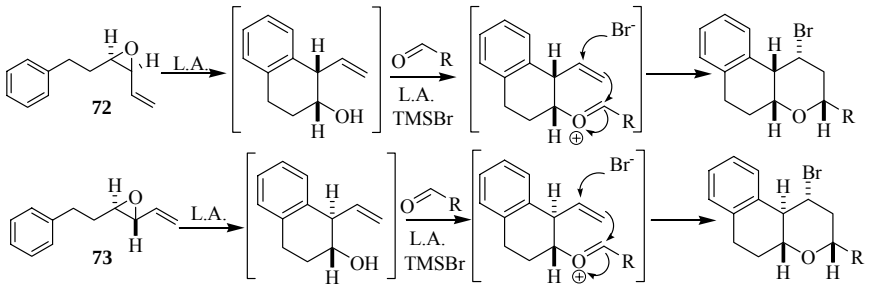


Figure 4.4 Crystal structure of **85**.

4.2.3 Mechanistic Interpretation of Friedel-Crafts-Prins Cascade Condensation of *cis*- and *trans*-Allylic Epoxides

As shown in scheme 4.14, a mechanistic interpretation could be deduced from our experimental results. When treated with the vigorously stirred suspension of indium triflate catalyst in dichloromethane at 0 ^{o}C, allylic epoxides, *cis*-isomer **72** and *trans*-isomer **73** underwent a regio- and stereoselective epoxide-opening-Friedel-Crafts cyclization with the assistance of the π-orbitals on the double bond, and were transformed into the corresponding cyclic homoallylic alcohols respectively. After the introduction of aldehyde and slightly excessive TMSBr as counterion source, Prins cyclization occurred smoothly between the cyclic homoallylic alchols and aldehydes to afford cyclized polycylic tetrahydropyrans with excellent stereocontrol. In each case, only one single diasteroisomer was obtained, as evidenced by the respective X-ray structure (Figure 4.3, and Figure 4.4).

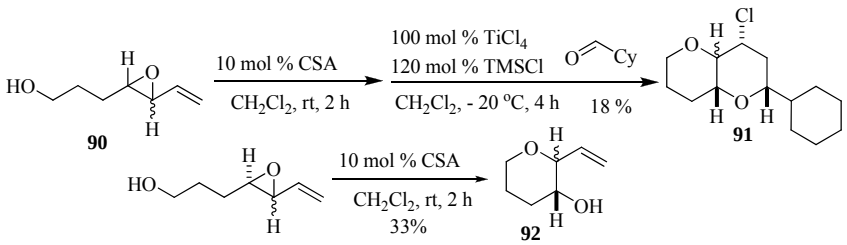


Scheme 4.14 Proposed reaction mechanism of Friedel-Crafts-Prins condensation of *cis*- and *trans*-allylic epoxides with aldehydes.

4.2.4 Prins Cascade Condensation of Allylic Epoxide with Hydroxy Function as Terminal Nucleophile

We also attempted to make bicyclic tetrahydropyrans by utilizing allylic epoxides containing a hydroxyl function as the terminal nucleophile. However, initial results revealed that $In(OTf)_3$, $InBr_3$, TMOTf were not competent catalysts for this cascade reaction, and only partially cyclized product **92** could be isolated in low yields (~ 30%) without any formation of desired bicyclic THP rings.

The reaction still proved quite sluggish even when following a reported method[4] to generate the reaction intermediate **92** *in situ*, followed with a subsequent Prins cyclization step using stoichiometric amount of $TiCl_4$ as promoter, affording target **91** in around 18% yield. Unexpectedly, it was found that the inefficient epoxide-opening cyclization should be responsible for the overall low efficiency of this cascade condensation, where only 33% of **92** could be isolated in a separate operation by treating **90** with camphorsulphonic acid. Our finding towards this low yield problem was consistent with Hoffmann's observations.[11c] Thus, we infer that the Prins cyclization should still be efficient for transforming **92** into the target bicyclic THP ring **91** in an estimated yield of around 60%.



Scheme 4.15 Synthesis of bicyclic THP ring *via* Prins cascade condensation.

4.3 CONCLUSION

In conclusion, we have developed a novel, efficient Friedel-Crafts-Prins cascade condensation reaction of allylic epoxides with various aldehydes catalyzed by indium triflate. The target polycyclic tetrahydropyrans were convergently synthesized from condensation of the corresponding allylic epoxide and aldehydes in a highly regio- and diastereoselective manner.

The main features of this reaction are as follows: (1) the regioselectivity in the epoxide-opening cyclization is assisted by the π-orbitals on the double bond, and the stereochemical outcome of the cyclization was controlled by the starting allylic epoxides; (2) desired polycyclic tetrahydropyrans are formed *via* Prins cyclization in a diastereoselctive manner as a single isomer.

Although our preliminary attempts to apply this reaction to construct the bicyclic THP ring system were unsuccessful due to the substrate problem, this could be overcome by substrate design, because it was revealed that the Prins cascade reaction itself is still an efficient approach with finely tailored substrates. Therefore, this catalytic, diastereoselective Prins cascade condensation reaction is of both academic importance and practical values.

CHAPTER 5

Prins Cyclization of Allenic Alcohols and Synthetic Study towards (+)-Sambutoxin

5.1 INTRODUCTION

5.1.1 Dihydropyran (DHP) Rings in Natural Proudcts

Dihydropyran (DHP) rings are core structural features found in natural products having important biological activities, such as jerangolid A, B, C, and D,[1] funiculosin, [2] (+)-ambruticin, [3] (+)-4,5-deoxyneodolabelline, [4] and methyl sarcophytoate (Figure 5.1).[5] These DHP backbones are attractive targets for synthetic chemists to devise novel methodology aimed at the efficient syntheses of the natural toxins, which are potential pharmaceutical candidates.

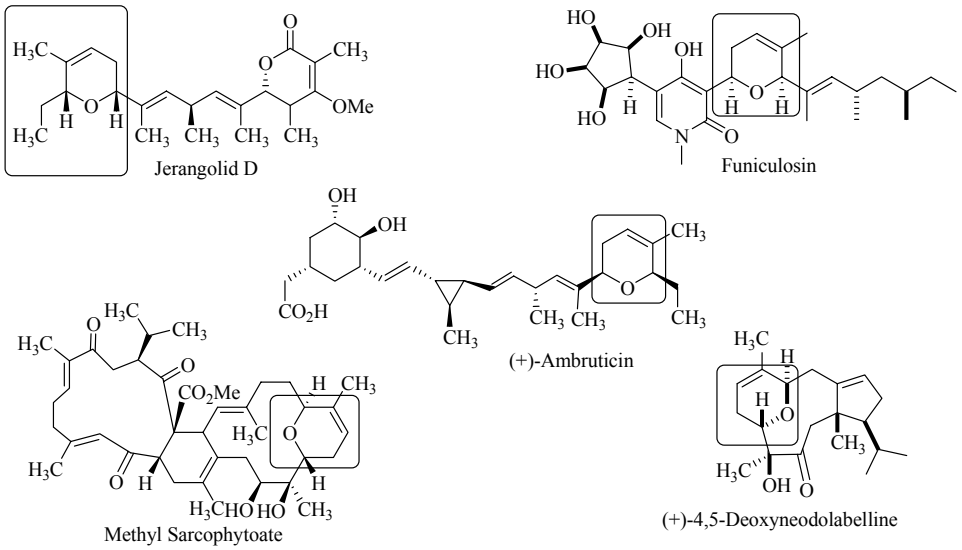


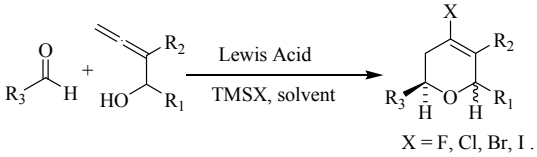
Figure 5.1 Natural products containing dihydropyran (DHP) ring backbones.

5.1.2 Development of Novel Prins Cyclization for DHP Sythesis

Based on our knowledge accumulated from our previous investigations towards Prins cyclization, we envisage that it would be an interesting and promising process to construct dihydropyrans using allenic alcohols as starting material (Scheme

[1] Gerth, K.; Washausen, P.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71.
[2] Ando, K.; Matsuura, I.; Nawata, Y.; Endo, H.; Sasaki, H.; Okytomi, T.; Saehi, T.; Tamura, G. *J. Antibiot.* **1978**, *31*, 533.
[3] Ringel, S. M.; Greenough, R. C.; Roemer, S.; Connor, D.; Gutt, A. L.; Blair, B.; Kanter, G.; von Strandtmann, M. *J. Antibiot.* **1977**, *30*, 371.
[4] Bowden, B. F.; Coll, J. C.; Gulbis, J. M.; Mackay, M. F.; Willis, R. H. *Aust. J. Chem.* **1986**, *39*, 803.
[5] Kusumi, T.; Igari, M.; Ishitsuka, M. O.; Ichikawa, A.; Itezono, Y.; Nakayama, N.; Kakisawa, H. *J. Org. Chem.* **1990**, *55*, 6286.

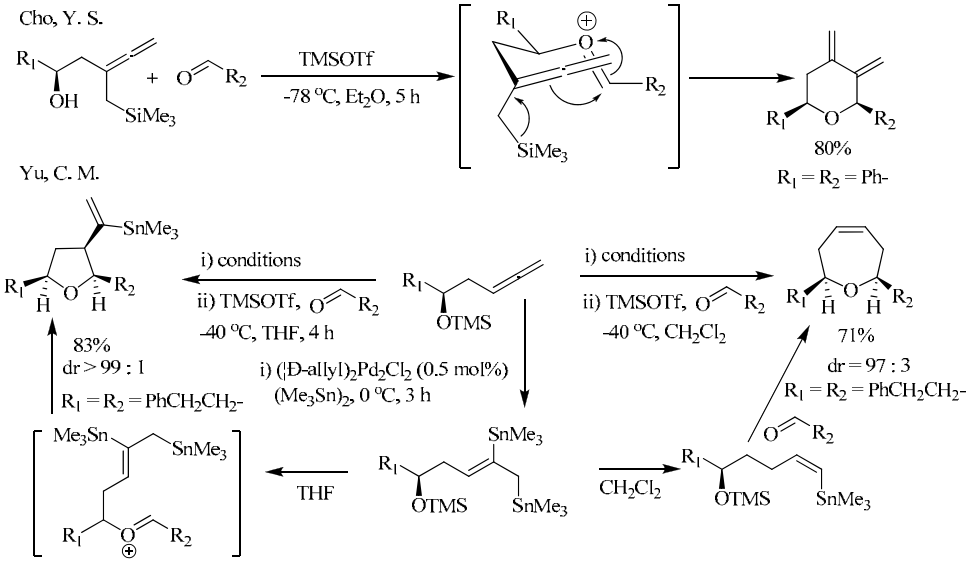
5.1).[6] This novel strategy would probably open a rapid and facile access to the dihydropyran backbone, which is highly valuable for synthetic purposes as inspired by the natural toxins with DHP backbones (Figure 5.1).



Scheme 5.1 Proposed protocol of Prins cyclization of allenic alcohols.

However, it still remains a great challenge to use allenic alcohols to do Prins cyclization reaction, and quite little has been documented in this area.

To the best of our knowledge, only some Prins-type cyclizations of homoallenyl alcohols have been reported for the construction of functionalized oxaheterocycles, including tetrahydropyrans, tetrahydrofurans and tetrahydrooxepines (Scheme 5.2).[7, 8]



Scheme 5.2 Prins-type cyclization of homoallenyl alcohols with aldehydes.

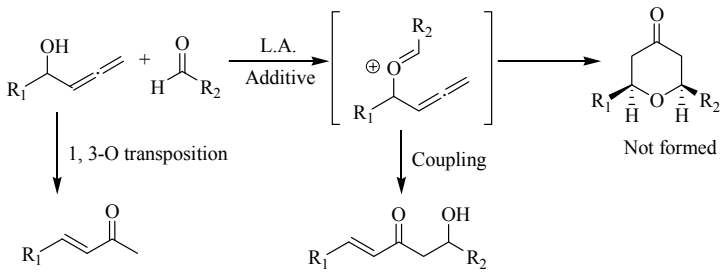
[6] (a) Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387. (b) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491. (c) Chan, K. P.; Ling, Y. H.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939. (d) Chan, K. P; Ling, Y. H.; Chan, J. L. T.; Loh, T. P. *J. Org. Chem.* **2007** *72* 2127. (e) Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2006**, *48*, 37. (f) Liu, F.; Loh, T. P. *Org. Lett.* **2007** *9* 2063.

One strategy developed by Cho, was the reaction of homoallenyl alcohols with aldehydes using TMSOTf as a promoter *via* a 6-*exo* mode cyclization to form 2,6-disubstituted-3,4-dimethylidene tetrahydropyrans.[7] The other strategy reported by Yu, was achieved through the Prins cyclization of homoallylic alcohol intermediate, which was generated *in situ* through palladium-complex assisted rearrangement of the homoallenyl alcohol in the presence of organostannane, affording the tetrahydrofurans.[10] Tetrahydrooxepines were obtained due to isomerization of the trimethyltin-substituted homoallylic alcohol when this reaction was performed in dichloromethane (Scheme 5.2).[8]

In an earlier separate account, Yu described a pioneer strategy aimed at synthesizing tetrahydropyranone *via* Prins-type cyclization of allenic alcohols with aldehydes using Lewis acid promoters (Scheme 5.3).[9] In spite of their efforts in surveying various reaction conditions, such as using different Lewis acids, including $In(OTf)_3$, TMSOTf, $TMSNTf_2$, $BF_3{\cdot}Et_2O$, $Sc(OTf)_3$, $Zn(OTf)_2$, $MgCl_2$, $HgCl_2$ and so on, their strategy failed to form the target tetrahydropyranones, which was rationalized as due to the lack of reactivity of the allenic alcohols. Instead, coupling products were obtained as the major outcome when this reaction was mediated by stoichoimetric amount of $InCl_3$ as a promoter at room temperature in dichloromethane. This coupling reaction readily afforded (*E*)-hydroxyenones as the major coupling products which are reminiscent of a convenient combination of both Wittig reaction and aldol reaction generated in an one-pot manner *via* a 1,3-*O*-transposition process. In addition, a trace amount of conjugated ketones were also observed as a side

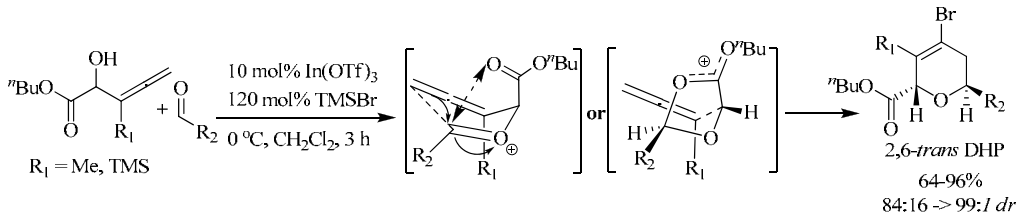
[7] Cho, Y. S.; Karupaiyan, K.; Kang, H. J.; Pae, A. N.; Cha, J. H.; Koh, H. Y.; Chang, M. H. *Chem. Commun.* **2003**, 2346.
[8] Kim, S. H.; Oh, S. J.; Ho, P. S.; Kang, S. C.; O, K. J.; Yu, C. M. *Org. Lett.* **2008**, *10*, 265.
[9] Yu, C. M.; Kim, Y. M.; Kim, J. M. *SynLett* **2003**, *10*, 1518. (b) Kim, S. H.; Oh, S. J.; Ho, P. S.; Kang, S. C.; O, K. J.; Yu, C. M. *Org. Lett.* **2008**, *10*, 265.

product in their studies which was thought be derived directly from the allenic allcohols *via* a 1,3-*O*-transposition process.



Scheme 5.3 Yu's attempts to develop a novel Prins cyclization of allenic alcohols.

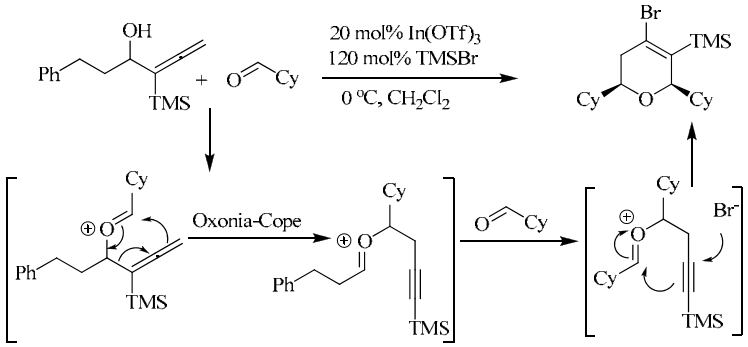
In contrast to Yu's findings, our group recently disclosed a novel *trans* Prins cyclization method for synthesizing 2,6-*trans*-disubstituted-4-halo-3,4-dihydropyrans by subjecting allenyl alcohol bearing α-alkoxycarbonyl group to Prins cyclization conditions (Scheme 5.4).[10] High 2,6-*trans* diastereoselectivity (> 86:14) was achieved for methyl-substituted allenyl alcohol bearing α-alkoxycarbonyl group, and was further enhanced to up to > 99:1 when using TMS substituted allenyl alcohol bearing α-alkoxycarbonyl group. The α-alkoxycarbonyl group adjacent to the allenyl alcohol motif played an essential role for the success of this 2,6-*trans*-diastereoselectivity: suppressing undesired oxonia-Cope rearrangement [11] and directing the α-alkoxycarbonyl group to adopt an axial orientation through stereoelectronic interaction between the lone pair on the carbonyl oxygen and the partially positive-charged oxonium carbon.



Scheme 5.4 *trans*-Prins cyclization of alkoxy-allenic alcohols with aldehydes.

[10] Hu, X. H.; Liu, F.; Loh, T. P. *Org. Lett.* **2009** *11* 1741.
[11] Roush, W. R.; Dilley, G. J. *SynLett.* **2001**, *S1*, 955.

However, prior to utilizing allenyl alcohol bearing α-alkoxycarbonyl group as the starting substrate, the oxonia-Cope rearrangement was encountered as a great setback (Scheme 5.1) during our initial stage for developing a novel Prins cyclization using common allenyl alcohols that do not bear α-alkoxycarbonyl group. Under standard Prins cyclization conditions developed in previous studies,[6a] our strategy (Scheme 5.1) was severely disturbed by the undesirable side reaction originating from the facile oxonia-Cope rearrangement, in which homopropargylic transfer process[12] predominated leading to the formation of undesired DHP ring (Scheme 5.5).



Scheme 5.5 Oxonia-Cope rearrangement encountered in Prins cyclization of common allenic alcohols with aldehydes.

With our previous experience and success in suppressing the epimerization by tuning reaction temperature and Lewis acidity, where mild Lewis acidity serves to retard the undesired allyl transfer process,[6b] we felt that it may be feasible to find the optimal reaction conditions by controlling the reaction temperatures, catalyst loading, and Lewis acidity.

In this chapter, we further our investigations in spite of the difficulties as mentioned above, aiming to developing a novel *cis* Prins cyclization using common allenic alcohols. The justification for development of this novel *cis* Pirns cyclization of common allenic alcohols also comes from our synthetic interests towards

[12] Lee, K. -C.; Lin, M. -J.; Loh, T. -P. *Chem. Commun.* **2004**, 2456.

funiculosin and (+)-Sambutoxin. Some progress has been achieved in developing this novel *cis* Prins cyclization using common allenic alcohols by effective suppression of the undesired oxonia-Cope rearrangement through a careful survey of reaction conditions, and the substrates factors have also been taken into account.

5.2 RESULTS AND DISCUSSIONS

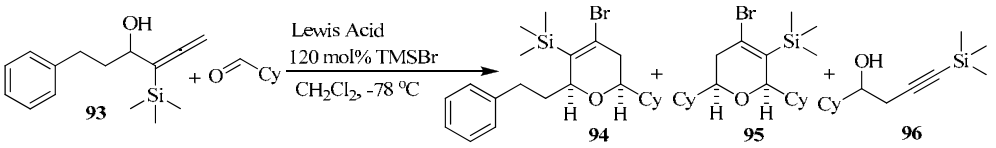
5.2.1 *cis* Prins Cyclization of TMS-substituted Allenic Alcohols

We ran the Prins cylization (Scheme 5.1) reaction at lower temperatures and at reduced concentrations, which was based on the empirical knowledge gained in suppressing the epimerization problem encountered in previous synthetic study towards (-)-Centrolobine.[6b]

The TMS-substituted allenic alcohol **93** was used as starting material to run Prins cyclization with cyclohexanecarboxaldehyde at -78 ^{o}C in dichloromethane. Different Lewis acids were screened for promoting this cyclization and results are summarized in Table 5.1. It could be seen that for robust Lewis acids, such as $In(OTf)_3$, TMSOTf, and $InBr_3$, the oxonia-Cope rearrangement process could not be effectively suppressed (Table 5.1, entries 1-3). To our delight, indium trifluoroacetate was found to be the suitable Lewis acid, where its mild acidity promoted the Prins cyclization smoothly at -78 ^{o}C over 18 hours with effective suppression of the undesired side reaction (Table 5.1, entries 5 and 6). It was also found that this Prins reaction was most efficiently promoted in terms of atom economy by 20 mol % $In(tfa)_3$ with 1.2 equivalent of TMSBr as additive (Table 5.1, entry 5) in dichloromethane over 18 hours to afford our desired crossed 2,6-*cis*-disubstituted-4-bromo-dihydropyran product in 81% yield as a single diastereoisomer without any observation of the 2,6-*trans*-dihydropyran diastereoisomer. However, it failed to

generate the desired product when this model Prins cyclization was performed at 0 °C, giving an intractable mixture (Table 5.1, entry 7). Thus, it could be seen that the low reaction temperature is essential for this reaction, and milder acidity helps to suppress the undesired oxonia-Cope rearrangement effectively.

Table 5.1 *cis* Prins cyclization of cyclohexanecarboxaldehyde with TMS-substituted allenic alcohol **93**.



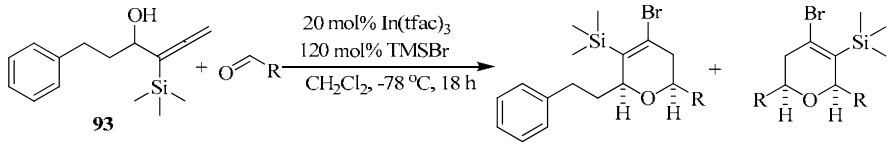
Entry	Lewis Acids	mol % L. A.	Concen.[a] (M)	Yield (%)[b]		
				94	**95**	**96**
1	$In(OTf)_3$	20	0.020	-	-	85
2	TMSOTf	20	0.020	15	7	55
3	$InBr_3$	20	0.020	-	-	33
4	$In(tfa)_3$	20	0.010	59	8	-
5	**$In(tfa)_3$**	**20**	**0.020**	**81**	**3**	**-**
6	$In(tfa)_3$	100	0.020	86	4	-
7[c]	$In(tfa)_3$	20	0.020	-	-	-

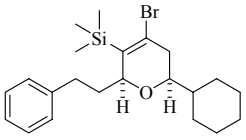
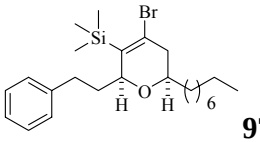
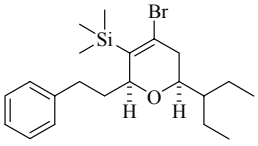
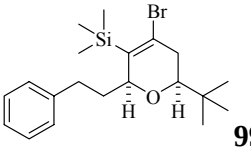
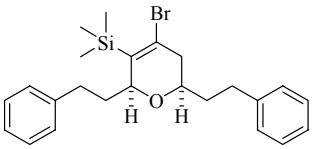
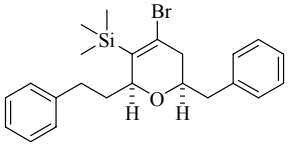
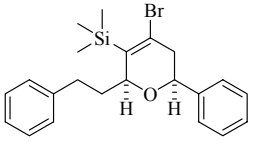
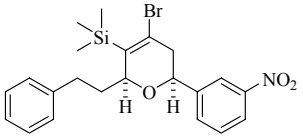
[a] Concen. denotes concentration of **93** with respect to CH_2Cl_2 in mol L^{-1}. [b] isolated yields. [c] Reaction was done at 0 °C for 18 h.

Under optimal reaction conditions, we explored the scope of this *cis* Prins cyclization by reacting the TMS-substituted allenic alcohol **93** with various aldehydes. Results are summarized in Table 5.2. Desired crossed 2,6-*cis*-disubstituted-4-bromo-dihydropyran products were obtained in moderate to good yields with excellent diasteroselectivity. Aliphatic aldehydes were found to react readily with the allenic alcohol to afford the target products in good yields, while

aromatic aldehydes are less reactive resulting in a lower yield. No reaction could be observed for conjugated aldehydes in this Prins cyclization.

Table 5.2 *cis* Prins cyclization of TMS-substituted allenic alcohols **93** with various aldehydes.

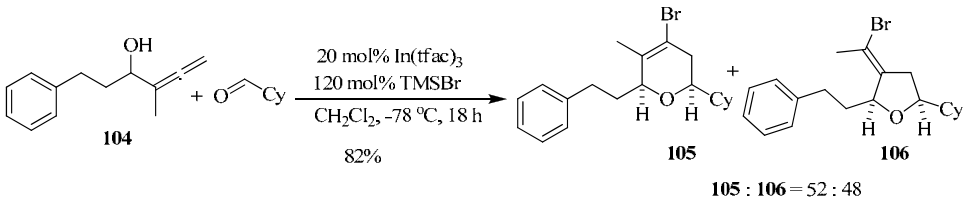


Entry	R	Product	Yield [a] (%)	Ratio [b]
1	Cy-	 **94**	81	87:13
2	$CH_3(CH_2)_7$-	 **97**	73	97:3
3	$(C_2H_5)_2CH$-	 **98**	62	98:2
4	$(CH_3)_3C$-	 **99**	72	> 99:1
5	$PhCH_2CH_2$-	 **100**	77	100:0
6	$PhCH_2$-	 **101**	NR [c]	-
7	Ph-	 **102**	36[d]	> 99:1
8	*m*-nitro-phenyl	 **103**	N.R.	-

[a] isolated yield. [b] the ratio of crossed DHP ring versus side product *via* oxonia-Cope rearrangement, determined by ^{1}H nmr. [c] N.R. denotes no reaction with the recovery of starting materials. [d] 100 mol % $In(tfa)_3$ was used as promoter.

5.2.2 *cis* Prins Cyclization of Methyl-substituted Allenic Alcohols

With the success in performing the *cis* Prins cyclization using the TMS-substituted allenic alcohol **93**, we progressed to extend this Prins cyclization to methyl-substituted allenic alcohol **104** (Scheme 5.6). Under the optimal reaction conditions as described above, a mixture of **105** and **106** was obtained in a combined yield of 82% with a ratio of 52:48 (**105**:**106)**.

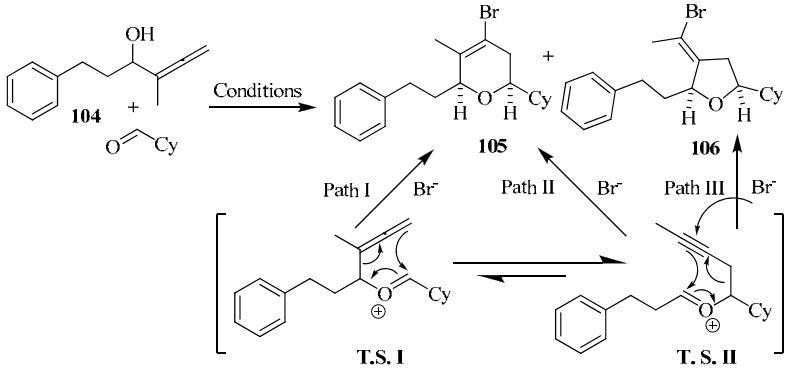


Scheme 5.6 Prins cyclization of Me-substituted allenic alcohol **104** with cyclohexanecarboxaldehyde.

This outcome was beyond our expectation that at -78 °C indium trifluoroacetate failed to afford our desired crossed 2,6-cis-disubstituted-3-methyl-4-bormo-dihydropyran as the major product. It turned out to be futile despite our efforts to optimize this reaction, such as slow introduction of the Me-substituted allenic alcohol **104** *via* using syringe pump, and using excess TMSBr (3.0 equiv.) aiming for more efficient trapping of the cationic reaction intermediate, dihydropyranyl carbocation.[13] We speculate over this phenomenon and that this cyclization could probably be interfered again by the undesired oxonia-Cope rearrangement process: the conversion from the transition state **I** to **II**. Here we rationalized our observations by invoking such a hypothesis that dihydropyran product **105** could be generated either from transition state **I** (path I) or transition states **II** (path II), while **106** should only be formed through transition states **II** (path III) (Scheme 5.7). It seems that this hypothesis is somewhat plausible because we observed similar results when stronger

[13] Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Chem. Eur. J.* **2008**, 14, 6260.

acids like $In(OTf)_3$ and $InBr_3$ were utilized to promote this reaction (Table 5.3, entries 2 and 3). As expected, no improvements could be achieved at -40 ^oC (Table 5.3, entries 5 to 7), and decompositions of allenic alcohols **104** occurred at elevated temperatures (Table 5.3, entries 8 to 13).



Scheme 5.7 Interpretation towards the Prins cyclization of **104** with cyclohexanecarboxaldehyde.

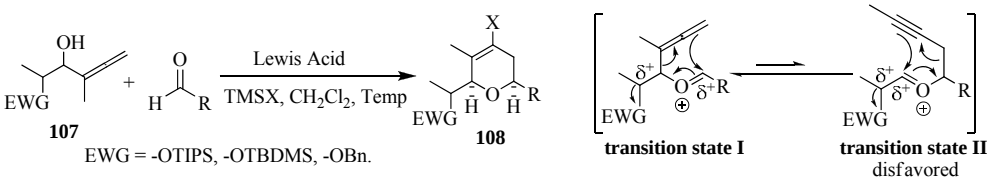
Table 5.3 Prins cyclization of **104** with cyclohexanecarboxaldehyde under various conditions.

Entry	Lewis Acids	mol % L. A.	Temperature (^oC)	Ratio: (105:106)[a]
1	$In(tfa)_3$	20	-78	52 : 48
2	$In(OTf)_3$	20	-78	50 : 50
3	$InBr_3$	20	-78	52 : 48
4	$InCl_3$[b]	20	-78	N. R.[c]
5	$In(tfa)_3$	20	-40	54 : 46
6	$InBr_3$	20	-40	54 : 46
7	$InCl_3$[b]	20	-40	56 : 44
8	$In(tfa)_3$	20	0	-[d]
9	$InBr_3$	20	0	-[d]
10	$InCl_3$[b]	20	0	-[d]
11	$In(tfa)_3$	20	25	-[d]
12	$InBr_3$	20	25	-[d]
13	$InCl_3$[b]	20	25	-[d]

[a] Ratio determined by ^1H nmr spectrum, combined yield for entry 1 was 82%, yields were not determined for other tests. [b] TMSCl was used as additive. [c] N.R. denotes no reaction with the recovery of starting materials. [d] Decomposition of the starting Me-substituted allenic alcohol **104** occurred without any formation of desired dihydropyran products.

5.2.3 Prins Cyclization of Acetyl Allenic Alcohol

From a mechanistic point of view, we are highly interested in deciphering the reasons for the different outcome when we changed the starting TMS-substituted allenic alcohol **93** into Me-substituted allenic alcohol **104** under the same cyclization conditions. We infer that the transition state II (**T. S. II**) is probably favored because of its lower energy as compared with transition state I (**T. S. I**) **(**Scheme 5.7), resulting in the facile occurrence of the undesired oxonia-Cope rearrangement. We wonder whether this rearrangement could be suppressed by incorporating an electron-withdrawing group (EWG) adjacent to the hydroxyallenyl moiety (Scheme 5.8).

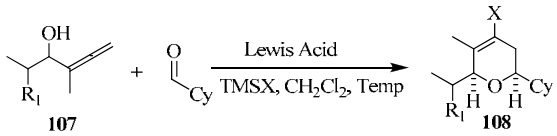


Scheme 5.8 Prins cyclization of Me-substituted allenic alcohol with aldehydes.

Me-substituted allenic alcohols **107** were prepared for testing our planned protocol by installing a protected hydroxyl group, including –OTIPS, -OTBDMS, -OBn, which is placed adjacent to the hydroxyallenyl function. We envisage that the electronegative oxygen atom would disfavour the formation of **T. S. II** type species (Scheme 5.7), helping to suppress the undesired oxonia-Cope rearrangement during cyclization.

Unfortunately, this strategy failed to afford our desired products. Only negative results were observed, such as no reaction, decomposition of starting allenic alcohols, or intractable reaction crude, in spite of our attempts in screening the reaction conditions, including using different Lewis acid promoters, running this cyclization reaction at different temperatures (from -78 ^{o}C to room temperature), and using different additives as counterion source (Table 5.4).

Table 5.4 Prins cyclization of electronically modified **107** with cyclohexanecarboxaldehyde.

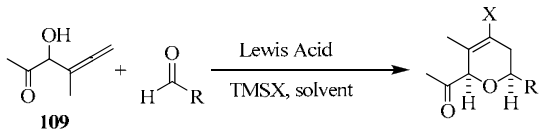


Entry	R_1	Lewis Acids	Lewis Acid (mol %)	TMSX (120 mol%)	Temperature (^oC)	Result
1	-OTIPS	$In(tfa)_3$	20	TMSBr	-78	- [a]
2	-OTIPS	$In(tfa)_3$	100	TMSBr	-78	- [a]
3	-OTIPS	TMSOTf	110	TMSBr	-78	- [b]
4	-OTIPS	TMSOTf	10	TMSCl	-78	N.R. [c, d]
5	-OTIPS	$In(OTf)_3$	100	TMSBr	-78	- [a]
6	-OTIPS	$In(OTf)_3$	20	TMSBr	-40	- [a]
7	-OTIPS	$In(OTf)_3$	20	TMSCl	-40	N.R.
8	-OTIPS	$In(OTf)_3$	20	TMSBr	0	- [a]
9	-OTIPS	$TiCl_4$	200	TMSCl	-60	N.R.
10	-OTIPS	$SnCl_4$	200	TMSCl	-60	- [b]
11	-OTIPS	$AlCl_3$	200	TMSCl	-60	- [b]
12	-OTIPS	$Sn(OTf)_2$	20	TMSBr	-40	- [a]
13	-OTIPS	$InCl_3$	100	TMSCl	25	- [a]
14	-OTIPS	$InCl_3$	20	TMSBr	25	- [b]
15	-OTBDMS	$In(OTf)_3$	100	TMSCl	0	- [b]
16	-OTBDMS	$InCl_3$	100	TMSCl	25	- [a]
17	-OBn	TMSOTf	110	TMSBr	-78	N.R.
18	-OBn	$In(OTf)_3$	100	TMSBr	-78	- [b]
19	-OBn	$InCl_3$	100	TMSCl	25	- [a]

[a] Messy reaction crude observed. [b] starting material decomposed. [c] N. R. denotes no reation occurred with starting materials recovered. [d] 1.0 equiv. of 2,6-di-*tert*-butylpyridine added as proton scavenger.

Despite of the negative results observed above, we furthered our study by incorporating a carbonyl function nearby the hydroxyallenyl moiety as the electronic withdrawing group (Scheme 5.9). We planned to use methyl-substituted acetyl allenic

alcohol **109**[14] to conduct this Prins cyclization with aldehydes by exploiting the carbonyl function to suppress the undesired oxonia-Cope rearrangement. In addition, this *cis* Prins cyclization methodology development here exploiting acetyl allenic alcohol also serves as a model study for our synthetic studies towards Funiculosin and (+)-Sambutoxin.

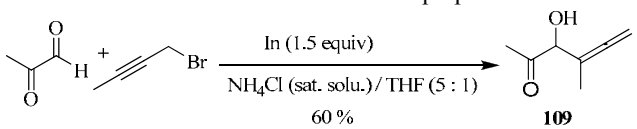


Scheme 5.9 Prins cyclization of acetyl allenic alcohol **109** with aldehydes.

We continued to screen the reaction conditions by subjecting the acetyl allenic alcohol **109** and 2-ethyl-butylraldehyde to Prins cyclization conditions using different Lewis acid promoters. Our preliminary observations revealed that the acetyl allenic alcohol **109** exhibited low reactivity over aldehyde in this Prins cyclization at low temperatures. No reaction could be observed at low temperatures (-78 ^{o}C and -60 ^{o}C) in dichloromethane with a variety of Lewis acid promoters in either catalytic or stoichoimetric amounts, including $In(OTf)_3$, TMSOTf, $TMSNTf_2$, $Sn(OTf)_2$, $La(OTf)_3$, $Sc(OTf)_3$, $In(tfa)_3$, $InBr_3$, $InCl_3$, $TiCl_4$, $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ with either TMSBr or TMSCl as additive. At elevated temperatures (such as -40 ^{o}C, 0 ^{o}C, and room temperature), strong Lewis acids, such as $In(OTf)_3$, TMSOTf, $TMSNTf_2$, $La(OTf)_3$, $In(tfa)_3$, $InBr_3$, and $BF_3{\cdot}OEt_2$ caused the decomposition of the starting acetyl allenic alcohol **109** without any formation of the target dihydropyran products.

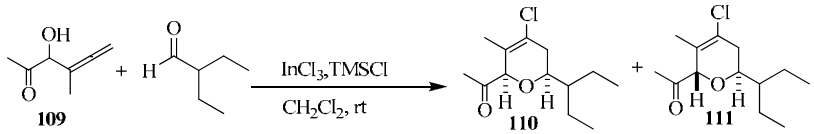
After screening numerous reaction conditions, we came to several key findings: 1) $InCl_3$ was found by far, to be the most suitable Lewis acid for promoting

[14] Me-substituted allenic alcohol **109** was prepared as follows:



this Prins cyclization, which is superior in terms of forming our desired dihydropyrans, and thus was selected for further systematic studies; 2) TMSCl is superior to TMSBr as counterion source, because TMSBr caused decomposition of the starting alcohol **109**; 3) the cyclization reaction turned out to be sluggish when $InCl_3$ was used in catalytic amount at both room temperature and 0 ^oC even with prolonged reaction time; 4) in terms of chemical yields and reaction rate, this Prins cyclization was found to proceed well only at room temperature with a stoichoimetric amount of $InCl_3$ as promoter in CH_2Cl_2; 5) our desired cyclization product 2,6-*cis*-dihydropyran was obtained as a major diastereoisomer in low yields with the concurrent formation of the 2,6-*trans*-dihydropyran isomer with a moderate diastereoselectivity of ~ 75 : 25 (*cis*/*trans*). Details and results of the screening of reaction conditions are summarized in Table 5.5. Results of Prins cyclization of **109** with various aldehydes are tabulated in Table 5.6.

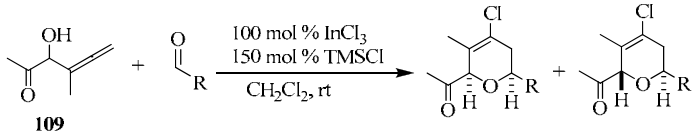
Table 5.5 Reaction condition screening of Prins cyclization of **109** with 2-ethylbutylraldehyde.

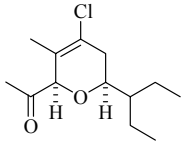
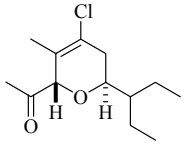
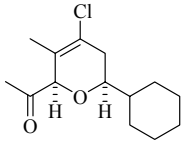
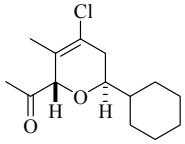
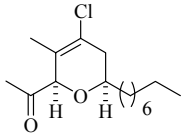
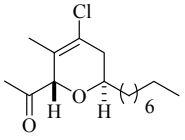
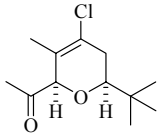
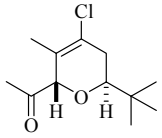
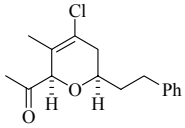
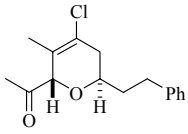
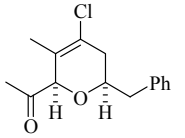
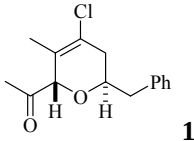
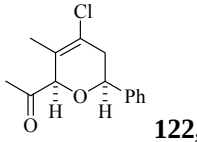
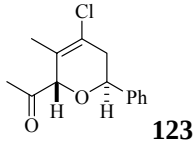
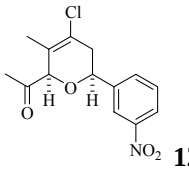
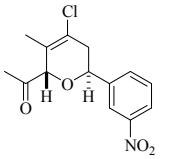


Entry	mol % $InCl_3$	TMSCl	Aldehyde	Yield (%)[a]	Ratio: (110:111)[b]
1	20	1.5 equiv	1.0 equiv	< 5%	-
2	50	1.5 equiv	1.5 equiv	31	67:33
3	50	3.0 equiv	3.0 equiv	30	74:26
4	**100**	**1.5 equiv**	**1.5 equiv**	**55**[c]	**69:31**
5	100	3.0 equiv	3.0 equiv	33	75:25
6	100	3.0 equiv	1.0 equiv	32[d]	70:30

[a] combined yield. [b] determined by ^1H nmr spectrum. [c] **109** was added *via* using syringe pump over 3 hours. [d] 3.0 equiv of **109** was used.

Table 5.6 Prins cyclization of **109** with various aldehydes to *crossed* 2,6-disubstituted-4-chloro-dihydropyrans.[a]



Entry	R	Product	Yield (%)[b]	Ratio: (*cis*:*trans*) [c]
1	$(C_2H_5)_2CH$-	 **110,**  **111**	55	69:31
2	Cy-	 **112,**  **113**	51	74:26
3	$CH_3(CH_2)_7$-	 **114,**  **115**	Trace	73:27
4	$(CH_3)_3C$-	 **116,**  **117**	Trace	71:29
5	$PhCH_2CH_2$-	 **118,**  **119**	45	69:31
6	$PhCH_2$-	 **120,**  **121**	Trace	>99:1
7	Ph-	 **122,**  **123**	N.R.[d]	-
8	m-NO_2-Ph-	 **124,**  **125**	N.R.	-

[a] Acetyl allenic alcohol **109** (0.3 mmol, in 1mL CH_2Cl_2) was introduced *via* syringe pump over 3 hours into the vigouously stirred suspension of a mixture of $InCl_3$ (0.3 mmol) with TMSCl (0.45 mmol) and the corresponding aldehyde (0.45 mmol) in 5 mL CH_2Cl_2 at 25 °C, stirred for another 2 hours after finishing introducing **109**, followed by aqueous workup and purification. [b] combined yield. [c] Determined by ^{1}H nmr spectrum. [d] N.R. denotes no reaction with the recovery of starting materials.

We could see that our strategy did afford us with the desired 2,6-*cis*-disubstituted-3-methyl-4-chloro-dihydropyans as the major product (Table 5.5). However, the overall yields were quite low and the *cis*/*trans* diastereoselectivity was moderate. Undesired side reactions may probably contribute to the low yield problem during this Prins cyclization, including dimerization, polymerization and decomposition of the starting allenic alcohol.[15] The exact reasons were not established, however, our experimental observations indicated low stability of the acetyl allenic alcohol **109** under the harsh acidic conditions in Prins cyclization, and the volatility, low stability of dihydropyran products during isolation and purification. Obviously, further efforts are necessary to solve all these problems.

The formation of 2,6-*trans*-dihydropyrans was believed to be of the same mechanism, originating from the directing stereoelectronic interaction between the lone pair on carbonyl oxygen and the positive-charged oxocarbenium carbon during the cyclization.[10]

5.3 SYNTHETIC STUDIES TOWARDS (+)-SAMBUTOXIN

5.3.1 Introduction to (+)-Sambutoxin

(+)-Sambutoxin is an interesting mycotoxin isolated by Lee and co-workers in 1995 from the wheat cultures of *Fusarium sambucinum* PZF-4.[16] This metabolite is structurally representative of a small class of natural products, featured with its central 2,6-*cis*-tetrahydropyran ring backbone linked with the 4-hydroxy-2-pyridinone motif

[15] For dimerizaton of allenens, see: Horváth, A.; Bäckvall, J. E. in *Modern Allene Chemistry*, Krause, N.; Stephen, A.; Hashmi, K. Eds, Wiley-VCH: Verlag, **2004**, vol. 2, p 891; polymerization of allenes, see: Tomita, I.; Kondo, Y.; Takagi, K.; Endo, T. *Macromolecules* **1994**, *27*, 4413; for chemistry of aminoallenes and allenylamides, see: Wei, L. L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773.

[16] (a) Kim, J.-C.; Lee, Y.-W. *Appl. Environ. Microbiol.* **1994**, *60*, 4380. (b) Kim, J.-C.; Lee, Y.-W.; Tamura, H. T.; Yoshizawa, T. *Tetrahedron Lett.* **1995**, *36*, 1047.

and the 1,3-*anti*-dimethyl tail, examples including funiculosin[17] and oxysporidinone[18] (Figure 5.2). These toxins exhibit a broad spectrum of biological activities including antibiotic, antiinsecticidal, antifugal, and antitumor properties. These structural features with their interesting biological activities aroused our strong interest to carry our synthetic studies towards these natural products.

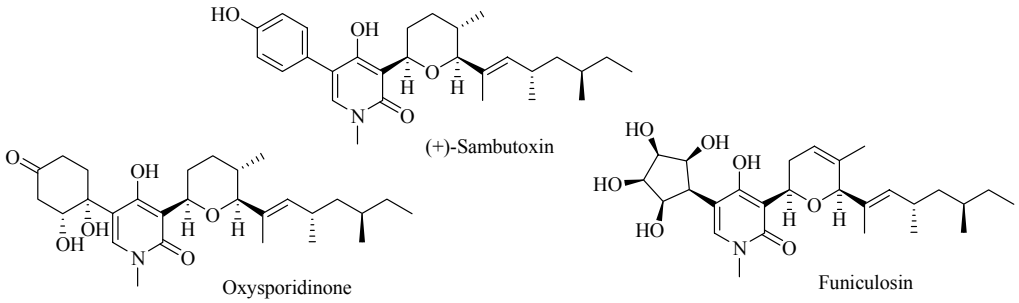


Figure 5.2 Natural products containing THP (DHP) ring backbone and pyridinone moiety.

5.3.2 Reported Synthesis of (+)-Sambutoxin

The first enantioselective total synthesis of (+)-Sambutoxin was reported by Williams, D.R. in 2000.[19] It is the first and the only completed total synthesis of this metabolite by far (Scheme 5.10), and this total synthesis featured four key operations: 1) an enantioenriched preparation of 1,3-*anti*-dimethyl array by asymmetric conjugate addition of Yamamoto's copper reagents onto the conjugate ketone with Hruby's 4-phenyloxazolidinone auxiliary [20] to establish the intermediate **I**. Excellent diastereofacial selectivity was observed due to a double induction stemming from the asymmetry of the homochiral copper species possessing a *syn-s-cis* chelation manner

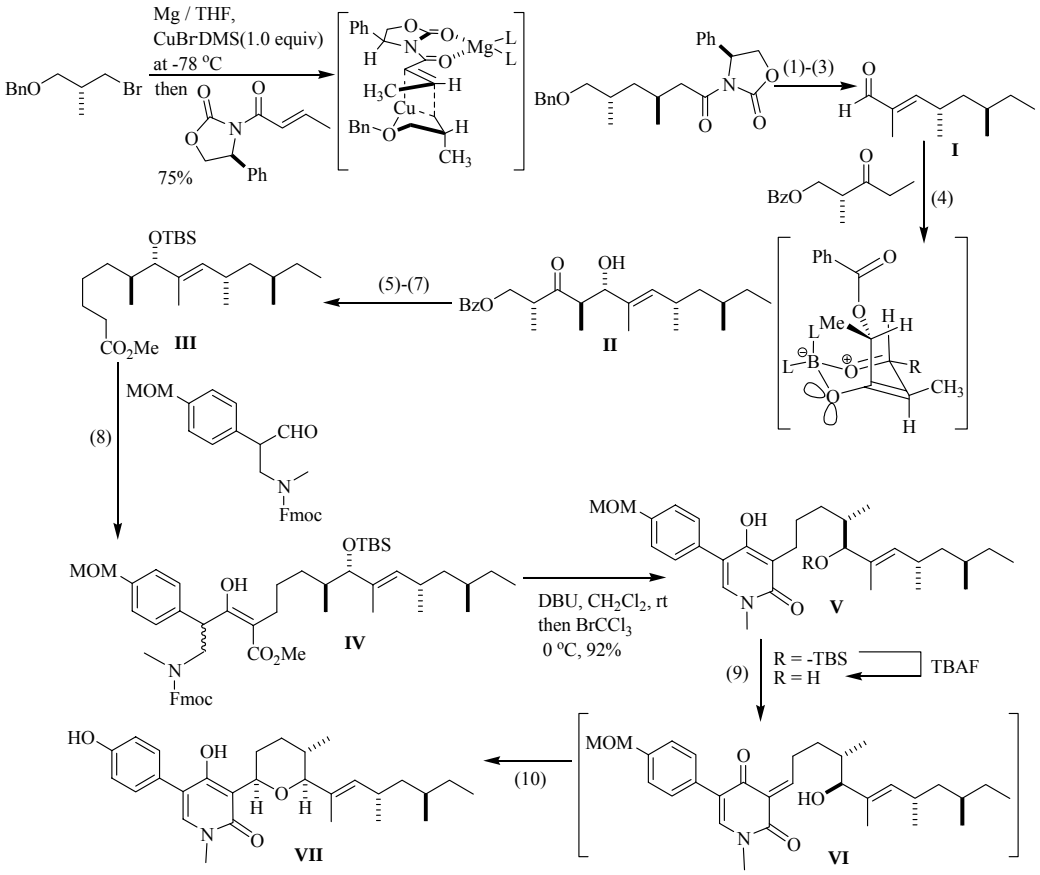
[17] (a) Ando, K.; Matsuura, I.; Nawata, Y.; Endo, H.; Sasaki, H.; Okytomi, T.; Saehi, T.; Tamura, G. *J. Antibiot.* **1978**, *31*, 533. (b) Nawata, Y.; Matsuura, I.; Ando, K.; Iitaka, Y. *Acta. Cryst.* **1990**, *C46*, 515.
[18] Breinholt, J.; Ludvigsen, S.; Rassing, B. R.; Rosendahl, C. N.; Nielsen, S. E.; Olsen, C. E. *J. Nat. Prod.* **1997**, *60*, 33.
[19] Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217, and references cited therin.
[20] (a) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766. (b) Williams, D. R.; Kissel, W. S.; Li, J. *Tetrahedron Lett.* **1998**, *39*, 8593.

as depicted in the transition state; 2) Paterson *anti*-Aldol reaction [21] to afford compound **II** with *E*-(O)-boron enolate, which was generated *in situ* by reacting the chiral ketone (derived from (*S*)-ethyl lactate) with boron-based chiral auxiliary $^{c}Hex_2BCl$. **II** was obtained in 78% yield as a single, crystalline diastereomer, and the complete stereocontrol was believed to be achieved *via* a boat-like transition state without a substantial barrier in energy based on theoretical calculations. Further elaborations transformed **II** into **III** by sequential standard chemical transformations, such as silyl ether formation, oxidative cleavage of the chiral auxiliary, and homologation of the carbon chain, and coupling condensation of **III** with the protected amino aldehyde yielded the precursor **IV** for construction of pyridinone; 3) the key intermediate pyridinone **V** was formed *via* an oxidative cyclization cascade from enol ether **IV** when treated with DBU and bromotrichloromethane;[22] 4) after removal of the TBS sily ether from **V** with TBAF, the formation of the central skeletal backbone of (+)-Sambutoxin **VII** was finished with the exclusive formation of the tetrahydropyran ring showing a 2,6-*cis*-diequatorial substitution pattern through a novel Saegusa oxidation cyclization cascade sequence mediated by palladium acetate *via* formation of the pridinone methide **VI** with a subsequent intramolecular conjugate addition. [23] Hydrolytic deprotection of the β–methoxymethyl ether afforded (+)-Sambutoxin, which was confirmed as the antipode of the natural product with identical nmr parameters but opposite optical rotational angle.

[21] (a) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (b) For a review: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. For other anit-aldol rections, see: (a) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T. -H. *J. Org. Chem*. **1996**, *61*, 2038. (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (c) Braun, M.; Sacha, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1318. (d) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61.

[22] Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.

[23] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.



Scheme 5.10 Williams' total synthesis of (+)-Sambutoxin.

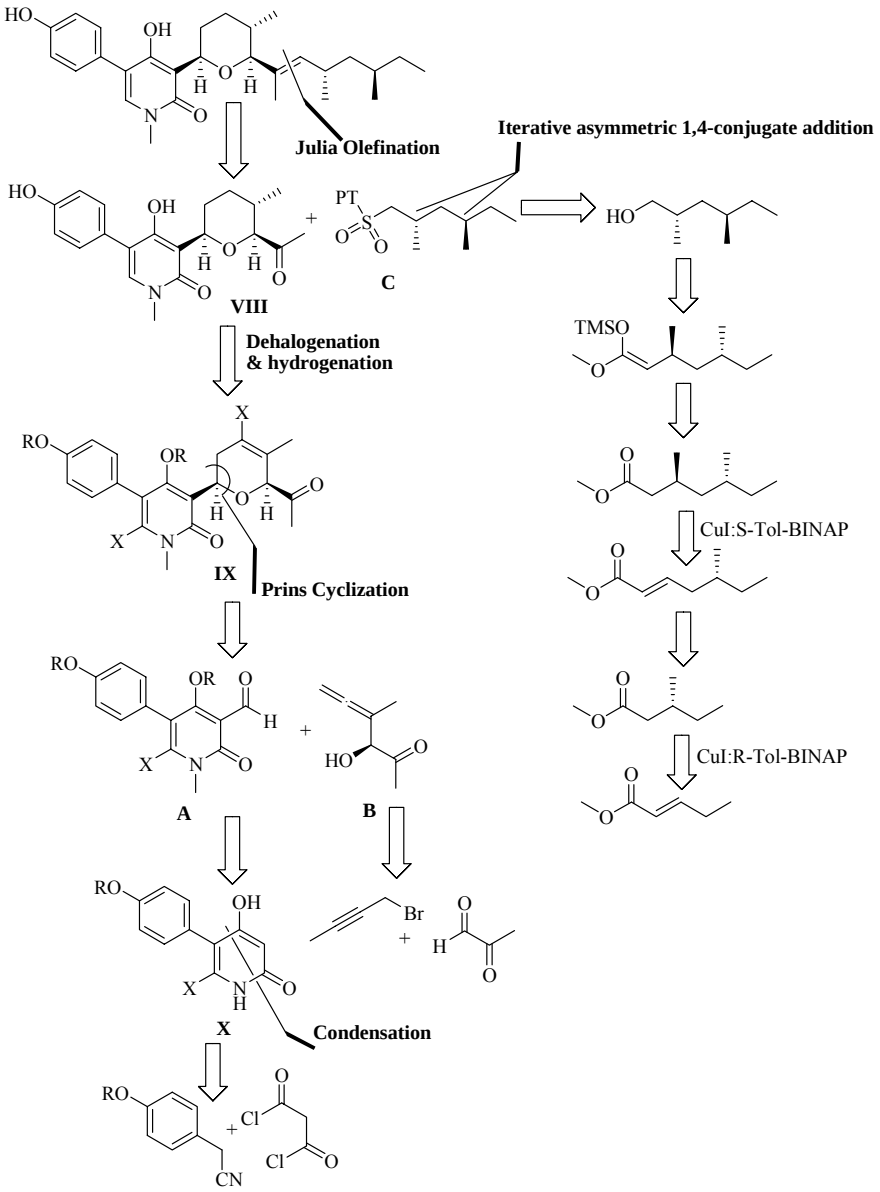
(1) $LiBH_4$, wet Et_2O, 84%; Ph_3P, I_2, imidazole, 96%; $LiEt_3BH$ then H_2O_2, NaOH, 98%. (2) 10% Pd/C, 10% HCO_2H in MeOH, 93%. (3) Swern oxidation, then add $PH_3P{=}C(CH_3)CO_2Et$, 83%; DIBAL, CH_2Cl_2, -78°C, 97%; MnO_2, CH_2Cl_2, 91%. (4) $^cHex_2BCl$, Me_2Net, 0 °C; **I**, -78°C, to -20 °C, 16h, H_2O_2, MeOH, pH7 buffer, 78%. (5) $Me^tBuSiOTf$, collidine, 98%; $LiBH_4$, THF, -78 °C, then aqu. $NaIO_4$; $NaBH_4$, MeOH, 92%; (6) Ph_3P, I_2, CH_2Cl_2, imidazole, 96%; (7) allylMgBr, CuBr·DMS, THF, -78 °C, to -35 °C; catecholborane, THF, then aqu. H_2O_2 at 0 °C, NaOH, 53%; PDC, wet DMF, then CH_2Cl_2, 82%. (8) LDA, THF, -78°C, then HMPA, 71%; DMSO, DCC, pyr-HCl, 89%. (9) DBU, CH_2Cl_2, rt, then $BrCCl_3$, 0 °C, 92%. (10) $Pd(OAc)_2$, K_2CO_3, CH_3CN, 22°C; actone, NaI, 22 °C, 10% aqu. HCl (1 drop).

5.3.3 Retrosynthetic analysis of (+)-Sambutoxin

In our opinion, the structural features of (+)-Sambutoxin come from its tetrahydropyran ring backbone and its 1,3-*anti*-dimethyl tail linked by a double bond. Based on our knowledge in Prins cyclization[6] and copper-tol-BINAP complex

catalyzed asymmetric conjugate addition,[24] a facile and straightforward retro-synthetic analysis was proposed, as depicted in Scheme 5.11. The skeleton of (+)-Sambutoxin was disconnected into **VIII** and fragment **C** upon a retro-Julia olefination reaction.[25] Fragment **C** was envisioned to be readily prepared through an iterative asymmetric 1,4-conjugate addition reaction using Cu-tol-BINAP catalyst to generate the 1,3-*anti*-dimethyl array.[24b] The precursor **VIII** could be derived from **IX** *via* a radical dehalogenation[26] and a subsequent stereoselective hydrogenation process.[27] A retro-Prins cyclization further cut **IX** into the protected pyridinone aldehyde **A** and acetyl allenic alchol **B**. Fragment **A** could be prepared *via* condensation of phenylacetonitrile with dimalonyl chloride[28] followed with incorporation of the aldehydic function,[29] and **B** could be readily obtained by allenation of the ketone-aldehyde.[30] In general, our synthetic strategy towards (+)-Sambutoxin could be highlighted as three key operations, including Prins cyclizaiton, asymmetric conjugate addition and Julia olefination reaction.

[24] (a) Wang, S.Y.; Ji, S. J.; Loh, T.P. *J. Am. Chem. Soc.* **2007**, *129*, 276. (b) Lum, T.K.; Wang, S. Y.; Loh, T.P. *Org. Lett.* **2008**, *10*, 761.
[25] Julia, M.; Paris, J. M. *Tetrahedron* **1973**, *14*, 4833. Synthetic application of Julia olefination in total syntheis see Pospíšil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 2516.
[26] For a summary of methods of radical dehalogenation, see (a) Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, 1986, pp 267-281. (b) Ryu, I.; Kusano, K.; Masumi, N.; Yamazaki, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* **1990**, *31*, 6887.
[27] For a stereoselctive hydrogenation of the dihydropyran to tetrahydropyran with methyl residing on equatorial position see: Nawata, Y.; Matsuura, I.; Ando, K.; Iitaka, Y. *Acta. Cryst.* **1990**, C*46*, 515.
[28] Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839.
[29] (a) Begley, M. J.; Madeley, J. P.; Pattenden, G.; Smith, G. F. *J. Chem. Soc. Perkin Trans. 1* **1992**, *1*, 57. (b) Buck, J.; Madeley, J. P.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1* **1992**, *1*, 67.
[30] (a) Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042-13043. (b) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496. (c)Inoue, M.; Nakada, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 252.

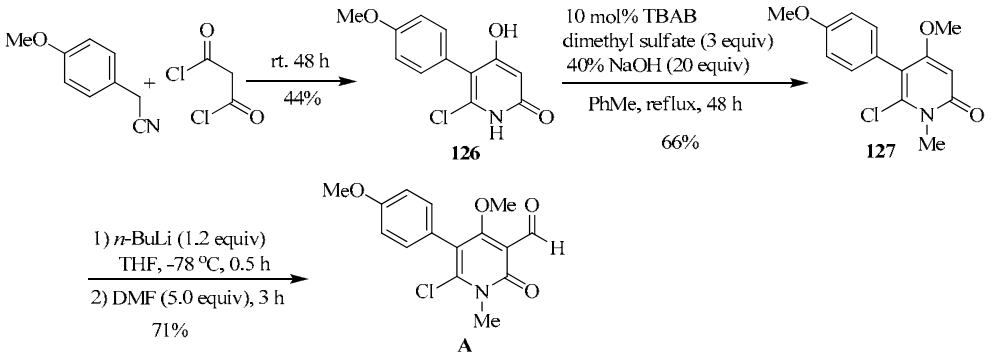


Scheme 5.11 Proposed retro-synthetic analysis of (+)-Sambutoxin.

5.3.4 Synthesis of Fragment A

As described in the retro-synthetic analysis, we started our synthetic study towards (+)-Sambutoxin by focusing our initial efforts on the key Prins cyclization step to form the skeletal tetrahydropyran backbone. The key precursor, fragment **A** for this Prins cyclization, was prepared over three steps by following literature reported methods (Scheme 5.12). Condensation of *p*-methoxyphenyl acetonitrile with malonyl

chloride afforded 44% of chloropyridinone **126**, where the black slurry-like reaction crude needs careful and tedious purification.[28] Double methylation product **127** was obtained in one step *via* methylation with dimethyl sulfate in the presence of aqueous sodium hydroxide.[28] Deprotonation of vinylic proton of **127** upon treatment with *n*-BuLi at -78 °C followed by reaction with DMF provided desired pyridinone aldehyde **A** in 71% yield.[28] In addition, the structures of **127** and fragment **A** could be readily seen from their respective X-ray single crystal structures (Figure 5.3 and Figure 5.4).



Scheme 5.16 Synthesis of fragment **A,** chloropyridinone aldehyde.

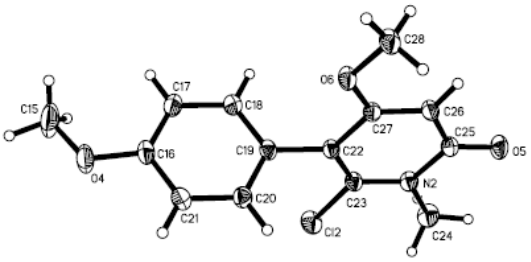


Figure 5.3 X-ray structure of **127**.

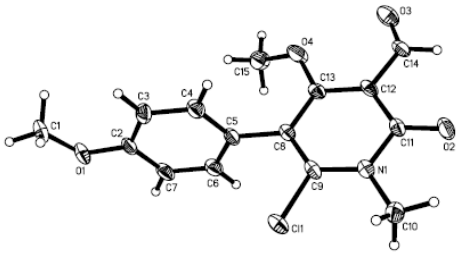


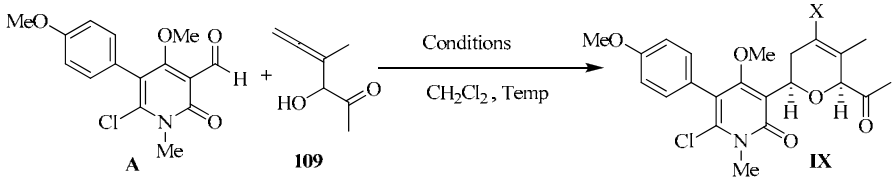
Figure 5.4 X-ray structure of fragment **A**.

5.3.5 Prins cyclization of pyridinone aldehyde (Fragment A) with acetyl allenic alcohol (Fragment B)

With the starting fragments **A** and racemic **B** (**109**) available in hand, we proceeded to carry out the key step of our strategy, the Prins cyclization reaction between fragment **A** and **109**. Unfortunately, no cyclization product could be observed when pyridinone aldehyde **A** was subjected to the optimal cyclization

conditions described above (Table 5.7, entry 1). We also attempted other cyclization conditions by using different Lewis acids and counterion additive, however, no desired product was formed in spite of our efforts (Table 5.7, entries 2 to 4). We suspect that the low reactivity might arise from the pyridinone aldehyde **A** because of its conjugate nature. Thus, we turned to the versatile catalyst $(O_3ReOSiPh_3)_3$, which is especially reactive for promoting Prins cyclization with aromatic and conjugate aldehydes.[31] However, it also failed to afford our desired cyclized dihydropyran backbone (Table 5.7, entries 5 to 7). Thus, it turns out that our Prins cyclization fails to work as the key strategy to generate the backbone of (+)-Sambutoxin and we temporarily ceased our synthesis at this stage. Further efforts are necessary with a new generation of Prins cyclization strategy for facile and rapid assembly of the backbone of this interesting mycotoxin.

Table 5.7 Synthesis of key precursor **IX** *via* Prins cyclization of A with **109**.



Entry	Conditions	Temperature	Time (h)	Yield (%)
1	$InCl_3$ (100 mol%), TMSCl (1.5 equiv.)	25 °C	5	N.R.[a]
2	$In(OTf)_3$ (20 mol%), TMSCl (1.5 equiv.)	0 °C	3	N.R.[a]
3	$In(tfa)_3$ (100 mol%), TMSBr (1.5 equiv.)	-78 °C	18	N.R.[a]
4	$In(tfa)_3$ (100 mol%), TMSCl (1.5 equiv.)	-78 °C	18	N.R.[a]
5	$(O_3ReOSiPh_3)_3$ (20 mol%), TMSCl (1.5 equiv.)	25 °C	24	N.R.[a]
6	$(O_3ReOSiPh_3)_3$ (20 mol%), TMSBr (1.5 equiv.)	25 °C	24	N.R.[b]
7	$(O_3ReOSiPh_3)_3$ (20 mol%)	25 °C	24	N.R.[a]

[a] N.R. denotes no reaction occurred with starting material recovered. [b] Starting allenic alcohol decomposed, pyridinone aldehyde recovered.

[31] Tadpetch, K.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 4839.

5.4 CONCLUSION

In conclusion, a novel *cis* Prins cyclization reaction of common allenic alcohols with aldehydes has been developed *via* suppression of undesirable oxonia-Cope rearrangement. At reduced reaction temperature and concentration, Prins cyclization of TMS-substituted allenic alcohol proceeds smoothly catalyzed by the mild Lewis acid indium trifluoroacetate with excellent chemical yields and stereoselectivity. While, it was a bit more complicated for Me-substituted allenic alcohols, the desired DHP products could only be formed by incorporating a carbonyl function adjacent to the hydroxyallenyl moiety so as to suppress the oxonia-Cope rearrangement, where the overall chemical yields were low with moderate stereoselectivities observed. The application of this methodology to the synthesis of (+)-Sambutoxin was unsuccessful due to the low reactivity of the starting pyridinone aldehyde.

CHAPTER 6

Experimental Section

6.1 GENERAL METHODS

Moisture and/or sensitive reactions 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 and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography.

Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 ^{o}C using Büchi rotary evaporator cooled with circulating ethylene glycol/water mixture (1:1) at -5 ^{o}C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[1] Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen.

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

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

Chromatography

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

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

Instruments & Equipments

Infrared Spectroscopy

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

Mass Spectroscopy

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

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and 500 NMR spectrometers. Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, $CDCl_3$ (^{1}H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.03, triplet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplets), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and ddt (doublet of doublet of triplets). Coupling constants (*J*) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by nH.

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 9.0 software.

6.2 *TRANS* PRINS CYCLIZATION

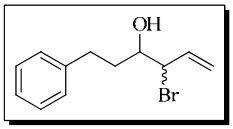
PRECEDURES AND DATA

Preparation of (*Z*)-*γ*-brominated-homoallylic alcohol.

1. To an oven dried (50 mL) round-bottom flask equipped with a magnetic stirring bar was added diisopropylamine (10.0 mmol, 1.40 mL), and anhydrous tetrahydrofuran (10 mL). The mixture was cooled to 0 ^{o}C prior to dropwise addition of *n*-butyl lithium (10.0 mmol, 6.3 mL, 1.6 M in hexane). The mixture was stirred at 0 ^{o}C for 30 minutes before being transferred into the other flask.

2. To an oven dried (100 mL) round-bottom flask equipped with a magnetic stirring bar was added $ZnBr_2$ (2.5 mmol, 0.5630 g, 1.25 equiv.), allyl bromide (5.0 mmol, 0.43 mL, 2.5 equiv.) and tetrahydrofuran (20 mL). The mixture was stirred and cooled to -78 ^{o}C. The preformed LDA was added dropwise *via* a plastic cannula and the mixture was stirred for around 20 minutes. Hydrocinnamaldehyde (2.0 mmol. 0.26 mL, 1.0 equiv.) was then added. Reaction was allowed to proceed for 3 hours at -78 ^{o}C. The reaction was quenched by pouring the reaction mixture into 1 M HCl solution (20 mL). The aqueous layer was extracted with diethyl ether (50 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (10% diethyl ether in hexane) to afford 4-bromo-1-phenylhex-5-en-3-ol (**1**) in 37% yield and (*Z*)-6-bromo-1-phenyl-hex-5en-3-ol (**4**) as a pale yellow oil in 62 % yield.

4-bromo-1-phenylhex-5-en-3-ol (1)



R*f*: 0.33 (hexane : diethyl ether = 4 : 1) (*syn* : *anti* = 3 : 1), yield: 37%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.16 (m, 5H), 6.01 (m, 1H,), 5.19 (m, 1H), 4.49 (m, 0.7H), 4.30 (m, 0.3H), 3.76 (s, 0.25H), 3.60 (s, 0.75H), 2.82 (m, 1H), 2.68 (m, 1H), 2.43 (s, 1H), 1.81-1.76 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.40, 141.37, 135.7, 135.0, 134.3, 133.8, 128.4, 125.9, 119.5, 119.3, 119.0, 118.7, 73.1, 68.8, 63.4, 61.4, 36.0, 35.28, 35.25, 31.7.

FTIR (neat) 3307, 3026, 2924, 2854, 1666, 1602, 1494, 1454, 1203, 1140, 1093, 1078, 968, 746, 698, 665 cm^{-1}.

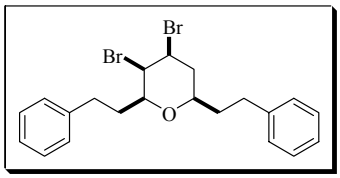
HRMS *m/z* Calcd for $C_{12}H_{16}{}^{79}BrO$ $[M+H]^+$: 255.0385, found: 255.0400.

Calcd for $C_{12}H_{16}{}^{81}BrO$ $[M+H]^+$: 257.0364, found: 257.0358.

Procedures for Prins cyclization of *syn* and *anti* bromohydrin with aldehyde

To an oven-dried (25mL) round-bottom flask equipped with a magnetic stirring bar was added indium triflate (67.4 mg, 0.12 mmol, 0.20 equiv.) and anhydrous dichloromethane (6 mL). The mixture was allowed to cool to 0 ^oC with vigorous stirring. 4-Bromo-1-phenylhex-5-en-3-ol **(1)** (154.8 mg, 0.60 mmol, 1.0 equiv.) in 1 mL dry CH_2Cl_2 was introduced into the suspension, and 5 minutes later bromotrimethylsilane (TMSBr, 0.12 mL, 0.90 mmol, 1.5 equiv.) was added. Hydrocinnamaldehyde (80.5 mg, 0.60 mmol, 1.0 equiv.) in 1 mL dry CH_2Cl_2 was slowly introduced over 10 minutes. The reaction was allowed to proceed at 0 ^oC for 3 hours before quenching with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane) to afford 3,4-dibromo-2,6-diphenethyl-tetrahydro-2H-pyran (**2**) and (**3**) in 47 % and 16% yield, respectively.

(2S*,3R*,4S*,6R*)-3,4-dibromo-2,6-diphenethyltetrahydro-2*H*-pyran (2)



R_f: 0.64 (hexane : diethyl ether = 4 : 1), yield: 47%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 10H), 4.27 (s, 1H), 4.19 (td, *J* = 3.87, 11.97 Hz, 1H), 3.34 (dddd, *J* = 2.25, 3.78, 8.61, 10.95 Hz, 1H), 3.20 (ddd, *J* = 0.87, 4.23, 8.61 Hz, 1H), 2.75 (m, 4H), 2.25 (m, 2H), 1.95 (m, 2H), 1.76 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 141.2, 128.49, 128.45, 128.41, 126.1, 125.9, 77.8, 77.3, 61.7, 49.5, 37.8, 37.1, 36.8, 31.5, 31.3.

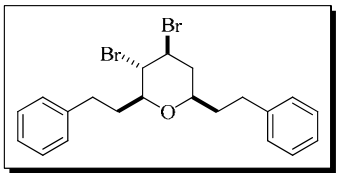
FTIR (KBr) 3024, 2924, 2848, 1602, 1495, 1454, 1435, 1329, 1290, 1222, 1182, 1153, 1122, 1086, 1057, 1028, 750, 698, 602 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{25}{}^{79}Br_2O$ $[M+H]^+$: 451.0272, found : 451.0257.

Calcd for $C_{21}H_{25}{}^{79}Br^{81}BrO$ $[M+H]^+$: 453.0252, found : 453.0247.

Calcd for $C_{21}H_{25}{}^{81}Br_2O$ $[M+H]^+$: 455.0231, found : 455.0324.

(2S*,3S*,4S*,6R*)-3,4-dibromo-2,6-diphenethyltetrahydro-2*H*-pyran (3)



R_f: 0.69 (hexane : diethyl ether = 4 : 1), yield: 16%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 10H), 4.12 (ddd, *J* = 5.05, 10.49, 12.11 Hz, 1H), 3.78 (t, *J* = 10.10, 10.20 Hz, 1H), 3.41 (dt, *J* = 2.19, 9.44 Hz, 1H), 3.34 (m, 1H), 2.80 (m, 4H), 2.46 (m, 1H) 2.34 (ddd, *J* = 1.81, 4.99, 13.30 Hz, 1H), 2.00 (q, *J* = 12.06 Hz, 1H), 1.88 (m, 2H), 1.73 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 141.35, 128.5, 128.4, 126.0, 125.9, 80.7, 76.2, 59.1, 54.0, 44.8, 36.8, 35.8, 31.6, 31.5.

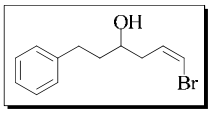
FTIR (neat) 3024, 2922, 2858, 1603, 1495, 1454, 1435, 1386, 1369, 1336, 1317, 1247, 1159, 1125, 1084, 1051, 1030, 962, 912, 872, 750, 698, 665 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{25}{}^{79}Br_2O$ $[M+H]^+$: 451.0272, found : 451.0294.

Calcd for $C_{21}H_{25}{}^{79}Br^{81}BrO$ $[M+H]^+$: 453.0252, found : 453.0259.

Calcd for $C_{21}H_{25}{}^{81}Br_2O$ $[M+H]^+$: 455.0231, found : 455.0247.

(*Z*)-6-bromo-1-phenylhex-5-en-3-ol (4)



R_f: 0.45 (hexane : ethyl acetate = 4 : 1) , yield: 62%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 5H), 6.23 (d, *J* = 7.08 Hz, 1H,), 6.16 (dd, *J* = 6.78, 13.68 Hz, 1H), 3.72 (m, 1H), 2.77 (td, *J* = 7.63, 13.53 Hz, 1H), 2.65 (td, *J* = 7.92, 13.95 Hz, 1H), 2.45-2.33 (m, 2H), 2.15 (s, 1H), 1.81-1.74 (m, 2H).

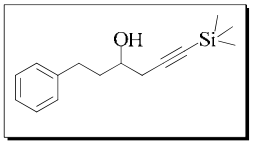
^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 130.8, 128.3, 128.2, 125.8, 109.8, 69.8, 38.4, 37.5, 31.8.

FTIR (neat) 3356, 3082, 3061, 3024, 2926, 2860, 1715, 1622, 1603, 1495, 1454, 1314, 1279, 1080, 1053, 1030, 748, 700, 675 cm^{-1}.

HRMS *m/z* Calcd for $C_{12}H_{15}BrO$ $[M^+]$: 254.0301, found: 254.0305.

Calcd for $C_{12}H_{15}{}^{81}BrO$ $[M^+]$: 256.0280, found: 256.0287.

1-Phenyl-6-trimethylsilanyl-hex-5-yn-3-ol



Trimethylsilylpropargyl bromide (956 mg, 5.0 mmol, 1.25 equiv.) was added to a suspension of the indium powder (574 mg, 5.0 mmol, 1.25 equiv.) and indium bromide (142 mg, 0.40 mmol, 0.1 equiv.) in 5 mL anhydrous THF at room temperature. After 15 minutes, hydrocinnamaldehyde (537 mg, 4.0 mmol, 1.0 equiv.) was added at room temperature. The mixture was refluxed overnight, and quenched with 50 mL 1M HCl solution. The aqueous layer was extracted with diethyl ether (50 mL × 3), and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and purified *via* flash chromatography (20% ethyl acetate in hexane) to afford 1-phenyl-6-trimethylsilanyl-hex-5-yn-3-ol in 60% yield as a yellow oil.

R_f: 0.45 (hexane : ethyl acetate = 4 : 1), yield: 60%.

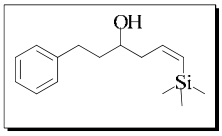
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 3.79-3.72 (m, 1H), 2.81 (td, *J* = 7.52, 13.72 Hz, 1H), 2.70 (td, *J* = 8.12, 13.88 Hz, 1H), 2.48 (dd, *J* = 4.76, 16.80 Hz, 1H), 2.38 (dd, *J* = 6.88, 16.76 Hz, 1H), 1.99 (d, *J* = 5.04 Hz, 1H), 1.99-1.84 (m, 2H), 0.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 128.4, 128.4, 125.9, 102.9, 87.8, 69.0, 37.8, 31.8, 29.0, 0.05.

FTIR (neat) 3356, 3026, 2957, 2174, 1495, 1454, 1418, 1250, 1080, 1030, 841, 760, 698, 648 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{21}OSi$ $[M-H]^+$: 245.1356, found $[M-H]^+$: 245.1366.

(*Z*)-1-phenyl-6-trimethylsilanyl-hex-5-en-3-ol



To an oven dried (50 mL) round-bottom flask equipped with a magnetic stirring bar was added 1-phenyl-6-trimethylsilanyl-hex-5-yn-3-ol (1.0 mmol, 246.4 mg, 1.0 equiv.) diluted with 1.5 mL anhydrous diethyl ether and stirred at 0 ^{o}C. DIBAL-H in heptane (1.0M in heptane, 2.6 mL, 2.6 mmol, 2.6 equiv.) was slowly added. The reaction was allowed to proceed at room temperature for 29 hours before quenching with methanol (10 mL) and saturated sodium potassium tartrate solution (10 mL). The aqueous layer was extracted with diethyl ether (20 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (5.0 % ethyl acetate in hexane) to afford the (*Z*)-1-phenyl-6-trimethylsilyl-hex-5-en-3-ol as a colorless oil in 64 % yield.

R_f: 0.47 (hexane : ethyl acetate = 4 : 1), yield: 64%.

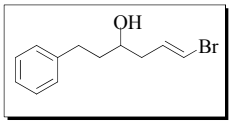
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 6.32 (ddd, *J* = 7.00, 7.96, 14.32 Hz, 1H), 5.70 (td, *J* = 1.16, 14.12 Hz, 1H) 3.70-3.67 (m, 1H), 2.82-2.73 (m, 1H), 2.71-2.67 (m, 1H), 2.36-2.30 (m, 1H), 1.83-1.77 (m, 1H), 1.57 (d, *J* = 4.00 Hz, 1H), 0.13 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 141.9, 133.2, 128.41, 128.39, 125.8, 70.5, 41.3, 38.5, 32.0, 0.25.

FTIR (neat) 3354, 3339, 2954, 2897, 1604, 1497, 1454, 1408, 1248, 1078, 1053, 858, 830, 764, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{24}OSi$ $[M^+]$: 248.1591, found : 248.1595.

(*E*)-6-bromo-1-phenylhex-5-en-3-ol (11)



To an oven dried (50 mL) round-bottom flask equipped with a magnetic stirring bar was added (*Z*)-1-phenyl-6-trimethylsilanyl-hex-5-en-3-ol (1126.9 mg, 5.11 mmol, 1.0 equiv.) diluted with 15 mL anhydrous dichloromethane, and cooled to -78 ^{o}C with stirring. Bromine (0.26 mL, 5.11 mmol, 1.0 equiv.) was added dropwise into the solution of (*Z*)-1-phenyl-6-trimethylsilanyl-hex-5-en-3-ol. The reaction was quenched by adding 10% Na_2SO_3 solution upon the persistence of brownish color. Reaction mixture was extracted with dichloromethane (50 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was cooled to -20 ^{o}C prior to addition of TBAF (10.22 mL, 10.22 mmol, 2.0 equiv.). The mixture was allowed to be stirred at -20 ^{o}C for 30 minutes. The reaction mixture was concentrated *in vacuo*. The residual crude was purified *via* flash chromatography (20% ethyl acetate in hexane) to afford (*E*)-γ-brominated-homoallylic alcohol as a yellow oil in 90% yield.

R_f: 0.34 (hexane : ethyl acetate = 4 : 1), yield: 90%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 6.20 (td, *J* = 7.36, 13.60 Hz, 1H), 6.12 (d, *J* = 13.60 Hz) 3.68-3.65 (m, 1H), 2.79 (td, *J* = 8.12, 13.39 Hz, 1H), 2.66 (td, *J* = 8.26, 13.96 Hz,1H), 2.29-2.22 (m, 1H), 2.17 (td, *J* = 7.49, 14.13 Hz, 1H), 1.79-1.73 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 133.9, 128.41, 128.36, 125.9, 106.9, 69.7, 40.8, 38.3, 31.9.

FTIR (neat) 3377, 3360, 3026, 2931, 2860, 1620, 1499, 1454, 1433, 1275, 1242, 1084, 1051, 943, 748, 700 cm^{-1}.

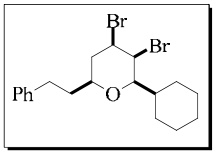
HRMS *m/z* Calcd for $C_{12}H_{15}BrO$ [M^{+}]: 254.0301, found : 254.0292.

Calcd for $C_{12}H_{15}{}^{81}BrO$ $[M^+]$: 256.0280, found : 256.0273.

General Procedures for the construction of 2,6-*cis*-dibromo-tetrasubstituted tetrahydropyrans.

To an oven-dried (25 mL) round-bottom flask equipped with a magnetic stirring bar was added indium bromide (106.0 mg, 0.30 mmol, 1.0 equiv.) and anhydrous dichloromethane (1.5 mL). The mixture was allowed to cool to 0 ^oC with vigorous stirring. (*Z*)-γ-Brominated-homoallylic alcohol (91.8 mg, 0.36 mmol, 1.2 equiv.) in 1 mL dry CH_2Cl_2 was introduced into the suspension, and 5 minutes later bromotrimethylsilane (TMSBr, 0.05 mL, 0.36 mmol, 1.2 equiv.) was added. Cyclohexanecarboxaldehyde (33.7 mg, 0.30 mmol, 1.0 equiv.) in 1 mL dry CH_2Cl_2 was slowly introduced over 10 minutes. The reaction was allowed to proceed at 0 ^oC for 90 minutes before quenching with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane) to afford **5** as a white solid in 95 % yield.

(2R*,3S*,4R*,6S*)-3,4-dibromo-2-cyclohexyl-6-phenethyl-tetrahydro-2*H*-pyran (5)



R_f: 0.69 (hexane : diethyl ether = 4 : 1), yield: 95%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.14 (m, 5H), 4.38 (d, *J* = 2.79 Hz, 1H), 4.22 (ddd, *J* = 3.12, 3.93, 12.19 Hz, 1H), 3.32-3.23 (m, 1H), 2.85-2.76 (m, 2H), 2.69 (td, *J* = 8.10, 13.75 Hz, 1H), 2.23-2.15 (m, 2H), 1.97-1.87 (m, 2H), 1.77-1.66 (m, 6H), 1.31-1.13 (m, 3H), 0.98 (m, 1H), 0.79 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 128.5, 128.3, 125.9, 83.8, 77.0, 59.5, 50.2, 41.5, 38.3, 36.9, 31.4, 29.9, 27.4, 26.3, 25.6, 25.5.

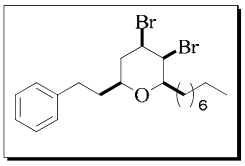
FTIR (KBr) 3021, 2930, 2918, 2851, 1450, 1433, 1313, 1224, 1080, 1067, 1055, 744, 696, 575 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{26}Br_2O$ [M^+]: 428.0345, found : 428.0332.

Calcd for $C_{19}H_{26}Br^{81}BrO$ [M^+]: 430.0324, found : 430.0311.

Calcd for $C_{19}H_{26}{}^{81}Br_2O$ [M^+]: 432.0304, found : 432.0294.

(2R*,3S*,4R*,6S*)-3,4-dibromo-2-octyl-6-phenethyl-tetrahydro-2*H*-pyran (6)



Yellow oil; **R_f:** 0.75 (hexane : diethyl ether = 4 : 1), yield: 87%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 4.31 (s, 1H), 4.29-4.26 (m, 1H), 3.37-3.31 (m, 1H), 3.22 (dd, *J* = 5.57, 7.27 Hz, 1H), 2.80 (ddd, *J* = 5.48, 8.77, 14.03 Hz, 1H), 2.70 (td, *J* = 8.13, 13.87 Hz, 1H), 2.23 (q, *J* = 11.99 Hz, 1H), 2.00-1.91 (m, 2H), 1.87-1.80 (m, 1H), 1.75-1.51 (m, 1H), 1.58-1.51 (m, 1H), 1.45-1.41 (m, 1H), 1.32-1.28 (m, 11H), 0.88 (t, *J* = 7.21 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 128.5, 128.4, 125.9, 79.3, 77.2, 61.8, 49.8, 37.9, 36.8, 35.4, 31.8, 31.4, 29.5, 29.4, 29.2, 25.2, 22.7, 14.1.

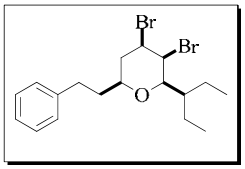
FTIR (neat) 2951, 2924, 2855, 1495, 1454, 1114, 1084, 910, 735, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{32}Br_2O$ [M^+]: 458.0814, found : 458.0802.

Calcd for $C_{21}H_{32}Br^{81}BrO$ [M^+]: 460.0794, found : 460.0785.

Calcd for $C_{21}H_{32}{}^{81}Br_2O$ [M^+]: 462.0773, found : 462.0767.

(2R*,3S*,4R*,6S*)-3,4-dibromo-2-(pentan-3-yl)-6-phenethyl-tetrahydro-2*H*-pyran (7)



Yellow oil; **R_f:** 0.67 (hexane : diethyl ether = 4 : 1), yield: 68%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5H), 4.41 (d, *J* = 2.90 Hz, 1H), 4.27 (td, *J* = 4.01, 12.21 Hz), 3.35-3.29 (m, 1H), 2.99 (d, *J* = 9.96 Hz, 1H), 2.83 (ddd, *J* = 5.22, 8.76, 13.98 Hz, 1H), 2.68 (dt, *J* = 8.11, 13.95 Hz, 1H), 2.23 (q, *J* = 12.45 Hz, 1H), 2.02-1.91 (m, 2H), 1.86-1.78 (m, 2H), 1.76-1.67 (m, 2H), 1.62-1.51 (m, 1H), 1.48-1.39 (m, 1H), 1.28-1.19 (m, 1H), 0.88 (t, *J* = 7.34 Hz, 6H).

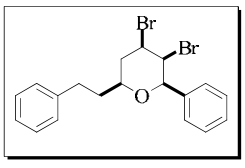
^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 128.5, 128.4, 125.9, 80.9, 77.4, 60.2, 50.3, 43.1, 38.3, 36.9, 31.5, 19.8, 18.9, 9.7, 9.6.

FTIR (neat) 3024, 2961, 2934, 2874, 1495, 1454, 1381, 1290, 1220, 1112, 1082, 746, 698, 600 cm^{-1}.

HRMS *m/z* Calcd for $C_{18}H_{26}Br^{81}BrO$ [M^+]: 418.0324, found : 418.0319.

Calcd for $C_{18}H_{26}{}^{81}Br_2O$ [M^+]: 420.0304, found : 420.0300.

(2R*,3S*,4R*,6S*)-3,4-dibromo-6-phenethyl-2-phenyl-tetrahydro-2*H*-pyran (8)



Pale yellow oil; **R_f:** 0.50 (hexane : diethyl ether = 4 : 1), yield: 71%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.18 (m, 10H), 4.58 (t, *J* = 1.48 Hz, 1H), 4.56 (s, 1H), 4.50 (dt, *J* = 4.12, 11.36 Hz, 1H), 3.63-3.55 (m, 1H), 2.87 (ddd, *J* = 5.53, 8.99 14.05 Hz, 1H), 2.79 (td, *J* = 8.15, 13.86 Hz, 1H), 2.38 (q, *J* = 12.46 Hz, 1H), 2.15-2.02 (m, 2H), 1.92-1.82 (m, 1H).

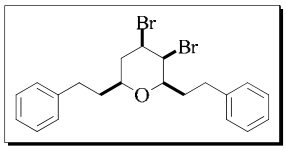
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.5, 128.5, 128.4, 128.2, 127.8, 125.9, 125.4, 79.7, 77.4, 62.4, 49.3, 37.5, 36.9, 31.4.

FTIR (neat) 3061, 3026, 2930, 2855, 2174, 1732, 1602, 1495, 1452, 1418, 1228, 1123, 1088, 1066, 955, 741, 698, 573 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{20}Br_2O$ $[M^+]$: 421.9875, found : 421.9896.

Calcd for $C_{19}H_{20}Br^{81}BrO$ $[M^+]$: 423.9855, found : 423.9845.

(2R*,3S*,4R*,6S*)-3,4-dibromo-2,6-diphenethyl-tetrahydro-2*H*-pyran (9)



White solid, m.p. 91.6-92.3 ^oC; **R_f:** 0.67 (hexane : diethyl ether = 4 : 1), yield: 91%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.16 (m, 10H), 4.22 (s, 1H), 4.17 (td, J = 3.88, 11.84 Hz, 1H), 3.33-3.27 (m, 1H), 3.15 (dd, *J* = 3.80, 8.40 Hz, 1H), 2.83-2.66 (m, 4H), 2.27-2.16 (m, 2H), 2.00-1.87 (m, 2H), 1.79-1.68 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.1, 128.43, 128.38, 128.34, 126.0, 125.9, 77.7, 77.1, 61.7, 49.5, 37.8, 37.0, 36.7, 31.4, 31.3.

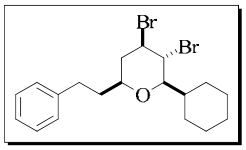
FTIR (KBr) 3024, 2957, 2924, 2852, 1597, 1495, 1452, 1314, 1255, 1220, 1123, 1087, 1026, 935, 743, 696, 602, 511, 482 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{24}Br_2O$ $[M^+]$: 450.0188, found : 450.0193.

Calcd for $C_{21}H_{24}Br^{81}BrO$ $[M^+]$: 452.0168, found : 452.0168.

Calcd for $C_{21}H_{24}{}^{81}Br_2O$ $[M^+]$: 454.0147, found : 454.0155.

(2R*,3R*,4R*,6S*)-3,4-dibromo-2-cyclohexyl-6-phenethyl-tetrahydro-2*H*-pyran (12)



Pale yellow oil; **R_f:** 0.81 (hexane : diethyl ether = 4 : 1), yield: 92%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 4.15 (ddd, J = 4.92, 10.44, 12.00 Hz, 1H), 3.92 (t, J = 10.28 Hz, 1H), 3.26-3.23 (m, 2H), 2.77 (ddd, *J* = 5.24, 8.57, 13.80 Hz 1H), 2.67 (td, *J* = 8.15, 13.74 Hz, 1H), 2.30 (ddd, *J* = 1.64, 4.92, 13.24 Hz, 1H), 2.01 (s, 1H), 1.95 (q, *J* = 12.27 Hz, 1H), 1.86-1.77 (m, 3H), 1.70-1.64 (m, 2H), 1.60-1.50 (m, 3H), 1.35-1.13 (m , 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 128.4, 128.3, 125.9, 85.1, 76.0, 56.7, 55.0, 44.9, 39.9, 36.7, 31.4, 30.8, 26.6, 26.4, 26.2, 24.4.

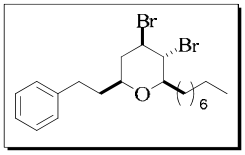
FTIR (neat) 3026, 2928, 2853, 1495, 1450, 1161, 1126, 1088, 1057, 1032, 1001, 750, 736, 698, 492 cm^{-1}.

HRMS m/z Calcd for $C_{19}H_{26}Br_2O$ $[M^+]$: 428.0345, found : 428.0352.

Calcd for $C_{19}H_{26}Br^{81}BrO$ $[M^+]$: 430.0324, found : 430.0335.

Calcd for $C_{19}H_{26}{}^{81}Br_2O$ $[M^+]$: 432.0304, found : 432.0314.

(2R*,3R*,4R*,6S*)-3,4-dibromo-2-octyl-6-phenethyl-tetrahydro-2*H*-pyran (13)



Pale yellow oil; **R_f:** 0.78 (hexane : diethyl ether = 4 : 1), yield: 82%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5H), 4.14 (ddd, *J* = 4.96, 10.56, 12.08 Hz, 1H), 3.75 (t, *J* = 10.20 Hz, 1H), 3.39 (dt, *J* = 2.12, 10.24 Hz, 1H), 3.31-3.24 (m, 1H), 2.75 (ddd, *J* = 5.25, 8.64, 13.74 Hz, 1H), 2.66 (td, *J* = 8.18, 13.74 Hz, 1H), 2.32 (ddd, *J* = 1.40, 4.84, 13.20 Hz, 1H), 2.12-2.07 (m, 1H), 1.99 (q, *J* = 12.16 Hz, 1H), 1.89-1.80 (m, 1H), 1.72-1.64 (m, 1H), 1.72-1.64 (m, 1H), 1.59-1.51 (m, 2H), 1.31-1.29 (m, 11H), 0.90-0.87 (t, *J* = 6.96 Hz, 3H).

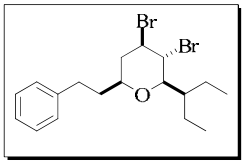
^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 128.43, 128.41, 125.9, 81.6, 75.9, 59.5, 54.3, 44.9, 36.7, 34.2, 31.9, 31.4, 29.5, 29.3, 29.2, 25.3, 22.7, 14.1.

FTIR (neat) 3356, 3026, 2957, 2174, 1495, 1454, 1418, 1250, 1080, 1030, 841, 760, 698, 648 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{32}Br^{81}BrO$ $[M^+]$: 460.0794, found : 460.0782.

Calcd for $C_{21}H_{32}{}^{81}Br_2O$ $[M^+]$: 462.0773, found : 462.0777.

(2R*,3R*,4R*,6S*)-3,4-dibromo-2-(pentan-3-yl)-6-phenethyl-tetrahydro-2*H*-pyran (14)



Pale yellow oil; **R_f:** 0.72 (hexane : diethyl ether = 4 : 1), yield: 90%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5H), 4.18 (ddd, *J* = 4.92, 10.32, 12.12 Hz, 1H), 3.98 (t, *J* = 10.20 Hz, 1H), 3.47 (dd, *J* = 1.92, 10.12 Hz, 1H), 3.30-3.23 (m, 1H), 2.77 (ddd, *J* = 5.21, 8.90, 13.89 Hz 1H), 2.64 (td, *J* = 8.25, 13.78 Hz, 1H), 2.32 (ddd, *J* = 1.72, 4.88, 13.24 Hz, 1H), 1.97 (q, *J* = 12.28 Hz, 1H), 1.88-1.78 (m, 2H), 1.73-1.64 (m, 1H), 1.60-1.38 (m, 3H), 1.32-1.19 (m, 1H), 0.93 (t, *J* = 7.47 Hz, 6H).

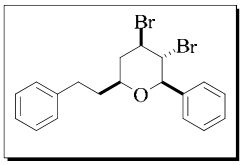
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 128.4, 125.9, 82.5, 76.3, 57.3, 55.0, 45.0, 43.1, 36.9, 31.4, 23.2, 20.6, 12.3, 11.9.

FTIR (neat) 3026, 2953, 2924, 2854, 1495, 1454, 1369, 1159, 1130, 1114, 1082, 1053, 748, 735, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{18}H_{26}Br^{81}BrO$ $[M^+]$: 418.0324, found : 418.0326.

Calcd for $C_{18}H_{26}{}^{81}Br_2O$ $[M^+]$: 420.0304, found : 420.0306.

(2R*,3R*,4R*,6S*)-3,4-dibromo-6-phenethyl-2-phenyl-tetrahydro-2*H*-pyran (15)



White solid, m.p.76.0-77.0 °C; **R_f:** 0.58 (hexane : diethyl ether = 4 : 1), yield: 77%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.11 (m, 10H), 4.39 (d, *J* = 10.00 Hz, 1H), 4.28 (ddd, *J* = 4.88, 10.72, 11.76 Hz, 1H), 4.05 (t, *J* = 10.20 Hz, 1H), 3.53-3.44 (m, 1H), 2.73-2.63 (m, 2H), 2.48 (ddd, *J* = 1.16, 4.68, 13.36 Hz, 1H), 2.17 (q, *J* = 12.28 Hz, 1H), 1.97-1.88 (m, 1H), 1.81-1.72 (m, 1H).

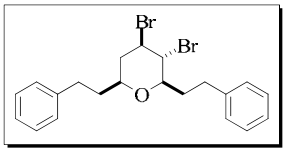
^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 138.9, 128.7, 128.4, 128.4, 128.3, 127.7, 125.9, 84.9, 76.7, 59.2, 53.7, 44.4, 36.5, 31.2.

FTIR (KBr) 3055, 3022, 2980, 2931, 2918, 2848, 1495, 1452, 1433, 1364, 1305, 1281, 1215, 1165, 1149, 1076, 1057, 763, 725, 704, 698, 527 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{20}Br_2O$ $[M^+]$: 421.9875, found : 421.9879.

Calcd for $C_{19}H_{20}Br^{81}BrO$ $[M^+]$: 423.9855, found : 423.9859.

(2R*,3R*,4R*,6S*)-3,4-dibromo-2,6-diphenethyl-tetrahydro-2*H*-pyran (16)



Yellow oil; **R_f:** 0.64 (hexane : diethyl ether = 4 : 1), yield: 90%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.16 (m, 10H), 4.12 (ddd, *J* = 4.96, 10.48, 12.12 Hz, 1H), 3.78 (t, *J* = 10.20 Hz, 1H), 3.43 (dt, *J* = 2.04, 9.52 Hz, 1H), 3.33-3.27 (m, 1H), 2.90 (ddd, *J* = 4.81, 9.80, 14.06 Hz 1H), 2.82 (ddd, *J* = 5.36, 8.88, 13.87 Hz, 1H), 2.74-2.68 (m, 2H), 2.50-2.41 (m, 1H) 2.34 (ddd, *J* = 1.64, 4.92, 13.28 Hz, 1H), 2.00 (q, *J* = 12.24 Hz, 1H), 1.94-1.82 (m, 2H), 1.76-1.68 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 141.3, 128.5, 128.4, 126.0, 125.9, 80.6, 76.1, 59.1, 53.9, 44.8, 36.8, 35.8, 31.6, 31.5.

FTIR (neat) 3024, 2947, 2920, 2859, 1495, 1454, 1155, 1124, 1084, 1051, 750, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{24}Br^{81}BrO$ $[M^+]$: 452.0168, found : 452.0179.

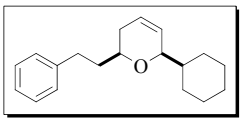
Calcd for $C_{21}H_{24}{}^{81}Br_2O$ $[M^+]$: 454.0147, found : 454.0160.

Procedures of debromination of 2,6-*cis*-4,5-dibromo-tetrahydropyran.

Approach 1.To an oven-dried (25 mL) round-bottom flask equipped with a magnetic stirring bar was added **5** (44.9 mg, 0.10 mmol, 1.0 equiv.) in 2.5 mL anhydrous glacial acetic acid and activated zinc (68.8 mg, 1.0 mmol, 10.0 equiv.). The reaction was allowed to proceed at room temperature for 24 hrs before diluting with diethyl ether (10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.4% diehthyl ether in hexane) to afford **18** as a pale yellow oil in 70% yield.

Approach 2.To an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added **5** (24.5 mg, 0.06 mmol, 1.0 equiv.) and tributyltin hydride (0.015 mL, 0.06 mmol, 1.0 equiv.) in 1 mL anhydrous toluene and ACCN (1,1'-azobis(cyclohexane) carbonitrile, 1.2 mg, 0.005 mmol, 0.10 equiv.). The reaction was allowed to proceed at 110 ^{o}C for 24 hrs before quenching with saturated KF solution (15 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (1% diehthyl ether in hexane) to afford (2S*,6R*)-6-cyclohexyl-2-phenethyl-3,6-dihydro-2*H*-pyran **18** as a pale yellow oil in 71% yield.

(2S*,6R*)-6-cyclohexyl-2-phenethyl-3,6-dihydro-2*H*-pyran (18)



R$_f$: 0.75 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.09 (m, 5H), 5.71 (ddd, *J* = 2.72, 5.40, 10.28 Hz, 1H), 5.60 (td, *J* = 1.04, 10.28 Hz, 1H), 3.76 (d, *J* = 1.80 Hz, 1H), 3.39-3.33 (m, 1H), 2.70 (ddd, *J* = 5.33, 8.95, 13.90 Hz, 1H) 2.65 (td, *J* = 8.28, 13.71 Hz, 1H), 1.83-1.76 (m, 4H), 1.70-1.60 (m, 5H), 1.36-1.33 (m, 1H), 1.18-1.03 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 129.0, 128.6, 128.2, 125.6, 125.0, 79.0, 72.4, 42.8, 37.6, 31.6, 31.5, 28.7, 28.3, 26.6, 26.30, 26.29.

FTIR (neat) 3026, 2924, 2851, 1495, 1450, 1188, 1130, 1088, 1070, 746, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{26}O$ [M^+]: 270.1978, found: 270.1967.

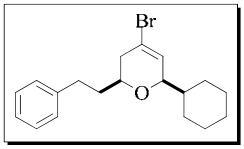
Procedures of elimination of 2,6-*cis*-4,5-dibromo-tetrahydropyran (5)

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added **5** (136.3 mg, 0.32 mmol, 1.0 equiv.) in 1 mL dry ethanol and potassium *tert*-butoxide (0.64 mL, 0.64 mmol, 2.0 equiv.).The reaction was allowed to proceed at room temperature for 24 hrs before quenching with saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.4% diehthyl ether in hexane) to afford (2S*,6R*)-4-bromo-6-cyclohexyl-2-phenethyl-3,6-dihydro-2*H*-pyran (**19**) as a colorless oil in 69% yield.

Procedures of elimination of 2,6-*cis*-4,5-dibromo-tetrahydropyran (12)

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added **12** (86.0 mg, 0.20 mmol, 1.0 equiv.) in 2 mL dry α,α,α-trifluorotoluene and potassium *tert*-butoxide (0.40 mL, 0.40 mmol, 2.0 equiv.).The reaction was allowed to proceed at reluxing temperature (~110 ^{o}C) for 24 hrs before quenching with saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.4% diethyl ether in hexane) to afford (2S*,6R*)-4-bromo-6-cyclohexyl-2-phenethyl-3,6-dihydro-2*H*-pyran (**19**) as a colorless oil in 59% yield.

(2S*,6R*)-4-bromo-6-cyclohexyl-2-phenethyl-3,6-dihydro-2*H*-pyran (19)



R_f: 0.79 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.09 (m, 5H), 5.96 (s, 1H), 3.77 (m, 1H), 3.47-3.38 (m, 1H), 2.70 (ddd, *J* = 5.49, 8.67, 13.86 Hz 1H), 2.63 (td, *J* = 6.01, 13.72 Hz, 1H) 2.39-2.28 (m, 1H), 2.17 (td, *J* = 2.92, 16.79 Hz, 1H), 1.85-1.62 (m, 8H), 1.18-0.99 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 130.1, 128.5, 128.3, 125.8, 119.0, 80.4, 73.5, 42.6, 41.1, 36.9, 31.4, 28.7, 28.0, 26.5, 26.2, 26.1.

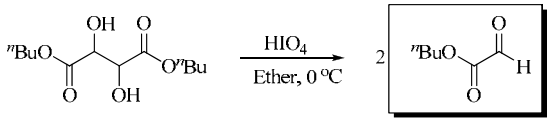
FTIR (neat) 2926, 2853, 1649, 1602, 1495, 1450, 1341, 1317, 1123, 746, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{25}BrO$ [M^+]: 348.1083, found: 348.1086.

Calcd for $C_{19}H_{25}{}^{81}BrO$ [M^+]: 350.1063, found: 350.1074.

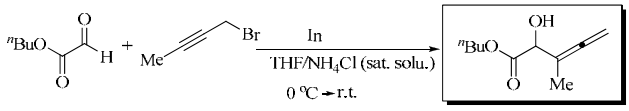
General Procedure for *trans* Prins Cyclization of carboalkoxyl Allenic Alcohols

Preaprations of *n*-butyl glyoxylate



To a solution of di-*n*-butyl tartrate (2.62 g, 10 mmol) in dry ether (60 mL) cooled was added periodic acid (2.28 g, 10 mmol) in portions over 1 h under N_2 at 0 °C. The resulting reaction was stirred for 4 h, decanted from the solid precipitate, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was distilled under reduced pressure to give *n*-butyl glyoxylate (2.45 g) as a viscous oil in 94% yield; b. p. 55-63 °C/12 mmHg.

Preparation of butyl 2-hydroxy-3-methylpenta-3,4-dienoate (20)



1-Bromo-2-butyne (1.33 g, 10 mmol, 2.0 equiv) was added to a mixture of *n*-butyl glyoxylate (0.65 g, 5 mmol, 1.0 equiv) and indium power (1.15 g, 10 mmol, 2.0 equiv) in THF/NH_4Cl(aq. sat.) (1:5, 20 mL) at 0 ^oC with vigorous stirring. After 0.5 hour, the mixture was warmed to room temperature and kept for another 6 hours, and finally quenched with 20 mL of 1 M HCl solution. The aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by flash gel column chromatogragh to provide **20** in 83% yield as a clear oil.

R_f: 0.30 (Hexane: Ethyl acetate = 4 : 1)

^{1}H NMR (300 MHz, $CDCl_3$): 4.79-4.83 (m, 2H), 4.56 (s, 1H), 4.13-4.25 (m, 2H), 3.03 (s, 1H), 1.72 (t, *J* = 3.2 Hz, 3H), 1.59-1.69 (m, 2H), 1.32-1.44 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): 206.6, 173.3, 97.9, 77.1, 72.3, 65.8, 30.6, 19.0, 14.3, 13.6

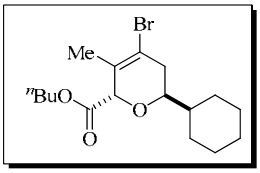
FTIR (NaCl): 3462, 2961, 2874, 1962, 1732, 1462, 1273, 1198, 1080, 850 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{10}H_{16}NaO_3$ $[M + Na]^+$: 207.0997, Found: 207.0988

To an oven dried 10 mL round-bottom flask with a magnetic stirring bar was added indium(III) triflate (16.9 mg, 0.03 mmol, 0.1 equiv) in 2 mL anhydrous CH_2Cl_2. The mixture was allowed to cool to 0 ^oC prior to addition of trimethylsilylbromide (55.1 mg, 0.36 mmol, 1.2 equiv). Cyclohexanecarboxaldehyde (40.4 mg, 0.36 mmol, 1.2 equiv) was added within 5 minutes. Then a solution of butyl 2-hydroxy-3-methylpenta- 3,4-dienoate (**20**, 55.3 mg, 0.3 mmol, 1.0 equiv) dissolved in 1 mL anhydrous CH_2Cl_2 was added using syringe pump addition over a period of 1 hour. The reaction was stirred at 0 ^oC for 2 hours, warming up to room temperature. The

mixture was quenched with saturated $NaHCO_3$ aqueous solution (10 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3). The combined organic layers were washed with water, brine, and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue crude product was purified by flash column chromatography to afford dihydropyrans **21** in 84% yield and **21'** in 12% yield as colorless oil.

(2S*,6S*)-butyl 4-bromo-6-cyclohexyl-3-methyl-5,6-dihydro-2*H*-pyran-2-carboxylate (21)



R_f: 0.46 (Hexane: Diethyl ether = 8 : 1), yield: 84%.

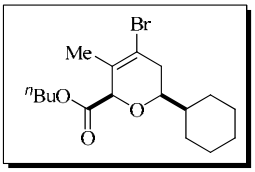
^{1}H NMR (400 MHz, $CDCl_3$): 4.57 (s, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 3.90 (ddd, *J* = 3.7, 7.1, 10.5 Hz, 1H), 2.19-2.56 (m, 2H), 1.95 (d, *J* = 12.9 Hz, 1H), 1.88 (s, 3H), 1.61-1.75 (m, 6H), 1.35-1.46 (m, 3H), 1.13-1.26 (m, 3H), 0.98-1.08 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 128.2, 119.6, 77.5, 76.1, 65.1, 42.2, 38.7, 30.6, 28.8, 28.1, 26.5, 26.0, 25.9, 19.4, 19.2, 13.7

FTIR (NaCl) 2926, 2853, 1732, 1454, 1383, 1346, 1305, 1280, 1179, 1130, 1063, 1020, 972, 831, 737 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{17}H_{27}{}^{79}BrNaO_3$ $[M + Na]^+$: 381.1041, Found: 381.1031

(2R*,6S*)-butyl 4-bromo-6-cyclohexyl-3-methyl-5,6-dihydro-2*H*-pyran-2-carboxylate (21')



R_f: 0.40 (Hexane: Diethyl ether = 8 : 1), yield: 12%.

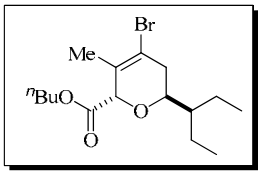
^{1}H NMR (400 MHz, $CDCl_3$): 4.63 (s, 1H), 4.13-4.22 (m, 2H), 4.31-4.37 (m, 1H), 2.19-2.68 (m, 2H), 1.97 (d, *J* = 12.4 Hz, 1H), 1.74 (s, 3H), 1.62-1.72 (m, 6H), 1.46-1.54 (m, 1H), 1.34-1.44 (m, 2H), 1.09-1.25 (m, 4H), 0.96-1.01 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.3, 128.3, 119.5, 80.1, 79.2, 65.3, 42.0, 38.9, 30.5, 29.1, 28.1, 26.4, 26.0, 25.8, 19.1, 17.5, 13.7

FTIR (NaCl) 2930, 2855, 1732, 1678, 1607, 1369, 1344, 1250, 1219, 1169, 1069, 756 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{17}H_{27}{}^{79}BrNaO_3$ $[M + Na]^+$: 381.1041, Found: 381.1047

(2S*,6S*)-butyl 4-bromo-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2*H*-pyran-2-carboxylate (22)



R_f: 0.48 (Hexane: Diethyl ether = 8 : 1), yield: 75%.

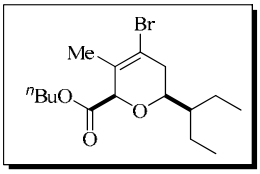
^{1}H NMR (400 MHz, $CDCl_3$): 4.60 (s, 1H), 4.12-4.19 (m, 3H), 2.19-2.63 (m, 2H), 1.91 (s, 3H), 1.64-1.71 (m, 2H), 1.22-1.56 (m, 7H), 0.89-0.98 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 128.2, 119.6, 77.5, 73.6, 65.1, 45.3, 38.6, 30.6, 21.1, 21.0, 19.3, 19.2, 13.7, 11.3, 11.1

FTIR (NaCl) 2961, 2874, 1744, 1462, 1381, 1221, 1179, 1128, 1099, 1020, 972, 792 cm^{-1}

HRMS (ESI) ***m/z*** calculated for $C_{16}H_{27}{}^{79}BrNaO_3$ $[M + Na]^+$: 369.1041, Found: 369.1040

(2R*,6S*)-butyl 4-bromo-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2*H*-pyran-2-carboxylate (22')



R_f: 0.45 (Hexane: Diethyl ether = 8 : 1), yield: 6%.

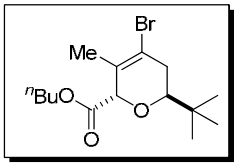
^{1}H NMR (400 MHz, $CDCl_3$): 4.64 (s, 1H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.56-3.63 (m, 1H), 2.18-2.75 (m, 2H), 1.77 (s, 3H), 1.63-1.68 (m, 2H), 1.37-1.56 (m, 6H), 1.21-1.29 (m, 1H), 0.87-0.98 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.3, 128.2, 119.5, 80.1, 76.5, 65.3, 44.7, 38.5, 30.5, 21.3, 21.0, 19.1, 17.5, 13.7, 11.1, 11.0

FTIR (NaCl) 2961, 2874, 1738, 1462, 1381, 1279, 1177, 1121, 1099, 1022, 972, 758 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{16}H_{27}{}^{79}BrNaO_3$ $[M + Na]^+$: 369.1041, Found: 369.1040

(2S*,6S*)-butyl 4-bromo-6-tert-butyl-3-methyl-5,6-dihydro-2*H*-pyran-2-carboxylate (23)



R_f: 0.53 (Hexane: Diethyl ether = 8 : 1), yield (%): 84%, dr (*trans*/*cis*) = 92:8.

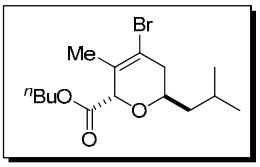
^{1}H NMR (400 MHz, $CDCl_3$): 4.58 (s, 1H), 4.09-4.18 (m, 2H), 3.81 (dd, *J* = 3.5, 10.9 Hz, 1H), 2.12-2.59 (m, 2H), 1.87 (s, 3H), 1.61-1.68 (m, 2H), 1.34-1.43 (m, 2H), 0.93 (s, 3H), 0.91 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 128.1, 119.9, 79.0, 77.7, 65.0, 36.2, 33.7, 30.6, 25.5, 19.3, 19.2, 13.6

FTIR (NaCl) 2958, 2872, 1734, 1678, 1466, 1396, 1365, 1300, 1242, 1179, 1128, 1107, 1015, 966, 837, 737 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{15}H_{25}{}^{79}BrNaO_3$ $[M + Na]^+$: 355.0885, Found: 355.0862

(2S*,6R*)-butyl 4-bromo-6-isobutyl-3-methyl-5,6-dihydro-2*H*-pyran-2-carboxylate (24)



R_f: 0.44 (Hexane: Diethyl ether = 8 : 1), yield: 73%.

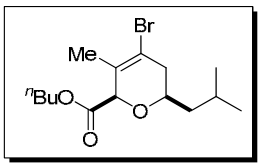
^{1}H NMR (400 MHz, $CDCl_3$): 4.56 (s, 1H), 4.22-4.29 (m, 1H), 4.15 (t, *J* = 6.6 Hz, 2H), 2.23-2.44 (m, 2H), 1.88 (s, 3H), 1.79-1.86 (m, 1H), 1.61-1.68 (m, 2H), 1.47-1.55 (m, 1H), 1.34-1.43 (m, 2H), 1.20-1.28 (m, 1H), 0.91-0.95 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 128.1, 119.0, 77.4, 70.4, 65.1, 44.6, 41.6, 30.6, 24.3, 23.2, 22.3, 19.3, 19.2, 13.7

FTIR (NaCl) 2957, 2872, 1732, 1682, 1468, 1383, 1342, 1269, 1225, 1179, 1126, 1101, 1069, 970, 802 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{15}H_{25}{}^{79}BrNaO_3$ $[M + Na]^+$: 355.0885, Found: 355.0885

(2R*,6R*)-butyl 4-bromo-6-isobutyl-3-methyl-5,6-dihydro-2*H*-pyran-2-carboxylate (24')



R_f: 0.41 (Hexane: Diethyl ether = 8 : 1), yield: 8%.

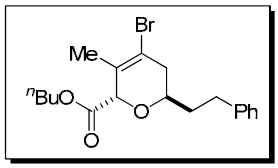
^{1}H NMR (400 MHz, $CDCl_3$): 4.66 (s, 1H), 4.13-4.23 (m, 2H), 3.66-3.74 (m, 1H), 2.18-2.64 (m, 2H), 1.75-1.83 (m, 1H), 1.77 (s, 3H), 1.62-1.69 (m, 3H), 1.36-1.43 (m, 2H), 1.28-1.35 (m, 1H), 0.91-0.98 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.3, 128.3, 119.0, 80.0, 73.4, 65.4, 43.9, 41.6, 30.5, 24.3, 22.9, 22.4, 19.1, 17.5, 13.7

FTIR (NaCl) 2959, 2872, 1732, 1682, 1614, 1470, 1454, 1371, 1252, 1229, 1171, 1142, 1069, 988, 891 cm^{-1}

HRMS (ESI) m/z Calcd for $C_{15}H_{25}{}^{79}BrNaO_3$ $[M + Na]^+$: 355.0885, Found: 355.0878

(2S*,6R*)-butyl 4-bromo-3-methyl-6-phenethyl-5,6-dihydro-2*H*-pyran-2-carboxylate (25)



R_f: 0.46 (Hexane: Diethyl ether = 8 : 1), yield: 70%.

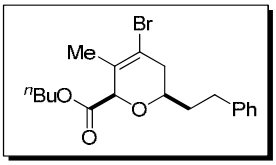
^{1}H NMR (400 MHz, $CDCl_3$): 7.18-7.31 (m, 5H), 4.63 (s, 1H), 4.21-4.27 (m, 1H), 4.18 (t, J = 6.7 Hz, 2H), 2.84-2.92 (m, 1H), 2.66-2.73 (m, 1H), 2.25-2.57 (m, 2H), 1.91 (s, 3H), 1.76-1.89 (m, 2H), 1.62-1.69 (m, 2H), 1.36-1.46 (m, 2H), 0.96 (t, J = 7.4 Hz. 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 141.9, 128.4, 128.4, 128.4, 125.9, 118.8, 77.4, 71.7, 65.2, 41.1, 37.1, 31.6, 30.6, 19.4, 19.2, 13.7

FTIR (NaCl) 3061, 3026, 2959, 2872, 1742, 1668, 1603, 1495, 1454, 1383, 1352, 1248, 1223, 1179, 1128, 1115, 1059, 974, 910, 735, 700 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{19}H_{25}{}^{79}BrNaO_3$ $[M + Na]^+$: 403.0885, Found: 403.0899

(2R*,6R*)-butyl 4-bromo-3-methyl-6-phenethyl-5,6-dihydro-2*H*-pyran-2-carboxylate (25')



R_f: 0.39 (Hexane: Diethyl ether = 8 : 1), yield: 13%.

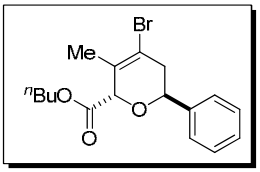
^{1}H NMR (400 MHz, $CDCl_3$): 7.26-7.30 (m, 2H), 7.17-7.21 (m, 3H), 4.65 (s, 1H), 4.15-4.25 (m, 2H), 3.54-3.63 (m, 1H), 2.18-2.82 (m, 4H), 1.93-2.05 (m, 1H), 1.64-1.85 (m, 6H), 1.36-1.48 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.2, 141.5, 128.5, 128.4, 128.3, 125.9, 118.8, 79.9, 73.9, 65.4, 41.2, 36.3, 31.3, 30.5, 19.1, 17.5, 13.7

FTIR (NaCl) 3061, 3026, 2959, 2872, 1738, 1682, 1603, 1495, 1454, 1381, 1368, 1250, 1215, 1179, 1117, 1067, 983, 910, 750, 700 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{19}H_{25}{}^{79}BrNaO_3$ $[M + Na]^+$: 403.0885, Found: 403.0878

(2S*,6S*)-butyl 4-bromo-3-methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-carboxylate (26)



R_f: 0.39 (Hexane: Diethyl ether = 8 : 1), yield: 75%.

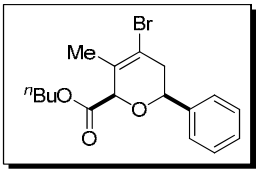
^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.41 (m, 5H), 5.31 (dd, *J* = 3.7, 10.5 Hz, 1H), 4.75 (s, 1H), 4.19 (t, *J* = 6.8 Hz, 2H), 2.68-2.89 (m, 2H), 1.95 (s, 3H), 1.63-1.70 (m, 2H), 1.35-1.44 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 140.4, 128.6, 128.1, 128.0, 126.2, 118.7, 77.7, 73.8, 65.3, 42.3, 30.6, 19.2, 19.1, 13.7

FTIR (NaCl) 3063, 3032, 2959, 2872, 1738, 1668, 1495, 1454, 1275, 1179, 1126, 1101, 1012, 820, 760, 700 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{17}H_{21}{}^{79}BrNaO_3$ $[M + Na]^+$: 375.0572, Found: 375.0558

(2R*,6S*)-butyl 4-bromo-3-methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-carboxylate (26')



R_f: 0.38 (Hexane: Diethyl ether = 8 : 1), yield: 8%.

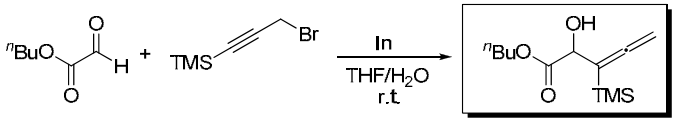
^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.41 (m, 5H), 4.88 (d, *J* = 0.9 Hz, 1H), 4.71 (dd, *J* = 3.2, 10.7 Hz, 1H), 4.20 (t, *J* = 6.7 Hz, 2H), 2.90-2.99 (m, 1H), 2.68 (d, *J* = 16.9 Hz, 1H), 1.83 (s, 3H), 1.64-1.71 (m, 2H), 1.37-1.46 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 140.2, 128.5, 128.3, 128.1, 126.0, 118.5, 80.2, 76.5, 65.5, 43.1, 30.5, 19.1, 17.7, 13.7

FTIR (NaCl) 3065, 3036, 2959, 2872, 1738, 1614, 1454, 1277, 1179, 1123, 1103, 1055, 1021, 970, 756, 700 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{17}H_{21}{}^{79}BrNaO_3$ $[M + Na]^+$: 375.0572, Found: 375.0555

Preparation of butyl 2-hydroxy-3-(trimethylsilyl)penta-3,4-dienoate (27)



To a suspension of indium power (1.15 g, 10 mmol, 2.0 equiv) in H_2O/THF (5:1, 10 mL) was added *n*-butyl glyoxylate (0.65 g, 5 mmol, 1.0 equiv) and then trimethylsilyl propargyl bromide (1.91 g, 10 mmol, 2.0 equiv). The mixture was vigorously stirred at room temperature for 8 hours. Standard workup and purified by flash silica gel column chromatograph gave **27** in 55% yield as a clear oil.

$\mathbf{R}_f$: 0.42 (Hexane: Ethyl acetate = 4 : 1)

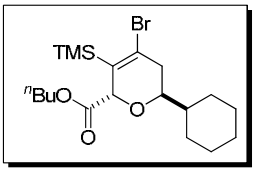
^{1}H NMR (400 MHz, $CDCl_3$): 4.67 (t, J = 2.1 Hz, 1H), 4.53-4.59 (m, 2H), 4.12-4.23 (m, 2H), 2.78 (br, 1H), 1.61-1.68 (m, 2H), 1.34-1.43 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H), 0.16 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 209.0, 173.7, 96.5, 72.0, 70.5, 65.5, 30.6, 19.0, 13.6, -1.0

FTIR (NaCl) 3470, 3065, 2959, 2874, 1932, 1730, 1630, 1458, 1406, 1381, 1248, 1205, 1082, 1035, 843, 760, 696 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{12}H_{23}O_3Si$ $[M + H]^+$: 243.1416, Found: 243.1424

(2R*,6S*)-butyl 4-bromo-6-cyclohexyl-3-(trimethylsilyl)-5,6-dihydro-2*H*-pyran-2-carboxylate (28)



R_f: 0.67 (Hexane: Diethyl ether = 8 : 1), yield: 90%, dr (*trans*/*cis*) = 96:4.

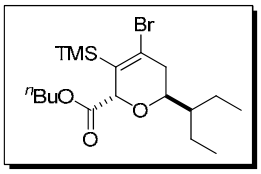
^{1}H NMR (400 MHz, $CDCl_3$): 4.78 (s, 1H), 4.09-4.21 (m, 2H), 3.46 (ddd, *J* = 3.8, 6.8, 10.6 Hz, 1H), 2.59 (ddd, *J* = 1.9, 10.6, 17.6 Hz, 1H), 3.42 (dd, *J* = 3.8, 17.6 Hz, 1H), 1.94 (d, *J* = 13.0 Hz, 1H), 1.69-1.74 (m, 2H), 1.62-1.67 (m, 4H), 1.35-1.45 (m, 3H), 1.13-1.26 (m, 5H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.24 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 134.1, 132.1, 77.6, 75.8, 65.3, 42.3, 41.0, 30.6, 28.6, 27.9, 26.4, 25.9, 25.8, 19.1, 13.6, -1.0

FTIR (NaCl) 2928, 2853, 1734, 1667, 1611, 1450, 1306, 1248, 1182, 1126, 1070, 935, 885, 843, 762, 689 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{19}H_{34}{}^{79}BrO_3Si$ $[M + H]^+$: 439.1280, Found: 439.1276

(2R*,6S*)-butyl 4-bromo-6-(pentan-3-yl)-3-(trimethylsilyl)-5,6-dihydro-2*H*-pyran-2-carboxylate (29)



R_f: 0.51 (Hexane: Diethyl ether = 8 : 1), yield: 84%, dr (*trans*/*cis*) = 96:4.

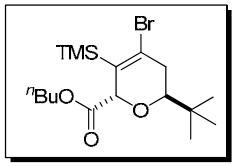
^{1}H NMR (400 MHz, $CDCl_3$): 4.78 (d, *J* = 1.7 Hz, 1H), 4.15 (t, *J* = 6.8 Hz, 2H), 3.66-3.71 (m, 1H), 2.61 (ddd, *J* = 2.0, 10.7, 17.5 Hz, 1H), 2.41 (dd, *J* = 3.7, 17.5 Hz, 1H), 1.62-1.69 (m, 2H), 1.34-1.54 (m, 5H), 1.18-1.32 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 6H), 0.24 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 134.0, 132.1, 77.6, 73.2, 65.3, 45.3, 41.0, 30.6, 20.8, 20.7, 19.1, 13.6, 11.2, 11.0, -1.0

FTIR (NaCl) 2959, 2874, 1732, 1612, 1462, 1422, 1381, 1304, 1248, 1180, 1125, 1069, 1024, 934, 843, 762 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{18}H_{34}{}^{79}BrO_3Si$ $[M + H]^+$: 405.1461, Found: 405.1450

(2R*,6S*)-butyl 4-bromo-6-tert-butyl-3-(trimethylsilyl)-5,6-dihydro-2*H*-pyran-2-carboxylate (30)



R_f: 0.67 (Hexane: Diethyl ether = 8 : 1), yield: 86%, dr (*trans*/*cis*) = 94:6

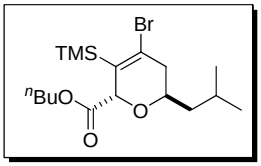
^{1}H NMR (400 MHz, $CDCl_3$): 4.80 (d, *J* = 1.8 Hz, 1H), 4.08-4.19 (m, 2H), 3.37 (dd, *J* = 3.6, 11.0 Hz, 1H), 2.62 (ddd, *J* = 2.0, 11.0, 17.5 Hz, 1H), 2.38 (dd, *J* = 3.6, 17.5 Hz, 1H), 1.62-1.69 (m, 2H), 1.35-1.44 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.24 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 133.9, 132.4, 78.9, 77.9, 65.3, 38.5, 33.7, 30.6, 25.3, 19.1, 13.6, -1.0.

FTIR (NaCl) 2957, 2872, 1734, 1612, 1466, 1396, 1366, 1296, 1248, 1180, 1128, 1086, 1059, 920, 841, 762, 689 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{17}H_{32}{}^{79}BrO_3Si$ $[M + H]^+$: 391.1304, Found: 391.1304

(2R*,6R*)-butyl 4-bromo-6-isobutyl-3-(trimethylsilyl)-5,6-dihydro-2*H*-pyran-2-carboxylate (31)



R_f: 0.49 (Hexane: Diethyl ether = 8 : 1), yield: 80%, dr (*trans*/*cis*) >= 99:1

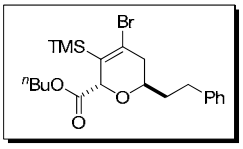
^{1}H NMR (500 MHz, $CDCl_3$): 4.76 (d, *J* = 1.5 Hz, 1H), 4.11-4.18 (m, 2H), 3.81 (ddd, *J* = 4.0, 8.6, 12.9 Hz, 1H), 2.41-2.49 (m, 2H), 1.76-1.85 (m, 1H), 1.62-1.68 (m, 2H), 1.45-1.51 (m, 1H), 1.36-1.42 (m, 2H), 1.15-1.24 (m, 1H), 0.86-0.94 (m, 9H), 0.23 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$): 170.5, 134.0, 131.6, 77.5, 70.0, 65.3, 44.7, 43.8, 30.6, 24.2, 23.2, 22.2, 19.1, 13.7, -1.0

FTIR (NaCl) 2957, 2872, 1732, 1614, 1468, 1381, 1368, 1306, 1248, 1180, 1123, 1067, 1034, 932, 843, 762 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{17}H_{32}{}^{79}BrO_3Si$ $[M + H]^+$: 391.1304, Found: 391.1279

(2R*,6R*)-butyl 4-bromo-6-phenethyl-3-(trimethylsilyl)-5,6-dihydro-2*H*-pyran-2-carboxylate (32)



R_f: 0.59 (Hexane: Diethyl ether = 8 : 1), yield: 83%, dr (*trans*/*cis*) >= 93:7

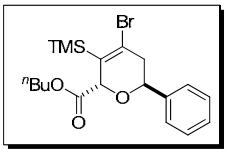
^{1}H NMR (500 MHz, $CDCl_3$): 7.29-7.32 (m, 2H), 7.20-7.23 (m, 3H), 4.86 (d, *J* = 1.5 Hz, 1H), 4.14-4.23 (m, 2H), 3.81 (ddd, *J* = 4.1 Hz, 8.1, 12.1 Hz, 1H), 2.86 (ddd, *J* = 5.4, 10.0, 14.3 Hz, 1H), 2.65-2.72 (m, 1H), 2.60 (ddd, *J* = 1.9, 10.4, 17.6 Hz, 1H), 2.51 (dd, *J* = 3.9, 17.6 Hz, 1H), 1.78-1.92 (m, 2H), 1.66-1.71 (m, 2H), 1.40-1.47 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.29 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$): 170.4, 141.7, 134.1, 131.3, 128.4, 128.3, 125.9, 77.6, 71.1, 65.4, 43.3, 37.2, 31.3, 30.6, 19.1, 13.7, -0.9

FTIR (NaCl) 3063, 3019, 2958, 2874, 1730, 1612, 1454, 1301, 1250, 1215, 1184, 1123, 1069, 1030, 843, 756, 700 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{21}H_{32}{}^{79}BrO_3Si$ $[M + H]^+$: 439.1304, Found: 439.1300

(2R*,6S*)-butyl 4-bromo-6-phenyl-3-(trimethylsilyl)-5,6-dihydro-2*H*-pyran-2-carboxylate (33)



R_f: 0.42 (Hexane: Diethyl ether = 8:1) yield: 68%, dr (*trans*/*cis*) >= 99:1

^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.38 (m, 5H), 4.95 (d, *J* = 1.4 Hz, 1H), 4.85 (dd, *J* = 4.0, 10.5 Hz, 1H), 4.12-4.23 (m, 2H), 2.87 (ddd, *J* = 1.9, 10.5, 17.6 Hz, 1H), 2.75 (dd, *J* = 4.1, 17.6 Hz, 1H), 1.62-1.69 (m, 2H), 1.32-1.41 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.29 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 140.5, 134.0, 131.1, 128.5, 128.0, 125.9, 77.9, 73.4, 65.5, 44.6, 30.5, 19.0, 13.6, -0.9

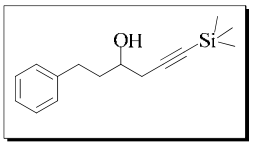
FTIR (NaCl) 3063, 3032, 2958, 2872, 1730, 1611, 1496, 1452, 1309, 1248, 1182, 1123, 1069, 885, 842, 754, 698 cm^{-1}

HRMS (ESI) ***m/z*** Calcd for $C_{19}H_{27}{}^{79}BrNaO_3Si$ $[M + Na]^+$: 433.0811, Found: 433.0795

6.3 FCP CASCADE CONDESATION OF PROPARGYLIC EPOXIDES

PRECEDURES AND DATA

Preparation of 1-Phenyl-6-trimethylsilanyl-hex-5-yn-3-ol (34)



Trimethylsilylpropargyl bromide (956 mg, 5.0 mmol, 1.25 equiv.) was added to a suspension of the indium powder (574 mg, 5.0 mmol, 1.25 equiv.) and indium bromide (142 mg, 0.40 mmol, 0.1 equiv.) in 5 mL anhydrous THF at room temperature. After 15 minutes, hydrocinnamaldehyde (537 mg, 4.0 mmol, 1.0 equiv.) was added at room temperature. The mixture was refluxed overnight, and quenched with 50 mL 1M HCl solution. The aqueous layer was extracted with diethyl ether (50 mL × 3), and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, concentrated *in vacuo*, and purified *via* flash chromatography (20% ethyl acetate in hexane) to afford 1-phenyl-6-trimethylsilanyl-hex-5-yn-3-ol in 60% yield as a yellow oil.

R_f: 0.45 (hexane : ethyl acetate = 4 : 1)

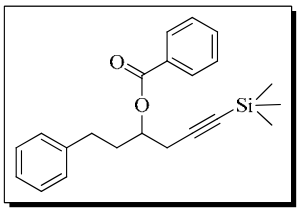
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 3.79-3.72 (m, 1H), 2.81 (td, *J* = 7.52, 13.72 Hz, 1H), 2.70 (td, *J* = 8.12, 13.88 Hz, 1H), 2.48 (dd, *J* = 4.76, 16.80 Hz, 1H), 2.38 (dd, *J* = 6.88, 16.76 Hz, 1H), 1.99 (d, *J* = 5.04 Hz, 1H), 1.99-1.84 (m, 2H), 0.16 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 128.4, 128.4, 125.9, 102.9, 87.8, 69.0, 37.8, 31.8, 29.0, 0.05.

FTIR (neat) 3356, 3026, 2957, 2174, 1495, 1454, 1418, 1250, 1080, 1030, 841, 760, 698, 648 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{21}OSi$ $[M-H]^+$: 245.1356, found $[M-H]^+$: 245.1366.

Preparation of 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-yl benzoate (35)



To an oven dried (10 mL) round-bottom flask equipped with a magnetic stirring bar was added with 1-phenyl-6-trimethylsilanyl-hex-5-yn-3-ol (**34**) (0.5 mmol, 123.2 mg, 1.0 equiv.), DMAP (0.05 mmol, 6.1 mg, 0.1 equiv.) and triethylamine (1.5 mmol, 0.21 mL, 3.0 equiv.), diluted with 3 mL anhydrous dichloromethane and stirred at 0 ^{o}C. Benzoyl chloride (0.15. mL, 0.6 mmol, 1.2 equiv.) was slowly added. The reaction was allowed to warm up to room temperature and stirred for overnight before quenching saturated sodium bicarbonate solution (10 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (1% diethyl ether in hexane) to afford the 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-yl benzoate **35** in 96 % yield as a colorless oil.

R_f: 0.56 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.52 (m, 1H), 7.29 (m, 2H), 7.19 (m, 5H), 5.21 (m, 1H), 2.66 (m, 4H), 2.18 (m, 2H), 0.13 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 141.2, 132.9, 130.3, 129.6, 128.4, 128.3, 128.2, 126.0, 101.9, 87.4, 71.8, 34.8,1 31.5, 25.4, 0.11.

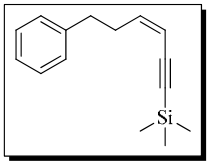
FTIR (neat) 2957, 2178, 1718, 1602, 1452, 1271, 1249, 1111, 1026, 840,758, 711, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{22}H_{27}O_2Si$ $[M+H]^+$: 351.1780, found $[M+H]^+$: 351.1777.

Preparation of (*Z*)-trimethyl(6-phenylhex-3-en-1-ynyl)silane (36)

1. To an oven dried (25 mL) round-bottom flask equipped with a magnetic stirring bar was added diisopropylamine (1.10 mmol, 0.15 mL, 2.0 equiv.), and anhydrous THF (5 mL). The mixture was cooled to 0 ^{o}C prior to dropwise addition of *n*-butyl lithium (1.6 M in hexane) (1.10 mmol, 0.68 mL, 2.0 equiv.). The mixture was stirred at 0 ^{o}C for 30 minutes before being transferred into the target flask.

2. To an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-yl benzoate (**35**, 1.839 g, 0.52 mmol, 1.0 equiv.) and TIPSCl (1.10 mmol, 0.23 mL, 2.0 equiv.) and was diluted with 5 mL anhydrous THF, stirred and cooled to around -93 ^{o}C (low temperature was generated by using toluene and liquid nitrogen). The preformed LDA was transferred *via* a plastic cannula in a dropwise manner into the solution of **35**. The reaction was allowed to proceed at –93 ^{o}C for 3 hours. The reaction was quenched by pouring the reaction mixture into 1 M HCl solution (10 mL). The reaction mixture was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered. The reaction mixture was concentrated *in vacuo*. The residual crude was purified *via* flash chromatography (0.2 % diethyl ether in hexane) to afford **36** and **37** (*Z*/*E* = 90:10) in an overall 77 % yield as a colorless oil.



R*f*: 0.58 (hexane : diethyl ether = 40 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.98 (td, *J* = 7.32, 10.90 Hz, 1H), 5.50 (dd, *J* = 1.16, 10.96 Hz, 1H) 2.80 (m, 2H), 2.65 (m, 2H), 0.21 (s, 9H).

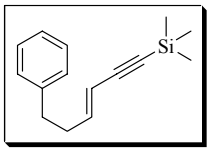
^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 141.4, 128.4, 128.3, 125.9, 109.9, 101.8, 98.9, 34.9, 31.9, 0.05.

FTIR (neat) 3469, 2924, 2852, 2150, 1454, 1249, 842, 759, 732, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{20}Si$ [M^+]: 228.4048, found [M^+]: 228.1321.

Preparation of (*E*)-trimethyl(6-phenylhex-3-en-1-ynyl)silane (37)

To an oven dried 50 mL sealed tube was added 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-yl benzoate (**35**, 0.7011 g, 2.0 mmol, 1.0 equiv.) and NaH (70% dispersed in mineral oil, 20.0 mmol, 0.6857 g, 20.0 equiv.), diluted with 10 mL anhydrous $PhCF_3$, sealed and set into 120 ^oC silicon oil bath. The reaction was allowed to proceed at 120 ^oC for 13 hours. The reaction was quenched by pouring the reaction mixture into 1 M NH_4Cl solution (20 mL). The reaction mixture was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered. The reaction mixture was concentrated *in vacuo*. The residual crude was purified *via* flash chromatography (0.2 % diethyl ether in hexane) to afford **36** and **37** (*Z*/*E* = 9:91) in an overall 66 % yield as a colorless oil.



R_f: 0.47 (hexane : diethyl ether = 40 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 5H), 6.25 (td, *J* = 6.94, 15.93 Hz, 1H), 5.55 (td, *J* = 1.56, 15.92 Hz, 1H) 2.69 (t, *J* = 8.08 Hz, 2H), 2.40 (m, 2H), 0.18 (s, 9H).

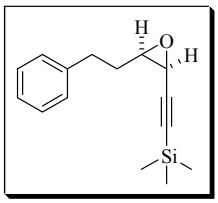
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 141.1, 128.4, 128.3, 126.0, 110.3, 103.9, 93.0, 34.9, 34.8, 0.04.

FTIR (neat) 3446, 2956, 2920, 2848, 2129, 1496, 1454, 1247, 842, 1084, 952, 842, 760, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{20}Si$ $[M^+]$: 228.4048, found $[M]^+$: 228.1325.

Preparation of trimethyl(((2S*,3R*)-3-phenethyloxiran-2-yl)ethynyl)silane (38)

To an oven dried (100 mL) round-bottom flask equipped with a magnetic stirring bar was added with *m*-CPBA (70% assay, 4.60 mmol, 1.1344 g, 2.5 equiv), diluted with 30 mL anhydrous dichloromethane and stirred at 0 ^oC (ice bath). (*Z*)-Trimethyl(6-phenylhex-3-en-1-ynyl)silane (**36**, 1.84 mmol, 420.4 mg, 1.0 equiv, dissolved in 10 mL CH_2Cl_2) was added in a dropwise manner, and the reaction was allowed to proceed for around 12 hours from 0 ^oC to room temperature. Reaction was quenched using saturated $Na_2S_2O_3$ solution (20 mL). The aqueous layer was extracted with dichloromethane (30 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (5% diethyl ether in hexane) to afford the trimethyl(-3-phenethyloxiran-2-yl)ethynyl)silane **38** in 72 % yield as a colorless oil.



R_f: 0.61 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 5H), 3.24 (d, *J* = 4.0 Hz, 1H), 2.88 (m, 1H) 2.64 (m, 2H), 1.90 (m, 2H), 0.01 (s, 9H).

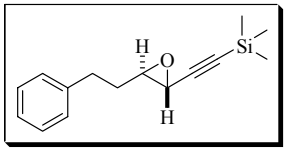
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 128.4, 128.3, 126.0, 100.1, 91.3, 57.5, 45.4, 32.0, 31.1, 0.31.

FTIR (neat) 3026, 2958, 2181, 1602, 1496, 1454, 1417, 1357, 1249, 1041, 845, 760, 698 cm^{-1}.

HRMS *m/z* Calcd for $[M+H]^+$ $C_{15}H_{21}OSi$: 245.1362, found : 245.1369.

Preparation of trimethyl(((2R*,3R*)-3-phenethyloxiran-2-yl)ethynyl)silane (39)

To an oven dried (250 mL) round-bottom flask equipped with a magnetic stirring bar was added with *m*-CPBA (70% assay, 16.2 mmol, 3.99 g, 1.5 equiv), diluted with 100 mL anhydrous dichloromethane and stirred at 0 ^oC (ice bath). (*E*)-Trimethyl(6-phenylhex-3-en-1-ynyl)silane (**37**, 10.79 mmol, 2.4653 g, 1.0 equiv, dissolved in 30 mL CH_2Cl_2) was added in a dropwise manner, and the reaction was allowed to proceed for around 12 hours from 0 ^oC to room temperature. Reaction was quenched using saturated $Na_2S_2O_3$ solution (100 mL). The aqueous layer was extracted with dichloromethane (50 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (5% diethyl ether in hexane) to afford the trimethyl(-3-phenethyloxiran-2-yl)ethynyl)silane **39** in 67 % yield as a colorless oil.



R_f: 0.56 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 3.13 (m, 1H), 3.08 (d, *J* = 2.04 Hz, 1H), 2.79 (m, 2H) 1.94 (m, 1H), 1.81 (m, 1H), 0.17 (s, 9H).

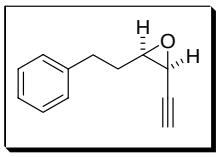
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8, 128.5, 128.4, 126.2, 101.7, 89.4, 60.1, 45.7, 33.6, 31.9, 0.30.

FTIR (neat) 3442, 2958, 2179, 1633, 1454, 1249, 1062, 1035, 842, 759, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{21}OSi$ $[M+H]^+$: 245.1362, found $[M+H]^+$: 245.1364.

Preparation of (2S*,3R*)-2-ethynyl-3-phenethyloxirane (40)

To an oven dried (25 mL) round-bottom flask equipped with a magnetic stirring bar was added with trimethyl(((2S*,3R*)-3-phenethyloxiran-2-yl)ethynyl)silane (**38**, 2.0 mmol, 0.4568 g, 1.0 equiv) and 5 mL anhydrous THF, stirred at room temperature. TBAF (1.0 M in THF, 4 mL, 2.0 equiv) was added in a dropwise manner. Reaction was allowed to proceed for around 2 hours at room temperature. Reaction was quenched using saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (3 % diethyl ether in hexane) to afford the 2-ethynyl-3-phenethyloxirane **40** in 87 % yield as a colorless oil.



R_f: 0.64 (hexane : diethyl ether = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 3.43 (dd, *J* = 1.69, 4.02 Hz, 1H), 3.06 (m, 1H), 2.84 (m, 2H), 2.34 (d, *J* = 1.68 Hz, 1H), 2.01 (m, 2H).

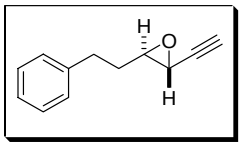
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 128.5, 128.4, 126.1, 78.7, 73.7, 57.1, 44.8, 32.1, 31.0.

FTIR (neat) 2957, 2179, 1603, 1497, 1454, 1323, 1249, 1072, 1037, 935, 844, 760, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{12}H_{12}ONa$ $[M+Na]^+$: 195.0786, found $[M+Na]^+$: 195.0804.

Preparation of (2R*,3R*)-2-ethynyl-3-phenethyloxirane (41)

To an oven dried (25 mL) round-bottom flask equipped with a magnetic stirring bar was added with trimethyl(((2R*,3R*)-3-phenethyloxiran-2-yl)ethynyl)silane (**39**, 3.0 mmol, 0.7454 g, 1.0 equiv) and 8 mL anhydrous THF, stirred at room temperature. TBAF (1.0 M in THF, 6 mL, 2.0 equiv) was added in a dropwise manner. Reaction was allowed to proceed for around 2 hours at room temperature. Reaction was quenched using saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (3 % diethyl ether in hexane) to afford the 2-ethynyl-3-phenethyloxirane **41** in 86 % yield as a colorless oil.



R_f: 0.56 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 3.13 (m, 1H), 3.07 (t, *J* = 1.69, 1.84 Hz, 1H), 2.77 (m, 2H), 2.29 (d, *J* = 1.56 Hz, 1H), 1.87 (m, 1H).

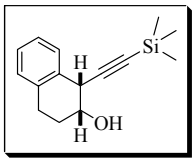
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 128.5, 128.3, 126.1, 80.3, 71.8, 59.6, 44.9, 33.4, 31.7.

FTIR (neat) 3286, 3026, 2927, 2123, 1602, 1496, 1454, 1327, 1029, 935, 883, 750, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{12}H_{12}ONa$ $[M+Na]^+$: 195.0786 , found $[M+Na]^+$: 195.0782 .

Preparation of (1R*,2R*)-1-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-2-ol (42)

To an oven dried (10 mL) round-bottom flask equipped with a magnetic stirring bar was added with indium triflate (0.037 mmol, 21.0 mg, 0.2 equiv) and 2 mL anhydrous dichloromethane, stirred at –78 ^{o}C. Trimethyl(((2S*,3R*)-3-phenethyloxiran-2-yl)ethynyl)silane (**38**, 0.184 mmol, 44.9 mg, 1.0 equiv, dissolved in 1 mL CH_2Cl_2) was added in a dropwise manner into the stirred suspension of indium triflate. Reaction was allowed to proceed for around half an hour at -78 ^{o}C, and followed with another 14 hours at -10 ^{o}C. Reaction was quenched using saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with dichloromethane (5 mL × 3) and the combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (10 % ethyl acetate in hexane) to afford **42** in 91 % yield as a colorless solid.



R_f: 0.28 (hexane : diethyl ether = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.25-7.08 (m, 3H), 4.15 (m, 1H), 4.01 (d, *J* = 4.12 Hz, 1H), 3.04 (m, 1H) 2.75 (m, 1H) 2.29 (d, *J* = 5.84 Hz, 1H) 2.12 (m, 1H), 1.91 (m, 1H), 0.18 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 133.4, 129.6, 128.7, 126.9, 126.2, 105.1, 89.4, 67.3, 40.2, 27.9, 25.7, 0.04.

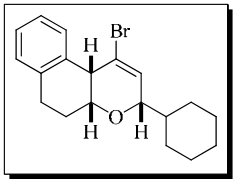
FTIR (neat) 2955, 2897, 2162, 1491, 1452, 1248, 1059, 972, 845, 762, 740 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{21}OSi$ $[M+H]^+$: 245.1362, found $[M+H]^+$: 245.1364.

General procedures for preaparing polycyclic pyrans *via* Lewis acid catalyzed Friedel-Crafts-Prins cascade condensation of *cis* propargylic epoxide with aldehydes

To an oven-dried (10 mL) round-bottom flask equipped with a magnetic stirring bar was added indium triflate (11.2 mg, 0.020 mmol, 0.20 equiv.) and anhydrous dichloromethane (1 mL). The mixture was vigorous stirred at 0 ^{o}C. Propargylic epoxide **40** (17.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension, stirred at 0 ^{o}C for 4 hour. The mixture was then warmed up to room temperature. Bromotrimethylsilane (TMSBr, 0.016 mL, 0.12 mmol, 1.20 equiv) was added. Cyclohexanecarboxaldehyde (11.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced in a dropwise manner. The reaction was allowed to proceed at room temperature for 6 hours before quenching with saturated sodium bicarbonate solution (3 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane) to afford **43** in 21 % yield as a colorless oil.

(3S*,4aR*,10bS*)-1-bromo-3-cyclohexyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (43)



R_f: 0.67 (hexane : diethyl ether = 4 : 1), yield: 21%.

^{1}H NMR (500 MHz, $CDCl_3$) δ.7.69 (d, *J* =7.15 Hz, 1H), 7.17 (m, 4H), 6.22 (d, *J* = 2 Hz, 1H), 4.18 (ddd, *J* =4.25, 5.6, 8.95 Hz, 1H), 4.06 (m, 1H), 3.38 (s, 1H) 2.89 (td, *J*

= 6.68, 15.38 Hz, 1H), 2.55 (ddd, *J* = 6.05, 8.00, 15.50 Hz, 1H), 2.18 (m, 1H), 1.73 (m, 1H), 1.58 (m, 3H), 1.37 (d, *J* = 7.04 Hz, 2H), 1.10 (m, 3H), 1.05 (m, 1H), 0.94 (m, 2H)

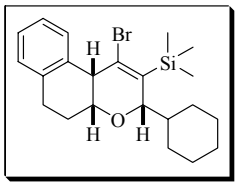
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.9, 132.2, 127.6, 127.2, 126.2, 126.0, 120.2, 80.9, 72.9, 47.0, 42.5, 28.9, 28.2, 27.8, 26.4, 26.2, 26.1, 25.8.

FTIR (KBr) 2928, 2853, 1714, 1645, 1593, 1450, 1244, 1122, 1057, 860, 746 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{24}{}^{79}BrO$ $[M+H]^+$: 347.1011, found $[M+H]^+$: 347.1061.

Calcd for $C_{19}H_{24}{}^{81}BrO$ $[M+H]^+$: 349.0990, found $[M+H]^+$: 349.0998.

((3S*,4aR*,10bS*)-1-bromo-3-cyclohexyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromen-2-yl)trimethylsilane (43')



R_f: 0.67 (hexane : diethyl ether = 4 : 1), yield: 33%.

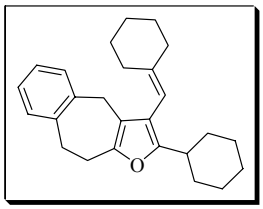
^{1}H NMR (500 MHz, $CDCl_3$) δ.7.72 (t, *J* = 3.1, 5.55 Hz, 1H), 7.05 (m, 3H), 4.18 (s, 1H), 3.98 (q, *J* = 2.95, 4.2 Hz, 1H), 3.47 (m, 1H), 3.38 (s, 1H) 2.86 (ddd, *J* = 6.5, 8.50, 15.10 Hz, 1H), 2.50 (td, *J* = 6.4, 15.75 Hz, 1H), 2.04 (m, 1H), 1.73 (m, 1H), 1.58 (d, *J* = 13.55 Hz, 1H), 1.41 (m, 2H), 1.37 (m, 3H), 1.28 (m, 1H), 0.90 (d, *J* = 15.15 Hz, 1H), 0.83 (m, 3H), 0.24 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.2, 135.8, 130.6, 127.7, 126.2, 126.0, 125.6, 83.5, 72.4, 50.8, 42.5, 30.4, 28.4, 27.1, 26.5, 26.1, 25.6, 24.8, 0.2.

FTIR (KBr) 3309, 2926, 2851, 1635, 1450, 1247, 1111, 1072, 841, 740 cm^{-1}.

HRMS *m/z* Calcd for $C_{22}H_{31}{}^{79}BrOSi$ $[M]^+$: 418.1322, found $[M^+]$: 418.1317.

Calcd for $C_{22}H_{31}{}^{81}BrOSi$ $[M]^+$: 420.1302, found $[M^+]$: 420.1294.



(46)

R_f: 0.83 (hexane : diethyl ether = 8 : 1), yield: 17%.

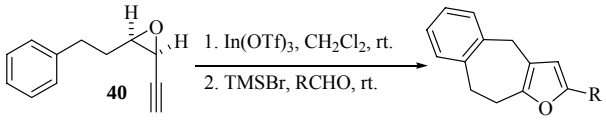
^{1}H NMR (300 MHz, $CDCl_3$) δ.7.25-7.11 (m, 4H), 5.76 (s, 1H), 3.56 (s, 2H), 3.06 (t, *J* = 5.82, 6.64 Hz), 2.86 (m, 2H), 2.45 (m, 1H), 2.29 (t, *J* = 5.48, 5.88 Hz, 2H), 2.06 (t, *J* = 5.81, 5.88 Hz, 2H), 1.72 (s, 3H), 1.67 (s, 4H), 1.49 (m, 2H), 1.25 (s, 4H), 0.87 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 146.4, 145.5, 142.0, 140.8, 129.2 128.1, 126.5, 126.3, 117.4, 115.6, 111.9, 36.8, 36.7, 31.5, 31.0, 30.3, 29.1, 28.85, 27.86, 27.82, 26.7, 26.6, 26.0.

FTIR (KBr) 2926, 2853, 1681, 1511, 1446, 1259, 1089, 1018, 798, 754, 736, 702, 665 cm^{-1}.

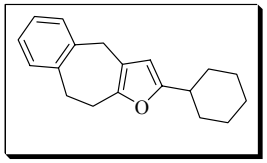
HRMS *m/z* Calcd for $C_{26}H_{33}O$ $[M+H]^+$: 361.2531, found $[M+H]^+$: 361.2547.

General procedures for preaparing polycyclic furans *via* indium triflate-mediated Friedel-Crafts-Prins cascade condensation of *cis* propargylic epoxide with aldehydes



To an oven-dried (10 mL) round-bottom flask equipped with a magnetic stirring bar was added indium triflate (56.2 mg, 0.1 mmol, 1.0 equiv.) and anhydrous dichloromethane (1 mL), vigorously stirred at room temperature. Propargylic epoxide

40 (17.2 mg, 0.1 mmol, 1 equiv., dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension, stirred at room temperature for 1 hour. Bromotrimethylsilane (TMSBr, 0.03 mL, 0.20 mmol, 2 equiv.) was added. Cyclohexanecarboxaldehyde (11.2 mg, 0.1 mmol, 1.0 equiv.) in 1 mL dry CH_2Cl_2 was introduced in a dropwise manner. The reaction was allowed to proceed at room temperature for 2 hours before quenching with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (10 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane 0.5%) to afford **44** in 81 % yield as a colorless oil.



(44)

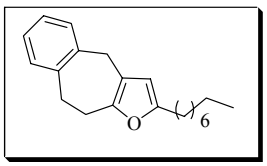
R_f: 0.73 (hexane : diethyl ether = 8 : 1), ratio (furan / pyran) >= 99:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 4H), 5.76 (s, 1H), 3.72 (s, 2H), 3.05 (m, 2H), 2.85 (m, 2H), 2.49 (s, 1H), 1.94 (m, 2H), 1.74 (m, 2H), 1.67 (d, J = 11.88 Hz, 1H), 1.21 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 147.1, 141.7, 140.5, 129.2, 127.9, 126.6, 126.3, 116.9, 105.2, 37.1, 31.7, 31.1, 31.0, 27.7, 26.1, 25.9.

FTIR (KBr) 2928, 2853, 1531, 1450, 1265, 756, 736 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{23}O$ $[M+H]^+$: 267.1749, found $[M+H]^+$: 267.1733.



(47)

R_f: 0.81 (hexane : diethyl ether = 8 : 1), yield: 73%, ratio (furan / pyran) = 97:3.

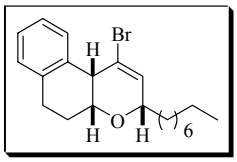
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 4H), 5.79 (s, 1H), 3.71 (s, 2H), 3.05 (t, *J* = 5.88, 6.68 Hz, 2H), 2.86 (t, *J* = 5.96, 6.28 Hz, 2H), 2.49 (t, *J* = 7.52, 7.68 Hz, 2H), 1.56 (t, *J* = 6.96, 8.08 Hz, 2H), 1.28 (m, 10H), 1.67 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 147.4, 141.7, 140.4, 129.2, 127.9, 126.6, 126.3, 117.1, 77.2, 31.9, 31.1, 30.9, 29.4, 29.3, 29.2, 28.2, 27.9, 27.7, 22.7, 14.1.

FTIR (KBr) 2924, 2852, 1489, 1454, 1377, 1259, 1105, 756 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{29}O$ $[M+H]^+$: 297.2218, found $[M+H]^+$: 297.2216.

(3S*,4aR*,10bS*)-1-bromo-3-octyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (47')



R_f: 0.77 (hexane : diethyl ether = 8:1)

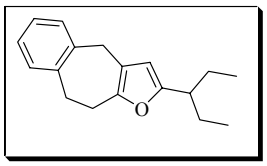
^{1}H NMR (400 MHz, $CDCl_3$) δ7.70 (d, *J* =7.0 Hz, 1H), 7.20 (m, 3H), 6.21 (d, *J* = 1.88 Hz, 1H), 4.22 (m, 2H), 3.39 (s, 1H) 2.89 (td, *J* = 6.56, 15.16 Hz, 1H), 2.56 (ddd, *J* = 6.08, 8.32, 14.64 Hz, 1H) 2.20 (m, 1H), 1.70 (m, 1H), 1.40 (m, 2H), 1.20 (m, 12H), 0.86 (t, *J* = 6.92 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 135.9, 133.6, 127.6, 127.2, 126.3, 126.1, 119.9, 76.7, 73.2, 46.8, 34.7, 31.9, 29.5, 29.4, 29.2, 28.8, 25.8, 24.6, 22.7, 14.1.

FTIR (KBr) 2953, 2926, 2853, 1716, 1651, 1603, 1456, 1246, 1109, 746 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{30}{}^{79}BrO$ $[M+H]^+$: 377.1480, found $[M+H]^+$: 377.1456.

Calcd for $C_{21}H_{30}{}^{81}BrO$ $[M+H]^+$: 379.1460, found $[M+H]^+$: 379.1479.



(48)

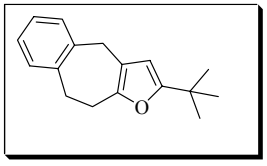
R_f: 0.91 (hexane : diethyl ether = 8 : 1), yield: 91%, ratio (furan / pyran) >= 99:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (m, 4H), 5.71 (s, 1H), 3.65 (s, 2H), 2.97 (t, *J* = 5.8, 6.68 Hz, 2H), 2.79 (t, *J* = 6.08, 6.20 Hz, 2H), 2.49 (quint, *J* = 6.88 Hz, 1H), 1.47 (m, 4H), 1.28 (m, 10H), 0.74 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 147.3, 141.8, 140.6, 129.2, 128.0, 126.6, 126.3, 116.6, 107.3, 42.1, 31.2, 31.1, 27.7, 26.4, 11.8.

FTIR (KBr) 2960, 2930, 2872, 1568, 1489, 1454, 1377, 1211, 1184, 1168, 1103, 972, 796, 756, 716 cm^{-1}.

HRMS *m/z* Calcd for $C_{18}H_{23}O$ $[M+H]^+$: 255.1749, found $[M+H]^+$: 255.1739.



(49)

R_f: 0.83 (hexane : diethyl ether = 8 : 1), yield: 64%, ratio (furan / pyran) = 90:10.

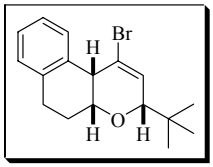
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 4H), 5.77 (s, 1H), 3.72 (s, 2H), 3.06 (t, *J* = 5.64, 6.76 Hz, 2H), 2.87 (t, *J* = 5.44, 6.24 Hz, 2H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 147.3, 141.8, 140.5, 129.2, 128.0, 126.6, 126.3, 116.7, 104.4, 32.3, 31.1, 31.0, 29.1, 27.7.

FTIR (KBr) 2962, 2866, 1566, 1490, 1454, 1361, 1286, 1192, 1095, 968, 950, 798, 756, 711 cm^{-1}.

HRMS *m/z* Calcd for $C_{17}H_{21}O$ $[M+H]^+$: 241.1592, found $[M+H]^+$: 241.1596.

(3R*,4aR*,10bS*)-1-bromo-3-tert-butyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (49')



R_f: 0.77 (hexane : diethyl ether = 8:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.73 (d, *J* = 8.13 Hz, 1H), 7.20 (m, 4H), 6.30 (d, *J* = 1.91 Hz, 1H), 4.17 (q, *J* = 3.65, 4.02, 4.38 Hz, 1H), 3.85 (s, 1H), 3.43 (s, 1H), 2.95 (m, 1H), 2.58 (td, *J* = 6.74, 15.35 Hz, 1H) 2.12 (m, 1H), 1.81 (m, 1H), 1.54 (s, 9H).

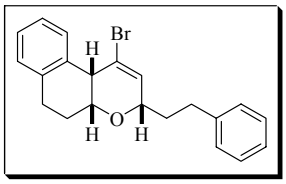
^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.0, 130.9, 127.7, 127.3, 126.1, 125.9, 121.2, 84.2, 72.5, 46.9, 35.1, 28.7, 25.6, 25.5.

FTIR (KBr) 2962, 2930, 2868, 1643, 1593, 1479, 1354, 1361, 1249, 1122, 1066, 970, 748 cm^{-1}.

HRMS *m/z* Calcd for $C_{17}H_{22}{}^{79}BrO$ $[M+H]^+$: 321.0854, found $[M+H]^+$: 321.0831.

Calcd for $C_{17}H_{22}{}^{81}BrO$ $[M+H]^+$: 323.0834, found $[M+H]^+$: 323.0828.

(3S*,4aR*,10bS*)-1-bromo-3-phenethyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (50')



R_f: 0.72 (hexane : diethyl ether = 4 : 1), ratio (furan / pyran) = 84:16.

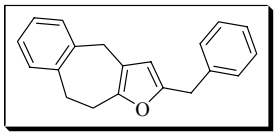
^{1}H NMR (400 MHz, $CDCl_3$) δ.7.75 (d, *J* =6.72 Hz, 1H), 7.20 (m, 8H), 6.21 (d, *J* =1.88 Hz, 1H), 4.27 (m, 1H), 4.22 (m, 1H), 3.42 (s, 1H), 2.92 (m, 1H), 2.30 (m, 3H), 2.18 (m, 1H), 1.75 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 137.6, 135.8, 133.2, 128.4, 128.3, 127.7, 127.2, 126.4, 126.1, 125.7, 120.5, 75.6, 73.1, 46.8, 36.1, 30.5, 28.9, 25.7.

FTIR (KBr) 3024, 2926, 2855, 1645, 1603, 1493, 1454, 1246, 1117, 1101, 1074, 746, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{22}{}^{79}BrO$ $[M+H]^+$: 369.0854, found $[M+H]^+$: 369.0873.

Calcd for $C_{21}H_{22}{}^{81}BrO$ $[M+H]^+$: 371.0834, found $[M+H]^+$: 371.0834.



(51)

R_f: 0.71 (hexane : diethyl ether = 8 : 1), yield: 55%, ratio (furan / pyran) >= 99:1.

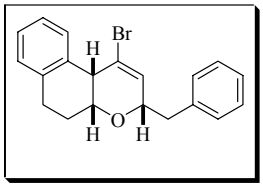
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.12 (m, 9H), 5.79 (s, 1H), 3.85 (s, 2H), 3.70 (s, 2H), 3.05 (t, J = 6.05 Hz, 2H), 2.86 (t, J = 6.30 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 148.4, 141.6, 140.4, 138.4, 129.3, 128.7, 128.4, 128.0, 126.7, 126.39, 126.37, 117.4, 108.8, 34.4, 31.0, 30.9, 27.7.

FTIR (KBr) 2924, 2852, 1745, 1489, 1454, 1265, 1188, 964, 916, 750, 738, 702, 665 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{19}O$ $[M+H]^+$: 275.1436, found $[M+H]^+$: 275.1432.

(3S*,4aR*,10bS*)-3-benzyl-1-bromo-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (51')



R_f: 0.50 (hexane : diethyl ether = 8 : 1)

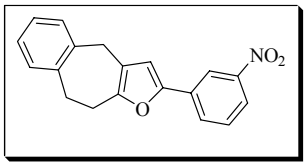
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (t, *J* = 5.07, 3.66 Hz, 1H), 7.19-7.07 (m, 8H), 6.17 (d, *J* = 1.96 Hz, 1H), 4.44 (tt, *J* = 2.08, 6.62 Hz, 1H), 4.22 (ddd, *J* = 3.45, 4.40. 7.77 Hz, 1H), 3.39 (s, 1H), 2.92 (ddd, *J* = 5.99, 7.27, 15.40 Hz, 1H), 2.78 (dd, *J* = 6.11, 13.50 Hz, 1H), 2.60 (dd, *J* = 6.82, 13.50 Hz, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 1.76 (m, 1H), 3.05 (t, *J* = 6.05 Hz, 2H), 2.86 (t, *J* = 6.30 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ137.4, 137.1, 135.6, 132.4, 129.50, 128.12, 127.7, 127.2, 126.34, 126.30, 126.15, 120.6, 77.52, 73.3, 46.7, 41.3, 28.8, 25.7.

FTIR (KBr) 3026, 2924, 2853, 1728, 1599, 1494, 1454, 1261, 1188, 1109, 1080, 1056, 1030, 970, 746, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{20}{}^{79}BrO$ $[M+H]^+$: 355.0698, found $[M+H]^+$: 355.0714.

Calcd for $C_{20}H_{20}{}^{81}BrO$ $[M+H]^+$: 357.0677, found $[M+H]^+$: 357.0694.



(53)

R_f: 0.40 (hexane : diethyl ether = 8 : 1), yield: 63%, ratio (furan / pyran) >= 99:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.8 Hz, 1H) 8.02 (dd, *J* = 1.96, 8.16 Hz, 1H) 7.48 (t, *J* = 8.0 Hz, 1H) 7.20 (m, 4H), 6.65 (s, 1H), 3.82 (s, 2H), 3.13 (dd, *J* = 5.6, 7.88 Hz, 2H), 3.00 (t, *J* = 5.88, 6.16 Hz, 2H).

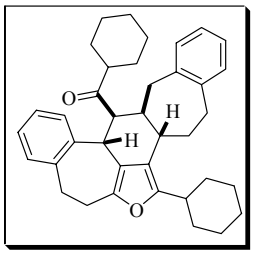
^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.7, 148.3, 140.9, 140.0, 132.5, 129.5, 129.4, 128.6, 128.1, 127.0, 126.6, 121.0, 119.7, 117.8, 109.9, 30.9, 30.7, 27.9.

FTIR (KBr) 3442, 2920, 1651, 2860, 1610, 1556, 1520, 1454, 1344, 1091, 866, 796, 759, 738, 702, 675 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{16}NO_3$ $[M+H]^+$: 306.1130, found $[M+H]^+$: 306.1126.

General procedures for preaparing polycyclic furans *via* [3+3] type annulation

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added trifluoroborate etherate (0.013 mL, 0.10 mmol, 1.0 equiv) and anhydrous dichloromethane (1 mL). The mixture was vigorous stirred at room temperature. Propargylic epoxide **40** (17.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension, and stirred at room temperature for 1 hour. Cyclohexanecarboxaldehyde (11.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced in a dropwise manner. The reaction was allowed to proceed at room temperature for 2 hours before quenching with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.3% diethyl ether in hexane) to afford **45** as a colorless oil in 20 % yield.



(45)

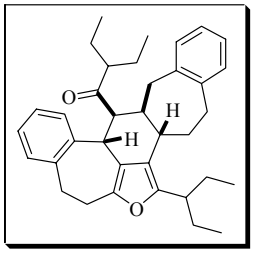
R_f: 0.58 (hexane : diethyl ether = 8 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.27 (m, 2H), 7.12 (m, 6H), 4.30 (s, 1H), 3.70 (d, *J* = 3.34 Hz, 1H), 3.45 (dd, *J* = 2.96, 10.95 Hz, 1H), 3.28 (m, 1H), 3.03 (m, 2H), 2.88 (td, *J* =4.41, 13.92 Hz, 1H), 2.79 (m, 2H), 2.66 (m, 2H), 2.56 (m, 2H), 1.94 (d, *J* = 12.31 Hz, 1H), 1.82 (m, 7H), 1.66 (d, *J* = 11.59 Hz, 3H), 1.39 (m, 3H), 1.23 (m, 6H), 0.86 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 151.2, 144.9, 143.6, 142.9, 141.7, 140.2, 130.1, 128.7, 126.54, 126.46, 126.35, 126.18, 121.4, 117.9, 117.1, 52.5, 52.1, 42.3, 41.7, 39.2, 38.5, 34.9, 33.7, 33.5, 32.3, 32.0, 30.0, 29.7, 28.9, 28.4, 27.4, 26.74, 26.69, 26.02, 25.81, 25.75, 25.6.

FTIR (KBr) 2926, 2851, 1703, 1510, 1454, 1265, 1242, 1211, 1144, 981, 891, 829, 756, 739, 665 cm^{-1}.

HRMS *m/z* Calcd for $C_{38}H_{45}O_2$ $[M+H]^+$: 533.3420, found $[M+H]^+$: 533.3425.



(56)

R_f: 0.72 (hexane : diethyl ether = 8 : 1), yield: 18%.

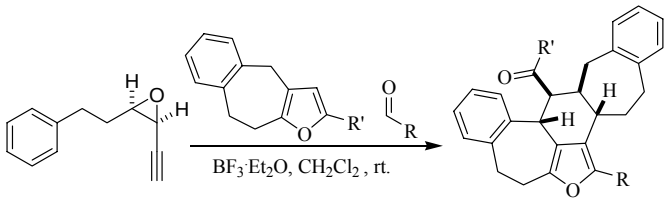
^{1}H NMR (400 MHz, $CDCl_3$) δ.7.17 (m, 8H), 4.45 (s, 1H), 3.55 (d, *J* = 3.0 Hz, 1H), 3.51 (dd, *J* = 3.04, 10.96 Hz, 1H), 3.42 (dd, *J* =10.56, 13.84 Hz, 1H), 3.33 (dt, *J* = 4.54, 13.96 Hz, 1H), 3.05 (m, 2H), 2.88 (td, *J* = 3.36, 13.64, 15.56 Hz, 1H), 2.75 (m, 3H), 2.59 (m, 3H), 1.87 (dt, *J* = 3.04, 10.44 Hz, 1H), 1.73 (m, 1H), 1.69 (m, 1H), 1.53 (m, 5H), 1.13 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.85 (m, 4H), 0.77 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 149.0, 145.1, 143.7, 142.9, 141.9, 140.3, 130.1, 128.6, 126.5, 126.4, 126.3, 126.2, 121.4, 120.9, 116.8, 54.9, 54.1, 42.8, 42.3, 41.8, 38.9, 34.8, 34.1, 32.9, 30.3, 29.7, 27.6, 27.5, 26.9, 24.0, 23.4, 12.4, 12.2, 12.0, 11.9.

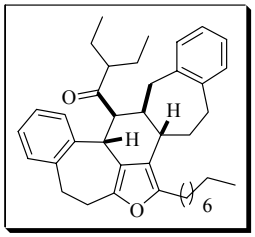
FTIR (KBr) 2961, 2928, 2872, 1705, 1454, 1381, 1263, 1051, 752 cm^{-1}.

HRMS *m/z* Calcd for $C_{36}H_{45}O_2$ $[M+H]^+$: 509.3420, found $[M+H]^+$: 509.3419.

General procedures for preaparing polycyclic furans *via* crossed [3+3] type annulation



To an oven-dried (10 mL) round-bottom flask equipped with a magnetic stirring bar was added trifluoroborate etherate (0.013 mL, 0.10 mmol, 1.0 equiv) and anhydrous dichloromethane (1 mL), vigorously stirred at room temperature. Propargylic epoxide **40** (17.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension, and stirred at room temperature for 1 hour. Furan **48** (25.4 mg, 0.10 mmol, 1.0 equiv., in 1 mL CH_2Cl_2) was added. Nonyl aldehyde (14.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced slowly over 15 minutes. The reaction was allowed to proceed at room temperature for 3 hours before quenching with saturated $NaHCO_3$ solution. The aqueous layer was extracted with dichloromethane (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.3% diethyl ether in hexane) to afford **57** as a colorless oil in 47 % yield.



(57)

R_f: 0.64 (hexane : diethyl ether = 8 : 1), yield: 47%.

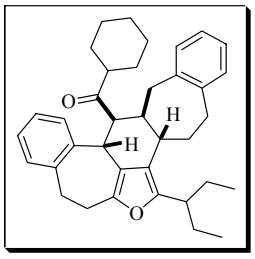
^{1}H NMR (500 MHz, $CDCl_3$) δ.7.27 (m, 2H), 7.15 (m, 5H), 7.06 (d, *J* = 7.85 Hz, 1H), 4.41 (s, 1H), 3.60 (d, *J* = 3.30 Hz, 1H), 3.50 (dt, *J* = 3.19, 11.20 Hz, 1H), 3.39 (dd, *J*

=10.90, 14.09 Hz, 1H), 3.30 (dt, *J* = 4.79, 14.09 Hz, 1H), 3.05 (m, 2H), 2.90 (td, *J* = 4.48, 13.77 Hz, 1H), 2.80 (m, 2H), 2.66 (m, 1H), 2.54 (m, 4H), 1.86 (dt, *J* = 3.08, 10.69 Hz, 1H), 1.78 (m, 1H), 1.69 (m, 1H), 1.48 (m, 4H), 1.26 (s, 10H), 1.16 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.86 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 147.5, 144.9, 143.7, 142.9, 141.7, 140.1, 130.1, 128.69, 128.65, 126.4, 126.3, 126.2, 121.4, 119.1, 117.5, 55.3, 53.9, 42.2, 41.6, 38.8, 34.7, 34.4, 32.9, 31.9, 30.2, 29.70, 29.50, 29.31, 29.27, 29.23, 29.17, 27.4, 23.7, 23.3, 22.7, 14.1, 12.0, 11.9.

FTIR (KBr) 2924, 2852, 1701, 1651, 1514, 1456, 1361, 1240, 1211, 1099, 1047, 829, 756 cm^{-1}.

HRMS *m/z* Calcd for $C_{39}H_{51}O_2$ $[M+H]^+$: 551.3889, found $[M+H]^+$: 551.3813.



(58)

R_f: 0.51 (hexane : diethyl ether = 8 : 1), yield: 40%.

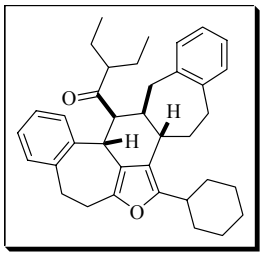
^{1}H NMR (400 MHz, $CDCl_3$) δ.7.15 (m, 8H), 4.32 (s, 1H), 3.68 (d, *J* = 3.17 Hz, 1H), 3.42 (dt, *J* = 1.51, 10.77 Hz, 1H), 3.34 (dt, *J* =4.73, 14.18 Hz, 1H), 3.23 (dd, *J* = 10.77, 13.99 Hz, 1H), 3.03 (m, 2H), 2.88 (td, *J* = 3.59, 13.61 Hz, 1H), 2.75 (m, 3H), 2.59 (m, 3H), 1.95 (d, *J* = 12.66 Hz, 1H), 1.83 (m, 4H), 1.68 (m, 1H), 1.53 (m, 4H), 1.38 (m, 1H), 1.26 (m, 4H), 1.13 (m, 1H), 0.80 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 149.1, 145.0, 143.8, 142.9, 141.7, 140.2, 130.1, 128.72, 128.66, 126.5, 126.4, 126.3, 126.2, 121.4, 120.8, 116.8, 52.7, 52.1, 42.8, 42.3,

41.7, 39.2, 34.8, 33.85, 33.45, 30.25, 29.0, 28.5, 27.7, 27.5, 26.8, 25.82, 25.78, 25.6, 12.42, 12.36.

FTIR (KBr) 3442, 2958, 2928, 2853, 1703, 1489, 1454, 1379, 1265, 1144, 736 cm^{-1}.

HRMS *m/z* Calcd for $C_{37}H_{45}O_2$ $[M+H]^+$: 521.3420, found $[M+H]^+$: 521.3437.



(59)

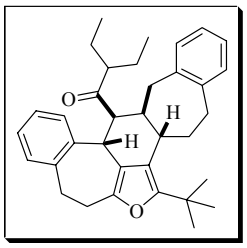
R_f: 0.43 (hexane : diethyl ether = 8 : 1), yield: 42%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.26 (m, 2H), 7.15 (m, 5H), 7.05 (d, *J* = 7.05 Hz, 1H), 4.41 (s, 1H), 3.58 (d, *J* = 3.11 Hz, 1H), 3.50 (dt, *J* = 3.29, 11.07 Hz, 1H), 3.39 (dd, *J* =10.72, 14.00 Hz, 1H), 3.30 (dt, *J* = 4.50, 14.00 Hz, 1H), 3.05 (t, J = 11.93 Hz, 2H), 2.88 (td, *J* = 4.32, 13.83 Hz, 1H), 2.79 (m, 3H), 2.63 (m, 4H), 1.78 (m, 10H), 1.73 (m, 4H), 1.26 (m, 8H), 1.15 (m, 1H), 0.96 (t, *J* = 7.43 Hz, 3H), 0.85 (t, *J* = 7.43 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 151.1, 145.0, 143.5, 142.9, 141.8, 140.2, 130.1, 128.7, 128.6, 126.5, 126.4, 126.32, 126.29, 121.4, 117.9, 117.1, 55.3, 53.9, 42.3, 41.8, 39.2, 38.5, 34.8, 33.7, 32.8, 31.9, 30.2, 27.4, 26.90, 26.71, 25.72, 25.60, 23.6, 23.3, 12.0, 11.90.

FTIR (KBr) 2927, 2853, 1712, 1489, 1454, 1385, 1265, 1049, 893, 739 cm^{-1}.

HRMS *m/z* Calcd for $C_{37}H_{45}O_2$ $[M+H]^+$: 521.3420, found $[M+H]^+$: 521.3458.



(60)

R_f: 0.47 (hexane : diethyl ether = 8 : 1), yield: 35%.

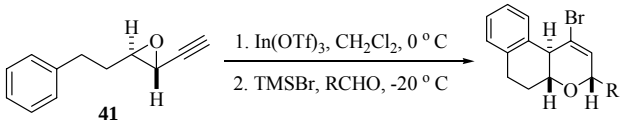
^{1}H NMR (500 MHz, $CDCl_3$) δ.7.25 (m, 2H), 7.16 (m, 5H), 7.04 (t, *J* = 3.57, 5.06 Hz), 4.47 (s, 1H), 3.51 (d, *J* = 3.01 Hz, 1H), 3.48 (dd, *J* = 1.81, 9.63 Hz, 1H), 3.38 (dd, *J* =10.05, 14.28 Hz, 1H), 3.07 (dt, *J* = 1.84, 14.28 Hz, 1H), 3.06 (d, *J* = 12.35 Hz, 1H), 2.92 (td, *J* = 4.24, 13.92 Hz, 1H), 2.83 (d, *J* = 7.37, 14.38 Hz, 1H), 2.76 (d, *J* = 14.28 Hz, 1H), 2.65 (dd, J = 8.20, 13.27 Hz, 1H), 2.57 (m, 1H), 1.85 (dt, *J* = 3.32, 9.86 Hz, 1H), 1.76 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.44 (m, 1H), 1.32 (s, 9H), 1.09 (m, 1H), 0.96 (t, *J* = 7.46 Hz, 3H), 0.84 (m, *J* = 7.46 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 153.3, 145.0, 142.8, 142.6, 142.2, 140.1 130.2, 129.1, 128.9, 126.6, 126.31, 126.29, 126.09, 121.4, 119.2, 117.2, 54.4, 53.9, 43.3, 42.7, 41.0, 38.6, 35.5, 33.7, 32.7, 30.5, 29.94, 29.72, 29.07, 27.2, 24.2, 23.0, 12.2, 11.7.

FTIR (KBr) 2961, 2926, 2872, 1709, 1454, 1362, 1263, 1032, 912, 752 cm^{-1}.

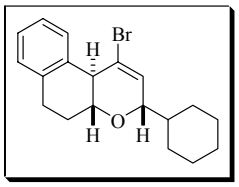
HRMS *m/z* Calcd for $C_{35}H_{43}O_2$ $[M+H]^+$: 495.3263, found $[M+H]^+$: 495.3268.

Procedures for preaparing polycyclic pyrans *via* indium triflate-catalyzed Friedel-Crafts-Prins cascade condensation of *trans* Propargylic epoxide with aldehydes



To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added indium triflate (11.2 mg, 0.02 mmol, 0.2 equiv.) and anhydrous dichloromethane (1.5 mL). The mixture was cooled to 0 ^{o}C with vigorous stirring. Propargylic epoxide **41** (17.2 mg, 0.1 mmol, 1.0 equiv. dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension, stirred at 0 ^{o}C for 4 hour, then cooled to -20 ^{o}C. Bromotrimethylsilane (TMSBr, 0.016 mL, 0.12 mmol, 1.2 equiv.) was added. Cyclohexanecarboxaldehyde (11.2 mg, 0.1 mmol, 1.0 equiv. dissolved in 1.0 mL dry CH_2Cl_2) was introduced in a dropwise manner. The reaction was allowed to proceed at -20 ^{o}C for 6 hours before quenching with saturated sodium bicarbonate solution (3 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane) to afford **62** in 87 % yield.

(3S*,4aR*,10bR*)-1-bromo-3-cyclohexyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (62)



R_f: 0.77 (hexane : diethyl ether = 8 : 1), yield: 87%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.67 (d, *J* =7.48 Hz,1H), 7.19 (m, 3H), 6.38 (t, *J* = 1.6 Hz, 1H), 3.88 (m, 1H), 3.57 (d, *J* =9.68 Hz, 1H), 3.40 (q, *J* = 8.6, 8.7, 9.6 Hz, 1H) 3.0 (td, *J* = 9.61, 15.48 Hz, 1H), 2.77 (ddd, *J* = 1.90, 8.62, 15.59 Hz, 1H), 2.16 (m, 1H), 1.90 (m, 1H), 1.88 (m, 4H), 1.76 (d, *J* = 7.04 Hz, 1H), 1.22 (m, 6H).

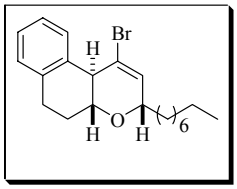
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.4, 135.1, 127.6, 126.4, 125.8, 124.9, 120.9, 80.9, 79.1, 48.4, 42.5, 28.4, 28.1, 26.7, 26.5, 26.4, 26.2, 26.1.

FTIR (KBr) 2928, 2850, 2812, 1639, 1479, 1448, 1354, 1317, 1288, 1178, 1124, 1074, 943, 887, 867, 833, 765, 748 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{24}{}^{79}BrO$ $[M+H]^+$: 347.1011, found $[M+H]^+$: 347.0996.

Calcd for $C_{19}H_{24}{}^{81}BrO$ $[M+H]^+$: 349.0990, found $[M+H]^+$: 349.0991.

(3S*,4aR*,10bR*)-1-bromo-3-octyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (63)



R_f: 0.66 (hexane : diethyl ether = 8 : 1), yield: 77%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.67 (d, *J* =7.48 Hz,1H), 7.18 (m, 3H), 6.33 (s, 1H), 4.0 (m, 1H), 3.59 (d, *J* =9.60 Hz, 1H), 3.41 (q, *J* = 8.72, 8.96, 9.24 Hz, 1H) 3.0 (td, *J* = 9.52, 15.48 Hz, 1H), 2.76 (dd, *J* = 7.36, 15.60 Hz, 1H), 2.17 (m, 1H), 1.90 (m, 1H), 1.87 (m, 2H), 1.65 (m, 2H), 1.45 (m, 10H), 0.88 (t, *J* = 6.44, 6.96 Hz, 3H).

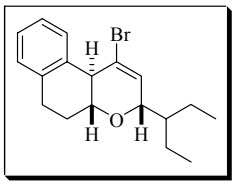
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.4, 136.3, 127.6, 126.5, 125.9, 124.8, 120.7, 79.2, 76.9, 48.3, 35.1, 31.9, 29.6, 29.5, 29.3, 26.7, 26.5, 25.0, 22.7, 14.1.

FTIR (KBr) 2924, 2852, 1633, 1456, 1370, 1116, 1124, 1082, 943, 775, 742 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{30}{}^{79}BrO$ $[M+H]^+$: 377.1480, found $[M+H]^+$: 377.1489.

Calcd for $C_{21}H_{30}{}^{81}BrO$ $[M+H]^+$: 379.1460, found $[M+H]^+$: 379.1501.

(3S*,4aR*,10bR*)-1-bromo-3-(pentan-3-yl)-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (64)



R_f: 0.69 (hexane : diethyl ether = 8 : 1), yield: 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.68 (d, *J* =7.48 Hz,1H), 7.18 (m, 3H), 6.34 (t, *J* = 1.48, 1.52 Hz, 1H), 4.13 (d, *J* = 1.16, 1H), 3.58 (d, *J* = 9.68 Hz, 1H), 3.41 (q, *J* = 8.64, 8.8, 9.4 Hz, 1H), 2.99 (td, *J* = 9.64, 15.44 Hz, 1H), 2.78 (ddd, *J* = 1.76, 8.68, 15.52 Hz, 1H), 2.15 (m, 1H), 1.89 (m, 1H), 1.55 (m, 1H), 1.42 (m, 3H), 1.37 (m, 1H), 0.90 (m, 6H).

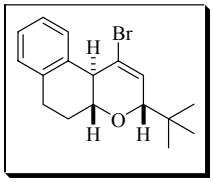
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.5, 135.4, 127.6, 126.4, 125.8, 124.9, 120.8, 79.2, 78.4, 48.4, 45.9, 26.7, 26.6, 22.3, 22.0, 12.1, 12.0.

FTIR (KBr) 2959, 2926, 2852, 2852, 1456, 1377, 1357, 1259, 1118, 1092, 750 cm^{-1}.

HRMS *m/z* Calcd for $C_{18}H_{24}{}^{79}BrO$ $[M+H]^+$: 335.1011, found $[M+H]^+$: 335.1015.

Calcd for $C_{18}H_{24}{}^{81}BrO$ $[M+H]^+$: 337.0990, found $[M+H]^+$: 337.0998.

(3R*,4aR*,10bR*)-1-bromo-3-tert-butyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (65)



R_f: 0.83 (hexane : diethyl ether = 8 : 1), yield: 89%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.62 (d, *J* =7.52 Hz, 1H), 7.15 (m, 3H), 6.38 (s, 1H), 3.61 (dd, *J* = 1.32, 3.48, 1H), 3.49 (d, *J* = 9.76 Hz, 1H), 3.31 (q, *J* = 8.6, 8.76, 9.4 Hz, 1H), 2.90 (td, *J* = 9.36, 15.6 Hz, 1H), 2.68 (ddd, *J* = 1.92, 8.6, 15.56 Hz, 1H), 2.12 (m, 1H), 1.83 (m, 1H), 0.96 (s, 9H).

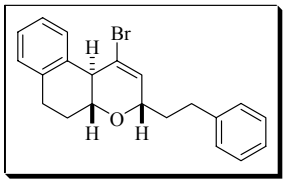
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 137.5, 134.1, 127.6, 126.4, 125.8, 124.9, 121.6, 84.4, 79.0, 48.3, 34.7, 26.8, 26.5, 25.7.

FTIR (KBr) 2956, 2864, 1634, 1479, 1456, 1361, 1307, 1259, 1122, 1097, 1060, 1012, 906, 800, 756, 737, 669 cm^{-1}.

HRMS *m/z* Calcd for $C_{17}H_{22}{}^{79}BrO$ $[M+H]^+$: 321.0854, found $[M+H]^+$: 321.0863.

Calcd for $C_{17}H_{22}{}^{81}BrO$ $[M+H]^+$: 323.0834, found $[M+H]^+$: 323.0859.

(3S*,4aR*,10bR*)-1-bromo-3-phenethyl-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (66)



R_f: 0.54 (hexane : diethyl ether = 8 : 1), yield: 83%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.66 (d, *J* =7.4 Hz, 1H), 7.22 (m, 8H), 6.32 (s, 1H), 4.07 (m, 1H), 3.62 (d, *J* = 9.64, 1H), 3.41 (q, *J* = 8.84, 8.92, 9.2 Hz, 1H), 3.03 (td, *J* = 9.72, 15.48 Hz, 1H), 2.76 (m, 3H), 2.17 (m, 1H), 1.88 (m, 3H).

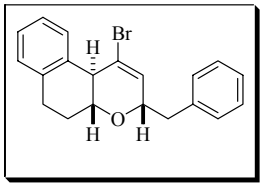
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.4, 137.3, 136.0, 128.5, 128.4, 127.6, 126.5, 125.9, 124.8, 121.0, 79.2, 75.8, 48.3, 36.5, 31.2, 26.7, 26.5.

FTIR (KBr) 3026, 2929, 2850, 1602, 1494, 1454, 1265, 1120, 1076, 738, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{22}{}^{79}BrO$ $[M+H]^+$: 369.0854, found $[M+H]^+$: 369.0867.

Calcd for $C_{21}H_{22}{}^{81}BrO$ $[M+H]^+$: 371.0834, found $[M+H]^+$: 371.0851.

(3S*,4aR*,10bR*)-3-benzyl-1-bromo-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (67)



R_f: 0.66 (hexane : diethyl ether = 8 : 1), yield: 69%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.7.62 (d, *J* =7.24 Hz, 1H), 7.21 (m, 8H), 6.33 (t, *J* = 1.48, 1.56 Hz,1H), 4.32 (m, 1H), 3.62 (d, *J* = 9.76, 1H), 3.41 (q, *J* = 8.6, 8.72, 9.6 Hz, 1H), 3.08 (dd, *J* = 6.48, 13.56 Hz, 1H), 3.00 (td, *J* = 9.52, 15.8 Hz, 1H), 2.77 (m, 2H), 2.15 (m, 1H), 1.90 (m, 1H).

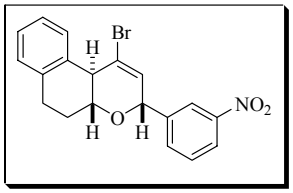
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.2, 137.0, 134.9, 129.6, 128.5, 127.6, 126.6, 126.5, 125.9, 124.8, 121.3, 79.3, 77.7, 48.2, 41.2, 26.6, 26.5.

FTIR (KBr) 2930, 2849, 1633, 1494, 1454, 1357, 1120, 1099, 744, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{20}{}^{79}BrO$ $[M+H]^+$: 355.0698, found $[M+H]^+$: 355.0682.

Calcd for $C_{20}H_{20}{}^{81}BrO$ $[M+H]^+$: 357.0677, found $[M+H]^+$: 357.0695.

(3R*,4aR*,10bR*)-1-bromo-3-(3-nitrophenyl)-4a,5,6,10b-tetrahydro-3*H*-benzo[f]chromene (69)



R_f: 0.46 (hexane : ethyl acetate = 4 : 1), yield: 75%.

^{1}H NMR (400 MHz, $CDCl_3$) δ.8.30 (S, 1h), 8.20 (d, *J* =7.96 Hz, 1H), 7.73 (m, 2H), 7.57 (t, *J* = 7.92 Hz,1H), 7.23 (M, 3H), 6.41 (s, 1H), 5.24 (d, *J* = 2.36 Hz, 1H), 3.77 (d, *J* = 9,72 Hz, 1H), 3.66 (q, *J* = 8.56, 8.92, 9.32, 1H), 3.06 (td, *J* = 9.64, 15.48 Hz, 1H), 2.82 (ddd, *J* = 7.76, 8.76, 15.64 Hz, 1H), 2.23 (m, 1H), 2.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 141.9, 138.4, 136.7, 134.4, 132.9, 129.7, 127.8, 126.8, 126.1, 124.9, 123.3, 122.2, 122.1, 79.4, 78.1, 47.7, 26.7, 26.5.

FTIR (KBr) 2926, 2854, 1728, 1531, 1456, 1348, 1265, 1122, 1070, 746 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{17}{}^{79}BrNO_3$ $[M+H]^+$: 386.0392, found $[M+H]^+$: 386.0394.

Calcd for $C_{19}H_{17}{}^{81}BrNO_3$ $[M+H]^+$: 388.0371, found $[M+H]^+$: 388.0351.

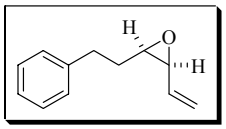
6.4 FCP CASCADE CONDESATION OF ALLYLIC EPOXIDES

PRECEDURE AND DATA

General procedures for preparation of Allylic Epoxide 72 and 73

To an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was added **40** (411.8 mg, 2.39 mmol, 1.0 equiv.) and Lindlar catalyst (palladium on $CaCO_3$ poisoned with 3.5% Pb, 50.9 mg, 0.48 mmol, 0.20 equiv.). The mixture was diluted with 30 mL ethyl acetate, vigoruously stirred at -20 ^oC under the atmosphere of hydrogen gas. Reaction was allowed to proceed at -20 ^oC for 2.5 hours before quenching with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with diethyl ether (10 mL × 3) and the combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (1% diehthyl ether in hexane) to afford **72** in 96% yield as a colorless oil.

(2R*,3S*)-2-phenethyl-3-vinyloxirane (72)



R_f: 0.67 (hexane : diethyl ether = 4 : 1), yield: 96%.

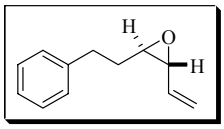
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 5.67 (m, 1H), 5.43 (d, *J* = 16.82 Hz, 1H), 5.13 (d, *J* = 10.60 Hz, 1H), 3.41 (dd, *J* = 4.31, 6.96 Hz, 1H), 3.12 (ddd, *J* = 4.57, 6.11, 10.55 Hz, 1H), 2.82 (m, 1H), 2.72 (m, 1H), 1.91 (m, 1H), 1.82 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 132.3, 128.5, 128.4, 126.1, 120.4, 58.1 57.3, 32.5, 29.6.

FTIR (neat) 3456, 3026, 2964, 2926, 2858, 1639, 1602, 1494, 1454, 1409, 987, 924, 812, 750, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123, found $[M+H]^+$: 175.1126.

(2R*,3R*)-2-phenethyl-3-vinyloxirane (73)



R_f: 0.58 (hexane : ethyl acetate = 4 : 1), yield: 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 5.56 (ddd, *J* = 7.58, 10.21, 17.38 Hz, 1H), 5.39 (d, *J* = 1.15, 17.11 Hz, 1H), 5.23 (d, *J* = 1.08, 10.28 Hz, 1H), 3.06 (dd, *J* = 2.03, 7.59 Hz, 1H), 2.87 (dt, *J* = 2.07, 5.67 Hz, 1H), 2.82 (m, 1H), 2.74 (m, 1H), 1.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.6, 128.4, 128.3, 126.0, 119.0, 59.7 58.8, 33.8, 32.1.

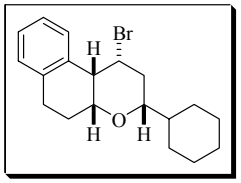
FTIR (neat) 3026, 2926, 2856, 1643, 1603, 1494, 1454, 1404, 1259, 1029, 987, 927, 879, 750, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{12}H_{15}O$ $[M+H]^+$: 175.1123, found $[M+H]^+$: 175.1119.

General procedures for preaparing polycyclic tetrahydropyrans *via* indium triflate-mediated Friedel-Crafts-Prins cascade condensation of *cis* allylic epoxide with aldehydes

To an oven-dried (10 mL) round-bottom flask equipped with a magnetic stirring bar was added indium triflate (11.2 mg, 0.020 mmol, 0.20 equiv) and anhydrous dichloromethane (1 mL). The mixture was vigorous stirred at 0 ^{o}C. Allylic epoxide **40** (17.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension, stirred at 0 ^{o}C for 2 hour. Bromotrimethylsilane (TMSBr, 0.016 mL, 0.12 mmol, 1.20 equiv) was added. Cyclohexanecarboxaldehyde (11.2 mg, 0.1 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced in a dropwise manner. The reaction was allowed to proceed at 0 ^{o}C for 4 hours before quenching with saturated $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with dichloromethane (10 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane) to afford **74** in 91 % yield.

(1R*,3R*,4aR*,10bS*)-1-bromo-3-cyclohexyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (74)



R_f: 0.75 (hexane : diethyl ether = 4 : 1), yield: 91%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.47 Hz, 1H), 7.18 (m, 3H), 4.77 (td, *J* = 3.99, 12.37 Hz, 1H), 3.91 (m, 1H), 3.17 (ddd, *J* = 2.53, 6.52, 9.93 Hz, 1H), 3.08 (s, 1H), 2.80 (td, *J* = 6.52, 15.39 Hz, 1H), 2.47 (m, 4H), 2.16 (q, *J* = 11.03, 11.84, 12.44

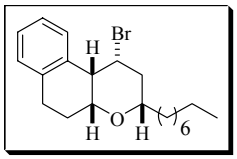
Hz, 1H) 2.03 (m, 2H), 1.69 (m, 2H), 1.56 (m, 2H),, 1.45 (m, 2H), 1.18 (m, 2H), 1.02 (m, 2H), 0.76 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 134.5, 128.1, 127.5, 126.1, 125.4, 82.6, 76.7, 52.1, 44.1, 42.6, 35.2, 29.3, 29.0, 28.2 26.5, 26.3, 26.0, 25.9.

FTIR (KBr) 2924, 2850, 1489, 1448, 1300, 1267, 1242, 1064, 989, 893, 812, 740 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{26}{}^{79}BrO$ $[M+H]^+$: 349.1167, found $[M+H]^+$: 349.1199;
Calcd for $C_{19}H_{26}{}^{81}BrO$ $[M+H]^+$: 351.1147, found $[M+H]^+$: 351.1120.

(1R*,3S*,4aR*,10bS*)-1-bromo-3-octyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (75)



R*f*: 0.83 (hexane : diethyl ether = 4 : 1), yield: 84%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.51 Hz, 1H), 7.15 (m, 3H), 4.77 (td, *J* = 4.06, 12.39 Hz, 1H), 4.01 (m, 1H), 3.48 (m, 1H), 3.14 (s, 1H), 2.85 (td, *J* = 6.10, 15.36 Hz, 1H), 2.53 (ddd, *J* = 6.70, 8.41 15.24 Hz, 1H), 2.21 (m, 2H), 2.09 (td, *J* = 3.05, 12.76 Hz, 1H), 1.72 (m, 1H), 1.40 (m, 1H), 1.27 (m, 3H), 1.21 (s, 10H), 0.86 (t, *J* = 7.09 Hz, 3H).

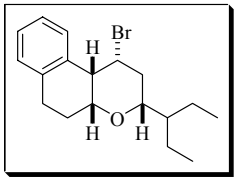
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 134.5, 128.1, 127.5, 126.1, 125.5, 78.6, 76.9, 51.2, 44.0, 38.1, 35.7, 31.9, 29.52, 29.48, 29.45, 29.23, 26.4, 25.3, 22.7, 14.1.

FTIR (KBr) 3442, 2924, 2852, 1487, 1456, 1377, 1240, 1134, 1099, 1064, 979, 750, 721 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{32}{}^{79}BrO$ $[M+H]^+$: 379.1637, found $[M+H]^+$: 379.1662;

Calcd for $C_{21}H_{32}{}^{81}BrO$ $[M+H]^+$: 381.1616, found $[M+H]^+$: 381.1605.

(1R*,3R*,4aR*,10bS*)-1-bromo-3-(pentan-3-yl)-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (76)



R_f: 0.78 (hexane : diethyl ether = 4 : 1), yield: 85%.

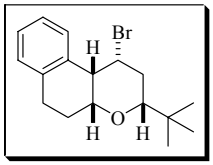
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.22 Hz, 1H), 7.16 (m, 3H), 4.78 (td, *J* = 3.85, 12.51 Hz, 1H), 3.97 (m, 1H), 3.49 (ddd, *J* = 2.69, 4.94, 10.77 Hz, 1H), 3.17 (s, 1H), 2.88 (td, *J* = 6.88, 15.56 Hz, 1H), 2.55 (td, *J* = 6.88, 14.21 Hz, 1H), 2.25 (q, *J* = 12.57 Hz, 1H), 2.10 (m, 1H), 1.99 (td, *J* = 2.84, 12.72 Hz, 1H), 1.78 (m, 1H), 1.24 (m, 4H), 1.09 (m, 1H), 0.76 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 134.5, 128.2, 127.5, 126.1, 125.4, 80.1, 76.8, 52.4, 45.5, 44.1, 34.6, 29.3, 26.3, 21.7, 21.6, 11.5, 11.4.

FTIR (KBr) 2958, 2931, 2872, 1490, 1458, 1379, 1300, 1263, 1236, 1211, 1184, 1145, 1083, 1064, 966, 742, 671 cm^{-1}.

HRMS *m/z* Calcd for $C_{18}H_{26}{}^{79}BrO$ $[M+H]^+$: 337.1167, found $[M+H]^+$: 337.1174;
Calcd for $C_{18}H_{26}{}^{81}BrO$ $[M+H]^+$: 339.1147, found $[M+H]^+$: 339.1172.

(1R*,3R*,4aR*,10bS*)-1-bromo-3-tert-butyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (77)



R_f: 0.75 (hexane : diethyl ether = 4 : 1), yield: 72%.

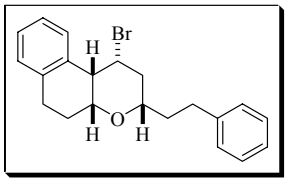
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.22 Hz, 1H), 7.15 (m, 3H), 4.78 (td, *J* = 3.82, 12.32 Hz, 1H), 3.96 (m, 1H), 3.49 (ddd, *J* = 2.69, 4.94, 10.77 Hz, 1H), 3.17 (s, 1H), 3.15 (dd, *J* =2.55, 10.83 Hz, 1H), 2.93 (td, *J* = 7.01, 15.08 Hz, 1H), 2.56 (td, *J* = 6.58, 15.50 Hz, 1H), 2.20 (q, *J* = 12.53 Hz, 1H), 2.04 (m, 2H), 1.83 (m, 1H), 0.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 134.5, 128.2, 127.6, 126.0, 125.3, 85.5, 76.4, 52.9, 43.9, 34.4, 32.8, 29.2, 26.2, 25.7.

FTIR (KBr) 2953, 2866, 1479, 1456, 1394, 1373, 1361, 1298, 1257, 1238, 1215, 1166, 1101, 1080, 1066, 1028, 989, 813, 742, 729, 707, 576 cm^{-1}.

HRMS *m/z* Calcd for $C_{17}H_{34}{}^{79}BrO$ $[M+H]^+$: 333.1793, found $[M+H]^+$: 333.1796;
Calcd for $C_{17}H_{34}{}^{81}BrO$ $[M+H]^+$: 335.1773, found $[M+H]^+$: 335.1773.

(1R*,3S*,4aR*,10bS*)-1-bromo-3-phenethyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (78)



R_f: 0.64 (hexane : diethyl ether = 4 : 1), yield: 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.46 Hz, 1H), 7.18 (m, 8H), 4.74 (td, *J* = 4.04, 12.53 Hz, 1H), 4.00 (m, 1H), 3.48 (m, 1H), 3.15 (s, 1H), 2.87 (td, *J* = 6.33, 15.49 Hz, 1H), 2.59 (m, 3H), 2.27 (q, *J* = 12.60 Hz, 1H), 2.20 (m, 1H), 2.06 (td, *J* = 2.85, 12.78 Hz, 1H), 1.77 (m, 2H), 1.63 (m, 1H).

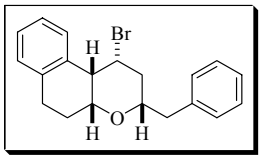
^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 139.2, 134.5, 128.4, 128.3, 128.1, 127.6, 126.2, 125.8, 125.6, 77.3, 76.9, 50.9, 43.9, 38.0, 37.0, 31.4, 29.4, 26.4.

FTIR (KBr) 3024, 2929, 2852, 1602, 1492, 1454, 1317, 1301, 1271, 1251, 1213, 1199, 1107, 1064, 985, 750, 700, 669, 565 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{24}{}^{79}BrO$ $[M+H]^+$: 371.1011, found $[M+H]^+$: 371.1010;

Calcd for $C_{21}H_{24}{}^{81}BrO$ $[M+H]^+$: 373.0990, found $[M+H]^+$: 373.0992.

(1R*,3S*,4aR*,10bS*)-3-benzyl-1-bromo-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (79)



R_f: 0.67 (hexane : diethyl ether = 4 : 1), yield: 63%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.22 Hz, 1H), 7.19 (m, 8H), 4.74 (td, *J* = 4.02, 12.70 Hz, 1H), 4.02 (m, 1H), 3.71 (m, 1H), 3.15 (s, 1H), 2.90 (td, *J* = 6.39, 15.44 Hz, 1H), 2.83 (dd, *J* = 6.03, 13.66 Hz, 1H), 2.56 (m, 2H), 2.24 (q, *J* = 8.83, 12.68, 12.70 Hz, 1H), 2.14 (m, 1H), 1.77 (m, 1H).

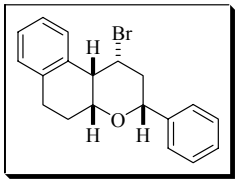
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.8, 134.4, 129.4, 128.3, 128.2, 127.5, 126.3, 126.2, 125.5, 79.4, 77.0, 50.9, 43.8, 42.1, 37.3, 29.3, 26.3.

FTIR (KBr) 3026, 2927, 2850, 1600, 1494, 1454, 1377, 1305, 1265, 1240, 1062, 981, 752, 700, 599 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{22}{}^{79}BrO$ $[M+H]^+$: 357.0854, found $[M+H]^+$: 357.0813;

Calcd for $C_{20}H_{22}{}^{81}BrO$ $[M+H]^+$: 359.0834, found $[M+H]^+$: 359.0840.

(1R*,3R*,4aR*,10bS*)-1-bromo-3-phenyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (80)



R_f: 0.56 (hexane : diethyl ether = 4 : 1), yield: 70%.

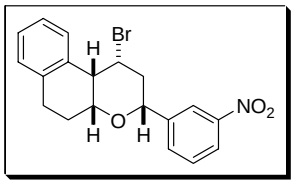
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (t, *J* = 3.44, 4.67 Hz, 1H), 7.21 (m, 8H), 4.74 (td, *J* = 3.69, 12.78 Hz, 1H), 4.59 (dd, J = 2.46, 10.56 Hz, 1H), 4.20 (m, 1H), 3.28 (s, 1H), 3.00 (td, *J* = 6.88, 14.99 Hz, 1H), 2.63 (dd, *J* = 6.88, 13.76 Hz, 1H), 2.48 (q, J = 11.06, 12.78 Hz, 1H), 2.29 (td, *J* = 2.95, 13.02 Hz, 1H), 2.18 (m, 1H), 1.91 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 139.0, 134.1, 128.3, 127.7, 127.6, 126.2, 125.7, 125.6, 80.5, 77.1, 50.6, 43.7, 40.2, 29.3, 26.1.

FTIR (KBr) 3028, 2929, 2852, 1602, 1597, 1492, 1454, 1377, 1301, 1265, 1238, 1211, 1095, 1060, 985, 914, 840, 754, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{20}{}^{79}BrO$ $[M+H]^+$: 343.0698, found $[M+H]^+$: 343.0692;
Calcd for $C_{19}H_{20}{}^{81}BrO$ $[M+H]^+$: 345.0616, found $[M+H]^+$: 345.0623.

(1R*,3R*,4aR*,10bS*)-1-bromo-3-(3-nitrophenyl)-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (81)



R_f: 0.4 (hexane : ethyl acetate = 4 : 1), yield: 84%.

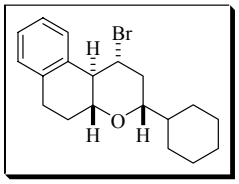
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (q, *J* = 2.94 Hz, 1H), 8.06 (td, *J* = 1.30, 7.95 Hz, 1H), 8.03 (s, 1H), 7.47 (d, *J* = 7.67 Hz, 1H), 7.40 (t, *J* = 7.67 Hz, 1H), 7.22 (m, 3H), 4.92 (td, *J* = 4.34, 11.82 Hz, 1H), 4.72 (dd, *J* = 3.98, 9.76Hz, 1H), 4.26 (m, 1H), 3.32 (s, 1H), 3.01 (td, *J* = 7.19, 15.45 Hz, 1H), 2.66 (td, *J* = 6.77, 15.77 Hz, 1H), 2.41 (m, 2H), 2.22 (m, 1H), 1.93 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 143.3, 138.9, 133.7, 131.7, 129.4, 128.5, 127.5, 126.5, 125.7, 122.6, 120.8, 78.9, 77.4, 49.5, 43.5, 39.7, 29.2, 26.1.

FTIR (KBr) 3072, 2929, 2854, 1703, 1614, 1583, 1525, 1485, 1446, 1348, 1267, 1201, 1165, 1097, 1062, 989, 906, 831, 808, 734, 688, 570 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{19}{}^{79}BrNO_3$ $[M+H]^+$: 388.0548, found $[M+H]^+$: 388.0566; Calcd for $C_{19}H_{19}{}^{81}BrNO_3$ $[M+H]^+$: 390.0528, found $[M+H]^+$: 390.0516.

(1R*,3R*,4aR*,10bR*)-1-bromo-3-cyclohexyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (82)



R*f*: 0.72 (hexane : diethyl ether = 8 : 1), yield: 83%.

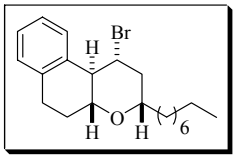
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.66 Hz, 1H), 7.18 (m, 3H), 4.77 (dt, *J* = 4.90, 11.34 Hz, 1H), 3.20 (ddd, *J* = 6.91, 8.34, 15.35 Hz, 1H), 3.06 (ddd, *J* = 1.42, 6.61, 11.28 Hz, 1H), 2.96 (td, *J* = 9.05, 15.35 Hz, 1H), 2.88 (t, *J* = 10.26 Hz, 1H), 2.73 (ddd, *J* = 3.20, 7.66, 15.40 Hz, 1H), 2.54 (ddd, *J* = 1.64, 4.96, 13.24 Hz, 1H), 2.11 (m, 2H), 1.89 (m, 2H), 1.74 (m, 3H), 1.66 (d, *J* = 11.67 Hz, 1H), 1.45 (m, 1H), 2.03 (m, 2H), 1.22 (m, 3H), 1.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.6, 127.3, 126.6, 125.9, 125.3, 81.9, 78.5, 50.6, 50.0, 42.6, 41.4, 29.1, 28.7, 28.6, 27.2, 26.5, 26.2, 26.1.

FTIR (KBr) 2924, 2848, 1597, 1485, 1446, 1357, 1273, 1165, 1134, 1076, 1045, 987, 891, 742, 705 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{26}{}^{79}BrO$ $[M+H]^+$: 349.1167, found $[M+H]^+$: 349.1169; Calcd for $C_{19}H_{26}{}^{81}BrO$ $[M+H]^+$: 351.1147, found $[M+H]^+$: 351.1129.

(1R*,3S*,4aR*,10bR*)-1-bromo-3-octyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (83)



R_f: 0.74 (hexane : diethyl ether = 8 : 1), yield: 81%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.43 Hz, 1H), 7.17 (m, 3H), 4.77 (dt, *J* = 4.95, 11.46 Hz, 1H), 3.30 (ddd, *J* = 5.48, 7.11, 15.08 Hz, 1H), 3.22 (ddd, *J* = 7.11, 9.95, 15.54 Hz, 1H), 2.96 (td, *J* = 9.04, 15.44 Hz, 1H), 2.90 (t, *J* = 10.36 Hz, 1H), 2.73 (ddd, *J* = 3.17, 7.70, 15.40 Hz, 1H), 2.54 (ddd, *J* = 1.49, 4.80, 13.03 Hz, 1H), 2.13 (m, 2H), 1.90 (m, 1H), 1.89 (m, 2H), 1.59 (m, 1H), 1.41 (m, 2H), 1.27 (m, 11H), 0.88 (t, J = 6.47 Hz, 3H).

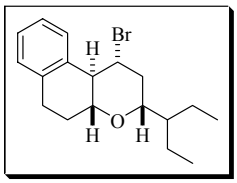
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.5, 127.3, 126.7, 125.9, 125.3, 78.4, 77.7, 49.84, 49.80, 44.2, 35.7, 31.9, 29.6, 29.5, 29.3, 28.8, 27.1, 25.4, 22.7, 14.1.

FTIR (KBr) 2951, 2924, 2852, 1485, 1456, 1375, 1336, 1165, 1141, 1082, 742 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{32}{}^{79}BrO$ $[M+H]^+$: 379.1637, found $[M+H]^+$: 379.1642;

Calcd for $C_{21}H_{32}{}^{81}BrO$ $[M+H]^+$: 381.1616, found $[M+H]^+$: 381.1592.

(1R*,3R*,4aR*,10bR*)-1-bromo-3-(pentan-3-yl)-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (84)



R_f: 0.58 (hexane : diethyl ether = 4 : 1), yield: 85%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.45 Hz, 1H), 7.16 (m, 3H), 4.47 (dt, *J* = 5.02, 11.33 Hz, 1H), 3.27 (dd, *J* = 5.45, 11.21 Hz, 1H), 3.20 (ddd, *J* = 7.14, 8.50, 15.64 Hz, 1H), 2.93 (td, *J* = 9.10, 15.57 Hz, 1H), 2.86 (t, *J* = 10.54 Hz, 1H), 2.72 (ddd, *J* = 2.98, 7.76, 15.22 Hz, 1H), 2.54 (ddd, *J* = 1.04, 4.92, 13.13 Hz, 1H), 2.14 (m, 2H), 1.89 (m, 1H), 1.51 (m, 1H), 1.44 (m, 2H), 1.35 (m, 1H), 1.27 (m, 1H), 0.88 (m, 6H).

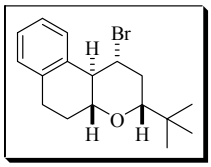
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.6, 127.3, 126.6, 125.8, 125.2, 79.2, 78.6, 50.6, 50.0, 45.4, 40.9, 28.6, 27.1, 21.6, 11.44, 11.39.

FTIR (KBr) 2960, 2933, 2872, 1485, 1456, 1379, 1307, 1168, 1141, 1083, 1047, 742, 690 cm^{-1}.

HRMS *m/z* Calcd for $C_{18}H_{26}{}^{79}BrO$ $[M+H]^+$: 337.1167, found $[M+H]^+$: 337.1169;

Calcd for $C_{18}H_{26}{}^{81}BrO$ $[M+H]^+$: 339.1147, found $[M+H]^+$: 339.1147.

(1R*,3R*,4aR*,10bR*)-1-bromo-3-tert-butyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (85)



R_f: 0.76 (hexane : diethyl ether = 8 : 1), yield: 75%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.57 Hz, 1H), 7.17 (m, 3H), 4.47 (dt, *J* = 5.10, 11.26 Hz, 1H), 3.19 (q, *J* = 8.15, 8.39, 8.97 Hz, 1H), 2.94 (m, 2H), 2.86 (t, *J* = 10.28 Hz, 1H), 2.72 (ddd, *J* = 3.10, 7.80, 15.43 Hz, 1H), 2.50 (dd, *J* = 4.13, 12.38 Hz, 1H), 2.12 (m, 2H), 1.89 (m, 1H), 0.94 (s, 9H).

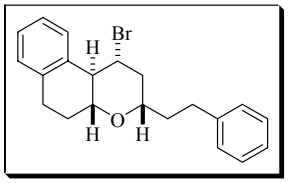
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.7, 127.3, 126.5, 125.8, 125.2, 85.1, 78.7, 51.3, 50.0, 38.9, 34.1, 28.5, 27.1, 26.0.

FTIR (KBr) 3417, 2954, 2868, 1633, 1479, 1456, 1361, 1257, 1138, 1093, 1082, 742, 684 cm^{-1}.

HRMS *m/z* Calcd for $C_{17}H_{34}{}^{79}BrO$ $[M+H]^+$: 333.1793, found $[M+H]^+$: 333.1799;

Calcd for $C_{17}H_{34}{}^{81}BrO$ $[M+H]^+$: 335.1773, found $[M+H]^+$: 335.1768.

(1R*,3S*,4aR*,10bR*)-1-bromo-3-phenethyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (86)



R_f: 0.64 (hexane : diethyl ether = 4 : 1), yield: 76%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.63 Hz, 1H), 7.17 (m, 8H), 4.47 (dt, *J* = 5.13, 11.58 Hz, 1H), 3.26 (m, 1H), 3.20 (ddd, *J* = 6.85, 8.51, 15.44 Hz, 1H), 2.95 (td, J = 9.19, 15.43 Hz, 1H), 2.86 (t, *J* = 10.26 Hz, 1H), 2.73 (m, 3H), 2.46 (ddd, *J* = 1.64, 5.01, 13.15 Hz, 1H), 2.14 (m, 2H), 1.91 (m, 2H), 1.74 (m, 1H).

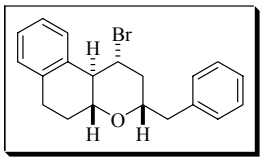
^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.6, 139.0, 136.4, 128.4, 128.3, 127.3, 126.6, 125.8, 125.2, 78.3, 76.2, 49.7, 49.4, 44.1, 37.0, 31.4, 28.7, 27.0.

FTIR (KBr) 3442, 2945, 2848, 1602, 1494, 1487, 1454, 1338, 1139, 1265, 1101, 1080, 1029, 744, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{24}{}^{79}BrO$ $[M^+]$: 370.0927, found $[M^+]$: 370.0919;

Calcd for $C_{21}H_{24}{}^{81}BrO$ $[M^+]$: 372.0906, found $[M^+]$: 372.0899.

(1R*,3S*,4aR*,10bR*)-3-benzyl-1-bromo-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (87)



R_f: 0.56 (hexane : diethyl ether = 4 : 1), yield: 70%.

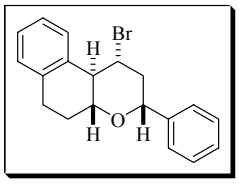
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.52 Hz, 1H), 7.20 (m, 8H), 4.47 (dt, *J* = 4.98, 11.38 Hz, 1H), 3.55 (m, 1H), 3.25 (ddd, *J* = 6.89, 8.44, 15.47 Hz, 2H), 3.00 (dd, *J* = 5.92, 13.62 Hz, 1H), 2.91 (m, 2H), 2.72 (m, 2H), 2.47 (ddd, *J* = 1.46, 4.91, 13.08 Hz, 1H), 2.13 (m, 2H), 1.92 (m, 1H), 0.94 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 137.6, 136.4, 129.5, 128.4, 127.3, 126.7, 126.5, 125.9, 125.2, 78.5, 78.4, 49.6, 49.4, 43.4, 42.2, 28.7, 27.1.

FTIR (KBr) 3026, 2941, 2848, 1602, 1494, 1485, 1454, 1435, 1365, 1338, 1265, 1219, 1165, 1139, 1080, 1031, 981, 744, 702 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{22}{}^{79}BrO$ $[M+H]^+$: 357.0854, found $[M+H]^+$:357.0874;
Calcd for $C_{20}H_{22}{}^{81}BrO$ $[M+H]^+$: 359.0834, found $[M+H]^+$: 359.0815.

(1R*,3R*,4aR*,10bR*)-1-bromo-3-phenyl-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (88)



R_f: 0.50 (hexane : diethyl ether = 4 : 1), yield: 70%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.60 Hz, 1H), 7.42 (m, 3H), 7.31 (m, 2H), 7.25 (t, *J* = 7.13 Hz, 1H), 7.19 (d, *J* = 7.28 Hz, 1H), 4.66 (dt, *J* = 4.96, 11.46 Hz, 1H), 4.46 (dd, *J* = 1.72, 11.47Hz, 1H), 3.48 (ddd, *J* = 6.83, 8.55, 15.38 Hz, 1H), 3.07 (d, *J* = 10.41 Hz, 1H), 3.03 (m, 1H), 2.82 (ddd, *J* = 2.98, 7.76, 15.58 Hz, 1H), 2.77 (ddd, *J*

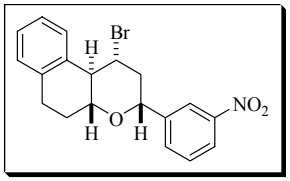
= 1.92, 4.91, 11.28 Hz, 1H), 2.50 (td, *J* = 11.67, 13.39 Hz, 1H), 2.24 (m, 1H), 2.07 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.1, 136.3, 128.5, 127.9, 127.4, 126.7, 125.95, 125.87, 125.22, 79.5, 78.8, 49.4, 49.1, 45.9, 28.6, 27.0.

FTIR (KBr) 3030, 2945, 2848, 1602, 1494, 1485, 1454, 1354, 1265, 1166, 1138, 1091, 1074, 1047, 979, 744, 700, 555 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{20}{}^{79}BrO$ $[M+H]^+$: 343.0698, found $[M+H]^+$: 343.0708;
Calcd for $C_{19}H_{20}{}^{81}BrO$ $[M+H]^+$: 345.0677, found $[M+H]^+$: 345.0680.

(1R*,3R*,4aR*,10bR*)-1-bromo-3-(3-nitrophenyl)-2,3,4a,5,6,10b-hexahydro-1*H*-benzo[f]chromene (89)



R*f*: 0.56 (hexane : ethyl acetate = 4 : 1), yield: 86%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.15 (d, *J* = 8.25 Hz, 1H), 7.69 (d, *J* = 7.41 Hz, 2H), 7.53 (t, *J* = 7.91 Hz, 1H), 7.24 (m, 3H), 4.59 (dt, *J* = 4.88, 11.11 Hz, 1H), 4.50 (d, *J* = 11.45 Hz, 1H), 3.45 (m, 1H), 3.03 (m, 2H), 2.79 (m, 2H), 2.40 (q, *J* = 11.95 Hz, 1H), 2.21 (m, 1H), 2.05 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 142.9, 139.0, 135.8, 131.8, 129.5, 127.4, 126.9, 126.0, 125.2, 122.8, 120.9, 78.9, 78.1, 49.2, 48.0, 45.7, 28.5, 26.9.

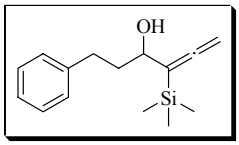
FTIR (KBr) 3064, 2945, 2850, 1531, 1485, 1348, 1265, 1166, 1139, 1095, 1076, 983, 894, 825, 808, 736, 686 cm^{-1}.

HRMS *m/z* Calcd for $C_{19}H_{19}{}^{79}BrNO_3$ $[M+H]^+$: 388.0548, found $[M+H]^+$: 388.0505.
Calcd for $C_{19}H_{19}{}^{81}BrNO_3$ $[M+H]^+$: 390.0528, found $[M+H]^+$: 390.3558.

6.5 *CIS* PRINS CYCLIZATION OF ALLENIC ALCOHOLS

PRECEDURES AND DATA

Preparation of 1-phenyl-4-(trimethylsilyl)hexa-4,5-dien-3-ol (93)



(3-Bromoprop-1-ynyl)trimethylsilane (0.85 mL, 6 mmol, 2.0 equiv) was added to a vigorous stirred mixture of hydrocinnamaldehyde (0.40 mL, 3.0 mmol, 1.0 equiv) and indium power (0.516 g, 4.5 mmol, 1.5 equiv) in THF/NH_4Cl(aq. sat.) (1:5, 18 mL) at 0 ^oC. Reaction was allowed to warm up to room temperature and proceed for around 12 hours before quenching with 10 mL of 1 M HCl solution. The aqueous layer was extracted with diethyl ether (20 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by flash chromatograghy (3% ethyl acetate in hexane) to afford **93** in 48% yield as a clear oil.

R_f: 0.5 (Hexane: diethyl ether = 4 : 1)

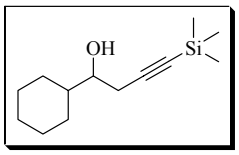
^1H NMR (400 MHz, $CDCl_3$): 7.29 (m, 2H), 7.19 (m, 3H), 4.56 (m, 2H), 4.18 (s, 1H), 2.76 (m, 1H), 2.70 (m, 1H), 1.96 (m, 1H0, 1.84 (m, 1H), 1.66 (d, J = 5.98 Hz, 1H), 0.14 (s, 9H)

^{13}C NMR (100.0 MHz, $CDCl_3$): 207.2, 142.1, 128.5, 128.4, 125.8, 100.6, 72.2, 69.9, 39.6, 32.0, -0.87.

FTIR (neat) 3417, 2953, 1927, 1602, 1495, 1454, 1247, 1029, 840, 754, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{23}OSi$ $[M+H]^+$: 247.1518, found $[M+H]^+$: 247.1522.

1-cyclohexyl-4-(trimethylsilyl)but-3-yn-1-ol (96)



R_f: 0.38 (Hexane : Diethyl ether = 4 : 1)

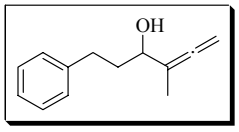
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (m, 1H), 2.47 (dd, *J* = 4.02, 16.86 Hz, 1H), 2.35 (dd, *J* = 7.93, 16.86 Hz, 1H), 2.03 (d, *J* = 4.14Hz, 1H), 1.86 (d, *J* = 12.77 Hz, 1H), 1.75, (m, 2H), 1.62, (m, 2H), 1.42, (m, 1H), 1.21, (m, 3H), 1.00, (m, 2H), 0.14 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 103.8, 87.5, 73.9, 42.7, 28.9, 28.2, 26.4, 26.2, 26.0, 0.07.

FTIR (neat) 3402, 2928, 2851, 2663, 2174, 1713, 1450, 1422, 1349, 1249, 1198, 1103, 1086, 1015, 842, 760, 698, 651 cm^{-1}.

HRMS *m/z* Calcd for $C_{13}H_{25}OSi$ [M^+]: 225.1675, found [M^+]: 225.1678.

4-methyl-1-phenylhexa-4,5-dien-3-ol (104)



1-Bromobut-2-yne (0.92 mL, 10 mmol, 2.0 equiv) was added to a vigorous stirred mixture of hydrocinnamaldehyde (0.67 mL, 5.0 mmol, 1.0 equiv) and indium power (0.8612 g, 7.5 mmol, 1.5 equiv) in THF/NH_4Cl(aq. sat.) (1:5, 24 mL) at 0 ^oC. Reaction was allowed to warm up to room temperature and proceed for around 12 hours before quenching with 15 mL of 1 M HCl solution. The aqueous layer was extracted with diethyl ether (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by flash chromatograghy (5% ethyl acetate in hexane) to afford **104** in 90% yield as a clear oil.

R_f: 0.47 (Hexane : Ethyl Acetate = 4 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 4.80 (m, 2H), 4.06 (m, 1H), 2.75 (m, 1H), 2.66 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H), 1.72 (t, *J* = 3.11 Hz, 1H), 1.64 (d, *J* = 5.16 Hz, 1H).

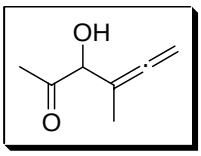
^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 141.9, 128.4, 128.3, 125.7, 101.7, 76.7, 71.7, 36.8, 31.8, 14.3.

FTIR (neat) 3379, 2943, 2860, 1957, 1714, 1602, 1494, 1454, 1371, 1029, 848, 750, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{13}H_{17}O$ $[M+H]^+$: 189.1279, found $[M+H]^+$: 189.1288.

1-Bromobut-2-yne (0.96 mL, 10 mmol, 1.0 equiv) was added to a vigorous stirred mixture of Pyruvic aldehyde (40% in water, 2.70 mL, 15 mmol, 1.5 equiv) and indium power (1.15 g, 10 mmol, 1.0 equiv) in THF/NH_4Cl(aq. sat.) (1:5, 12 mL) at 0 ^oC. Reaction was allowed to warm up to room temperature and proceed for around 12 hours before quenching with 10 mL of 1 M HCl solution. The aqueous layer was extracted with diethyl ether (30 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by flash chromatograghy to afford **109** in 60% yield as a clear oil.

3-hydroxy-4-methylhexa-4,5-dien-2-one (109)



R_f: 0.39 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (m, 1H), 4.81 (m, 1H), 4.66 (d, *J* = 5.19 Hz, 1H), 3.71 (d, *J* = 5.30 Hz, 1H), 2.24 (s, 3H), 1.60 (t, *J* = 3.32 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 207.5, 96.7, 78.9, 75.7, 24.8, 12.9.

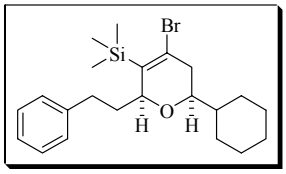
FTIR (neat) 3441, 2987, 2851, 1960, 1717, 1630, 1427, 1359, 1234, 1180, 1078, 974, 860 cm^{-1}.

HRMS *m/z* Calcd for $C_7H_{11}O_2$ $[M+H]^+$: 127.0759, found $[M+H]^+$: 127.0754.

General procedures for carrying out Prins cyclization using allenic alcohol 93 with various aldehydes at reduced reaction temperature and concentration

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added indium trifluoroacetate (17.4 mg, 0.040 mmol, 0.20 equiv) and anhydrous dichloromethane (1 mL), stirred at -78 ^{o}C. Bromotrimethylsilane (TMSBr, 0.032 mL, 0.24 mmol, 1.20 equiv) was added, and followed with the introduction of cyclohexanecarboxaldehyde (22.4 mg, 0.2 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2). Allenic alcohol **93** (49.6 mg, 0.20 mmol, 1.0 equiv, dissolved in 1 mL dry CH_2Cl_2) was introduced into the suspension over around 10 minutes. The reaction was allowed to proceed at -78 ^{o}C for 18 hours before quenching with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with dichloromethane (15 mL × 3) and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.5% diethyl ether in hexane) to afford **94** in 81 % yield.

((2S*,6S*)-4-bromo-6-cyclohexyl-2-phenethyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (94)



R*f*: 42 (Hexane : Diethyl ether = 8 : 1), yield: 81%.

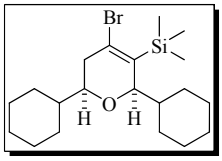
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.23 (m, 3H), 4.30 (m, 1H), 3.25 (t, *J* = 8.72 Hz, 1H), 2.80 (m, 2H), 2.60 (ddd, *J* = 2.62, 9.78, 17.14 Hz, 1H), 2.52 (d, *J* = 17.09 Hz, 1H), 2.04 (m, 2H), 1.80 (m, 2H), 1.75 (m, 3H), 1.47 (m, 1H), 1.27 (m, 3H), 1.08 (m, 2H), 0.27 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 138.9, 130.6, 128.7, 128.3, 125.7, 78.5, 77.9, 42.9, 42.4, 37.7, 31.5, 29.0, 28.4, 26.6, 26.1, 26.0, 0.31.

FTIR (neat) 3024, 2945, 2850, 1598, 1494, 1450, 1355, 1298, 1249, 1176, 1103, 841, 756, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{22}H_{34}{}^{79}BrOSi$ $[M+H]^+$: 421.1562, found $[M+H]^+$: 421.1556;
Calcd for $C_{22}H_{34}{}^{81}BrOSi$ $[M+H]^+$: 423.1542, found $[M+H]^+$: 423.1536.

((2R*,6R*)-4-bromo-2,6-dicyclohexyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (95)



R*f*: 0.86 (Hexane : Diethyl ether = 8 : 1), yield: 3%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (s, 1H), 3.15 (m, 1H), 2.43 (ddd, *J* = 3.12, 9.84, 16.84Hz, 1H), 2.36 (td, *J* = 2.65, 16.84 Hz, 1H), 1.88 (d, *J* = 12.62 Hz, 1H), 1.73 (m,

4H), 1.65 (m, 3H), 1.50 (M, 1H), 1.41 (d, *J* = 12.21 Hz, 1H), 1.35 (m, 1H), 1.17 (m, 9H), 1.00 (m, 2H), 0.24 (s, 9H).

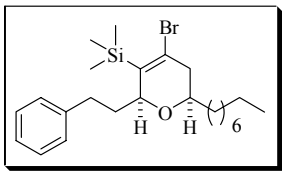
^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 130.0, 116.2, 83.1, 77.33, 43.0, 42.6, 42.4, 30.6, 28.8, 28.4, 27.1, 26.7, 26.5, 26.2, 26.1, 24.8, 0.13.

FTIR (neat) 2926, 2851, 1601, 1450, 1354, 1248, 1114, 1072, 839, 758 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{35}{}^{79}BrOSiNa$ $[M+Na]^+$: 421.1538,

found $[M+Na]^+$: 421.1542.

((2S*,6R*)-4-bromo-6-octyl-2-phenethyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (97)



R_f: 0.68 (Hexane : diethyl ether = 20 : 1), yield: 73%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.17 (m, 3H), 4.27 (m, 1H), 3.45 (m, !H), 2.74 (m, 2H), 2.48 (ddd, *J* = 3.25, 9.41, 17.11 Hz, 1H), 2.44 (td, *J* = 2.91, 16.94 Hz, 1H), 1.99 (m, 1H), 1.71 (m, 1H), 1.46 (m, 3H), 1.29 (m, 11H), 0.88 (t, *J* = 6.93 Hz, 3H), 0.22 (s, 9H).

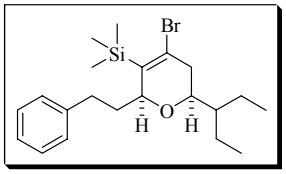
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 138.9, 130.2, 128.7, 128.3, 125.7, 78.5, 73.7, 45.3, 37.7, 35.2, 31.9, 31.4, 29.63, 29.61, 29.32, 25.4, 22.7, 14.1, 0.31.

FTIR (neat) 2924, 1599, 1454, 1367, 1249, 1099, 839, 752, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{24}H_{40}{}^{79}BrOSi$ $[M+H]^+$: 451.2032, found $[M+H]^+$: 451.2040;

Calcd for $C_{24}H_{40}{}^{81}BrOSi$ $[M+H]^+$: 453.2011, found $[M+H]^+$: 453.2011.

((2S*,6S*)-4-bromo-6-(pentan-3-yl)-2-phenethyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (98)



R_f: 0.83 (Hexane : diethyl ether = 20 : 1), yield: 62%.

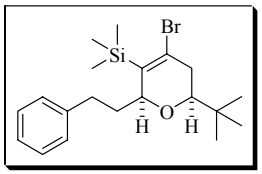
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.18 (m, 3H), 4.22 (m, 1H), 3.41 (ddd, *J* = 2.48, 6.43, 9.59 Hz, 1H), 2.74 (m, 2H), 2.58 (ddd, *J* = 3.27, 10.27, 17.04 Hz, 1H), 2.40 (td, *J* = 2.48, 17.04 Hz, 1H), 1.99 (m, 1H), 1.70 (m, 1H), 1.48 (m, 3H), 1.34 (m, 1H), 1.26 (m, 1H), 0.90 (t, *J* = 7.45 Hz, 6H), 0.21 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 138.9, 130.7, 128.7, 128.3, 125.7, 78.5, 75.3, 45.0, 42.8, 37.8, 31.5, 21.35, 21.32, 11.4, 11.1, 0.33.

FTIR (neat) 3452, 2960, 1599, 1494, 1454, 1250, 1101, 840, 752, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{21}H_{34}{}^{79}BrOSi$ $[M+H]^+$: 409.1562, found $[M+H]^+$: 409.1554;
Calcd for $C_{21}H_{34}{}^{81}BrOSi$ $[M+H]^+$: 411.1542, found $[M+H]^+$: 411.1525.

((2S*,6S*)-4-bromo-6-tert-butyl-2-phenethyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (99)



R_f: 0.75 (Hexane : diethyl ether = 20 : 1), yield: 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.18 (m, 3H), 4.25 (m, 1H), 3.12 (dd, *J* = 2.62, 10.40 Hz, 1H), 2.74 (m, 2H), 2.58 (ddd, *J* = 3.42, 10.34, 16.94 Hz, 1H), 2.52

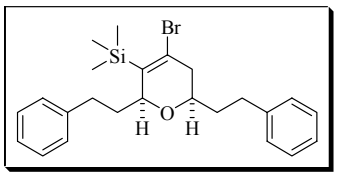
(s, 1H), 2.41 (td, J = 2.52, 16.94 Hz, 1H), 1.97 (m, 1H), 1.71 (m, 1H), 0.94 (s, 9H), 0.22 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 138.7, 130.9, 128.7, 128.3, 125.7, 80.9, 78.6, 40.2, 37.8, 34.2, 33.9, 31.4, 25.8, 0.29.

FTIR (neat) 2954, 2866, 2841, 1600, 1575, 1454, 1361, 1290, 1249, 1178, 1107, 1068, 1047, 840, 752, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{32}{}^{79}BrOSi$ $[M+H]^+$: 395.1406, found $[M+H]^+$: 395.1420; Calcd for $C_{20}H_{32}{}^{81}BrOSi$ $[M+H]^+$: 397.1385, found $[M+H]^+$: 397.1387.

((2S*,6R*)-4-bromo-2,6-diphenethyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (100)



R_f: 0.65 (Hexane : diethyl ether = 20 : 1), yield: 77%.

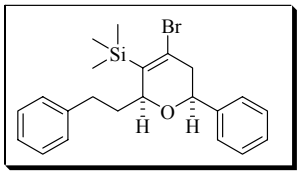
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.26 (m, 6H), 4.33 (m, 1H), 3.51 (m, 1H), 2.84 (m, 4H), 2.60 (ddd, J = 3.24, 10.19, 17.13 Hz, 1H), 2.58 (td, J = 2.47, 17.13 Hz, 1H), 2.08 (m, 1H), 1.92 (m, 1H), 1.82 (m, 2H), 0.28 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 142.0, 139.0, 129.8, 128.7, 128.5, 128.4, 128.3, 125.8, 125.7, 78.5, 72.6, 45.2, 37.7, 36.7, 31.5, 31.4, 0.32.

FTIR (neat) 3024, 2921, 2858, 1601, 1495, 1454, 1250, 1103, 839, 752, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{24}H_{32}{}^{79}BrOSi$ $[M+H]^+$: 443.1406, found $[M+H]^+$: 443.1422; Calcd for $C_{24}H_{32}{}^{81}BrOSi$ $[M+H]^+$: 445.1385, found $[M+H]^+$: 445.1381.

((2S*,6S*)-4-bromo-2-phenethyl-6-phenyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane (102)



R*f*: 0.56 (Hexane : diethyl ether = 20 : 1), yield: 36%.

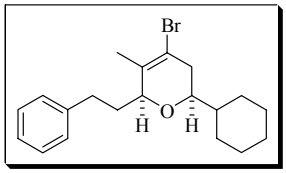
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 4H), 7.26 (m, 3H), 7.18 (m, 3H), 4.57 (dd, *J* = 3.34, 9.84 Hz, 1H), 4.53 (m, 1H), 2.83 (t, *J* = 8.28 Hz, 2H), 2.77 (ddd, *J* = 3.21, 9.63, 17.19 Hz, 1H), 2.70 (td, *J* = 2.80, 17.19 Hz, 1H), 2.11 (m, 1H), 1.86 (m, 1H), 0.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.6, 138.9, 129.4, 128.7, 128.5, 128.4, 127.7, 125.8, 79.0, 75.3, 47.1, 37.8, 31.2, 0.23.

FTIR (neat) 3026, 2951, 2926, 2852, 1599, 1494, 1454, 1250, 1176, 1099, 1072, 839, 752, 698 cm^{-1}.

HRMS *m/z* Calcd for $C_{22}H_{28}{}^{79}BrOSi$ $[M+H]^+$: 415.1093, found $[M+H]^+$: 415.1081;
Calcd for $C_{22}H_{28}{}^{81}BrOSi$ $[M+H]^+$: 417.1072, found $[M+H]^+$: 417.1066.

(2S*,6S*)-4-bromo-2-cyclohexyl-5-methyl-6-phenethyl-3,6-dihydro-2*H*-pyran (105)



R*f*: 0.78 (Hexane : diethyl ether = 20 : 1)

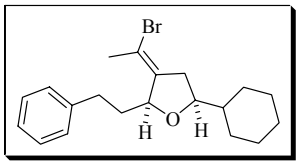
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.18 (m, 3H), 4.50 (d, *J* = 7.40 Hz, 1H), 3.62 (ddd, *J* = 5.40, 7.27, 12.54 Hz, 1H) 2.70 (m, 3H), 2.28 (m, 1H), 2.19 (s, 3H), 1.96 (m, 2H), 1.81 (q, *J* = 7.74 Hz, 1H), 1.75 (m, 2H), 1.66(m, 2H), 1.47 (m, 1H), 1.25 (m, 2H), 1.15(ttt, *J* = 2.90, 12.20 Hz, 1H), 1.03 (dd, *J* = 3.19, 12.20 Hz, 1H), 0.96 (dd, *J* = 3.19, 12.20 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 142.1, 128.5, 128.4, 125.8, 111.6, 82.6, 78.5, 43.1, 40.0, 37.0, 31.2, 29.7, 28.7, 26.6, 26.0, 25.9, 25.2

FTIR (neat) 2926, 2853, 1717, 1602, 1512, 1450, 1373, 1236, 1161, 1028, 981, 891, 750, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{20}H_{28}{}^{79}BrO$ $[M+H]^+$: 363.1324, found $[M+H]^+$: 363.1315;
Calcd for $C_{20}H_{28}{}^{81}BrO$ $[M+H]^+$: 365.1303, found $[M+H]^+$: 365.1329.

(2S*,5S*,*E*)-3-(1-bromoethylidene)-5-cyclohexyl-2-phenethyltetrahydrofuran (106)



R_f: 0.56 (Hexane : diethyl ether = 20 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.18 (m, 3H), 4.01 (m, 1H), 3.28 (ddd, *J* = 3.29, 7.32, 10.52 Hz, 1H) 2.71 (m, 2H), 2.53 (m, 1H), 2.36 (d, *J* = 16.43 Hz, 1H), 2.01 (m, 2H), 1.75 (m, 3H), 1.70 (s, 3H), 1.66 (m, 2H), 1.44 (m, 1H), 1.25 (m, 2H), 1.16 (ttt, *J* = 3.16, 12.38 Hz, 1H), 1.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 133.8, 128.6, 128.3, 125.7, 117.6, 78.7, 77.9, 42.5, 39.9, 35.2, 31.1, 29.1, 28.4, 26.6, 26.1, 25.9, 18.2

FTIR (neat) 2926, 2853, 1730, 1600, 1512, 1452, 1396, 1373, 1338, 1144, 1029, 972, 750, 698 cm^{-1}.

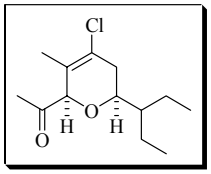
HRMS *m/z* Calcd for $C_{20}H_{28}{}^{79}BrO$ $[M+H]^+$: 363.1324, found $[M+H]^+$: 363.1331;

Calcd for $C_{20}H_{28}{}^{81}BrO$ $[M+H]^+$: 365.1303, found $[M+H]^+$: 365.1293.

General procedures for carrying out Prins cyclization using allenic alcohol 109 with various aldehydes at room temperature

To an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added indium trichloride (66.4 mg, 0.30 mmol, 1.0 equiv.) and anhydrous dichloromethane 4 mL, vigorously stirred at room temperature, followed with the introduction of 2-ethylbutylraldehyde (45.0 mg, 0.45 mmol, 1.50 equiv., dissolved in 1 mL dry CH_2Cl_2) and TMSCl (0.60 mL, 0.45 mmol, 1.50 equiv.). Acetyl allenic alcohol **109** (39.8 mg, 0.30 mmol, 1.0 equiv. dissolved in 1 mL dry CH_2Cl_2) was slowly introduced into the stirred mixture using syringe pump over 3 hours. After the addition of **109,** reaction was allowed to proceed for another 2 hours at room temperature before quenching with saturated $NaHCO_3$ solution. The crude was extracted with dichloromethane (15 mL x 3). Combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (0.3% diethyl ether in hexane) to afford 4-chloro-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2*H*-pyran-2-yl)ethanone **110** and **111** in an overall 55% yield with a ratio (cis/trans) of 69:31.

1-((2R*,6S*)-4-chloro-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2*H*-pyran-2-yl)ethanone (110)



R_f: 0.75 (Hexane : Ethyl Acetate = 4:1)

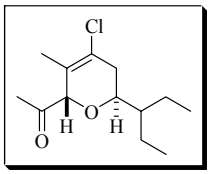
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (s, 1H), 3.63 (ddd, *J* = 3.02, 5.33, 10.65Hz, 1H), 2.58 (m, 1 H), 2.22 (d, *J* = 16.59 Hz, 1H), 2.09 (s, 3H), 1.65 (d, *J* = 1.14 Hz, 3H), 1.51 (m, 1H), 1.40 (m, 3H), 1.26 (m, 1H), 0.88 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 127.7, 125.3, 85.7, 75.2, 45.0, 36.1, 24.9, 21.45, 21.41, 13.98, 11.4, 11.3.

FTIR (neat) 3454, 2963, 2929, 2876, 1732, 1460, 1379, 1136, 1037, 970, 804 cm^{-1}.

HRMS *m/z* Calcd for $C_{13}H_{22}{}^{35}ClO_2$ $[M+H]^+$: 245.1308, found $[M+H]^+$: 245.1318;
Calcd for $C_{13}H_{22}{}^{37}ClO_2$ $[M+H]^+$: 247.1279, found $[M+H]^+$: 247.1274.

1-((2S*,6S*)-4-chloro-3-methyl-6-(pentan-3-yl)-5,6-dihydro-2*H*-pyran-2-yl)ethanone (111)



R_f: 0.64 (Hexane : Ethyl Acetate = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (s, 1H), 3.54 (ddd, *J* = 3.83, 5.57, 9.80Hz, 1H), 2.38 (m, 1 H), 2.28 (s, 3H), 2.18 (d, *J* = 14.55 Hz, 1H), 1.78 (s, 3H), 1.53 (m, 1H), 1.47 (m, 3H), 1.25 (m, 1H), 0.85 (m, 6H).

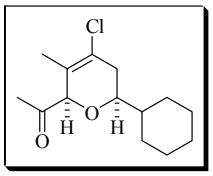
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 126.6, 125.9, 82.6, 73.7, 45.1, 36.0, 27.4, 21.1, 20.9, 16.7, 11.3, 10.9.

FTIR (neat) 3454, 2962, 2875, 1730, 1456, 1379, 1186, 1080, 970, 895 cm^{-1}.

HRMS *m/z* Calcd for $C_{13}H_{22}{}^{35}ClO_2$ $[M+H]^+$: 245.1308, found $[M+H]^+$: 245.1324;

Calcd for $C_{13}H_{22}{}^{37}ClO_2$ $[M+H]^+$: 247.1279, found $[M+H]^+$: 247.1296.

1-((2R*,6S*)-4-chloro-6-cyclohexyl-3-methyl-5,6-dihydro-2*H*-pyran-2-yl)ethanone (112)



R_f: 0.39 (Hexane : Diethyl ether = 8 : 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (s, 1H), 3.37 (ddd, *J* = 3.09, 6.44, 9.96Hz, 1H), 2.52 (m, 1 H), 2.25 (d, *J* = 16.27 Hz, 1H), 2.10 (s, 3H), 1.91 (d, *J* = 12.98 Hz, 1H), 1.75 (m, 2H), 1.68 (s, 1H), 1.65 (s, 3H), 1.48 (m, 1H), 1.21 (m, 4H), 1.00 (m, 2H).

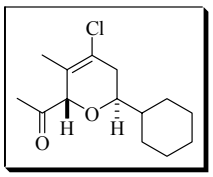
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 127.6, 125.3, 85.7, 77.7, 42.2, 36.3, 28.6, 28.2, 26.5, 26.0, 25.9, 25.0, 14.1.

FTIR (neat) 2927, 2852, 1728, 1714, 1448, 1255, 1022, 891, 750 cm^{-1}.

HRMS *m/z* Calcd for $C_{14}H_{22}{}^{35}ClO_2$ $[M+H]^+$: 257.1308, found $[M+H]^+$: 257.1320;

Calcd for $C_{14}H_{22}{}^{37}ClO_2$ $[M+H]^+$: 259.1279, found $[M+H]^+$: 259.1287.

1-((2S*,6S*)-4-chloro-6-cyclohexyl-3-methyl-5,6-dihydro-2*H*-pyran-2-yl)ethanone (113)



R_f: 0.25 (Hexane : Diethyl ether = 8 : 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (s, 1H), 3.30 (ddd, *J* = 3.84, 7.31, 10.78 Hz, 1H), 2.36 (m, 1 H), 2.28 (s, 3H), 2.22 (d, *J* = 15.37 Hz, 1H), 2.03 (m, 1H), 1.78 (s, 3H), 1.66 (m, 3H), 1.48 (m, 1H), 1.21 (m, 4H), 0.97 (m, 2H).

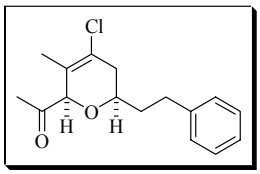
^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 126.5, 126.0, 82.7, 76.4, 42.2, 36.3, 29.1, 28.4, 27.4, 26.4, 26.0, 25.9, 16.8.

FTIR (KBr) 3441, 2926, 2852, 1730, 1643, 1450, 1270, 736 cm^{-1}.

HRMS *m/z* Calcd for $C_{14}H_{22}{}^{35}ClO_2$ $[M+H]^+$: 257.1308, found $[M+H]^+$: 257.1317;

Calcd for $C_{14}H_{22}{}^{37}ClO_2$ $[M+H]^+$: 259.1279, found $[M+H]^+$: 259.1295.

1-((2R*,6R*)-4-chloro-3-methyl-6-phenethyl-5,6-dihydro-2*H*-pyran-2-yl)ethanone (118)



R_f: 0.58 (Hexane : Diethyl ether = 4 : 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 4.40 (s, 1H), 3.60 (m, 1H), 2.80 (ddd, *J* = 5.71, 9.09, 14.12 Hz, 1H), 2.72 (td, *J* = 7.93, 14.51 Hz, 1H), 2.52 (m, 1H), 2.25 (dd, *J* = 1.06, 16.73 Hz, 1H), 2.13 (s, 3H), 1.94 (m, 1H), 1.85 (m, 1H), 1.65 (s, 3H).

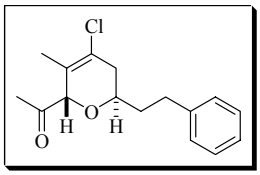
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 141.4, 128.48, 128.46, 127.0, 126.0, 125.4, 85.6, 72.6, 39.0, 36.6, 31.3, 24.9, 14.1.

FTIR (KBr) 2928, 1728, 1714, 1494, 1454, 1354, 1199, 1141, 752, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{16}H_{20}{}^{35}ClO_2$ $[M+H]^+$: 279.1152, found $[M+H]^+$: 279.1147;

Calcd for $C_{16}H_{20}{}^{37}ClO_2$ $[M+H]^+$: 281.1122, found $[M+H]^+$: 281.1123.

1-((2S*,6R*)-4-chloro-3-methyl-6-phenethyl-5,6-dihydro-2*H*-pyran-2-yl)ethanone (119)



R_f: 0.33 (Hexane : Diethyl ether = 4 : 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 4.47 (s, 1H), 3.69 (m, 1H), 2.84 (ddd, *J* = 5.60, 10.59, 15.88 Hz, 1H), 2.63 (ddd, *J* = 6.17, 10.33, 16.33 Hz, 1H), 2.33 (m, 1H), 2.27 (s, 3H), 1.92 (m, 1H), 1.83 (m, 1H), 1.79 (s, 3H).

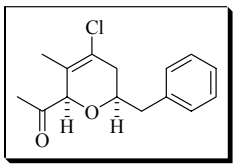
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 141.3, 128.5, 128.3, 126.1, 126.0, 125.9, 82.5, 71.7, 38.4, 36.7, 31.7, 27.2, 16.6.

FTIR (KBr) 2927, 1714, 1681, 1602, 1494, 1454, 1172, 1029, 748, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{16}H_{20}{}^{35}ClO_2$ $[M+H]^+$: 279.1152, found $[M+H]^+$: 279.1150;

Calcd for $C_{16}H_{20}{}^{37}ClO_2$ $[M+H]^+$: 281.1122, found $[M+H]^+$: 281.1136.

1-((2R*,6R*)-6-benzyl-4-chloro-3-methyl-5,6-dihydro-2*H*-pyran-2-yl)ethanone (120)



R_f: 0.39 (Hexane : Diethyl ether = 8 : 1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (m, 5H), 4.41 (s, 1H), 3.87 (m, 1H), 2.99 (dd, *J* = 6.39, 13.89 Hz, 1H), 2.83 (dd, *J* = 6.17, 13.89 Hz, 1H), 2.52 (m, 1H), 2.21 (d, *J* = 17.86 Hz, 1H), 2.11 (s, 3H), 1.65 (s, 3H).

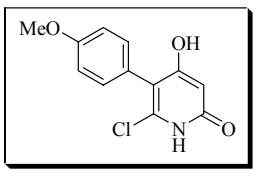
^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 137.2, 129.5, 128.4, 127.0, 126.6, 125.3, 85.5, 74.3, 41.5, 38.3, 25.0, 14.1.

FTIR (KBr) 3454, 2924, 1716, 1672, 1494, 1454, 1354, 1203, 1128, 752, 700 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{18}{}^{35}ClO_2$ $[M+H]^+$: 265.0995, found $[M+H]^+$: 265.1006;
Calcd for $C_{15}H_{18}{}^{37}ClO_2$ $[M+H]^+$: 261.0966, found $[M+H]^+$: 261.0978.

Procedures for preparing the 6-chloro-4-hydroxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (126)

To an oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar was added 4-methoxy-phenylacetonitrile (2.71 mL, 20 mmol, 1.0 equiv.). Freshly distilled malonyl chloride (7.0 mL, 36 mmol, 1.80 equiv.) was introduced in a dropwise manner. The mixture was stirred at room temperature for around 48 hours until slurry-like mixture was formed. Methanol (5 mL) was added dropwise to the mixture. The residual crude was then dissolved in saturated KOH solution (~ 10 mL), and was extracted with diethyl ether (10 mL x 3). The aqueous solution was acidified with concentrated HCl. The precipitate was filtered off under reduced pressure, and was washed with chloromethane (5 mL) and diethyl ether (5 mL). Solid was collected for chromatography (25% chloroform in methanol) to afford 6-chloro-4-hydroxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one **126** in 44 % yield as a pale yellow solid.



R_f: 46 (Chloroform : Methanol = 1:1)

^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.08 (d, *J* = 8.72 Hz, 2H), 6.83 (d, *J* = 8.72 Hz, 2H), 6.07 (s, 1H), 3.70 (s, 1H), 3.69 (s, 3H).

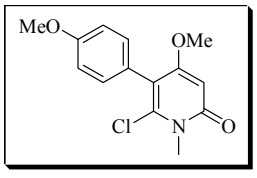
^{13}C NMR (100 MHz, CD_3COCD_3) δ 165.5, 159.2, 131.9, 131.5, 131.4, 125.9, 117.2, 113.4, 113.0, 48.9.

FTIR (KBr) 3358, 1687, 1589, 1510, 1249, 1176, 1029, 831, 792, 740 cm^{-1}.

HRMS *m/z* Calcd for $C_{12}H_{11}{}^{35}ClNO_3$ $[M+H]^+$: 252.0427, found $[M+H]^+$: 252.0421;
Calcd for $C_{12}H_{11}{}^{37}ClNO_3$ $[M+H]^+$: 254.0398, found $[M+H]^+$: 254.0400.

Procedures for preparing the 6-chloro-4-methoxy-5-(4-methoxyphenyl)-1-methylpyridin-2(1*H*)-one (127)

To a two-necked 25 mL round-bottom flask equipped with a magnetic stirring bar and a condenser was added 6-chloro-4-hydroxy-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (**126**, 0.1200 g, 0.48 mmol, 1.0 equiv.), TBAB (tetrabutylammonium bromide, 15.5 mg, 1.15 mmol, 0.10 equiv.) followed with the introduction of 4 mL toluene, dimethyl sulfate (0.18 mL, 1.92 mmol, 4.0 equiv.) and 40% NaOH solution (1.0 mL). The mixture was stirred and refluxed for 48 hours. Reaction crude was extracted with dichloromethane (15 mL x 3). Combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (5 % diethyl ether in hexane) to afford 6-chloro-4-methoxy-5-(4-methoxyphenyl)-1-methylpyridin-2(1*H*)-one **127** in 66 % yield as a pale yellow solid.



R_f: 0.57 (Hexane : Diethyl Ether = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.60 Hz, 2H), 6.92 (d, *J* = 8.55 Hz, 2H), 5.95 (s, 1H), 3.83 (s, 3H), 3.68 (d, *J* = 3.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.5, 159.1, 137.6, 131.8, 125.2, 113.9, 113.6, 95.0, 56.0, 55.1, 33.2.

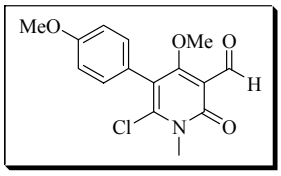
FTIR (KBr) 3452, 1651, 1608, 1504, 1454, 1415, 1286, 1242, 1155, 1030, 844 cm^{-1}.

HRMS *m/z* Calcd for $C_{14}H_{15}{}^{35}ClNO_3$ $[M+H]^+$: 280.0740, found $[M+H]^+$: 280.0742;

Calcd for $C_{14}H_{15}{}^{37}ClNO_3$ $[M+H]^+$: 282.0711, found $[M+H]^+$: 282.0725.

Procedures for preparing the 6-chloro-4-methoxy-5-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde (Fragment A)

To an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added 6-chloro-4-methoxy-5-(4-methoxyphenyl)-1-methylpyridin-2(1*H*)-one (**127**) (0.1444 g, 0.516 mmol, 1.0 equiv.) and anhydrous THF 10 mL, stirred at -78 °C. *n*-BuLi (0.39 mL, 1.6 M in hexane, 1.20 equiv.) was added dropwise into the mixture and stirred for half an hour. DMF (0.20 mL, 5.0 equiv.) was then introduced and reaction was allowed to proceed at -78 °C for 3 hours before quenching with 1M HCl solution (3 mL). Reactoin crude was extracted with diethyl ether (3 x 15 mL). Combined organic extracts were washed with water and brine, and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash chromatography (5 % diethyl ether in hexane) to afford 6-chloro-4-methoxy-5-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carbaldehyde in 71 % yield as a pale yellow solid.



R_f: 0.55 (Hexane : Diethyl Ether = 4:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.15 (dd, *J* = 2.05, 6.65 Hz, 2H), 6.96 (dd, *J* = 2.10, 6.70 Hz, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H).

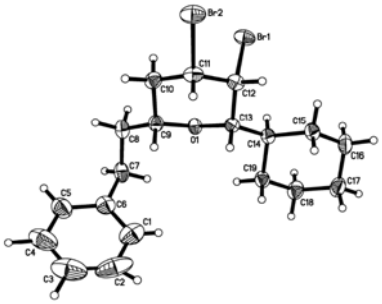
^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 170.3, 163.3, 159.5, 144.7, 131.7, 124.6, 116.8, 113.9, 112.3, 66.2, 55.2, 33.9.

FTIR (KBr) 2956, 2926, 2854, 1707, 1682, 1651, 1487, 1288, 1247, 1178, 1107, 1030, 794 cm^{-1}.

HRMS *m/z* Calcd for $C_{15}H_{15}{}^{35}ClNO_4$ $[M+H]^+$: 308.0690, found $[M+H]^+$: 308.0686;
Calcd for $C_{15}H_{15}{}^{37}ClNO_4$ $[M+H]^+$: 310.0660, found $[M+H]^+$: 310.0667.

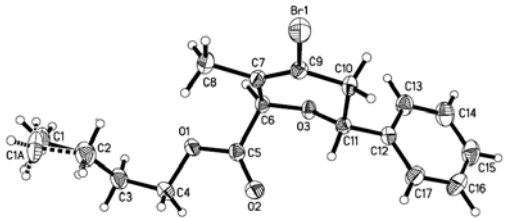
Appendix

Single crystal X-ray diffraction analysis of **5.**



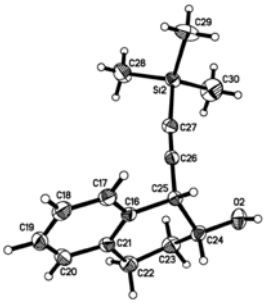
Empirical formula	C19 H26 Br2 O	
Formula weight	430.22	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.4511(4) Å	α= 90°.
	b = 18.9558(7) Å	β= 105.932(2)°.
	c = 9.7638(4) Å	γ = 90°.
Volume	1860.00(12) $Å^3$	
Z	4	
Density (calculated)	1.536 Mg/m^3	
Absorption coefficient	4.359 mm^{-1}	
F(000)	872	
Crystal size	0.40 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.15 to 30.55°.	
Index ranges	-14<=h<=14, -27<=k<=26, -13<=l<=13	
Reflections collected	23668	
Independent reflections	5664 [R(int) = 0.0272]	
Completeness to theta = 30.55°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4760 and 0.2745	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5664 / 0 / 303	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0264, wR2 = 0.0553	
R indices (all data)	R1 = 0.0426, wR2 = 0.0599	
Largest diff. peak and hole	0.541 and -0.335 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **26**



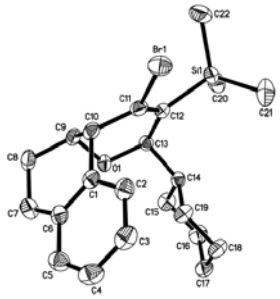
Empirical formula	C17 H21 Br O3	
Formula weight	353.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.5660(2) Å	α= 88.897(2)°.
	b = 9.7684(3) Å	β= 85.825(2)°.
	c = 11.5589(4) Å	γ = 74.451(2)°.
Volume	820.84(4) $Å^3$	
Z	2	
Density (calculated)	1.429 Mg/m^3	
Absorption coefficient	2.511 mm^{-1}	
F(000)	364	
Crystal size	0.22 x 0.22 x 0.08 mm^3	
Theta range for data collection	1.77 to 31.08°.	
Index ranges	-10<=h<=10, -13<=k<=14, -16<=l<=16	
Reflections collected	17908	
Independent reflections	5248 [R(int) = 0.0310]	
Completeness to theta = 31.08°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8244 and 0.6081	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5248 / 32 / 203	
Goodness-of-fit on F^2	1.087	
Final R indices [I>2sigma(I)]	R1 = 0.0339, wR2 = 0.0898	
R indices (all data)	R1 = 0.0526, wR2 = 0.1079	
Largest diff. peak and hole	0.786 and -0.398 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **42**



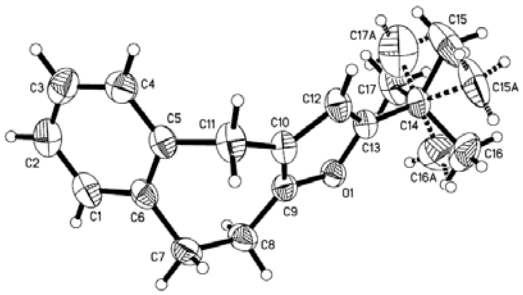
Empirical formula	C15 H20 O Si	
Formula weight	244.40	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.3807(3) Å	α= 112.4650(10)°.
	b = 11.6585(4) Å	β= 94.7320(10)°.
	c = 12.9026(4) Å	γ = 97.936(2)°.
Volume	1413.51(8) $Å^3$	
Z	4	
Density (calculated)	1.148 Mg/m^3	
Absorption coefficient	0.149 mm^{-1}	
F(000)	528	
Crystal size	0.30 x 0.25 x 0.15 mm^3	
Theta range for data collection	1.73 to 30.52°.	
Index ranges	-14<=h<=14, -16<=k<=16, -18<=l<=18	
Reflections collected	26719	
Independent reflections	8605 [R(int) = 0.0232]	
Completeness to theta = 30.52°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9780 and 0.9566	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8605 / 0 / 315	
Goodness-of-fit on F^2	1.024	
Final R indices [I>2sigma(I)]	R1 = 0.0385, wR2 = 0.1104	
R indices (all data)	R1 = 0.0531, wR2 = 0.1224	
Largest diff. peak and hole	0.432 and -0.230 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **43'**



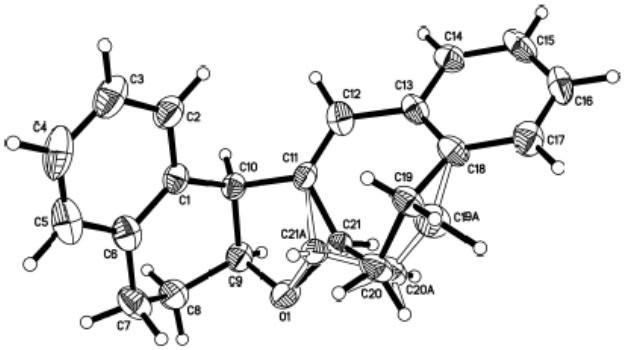
Empirical formula	C22 H31 Br O Si	
Formula weight	419.47	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.3206(3) Å	α= 90°.
	b = 22.4348(6) Å	β= 94.708(2)°.
	c = 10.1325(3) Å	γ = 90°.
Volume	2111.62(11) $Å^3$	
Z	4	
Density (calculated)	1.319 Mg/m^3	
Absorption coefficient	2.011 mm^{-1}	
F(000)	880	
Crystal size	0.30 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.82 to 30.61°.	
Index ranges	-13<=h<=12, -32<=k<=31, -13<=l<=14	
Reflections collected	21032	
Independent reflections	6446 [R(int) = 0.0304]	
Completeness to theta = 30.61°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8242 and 0.5837	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6446 / 0 / 229	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0319, wR2 = 0.0747	
R indices (all data)	R1 = 0.0513, wR2 = 0.0815	
Largest diff. peak and hole	0.635 and -0.345 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **49**



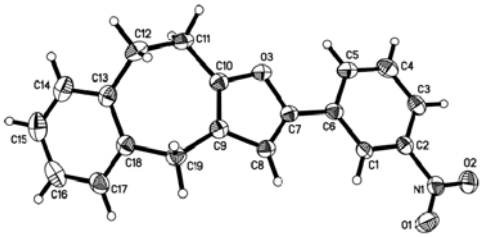
Empirical formula	C17 H20 O	
Formula weight	240.33	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.8244(3) Å	α= 90°.
	b = 10.1462(4) Å	β= 97.787(2)°.
	c = 15.7288(5) Å	γ = 90°.
Volume	1395.28(9) $Å^3$	
Z	4	
Density (calculated)	1.144 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	520	
Crystal size	0.36 x 0.34 x 0.34 mm^3	
Theta range for data collection	2.33 to 30.60°.	
Index ranges	-12<=h<=12, -14<=k<=14, -22<=l<=22	
Reflections collected	19659	
Independent reflections	4262 [R(int) = 0.0552]	
Completeness to theta = 30.60°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9769 and 0.9756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4262 / 69 / 198	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0690, wR2 = 0.2013	
R indices (all data)	R1 = 0.0996, wR2 = 0.2439	
Extinction coefficient	0.059(10)	
Largest diff. peak and hole	0.433 and -0.259 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **50**



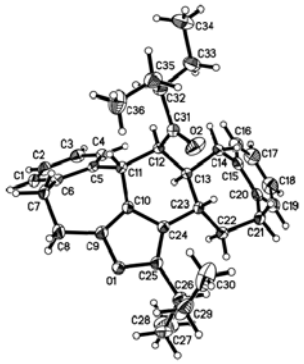
Empirical formula	C21 H20 O	
Formula weight	288.37	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.4202(4) Å	α= 90°.
	b = 15.0125(6) Å	β= 116.949(2)°.
	c = 10.9637(5) Å	γ = 90°.
Volume	1528.85(11) $Å^3$	
Z	4	
Density (calculated)	1.253 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	616	
Crystal size	0.25 x 0.25 x 0.15 mm^3	
Theta range for data collection	2.49 to 28.00°.	
Index ranges	-13<=h<=12, -19<=k<=19, -14<=l<=14	
Reflections collected	12430	
Independent reflections	3672 [R(int) = 0.0238]	
Completeness to theta = 28.00°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9888 and 0.9815	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3672 / 2 / 319	
Goodness-of-fit on F^2	1.160	
Final R indices [I>2sigma(I)]	R1 = 0.0561, wR2 = 0.1234	
R indices (all data)	R1 = 0.0654, wR2 = 0.1284	
Largest diff. peak and hole	0.270 and -0.279 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **53**



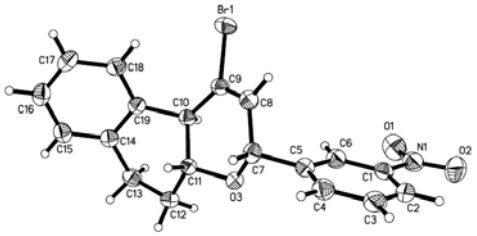
Empirical formula	C19 H15 N O3	
Formula weight	305.32	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.9772(4) Å	α= 90°.
	b = 6.6163(2) Å	β= 90.843(3)°.
	c = 27.7756(12) Å	γ = 90°.
Volume	1465.82(11) $Å^3$	
Z	4	
Density (calculated)	1.384 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	640	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	1.47 to 26.00°.	
Index ranges	-9<=h<=9, -8<=k<=8, -34<=l<=34	
Reflections collected	14210	
Independent reflections	2875 [R(int) = 0.0598]	
Completeness to theta = 26.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9814 and 0.9814	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2875 / 0 / 208	
Goodness-of-fit on F^2	1.102	
Final R indices [I>2sigma(I)]	R1 = 0.0621, wR2 = 0.1778	
R indices (all data)	R1 = 0.0772, wR2 = 0.2073	
Largest diff. peak and hole	0.440 and -0.396 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **56**



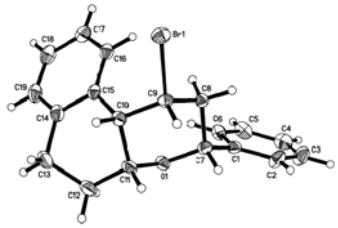
Empirical formula	C36 H44 O2	
Formula weight	508.71	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.5872(5) Å	α= 90°.
	b = 18.5669(10) Å	β= 100.717(3)°.
	c = 18.7066(10) Å	γ = 90°.
Volume	2930.5(3) $Å^3$	
Z	4	
Density (calculated)	1.153 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	1104	
Crystal size	0.30 x 0.25 x 0.20 mm^3	
Theta range for data collection	1.56 to 27.00°.	
Index ranges	-9<=h<=10, -23<=k<=21, -23<=l<=21	
Reflections collected	41190	
Independent reflections	6383 [R(int) = 0.0485]	
Completeness to theta = 27.00°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9863 and 0.9796	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6383 / 0 / 347	
Goodness-of-fit on F^2	1.087	
Final R indices [I>2sigma(I)]	R1 = 0.0536, wR2 = 0.1433	
R indices (all data)	R1 = 0.0691, wR2 = 0.1637	
Largest diff. peak and hole	0.324 and -0.270 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **69**



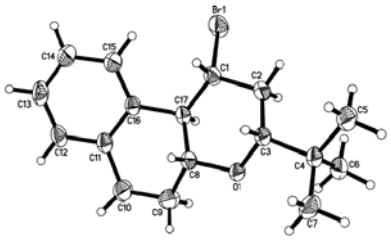
Empirical formula	C19 H16 Br N O3
Formula weight	386.24
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 13.2591(11) Å α= 90°.
	b = 8.8217(7) Å β= 105.986(4)°.
	c = 14.4696(12) Å γ = 90°.
Volume	1627.0(2) $Å^3$
Z	4
Density (calculated)	1.577 Mg/m^3
Absorption coefficient	2.543 mm^{-1}
F(000)	784
Crystal size	0.25 x 0.25 x 0.15 mm^3
Theta range for data collection	1.85 to 30.61°.
Index ranges	-18<=h<=18, -12<=k<=10, -20<=l<=20
Reflections collected	45798
Independent reflections	4987 [R(int) = 0.0354]
Completeness to theta = 30.61°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7015 and 0.5689
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4987 / 0 / 217
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0746
R indices (all data)	R1 = 0.0458, wR2 = 0.0816
Largest diff. peak and hole	0.398 and -0.486 $e.Å^{-3}$

Single crystal X-ray diffraction analysis of **80**



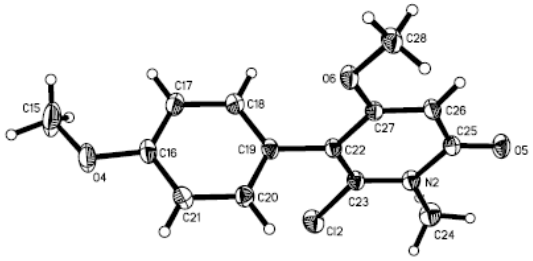
Empirical formula	C19 H19 Br O	
Formula weight	343.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.7055(3) Å	α= 90°.
	b = 18.9862(7) Å	β= 107.746(2)°.
	c = 9.6394(3) Å	γ = 90°.
Volume	1517.43(9) $Å^3$	
Z	4	
Density (calculated)	1.502 Mg/m^3	
Absorption coefficient	2.705 mm^{-1}	
F(000)	704	
Crystal size	0.25 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.15 to 30.58°.	
Index ranges	-11<=h<=12, -27<=k<=27, -12<=l<=13	
Reflections collected	22845	
Independent reflections	4650 [R(int) = 0.0282]	
Completeness to theta = 30.58°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6137 and 0.5512	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4650 / 0 / 190	
Goodness-of-fit on F^2	1.092	
Final R indices [I>2sigma(I)]	R1 = 0.0257, wR2 = 0.0652	
R indices (all data)	R1 = 0.0345, wR2 = 0.0692	
Largest diff. peak and hole	0.309 and -0.570 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **85**



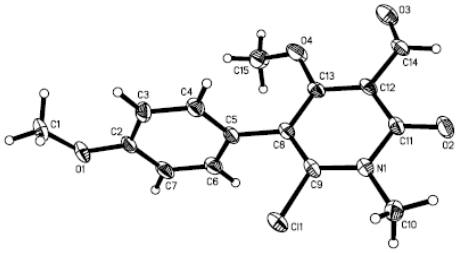
Empirical formula	C17 H23 Br O	
Formula weight	323.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.1844(3) Å	α= 90°.
	b = 12.2651(4) Å	β= 111.134(2)°.
	c = 13.0366(4) Å	γ = 90°.
Volume	1518.91(8) $Å^3$	
Z	4	
Density (calculated)	1.414 Mg/m^3	
Absorption coefficient	2.697 mm^{-1}	
F(000)	672	
Crystal size	0.30 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.14 to 30.59°.	
Index ranges	-14<=h<=14, -17<=k<=17, -18<=l<=18	
Reflections collected	33828	
Independent reflections	4650 [R(int) = 0.0319]	
Completeness to theta = 30.59°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6145 and 0.4983	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4650 / 0 / 175	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0400, wR2 = 0.0990	
R indices (all data)	R1 = 0.0597, wR2 = 0.1093	
Largest diff. peak and hole	1.329 and -1.168 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **127**



Empirical formula	C14 H14 Cl N O3	
Formula weight	279.71	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.4398(2) Å	α= 107.280(2)°.
	b = 11.7000(4) Å	β= 101.179(2)°.
	c = 14.1294(4) Å	γ = 95.394(2)°.
Volume	1289.74(6) $Å^3$	
Z	4	
Density (calculated)	1.441 Mg/m^3	
Absorption coefficient	0.299 mm^{-1}	
F(000)	584	
Crystal size	0.34 x 0.30 x 0.26 mm^3	
Theta range for data collection	1.55 to 34.00°.	
Index ranges	-13<=h<=13, -18<=k<=18, -22<=l<=22	
Reflections collected	47675	
Independent reflections	10512 [R(int) = 0.0372]	
Completeness to theta = 34.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9263 and 0.9051	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10512 / 0 / 349	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1327	
R indices (all data)	R1 = 0.0707, wR2 = 0.1531	
Largest diff. peak and hole	0.964 and -0.626 $e.Å^{-3}$	

Single crystal X-ray diffraction analysis of **A**



Empirical formula	C15 H14 Cl N O4	
Formula weight	307.72	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.5797(2) Å	α= 78.6810(10)°.
	b = 9.4629(3) Å	β= 80.0220(10)°.
	c = 11.4678(3) Å	γ = 85.1050(10)°.
Volume	688.57(4) $Å^3$	
Z	2	
Density (calculated)	1.484 Mg/m^3	
Absorption coefficient	0.293 mm^{-1}	
F(000)	320	
Crystal size	0.30 x 0.30 x 0.24 mm^3	
Theta range for data collection	1.83 to 25.50°.	
Index ranges	-7<=h<=7, -11<=k<=11, -13<=l<=13	
Reflections collected	11628	
Independent reflections	2553 [R(int) = 0.0439]	
Completeness to theta = 25.50°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9330 and 0.9172	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2553 / 0 / 192	
Goodness-of-fit on F^2	1.191	
Final R indices [I>2sigma(I)]	R1 = 0.0788, wR2 = 0.2356	
R indices (all data)	R1 = 0.0892, wR2 = 0.2624	
Largest diff. peak and hole	0.690 and -0.556 $e.Å^{-3}$	

List of Publication

1. Liu, F.; Lu, J.; Loh, T. P. Divergent Synthesis of Polycylic Pyrans and Furans by Condensation of Propargylic Epoxide with Aldehydes *via* An Efficient Friedel-Crafts-Prins Cascade Reaction. *Manuscript in preparation.* **2009.**

2. Liu, F.; Lu, J.; Loh, T. P. Fridel-Crafts-Prins Cascade Condensation of Allylic Epoxide with Aldehydes to Polycyclic Tetrahydropyrans. *Manuscript in preparation.* **2009.**

3. Hu, X. H.; Liu, F.; Loh, T. P. Stereoelectronic versus steric tuning in the prins cyclization reaction: synthesis of 2,6-trans pyranyl motifs. *Org. Lett.* **2009** *11(8)* 1741-1743.

4. Liu, F.; Loh, T. P. Highly Stereoselective Prins Cyclization of (***Z***)- and (***E***)- γ-Brominated Homoallylic Alcohols to 2,4,5,6-Tetrasubstituted Tetrahydropyrans. *Org. Lett.* **2007** *9 (11)* 2063-2066.

Conferences

1. Liu, F.; Loh, T. P. Construction of 4,5-Dibromo-Tetrahydropyrans *via* Prins Cyclization. Penang 1st Asia Young Chemist Conference, May 22-26, 2006, Maylasia.

2. Liu, F.; Loh, T. P. Cascade Condensation of Propargylic and Allylic Epoxides with Aldehydes. International Symposium on Catalysis and Fine Chemicals 2007, Dec 16-21, 2007, Singapore.