Development of New Methods in Tetrahydropyran Ring Synthesis: Application to the Enantioselective Synthesis of Natural Products

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To my family and friends,

Diligence paths the way to the door of success; perseverance holds the key to open it.

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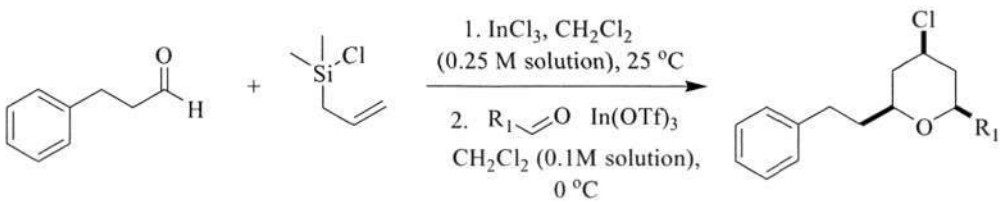
SUMMARY

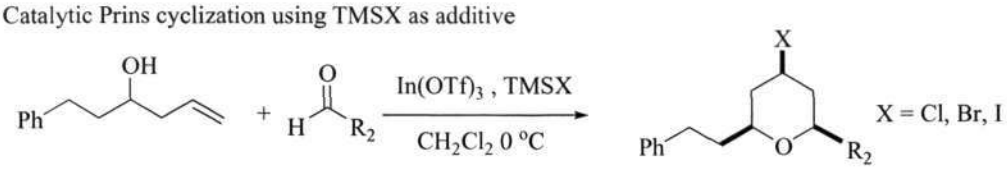
Prins cyclization is one of the most convergent strategies for the synthesis of 2,6-disubstituted tetrahydropyran rings from homoallylic alcohols and aldehydes. However, several limitations, such as the possibility of racemization of the homoallylic alcohol and substrate compatibility, have rendered this methodology a less preferred choice in the total synthesis of natural products containing the THP motifs. The emphasis of this thesis is placed on the evolution of a novel catalytic Prins cyclization to overcome these current limitations, and manifestation of its applicability to the enantioselective synthesis of natural products.

In the introductory chapter, the biological importance of the tetrahydropyran framework in therapeutic natural products is highlighted. This is followed by a general discussion of established methodologies for the formation of tetrahydropyran rings system. The need for a more sustainable and convergent method leads us to explore the Prins cyclization strategy, which we eventually developed into a one-pot catalytic process to obtain synthetically useful, unsymmetrical *syn*-4-chloro-2,6-disubstituted tetrahydropyran rings in Chapter 2.

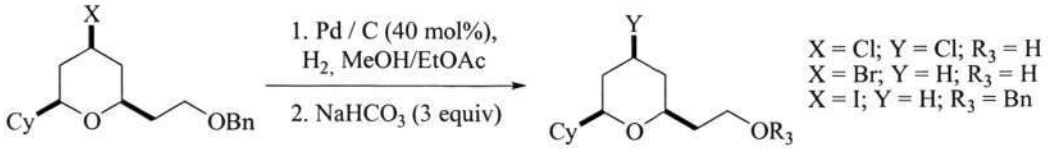


Further development of the catalytic Prins cyclization is discussed in Chapter 3, where versatile incorporation of halides at the 4-position of the tetrahydropyran ring can be achieved using trimethylsilylhalide additives. This versatility greatly enhances the synthetic value of this methodology, as demonstrated in the chemoselectivity of the newly developed stannane-free hydrodehalogenation protocol.

Catalytic Prins cyclization using TMSX as additive

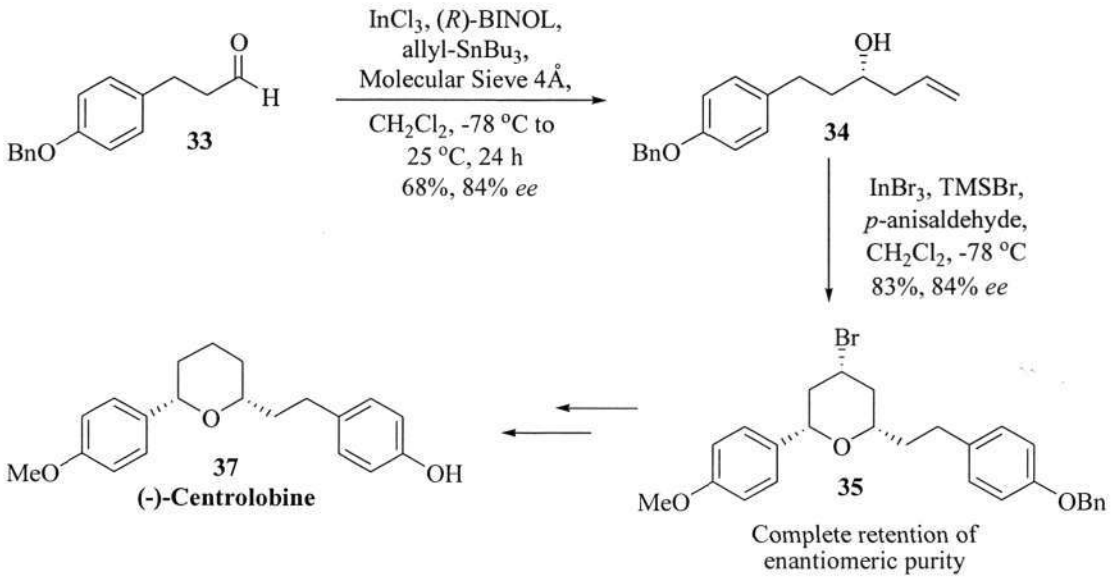


Chemoselective stannane-free hydrodehalogenation



An insight into the mechanistic pathway of racemization suppression is also discussed in Chapter 3. Using the total synthesis of (-)-Centrolobine as a model study, effective suppression of racemization can be achieved under optimized reaction conditions. A mechanism to control the racemization process based on product studies is also proposed in this chapter.

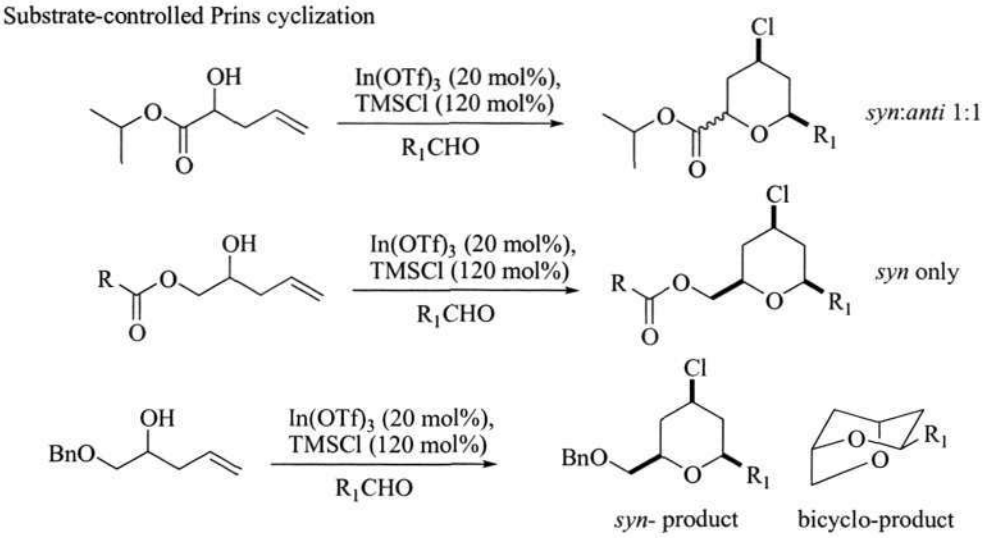
Total synthesis of (-)-Centrolobine



The scope of the catalytic Prins cyclization is extended to the diverse synthesis of both *syn*- and *anti*-2,6-disubstituted THP rings in Chapter 4. The development of substrate-controlled Prins cyclization offers a direct, one-pot synthesis of both the isomers in this otherwise exclusively *syn*-THP ring formation methodology. Investigations on the inductive effects of α-carbonyl lone pair stabilizing the

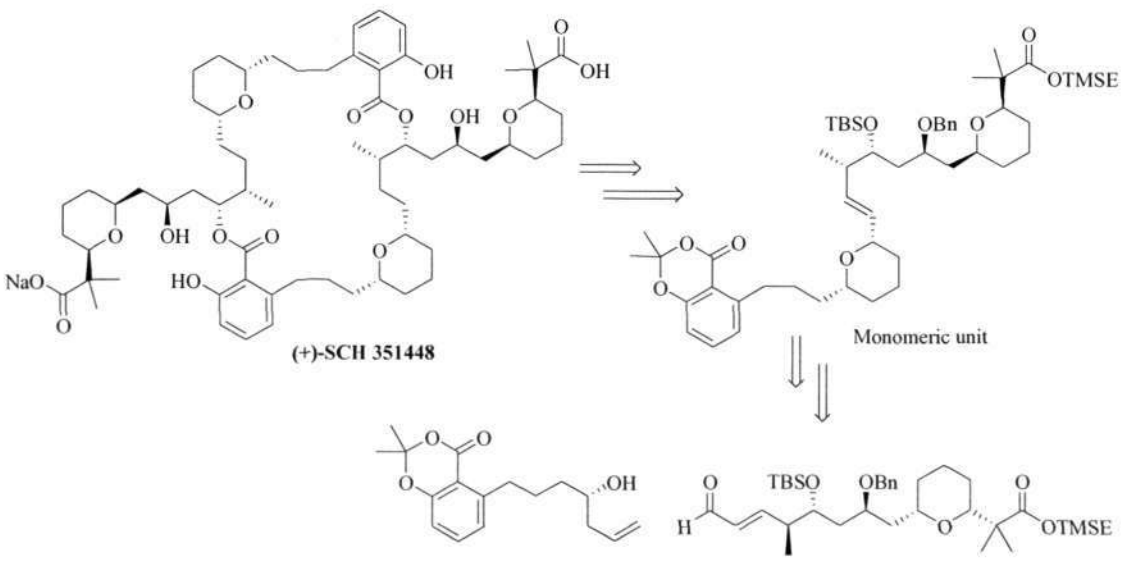
oxocarbenium transition state have been carried out to explain the stereochemical formation of the *anti*-isomers.

Substrate-controlled Prins cyclization



In the final part of this thesis, an elegant display of the catalytic Prins cyclization methodology is demonstrated in the formal synthesis of (+)-SCH 351448. Several strategies have been used in the construction of the molecule, 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 involving catalytic Prins cyclization in moderate yield without significant racemization.

Formal synthesis of **(+)-SCH 351448**



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	heat
↑↓	reflux
°C	degree centrigrade
ABq	AB quartet
Ac	acetyl
acac	acetoacetonate
AcCl	acetyl chloride
ACCN	*azo-bis*-cyclohexylcarbonitrile
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	*azo-bis*-isobutyronitrile
AllylBr	allylbromide
Alloc	allyloxycarbonyl
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
B:	Lewis base
Bn	benzyl
BOC	tert-butoxycarbonyl
BOP	benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate
br s	broad singlet
BuLi	butyl lithium
Bz	benzoyl
Cacld	calculated
Cat.	catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
COSY	correlated spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid

CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexane; cyclohexanyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublets of doublet
ddd	doublets of doublets of doublet
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DIPBr	B-bromodiisopinocampheylborane
DIPCl	B-chlorodiisopinocampheylborane
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dppf	diphenylphosphino ferrocenyl
dq	doublets of quartet
dt	doublets of triplet
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
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

FAB	fast atomic bombardment
$Fe(acac)_3$	Iron (III) acetoacetonate
Fmoc	9-fluorenylmethyl
FTIR	Fourier transform infrared spectroscopy
g	gram
Gly	glycine
h	hour
H	hydrogen
HDA	hetero Diels-Alder
hept	heptet
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HMQC	heteronuclear multiple quantum correlation
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
Hz	Hertz
IC	Inhibitory concentration
IR	infrared
Ipc	isopinocampheyl
i-Pr	isopropyl
J	coupling constants
kg	kilogram
L.A.	Lewis acid
LDA	lithium diisopropylamide
LDL-R	low density lipoprotein receptor
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxy methyl

MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)
NaHMDS	Sodium hexamethyl disilazide
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
nmr	nuclear magnetic resonance
NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
N.R.	no reaction
obs.	observed
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	trifluoromethanesulfonate
PBr_3	phophorus tribromide
PCC	pyridinium chlorochromate
Pd / C	palladium on carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PhH	benzene
PhMe	toluene
PMB	*p*-methoxybenzyl
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'd	saturated
s-Bu	*sec*-Butyl
SREBP	Sterol Regulating Element Binding Protein
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenyl silyl
t-BOC	*tert*-butoxycarbonyl
TBS	*tert*-butyldimethyl silyl
t-Bu	*tert*-butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TFA	trifluoroacetic acid
TfOH	triflate acid
Tf_2O	Triflate anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMSE	trimethylsiylethyl
TMEDA	N,N,N',N'-tetramethylethylenediamine
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
T.S.	transition state
vol	volume

CHAPTER 1

The Tetrahydropyran Framework in Natural Products

1.1 INTRODUCTION

Tetrahydropyran (THP) rings are an important feature in the vast array of natural products[1]. Over the past few decades, there has been an increase in the number of polyketides with THP backbones (Figure 1.1) isolated from marine sponges and microorganisms. These compounds are usually macrolides having unique structural configurations of THP arranged in a regular or random manner together with other functionalities. Compounds such as phorboxazole A (see Figure 1.1) which possesses anti-tumor activity, have complex molecular behavior in physiological systems and their biological properties are still being widely studied. Compounds with ionophoric structures, such as spirastrellolide A and bryostatin 1 (see Figure 1.1), are of particular interest because of the presence of multiple THP moieties and their therapeutic properties. The polycyclic-ethereal framework allows the molecules to function in two modes[2]:

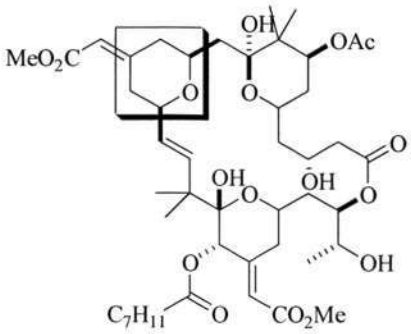
1. Binds to a particular ion which shields its charge from the surrounding environment. This facilitates the crossing of the ion through the hydrophobic interior of the lipid membrane in the physiological system.
2. Forms channels that introduce a hydrophilic pore into the membrane, thus allowing ions to pass through while avoiding contact with the membrane's hydrophobic interior.

Hence, ionophoric compounds disrupt transmembrane ion concentration gradients, which are essential for proper functioning and survival of microorganisms. This

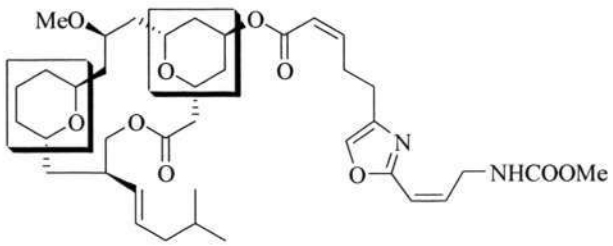
[1] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis* Wiley-VCH **1996**. (b) Nicolaou, K. C.; Synder, S. A. *Classics in Total Synthesis II* Wiley-VCH **2003**.

[2] (a) Bakker, E. P. *Antibiotics* **1979**, *5*, 67. (b) Chopra, I.; Roberts, M.; *Microbio. Mol. Bio. Rev.* **2001**, *65*, 232. (c) Schmid, E. E. *Antibiotics & chemotherapy* **1971**, *17*, 52. (d) Johnston, N. J.; Mukhtar, T. A.; Wright, G. D. *Curr. Drug Targets* **2002**, *3*, 334. (e) Zotchev, S. B. *Curr. Med. Chem.* **2003**, *10*, 211. (f) Delort, A.-M.; Jeminet, G.; Sareth, S.; Riddle, F. G. *Chem. Pharm. Bull.* **1998**, *46*, 1618. (g) Watanabe, K.; Watanabe, J.; Kuramitsu, S.; Maruyama, H. B. *Antimicrobial Agents and Chemotherapy* **1981**, *19*, 519. (h) Schadt, M.; Haeusler, G. *J. Membr. Biol.* **1974**, *18*, 277

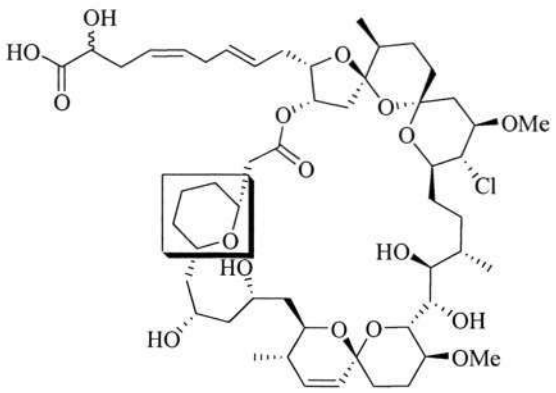
mainly accounts for the antibacterial[3], antifungal[4] and some cytotoxic[5] activities, although more research on these compounds needs to be done for greater understanding of their biological mechanism.



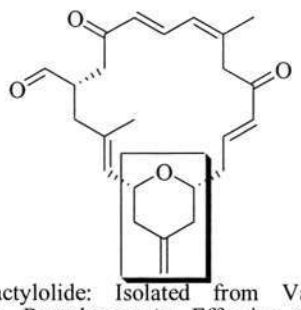
Bryostatin 1: Exhibit anticancer properties and has been shown to synergize the effects of other antineoplastic agents, promote apoptosis, reverse multidrug resistance, and stimulate the immune system



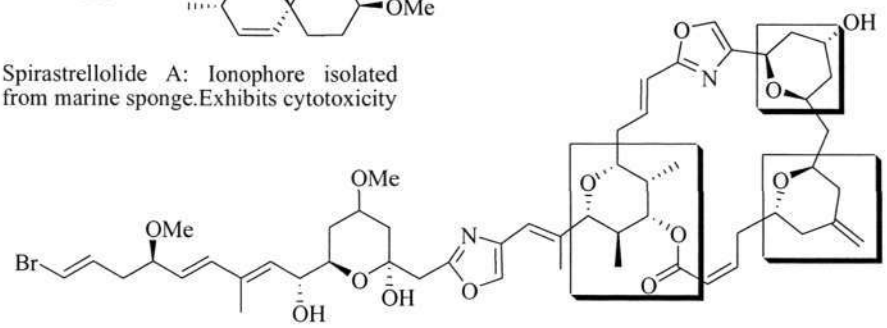
Leucascandrolide A: Isolated from thecalcareous sponge *Leucascandra caveolata.*Exhibit high cytotoxicity against human KB tumor cell lines and potent antifungal activity.



Spirastrellolide A: Ionophore isolated from marine sponge.Exhibits cytotoxicity



(+)-Dactylolide: Isolated from Vanuata sponge *Dactylospongia*. Effective against human broncho pulmonary, nasopharyageal, breast and colon tumor cell ines.



Phorboxazole A: Macrolactone with anti-tumour activity

Figure 1.1 Natural products containing tetrahydropyran backbone.

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

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

[5] (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.

With the invaluable benefits behind efficient synthesis of these compounds as the driving force, efforts devoted to develop various methods[6] to synthesize THP rings remained unabated. In the past decade, many methodologies have been formulated for both the racemic and stereospecific synthesis of substituted THP rings. The constraints of stereochemical outcomes, substrate compatibility and degree of substitution are determining factors on strategies towards THP rings construction. Despite the diversity of the methods available, the general approaches towards THP ring synthesis revolve around several concepts and these shall be discussed in the next section of this thesis. The challenge therein lies in the development of mild and versatile methods for the synthesis of the THP framework in the total synthesis of natural products.

1.2 GENERAL DISCUSSION ON TETRAHYDROPYRAN FORMATION

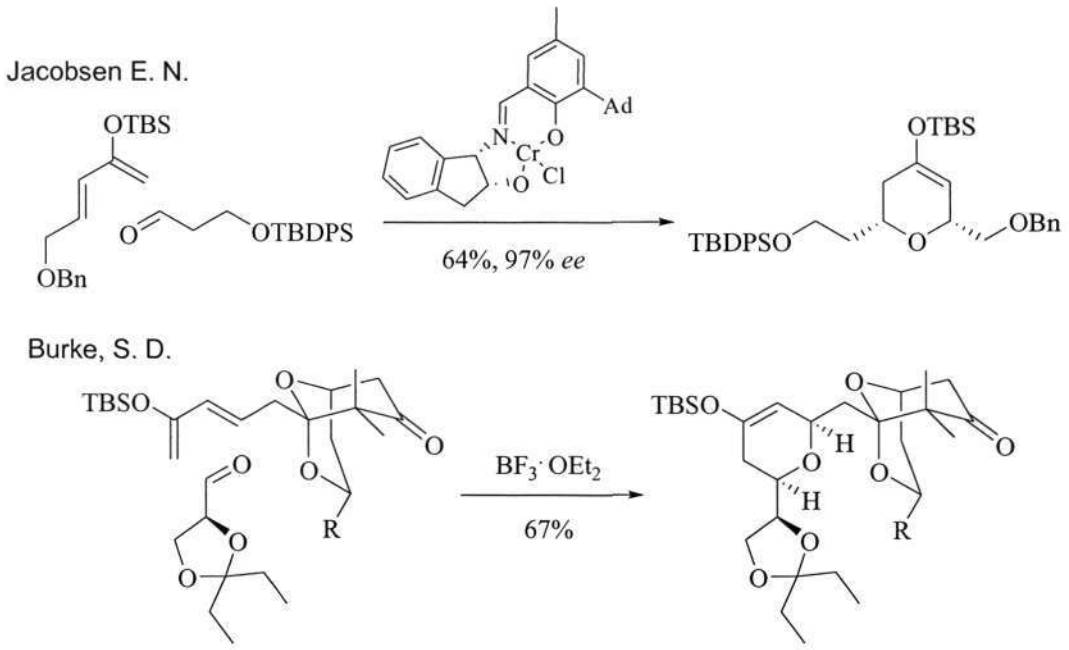
1.2.1 Hetero-Diels-Alder

The Hetero-Diels-Alder[7] reaction has been widely studied in the synthesis of THP rings. Being convergent in nature, the reaction introduces multiple stereocenters in a single reaction. Like the conventional Diels-Alder reaction, regio- and stereoselectivity are important considerations in the application to natural product

[6] For reviews see (a) Borvin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045.

[7] For reviews see (a) JØrgensen, K. A. *Eur. J. Org. Chem.* **2004**, *10*, 2093. (b) Schmidt, R. D. *Acc. Chem. Res.* **1986**, *19*, 250. (c) Herbert, W. *Synthesis*, **1994**, *6*, 535. (d) JØrgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (c)Weibreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (d) Ujaque, G.; Lee, P. S.; Houk, K. N.; Hentemann, M. F.; Danishefsky, S. J. *Chem. Eur. J.* **2002**, *8*, 3423. (e) Larson, E. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 6715. For other hetero-Diels-Alder literature, see (f) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. –L. *Tetrahedron* **2001**, *57*, 7575. (g) Sklenicka, H. M.; Hsung, R. P.; Wei, L. –L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J. (h) McLaughlin, M. J.; Shen, H. C.; Hsung, R. P. *Tetrahedron Lett.* **2001**, *42*, 609. (i) Wei, L. –L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516.

synthesis. Jacobsen[8] has demonstrated excellent stereoslectivity using a chiral chromium catalyst to synthesize the THP fragment of ambruticin with 97% *ee*. Burke has utilized a similar strategy for the stereoselective synthesis[9] of the northern C1-C16 section of bryostatin 1 (Scheme 1.1).



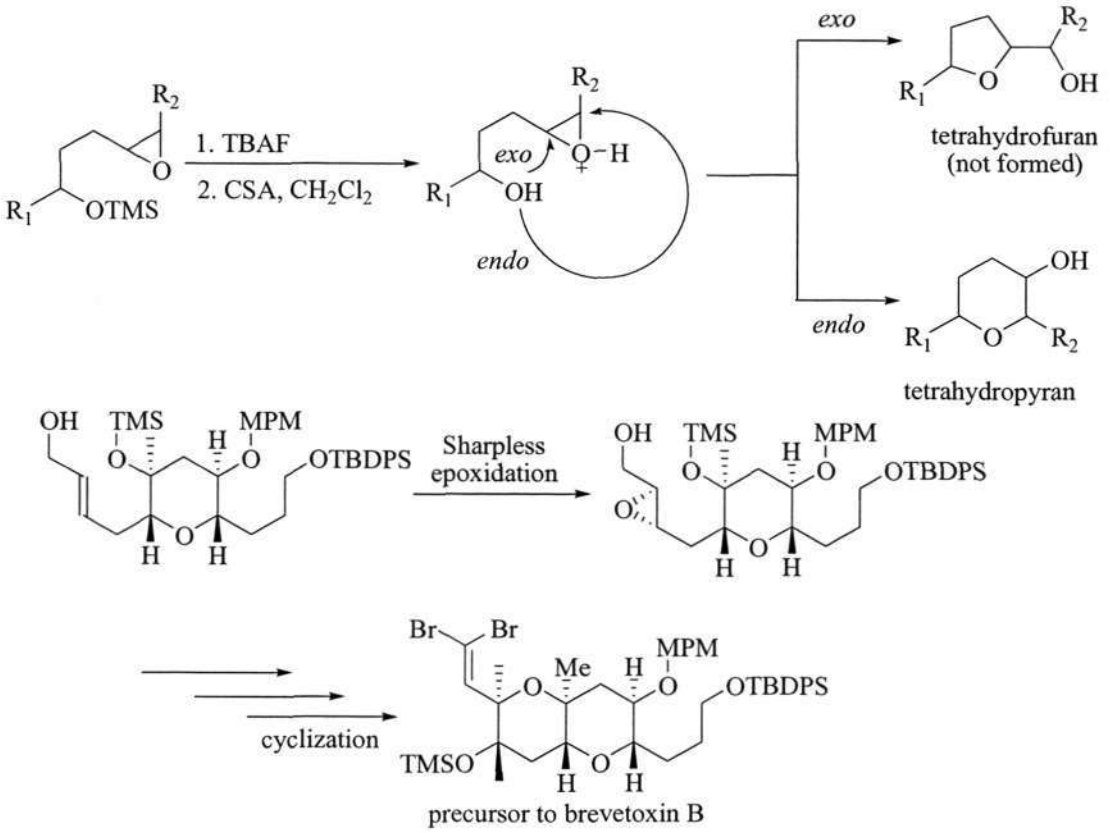
Scheme 1.1 Hetero-Diels-Alder strategy to form THP rings.

1.2.2 Hydroxyl Cyclization

Apart from cycloaddition reactions, hydroxyl cyclization with various functional groups such as alkenes or epoxides is also another widely used method to form tetrahydropyran rings. Enantiomerically pure 4,5-epoxy-alcohols are very good substrates for the formation of highly substituted asymmetric THP rings due to the ease of epoxy-ring-opening[10] and the feasibility of further derivatization on the secondary hydroxyl group on the THP ring. Nicolaou[11] has demonstrated

[8] Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.
[9] Voight, E. A.; Seradj, H.; Roethle, P. A.; Burke, S. D. *Org. Lett.* **2004**, *6*, 4045.
[10] For a review on epoxide ring openings, see (a) Smith, J. K. *Synthesis*, **1984**, 629. (b) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785.
[11] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. –K.; Somers, P. K. *J. Chem. Soc. Chem. Commun.* **1985**, *19*, 1359.

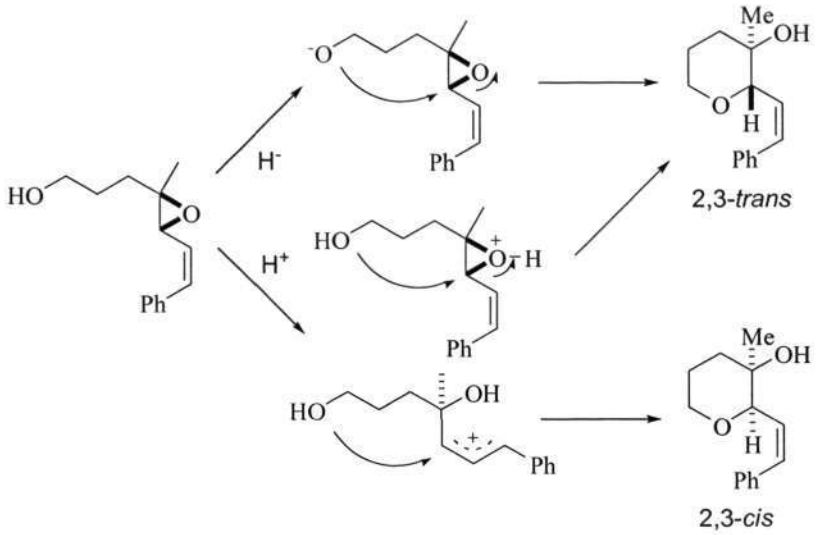
stereoselective syntheses of 2,3,6-trisubstituted THP system[12] using a chiral epoxy-alcohol under the influence of a Brønsted acid. The elegant activation of 6-*endo* over 5-*exo*- hydroxyl epoxide ring opening enhanced the applicability of this methodology (Scheme 1.2) in the synthesis of complex molecules such as brevetoxin B.



Scheme 1.2 6-*endo*-epoxide ring opening reaction and application towards the total synthesis of brevetoxin B.

Nakata[13] also investigated the mechanism of a similar strategy using hydroxyl styrylepoxides in both acid and base catalyzed THP ring formation. Under acidic conditions, a mixture of 2,3-*cis*- and 2,3-*trans*-isomers were obtained, indicating a competitive concerted and stepwise mechanism *via* the styryl cation. On the other hand, in the presence of NaH, the 2,3-*trans*-isomer was obtained exclusively (Scheme 1.3).

[12] For other application of this strategy see (a) Evans, P. A.; Murthy, S. *Tetrahedron Lett.* **1999**, *40*, 1253.
[13] Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.



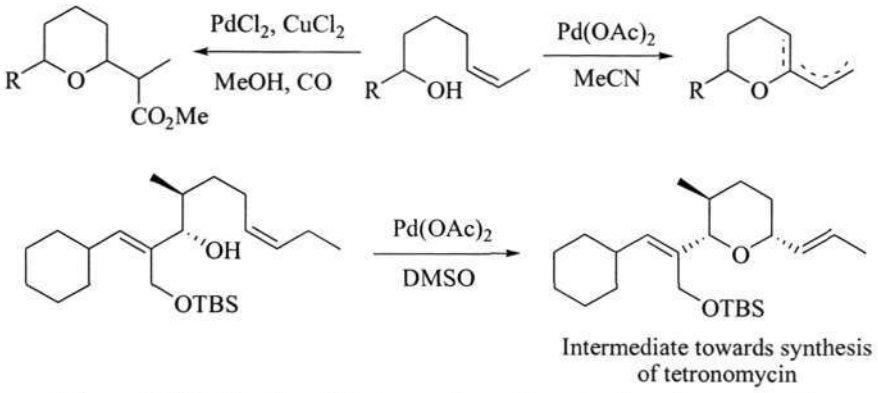
Scheme 1.3 Mechanistic studies on 6-*endo*-epoxide ring opening.

Tetrahydropyran ring synthesis has also been demonstrated successfully using hydroxyl-alkenyl group with a palladium[14] catalyst by Semmelhack[15]. Hydroxyalkenes[16] of appropriate hydrocarbon chain length can be activated by Pd(II) toward addition of the hydroxy group to the double bond (Scheme 1.4). The resulting alkylpalladium(II) complex can be usefully cleaved by CO or other reagents to form THP-esters or other functional groups. In the later examples, β-elimination can be achieved to form *exocyclic* or *endocyclic* unsaturated THP rings depending on the reaction conditions. A partial enantioselective synthesis of tetronomycin has been demonstrated using a tandem cyclization activated by palladium (II) acetate.

[14] For other examples on palladium mediated cyclization, see (a) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927. (b) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron Asym.* **2005**, *16*, 1299. (c) Hansen, E. C.; Lee, D. *Tetrahedron Lett.* **2004**, *45*, 7151.

[15] (a) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (c) Semmelhack, M. F.; Bodurow, C. *Tetrahedron Lett.* **1984**, *30*, 3171. (d) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205.

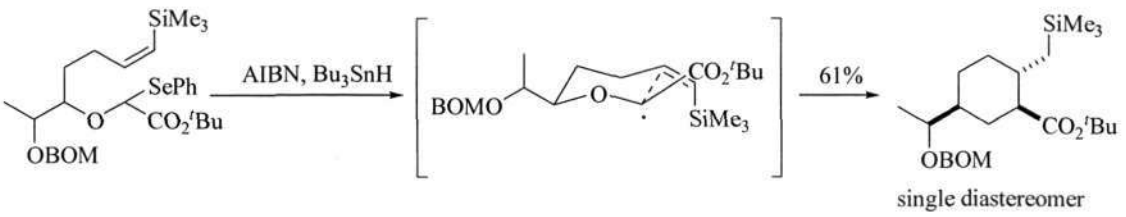
[16] (a) Sperka, J.; Liotta, D. C. *Heterocycles* **1993**, *35*, 701. (b) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. III. *J. Org. Chem.* **1987**, *52*, 4191.



Scheme 1.4 Cyclization of hydroxyalkenes in natural product synthesis.

1.2.3 Radical Cyclization

Similar to the hydroxyl-cyclization methodology, the radical cyclization[17] is another highly acclaimed concept in the synthesis of THP rings. The intramolecular cyclization reported by Burke[18] displayed excellent control of diastereoselectivity to form 2,6-*syn*-2,3-*anti*-trisubstituted THP rings using tethered sulfinyl or selenyl ether-alkenyl substrates (Scheme 1.5). Homolytic cleavage of the carbon-selenium bond with AIBN resulted in a chair-like transition state to facilitate 6-*exo-trig* radical cyclization. The ring closure followed by entrapment of radical using tributyltin hydride produces a single 2,6-*syn*-stereoisomer exclusively.

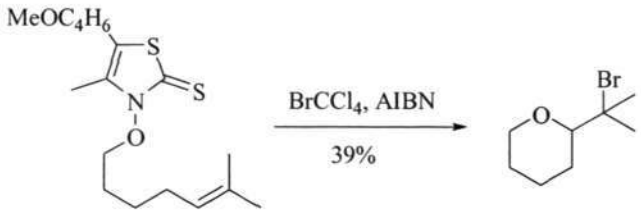


Scheme 1.5 Selenide promoted radical cyclization.

An interesting alternative radical-based precursor to 2,6-*syn*-THP ring is the thiazo-thione alkoxyl alkene reported by Hartung[19]. Also initiated by AIBN, the 6-*exo-trig* cyclization of 6-substituted-5-hexen-1-oxyl radicals effectively compete with

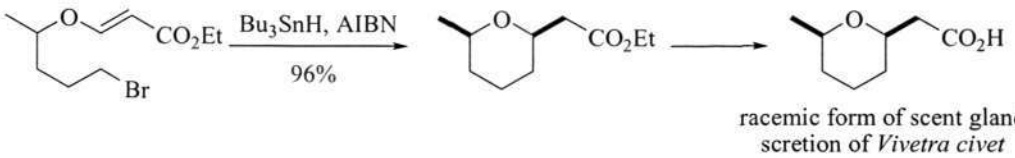
[17] For reviews see (a) Curran, D. P. *Synthesis* **1988**, *417*, 489. (b) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
[18] Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335.
[19] Hartung, J.; Gottwald, T. *Tetrahedron Lett.* **2004**, *45*, 5619.

δ-hydrogen atom transfer reactions, leading to bromomethylsubstituted tetrahydropyrans upon bromine atom trapping (Scheme 1.6).



Scheme 1.6 THP formation using alkoxyl alkene.

Another noteworthy strategy, promoted by Lee[20], is the radical cyclization of β-alkoxyacrylates in the formation of oxacycles. Since vinyl ethers[21] have been known to be good radical acceptors in cyclic ether synthesis, β-alkoxyacrylates can exhibit better reactivity and selectivity due to effective interactions between the large orbital coefficient[22] at the β-carbon in the LUMO of the β-alkoxyacrylates and the relatively high-energy SOMO of alkyl and stannylvinyl radicals. High efficiency of cyclization and excellent 2,6-*syn* diastereoselectivity mode of cyclization between the alkyl and stannylvinyl radicals rendered this methodology very useful in THP ring synthesis (Scheme 1.7).



racemic form of scent gland scretion of *Vivetra civet*

Scheme 1.7 Radical cyclization using β-alkoxyacrylates to form THP rings.

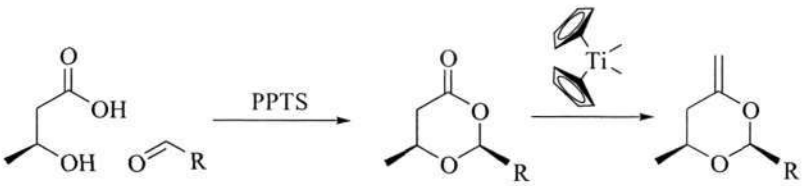
[20] (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831. For other applications of radical cyclization of β-alkoxyacrylates, see (b) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127. (c) Hwang, C. H.; Keum, G.; Sohn, K. I.; Lee, D. H.; Lee, E. *Tetrahedron Lett.* **2005**, *46*, 6621.

[21] Middleton, D. S.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 545.

[22] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons; Chichester, **1976**.

1.2.5 Petasis-Ferrier Rearrangement

Vinyl acetals can undergo a stereocontrolled aluminum-mediated rearrangement to afford substituted tetrahydropyrans as demonstrated by Petasis[23]. The precursor can be easily synthesized from acetalization of aldehydes with β-hydroxyacids followed by methylenation of the carbonyl group with dimethyl titanocene[24] (Scheme 1.8).



Scheme 1.8 Synthesis of vinyl acetal.

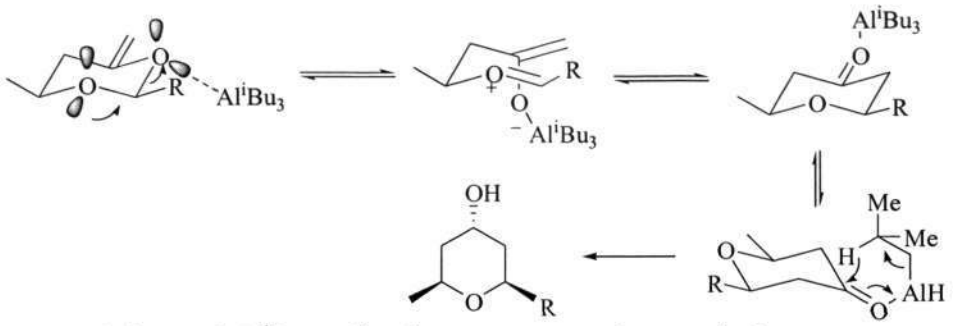
The mechanism for THP formation was proposed to be a [1,3]-sigmatropic rearrangement of vinyl-acetal, presumably initiated upon the coordination of the aluminum with the enolic moiety during the formation of an oxocarbenium ion. Subsequent reduction by triisobutyl aluminum *via* a Meerwein-Ponndorf-Verley[25] pathway formed the 2,6-*syn*-trisubstituted tetrahydropyran (Scheme 1.9).

---

[23] (a) Petasis, N. A.; Lu, S. –P. *Tetrahedron Lett.* **1996**, *37*, 141. (b) Petasis, N. A.; Lu, S. –P. *J. Am. Chem. Soc.* **1995**, *117*, 6394.

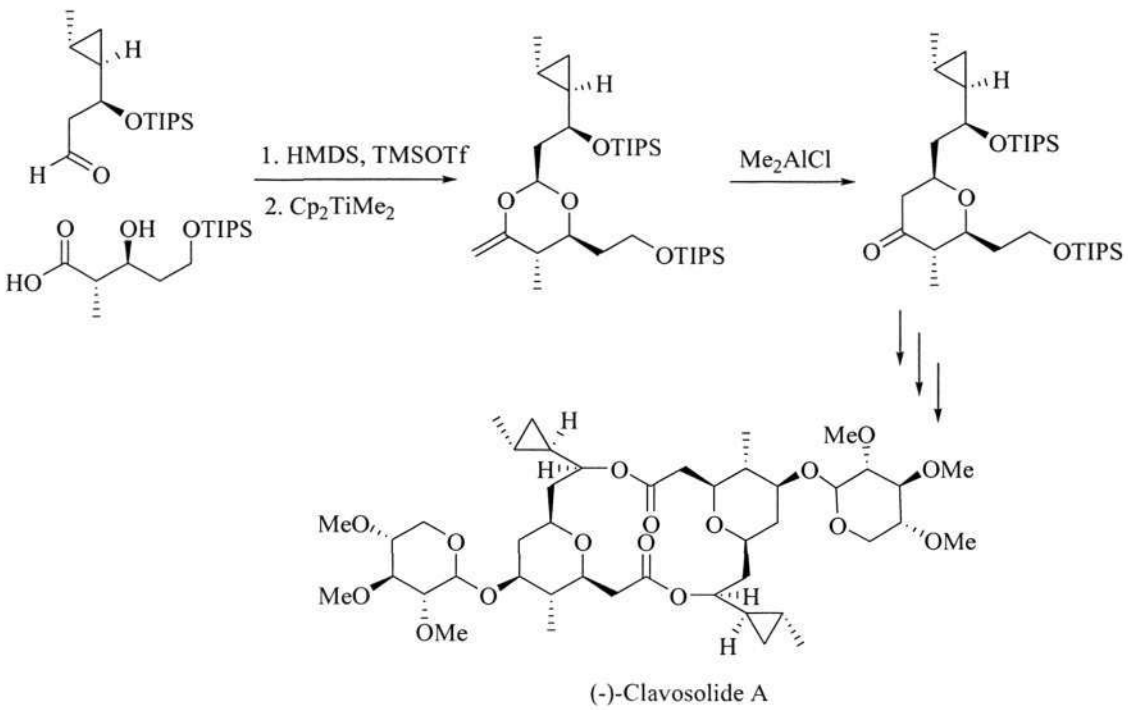
[24] (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112,* 6392. (b) Petasis, N. A.; Lu, S, -P. *Tetrahedron Lett.* **1995**, *36,* 2393.

[25] For mechanism, see (a) Screttas, C. G.; Cazianis, C. T. *Tetrahedron* **1978**, *34*, 933. (b) Ashbey, E. C.; Goel, A. B.; Argyropoulos, J. N. *Tetrahedron Lett.* **1982**, *23*, 2273. (c) Nasipuri, D.; Gupta, M. D.; Banerjee, S. *Tetrahedron Lett.* **1984**, *25*, 5551. (d) Ashbey, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *51*, 3593. (e) Yamataka, H.; Hanafusa, T. *Chem. Lett.* **1987**, 643. For reviews, see (f) Graves, C. R.; Campell, E. J.; Nguyen, S. T. *Tetrahedron Asym.* **2005**, *16*, 3460. (g) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, *10*, 1007. (h) Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414 and references therein.



Scheme 1.9 Al^iBu_3 mediated rearrangement to form tetrahydropyran.

Smith has demonstrated elegant applications of the Petasis-Ferrier rearrangement as the key step in the synthesis of biologically active natural products. Some examples include (+)-phorboxazole A[26], (-)-kendomycin[27] and (+)-zampanolide[28]. In the most recent showcase, the total synthesis of (-)-clavosolide A[29] was accomplished using this strategy to assemble two synthetically challenging fragments (Scheme 1.10).



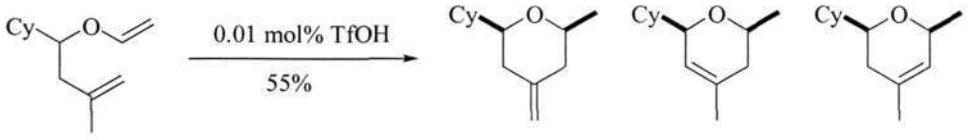
(-)-Clavosolide A

Scheme 1.10 Total synthesis of (-)-clavosolide A.

[26] Smith, A. B.; Minbiole, K. P.; Verhoest, P. R.; Schelhass, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942.
[27] Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948.
[28] Smith, A. B.; Saffonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.
[29] Smith, A. B.; Simov, V. *Org. Lett.* **2006**, *8*, 3315.

1.2.6 Other Cyclization Methods

An extension of the enol-ether cyclization was recently reported by Hoveyda[30]. This operationally simply and inexpensive Br∅nsted acid catalyzed reaction afforded a mixture of 2,6-*syn*-olefinic THP products in moderate yields (Scheme 1.11). Although further studies were not reported, this potentially useful reaction generates a major isomer that resembles the key molecular framework in biologically active natural products such as (-)-dactylolide[31].



isomeric ratio 4:1:1

Scheme 1.11 TfOH catalyzed cyclization.

Cyclic lactones can be reduced[32] to form cyclic hemi-ketals, which can be further derivatized to form 2,6-disubstituted THP rings[33]. Jennings[34] has reported that, in the synthesis of (-)-dactylolide, the nucleophilic addition of allylmagnesium bromide to a *β*-hydroxy lactone furnished a lactol, which was immediately transformed into the oxocarbenium[35] cation in the presence of TFA. Consecutive reduction with Et_3SiH afforded the desired *cis*-2,6-disubstituted tetrahydropyran (Scheme 1.12).

---

[30] Puglisi, A.; Lee, A.-L.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2006**, *8*, 1871.

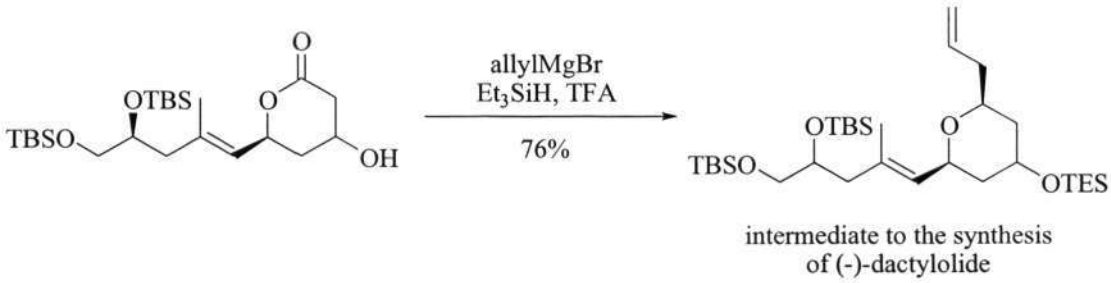
[31] For total synthesis of (+)-dactylolide, see Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005**, *7*, 3053.

[32] (a) Estevez, J. C.; Fairbanks, A. J.; Hsia, K. Y.; ward, P.; Fleet, W. J. *Tetrahedron Letters* **1994**, *35*, 3361. (b) Tsurugi, J.; Nakao, R.; Fukumoto, T. *J. Org. Chem.* **1972**, *37*, 76. (c) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, *21*, 1568. (d) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417.

[33] For other examples of reduction of lactones in natural product synthesis, see (a) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833. (b) Bolitt, V.; Mioskoski, C. *J. Am. Chem. Soc.* **1991**, *113*, 6320.

[34] (a) Ding, F.; Jennings, M. P. *Org. Lett.* **2005**, *7*, 2321. (b) Sawant, K. B.; Ding, F.; Jennings, M. P. *Tetrahedron Lett.* **2006**, *47*, 939.

[35] For strategies involving the formation of THP rings *via* oxocarbenium ion, see Chapter 2 in this thesis.



intermediate to the synthesis of (-)-dactylolide

Scheme 1.12 Reductive addition of lactones in the synthesis of (-)-dactylolide.

1.3 DEVELOPMENT OF NEW METHODS IN THP RING FORMATION

With the comprehensive discussion of the some of the elegant methods used to form THP rings, it is notable that each method also possesses some disadvantages in the application to natural product synthesis. In many cases, the application has been confined to small molecule synthesis and the construction of small fragments in natural product synthesis. Such methodologies[36] are thus seldom are used as a convergent strategy to conjoin complex molecular fragments and form the THP ring simultaneously. The difficulty in demonstrating convergence in these methods is largely attributed to the incompatibility of functional groups and protecting groups present with the reaction conditions used.

The issue of non-convergence is clearly displayed by intramolecular cyclization towards synthesis of THP rings. Despite high yielding and excellent selectivity, intramolecular cyclization requires tedious construction of the desired functionalities on complex fragments of intermediates to natural products. The synthesis of long chained molecules is often time consuming, and entails a significant level of complications because of delicate sensitivity towards harsh reaction conditions.

[36] For some examples on methods for intermolecular C-C bond formation in conjoining two large molecular fragments in natural products synthesis, see (a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *117*, 7001. (b) Meyers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072. (c) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Tetrahedron Lett.* **1986**, *27*, 4741.

The alluring need for development of an elegant method to overcome these odds in natural product synthesis remains uncompromised. Thus we invoke in the research of 2,4,6-trisubstituted THP rings synthesis based on Prins-type cyclization using mild reagents. The problem of racemization in Prins cyclization has been studied and well-addressed based on mechanistic investigations. Applications in the total synthesis of (-)-Centrolobine and (+)-SCH 351448 evinces the significance of this novel methodology in the realm of organic synthesis.

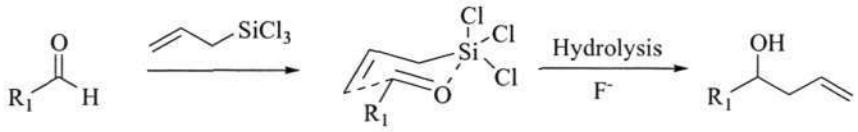
CHAPTER 2

Catalytic Prins Cyclization Using Allylchlorosilane

2.1 INTRODUCTION

2.1.1 Allylsilane reagents

Silicon based reagents are widely used in organic synthesis. Apart from the common protecting groups[37], organosilicon reagents such as allyltrimethylsilane[38] are excellent allylating agents in C-C bond formation reactions. Sakurai[39] and Hosomi had pioneered the use of silicon-based allylation of aldehydes. The strong affinity of silicon towards fluoride ions and the ability to form a pentavalent transition state gave such reactions an edge over many other metal-mediated C-C bond formation methods (Scheme 2.1).



Scheme 2.1 Silicon mediated allylation reaction.

To date, there have been numerous examples on silicon based carbon-carbon bond formation[40]. Lately Denmark[41] and co-workers have also established chiral Lewis base mediated organosilicon allylation reactions (Scheme 2.2), achieving satisfactory yields and enantioselectivity on reactions previously dominated by Lewis acids.

---

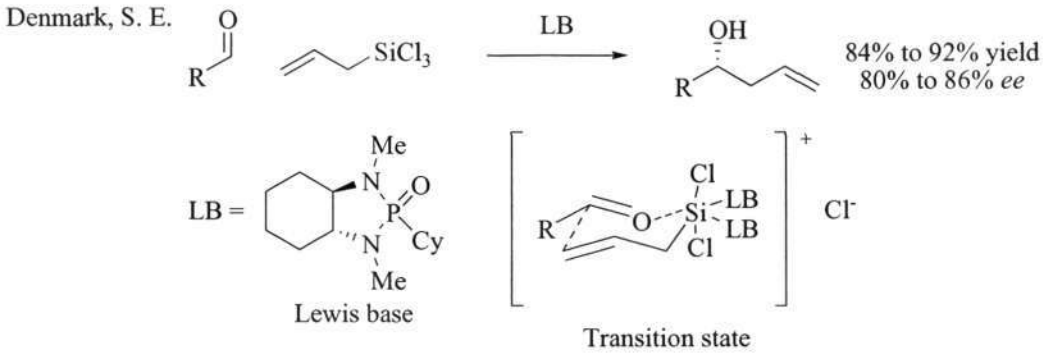
[37] Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, Wiley-Interscience, **1999**

[38] For reviews, see (a) Hwu, J. R.; Shiao, S. S.; Hakimelahi, G. H. *Appl. Organomet. Chem.* **1997**, *11*, 381. (b) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732 and references therein.

[39] (a) Sakurai, H.; Hosomi, A. *Tetrahedron Lett.* **1976**, 1295. (b) Sakura, H. *Pure and Applied Chem.* **1982**, *54*, 1.

[40] For reviews, see (a) Sebastian, R.; Martin, O. *Synthesis* **2005**, *11*, 1727. (b) Dilman, A. D.; L. Loffe, S. *Chem. Rev.* **2003**, *103*, 733 and references therein.

[41] (a) Denmark, S., E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000,** *122*, 12021. (c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001,** *123*, 9488. (d) Denmark, S. E.; Fu, J. *Org. Lett.* **2002,** *4*, 1951.



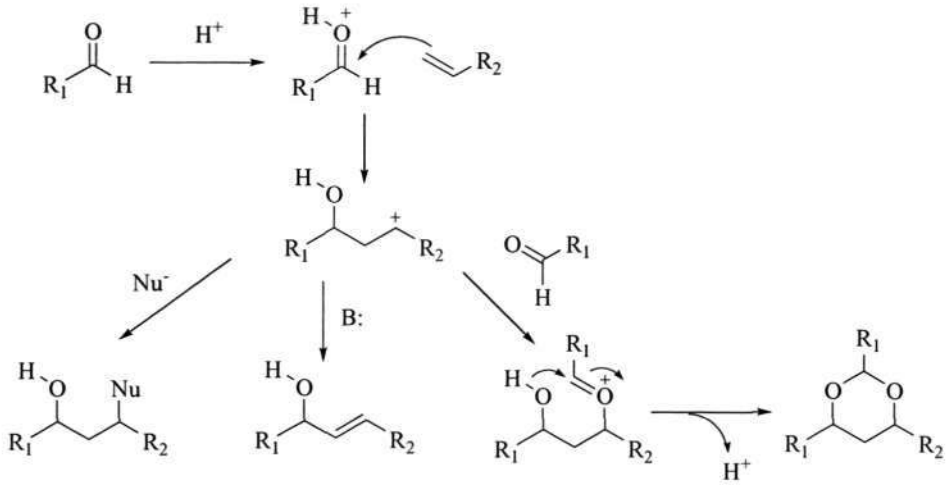
Scheme 2.2 Lewis base mediated organosilicon allylation.

2.1.2 Prins Cyclization in Organic Synthesis

Prins-type reaction is an acid mediated addition of an alkene to an aldehyde established by Hendrik Jacobus Prins[42] (1889-1958). The final product obtained varied according to different reaction conditions. The reaction mechanism is somewhat similar to the *ene*-reaction[43] whereby the aldehyde is activated by an acid, followed by an attack by an electron-rich alkene moiety. A very important distinction between the *ene*-reaction and Prins-reaction is that the latter is a stepwise mechanism, whereas the former proceeds in a concerted manner. The resultant formation of a carbocation in the Prins reaction (Scheme 2.3) can then undergo elimination, nucleophilic attack or acetalization with excess aldehydes to form different products. Although this reaction has been widely studied, attempts to improve the regio- and chemo-selectivity are rather unsuccessful, thus limiting its application in organic synthesis.

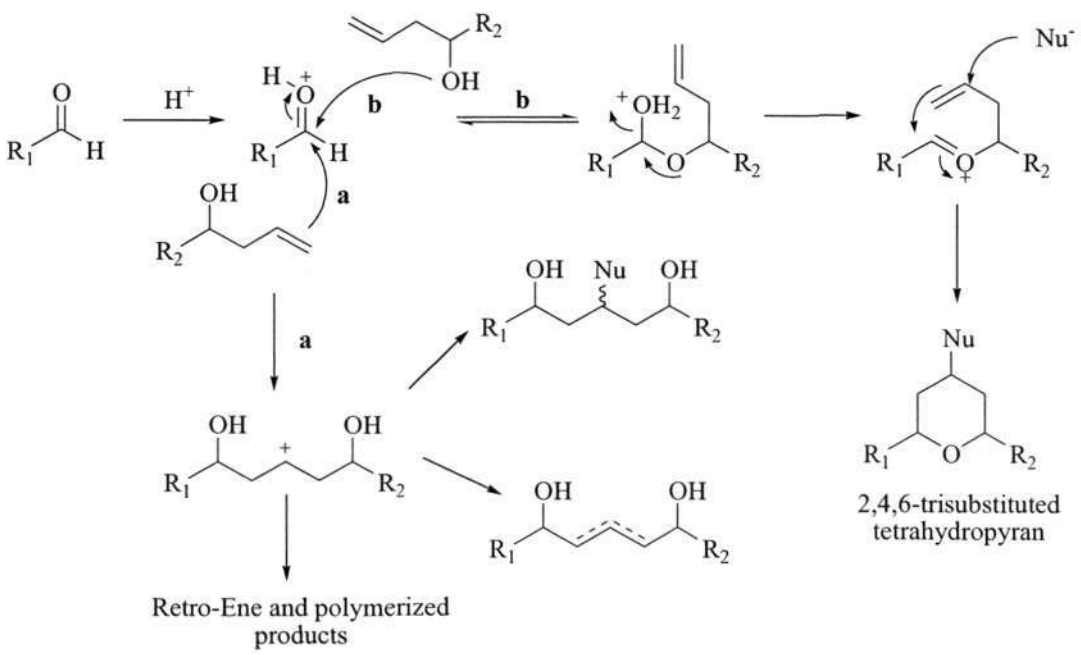
[42] (a) Prins, H. J.; *Chem. Weekblad.* **1917**, *14*, 932. (b) Prins, H. J.; *Chem. Weekblad.* **1919**, *16*, 1072. (c) Prins, H. J.; *Chem. Weekblad.* **1919**, *16*, 1510. (d) Prins, H. J.; *Proc. Acad. Sci. Amsterdam* **1919**, *22*, 51.

[43] (a) Alder, K.; von Brachel, H. *Liebigs Ann. Chem.* **1962**, *651*, 141. (b) Carruthers. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Elmsford, NY, 1990. (d) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed.* **1978**, *17*, 476. (e) Benn, F.R.; Dwyer, J.; Chappel, I. *J. Chem. Soc., Perkin Trans. 2* **1977**, *5*, 533. (f) Jenner, G.; Salem, B.; El'yanor, B.; Gonikberg, E.M. *J. Chem. Soc., Perkin Trans. 2* **1989**, *11*, 1671. (g) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.



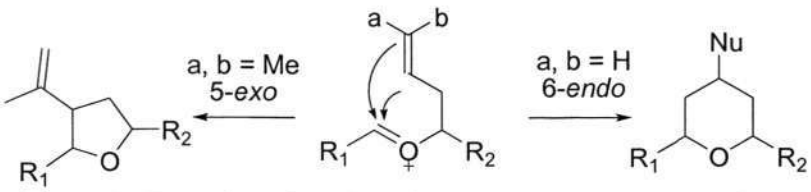
Scheme 2.3 Mechanistic interpretation of Prins reaction

An aldehyde subjected to an allylic fragment of a molecule (e.g a homoallylic alcohol) can proceed *via* two pathways (Scheme 2.4). The conventional Prins reaction (pathway **a**) will yield several products in an uncontrollable manner. On the other hand, in the presence of excess acid, an oxocarbenium cation transition state can be formed to yield a 2,4,6-trisubstituted tetrahydropyran (pathway **b**). Such competing pathways in strong mineral acids are often not selective and are prone to generate many undesired polymerized products.



Scheme 2.4 Prins-type reaction between an aldehyde and homoallylic alcohol.

From a different perspective, the cyclization pathway can be a powerful tool to build 2,6-disubstituted tetrahydropyran ring motifs in natural products. Since homoallylic alcohols and aldehydes can be easily synthesized, and some are even commercially available, this reaction is highly sought after in of methodology studies. The cyclization can take place either through a 5-*exo* or a 6-*endo* pathway[44] depending on the structure of the allylic fragment and the reaction conditions. The latter (6-*endo*) will form a pyran ring whereas the former produces a furan moiety (Scheme 2.5). Our group has demonstrated the formation of tetrahydrofuran ring catalyzed by $In(OTf)_3$ in good yields and selectivity[45]. Since tetrahydropyrans are important skeletal structure in some natural products, establishing the functionality of catalytic Prins cyclization using a synergetic approach of indium, silicon and oxocarbenium chemistry will be of significance in organic synthesis.



Scheme 2.5 Formation of tetrahydrofuran and tetrahydropyran products.

2.2 PRINS CYCLIZATION

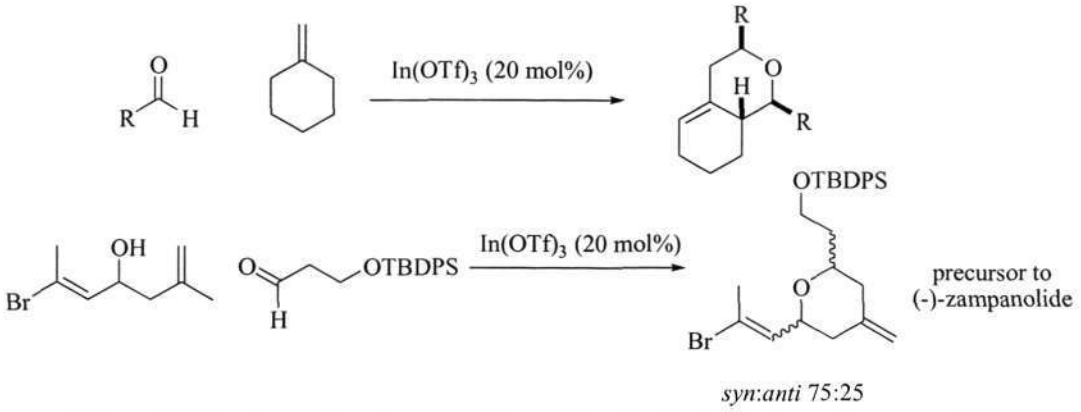
The concept of Prins cyclization has been studied and applied over the past few decades. Our group has demonstrated indium (III) complex catalyzed tandem carbonyl-ene reaction in the efficient construction of tetrahydropyran rings[46]. This

[44] (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.

[45] 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.

[46] Loh, T. P.; Feng, L. –C.; Yang, J. –Y. *Synthesis* **2002**, *7*, 937.

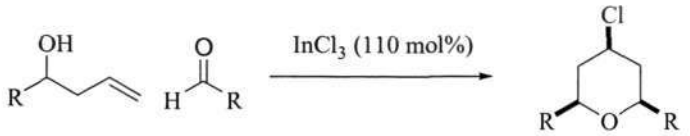
method was extended to synthetic studies towards total of zampanolide and dactylolide[47] (Scheme 2.6).



syn:*anti* 75:25

Scheme 2.6 Tandem carbonyl-ene reaction and synthetic studies towards zampanolide.

Prins cyclization proceeds *via* the formation of an oxocarbenium ion, followed by subsequent trapping with a nucleophile, which is usually the counterion. Li[48] has demonstrated the stoichiometric use of Lewis acid to introduce the heteroatom at the 4-position of the THP ring in Prins cyclization (Scheme 2.7). Unfortunately, only the *meso*-products were isolated, which were of very little synthetic value.

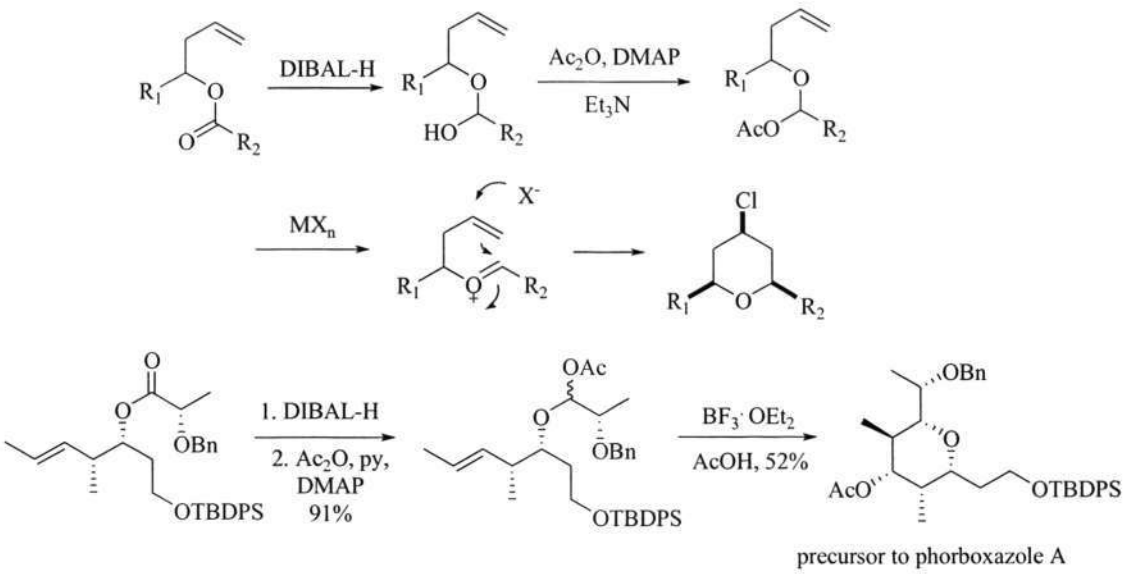


Scheme 2.7 Stoichiometric Prins cyclization in the formation of *meso*-THP ring.

In the perspective of generating an oxocarbenium ion, Rychnovsky[49] has reported an elegant THP synthesis using segment-coupling Prins cyclization (Scheme 2.8). DIBAL-H reduction of a homoallylic ester followed by acetate protection of the acetal product affords the acetoxy-alkene. Under acidic conditions, spontaneous generation of the oxocarbenium transition state can occur, which cyclized in the presence of excess halide ions to form cross-THP rings.

---

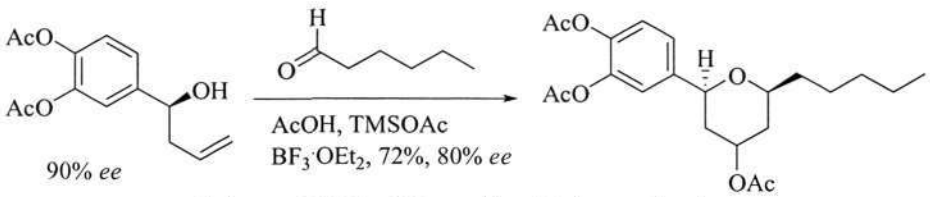
[47] Loh, T. P.; Yang, J. –Y; Feng, L. –C.; Zhou, Y. *Tetrahedron Lett.* **2002**, *43*, 7193.
[48] (a) Yang, J.; Viswanthan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. (b) Yang, X. –F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739.
[49] (a) Rychnovsky, S. D.; Hu, Y. Q.; 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.



precursor to phorboxazole A

Scheme 2.8 Segment-coupling Prins cyclization

An interesting observation was reported by Willis[50] whereby $BF_3{\cdot}OEt_2$ mediated Prins cyclization afforded the 4-acetyl-THP ring in the presence of acetic acid (Scheme 2.9). The mechanism for the formation of *meso*-THP side products has also been proposed in her studies.



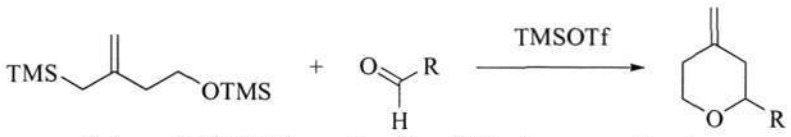
Scheme 2.9 $BF_3{\cdot}OEt_2$ mediated Prins cyclization

Silylated molecules with alkenyl functionality can undergo Prins cyclization to yield both *exocyclic* and *endocyclic* unsaturated THP products. Markó has developed an ISMS (intramolecular silyl modified Sakurai) reaction[51] for efficient pyran synthesis employing the Noyori method[52] to generate oxocarbenium ions with intramolecular allylsilane trapping (Scheme 2.10).

[50] (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.

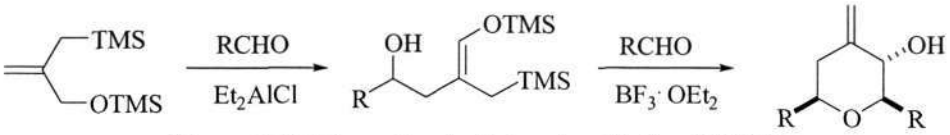
[51] (a) Mekhalfia, A.; Markó, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779. (b) Mekhalfia, A. Markó, I. E.; Adams,H. *Tetrahedron Lett.* **1991**, *32*, 4783.

[52] Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259.



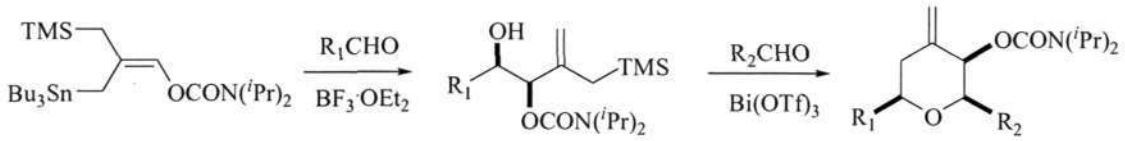
Scheme 2.10 ISMS reaction for efficient pyran synthesis.

Studies by Markó have also documented the use of racemic hydroxyl allylsilanes in sequences leading to THP formation *via* an initial ene reaction, and this was referred to as IMSC (intramolecular Sakurai cyclization)[53] (Scheme 2.11).



Scheme 2.11 Intramolecular Sakurai cyclization (IMSC).

In a later report, Leroy and Markó demonstrated the use of a functionalized allylstannane in $BF_3{\cdot}OEt_2$-promoted reactions with aldehydes to form the corresponding silyl-homoallylic alcohol (Scheme 2.12). This was followed by a $Bi(OTf)_3$-promoted cyclocondensation with a second aldehyde, to yield differentially substituted pyrans with excellent stereochemical control[54].



Scheme 2.12 Allylstananne mediated pyran formation.

An extension of this method was demonstrated by Keck[55] in an iterative pyran annulation to form a bis-pyran, which contains three differentiated and highly malleable functional groups on the THP ring (Scheme 2.13). This method allows adequate flexibility since the annulation can be approached from two different directions for any given pyran, thus enhancing its utility in natural product synthesis.

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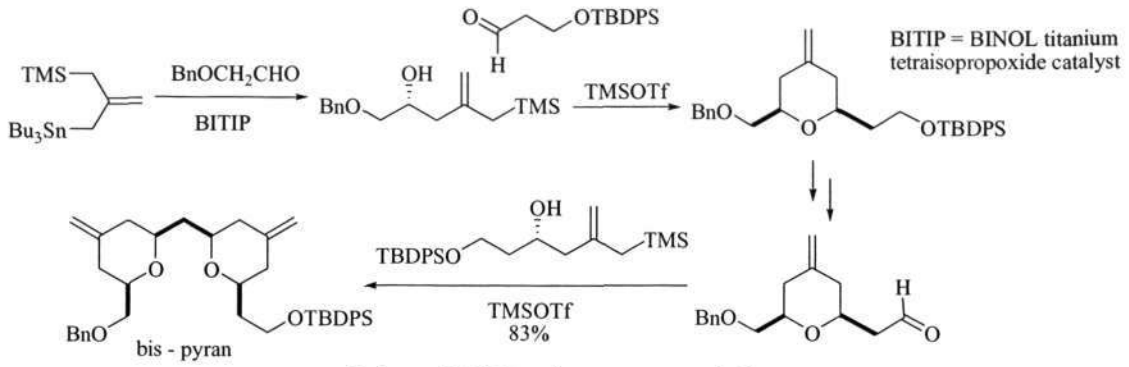
[53] (a) Marko, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595. (b) Marko, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141. (c) Marko, I. E.; Mekhalfia, A.; Murphy, F.; Bayston, D. J.; Bailey, M.; Janousek, Z.; Dolan, S. *Pure Appl. Chem.* **1997**, *69*, 565. (d) Marko, I. E.; Plancher, J. -M.; *Tetrahedron Lett.* **1999**, *40*, 5259.

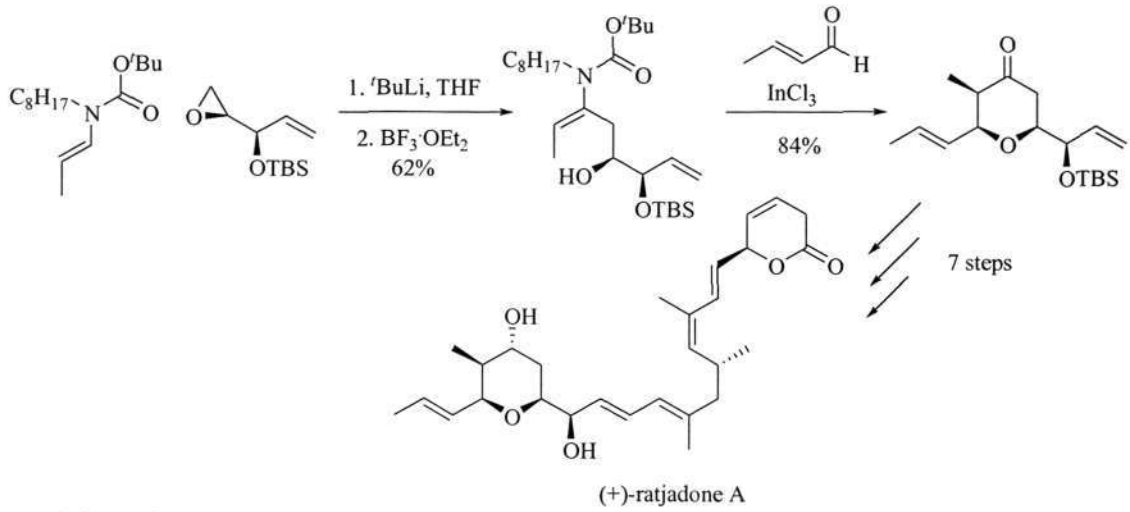
[54] Leroy, B.; Markó, I. E.; *Tetrahedron Lett.* **2001**, *41*, 8685.

[55] Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. *Org. Lett.* **2002**, *4*, 1189.



Scheme 2.13 Iterative pyran annulation.

In a separate account, enecarbamates have been reported by Funk[56] to participate in highly diastereoselective Prins cyclizations with oxocarbenium ions to form an all-*cis*-2,3,6-trisubstituted tetrahydropyran-4-ones. These unique cyclization substrates can be readily assembled from synthetically viable optically pure epoxides in the context of a formal total synthesis of (+)-ratjadone A (Scheme 2.14).

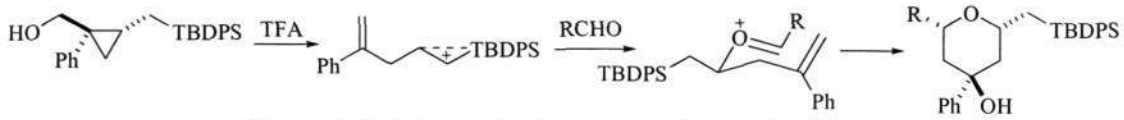


Scheme 2.14 Prins cyclization using enecarbamates: Formal total synthesis of (+)-ratjadone A.

Other precursors such as cyclopropyl carbinols have also been used to form 2,4,6-trisubstituted tetrahydropyrans *via* Prins cyclization as reported by Yadav[57]. Upon treatment with an acid, cyclopropyl carbinol will give a cyclopropyl carbonyl cation which can undergo either ring expansion to a cyclobutyl cation[58] or ring

[56] Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216.
[57] Yadav, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652.
[58] (a) Kanemoto, S.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1987**, *28*, 6313. (b) Hardouin, C.; Taran, F.; Doris, E. *J. Org. Chem.* **2001**, *66*, 4450.

cleavage to a homoallyllic cation[59] to relieve ring strain. The ring-cleavage pathway was promoted through stabilization of the homoallyllic cation by a silylmethyl functional group[60]. Subsequent intramolecular nucleophilic capture of the oxocarbenium ion by the intramolecular olefinic moiety afforded a multiply substituted tetrahydropyran ring (Scheme 2.15).



Scheme 2.15 Prins cyclization using cyclopropyl carbinols.

Although there is a diversity of substrates and techniques in Prins cyclization, there is still a need for a milder, more direct and convergent method involving easily prepared homoallylic alcohols and aldehydes. The use of harsh reagents such as DIBAL-H which may be incompatible with other functional and protecting groups like esters should be avoided. Especially in the total synthesis of natural products, the ease of synthesis of the precursors is an extremely important consideration in order not to jeopardize other functionalities in the fragment. In view of the flourishing field of alkyl halide coupling reactions, the versatile incorporation of halides onto the THP rings can enhance the synthetic values of such methodology[61]. Hence, the flexibility of further derivatization on the 4-position of the THP ring is also an important criterion in tetrahydropyran synthesis.

[59] (a) Sarel, S.; Yovell, J.; Sarel0Imber, M. *Angew. Chem. Int. Ed.* **1968**, *7*, 577. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W. Yip. Y. C.; Tanko, J.; Huldicky, T. *Chem. Rev.* **1989**, *89*, 165.
[60] (a) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717. (b) Yadav, V. K.; Balamurugan, R. *Chem. Commun.* **2002**, 514. (c) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669.
[61] For details on this methodology, refer to Chapter 3 in this thesis.

2.3 INDIUM TRIFLATE CATALYZED PRINS CYCLIZATION

2.3.1 Allyltrichlorosilane as Allylating Reagent

Indium chemistry has been widely established in various aspects of organic synthesis, and studies of indium mediated C-C bond formation by Araki[62] are of particular interest to us. Indium-based Lewis acids are mild to most functional groups and are relatively easy to handle compared to its boron and aluminum counterparts. For example, indium trichloride exhibits extreme moisture tolerance, enabling aqueous medium reaction to proceed with good yields and selectivities[63].

Prins cyclization is often carried out in the presence of a stoichiometric amount of Lewis acid. Although ensuring rapid and high yielding cyclization, the use of stoichiometric amounts of expensive Lewis acids becomes unviable in scale-up reactions. In addition, the formation of by-products is also more significant as a result of competitive reactions in the presence of excess Lewis acids. To the best of our knowledge, the chemistry of the catalytic Prins cyclization has not been fully established. Hence, the idea of a catalytic Prins cyclization was conceptualized during our attempts to demonstrate THP ring formation mediated by indium-based Lewis acids.

Our investigation began with studying the effects of Lewis acids on the condensation reaction between a homoallylic alcohol and an aldehyde. The construction of *meso*-THP rings with 20 mol% of Lewis acids yielded less than 30%

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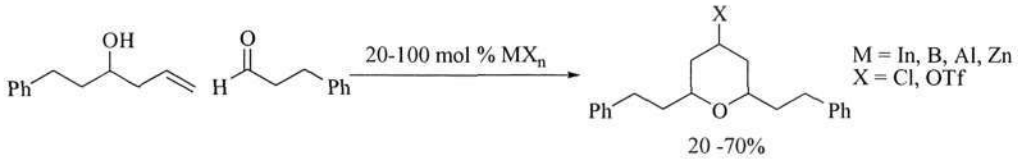
[62] (a) Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* **2003**, *68*, 1309. (b) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (c) Hirashita, T.; Toumatsu, S.; Imagawa, Y.; Araki, S.; Setsune, J. I. *Tetrahedron Lett.* **2006**, *47*, 1613. (d) Hirashita, T.; Mitsui, K.; Hayashi,Y.; Araki, S. *Tetrahedron Lett.* **2004**, *45*, 9189.

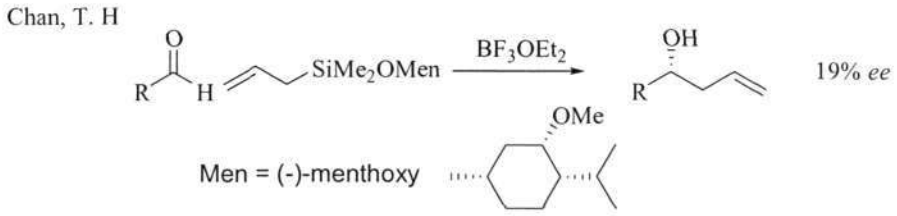
[63] (a) Loh T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L. *Tetrahedron* **2000**, *56*, 3227. (b) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (c) Loh T. P.; Wei, L. L. *Tetrahedron Lett.* **1998**, *39*, 323. (d) Loh, T. P.; Chua, G. L.; Vital, J. J.; Wong, M. W. *J. Chem. Soc., Chem. Commun.* **1998**, 861. (e) Loh, T. P.; Pei, J.; Koh, K. S. V.; Cao, G. Q. Li, X. R. *Tetrahedron Lett.* **1997**, *38*, 3465. (f) Loh, T. P.; Li, X. R. *Tetrahedron Asym.* **1996**, *7*, 1535. (g) Loh, T. P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2315. For reviews, see (h) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739. (i) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149.

of the desired product, alongside with unreacted starting materials and some 4-hydroxy-THP products. Progressive increments of molar equivalents of Lewis acids up to the stoichiometric amount raised the yield to about 70% (Scheme 2.16). The direct relationship between the Lewis acid molar equivalent and product yields seemed to suggest that the incorporation of the heteroatom at the 4-position was solely contributed by a single substituent on the Lewis acids.



Scheme 2.16 Construction to THP ring using catalytic amount of Lewis acids.

Taddei[64] and co-workers have demonstrated the synthesis of 2,4,6-trisubstituted THP ring in a one-pot allylation / Prins cyclization of aldehydes in the presence of allylsilanes and $TiCl_4$. Both *meso*- and synthetically useful crossed Prins cyclized products could be obtained with reasonable yields and excellent all-*syn* selectivity. Chan[65] and co-workers have also demonstrated Lewis acid promoted Prins cyclization using allylalkoxysilanes to form unsymmetrical 2,4,6-trisubstituted THP rings. In both cases, the respective homoallylic alcohols were formed as intermediates before proceeding with Prins cyclization in the presence of excess Lewis acids (Scheme 2.17).



Scheme 2.17 Chiral silicon auxiliary in silicon-mediated allylation.

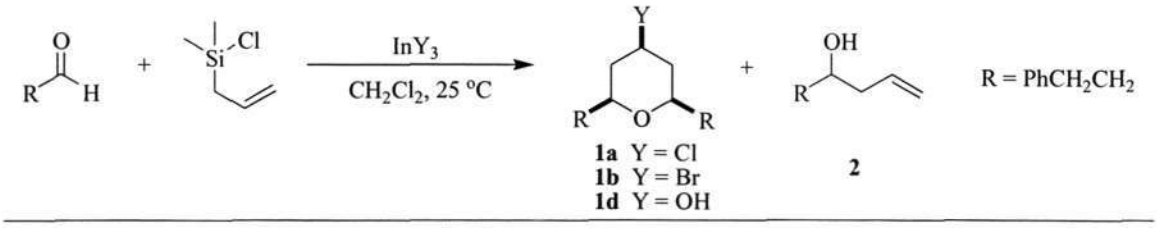
[64] Taddei, M.; Coppi, L.; Ricci, A. *Tetrahedron Lett.* **1987**, *28*, 973.
[65] Chan, T. H.; Wei, Z. Y.; Wang, D.; Li, S. J. *J. Org. Chem.* **1989**, *54*, 5768.

The formation of homoallylic alcohol with allylsilanes under such conditions has also been well-reported by Sakurai and Hosomi[66]. This led us to investigate the possibility of using allylsilanes[67] as allylating reagent as well as a source for the heteroatoms at the 4-position of the THP ring.

Based on the above-mention discussion, we envisaged the feasibility of a catalytic one-pot allylation / Prins cyclization mediated by allylsilane. Allylchlorodimethylsilane was chosen as the allylating reagent because of the presence of labile chloride moieties and its capability to form hypervalent silicon species, which is crucial in activating the substrates for one pot allylation / Prins-type reaction. Subjecting hydrocinnamaldehyde to allylchlorodimethylsilane and various indium based Lewis acids in dichloromethane yielded a mixture of homoallylic alcohol and Prins cyclized product as shown in Table 2.1.

[66] Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200. For other literature, refer to reference no. 38 in this chapter.
[67] For recent review on allylsilanes, Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173.

Table 2.1 Preliminary results of Prins cyclization of hydrocinnamaldehyde with allylchlorodimethylsilane.



1a Y = Cl
1b Y = Br
1d Y = OH

2

Entry	Y	mol % InY_3	Amt. allylsilane w.r.t. aldehyde	Conc[a] (*M*)	Yield (%)			
					1a	**1b**	**1d**	**2**
1	Cl	100	1.2 equiv	1	59	-	-	28
2	Cl	50	1.2 equiv	1	60	-	-	28
3	Cl	20	1.2 equiv	1	57	-	-	24
4	Cl	10	1.2 equiv	1	41	-	-	12
5	Cl	20	1.2 equiv	5	22	-	25	32
6	Cl	20	1.2 equiv	0.1	67	-	-	14
7	Cl	20	2.0 equiv	0.1	10	-	-	76
8	Cl	20	3.0 equiv	0.1	6	-	-	83
9	Br	20	1.2 equiv	0.1	41	21	9	10
10	F	20	1.2 equiv	0.1	23	-	12	27
11	**OTf**	**20**	**1.2 equiv**	**0.1**	**90**	**-**	**5**	**-**

[a] Conc denotes concentration with respect to aldehyde.

Our attempts with stoichiometric amount of $InCl_3$ yielded only moderate amount of THP product and significant proportions of the respective homoallylic alcohol. Decreasing the Lewis acid loading had no apparent effect on the yields of both the THP and homoallylic alcohol products, with 20 mol% of $InCl_3$ being the threshold catalyst loading.

The results also showed that reactions with higher molar concentration were non-selective, with the formation of THP products and homoallylic alcohol and other unidentifiable side products. The use of $In(OTf)_3$ (entry 11) at low concentration (0.1 M) gave the best result with predominant formation of the *meso*-4-chloro-2,6-

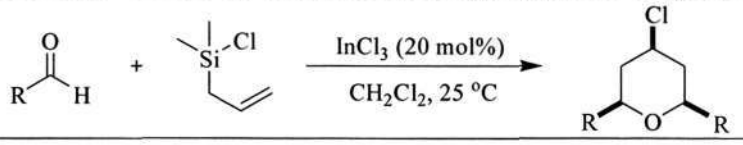
disubstituted tetrahydropyran and no homoallylic alcohol was isolated. The reaction was clean, with only a minute quantity of the 4-hydroxy-THP ring **1d**. With non-chloro Lewis acids (entries 9, 10 and 11), the formation of 4-chloro-THP product **1a** implied that the chloride source must have come from the allylsilane instead of the Lewis acids. Interestingly, the 4-fluoro-THP product was not observed with InF_3, possibly due to the high affinity of fluoride to silicon.

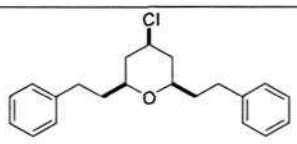
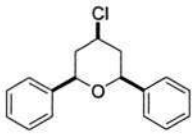
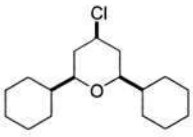
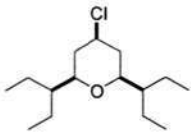
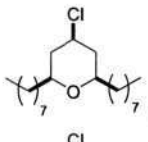
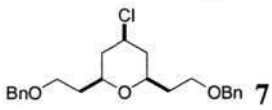
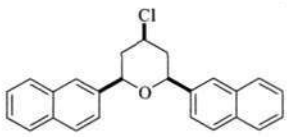
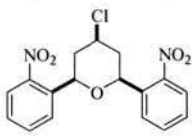
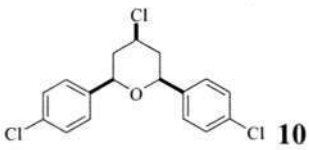
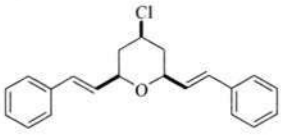
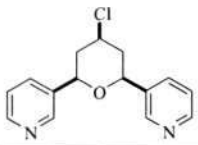
The homoallylic alcohol was predominantly formed with excess allylchlorodimethylsilane (entries 7 and 8). It was also observed that higher concentration enhanced the yield of the homoallylic alcohol (entry 5). In order to suppress its formation, a mixture of allylchlorodimethylsilane and aldehyde was added into a dilute solution of the Lewis acid, which gave the desired 4-chloro-THP product almost exclusively.

Delighted by our findings, various aldehydes were subjected to the optimized reaction conditions[68] to form *meso*-4-chloro-tetrahydropyrans (Table 2.2).

[68] 20 mol% $In(OTf)_3$, 1.2 equiv of allylchlorodimethylsilane in a total aldehyde concentration of 0.1 M in dichloromethane. Refer to experimental section in Chapter 6 for the detailed experimental procedure.

Table 2.2 Synthesis of *meso*-4-chloro-2,6-disubstituted tetrahydropyran *via* one-pot Prins cyclization



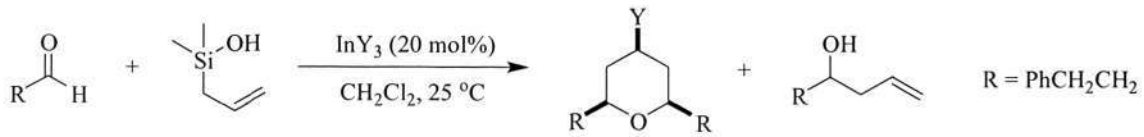
Entry	R	Time (h)	Product	Yield (%)
1	$PhCH_2CH_2$-	2	 **1a**	90
2	Ph-	4	 **3**	45
3	Cy-	2	 **4**[a]	65
4	$(C_2H_5)_2CH$-	1	 **5**	94
5	$CH_3(CH_2)_7$-	1	 **6**	65
6	$BnO(CH_2)_2$-	4	 **7**	45
7	3-napthyl	8	 **8**	26
8	2-nitrophenyl	8	 **9**	25
9	4-chlorophenyl	8	 **10**	36
10	cinnamyl	24	 **11**	N.R.[b]
11	3-pyridinyl	24	 **12**	N.R.

[a] An X-ray crystal structure was obtained and shown in Figure 2.1. [b] N.R. denotes no reaction with recovery of starting materials.

The reaction gave moderate to high yields of the *meso*-THP product and excellent diastereoselectivities, with only the *syn*-isomer isolated. The yields of inactivated aldehydes (entries 2 and 6) were lower with longer reaction times compared to the aliphatic counterparts. Naphthyl and other substituted aromatic aldehydes (entries 7 to 9) also afforded lower yields, but without any compromise in diastereoselectivity. However, no reaction was observed with highly conjugated aldehyde such as cinnamaldehyde (entry 10). The same result was also observed in the case of 3-pyridinyl aldehyde, probably due to poisoning of the catalyst as a result of the pyridinyl moiety chelating to the Lewis acid.

Allyldimethylsilanol has also been known to be an excellent allylating reagent. We postulate a similar reaction pathway where the hydroxyl group will be incorporated instead of the chloride moiety. An investigation was carried out to establish the formation of 4-hydroxy-THP rings by subjecting allyldimethylsilanol to the established conditions with hydrocinnamaldehyde (Table 2.3).

Table 2.3 Prins cyclization of hydrocinnamaldehyde with allyldimethylsilanol using 0.2 equiv of Lewis acid.



1a Y = Cl
1b Y = Br
1d Y = OH

2

Entry	Y	Yield (%)			
		1a	**1b**	**1d**	**2**
1	Br	-	36	23	-
2	F	-	-	48	-
3	Cl	33	-	3	4
4	OTf	-	-	68	23

The results were unexpected as low or moderate yield of the 4-hydroxy THP product (**1d**) were obtained. The 4-halo-THP rings were still the major products when $InBr_3$ and $InCl_3$ were used. This could be due to the hydroxyl group on allyldimethylsilanol being less labile and not able to participate in the trapping of the oxocarbenium ion.

2.3.2 $In(OTf)_3$ Catalyzed Crossed Prins Cyclization

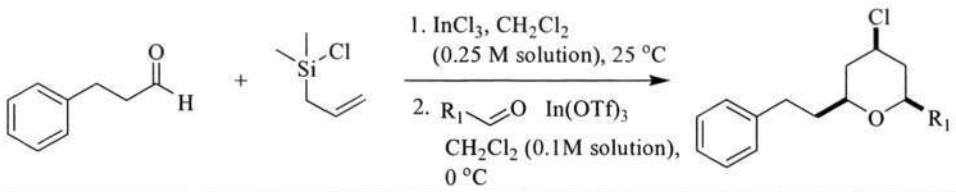
The controlled formation of homoallylic alcohol using allylchlorodimethylsilane can be achieved in two ways: -

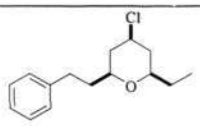
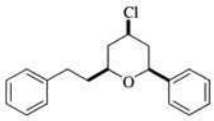
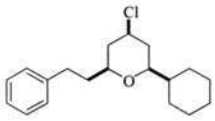
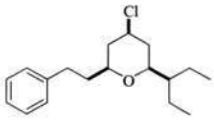
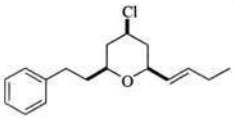
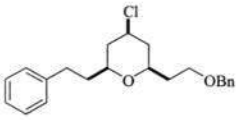
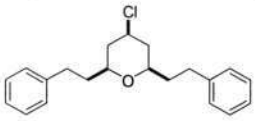
(a) Addition of more than 2 equivalent of allylating reagent in catalytic amount of Lewis acid; or

(b) Increasing the concentration of the reaction mixture to enhance rapid allyl transfer from allylsilane to aldehyde.

With the information gathered from the formation of *meso*-2,4,6-trisubstituted THP ring, we proposed to achieve catalytic crossed Prins cyclization using sequential aldehyde addition in a one pot reaction. We envisaged that by using a weaker Lewis acid, formation of the *meso*-product can be effectively suppressed, leading to generation of a homoallylic alcohol first. This can be then be followed by addition of a second aliquot of Lewis acid and a different aldehyde, thus obtaining the desired unsymmetrical THP ring in high yields and diastereoselectivity (Table 2.4).

Table 2.4 Catalytic crossed Prins cyclization using allylchlorodimethylsilane



Entry	R_1	Product[a]	Yield (%)
1	CH_3CH_2-	 **13**	83
2	Ph-	 **14**	85
3	Cy-	 **15**	68
4	$(C_2H_5)_2CH$-	 **16**	89
5	CH_3CH_2CH=CH-	 **17**	70
6	$BnO(CH_2)_2$-	 **18**	65
7	$PhCH_2CH_2$-	 **1a**	96

[a] It is noteworthy that only one single isomer was isolated in each case, determined by ^1H, ^{13}C and NOESY nmr spectra.

The use of both $InCl_3$ and $In(OTf)_3$ are essential in achieving good yields of the 2,4,6-trisubstituted THP product. In separate experiments, a total of 20 mol% of $InCl_3$ in the one-pot reaction yield less than 30% of the product, accompanied by comparable yields of *meso*-THP product and the respective homoallylic alcohols. A second addition of 20 mol% $InCl_3$ raised the yield of the desired product by merely 20%. Since a dilute solution is critical for the Prins cyclization, a stronger Lewis acid like $In(OTf)_3$ is essential for THP formation in limiting amount of homoallylic alcohol. Slow addition of the second aldehyde at a lower temperature is also important

to prevent allylation in the excess allylchlorodimethylsilane and allyl transfer from the freshly formed 1-phenylhex-5-en-3-ol, **2**.

Prins cyclization has been known to give low yields with inactivated aldehydes such as benzaldehyde and to a large extend, failed to give the desired product with α-β unsaturated aldehydes[69]. However, in this newly developed one-pot crossed Prins cyclization, conjugated aldehydes (entry 5) can be coupled successfully under the catalytic reaction condition to give moderate yields of alkenyl-THP product **17**, which is of high synthetic value.

2.4 MECHANISTIC INSIGHT TO CATALYTIC PRINS CYCLIZATION

One important observation in Prins cyclization is the exclusive diastereoselectivity during the cyclization process. An X-ray analysis of 4-chloro-2,6-dicyclohexyl-tetrahydro-2H-pyran, **4**, revealed the all-syn configuration of the final THP product (Figure 2.1). This is attributed to the preferential adoption of equatorial positions by the substituents in the favorable chair-like transition state so as to reduce repulsive 1,3-diaxial interactions (Scheme 2.18).

[69] Most reported Prins cyclization have shown to give very unsatisfactory results with α-β unsaturated aldehydes such as cinnamylaldehyde and acrolein. These aldehydes are prone to degradation or polymerization in acidic conditions.

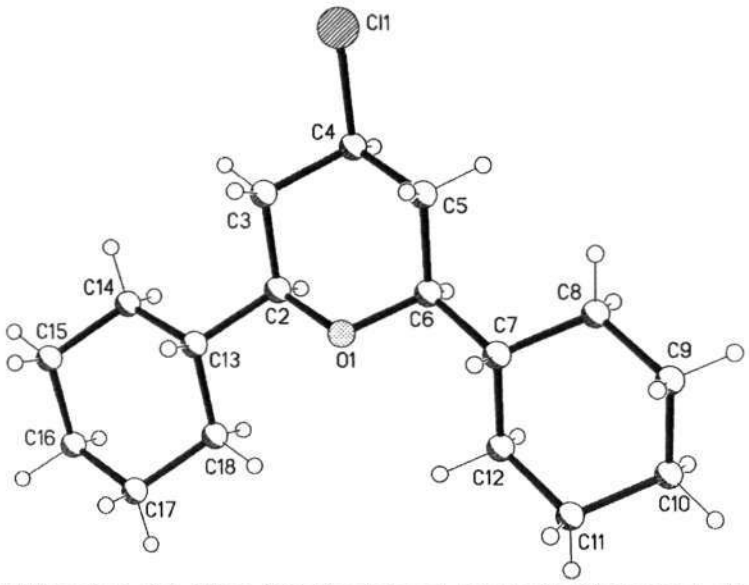
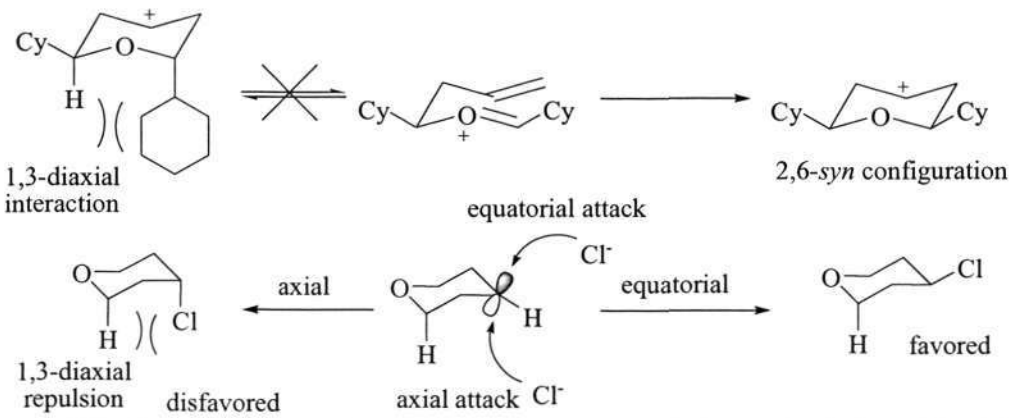


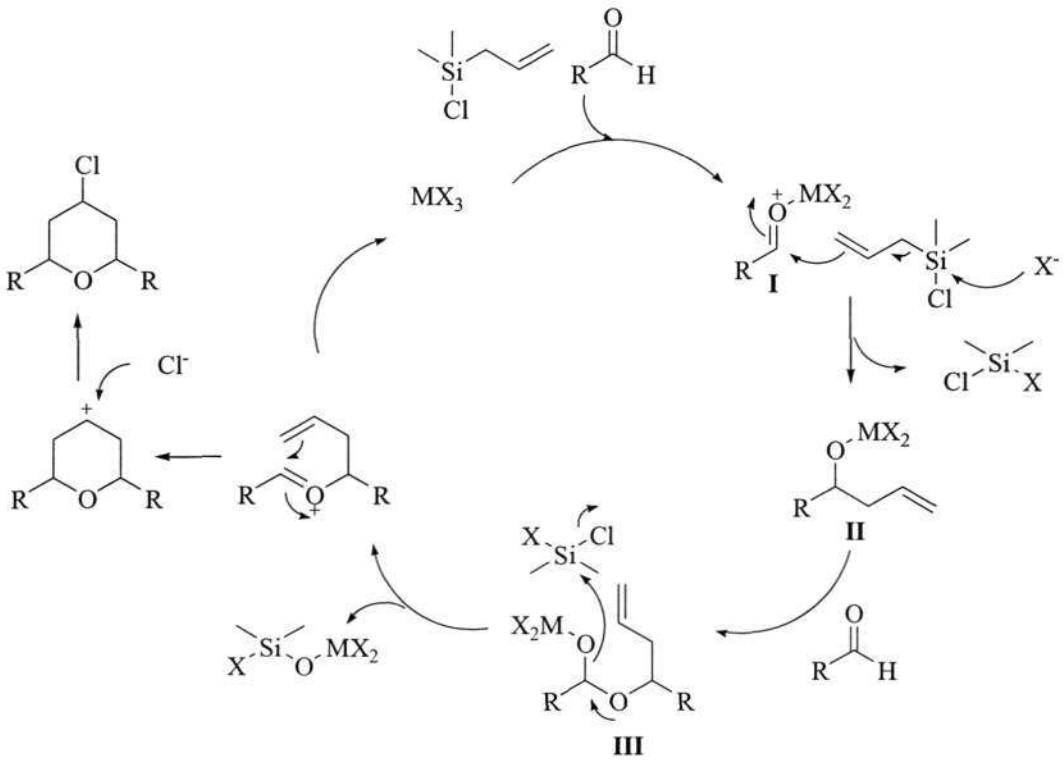
Figure 2.1 Crystal Structure of 4-chloro-2,6-dicyclohexyl-tetrahydro-2*H*-pyran **4**, showing all-*cis* configuration at the 2, 4 and 6 positions.



Scheme 2.18 Preferential adoption of equatorial positions by the substituents in the favorable chair-like transition state.

The fascinating feature in the catalytic Prins cyclization is the introduction of the nucleophile from the allylsilane. A sequential formation of homoallylic alcohol *via* allylsilylation of the aldehyde followed by condensation with other aldehydes to form a THP ring was proposed. A control experiment was carried to determine the level of participation of the Lewis acid in the allylation reaction. When hydrocinnamaldehyde was added to allylchlorodimethylsilane, TLC analysis showed formation of some homoallylic alcohol, with unreacted aldehyde remained as the major product. The reaction mixture remained unchanged for more than 24 hours

before it was quenched in 1*M* HCl to afford only less than 20% of homoallylic alcohol. The aldehyde and alcohol existed in a state of equilibrium favoring the dissociation of the allylsilane-aldehyde adducts. In the presence of a Lewis acid, the yield of THP product improved tremendously, indicating its importance in promoting allylation reaction. Hence we propose the mechanism of the catalytic Prins cyclization as shown in Scheme 2.19.



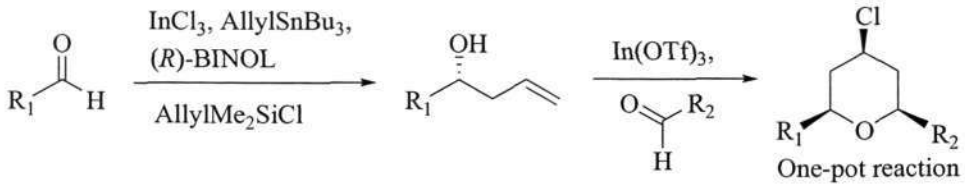
Scheme 2.19 Proposed mechanism for catalytic Prins cyclization

The proposed mechanism involves the formation of Lewis acid-activated aldehyde adduct (**I**) in the presence of a catalytic amount of Lewis acid. Subsequent open-chained allylation mediated by allylchlorosilane formed the homoallylic adduct (**II**). In the presence of excess aldehyde, spontaneous generation of the acetal (**III**) followed by formation of oxocarbenium ion proceeded readily due to anomeric effect. This brought about a release of the chloride ion from the cleavage of the labile Si-Cl bond, which served as a nucleophile to trap the oxocarbenium ion in a stepwise manner. The Lewis acid was then regenerated for subsequent catalytic reaction.

2.5 FUTURE WORK ON CATALYTIC PRINS CYCLIZATION

2.5.1 Enantioselective One-pot Prins Cyclization

With the achievement of cross-THP rings in excellent diastereoselectivity, future work on enantioselective one-pot Prins cyclization of aldehydes is in progress. With our recent development of enantioselective indium catalyzed allylation using BINOL and allyltributyltin, it may be possible to generate a chiral indium specie *in situ* which can then induce asymmetric allylation on the aldehyde (Scheme 2.20).



Scheme 2.20 Proposed enantioselective one-pot Prins cyclization reaction.

2.5.1 Synthesis of Morpholine-Type Skeleton Template

With the establishment of catalytic Prins cyclization, we proposed to extend the application to substrates[70] other than homoallylic alcohol. N-allylic-hydroxy amines offer a good model for multiple heteroatomic substrates due to the following reasons.

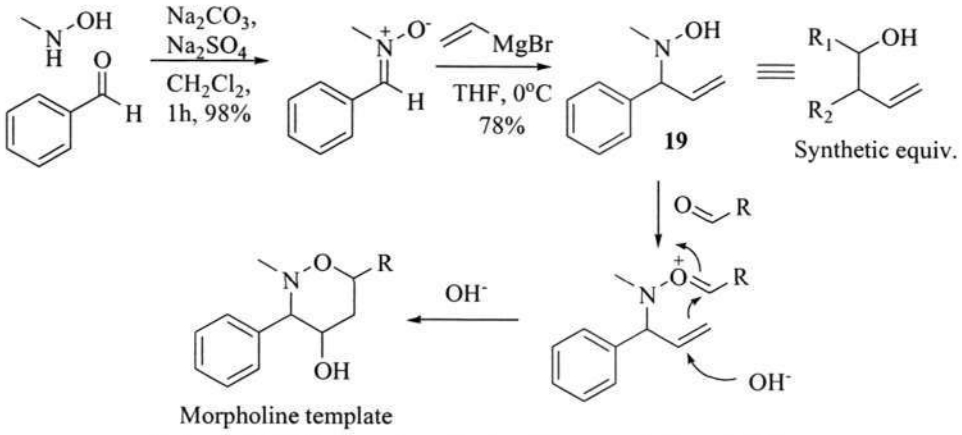
(a) Structurally similar to homoallylic alcohol.

(b) Easily synthesized from commercially available oxime or nitrones *via* vinyl Grignard reaction.

The synthetic plan of the morpholine skeleton was visualized in Scheme 2.21. The N-allylic-hydroxy amine **19** is a direct replicate of a homoallylic alcohol with a nitrogen in place of a carbon vicinal to OH, which can be synthesized from a nitrone

[70] For recent reviews on cyclization to form other heterocyclic structure apart from tetrahydropyran, see (a) Bates, R. W.; Sai-E, K. *Tetrahedron* **2002**, *58*, 5957. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (c) Felpin, F. –X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *19*, 3693. (c) Wijtmans, R.; Vin, M. K. S. Schoemaker, H. E.; Van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, *5*, 641. (d) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379.

with vinylmagnesium bromide. Generation of an oxocarbenium transition state in the presence of Lewis acid followed by trapping with a nucleophile can then afford the morpholine-type template[71].



Scheme 2.21 Proposed synthesis of the morpholine skeleton.

2.6 CONCLUSION

In conclusion, the catalytic Prins cyclization[72] offers several features that are superior to the methods that have been previously reported. The advantages are summarized below:

(a) Catalytic amount of indium Lewis acid;

(b) Heteroatom source from the allylsilane instead of the Lewis acid;

(c) High yields of the crossed Prins cyclized product, including activated and conjugated aldehydes;

(d) High stereoselectivity, with solely the *cis*-isomer of the THP product isolated.

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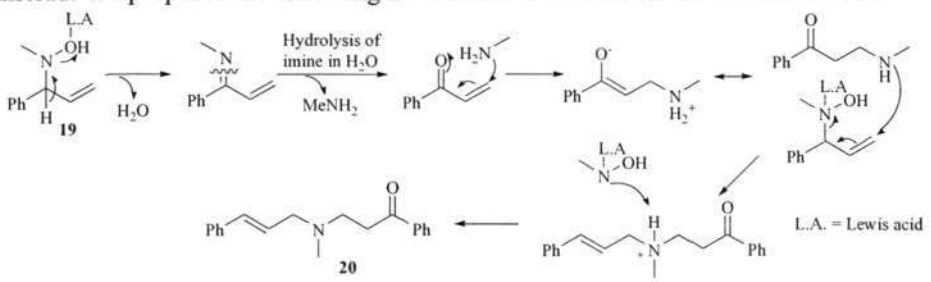
[71] Some trial reactions have been carried out using **19** and $In(OTf)_3$. However, a tertiary amine **20** was isolated instead. We proposed the following mechanism to account for the formation of **20**.



[72] Chan, K. P.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 8387-8390

(e) One-pot crossed Prins cyclization can be achieved without isolating the homoallylic alcohol, yet exercising control such that minimum side products are formed.

Further development on this method to enhance the applicability in natural product synthesis will be discussed in the next chapter.

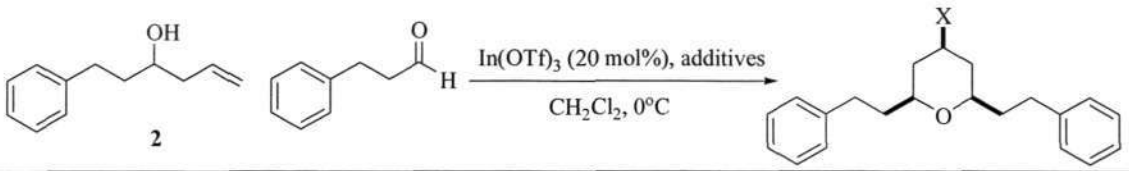
CHAPTER 3

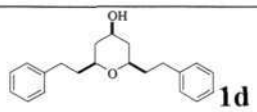
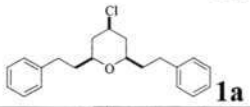
Versatile Synthesis of 4-Halo-2,6-Disubstituted Tetrahydropyran

3.1 IN(OTf)$_3$-CATALYZED PRINS CYCLIZATION USING TRIMETHYLSILYLHALIDE AS ADDITIVE

The work reported in the previous chapter not only provided some valuable insights into the mechanism of catalytic Prins cyclization, but intrigued us to investigate further the feasibility of using external silicon-based nucleophiles to trap the oxocarbenium ion. Since the condensation of aldehyde and homoallylic alcohol occurred in the presence of a Lewis acid, our attention was diverted to expanding the scope of catalytic Prins cyclization by using silicon-based additives to trap the oxocarbenium transition state. A comparison was done to establish the essentiality of additives in Prins cyclization as shown in Table 3.1.

Table 3.1 Catalytic Prins cyclization in various additives.

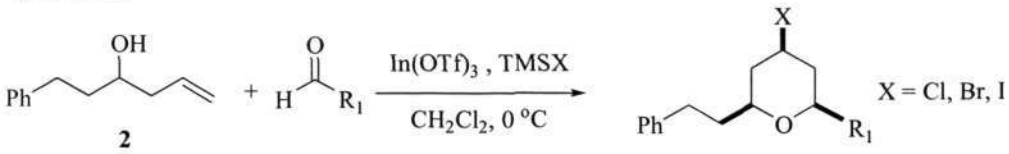


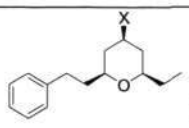
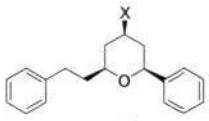
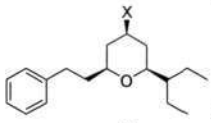
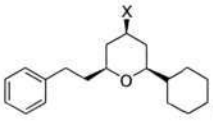
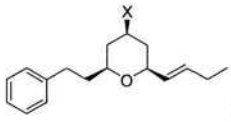
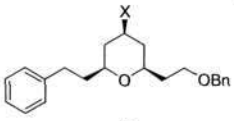
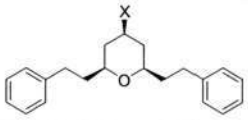
Entry	Additive	Time of reaction (h)	Expected Product	Isolated Product	Yield[a] (%)
1	none	8	 **1d**	**1d**	16
2	TMSCl	1	 **1a**	**1a**	94

[a] A series of experiments have been carried out to optimize the yields for both entries. The best yielding condition was found to be in 0.1 M CH_2Cl_2 solution, with 1.2 equiv of TMSCl at 0 °C.

The importance of trimethylsilylhalide additives in the activation of the reaction is clearly shown in the results obtained. The trimethylsilylhalides seemed to be the very efficient for introducing the heteroatom at the 4-position of the THP ring. The yield of the THP product was low without any additives (entry 1) and the reaction took 24 hours to afford a moderate yield. With this information, we extrapolated the utility of this method to incorporate chloride, bromide and iodide to various aldehydes as tabulated in Table 3.2.

Table 3.2 Versatile synthesis of 4-halo-2,6-trisubstituted tetrahydropyran via catalytic crossed-Prins cyclization



Entry	R_1	Product	Yield (%)		
			a (X = Cl)	b (X = Br)	c (X = I)
1	$-CH_2CH_3$	 **21**	71	76	82
2	-Ph	 **22**	74	82	82
3	$-CH(CH_3CH_2)_2$	 **23**	76	81	91
4	-Cy	 **24**	67	86	89
5	$-CH=CHCH_2CH_3$	 **25**	77	82	83
6	$-(CH_2)_2OBn$	 **26**	61	66	64
7	$-CH_2CH_2Ph$	 **1**	94	83	86

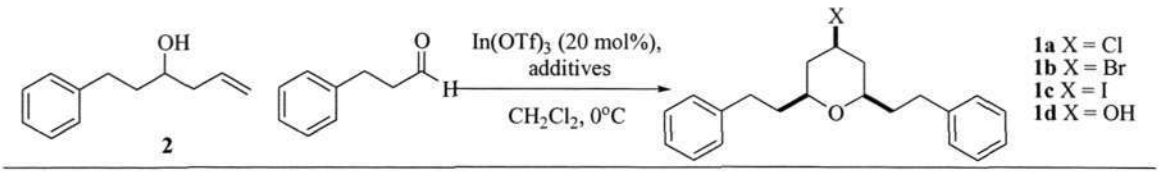
Note: 5% yield of the *meso*- product **1** was obtained in each of the entry 1 to 6. *Meso*- products containing fragments of $\mathbf{R_1}$ were not observed.

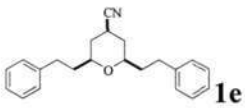
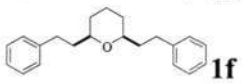
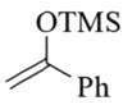
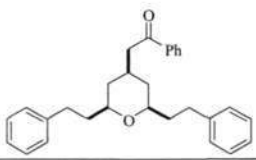
The display of versatility was overwhelming in the results obtained. In all cases, the Prins cyclization with various aldehydes proceeded to form crossed 4-halo-2,6-trisubstituted THP products with moderate to excellent yields. Especially noteworthy is the excellent stereoselectivity observed where only the all-*cis* configuration products were obtained. Furthermore, the reaction was also found to worked well for α,β-unsaturated aldehydes (entry 5) and was insensitive to the steric and electronic influences of the substrates (entries 2 and 3). The trimethylsilyl halide additives served as sources of halides, and have been shown to work well to afford the

corresponding halide containing THP compounds. No remarkable differences in yields of the THP products for the three trimethylsilylhalides were observed.

To extend the scope of this new development, 1-phenylhex-5-en-3-ol, **2**, was subjected to various additives in the presence of catalytic amount of $In(OTf)_3$ to form crossed-Prins cyclized products (Table 3.3). However, the results were rather unsatisfactory, yielding the 4-hydroxy THP ring **1d** instead of the desired products in all cases except for dichlorodimethylsilane (entry 1).

Table 3.3 Prins cyclization using other nucleophiles.



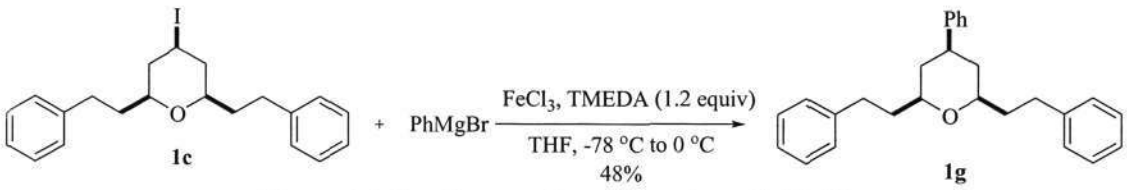
Entry	Additive	Time of reaction (h)	Expected Product	Isolated Product	Yield[a] (%)
1	Me_2SiCl_2	1	**1a**	**1a**	93
2	TMSCN	24	 **1e**	**1d**	5
3	Et_3SiH	24	 **1f**	**1d**	5
4	TEAB	24	**1b**	**1d**	7
5	TBAI	24	**1c**	**1d**	6
6	TBAB	24	**1b**	**1d**	7
7		24		**1d**	3

[a] Entries 2 – 7 were refluxed after TLC analysis showed absence of desired products. In these cases, the starting materials were recovered. No other side products were observed.

3.2 VERSATILE TRANSFORMATION OF 4-HALO-TETRAHYDROPYRAN

3.2.1 $FeCl_3$ Catalyzed C-C Bond Formation

Alkylhalides are important scaffolds used in the synthesis of natural products. They make excellent precursors for functional group interconversion[73] as well as C-C bond formations in coupling reactions[74], rendering a diverse usage of these compounds. As such, selective incorporation of various halides[75] onto the THP ring greatly enhances the synthetic value of catalytic Prins cyclization using trimethylsilylhalides additives. We have demonstrated a novel $FeCl_3$ catalyzed sp^2-sp^3 coupling, separately developed by both Fürstner[76] and Nakamura[77], using 4-iodo-tetrahydropyran **1c** to form 4-phenyl-THP product **1g** (Scheme 3.1).



Scheme 3.1 Coupling reaction of secondary alkyl halide.

3.2.2 De-halogenation of 4-halo-tetrahydropyran

De-halogenation is another widely used reaction in the synthesis of natural products, especially in the formation of the 2,6-disubstituted THP motifs. This usually

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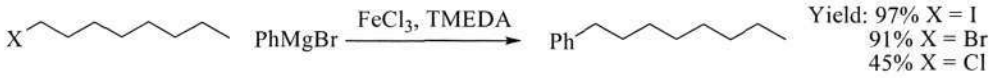
[73] (a) Harton, *Aliphatic Nucleophilic Substitution*; Cambridge University Press: Cambridge, 1973. For reviews, see (b) Katritzky; Brycki, *Chem. Soc. Rev.* **1990**, *19*, 83. (c) Richard, *Adv. Carbocation Chem.* **1989**, *1*, 121. (d) de le Mare; Swedlund, in Patai *The Chemistry of the Carbon-Halogen Bond*, part 1; Wiley: New York, 1973, pp 409-490. (e) Baciocchi, in Patai; Pappoport, *The Chemistry of Functional Groups, Supplement D*, part 2; Wiley: New York, 1983, pp 1173-1227.

[74] For reviews, see (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (d) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

[75] sp^3 bromides and iodides have been reported to provide better yields as compared to chlorides in the iron-catalyzed coupling reactions.

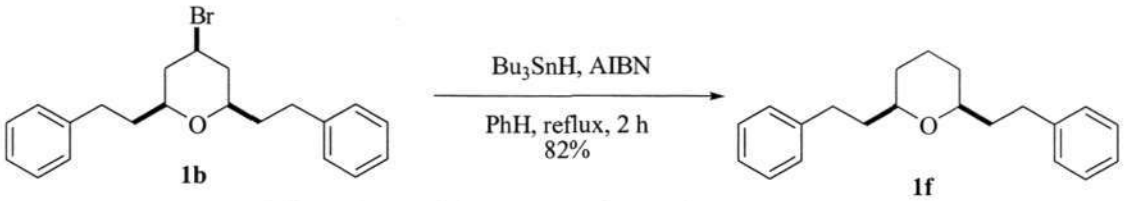


The reaction was also proposed to follow a radical mechanism, thus highlighting the importance of choice of alkyl halide for such reactions.

[76] Furstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624.

[77] Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.

involves a radical mechanism[78] using AIBN as a radical initiator and tributyltinhydride as hydride source (Scheme 3.2). The major drawback of this method is the environmental and safety issues associated with using stannane reagents, especially in scale-up reactions.



Scheme 3.2 De-halogenation of secondary alkyl halide.

In other examples, a nucleophilic hydride[79] (e.g. $NaBH_4$) can be used to displace the halide atom (usually bromide and iodide) directly to form the desired product. However, due to extreme basicity and nucleophilicity, such harsh conditions are usually not widely practiced in natural product synthesis.

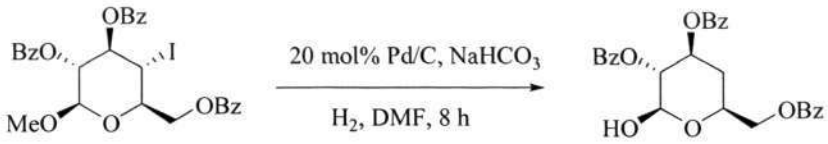
An interesting de-halogenation of iodo-glucose was reported by Kovac[80] using 20% palladium (in carbon) and sodium bicarbonate with hydrogen gas in DMF. Acknowledging this method as a convenient mean to achieve de-halogenation and de-benzylation concomitantly, we attempted to apply this to the 4-bromo-THP ring **1b**. The result was found to be unsatisfactory (Scheme 3.3) using DMF as a solvent. However, the ease of reaction was tremendously alleviated using a MeOH / EtOAc (9:1) solvent mixture, with sequential addition of $NaHCO_3$ followed by further hydrogenation.

[78] For a summary of methods of radical formation, 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.

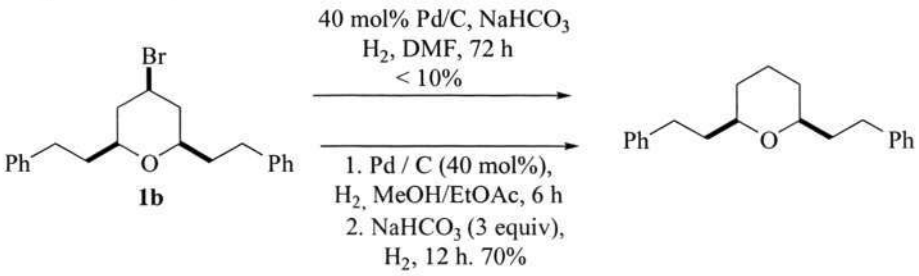
[79] (a) Hutchins, R. O.; Kandasamy, D.; Dux III, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistione, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259. (b) Miranda, L. S. M.; Meireles, B. A.; Costa, J. S. Pereira, V. L. P. ; Vasconcellos, M. L. A. A. *Synlett* **2005**, *5*, 869.

[80] (a) Lin, T. H.; Kovac, P.; Glaudemans, C. P. *Carbohydr. Res.* **1989**, *188*, 228. For other example, see (b) Dyong, I. ; Meyer, W. ; Thiem, J. *Liebigs Annalen der Chemie* **1986**, *4*, 613.

Kovac's dehalogenation procedure



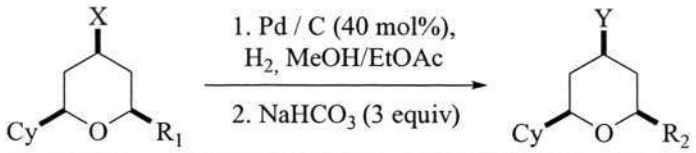
Our attempt on dehalogenation of 4-bromo-THP

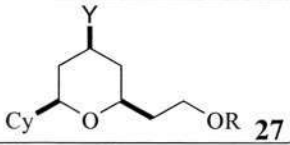
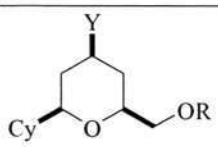
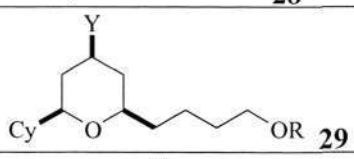
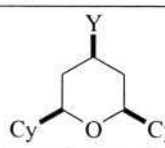
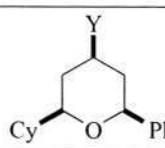


Scheme 3.3 Attempts on de-halogenation of 4-iodo-THP in DMF.

With these intriguing results, the scope of this reaction was extended to other 4-halo-THPs as well as one-pot de-halogenation / de-benzylation reaction (Table 3.4).

Table 3.4 One-pot de-halogenation of cyclic halides.



Entry	X	R_1	Product	Y	R_2	Yield (%)[a]
1	Cl	CH_2CH_2OBn	 **27**	Cl	H	79 (**a**)
2	Br			H	H	92 (**b**)
3	I			H	Bn	74 (**c**)
4	Cl	CH_2OBn	 **28**	Cl	H	65 (**a**)
5	Br			H	H	71 (**b**)
6	I			H	Bn	47 (**c**)
7	Cl	$(CH_2)_4OBn$	 **29**	Cl	H	60 (**a**)
8	Br			H	H	71 (**b**)
9	I			H	Bn	66 (**c**)
10	Cl	Cy	 **30**	Cl	Cy	N.R
11	Br			H	Cy	79
12	I			H	Cy	76
13	Cl	Ph	 **31**	Cl	Ph	N.R
14	Br			H	Ph	66
15	I			H	Ph	59

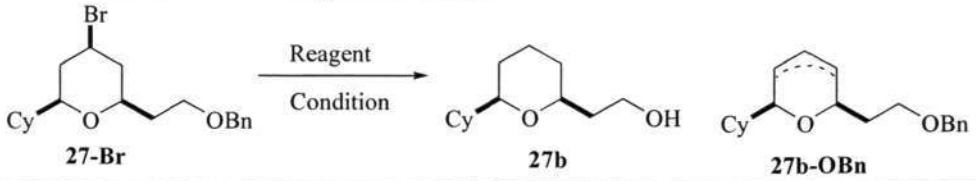
From the results, it was evident that this methodology was highly chemoselective. The chloro-THP substrates were de-benzylated but not de-halogenated (entry 1). On the contrary, the iodo-benzyloxy THPs were de-halogenated, but not de-benzylated (entry 3). The bromo-precursors were consistent with the earlier observations, whereby both de-halogenation and de-benzylation took place. Since hydrogenation should affect only the benzyl-protecting group, we envisaged that a greater distance between the halide and the benzyloxy-group may affect the regio- and chemoselectivity of the reaction. Therefore we conduct base-mediated hydrogenation experiments on different benzyloxy-substrates (entries 4 to 9). It was found that the proximity of the benzyloxy-group varied by chain length exerted no effect on the chemoselectivity of the products. It can be concluded that in the presence of an iodo- moiety on the 4-position of the THP, the molecule can be selectively de-halogenated without affecting the benzyl-protecting group.

The same phenomenon was observed in the cyclohexyl (entries 10 to 12) and phenyl (entries 13 to 15) moieties, with the 4-chloro-THP unaffected by the one-pot base-mediated palladium-catalyzed de-halogenation reaction. Such chemoselective reaction complemented our development of the TMSX-mediated Prins cyclization, where versatile incorporation of the halide on 4-position of the THP ring can now be selectively reduced in the presence of other functionality. This interesting finding not only allows one-pot de-bromination / de-benzylation reaction to obtain dehalo-THP products cleanly in a reasonable yield without the use of toxic stannane reagents, but more importantly, establishes groundwork for future endeavors in total synthesis of natural products.

This hydrodehalogenation protocol has shown that the equatorial halide can be removed in a basic environment, which defies the conventional *anti*-periplanar

conformational prerequisite base-mediated elimination pathway. A study was carried out to investigate on the mechanism of this reaction (Table 3.5).

Table 3.5 De-bromination / De-benzylation methods



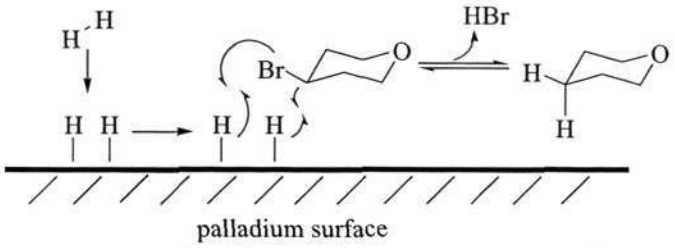
27-Br 27b 27b-OBn

Entry	Reagent	Condition	Yield (%)[a]	
			27b	27b-OBn
1	1. Pd / C (30 mol%), H_2, MeOH / EtOAc, 2. $NaHCO_3$, followed by further hydrogenation	25 °C, 18 h	89	N.R.
2	1. Pd / C (30 mol%), H_2, MeOH / EtOAc, 2. KOH[a], followed by further hydrogenation	25 °C, 18 h	91	N.R.
3	DBU, PhMe	reflux, 24 h	N.R.[b]	N.R.
4	KOH, THF	reflux, 24 h	N.R.	N.R.
5	Pd / C (40 mol%), $NaHCO_3$, MeOH / EtOAc	25 °C, 96 h	N.R.	N.R.
6	$NaHCO_3$, activated carbon, MeOH / EtOAc	25 °C, 48 h	N.R.	N.R.

[a] Another experiment was done with 4-chloro-benzyl-THP **27** using hydrogenation in KOH. It was found that the chloride remained intact, forming **27a**. This shows that the strength of base used has no apparent effect on de-halogenation of chloro-THP. [b] N.R. denotes no observable reaction.

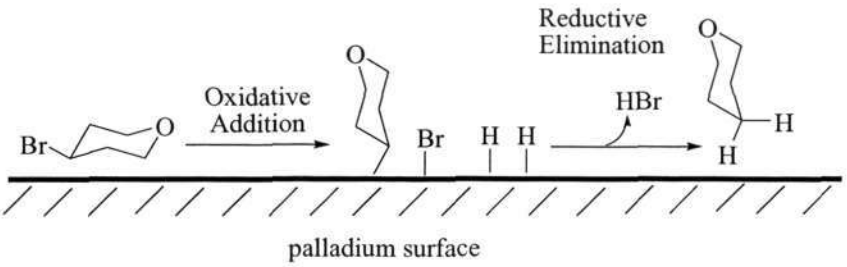
It can be concluded that the reaction was insensitive to the type of base used (entries 1 and 2). In the attempt to investigate the pre-requisition of an axial-halide, both DBU and KOH also failed to afford the elimination product **27b-OBn**, indicating the need of the *anti*-periplanar conformation for elimination reaction (entries 3 and 4). Further attempts to investigate the mechanism of dehalogenation in 4-bromo-THP ring indicated that both palladium and hydrogen are critical in the elimination of the halide, and that hydrogen is critical in initiating the dehalogenation reaction (entries 5 and 6).

Based on this information, a plausible explanation for this unusual phenomenon has been proposed. Upon adsorption of molecular hydrogen on the palladium surface, there could be an atom exchange process *via* a single electron transfer mechanism. This resulted in the formation of the dehalogenated THP product upon concurrent removal of HBr in the presence of a base (Scheme 3.4).



Scheme 3.4 Proposed mechanism for non-*anti*-periplanar elimination.

An alternative mechanistic possibility would involve an oxidative addition of palladium(0) to the C-Br bond, followed by a reductive elimination to afford the dehalogenated THP product (Scheme 3.5). However, it has been known that oxidative addition to a secondary C-Br bond is usually very slow, which probably explained the need of a high catalyst loading (40 mol%) in this reaction.



Scheme 3.5 Alternative proposed mechanism *via* oxidative addition / reductive elimination pathway.

3.2.3 Concluding Remark

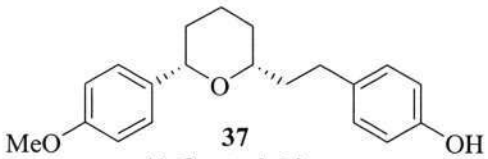
The application of the versatile Prins cyclization using trimethylsilylhalides have been demonstrated in the coupling reaction (Chapter 3.2.1) and stannane-free

hydrodehalogenation reaction[81]. The versatile incorporation of halides on THP moieties will have potential application values in the realm of natural product synthesis. Investigation of milder sources (e.g inorganic salts) of introducing the heteroatom at on the THP ring is in progress.

3.3 APPLICATION OF CATALYTIC PRINS CYCLIZATION USING TRIMETHYLSILYLHALIDES AS ADDITIVES: TOTAL SYNTHESIS OF (-)-CENTROLOBINE

3.3.1 Introduction to (-)-Centrolobine

(-)-Centrolobine **37** is a natural product isolated from the heartwood of *Centrolobium robustum*[82] and from the stem of *Brosinum potabile*[83] in the Amazon forest.



37
(-)-Centrolobine

Figure 3.1 Structure of (-)-Centrolobine.

It is a diarylheptanoid[84] which exhibits antimicrobial activity and possibly anti-leishmanial[85] effects. It has a simple structure consisting of a *cis*-2,6-disubstituted tetrahydropyan backbone with two phenolic moiety (Figure 3.1). Although its basic structure was elucidated in 1964 from the total synthesis of the racemic methyl ether, its absolute configuration had not been unequivocally established until 2002, when

[81] The other functional groups have been omitted for clarity purposes. HBr was quenched by excess $NaHCO_3$. For report on this methodology, see Chan, K. P.; Ling, H. Y.; Chan, L. T. J.; Loh, T. P. *J. Org. Chem.* **2007**, in press.

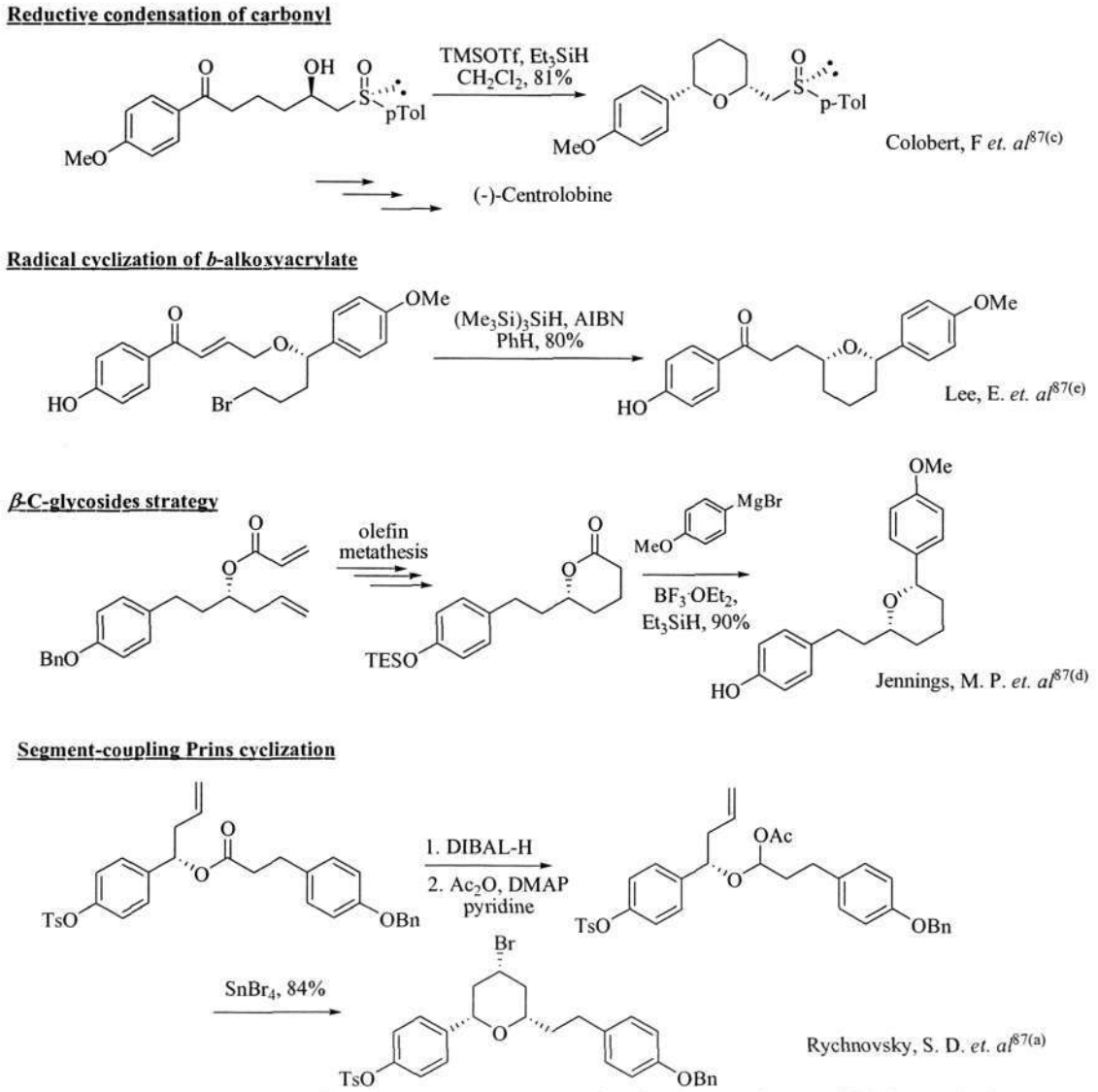
[82] (a) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1964**, 287. (b) Galeffi, C.; Casinovi, C. G.; Marini-Bettolo, G. B. *Gazz. Chim. Ital.* **1965**, 95. (c) Aragao Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson deAlbuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869.

[83] Alcantara, A. F. de C.; Souza, M. R.; Pilo´-Veloso, D. *Fitoterapia* **2000**, *71*, 613.

[84] Alegrio, L. V.; Braz-Filho, R.; Gottlieb, O. R. *Phytochemistry* **1989**, *28*, 2359.

[85] Araujo, C. A. C.; Alegrio, L. V.; Leon, L. L. *Phytochemistry* **1998**, *49*, 751.

Colobert[86] reported the first enantioselective total synthesis. To date, many strategies have been published towards both the racemic[87] and enantioselective[88] synthesis of Centrolobine (Scheme 3.6).



Scheme 3.6 Key strategies of representative enantioselective syntheses of (-)-Centrolobine.

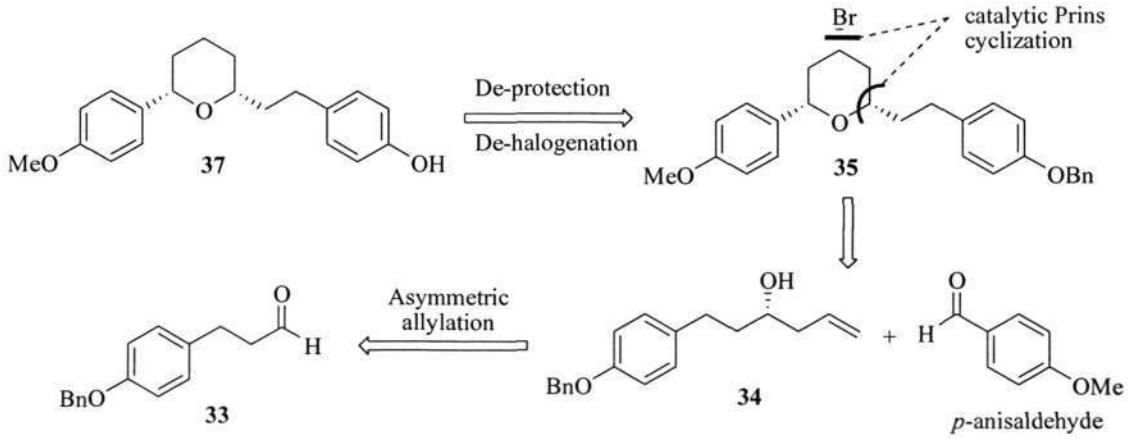
[86] Colobert, F.; Des Mazery, R.; Solladie´, G.; Carreno M. C. *Org. Lett.* **2002**, *4*, 1723-1725.

[87] (a) Clarke, P.A.; Martin, W. H. C.; *Tetrahedron Lett.* **2004**, *45*, 9061. (b) Sabitha, G.; Reddy, K. B.; Reddy, G. S. K. K.; Fatima, N.; Yadav, J. S. *Synlett*. **2005**, *15*, 2347.

[88] (a) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (b) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883. (c) Colobert, F.; Mazery, R. D.; Solladie, G.; Urbano, A.; Carreno, M. *Org. Lett.* **2002**, *4*, 1723. (d) Jennings, Michael P.; Clemens, Ryan T. *Tetrahedron Lett.* **2005**, *46*, 2021. (e) Lee, E.; Kim, H. J.; Jang, W. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1609. (f) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadere, B. *Tetrahedron Lett.* **2004**, *45*, 6603.

3.3.2 Retrosynthetic Analysis of (-)-Centrolobine

Our objective was to demonstrate the applicability of our newly developed catalytic Prins cyclization for the total synthesis of natural products. From (-)-Centrolobine **37**, a synthetically viable intermediate **35**, can be easily derived with benzylic deprotection and de-halogenation (Scheme 3.7). The key step exploited the convergent nature of Prins cyclization to construct the tetrahydropyran backbone from a homoallylic alcohol **34** and *p*-anisaldehyde.



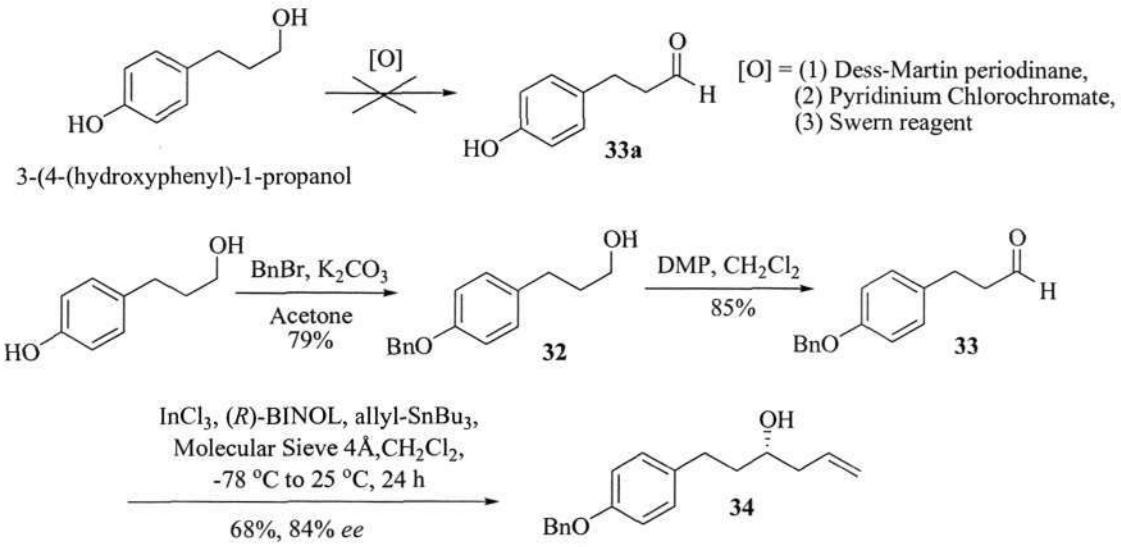
Scheme 3.7 Retrosynthesis of (-)-Centrolobine.

The aldehyde is commercially available and homoallylic alcohol **34** can be synthesized from aldehyde **33** *via* an asymmetric allylation reaction. The overall plan depicted a short, convergent and convenient enantioselective synthesis of (-)-Centrolobine.

3.3.3 Total Synthesis of (-)-Centrolobine

An ambitious attempt to synthesize **33a** directly from 3-(4-hydroxyphenyl)-1-propanol (Scheme 3.8) failed with various types of oxidation. The unprotected phenolic moiety was easily oxidized to quinone-type products which degraded almost instantaneously upon working up. Hence benzyl protection of the phenolic moiety

was absolutely necessary and was carried out using K_2CO_3 and benzylbromide[89] in acetone. The chemoselective reaction yielded 79% of the benzyl protected alcohol **32**, which was followed by Dess-Martin[90] oxidation to afford 85% of the aldehyde intermediate **33**.



Scheme 3.8 Synthesis of key intermediate **34**.

Although there are several methods to perform asymmetric allylations on aldehydes[91], indium catalyzed asymmetric allylation on aldehyde has not been widely developed and applied. With our group's vast experience in this arena[92], special interest was directed to the newly developed BINOL-$InCl_3$ system[93], attributing to the

[89] (a) Venuti, M. C.; Loe, B. E.; Jones, G. H. ; Young, M. *J. Med. Chem.* **1988**, *31*, 2132. (b) Kotecha, N. R.; Ley, S. V.; Montéganni, S. *Synlett* **1992**, 395. (c) Schmidhammer, H. ; Brossi, A. *J. Org. Chem.* **1983**, *48*, 1469.

[90] (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

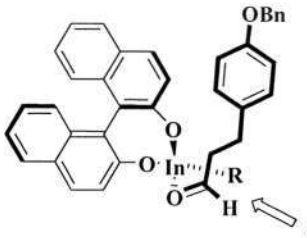
[91] For a review of enantioselective addition of allylic organometallic reagents to carbonyls, see (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763 and references therein. For representative examples, see (b) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (c) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (d) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (e) Ito, H.; Tanikawa, S.; Kobayashi, S. *Tetrahedron Lett.* **1996,** *37*, 1795. (f) Schreiber, S.; Groulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (f) Corey, E. J.; Yu, C. –M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

[92] (a) Loh, T. P.; Zhou, J. R. *Tetrahedron Lett.* **2000**, *41*, 5261. (b) Loh, T. P.; Zhou, J. R.; Zheng, Y. *Org. Lett.* **1999**, *1*, 1855. (c) Loh, T. P.; Zhou, J. R.; Li, X. R. *Tetrahedron Lett.* **1999**, *40*, 9115. (d) Teo, Y. C.; Goh, J. D.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2743. Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 159. (e) Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 5819.

[93] Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 1318.

high yielding, excellent enantioselectivities, and relative ease of use and compatibility on a variety of substrates. Aldehyde **33** was treated with $InCl_3$ / (*R*)-BINOL in allyltributyltin at -78 °C to afford homoallylic alcohol **34** with 61% yield and 84% enantiomeric excess (Scheme 3.8).

Subjecting homoallylic alcohol **34** and *p*-anisaldehyde to a catalytic amount of $In(OTf)_3$ in trimethylsilylbromide at 0 °C yielded 88% of the desired Prins cyclized product cleanly. However, a selectivity leakage was observed whereby the enantiomeric excess of the 4-bromo-THP product **35** decreased by 8% from the expected 84% *ee* to 76% *ee*. Such level of racemization[94] is consistent with the investigation on suppression of epimerization due to selectivity leakage[95] which our group has pioneered. From our previous work[96] on allyl-transfer mechanism, we were aware that the allylic fragment could be transferred to *p*-anisaldehyde, forming the corresponding homoallylic alcohol **38** (Scheme 3.9).

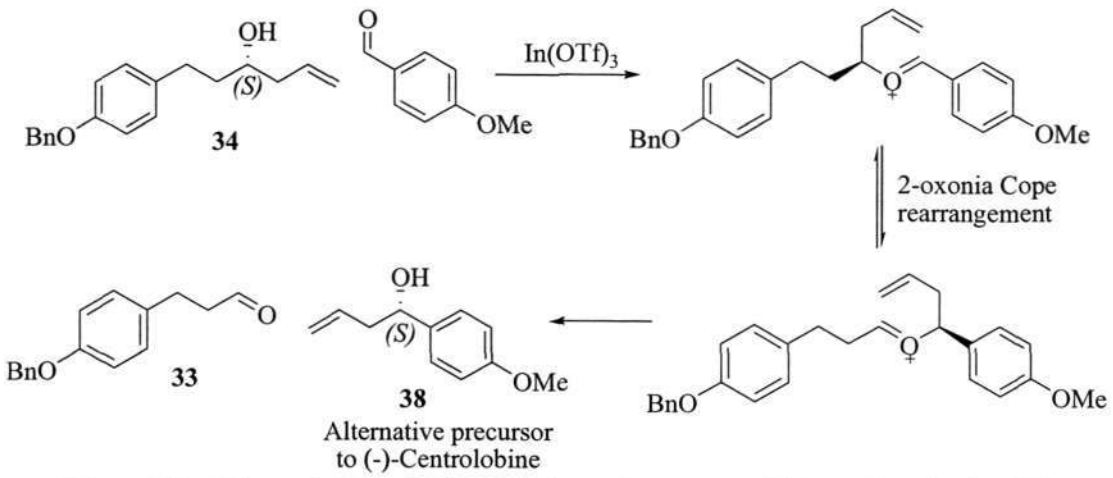


Postulated transition state in BINOL-In catalyzed asymmetric allylation.

[94] For reviews on racemization, see (a) Tanner, M. E. *Acc. Chem. Res.* **2002**, *35*, 237. (b) Huerta, F. F.; Minidis, A. B. E.; Baeckvall, J. *Chem. Soc. Rev.* **2001**, *30*, 321. (c) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417. For specific racemization of allyalcohols, see (d) Hussain, I.; Komasaka, T.; Ohga, M.; Nokami, J. *Synlett* **2002**, *4*, 640.

[95] Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 1641.

[96] (a) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (b) Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 5819. (c) Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 809. (d) Loh, T. P.; Lee, C. L. K.; Tan, K. T. *Org. Lett.* **2002**, *4*, 2985.

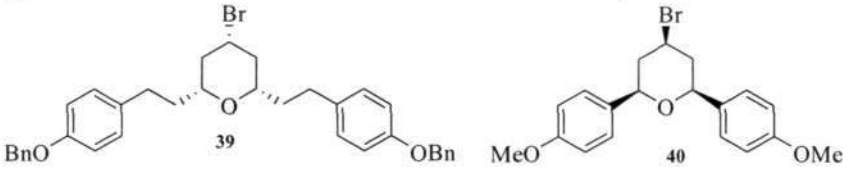


Scheme 3.9 Allyl-transfer from **34**, forming alternative precursor **38** to total synthesis of (-)-Centrolobine.

However, the chirality should be correctly induced since only *syn*- isomer can be formed in the chair-like transition state. Unless the aldehyde adopted a highly unfavorable axial position in the transition state, the allyl-transfer would result in the correct stereoisomeric precursor for the synthesis of (-)-Centrolobine. Furthermore, the mere difference of 8% in enantiomeric excess signified that direct Prins cyclization was still the dominant process. From these observations, we embarked on the investigation of the racemization mechanism in our methodology.

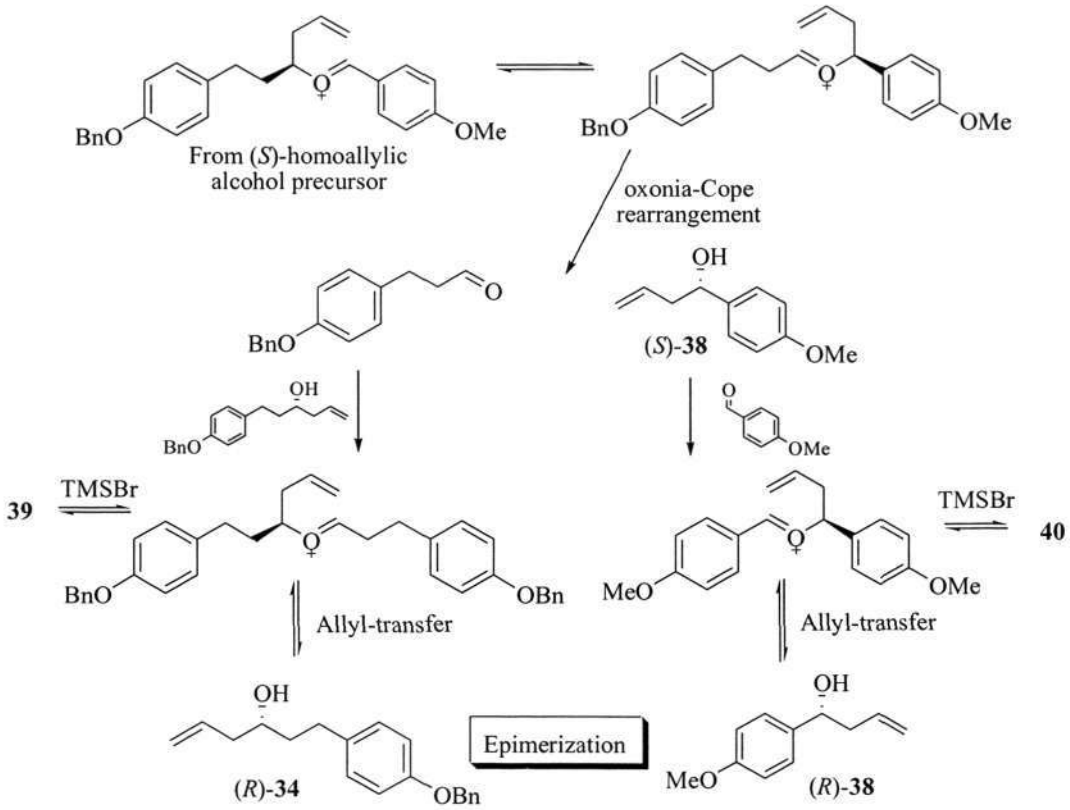
A very small amount (<10%) of both the *meso*-THP products[97] containing 4-benzoxy fragment **39** and the *p*-methoxyphenyl fragment **40** were isolated from the crude product. Such species indicated spontaneous formation of subsidiary oxocarbenium ions with the corresponding aldehydes (**33** and *p*-anisaldehyde). Hence we envisage that the chirality leakage could be due to a double allyl-transfer process *via* a 2-oxonia Cope rearrangement[98] mechanism. Two competing pathways were

[97] The trapping of oxocarbenium ion in Scheme 3.9 will lead to *meso*-products **39** and **40** respectively.



[98] For other examples of oxonia-Cope rearrangement, see (a) Jung, S. Y.; Min, J. H.; Oh, J. T.; Koo, S. *J. Org. Chem.* **2006**, ASAP. (b) Chen, Y. H.; McDonald, F. E. *J. Am. Chem. Soc.* **2006**, *128*, 4568. (c) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939. (d) Crosby, S. R.;

proposed (Scheme 3.10); (1) concerted trapping of oxocarbenium ion with TMSBr, and (2) allyl-transfer to the corresponding aldehyde resulting in epimerization of **34** and **38**. The latter pathway could have proceeded very much faster before the oxocarbenium ion can be trapped with an external halide source such as TMSBr.

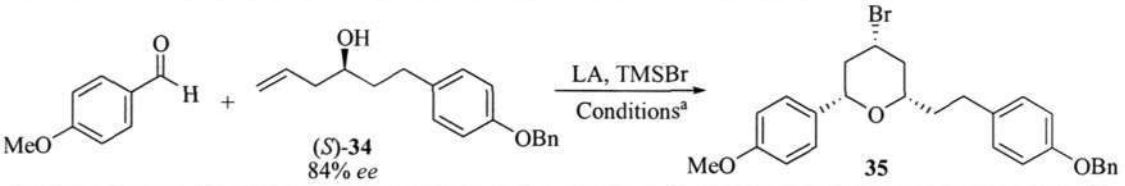


Scheme 3.10 Proposed racemization mechanism in Prins cyclization.

Therefore, the focus was directed towards developing ways to suppress the epimerization process. We postulated that the differential rate of the two competing pathways can be attenuated by thermodynamic or kinetic control of reaction conditions and the choice of Lewis acid. Homoallylic alcohol **34** was thus subjected to Prins cyclization under various conditions as shown in Table 3.6.

Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577. (e) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (f) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 4990.

Table 3.6 Model studies towards epimerization suppression in Prins cyclization.



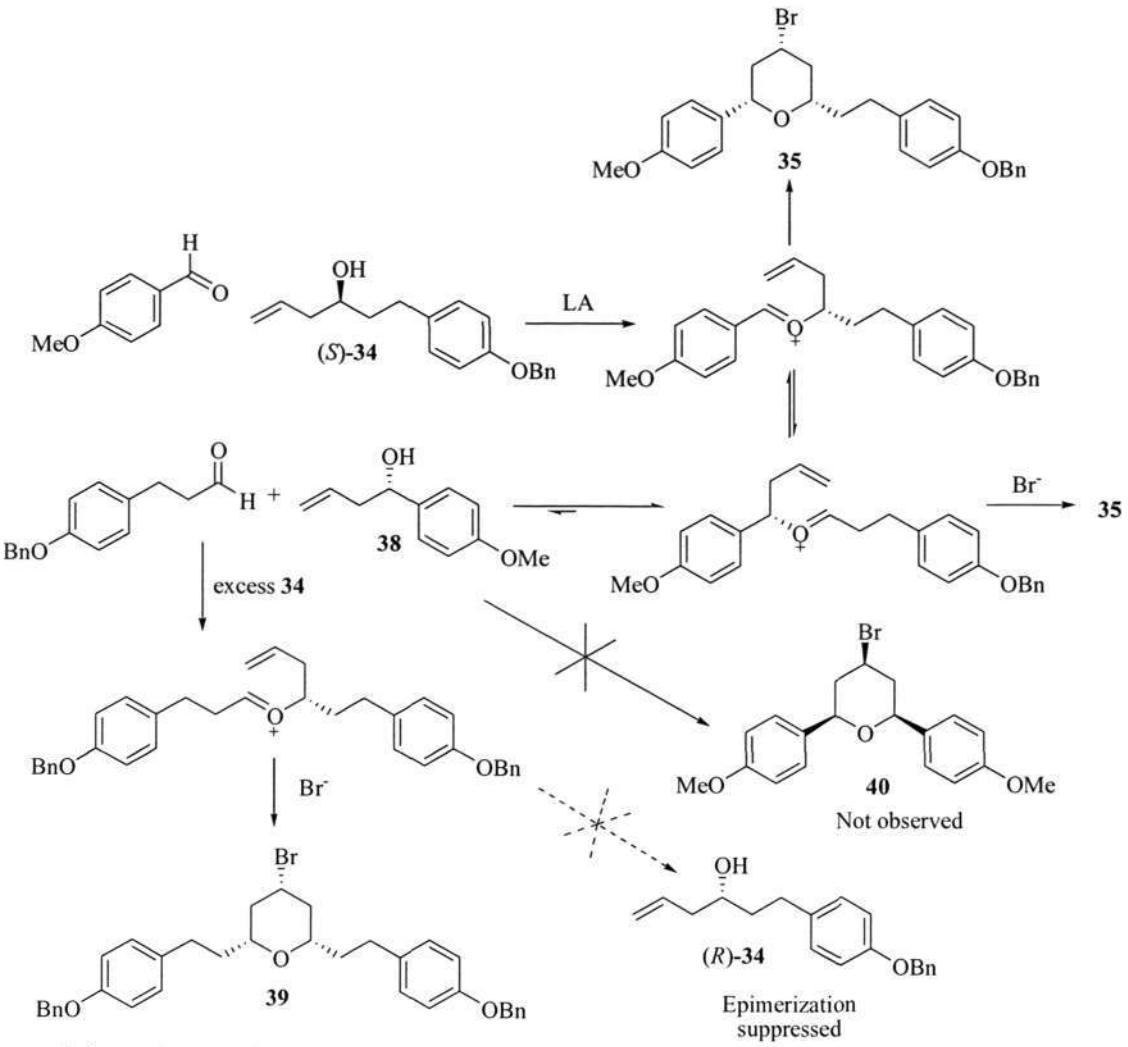
Entry	L.A. (equiv)[a]	TMSBr[b] (equiv)	Temp. (°C)	Time (h)	Yield (%)	*Ee*[c] (%)
1	$In(OTf)_3$ (0.2)	1.2	0	2	88	76
2	$In(OTf)_3$ (0.05)	1.2	-78	1	87	78
3	$In(OTf)_3$ (0.05)	2.5	0	1	72	76
4	$InBr_3$ (0.1)	1.2	0	1	88	79
5	**$InBr_3$ (0.1)**	**1.2**	**-78**	**1**	**83**	**84**

[a] Amount equivalent of Lewis acid in the reaction with respect to *p*-anisaldehyde. [b] Amount equivalent of TMSBr in the reaction with respect to *p*-anisaldehyde. [c] The reactions were carried out with the alcohol (1-(4-(benzyloxy)phenyl)hex-5-en-3-ol) with 84% *ee*.

Several conclusions could be drawn from the study. It was found that reduction in both temperature and catalyst loading failed to suppress epimerization. Using an increased amount of TMSBr in the reaction mixture to hasten the trapping of oxocarbenium ion also failed to retain the enantiomeric purity. However, with a weaker Lewis acid like $InBr_3$ at -78 °C, we were able to achieve comparable yield with complete retention of enantiomeric purity after the reaction. It can be concluded that Lewis acidity and temperature must have played an important role in reducing the rate of epimerization.

In all the experiments, approximately 5% of the *meso*-THP product **33** was obtained after purification. No formation of (*R*)-**34** and **40** were observed. It was obvious that the allyl transfer process has taken place with absolute chirality transfer to *p*-anisaldehyde, forming **38**. Since the rate of allyl transfer has been completely

retarded, asymmetric Prins cyclization became the dominant process, accomplished with complete retention of *ee* (Scheme 3.11). This study thus provided a valuable insight into the characteristics of the oxocarbenium species in Lewis acid mediated reactions. Most importantly, however, the surmounting of this second key step in our efforts towards the synthesis of (-)-Centrolobine allowed us to realize our synthetic strategy. Therefore, we proceeded with the synthesis of (-)-Centrolobine in accordance with our retrosynthetic plan (Scheme 3.7).



Scheme 3.11 Mechanistic interpretation of catalytic Prins cyclization without epimerization.

Another notable advantage of this novel catalytic Prins cyclization is that the use of indirect methods to generate the oxocarbenium intermediate can be avoided. As

compared to the method developed by Rychnovsky[99], this route offered a much more convergent strategy without engaging DIBAL-H reduction to form the acetoxy intermediate (Scheme 3.5). Such advantage is clearly visible in the total synthesis of many natural products where a plethora of ester protecting groups is very common. A more elaborate application of this novel methodology is demonstrated in the total synthesis of (+)-SCH 351448 which is described in Chapter 5 of this thesis.

With the formation of the 4-bromo-2,6-disubstituted intermediate **35**, we proceeded with radical de-halogenation[100] using 1,1'-azobis(cyclohexane) carbonitrile[101] (ACCN) as an initiator and tributyltinhydride to form the de-halogenation THP ring **36** with a 98% yield. This was followed by treatment of hydrogen in Pd/C[102] to yield (-)-Centrolobine **37** with 71% yield and 84% *ee*. The overall yield from the commercially starting material of 3-(4-hydroxyphenyl)-1-propanol was 26%, with complete retention of enantiomeric purity from the homoallylic alcohol intermediate (Scheme 3.12).

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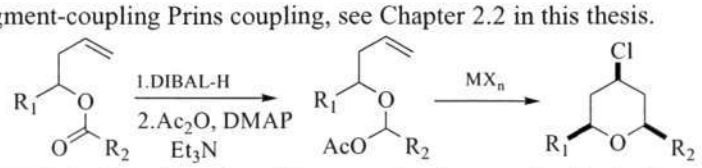
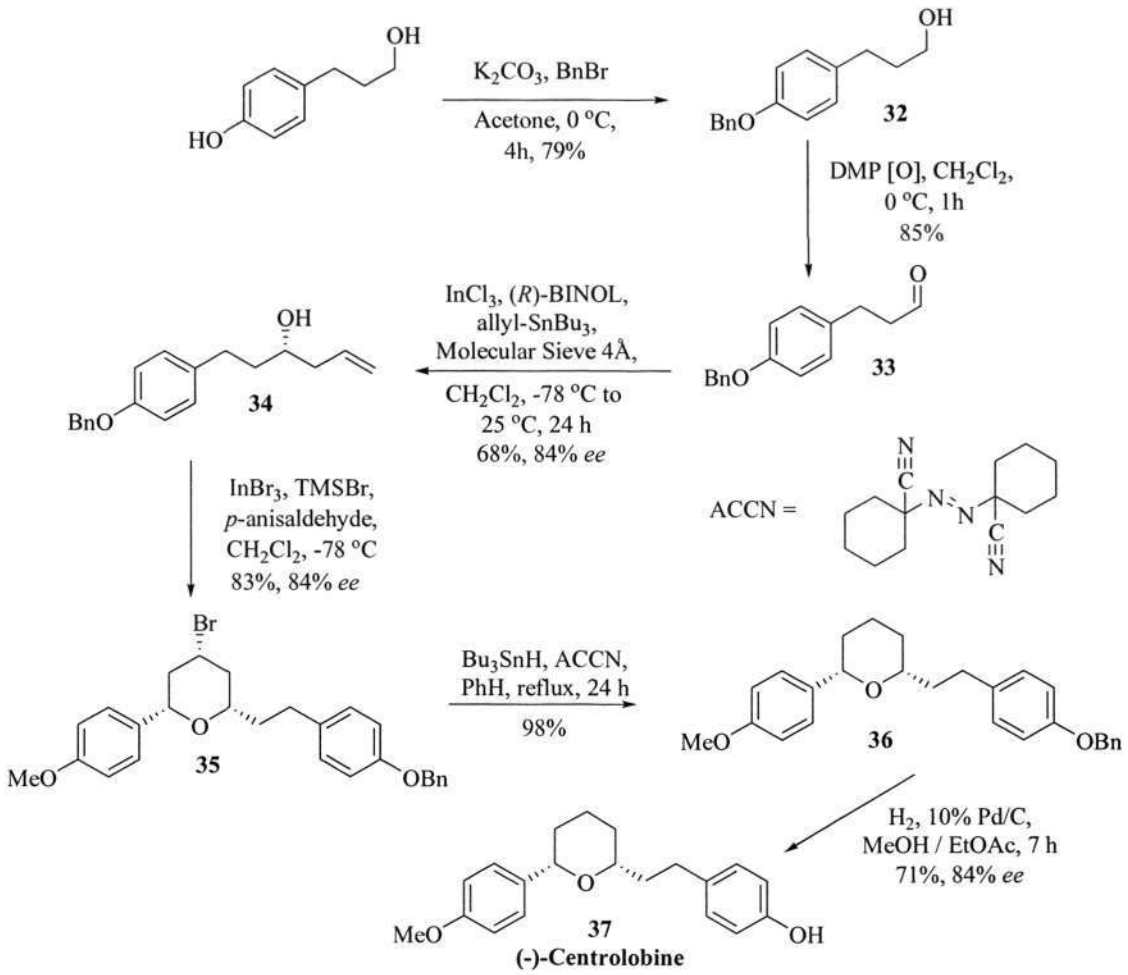
[99] For details in segment-coupling Prins coupling, see Chapter 2.2 in this thesis.



[100] (a) RajanBabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*: Paquette, L.; Ed.: Wiley: New York, **1995**, *7*, 5016. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Curran, D. P. *Synlett* **1991**, 63. (d) Glese, B.; *Radicals in Organic Synthesis*: *Formation of Carbon-Carbon Bonds*; Pergamon, New York, **1986**.

[101] ACCN is a synthetic equivalent of AIBN. Some examples of use were (a) Taniguchi, T.; Iwasaki, K.; Uchiyama, M.; Tamura, I.; Ishibashi, H. *Org. Lett.* **2005**, *7*, 4389. (b) McLoughlin, P. T. F.; Clyne, M. A.; Aldabbagh, F. *Tetrahedron*, **2004**, *60*, 8065. (c) Bacqué, E.; Pautrat, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 325. (d) Cassayre, J. ; Gagosz, F. ; Zard, S. Z. *Angew. Chem. Int. Ed.* **2002**, *41*, 1783.

[102] King, A. O.; Larsen, R. D.; Negishi, E.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*, **2002**, *2*, 2719.



Scheme 3.12 Total synthesis of (-)-Centrolobine.

3.4 CONCLUSION

A versatile, catalytic Prins cyclization[103] using trimethylsilylhalides as additives have been successfully developed. This direct condensation of homoallylic alcohol and aldehyde offers a convergent strategy in the formation of the tetrahydropyran skeleton of numerous natural products. Combined with the versatility of incorporating differing heteroatoms in the 4-position, this methodology exhibits diverse substrate compatibility and also addresses the problem of racemization in Prins cyclization. Its applicability have been demonstrated in the total synthesis of (-)-Centrolobine. This 6-step synthesis from commercially available starting material

[103] Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491.

afforded the natural product in an overall yield of 26% with complete retention of stereochemistry.

CHAPTER 4

Anti-Prins Cyclization

4.1 INTRODUCTION

The topic of Prins cyclization has been centered on the formation of *cis*-2,4,6-trisubstituted tetrahydropyranyl compounds. However, there are many natural products possessing the *anti*-2,6-tetrahydropyran backbone (Figure 4.1). These compounds exhibit potent cytotoxicity, making them attractive synthetic targets for organic chemists.

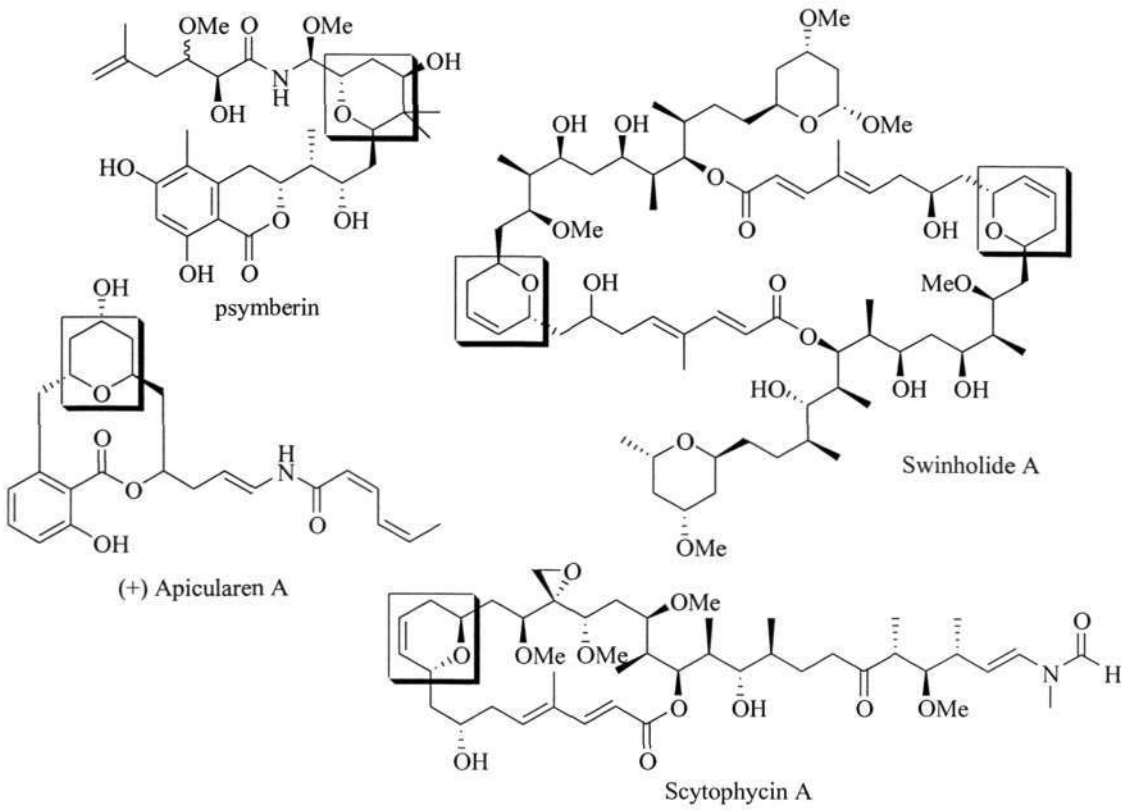


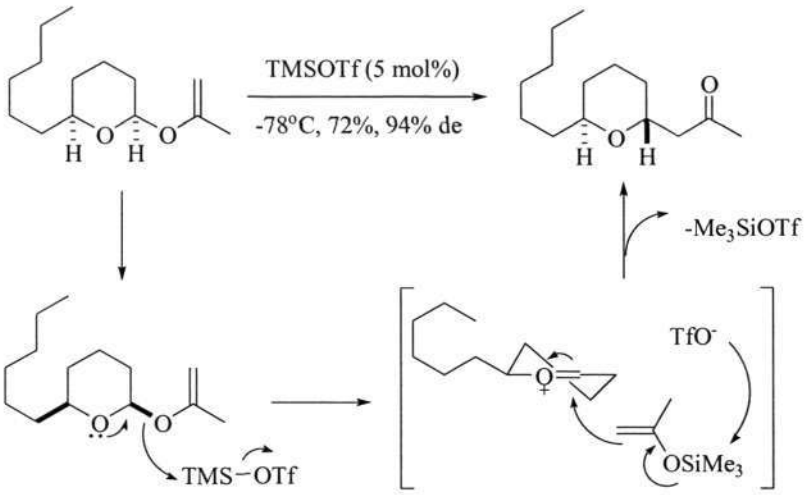
Figure 4.1 Natural products with 2,6-*anti*-tetrahydropyran framework.

4.2 GENERAL METHODS IN THE SYNTHESIS OF 2,6-*ANTI*-TETRAHYDROPYRAN

4.2.1 Isomerization of Cyclic Acetals

Several methods have been developed to form *anti*-2,6-disubstituted tetrahydropyran ring. Isomerization of 2,6-*syn*-tetrahydropyranyl enol ether under acidic conditions at low temperature can afford the *anti*-isomer in satisfactory yield

and excellent diastereomeric excess as demonstrated by Ley[104] (Scheme 4.1). Addition of TMSOTf activates the leaving group leading to the formation of an oxocarbenium ion and a silyl enol ether *in situ*. These components recombine kinetically to afford the *anti*-keto-tetrahydropyran product.



Scheme 4.1 Isomerization of 2,6-syn-tretrahydropyranyl enol ether.

It has been well reported[105] that carbohydrate derivatives undergo alkylation easily with preferential formation of the axial isomer in the presence of a Lewis acid and a soft nucleophilic agent (e.g. allyltrimethylsilane). In a recent example, Markó[106] has demonstrated a rapid assembly of highly substituted 2,6-*anti*-tetrahydropyran using isomerization of epimers in TMSOTf and allylsilane to yield the 2,6-*anti*-isomer exclusively in the synthesis of amphidinol 3[107] (Scheme 4.2).

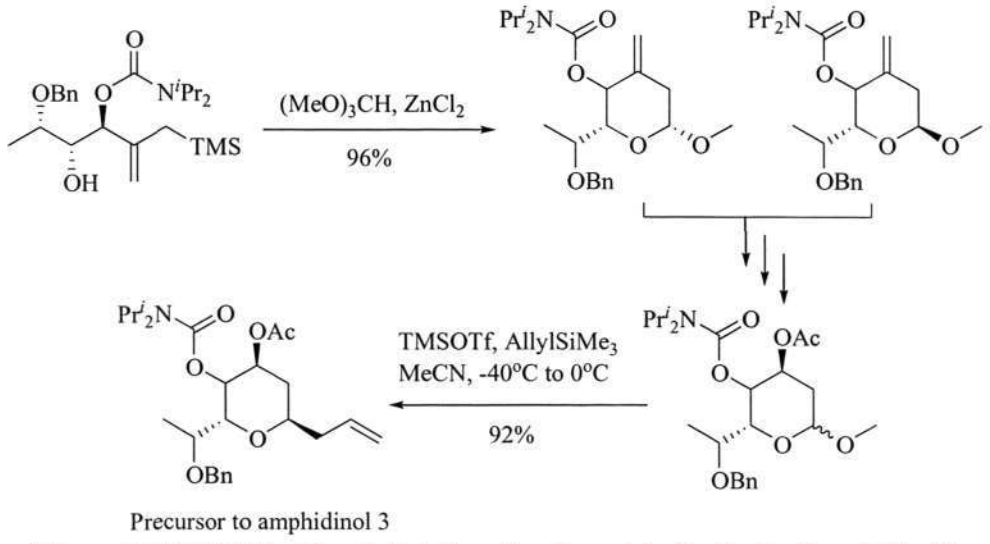
---

[104] (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.

[105] (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. (f) Berry, C. R.; Rameshkumar, C.; Tracey, M. R.; Wei, L. –L.; Hsung, R. P.; *Synlett* **2003**, *6*, 791.

[106] Dubost, C. ; Markó, I. E. ; Bryans, J. *Tetrahedron Lett.* **2005**, *46*, 4005.

[107] For other examples of synthesis of amphidinol 3, see (a) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509. (b) Chang, S. K. ; Paquette, L. A. *SynLett* **2005**, *19*, 2915. (c) BouzBouz, S. ; Cossy, J. *Org. Lett.* **2001**, *3*, 1451.



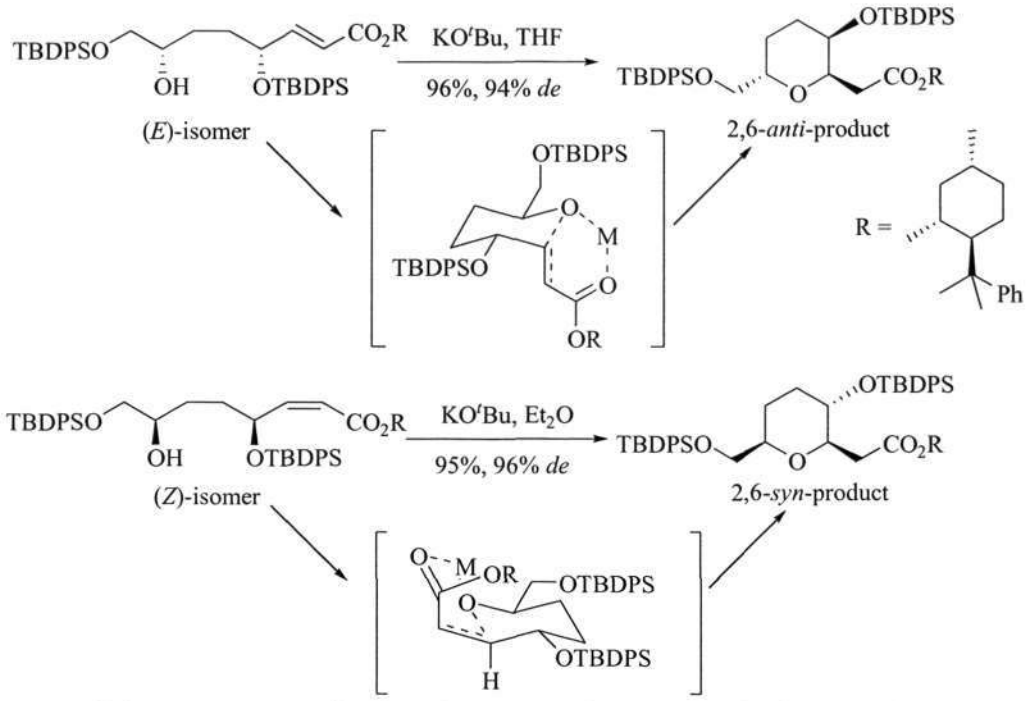
Precursor to amphidinol 3

Scheme 4.2 TMSOTf catalyzed allylation of cyclic acetals: Synthesis of amphidinol 3.

4.2.2 Stereochemical-controlled Cyclization

Intramolecular cyclization of hydroxy-alkene or hydroxyl-epoxide to form 2,6-disubstituted tetrahydropyran has been discussed in Chapter 1 in this thesis. As demonstrated by Rein[108], base mediated Michael type cyclization of (*E*)-hydroxy-acrylate affords the anti-isomer with excellent diastereoselectivity (Scheme 4.3). The acrylate group adopts an axial position in the favorable chair-like transition state as such to enhance maximum chelating effect with the metal counter ion (K^+). On the other hand, the (*Z*)-isomer is confined to the equatorial position leading to the corresponding 2,6-syn-product.

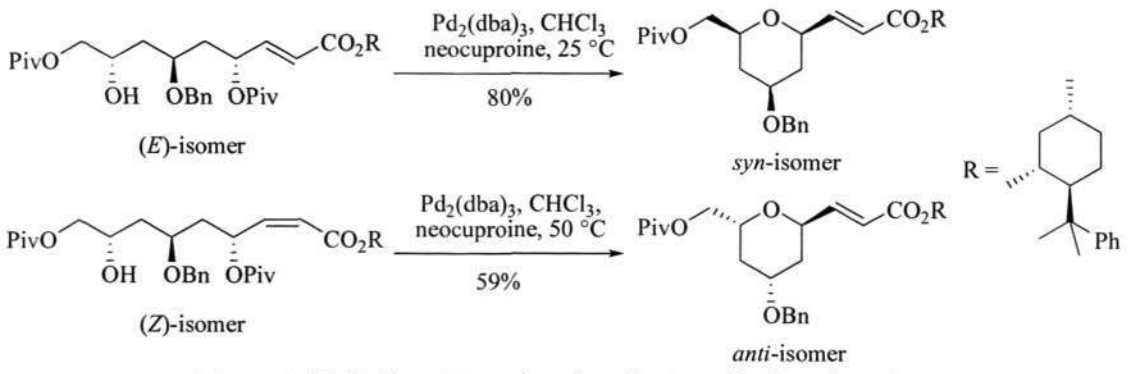
[108] Vares, L. ; Rein, T. *J. Org. Chem.* **2002**, *67*, 7226.



Scheme 4.3 Base mediated Michael type cyclization of (*E*)-hydroxy-acrylate.

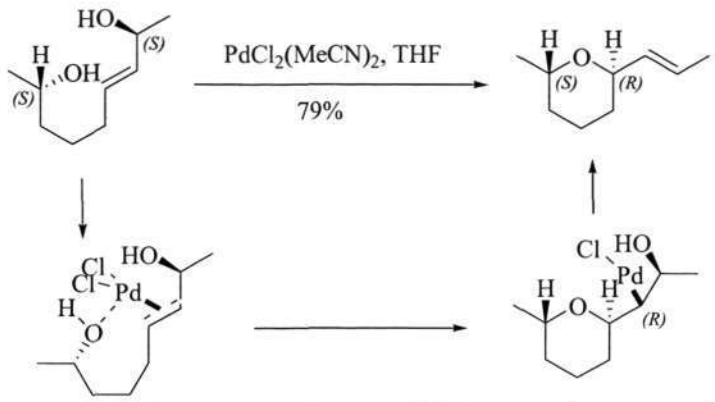
On the other hand, by controlling the geometry of the hydroxy-acrylate, palladium (II) catalyzed cyclization of the (*Z*)-isomer can selectively yield 2,6-*anti*-tetrahydropyran in high diastereomeric excess (Scheme 4.4). The value of this elegant display of stereochemically-controlled cyclization is elevated with the convenient synthesis of the precursors using the asymmetric Horner-Wadsworth-Emmons strategy[109].

[109] (a) Tömösközi, I.; Janszo´, G. *Chem. Ind. (London)* **1962**, 2085. For reviews, see: (b) Rein, T.; Reiser, O. *Acta Chem. Scand.* **1996**, *50*, 369. (c) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579. Asymmetric HWE reactions with dicarbonyl substrates: (d) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (e) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. (f) Kann, N.; Rein, T. *J. Org. Chem.* **1993**, *58*, 3802. (g) Tanaka, K.; Ohta, Y.; Fuji, K.; Taga, T. *Tetrahedron Lett.* **1993**, *34*, 4071. (h) Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847. (i) Tanaka, K.; Watanabe, T.; Ohta, Y.; Fuji, K. *Tetrahedron Lett.* **1997**, *38*, 8943. (j) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **1998**, *63*, 8284. (k) Rein, T.; Vares, L.; Kawasaki, I.; Pedersen, T. M.; Norrby, P.-O.; Brandt, P.; Tanner, D. *Phosphorus, Sulfur Silicon* **1999**, *144-146*, 169. (l) Tanaka, K.; Watanabe, T.; Shimamoto, K.-Y.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599. (m) Vares, L.; Rein, T. *Org. Lett.* **2000**, *2*, 2611.



Scheme 4.4 Palladium(II) catalyzed cyclization of hydroxyl-acrylate.

Oxypalladation reaction was also reported by Uenishi[110] in the synthesis of 2,6-*syn*- and 2,6-*anti*-tetrahydropyran rings. Treatment of enantiomerically pure ξ-hydroxy-α,β-unsaturated alcohols to $PdCl_2(MeCN)_2$ afford the corresponding (*E*)-tetrahydropyran products exclusively *via* a concerted 1,3-chirality transfer cyclic pathway. A preferential chelation of the allylic alcohol with palladium resulted in a facial selective hydroxyl S_N2' attack, thus forming the desire *anti*-isomer (Scheme 4.5). This elegant strategy was adopted in the total synthesis of (-)-Laulimalide[111].



Scheme 4.5 Oxypalladation and cyclization of ξ-hydroxy-α,β-unsaturated alcohols

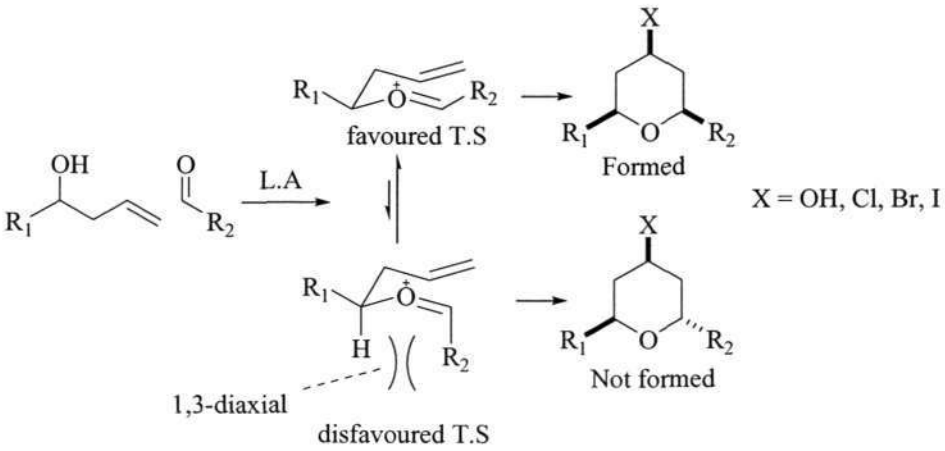
[110] (a) Kawai, N. ; Lagrange, J. –M. ; Ohmi, M. ; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530. (b) Uenishi, J.; Ohmi, M. ; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299. (c) Uenishi, J.; Ohmi, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2756.

[111] For total syntheses; see, a) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027. b) Paterson, I.; De Savi, C.; Tudge, M.; *Org. Lett.* **2001**, *3*, 3149. c) Mulzer, J.; Öhler, E. *Angew. Chem. Int. Ed.* **2001**, *40*, 3842. d) Wender, P. A.; Hegde, S. G., Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956. e) Crimmins, M. T.; Stanton, M. G. ; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958. f) Williams, D. R.; Mi, L.; Mullins, R. J.; Stites, R. E. *Tetrahedron Lett.* **2002**, *43*, 4841. g) Nelson, S. G.; Cheung, W. S.; Kassick, A. J.; Hilfiker, M. A.; *J. Am. Chem. Soc.* **2002**, *124*, 13654. h) Gallagher, B. M.; Fang, Jr., F. G.; Johannes, C.W.; Pesant, M.; Tremblay, M. R.; Zhao, H.; Akasaka, K.; Li, X.; Liu, J.; Littlefield, B. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 575.

4.3 SUBSTRATE-CONTROLLED *ANTI*-PRINS CYCLIZATION

4.3.1 Basis of Substrate-Controlled *anti*-Prins Cyclization

Despite the elegance displayed by methods discussed earlier, the need for an efficient and convergent way to assemble 2,6-*anti*-tetrahydropyran rings still remains. Prins cyclization offers an edge over other methods in terms of convergence in synthesis and ease of preparation of starting material. However, the predominant formation of the 2,6-*syn*-isomer rendered this method unsuitable in the synthesis of the *anti*-isomer. As described in Chapter 2.4 of this thesis, the formation of a favorable chair-like oxocarbenium transition state avoiding the 1,3-diaxial interaction results in the formation of the *syn*-isomer (Scheme 4.6).

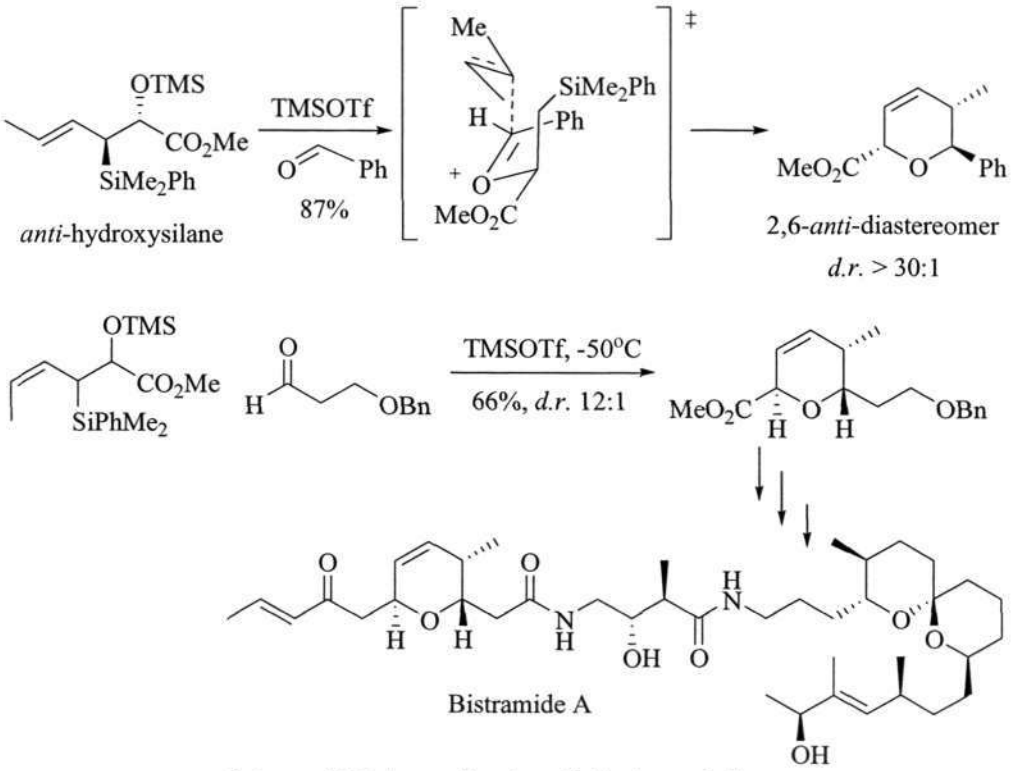


Scheme 4.6 1,3-diaxial interaction resulting in non-formation of *anti*-pyran.

Although uncommon in Prins cyclization, Panek[112] has reported a stereoselective synthesis of 2,6-*anti*-pyran ring using a formal [4+2] annulation of a chiral *anti*-hydroxycrotylsilane (Scheme 4.6). Through an *anti*-S_E' mode of addition, the configuration of the silane alcohol controls the stereochemical course of the cyclization. A favorable pseudo axial orientation for the silyl group has been proposed for effective σ-p overlap in a boatlike transition state. Based on both steric and

[112] (a) Huang, H.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836. For applications on total synthesis, see (b) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529. (c) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231. (d) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425.

electronic considerations, the bulky silyl group is in *anti* orientation to the neighboring ester group, thus resulting in the desired *anti*-isomer upon cyclization. This strategy has been widely used in the synthetic studies of many natural products such as Bistramide A[113].



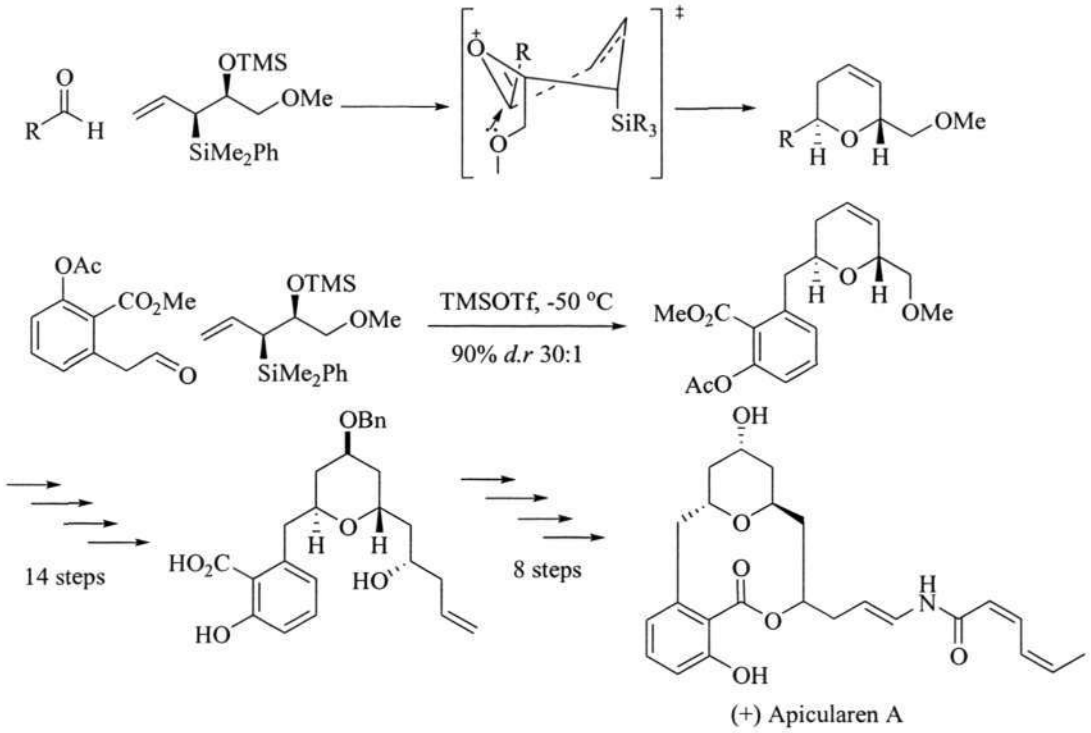
Scheme 4.7 Prins cyclization of chiral crotyl silane.

In a separate account, Panek also reported an interesting finding whereby a *syn*-crotylsilane can afford the *anti*-tetrahydropyran with modification on the terminal substitutent from a methyl ester to methyl ether. In the total synthesis of (-)-Apicularen A[114], he postulated that in a twist boatlike transition state, the electrostatic attraction between the nonbonding lone pair of electrons of methyl ether and the positively charged oxocarbenium (residing on the carbon atom) can stabilize the twist

[113] 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.

[114] 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.

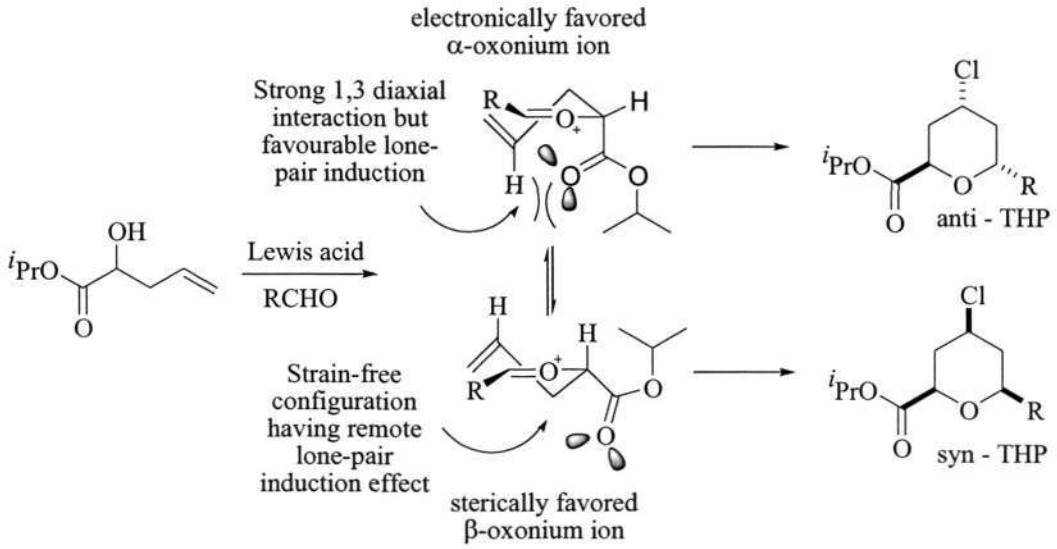
boat conformer and accelerate the annulation (Scheme 4.8). On the other hand, *syn*-crotyl silane methyl ester yielded molar equivalent of both the *syn*- and *anti*- THP products. The reaction was also reported to be substrate-dependant, with a greater proportion of the *syn*-isomer formed from conjugated and sterically hindered aldehydes.



Scheme 4.8 Synthesis of *anti*-THP using *syn*-methyl ether crotyl silane.

The postulate by Panek propelled our interest in the investigation of the lone pair directing effects on stabilizing the oxocarbenium ion in Prins cyclization. Concurrently, we envisaged that by incorporating suitable substitutents on the homoallylic alcohol, electronic interaction can overcome steric repulsion in the chair-like transition state, thus resulting in the formation of the *anti*-isomer (Scheme 4.9). Although the strategy is undoubtedly elegant, the synthesis of the hydroxyl-crotyl-silane is often tedious and low yielding. Therefore, we invoked a more direct and sustainable method to obtain the 2,6-*anti*-THP ring based on stereochemical and steric considerations. With an electron rich moiety such as isopropyl ester on the

homoallylic alcohol adopting the α-position to enhance the inductive effect in the transition state, we can establish a direct *anti*-Prins cyclization without the aid of a silyl-group in the precursor.



Scheme 4.9 Competing steric and electronic effects in substrate-controlled Prins cyclization.

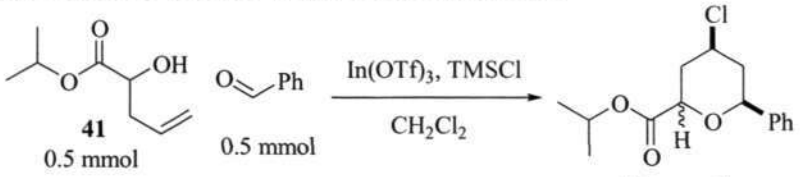
4.4 RESULTS AND DISCUSSION

4.4.1 Optimization of Conditions in *anti*-Prins Cyclization

We commenced the 2,6-*anti*-tetrahydropyran synthesis using our catalytic Prins cyclization protocol developed in Chapter 3. Benzaldehyde was used as the substrate since it was reported by Panek to give the poorest *anti*-selectivity. Isopropyl-4-hydroxy-pent-1-enoate **41** was treated with a catalytic amount of $In(OTf)_3$ and TMSCl in dichloromethane. We were fascinated with the isolation of the 2,6-*anti*-product[115], although the yield was low, with the *syn*-isomer being the major product. Optimization of the reaction conditions was carried as shown in Table 4.1.

[115] The conformation of the *anti*-2,6-isomer was determined by ^{1}H and NOESY nmr spectra.

Table 4.1 Prins cyclization of **41** under various reaction conditions.



42a - *syn* isomer
42b - *anti* isomer

Entry	$In(OTf)_3$ equiv	TMSCl equiv	Temperature (° C)	Conc. (*M*)[a]	Yield (%)	*d.r.* (*syn:anti*)
1	0.2	1.2	0	0.1	64	50:50
2	0.5	1.2	0	0.1	69	52:48
3	1.1	1.2	0	0.1	52	50:50
4	0.2	5	0	0.1	66	45:55
5	0.2	1.2	-78	0.1	35	82:18
6	0.2	1.2	-40	0.1	38	80:20
7	0.2	1.2	25	0.1	68	70:30
8	0.2	1.2	reflux	0.1	64	75:25
9	0.2	1.2	0	0.01	47	60:40
10	0.2	1.2	0	1	27	88:12
11	0.2	1.2	0	0.1[b]	42	66:33
12	0.2	1.2	0	0.1[c]	36	70:30

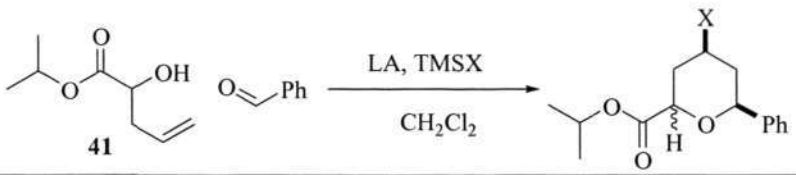
[a] Concentration of reaction mixture with respect to aldehyde. Except for entry 11 and 12, aldehyde (0.5 mmol) was dissolved in 0.5 mL of CH_2Cl_2 prior to addition to the mixture. [b] A solution of aldehyde (0.5 mmol in 4 mL) added to the mixture of homoallylic alcohol (0.5 mmol), $In(OTf)_3$ and TMSCl in 1 mL CH_2Cl_2. [c] Homoallylic alcohol was added to the mixture of aldehyde, $In(OTf)_3$ and TMSCl in 4.5 mL CH_2Cl_2.

The results showed that increasing the amount of Lewis acid does not improve the yields or selectivity. In contrast, the yield decreased with 1.1 equivalent of $In(OTf)_3$, together with unreacted homoallylic alcohol. The postulate of having a large reservoir of halide to rapidly trap the oxocarbenium ion during the electronically favored transition state (Scheme 4.9) was also refuted when 5 equivalent of TMSCl (entry 4) failed to increase the relative proportion of the *anti*-isomer. Variations in temperature had no apparent effect on the selectivity. It was found that increased concentration resulted in a lower yield of the desired product, with the formation of

diphenyl-*meso*-THP ring due to allyl-transfer in a concentrated system. A high diastereomeric ratio favoring the undesired *syn*-isomer was also observed. Changes in sequence of addition resulted in no significant improvement on either yields or selectivity. An investigation to study the solvent effects[116] on promoting axial configuration of the transition state was carried out. Various solvents such as methanol, THF, DMF, hexane and toluene were used in the Prins cyclization of **41** and benzaldehyde. It was found that dichloromethane and chloroform gave the best yields of both the *syn*- and *anti*-isomers.

Other Lewis acids and trimethylsilyl additives were also screened to optimize the reaction conditions and to establish any grounds of efficient coordination of the substrates and the catalysts (Table 4.2). The results showed that $In(OTf)_3$ yielded the highest proportion of the *anti*-isomer.

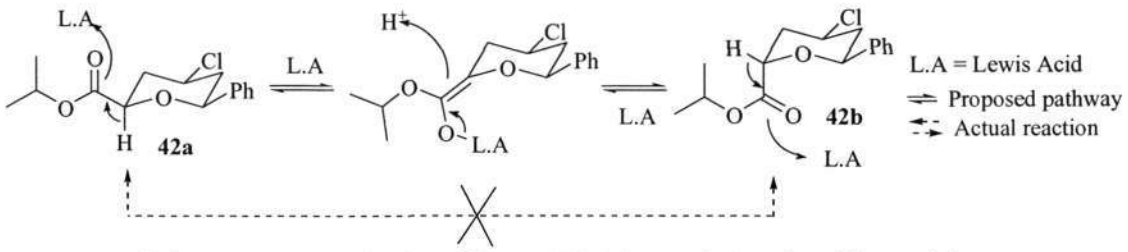
Table 4.2 Variation of Lewis acid and trimethylsilyl halide



Entry	LA	X	Yield (%)	*d.r.* (*syn:anti*)
1	$In(OTf)_3$	Cl	64	50:50
2	$In(OTf)_3$	Br	67	49:51
3	$In(OTf)_3$	I	59	50:50
4	$InBr_3$	Br	48	62:38
5	$InCl_3$	Cl	43	60:40
6	$TiCl_4$	Cl	51	50:50
7	$SnCl_4$	Cl	55	67:33
8	$SnBr_4$	Br	58	65:35

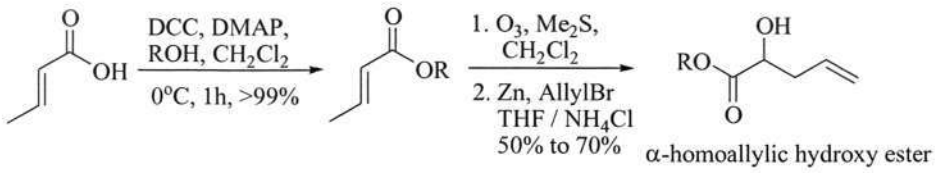
[116] Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd Ed. Wiley VCH Verlag GmbH & Co. KGaA, Weinheim, **2003**.

The possibility of isomerization of the products under Lewis acidic conditions has also been explored (Scheme 4.10). To substantiate this argument, both the *syn*- and *anti*-isomers of **42** were treated with $In(OTf)_3$ and TMSCl in dichloromethane at 0 °C on separate occasions. It was found that no isomerization was observed, with complete recovery of the starting material.



Scheme 4.10 Isomerization of 2-ester-THP ring under Lewis acidic condition.

Supported by the information from these studies, we proceeded with the investigation on the effects of substrates on the homoallylic alcohol. We embarked on the synthesis of α-homoallylic hydroxy-ester with coupling[117] of various alcohols and crotonic acid to form an αβ-unsaturated ester. Ozonolysis[118] followed by zinc mediated allylation afforded the desired products (Scheme 4.11) which were subsequently used in the methodology study for *anti*-Prins cyclization.



Scheme 4.11 Synthesis of α-homoallylic hydroxy-ester

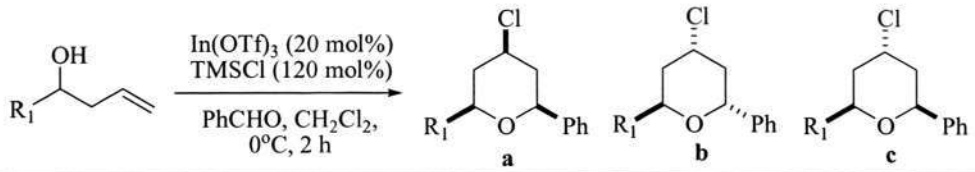
As proposed earlier, we were intrigued to determine whether the bulkiness of the ester group affects the selectivity of the Prins cyclization. Hence, various

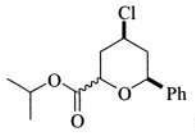
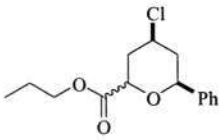
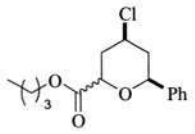
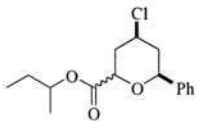
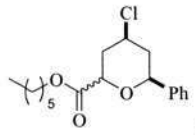
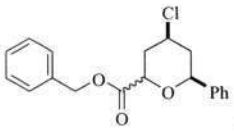
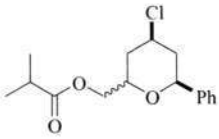
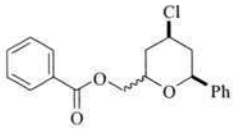
[117] (a) Smith, M.; Moffatt, J. G.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 6204. (b) Balcom, B. J.; Petersen, N. O. *J. Org. Chem.* **1989**, *54*, 1922. (c) Dolechall, G.; Lempert, K. *Tetrahedron Lett.* **1963**, 1195.

[118] For monograph, see (a) Razumovskii, S. D.; Zaikov, G. E. *Ozone and its Reaction with Organic Compounds* Elsevier: New York, **1984**. For reviews, see (b) Odinokov, V. N.; Tolstikov, G. A. *Russ. Chem. Rev.* **1981**, *50*, 636. (c) Menyailo, A. T.; Pospelov, M. V. *Russ. Chem. Rev.* **1967**, *36*, 284. (d) Bailey, P. S. *Chem. Rev.* **1958**, *58*, 990. (e) Knowles, W. S.; Thompson, Q. E. *J. Org. Chem.* **1960**, *25*, 1031 and references therein. For decomposition of ozonide with Me_2S, see (d) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

homoallylic alcohols were subjected to the optimized reaction conditions with benzaldehyde (Table 4.3).

Table 4.3 Prins cyclization of benzaldehyde with various homoallylic alcohols (I)



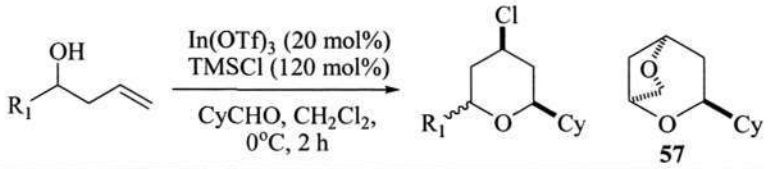
Entry	R_1	Product	Yield (%)		
			syn (a)	*anti* (b)	c
1	-COO^{i}Pr	 **42**	32	32	3
2	-COO^{n}Pr	 **43**	27	27	3
3	-COO^{n}Bu	 **44**	36	35	6
4	-COO^{s}Bu	 **45**	32	34	4
5	-COO^{n}Hex	 **46**	24	24	4
6	-COOBn	 **47**	26	25	8
7	-CH_2OCO^iPr	 **48**	65	-	-
8	- CH_2OCOPh	 **49**	69	-	-

Several conclusive findings established the existence of carbonyl lone-pair inductive effects on the oxocarbenium transition state. Firstly, the inductive effect of the *iso*-propyl ester group (entry 1) yielded equal amounts of *syn*- and *anti*- isomers of the 4-chloro-2,6-trisubstituted THP **42**. In addition, neither the chain length nor the bulkiness of the R-group exerts any effects on improving the selectivity. Interestingly, only the *syn*-isomer was isolated when benzoyl ester (entry 8) and *sec*-butyl ester (entry 7) underwent Prins cyclization with benzaldehyde. This gave us an understanding on the importance of the 1,2-carbonyl lone pair[119] in the formation of *anti*-pyran ring.

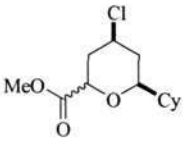
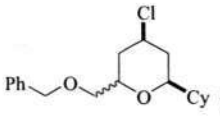
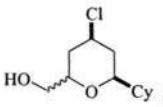
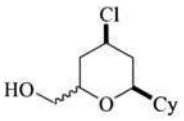
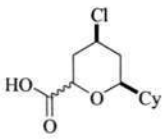
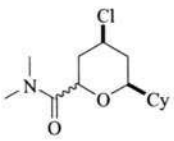
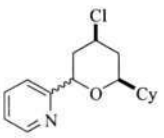
In order to further substantiate our postulate on the lone pair inductive effects, 1-protected-2-homoallylic diol (Table 4.4, entry 2 and 3) was subjected to Prins cyclization. In both cases, the formation of the 2,6-dioxa-bicyclo-[3,2,1]-octane, **57**, strongly indicates the adoption of the α-position in the oxocarbenium transition state. A noteworthy observation was that the unprotected acid and alcohol failed to give any bicyclic-product (entry 4, 5), suggesting a concerted removal of the bulky group at the axial position to relieve steric strain. Unfortunately, the lone-pair effect on amides and pyridinyl substrates were inconclusive as no Prins cyclized products were formed.

[119] For interactions of carbonyl lone pair, refer to (a) Roush, W. R.; Walts, A. E.; Lee, K. H. *J. Am. Chem Soc.* **1985**, *107*, 8186. (b) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692. (c) Roush, W. R.; Ratz, A. M.; Jablonomski, J. A. *J. Org. Chem.* **1992**, *57*, 2047. Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

Table 4.4 Prins cyclization of benzaldehyde with various homoallylic alcohols (II)



57

Entry	R_1	Prins-Product	Yield (%)		
			syn	*anti*	57 [c]
1	-COOMe[a]	 **50**	29	30	-
2	$-CH_2OBn$	 **51**	26	13	38
3	$-CH_2OTIPS$[b]	 **52**	38	-	40
4	$-CH_2OH$	 **53**	12	5	-
5	-COOH	 **54**	-	-	-
6	$-CONMe_2$	 **55**	-	-	-
7	$-2-C_5H_4N$	 **56**	-	-	-

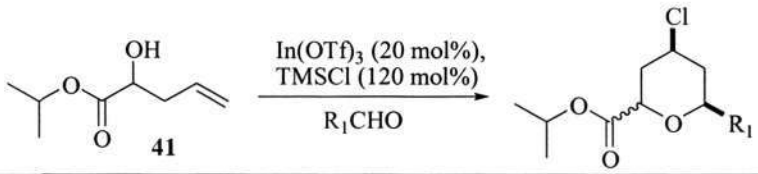
[a] Homoallylic hydroxyl methyl ester was used to reinforce the fact that bulkiness of the ester group have insignificant effect on the selectivity. Comparison between a more reactive aldehyde (cyclohexylcarboxyaldehyde) with benzaldehyde indicated that the selectivity is not dependent on aldehydes used. [b] TIPS protecting group was deprotected in this reaction condition, yielding the free alcohol. (c) Formation of **57** will be explained in the later section.

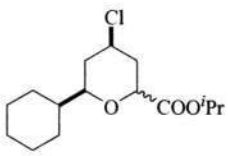
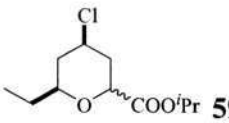
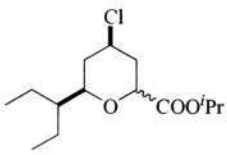
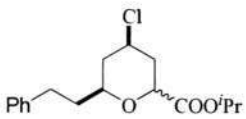
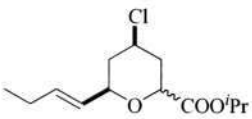
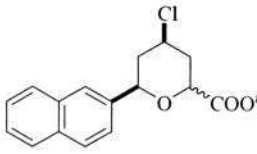
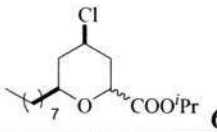
4.4.2 Formation of *Syn*- and *Anti*-THP rings with Various Aldehydes

Intrigued by these results, we explored the applicability of the methodology on a diverse selection of aldehydes. Isopropyl 2-hydroxypent-4-enoate **41** was subjected

to a series of aldehydes as shown in Table 4.5. The results were satisfactory with moderate yields and equivalent diastereomeric ratios. The isomers were also easily separated using flash column chromatography, enabling synthesis of both *syn*- and *anti*- products in a single reaction.

Table 4.5 Prins cyclization of **41** with various aldehydes.



Entry	R_1	Prins-Product	Yield	*d.r.* (*syn*:*anti*)
1	-cyclohexyl	 **58**	56	50:50
2	-ethyl	 **59**	62	50:50
3	-3-pentyl	 **60**	57	44:56
4	$-(CH_2)_2Ph$	 **61**	62	50:50
5	$-CH=CH-CH_3$	 **62**	58	51:49
6	-3-napthayl	 **63**	28	54:46
7	-octyl	 **64**	33	49:51

The diastereomeric ratios were comparable for all the aldehydes in Table 4.4, implying that the electronic and steric effects of the aldehydes do not influence the stereochemical course of the reaction. In contrast, Panek reported lower diastereomeric ratio in his synthetic studies, with the *syn*-product being the major isomer using benzaldehyde and more sterically hindered aldehydes. The lassitude of substrate dependency in the β-crotyl-silane method has been addressed in our use of synthetically convenient α-homoallylic hydroxyl-ester Prins cyclization.

An X-ray crystal structure of the *anti*-isomer **58b** (Figure 4.2) was obtained, showing the axial orientation of the isopropyl ester group, which was consistent with the nmr spectra.

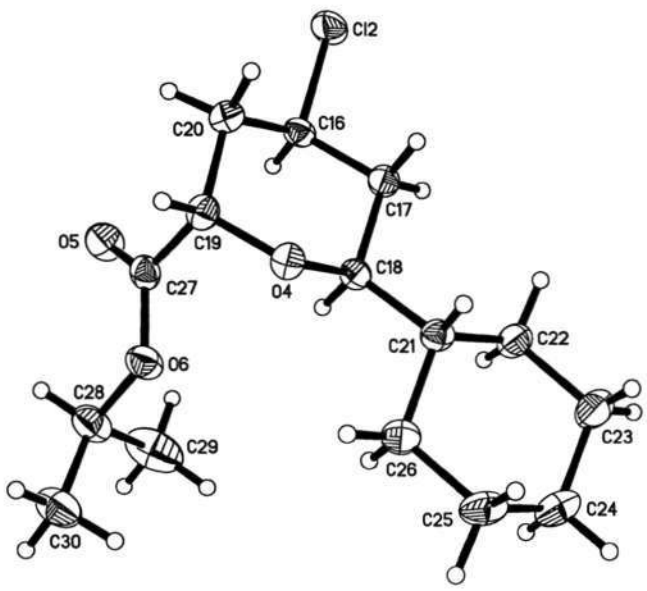
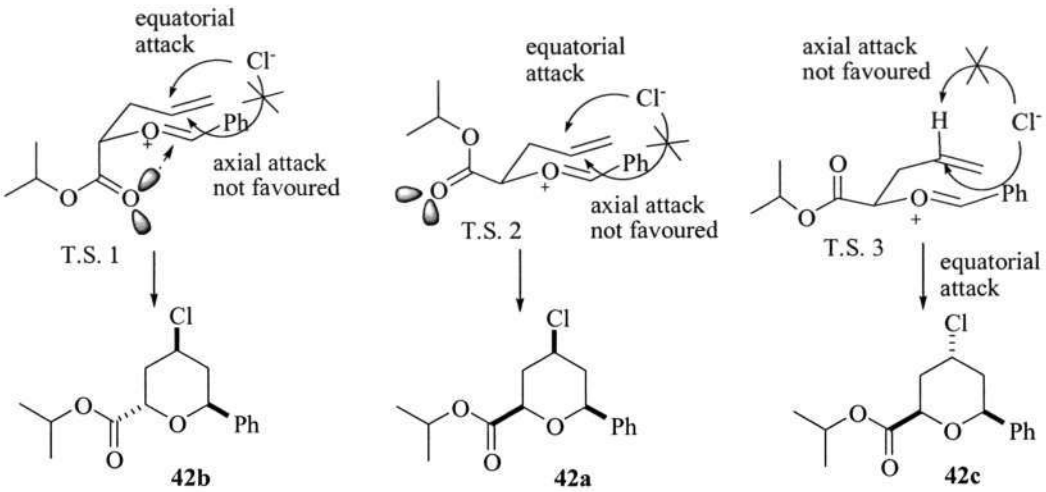


Figure 4.2 X-ray crystal structure of (2,4-*trans*-2,6-*trans*)-isopropyl 4-chloro-tetrahydro-6-phenyl-2H-pyran-2-carboxylate (**58b**). Note the carbonyl moiety is arranged such that the 1,3-diaxial interaction is minimized.

4.4.3 Mechanistic Interpretation

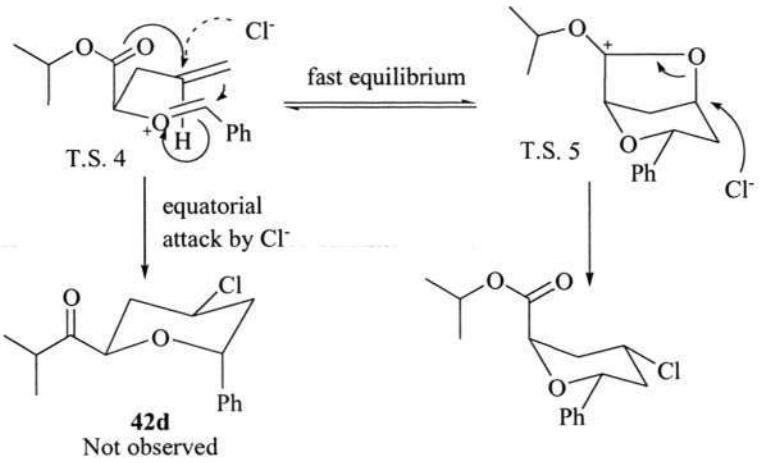
A plausible mechanism for the diversity of isomers formed has been proposed (Scheme 4.12). A competition exists between the electronically favored transition state (T.S.1) and the sterically preferred T.S.2. The latter leads to the conventional

syn-conformer (**42a**) while T.S.1 leads to the *anti*-conformer (**42b**). In both cases, axial nucleophilic attack by the external chloride at the 4-position is forbidden. The formation of axial 4-chloro-THP product (**42c**) is likely to proceed *via* a less stable boat transition state (T.S. 3), thus accounting for its comparatively lower yields.

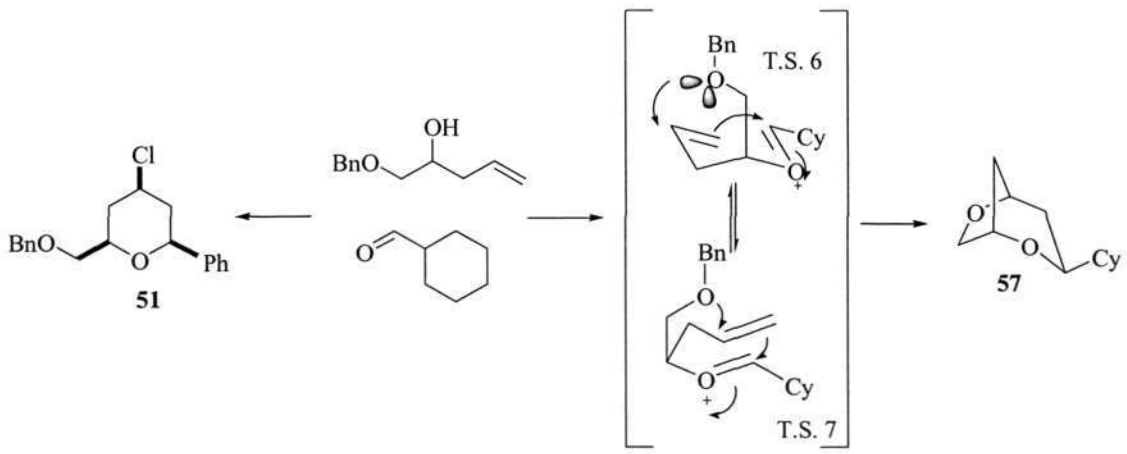


Scheme 4.12 Possible mechanisms for the formation of syn- and anti- products in Table 4.1.

Similarly, the sterically unstable boat-like T.S. 4 equilibrates rapidly to form the bicyclo-carbocation T.S.5, where the equatorial attack by chloride collapses the structure back to the *anti*-2,6-THP ring. Such pathway indicates evidently the strong electronic interaction of the ester moiety with the oxocarbenium ion. Interestingly, the formation of axial-phenyl product **42d** was not observed, indicating that the preferential adoption of T.S. 5 conformation (Scheme 4.13). In the case of the alkoxy homoallylic alcohol (Table 4.4 entry 2), the two lone pairs on the oxygen offered strong inductive effect in both T.S 6 and T.S 7, hence affording **48** (Scheme 4.14) and the respective *syn*-conformer **42**.

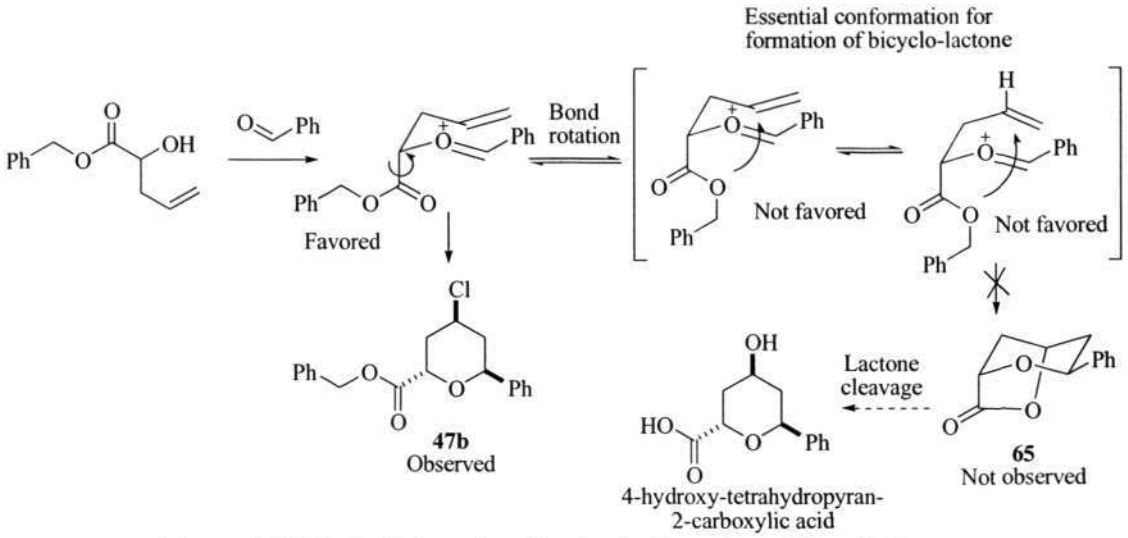


Scheme 4.13 Alternative mechanistic proposal following a bicyclic acetal-carbocation pathway.



Scheme 4.14 Mechanistic interpretation for the formation of **57**.

In lieu of this observation, we anticipated that a benzyl ester (Table 4.3, entry 6) R-group should be able to yield a bicyclolactone **65**, which could easily be hydrolyzed to 4-hydroxy-tetrahydropyran-2-carboxylic acid (Scheme 4.15). However, equivalent amounts of *syn*- (**47a**) and *anti*- (**47b**) products were formed, indicating that the lone pair of the carbonyl oxygen is essential for the transition state to adopt the axial conformation. The carbonyl lone-pair effect was reinforced by the fact that only the *syn*-isomers (**48** and **49**) were isolated when *iso*-butyl ester (Table 4.3, entry 7) and benzoate ester (Table 4.3, entry 8) underwent Prins cyclization with benzaldehyde. Evidently, we have established our postulation on the competitive adoption of *syn*- and *anti*- transition states based on steric and electronic attributes respectively.



Scheme 4.15 Mechanistic explanation for the formation of bicyclic-lactone.

4.5 CONCLUSION AND FUTURE WORK

In conclusion, the electronic and steric effects of α-homoallylic alcohol ester in Prins cyclization to form both *syn*- and *anti*-2,4,6-trisubstituted THP rings have been investigated[120]. The substrates afforded moderate yields of both products and were easily separated by flash column chromatographic means. Further improvements on yields and selectivity, together with the application of this method to the synthesis of diverse biologically active natural products is in progress.

[120] Chan, K. P.; Seow, A. –H.; Loh, T. P. *Tetrahedron Lett.* **2007**, *48*, 37.

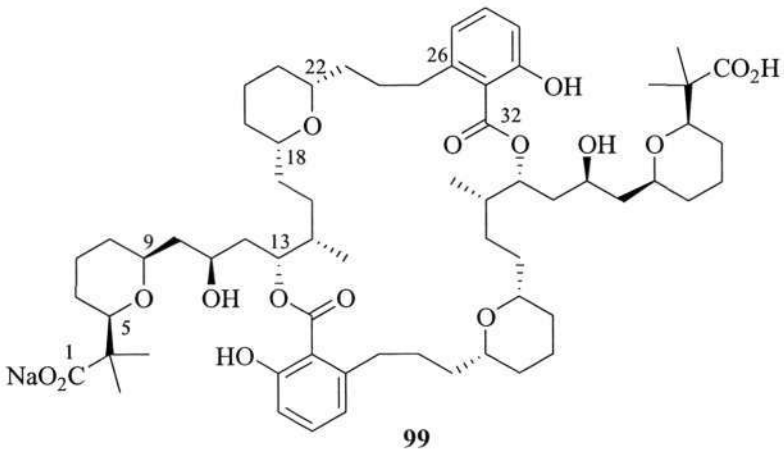
CHAPTER 5

Formal Synthesis of (+)-SCH 351448

5.1 BACKGROUND OF (+)-SCH 351448

5.1.1 Structural and Biological Aspects of (+)-SCH 351448

In 1999, Hedge[121] et al at Schering-Plough Research Institute discovered a novel microbial metabolite (+)-SCH 351448. It is a monosodium salt of a macrocyclic dilactone containing two identical diacids isolated from the fermentation broth of *Micromonospora sp.* The absolute stereochemistry has been determined, as shown in Figure 5.1.



99

Figure 5.1 (+)-SCH 351448

(+)-SCH 351448 possesses a very interesting structure. It features a 28-membered macrodiolide consisting of two identical hydroxyl carboxylic acid units. In the X-ray crystal structure of **99**, the sodium ion is surrounded by seven oxygen atoms, rendering pseudo-C_2 symmetry for the complex (Figure 5.2). It consists of four *cis*-2,6-disubstituted tetrahydropyran rings with opposite relative stereochemistry on each half of the molecule. Though the biosynthesis of this molecule has yet to be established, it has distinct features of a polyketide with 1,3- and 1,5-poly-ols. The stable 28-membered ring encompasses two tetrahydropyran rings of the same relative stereochemistry with respect to each other. On the exo-macrocycle, the poly-

[121] Hedge, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351.

oxygenated fragment can possibly form transient 16-membered cycles *via* hydrogen bonding between the carboxylate and phenolic moieties.

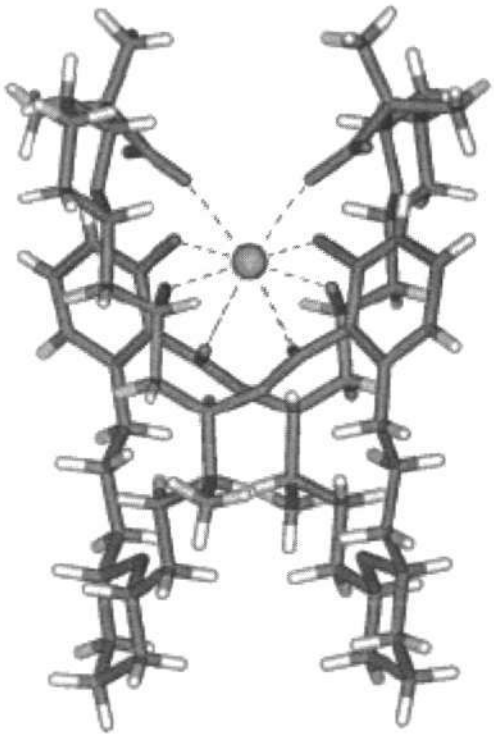


Figure 5.2 ORTEP diagram[122] of the structure of (+)-SCH 351448.

Micromonospora is a genus of bacteria of the family *Micromonosporaceae*. They are gram-positive, spore-forming and generally aerobic. They occur as saprophytic[123] forms in soil and water. The isolation and analysis of **99** from *Micromonospora sp.* is, however, beyond the scope of this thesis.

(+)-SCH 351448 acts as an activator of low density lipoprotein receptor promoter. LDL uptake by the LDL receptor (LDL-R) is an important mechanism for clearing serum cholesterol. LDL-R levels are regulated at the transcriptional level by the abundance of cholesterol and its metabolites in the cell membranes. High membrane cholesterol levels inhibit the cleavage of sterol response element binding

[122] The diagram of the X-ray structure is obtained from Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, *12*, 2777.
[123] A saprotroph is an organism that obtains its nutrients from non-living organic matter, usually dead and decaying plant or animal matter, by absorbing soluble organic compounds.

proteins (SREBPs)[124]. When cholesterol levels drop, SREBPs are cleaved from the membrane, allowing them to enter the nucleus and activate promoters containing sterol response elements, including LDL-R promoter.

(+)-SCH 351448 has an IC_{50}[125] of 25 μM in the LDL-R promoter transcription assay using hGH as reporter gene. However, it did not activate transcription of hGH from the SRα promoter, indicating its selectivity in activating transcription from the LDL-R promoter. To date, (+)-SCH 351448 is the first small molecule activator of the LDL-R promoter identified, thus its chemical synthesis posed significant value to many scientists investigating on serum cholesterol research.

5.1.2 Reported Synthesis of (+)-SCH 351448

The first enantioselective total synthesis of (+)-SCH 351448[126] was reported by Eun Lee[127] in 2004. Because of its highly symmetrical architecture, the synthesis can be highly convergent, with inherent problems of intramolecular side-reactions during the formation of the macrocycle. Eun Lee has demonstrated an excellent synthetic pathway to assemble the molecule, employing a radical cyclization strategy to construct the tetrahydropyran motifs. Further functional group interconversions and C-C bond formations yielded the resulting C1-C16 crotyl alcohol fragment **I** (Scheme 5.1).

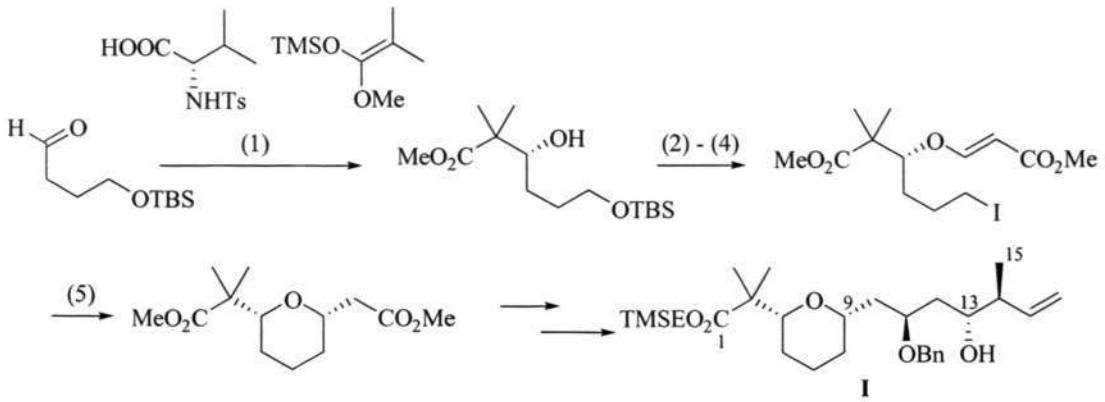
---

[124] For reviews, see (a) Brown, M. S.; Goldstein, J. L. *Cell* **1997**, *89*, 331. (b) Horton, J. D. *Biochem. Soc. Trans.* **2002**, *30*, 1091. (c) Osborne, T. F. *J. Bio. Chem.* **2000**, *275*, 32379.

[125] IC_{50} refers to half the maximal inhibitory concentration, which represents the concentration of an inhibitor of enzymes, cells, cell receptors or microorganisms.

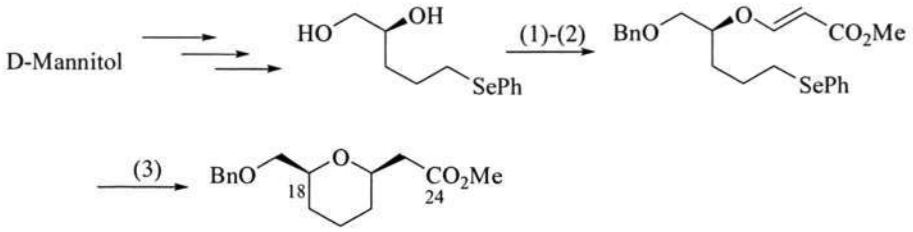
[126] Three cases of enantioselective synthesis of (+)-SCH 351448 will be discussed in this chapter. For other recent synthesis, see (a) Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, *12*, 2777. (b) Crimmins, M. T.; Grace, S. *Org. Lett.* **2006**, *8*, 2887.

[127] (a) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680. (b) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Young, E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J. S.; Kim, H. J.; Lee, S. G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321 and references therein. For review, see (c) Eun, K. ; Lee, E. *Chem. Rev.* **2005**, *105*, 4348.



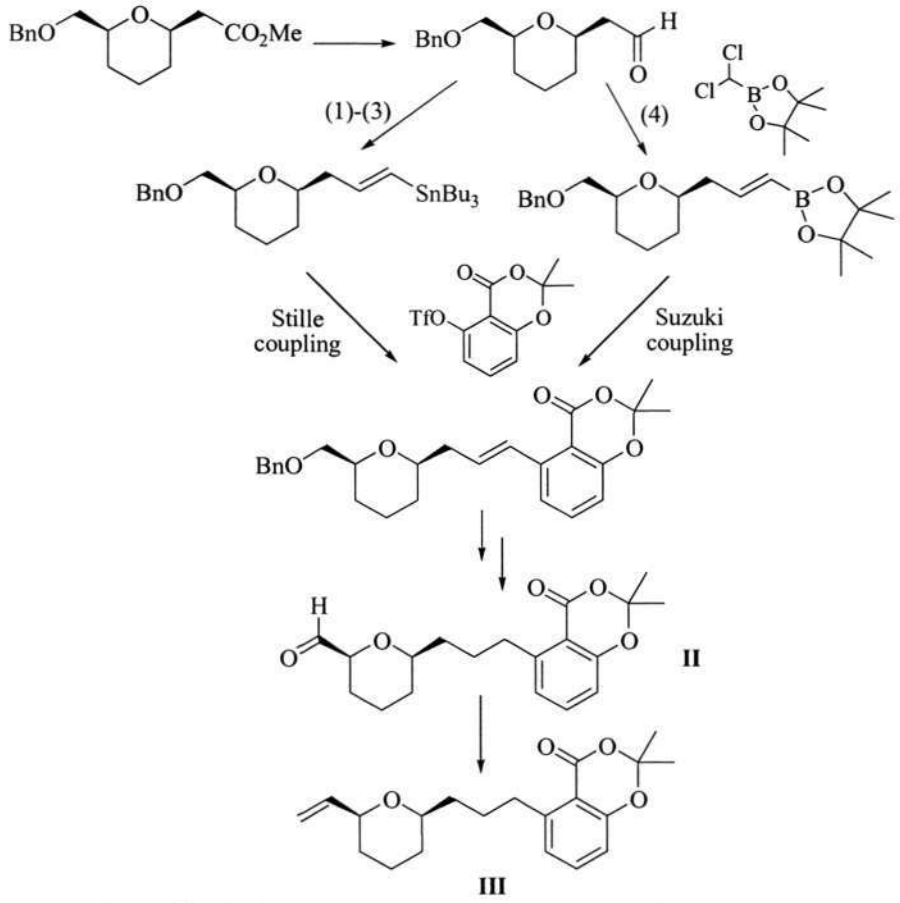
Scheme 5.1 Lee's synthesis of C1-C16 of (+)-SCH351448. (1) BH_3·THF, CH_2Cl_2 (2) $HCCCO_2Me$, NMM, MeCN, r.t. 48 h; (3) conc. HCl, MeOH, r.t. 30 min; (4) I_2, Ph_3P, imidazole, THF, 0 °C, 2 h. (5) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH, r.t. 30 min.

The second fragment was also assembled using the radical cyclization strategy. However, instead of iodide as a radical precursor, phenyl selenide was incorporated to the (D)-mannitol derived fragment. Reaction with methyl propiolate resulted in alkoxy-acrylate selenide which underwent radical cyclization with AIBN to form the C17-C24 fragment (Scheme 5.2).



Scheme 5.2 (1) Bu_2SnO, PhH, reflux, 16 h; BnBr, TBAI (2) $HCCCO_2Me$, NMM, MeCN (3) n-Bu_3SnH, AIBN, PhH.

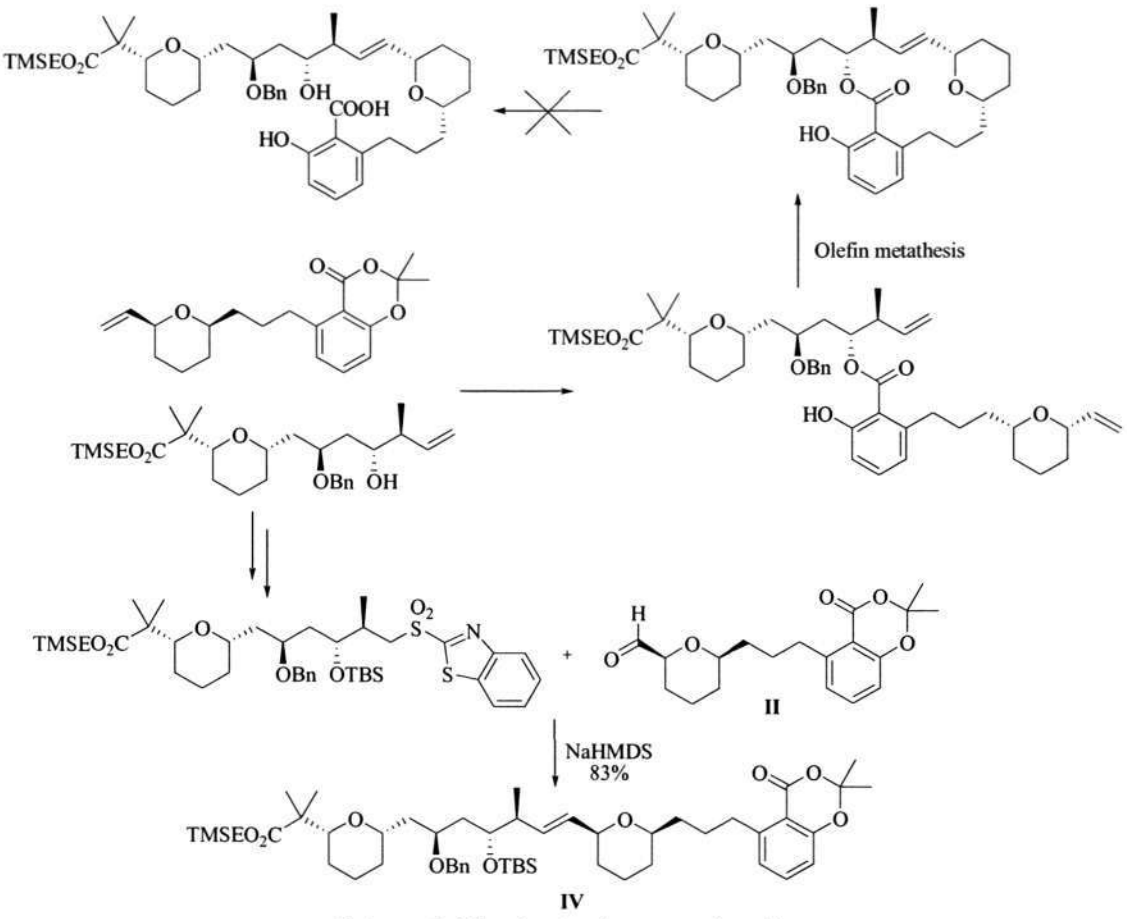
Lee has demonstrated the versatility of coupling of this fragment to the salicylate triflate by derivatizing it to either a vinylic stannane or a vinyl borate for Stille coupling and Suzuki coupling respectively. The product was dehydrogenated and debenzylated simultaneously, followed by further derivatization to yield the aldehydic fragment **II**.



Scheme 5.3 Synthesis of C17-C32 fragment (1) CBr_4, HMPT, THF (2) n-BuLi, THF, -78 °C (3) n-Bu_3SnH, AIBN, PhH, reflux, 8.0 (4) $CrCl_2$, LiI, THF.

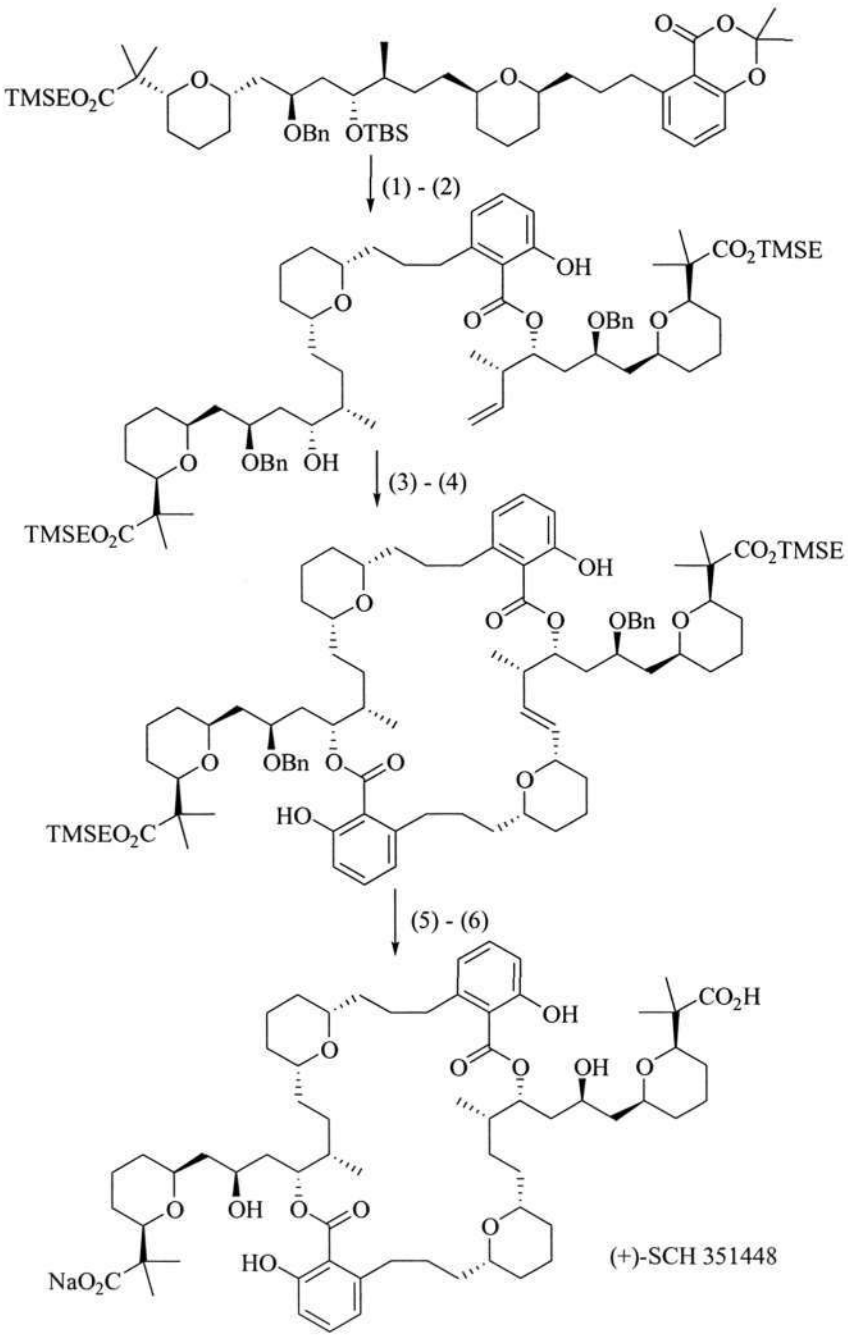
The next challenge highlighted was the assembling of the 2 fragments to form the monomeric unit (Scheme 5.4). Lee's initial attempts on acetonide coupling to form the salicylate ester followed by olefin metathesis failed to yield the desired product. Hence, his efforts were directed towards Julia olefination[128], although more steps were required to synthesize the sulfone precursor. Base-mediated coupling of the sulfone with **II** afforded the monomeric unit in 83% yield.

[128] (a) Kocienski, P. J. ; Lythgoe, B. *J. Chem. Soc. Perkin Trans.* **1980**, *1*, 1045. For reviews, see (b) Blakemore, P. R. *J. Chem. Soc. Perkin Trans. 1* **2002**, *23*, 2563. (c) van Staden, L. F. ; Gravestock, D. ; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195.



Scheme 5.4 Synthesis of monomeric unit.

Further functional group interconversions and base-mediated acetonide couplings provided the skeletal structure of (+)-SCH 351448. Intramolecular olefin metathesis afforded the 28-membered macrocycle which underwent deprotection of the benzyl and trimethylsilyl ethyl groups to afford the natural product (Scheme 5.5).

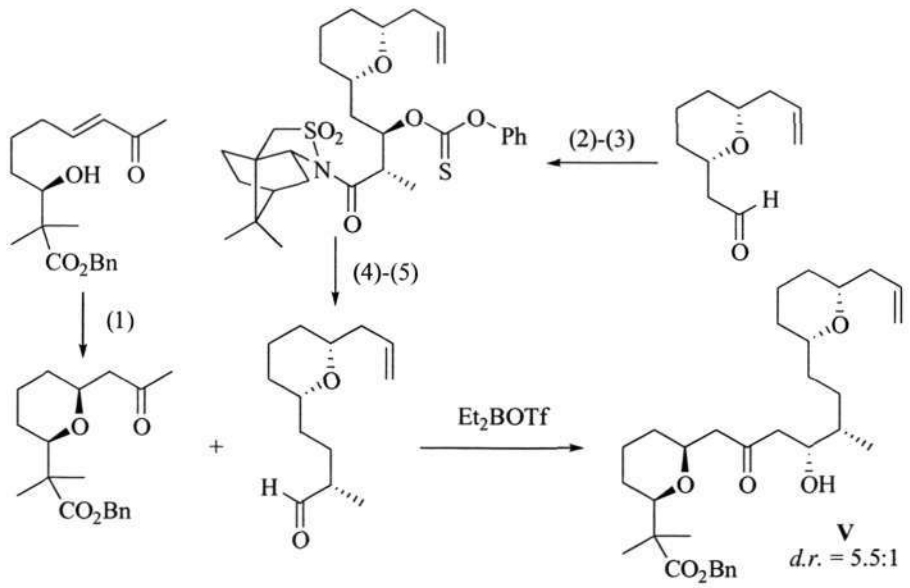


Scheme 5.5 Total synthesis of (+)-SCH 351448. (1) NaHMDS, THF, **I** (2) conc. HCl, MeOH (3) NaHMDS, THF, **III** (4) Grubbs 2nd generation cat., CH_2Cl_2 (0.003 M) (5) H_2, Pd/C, MeOH / EtOAc (3:1) (6) TBAF, THF; 4 N HCl (saturated with NaCl)

Two other groups have also worked on the total synthesis of (+)-SCH 35448 respectively. Brabander[129] reported an efficient synthesis of the molecule using a novel photochemical acylation[130] as the key step to combine two nearly identical but orthogonal fragments. An interesting boron ligand effect on the diastereoselectivity of

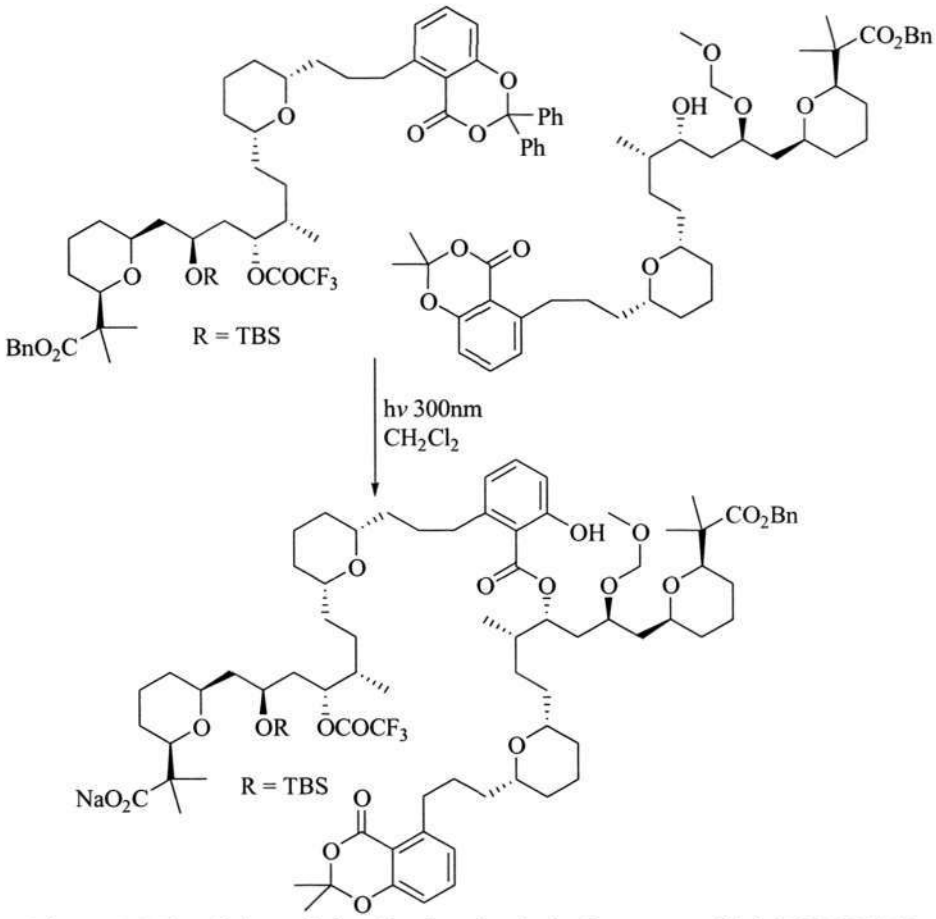
[129] (a) Soltani, O.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 2791. (b) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481 and references therein.
[130] Soltani, O.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1696.

a key aldol reaction with methyl ketone-derived enolborinates was also reported in the formation key intermediate **V** (Scheme 5.6). Though a shorter synthesis compared to Eun Lee's route, this 1,5-*anti*-asymmetric remote induction exhibited only moderate diastereocontrol in the formation of **V**.



Scheme 5.6 Brabander synthesis of intermediate **V**. (1) *t*-BuOK, THF, 0 °C (2) (2*S*)-*N*-propionyl bornanesultam, $TiCl_4$, *i*-Pr_2NEt, -78 °C (3) PhOC(S)Cl, py, CH_2Cl_2, 14 h (4) Bu_3SnH, 10% AIBN, PhH, 7 h, reflux (5) DIBAL-H, CH_2Cl_2, -78 °C, 1 h; then MeOH, -78 °C, 10 min.

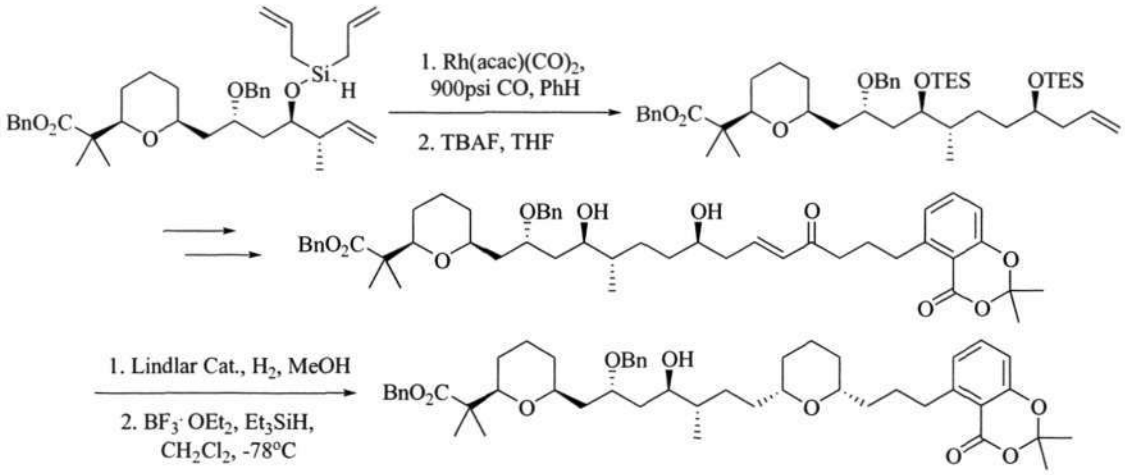
The final key step involved the dimerization of the two different acetonide protected monomeric units. Brabander reported that the diphenyl acetonide coupled selectively with the secondary alcohol at C-13 position using photolytic acylation, forming the basic skeletal structure. Further deprotection and acetonide coupling (as depicted by Lee) yielded the natural product.



Scheme 5.7 Photolytic acylation forming the skeletal structure of (+)-SCH 351448.

On a separate account, Leighton[131] delivered the natural product in a 23-step synthesis, featuring asymmetric allylation and crotylation using novel silane reagents (Scheme 5.8). In addition, he demonstrated an efficient synthesis of 1,5-*syn*-diols using a new protodesilylative version of tandem silylformylation/allylsilylation[132] reaction in the synthesis of the monomeric unit.

[131] Bolshakov, S.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 3809 and references therein.
[132] (a) Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587. (b) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915. (c) Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190. (d) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889.



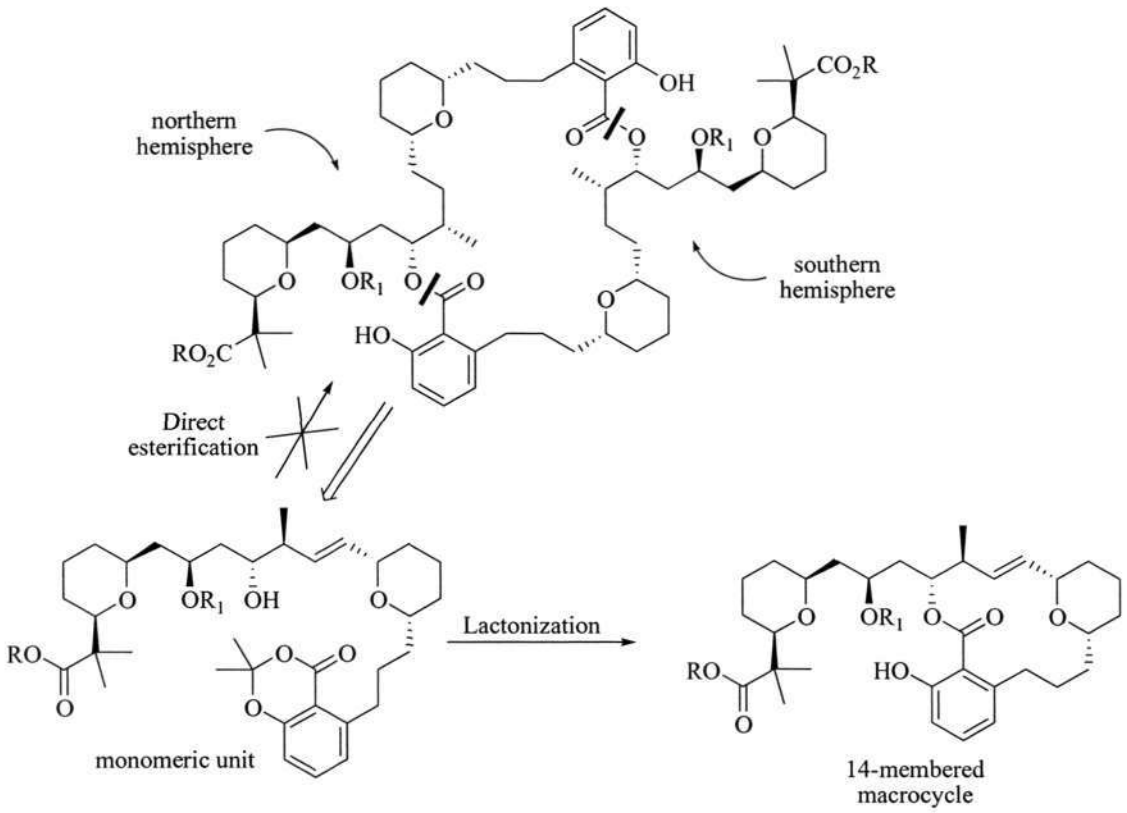
Scheme 5.8 Leighton's synthesis of the monomeric unit.

5.2 RETROSYNTHETIC ANALYSIS OF (+)-SCH 351448

5.2.1 Retrosynthesis of Macrodilactone

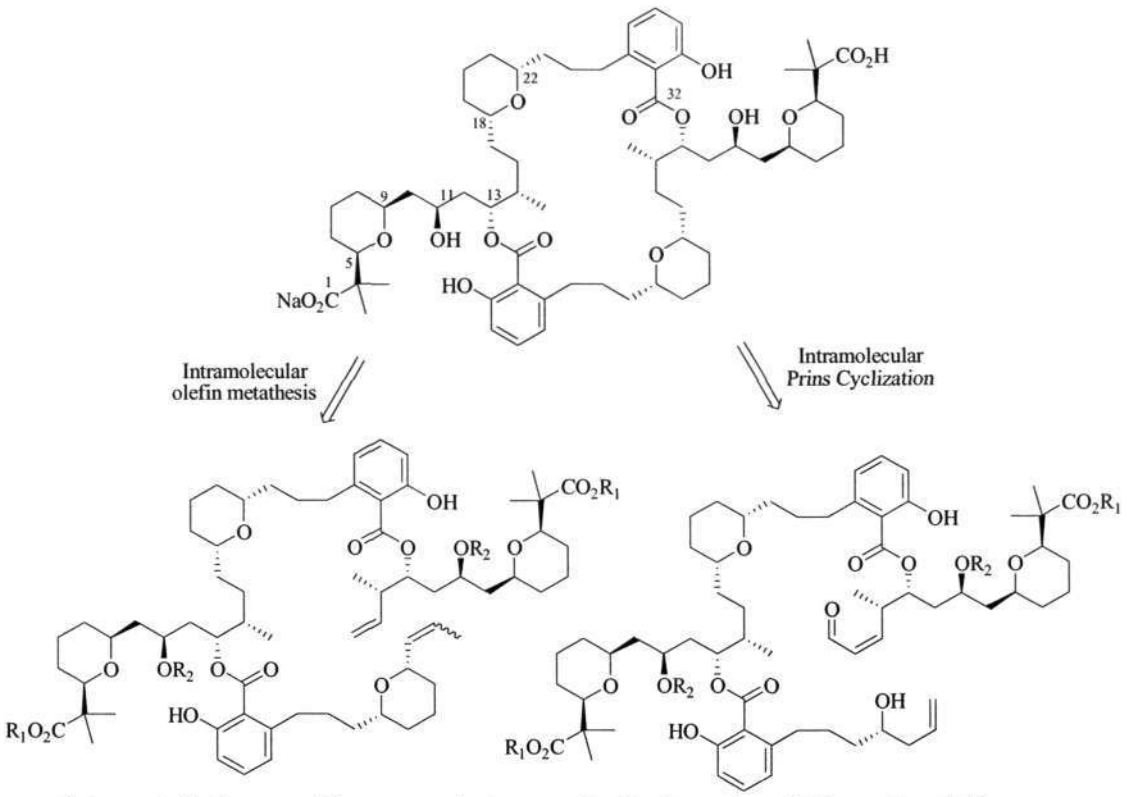
In the previous chapters, we emphasized the development of the catalytic Prins cyclization and epimerization suppression. We have also demonstrated its applicability on the total synthesis of (-)-Centrolobine, a relatively simple molecule which contain only one THP ring with two stereogenic centers. In the formal synthesis of (+)-SCH 351448, we hope to further demonstrate the versatility of Prins cyclization on various structurally challenging substrates.

We view the natural product as a dilactone having a C_2 symmetry which can be dissected into a north and a south hemisphere. The challenge then lies in the assembly of the two hemispheres without intramolcular lactonization to form a 14-membered lactone (Scheme 5.9) as described by Lee. Hence, direct esterification of the two monomeric units may not be feasible in this case.



Scheme 5.9 Intramolecular lactonization of the northern hemisphere.

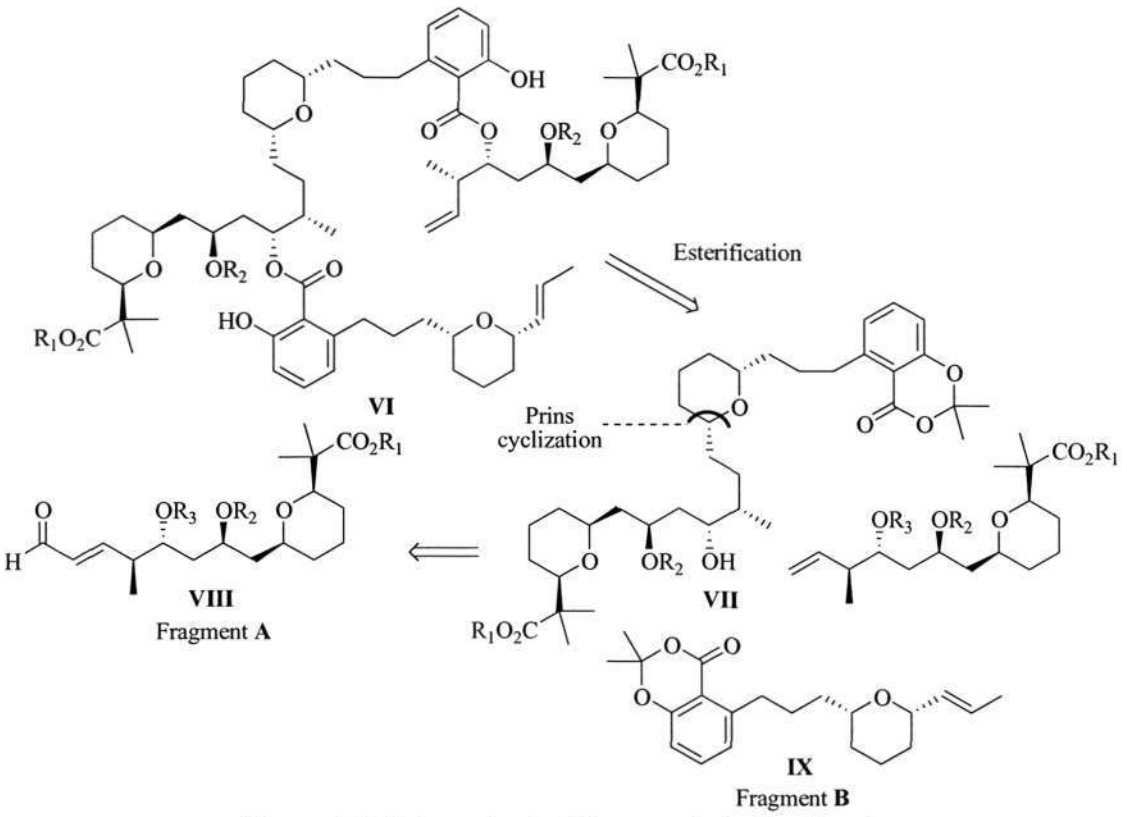
Two possible synthetic routes were proposed to assemble 28-membered dilactone (Scheme 5.10). The first route was modeled after Eun Lee's strategy where ring closing olefin metathesis was used to couple two alkenyl moieties to form the 28-membered macrodiolide (see intramolecular olefin metathesis route). The second route was to adopt catalytic Prins cyclization to close up the dilactone *via* formation of a THP ring. To the best of our knowledge, intramolecular Prins cyclization has not been demonstrated in any natural product synthesis.



Scheme 5.10 Two possible retrosynthetic route for the formation of 28-membered dilactone.

Following the dissection of macrodilactone, the two ester linkages at C-13 and C-32 can be cleaved to liberate the northern hemispheric hydroxy acid **VII** and the acetonide-THP alkene **IX** (Fragment **B**). Retro-Prins cyclization lead to two synthetically viable fragments: an αβ-unsaturated aldehyde (**VIII**) and an acetonide-homoallylic alcohol (**IX**) (Scheme 5.11). Although we have demonstrated Prins cyclization on simple conjugated aldehydes[133], we envisaged that the assembly of these two fragments might succumb to considerable level of difficulty due to the differential reactivity of the fragments and the stereochemical constraints. Hence, the northern hemisphere monomeric unit will be the target molecule in our formal synthesis of (+)-SCH 351448 employing the catalytic Prins cyclization strategy.

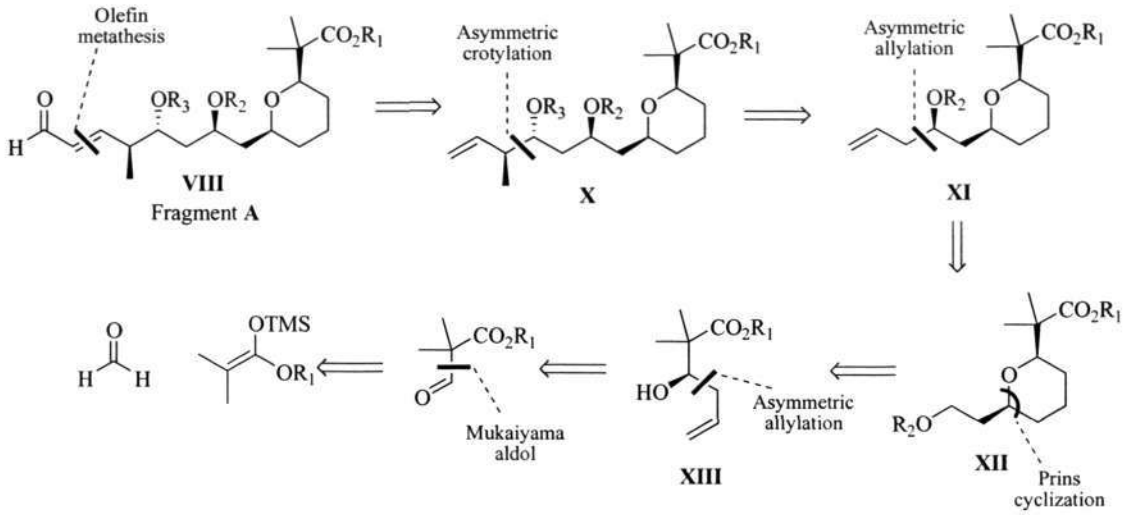
[133] For demonstration Prins cyclization with simple conjugated aldehydes, refer to Chapter 3.1 in this thesis.



Scheme 5.11 Retrosynthesis of the open-chain dimeric unit.

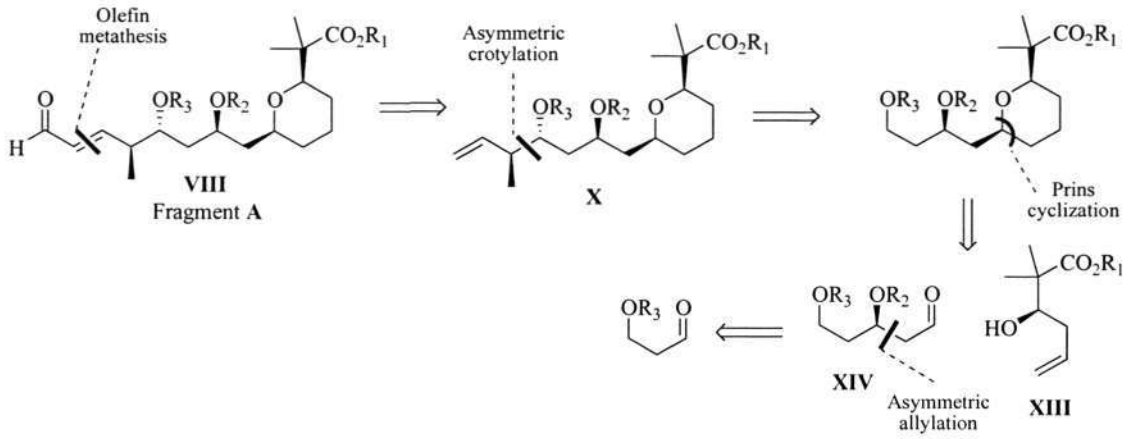
5.2.2 Retrosynthesis of Fragment **A**

Fragment **A** is an αβ-unsaturated aldehyde with a *cis*-2,6-disubstituted tetrahydropyran ring, containing a 1,3-*anti*-diol and an α-quaternary carboxylate ester. The aldehyde can be afforded from a homoallylic alcohol (**X**) and acrolein using olefin metathesis (Scheme 5.12). The *anti*-1,3-diol can be synthesized from asymmetric crotylation and allylation from a THP-ester (**XII**). The latter can be further disconnected into a 1,3-protected aldehyde and a homoallylic hydroxyl ester (**XIII**), which can be obtained from asymmetric allylation of a three-carbon chained aldehydic ester synthesized from Mukaiyama aldol reaction of trimethylsiloxypropene and formaldehyde.



Scheme 5.12 Retrosynthesis of Fragment **A**.

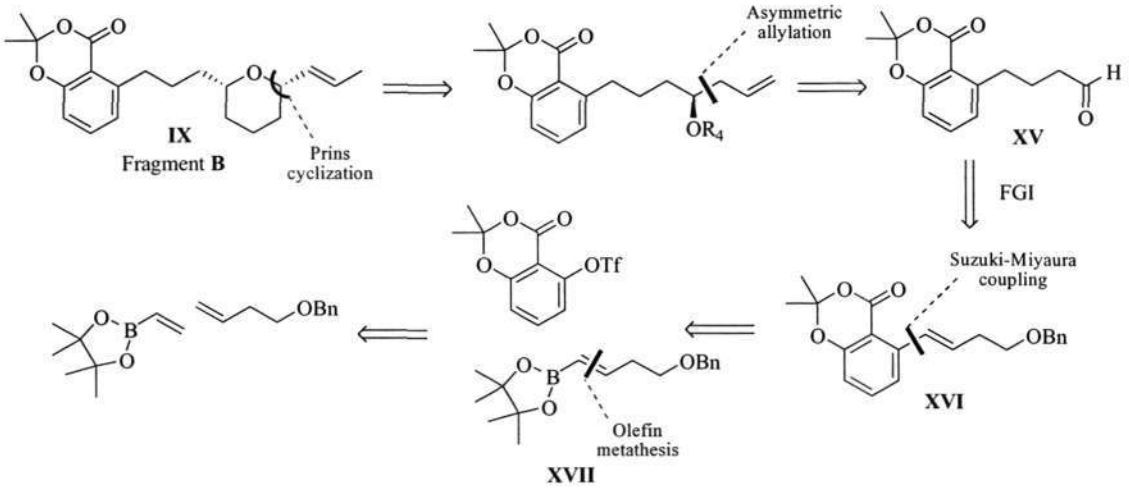
A more convergent strategy has also been proposed to synthesize Fragment **A** (Scheme 5.13). Similarly, we can adopt catalytic Prins cyclization as the key step to assemble the fragment using, in this case, a 1,3-protected-diol-5-aldehyde (**XIV**) with **XIII**. Both the strategies have been studied and shall be discussed in the later section of this thesis.



Scheme 5.13 Alternative retrosynthetic analysis of Fragment **A**.

5.2.3 Retrosynthesis of Fragment **B**

Fragment **B** consists of an unsaturated *syn*-2,6-disubstituted tetrahydropyranyl acetonide, which can be achieved from Prins cyclization using (*S*)-homoallylic alcohol with an acetonide protected salicylate moiety (Scheme 5.14).



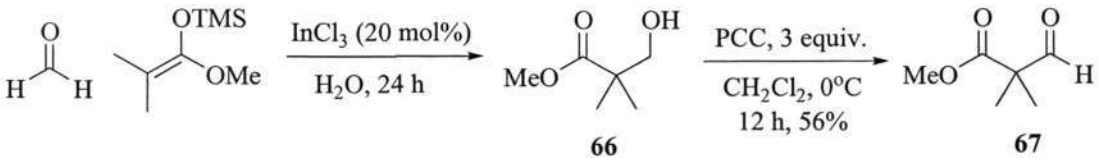
Scheme 5.14 Retrosynthetic analysis of Fragment **B**.

This can be easily afforded using asymmetric allylation on the respective aldehyde (**XV**). The challenge then lies in the C-C bond formation between the salicylic acid fragment and the aliphatic moiety to form the acetonide benzyl-ether **XVI**. We proposed a direct Suzuki-Miyaura coupling of a salicylate triflate with a vinylic 1,3,2-dioxaborolane **XVII**, which can be easily synthesized from commercially available starting materials *via* olefin metathesis.

5.3 SYNTHESIS OF FRAGMENT A

5.3.1 Synthesis of Methyl 2-formyl-2-methylpropanoate, **67**

Our highly convergent strategy commenced with the synthesis of a 2,2-dimethyl-3-hydroxy-methyl ester **66** from a silyl-enol-ether and formaldehyde. The generation of the achiral quaternary carbon using an indium mediated Mukaiyama aldol[134] condensation in aqueous media is well established in our group[135] (Scheme 5.15).



Scheme 5.15 Synthesis of methyl 2-formyl-2-methylpropanoate, **67**.

The isolated alcohol was subjected to oxidation to form the corresponding aldehyde. Due to its expected low boiling point, careful choice of oxidation method has to be considered. Swern oxidation[136] will create complications in the distillation of the aldehyde as the side products may have an azeotropic effect which can possibly contaminate the distillate. Dess-Martin periodinane[137] was first employed to perform the oxidation. However, difficulties were encountered during work-up and purification of the aldehyde, rendering this method rather low yielding. On the other

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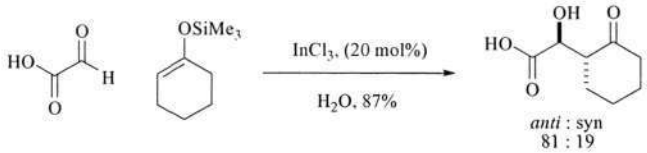
[134] (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. For reviews, see (b) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590. (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 66.

[135] Loh, T. P.; Pei, J.; Cao, G. Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819. This aqueous reaction is extremely applicable in this total synthesis due to its ease of synthesis, high-yielding and employment of catalytic amount of Lewis acid. The reaction was also reported to have moderate diastereoselectivity.



[136] (a) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, *4*, 297. (b) Omura, K.; Swern, D. *Tetrahedron* **1973**, *34*, 1651. For mechanism, see (c) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661. (d) Johnson, C. R.; Phillips, W. G. *J. Org. Chem.* **1967**, *32*, 1926.

[137] Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Lett.* **1993**, *58*, 2899.

hand, pyridinium chlorochromate[138] was able to afford the crude aldehyde in reasonable quantity after the reaction mixture was passed through a pad of silica gel using dichloromethane, followed by evaporation of the solvent at low temperature and moderate pressure. In order to remove moisture and unreacted alcohol, the crude aldehyde was stirred with molecular sieves for 24 hours, and was subjected to vacuum distillation to give the pure aldehyde **67** with an overall yield[139] of 56% (Scheme 5.15).

5.3.2 Synthesis of (*R*)-Methyl 3-hydroxy-2,2-dimethylhex-5-enoate, **68**

The introduction of the first chiral center was attempted using indium trichloride catalyzed asymmetric allylation[140] to yield 74% of (*R*)-methyl 3-hydroxy-2,2-dimethylhex-5-enoate **68** with 70% *ee*. In the attempts to improve the yields and enantiomeric purity of the product, we screened various methods of asymmetric allylation[141] (Table 5.1) and found that Brown's allylation[142] was the most desirable, yielding 71% of the homoallylic alcohol with 96% *ee*.

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[138] (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. (b) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 2641.

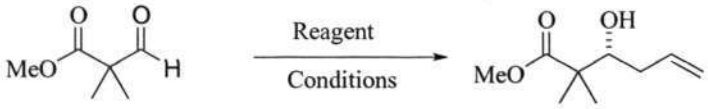
[139] The overall purified yield was computed over two steps, which excluded some remaining aldehyde in the residue. The latter was used for subsequent steps in racemic synthesis. The overall crude yield was approximately 87%, calculated from the crude nmr spectrum.

[140] (a) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 1318. (b) Teo, Y. C.; Goh, J. D.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2743. (c) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 159.

[141] Other methods of asymmetric allylation have been considered and carried out without much success. For references on these methods, see (a) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692. (b) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (c) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (d) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

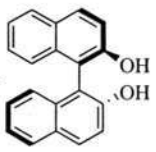
[142] (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1984**, *49*, 4089 (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S.; Perumal, T. *J. Org. Chem.* **1986**, *51*, 432 (d) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319 (e) Brown, H. C.; Randad, R. S.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1570 (f) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

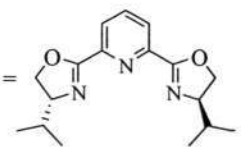
Table 5.1 Various allylation methods to synthesize (*R*)-homoallylic alcohol **68**.

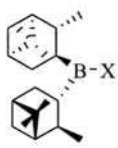


67 **68**

Entry	Reagent	Conditions	Yield (%)	*Ee* (%)
1	$InCl_3$ (20mol%), $Bu_3SnAllyl$ (2.0 equiv), (*R*)-BINOL[a] (22 mol%), 4Å mol. sieve[143]	-78 °C,	74	70
2	$In(OTf)_3$ (20mol%), $Bu_3SnAllyl$ (1.2 equiv), (*R*)-^{i}Pr-PYBOX[b] (22mol%), TMSCl (1.2 equiv), 4Å mol. sieve	-60°C	49	44
3	(+)-DIP[c]-Cl, AllylMgBr,	-78 °C	65	92
4	(+)-DIP-Br, AllylMgBr	-78 °C	71	96

[a] (*R*)-BINOL = 

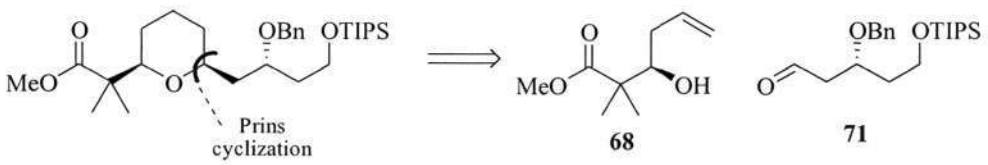
[b] (*R*)-^{i}Pr-PYBOX = 

[c] (+)-DIPX = 

X = Cl, Br

5.3.3 Synthesis of 3-(Benzyloxy)-5-triisopropylsilyloxy-pentanal **71**

The convergent retrosynthetic analysis proposed in Scheme 5.16 the strategy allowed us to investigate the 1,3-diastereoselectivity in Prins cyclization with a chiral aldehyde bearing a secondary protected alcohol.



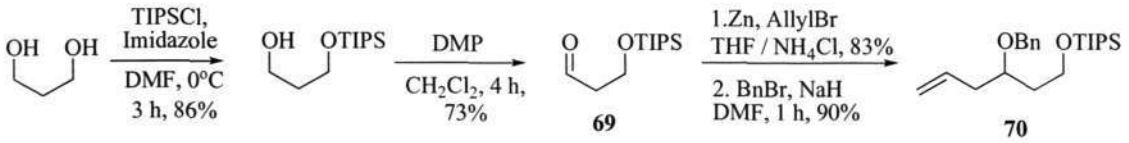
68 **71**

Scheme 5.16 Proposed alternative retrosynthetic route involving alcohol **68** and aldehyde **71**.

However, attempts to realize this strategy on racemic materials were futile. We began with a mono-TIPS protection on 1,3-propan-diol followed by Dess-Martin

[143] Other aldehydes such as benzaldehyde and cyclohexylcarboxylaldehyde have been demonstrated to show *ee* greater than 90% in excellent yields with the chiral indium catalyzed allylation. The unexpected results shown in Table 5.1 could be due to the steric effect caused by the quaternary carbon and competitive chelating effect due to the ester moiety.

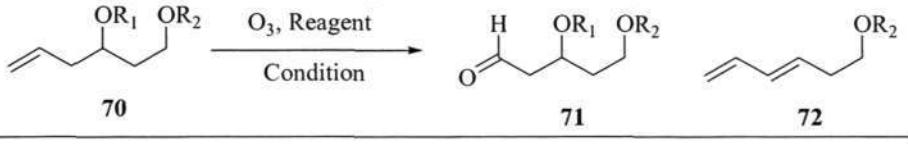
periodinane oxidation to afford 3-triisopropylsilyloxy-propanal **69**. Zinc allylation of aldehyde **69** yielded the racemic homoallylic alcohol, which was subsequently protected with a benzyl group to form the diol-protected alkene **70** (Scheme 5.17).



Scheme 5.17 Synthesis of *rac*-3,5-diprotected homoallylic alcohol **60**.

The synthesis proceeded smoothly until the ozonolysis of the diol-protected alkene **70** failed to yield the 3,5-diprotected pentanal **71**. Only a minute quantity (< 20% yield) of the desired product was obtained upon treatment with ozone followed by dimethyl sulfide reduction[144], together with eliminated and polymerized species as the major products. Several attempts were targeted at improving the yields of the **71** as shown in Table 5.2.

Table 5.2 Efforts to optimize[a] the yield of diprotected 3,5-diol-aldehyde.



70 **71** **72**

Entry	R_1	R_2	Reagent	Condition	Yield (%)[b]	
					71	**72**
1	Bn	TIPS	Me_2S (5 equiv)	-78 to 0 °C	3	34
2	Bn	TIPS	Me_2S (3 equiv)	-78 °C, 24 h	3	48
3	Bn	TIPS	PPh_3 (3 equiv)	-78 °C, 24 h	18	29
4	Ac	TIPS	PPh_3 (3 equiv)	-78 °C, 24 h	-	58
5	Bz	TIPS	PPh_3 (3 equiv)	-78 °C, 24 h	5	53
6	Bn	PMB	PPh_3 (3 equiv)	-78 °C, 24 h	-	56

[a] The reaction was monitored using TLC to ensure that all the alkenes were converted to ozonide prior to addition of reducing agents. [b] Apart from **71** and **72**, the rest of the products were degraded compounds which were not identified.

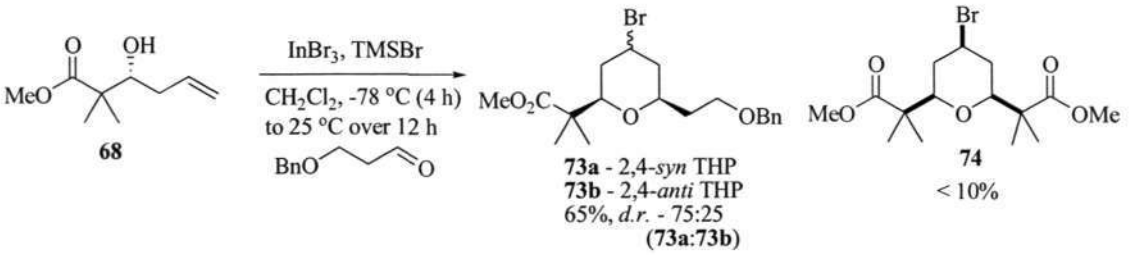
[144] We subject **60** to ozone at -78 °C and the reaction was monitored closely using TLC analysis. Dimethyl sulfide was immediately added upon completion of reaction and was allowed to warm up gradually to 0 °C over 8 hours.

Although there was a slight improvement in the yield at low temperature with triphenylphosphine as reducing agent, purification and storage of aldehyde **71** became a very significant problem. Albeit after flash column chromatography, the aldehyde was often contaminated with some remnant triphenylphophine residues. The aldehyde spontaneously underwent elimination to produce the conjugated aldehyde. This implied that the chiral secondary alcohol will eventually be destroyed in the subsequent asymmetric synthesis of this fragment. Such an undesirable process together with low yields at this early stage of the total synthesis outweighed the advantages that were proposed earlier. Therefore, a critical, though harsh decision was made to adopt the retrosynthetic strategy depicted in Scheme 5.12 instead.

5.3.4 Prins Cyclization – Stereoselectivity and Reactivity

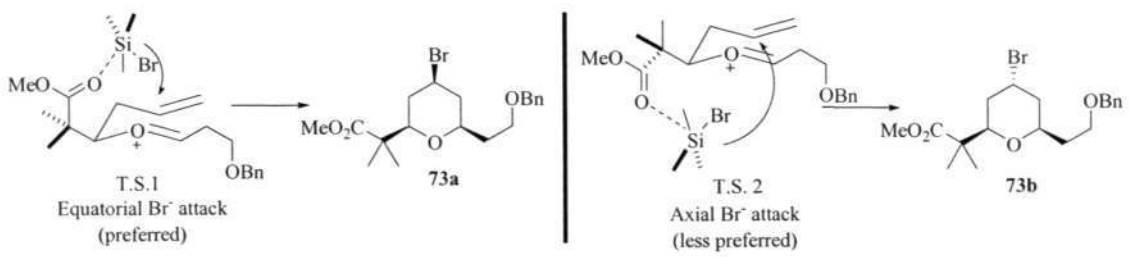
In our previous work, we demonstrated the all-*syn* stereochemical outcome in the InX_3 catalyzed Prins cyclization reaction. Homoallylic alcohol **68** was subjected to catalytic Prins cyclization with 3-(benzyloxy)propanal, catalyzed by $InBr_3$ with TMSBr as an additive at -78 °C to form the 2,4,6-trisubstituted THP ring **73**. The reaction appeared to be very sluggish, with the majority of starting material still present in the reaction mixture even after 24 hours. When the temperature was raised stepwise at 20 °C interval every 2 hours up to room temperature, the starting materials were fully consumed, yielding 28% of the desired product with many other by-products. Several attempts were made by varying the temperature to increase the yields of the THP products without compromising the risking selectivity leakage due to the allyl-transfer process. It was found that slow addition of the aldehyde at -78 °C and stirring for 4 hours before warming up gradually to room temperature for 12

hours was the optimal condition. Careful separation of the crude product using flash column chromatography isolated the products as shown in Scheme 5.18.



Scheme 5.18 Prins cyclization of **68** and 3-(benzyloxy)propanal under optimized condition.

As predicted from the observation in the total synthesis of (-)-Centrolobine, a small amount (< 10 %) of the *meso*-THP product **74** was obtained as a result of allyl-transfer mechanism in the oxy-Cope rearrangement. Apart from the expected *syn*-2,4,6-trisubstituted THP ring, we also observed a minor diastereomer of the *anti*-2,4-*syn*-2,6-THP product in a ratio of 3:1. This is consistent with the results we obtained in our *anti*-2,6-THP ring synthesis described in Chapter 4.4.3 of this thesis. However, in this case, it was postulated that with an adjacent quaternary centre restricting bond rotation, there could be momentary oxygen lone pair chelation to TMSBr, thus creating a pentavalent silicon species. This adduct promoted a concerted Br^- attack from both the equatorial and axial direction to the 4-position of the *pro*-THP transition states (T.S.1 and T.S.2, Scheme 5.19). However, since bromide coming from the axial direction was less preferred on the 4-position in a chair-like transition state, **73b** constituted the minor isomer as observed from the experimental results.



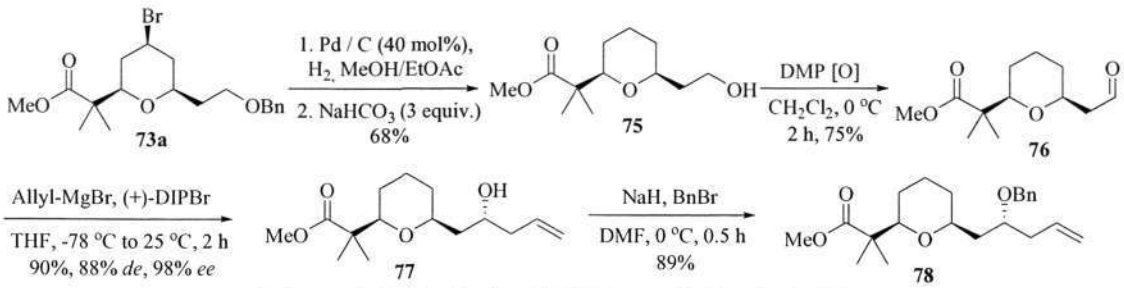
Scheme 5.18 Pentavalent silicon in the formation of axial-bromo THP product.

The failure to obtain a single 2,4,6-*syn*-isomer and the difficulty in purifying the two isomers using flash column chromatography in this reaction did not

discourage us from adopting the Prins cyclization approach. This is because there was no need to separate the diastereomers since the bromide on the 4-position of the THP ring will be removed in the subsequent step, giving the same *syn*-2,6-disubstituted THP intermediate. The enantiomeric excess of **73a** was found to be 96%, indicating complete suppression of epimerization in the catalytic Prins cyclization.

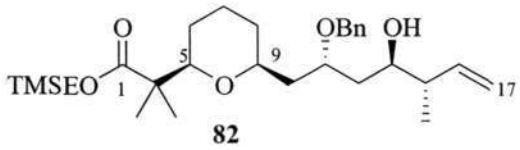
5.3.5 Synthesis of THP-homoallylic Alcohol **78**

We applied the hydrodehalogenation protocol on **73a** to provide the desired hydroxy-THP methyl ester **75** in 68% yield. Dess-Martin oxidation of **75** yielded 78% of the corresponding aldehyde, **76**. Brown's allylation of **76** using (+)-DIPBr afforded the 2,6-disubstituted-THP-homoallyllic alcohol **77**, with 88% yield and excellent diastereomeric ratio (*d.r.* 15:1). Benzyl protection was initially achieved using sodium bis(trimethylsilyl)amide and benzylbromide in THF. However, the reaction after 24 hours at room temperature only yielded 45% of the desired benzylether **78**. The reaction was repeated with the less sterically demanding sodium hydride at 0 °C for 30 minutes, and complete conversion of **77** to **78** was observed with 89% yield (Scheme 5.20). However, longer prolonged reaction under such conditions can result in the formation of some reduced methyl-ester side products.



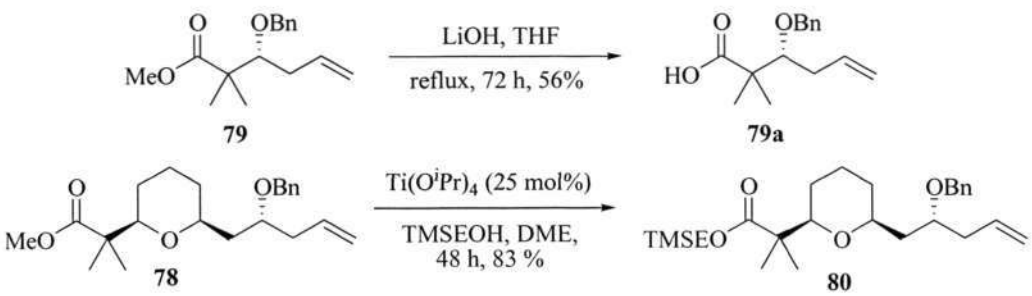
Scheme 5.20 Synthesis of THP-homoallylic alcohol **78**.

5.3.6 Synthesis of C1-C17 intermediate **82**



82

As mentioned in Eun Lee's total synthesis, he anticipated the problem of de-protection of the carboxylic acid at C-1 due to the steric hindrance of adjacent quaternary carbon. In order to verify this postulation, a model study (Scheme 5.21) was carried out using O-benzyl-methylester-homoallylic alcohol **79**, which was subjected to lithium hydroxide saponification. The deprotection was indeed very difficult to achieve at room temperature even after 48 hours. The free acid was finally obtained by refluxing with 20 equiv of LiOH over 72 hours in a moderate yield of 56 %. Taking into account the complexity of the natural product, such severe hydrolysis condition would probably disintegrate the molecule. Hence, transesterification[145] of **78** was carried out with trimethylsilylethanol and titanium (IV) isopropoxide to give the trimethylsilylethyl ester **80** in 83 % yield (Scheme 5.21).



79 **79a**

78 **80**

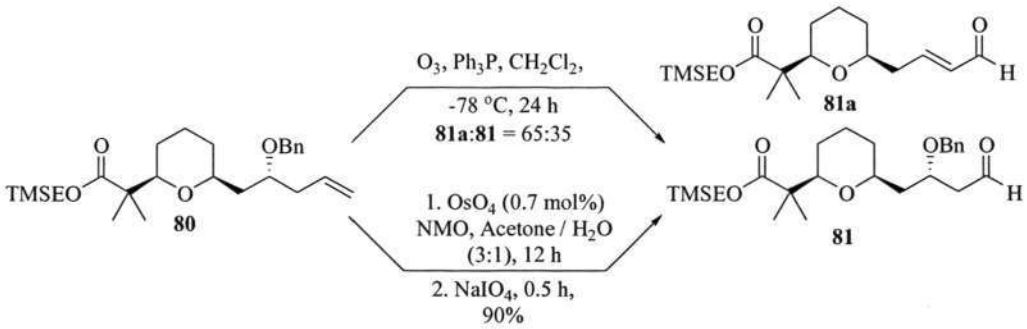
Scheme 5.21 Model study and transesterification. TMSEOH denotes trimethylsilylethanol; DME denotes dimethoxyethane.

From our experience with the synthesis of diprotected-3,5-diol-aldehyde[146], **71**, we envisaged that ozonolysis of **80** might result in elimination product (**81a**)

[145] Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis*, **1982**, 138.

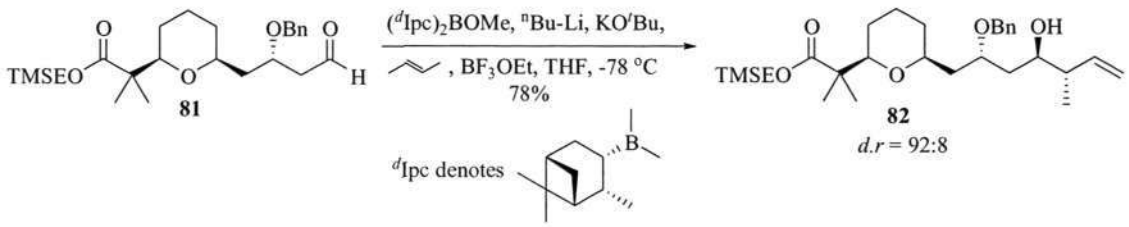
[146] Refer to Chapter 5.3.2 in this thesis for synthesis of diprotected-3,5-diol-aldehyde.

instead of the desired aldehyde **81**. Unsurprisingly, we obtained an estimated yield[147] of 43% of the products in the ratio of 65:35, with **81a** being the major product. Attempts to purify the minor product using flash column chromatography were futile. Hence, we focused our attention on osmium tetraoxide catalyzed dihydroxylation[148], followed by oxidative cleavage using sodium periodate in one pot. This method was clean and gave an excellent yield of the desired aldehyde **81** (Scheme 5.22).



Scheme 5.22 Synthesis of intermediate aldehyde **81**.

Asymmetric crotylation[149] is a widely used method to introduce a γ-allylic fragment to an aldehyde. Brown's crotylation[150] of aldehyde **81** using $(^{d}Ipc)_2BOMe$ (derived from (+)-pinene) and *trans*-but-2-ene afforded the *anti*-γ-homoallylic alcohol **82**, with 78% yield and satisfactory diastereomeric ratio of 92:8 (Scheme 5.23).



Scheme 5.23 Brown's crotylation of aldehyde **82**.

[147] Since the products cannot be separated, the yields were estimated based on the molecular weight of **75**. The relative ratio of the **75a**:**75** were determined by nmr intergration.

[148] For reviews, see (a) Bayer, A. *Comprehensive Asymmetric Catalysis* **2004**, *2*, 21. (b) Donohoe, T. J. *Synlett* **2002**, *8*

[149] For reviews, see (a) Brown H. C.; Ramachandran, P. V. *J. Organomet.Chem.* **1995**, *500*, 1. (b) Brown H. C.; Ramachandran, P. V. *Pure Appl.Chem.* **1994**, *66*, 201. (c) Hoffmann, R. W. *Pure Appl.Chem.* **1988**, *60*, 123. For other asymmetric crotylation, see (d) Roush, W. R.; Palkowitz, A. D.; Palmer, M. J. *J. Org. Chem.* **1987**, *109*, 953. (e) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (f) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

[150] (a) Brown, H. C.; Randad, R. S. *Tetrahedron* **1990**, *46*, 4157. (b) Brown, H. C.; Racherla, U. S.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608. (c) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (d) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

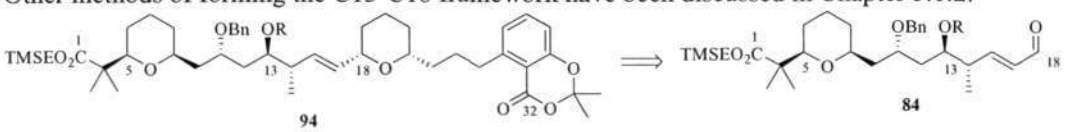
5.3.7 Synthesis of conjugated aldehyde intermediate **84**

One of the highlights in this formal synthesis was to demonstrate the versatility of catalytic Prins cyclization on natural product synthesis. Hence, in order to synthesize the monomeric unit *via* Prins cyclization, an aldehyde functionality has to be introduced to **82**. Exploitation of the double-bond in olefin metathesis[151] with acrolein seemed a very convenient mean of synthesizing the conjugated 5-hydroxy-aldehyde to match the C-13 to C-18[152] skeleton of the target molecule **94**.

Protection of **82** with *tert*-butyldimethylsilyl chloride under basic condition yielded the desired olefin **82a**. The latter was subjected to olefin metathesis under various conditions (Table 5.5) with acrolein. It was found that only Hoveyda-Grubbs 2nd generation catalyst[153] (**83d**) under sealed tube condition for 48 hours afforded **84a** (47 %) accompanied with some self-coupled products. However, when the unprotected homoallylic alcohol **82** was refluxed with the same catalyst for 8 hours, the desired conjugated aldehyde **84** was obtained in 79 % yield after purification by flash column chromatography. TBS protection[154] of **84** yielded the desired product **84a**.

[151] (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (b) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939. (c) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

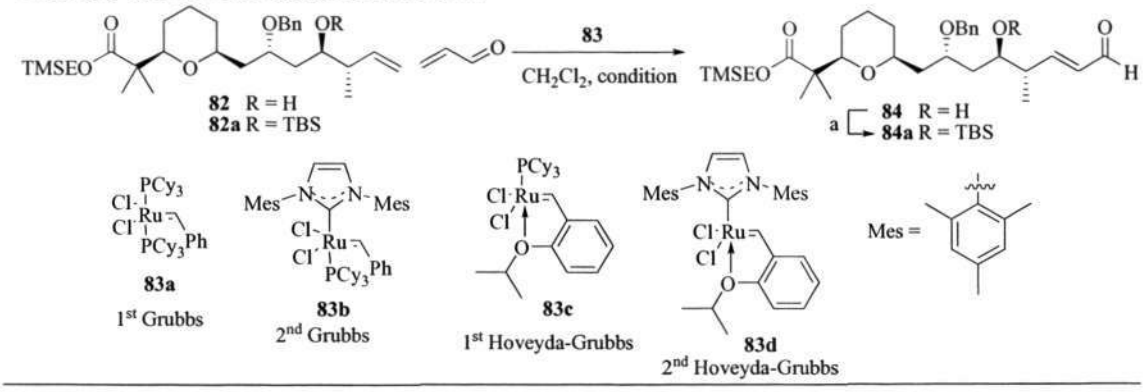
[152] Other methods of forming the C13-C18 framework have been discussed in Chapter 5.1.2.



[153] Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organometallic Chem.* **2001**, *634*, 216.

[154] (a) Askin, D.; Angst, D.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622. (b) Franck, X.; Figadere, B.; Cavé, A. *Tetrahedron Lett.* **1995**, *36*, 711. (c) Seebach, D.; Chow, H. F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *Liebigs Ann. Chem.* **1986**, 1281.

Table 5.5 Olefin metathesis of **84** and **84a**.



Entry	R	Catalyst (83)	Condition	Yield (%)	
				84	84a
1	TBS	**83b** (20 mol%)	reflux, 48 h	-	< 10
2	TBS	**83b** (20 mol%)	sealed tube, 120 °C, 48 h	-	15
3	TBS	**83a**, then **83b** (5 mol% each)	reflux, 48 h	-	N.R
4	TBS	**83c** (10 mol%)	sealed tube, 120 °C, 48 h	-	< 10
5	TBS	**83d** (20 mol%)	sealed tube, 120 °C, 48 h	-	47
6	H	**83b** (20 mol%)	reflux, 48 h	N.R	-
7	H	**83d** (5 mol%)	reflux, 8 h	79	-

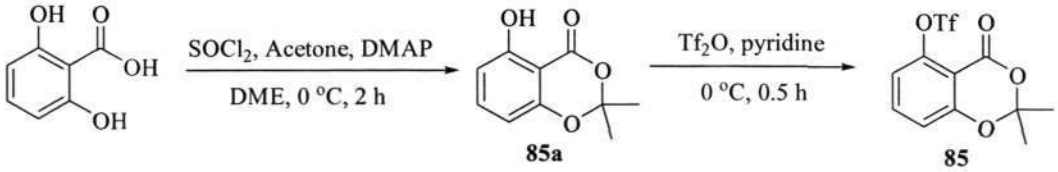
[a] TBSOTf, 2,6-lutidine, triethylamine, CH_2Cl_2, 0 °C, 0.5 h, 84 %.

5.4 SYNTHESIS OF FRAGMENT B

5.4.1 Synthesis of key intermediate **87**

The salicylate moiety of (+)-SCH 351448 can be derived from 2,6-dihydroxybenzoic acid. Protection[155] with an acetonide group using $SOCl_2$ and acetone with catalytic amount of DMAP yielded **85a**, which was subsequently functionalized to a stable acetonide-triflate **85** (Scheme 5.24).

[155] (a) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071. (b) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107. (d) Hasfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025. (e) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286. (f) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731.



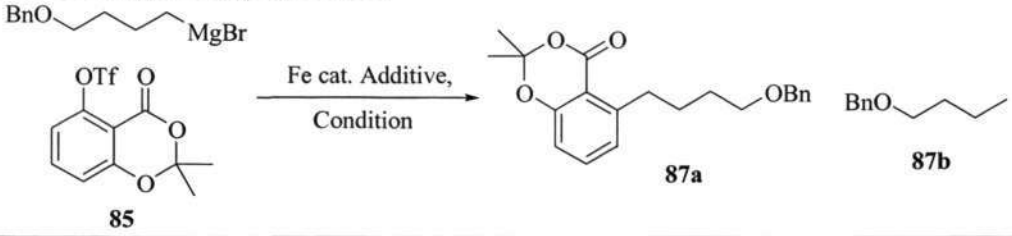
85a 85

Scheme 5.24 Synthesis of acetonide-triflate **85**.

Our initial idea for the synthesis of Fragment B revolved around direct sp^3-sp^2 coupling of 4-benzoxy-butylmagnesium bromide and acetonide-salicylate triflate **85**. This was adopted from Fürsnter's[156] work on iron-catalyzed cross-coupling reactions of alkyl-Grignard and aryl-triflates. Similar methodology has also been demonstrated by both Nakamura[157] and Hayashi[158], rendering this strategy very promising and straightforward for our application. However, no desired coupled product was obtained (Table 5.6). Instead, the Grignard reagent was quenched to become benzyloxylbutane. This novel methodology for our total synthesis was thus abandoned. Hence, the pursuit for a more suitable coupling method was directed towards Suzuki-Miyaura[159] coupling.

[156] (a) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Martin, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955.
[157] Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686.
[158] Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.
[159] (a) Suzuki, A. *Pure App. Chem.* **1991**, *63*, 419. (b) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

Table 5.6 Fe-catalyzed coupling reaction.



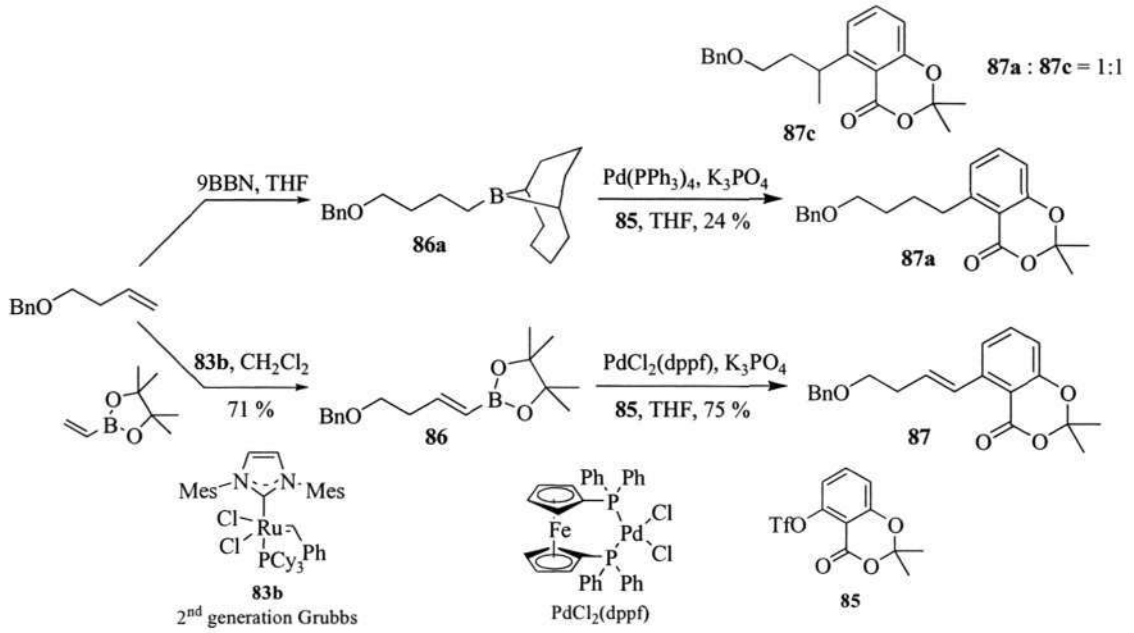
85 87a 87b

Entry	Fe cat.	Additive	Condition	Yield (%)		
				85[a]	87a	87b
1	$FeCl_3$	TMEDA	THF, -78 °C to 0 °C, 24 h	63	-	83
2	$Fe(acac)_3$	NMP	THF, 25 °C, 1 h	48	-	84
3	$Fe(acac)_3$	NMP	THF, 0 °C to 25 °C, 1 h	58	-	82

[a] The starting material was recovered using flash column chromatography, which may be partially degraded during the reaction or in the column.

The precursor of the boranyl compounds (**80** and **80a**) can be readily synthesized by benzyl protection of 3-buten-1-ol. From here, two strategies can be formulated (Scheme 5.25). The first was to perform a hydroboration on the benzyloxy-but-3-ene using 9-BBN to form alkyl borane **86a**, followed by Suzuki coupling[160] in one pot to form **87a**. However, this technically convenient strategy also yielded the undesired isomer **87c** together with **87a**. Furthermore, the hydroboration reaction was difficult to monitor using TLC, resulting in a poor overall yield of the coupling product.

[160] Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (b) Stewart, S. K.; Whiting, A. *J. Organometallic Chem.* **1994**, *482*, 293.



Scheme 5.25 Synthesis of key intermediate **87**.

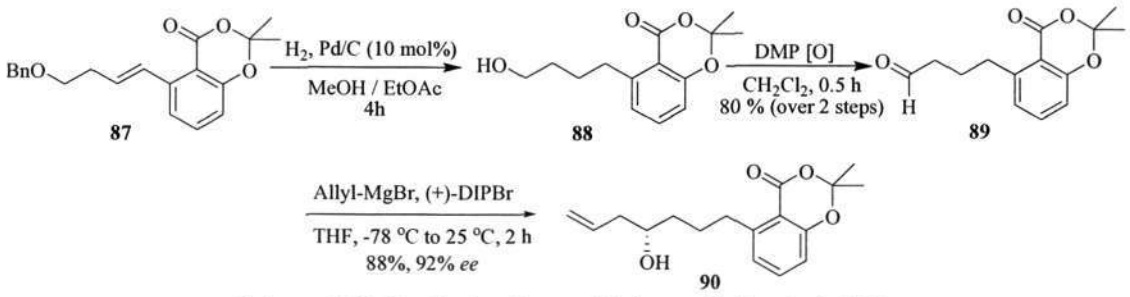
The second strategy involved olefin cross metathesis[161] between benzyloxy-but-3-ene and commercially available vinyl-pinocolate-borolane[162] using 2nd generation Grubbs catalyst (**83b**) to afford the 1,3,2-dioxaborolane **86** (Scheme 5.25). The electron deficient boron center is highly activated towards the ruthenium catalyst, hence resulting in a high yielding cross-metathesis with excellent stereo specificity, forming predominantly the (*E*)-isomer. This intermediate **86** was subjected to Suzuki[163] coupling with **85** in the presence of $PdCl_2$(dppf) and K_3PO_4 to afford the unsaturated acetonide benzylether **87** in 75% yield.

[161] (a) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187. (b) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031. (c) Chattejee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3171.
[162] For other examples of vinyl-pinocolate-borolane, see Njardarson, J. T.; Biswas, K.; Danishefsky, S. J. *Chem. Commun.* **2002**, 2759.
[163] Eastwood, P. E. *Tetrahedron Lett.* **2000**, *41*, 3705.

5.4.2 Synthesis of Fragment **B**

The unsaturated acetonide benzylether **87** was subjected to catalytic hydrogenation to de-protect the benzyl group and at the same time, reduce the double bond to form the alcohol **88**, which was then followed by Dess-Martin periodinane oxidation to afford aldehyde **89** in 80% yield over two steps (Scheme 5.26).

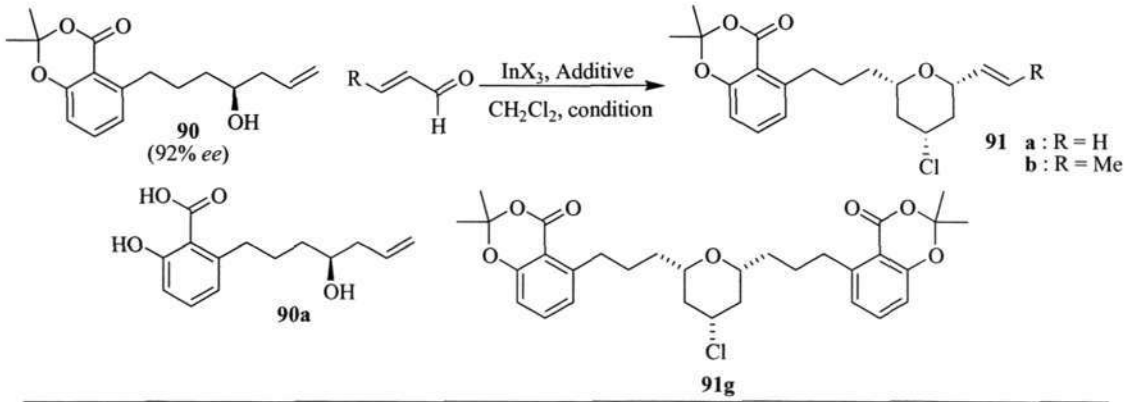
Asymmetric allylation of **89** using (+)-DIPBr and allylmagnesium bromide afforded the corresponding homoallylic alcohol **90** with 88 % yield and 92 % *ee*. This completed the synthesis of the precursor which will be combined with **84a** in the formal synthesis of (+)-SCH 351448. Apart from this purpose, **90** is be used in the synthesis of an αβ-unsaturated THP acetonide **91**, which constitutes part of the southern hemispheric fragment.



Scheme 5.26 Synthesis of acetonide homoallylic alcohol **90**.

Initially, we predicted that the αβ-unsaturated THP acetonide **91** can be synthesized using an $InBr_3$ catalyzed Prins cyclization with TMSBr and acrolein (Table 5.7, entry 1). However, no desired product was obtained and the acetonide-free homoallylic alcohol salicylic acid **90a** was isolated instead. Such a devastating outcome revealed that TMSBr could be too acidic for the acetonide group to remain intact. Disappointedly, further attempts using TMSCl also failed to yield the desired product, attributing to spontaneous polymerization of acrolein in the acidic $InCl_3$ / TMSCl solution. On the other hand, when crotonaldehyde was used, the desired Prins cyclized product was obtained with a yield of 64%.

Table 5.7 Prins cyclization of **90** and αβ-unsaturated aldehyde.



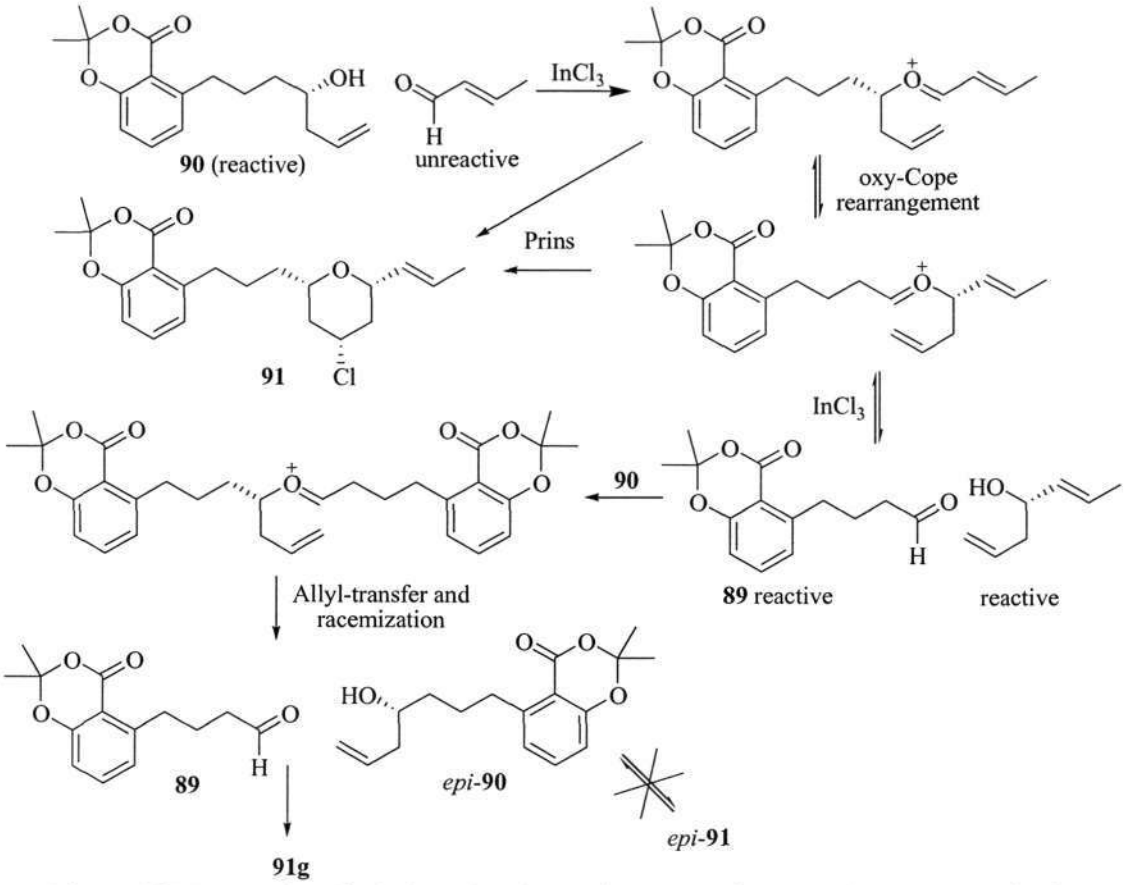
Entry	R	X	Additive[a]	Condition	Yield (%)		*Ee* (%)
					91	91g	
1	H	Br	TMSBr	0.1 M solution, -78 °C to 0 °C, 4 h	-	56	-
2	H	Cl	TMSCl	0.1 M solution , -78 °C to 0 °C, 4 h	-	48	-
3	H	Cl	TMSCl	0.1 M solution , -78 °C to -40 °C, 6 h	-	46	-
4	Me	Cl	TMSCl	0.01M solution, -78 °C to 0 °C, 4 h	33	29	82
5	Me	Cl	TMSCl (4.0 equiv)	0.1 M solution , -78 °C to -40 °C, 6 h	47	36	91
6	Me	Cl	TMSCl	0.03 M solution , -78 °C to -40 °C, 6 h	62	28	91

[a] The amount of additive added for the experiments were 1.2 equiv with respect to **90**, except for entry 6 where 4.0 equiv was used instead.

It was interesting to note the unusually high yield of the *meso*-product **91g** in this catalytic Prins cyclization[164] reaction. The homoallylic alcohol **90** seemed to be highly activated, thus facilitating allyl-transfer to form the respective aldehyde. The liberation of the corresponding aldehyde **89** spontaneously coupled with **90** to form **91g**. At the first glance, it seemed like severe racemization was unavoidable albeit stringent control on temperature and Lewis acidity. However, HPLC analysis revealed that although there was selectivity leakage[165] on the recovered alcohol **90** after the reaction, the product **91** retained its absolute configuration without significant

[164] The observed *meso*-products are usually less than 10% in Prins cyclization reaction (Refer to Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491 and Chapter 2 of this thesis).
[165] Recovered **90** has an enantiomeric purity of 65%.

racemization. Hence, it was proposed that the allyl-transfer process must have occurred through the crotonylaldehyde but ceased upon the formation of *meso*-product **91g** and *epi*-**90** (Scheme 5.27).

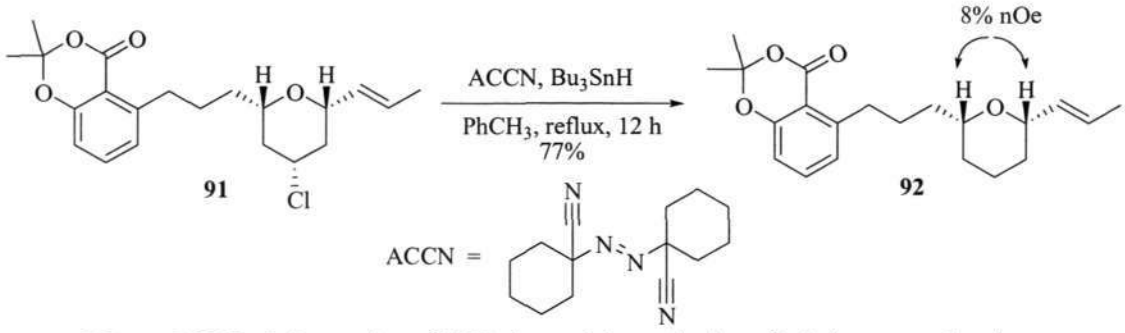


Scheme 5.27 Proposed mechanistic explanation on formation of *meso*-product and racemization suppression.

Such observations could be attributed to the reactivity of aldehyde species formed in the course of the reaction. In order for racemization to occur, the relatively unreactive crotonaldehyde must have formed the oxocarbenium ion, which proceeded directly to Prins product or underwent oxy-Cope rearrangement to liberate an acetonide aldehyde **89**. This reactive product was the key element responsible for racemization and formation of the *meso*- compound, and competed with the more unreactive crotonaldehyde for the reaction. Such competition, though brought about a lower yield of the desired product, was critical in the prevention of the formation of *epi*-**91**. Since the amount of acetonide aldehyde generated was dependent on the

molar equivalent of crotonaldeyde, the use of more homoallylic alcohol can effectively suppress racemization of **91**, but with no significant increased in yield. This valuable information set forth some indications on the feasibility of using Prins cyclization to assemble Fragment A and Fragment B in the formation of the monomeric unit[166].

Fragment B was furnished with radical dehalogenation of **91** using 1,1-azo-biscyclohexylcarboxylnitrile and tribuyltinhydride in 77% yield (Scheme 5.28). Intramolecular radical propagation with the alkenyl moiety was not observed due to conformational constraints. NMR analysis showed a 8% nOe correlation of the protons on the 2,6-position of the THP ring, indicating a *syn*-configuration of the ring structure.

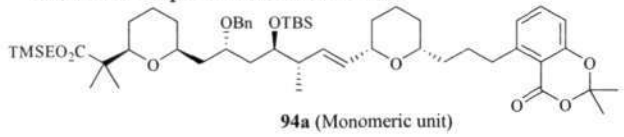


Scheme 5.28 De-halogenation of THP ring and determination of relative stereochemistry.

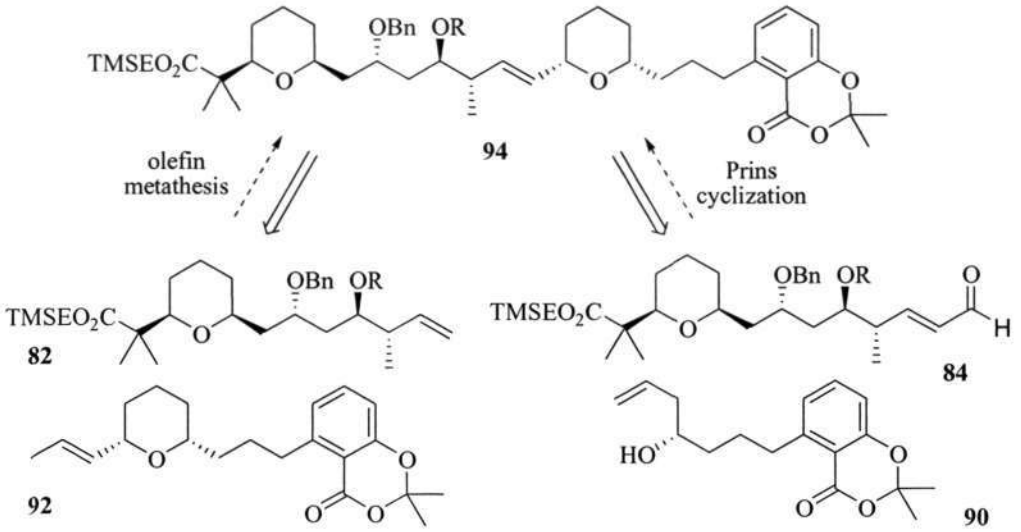
5.5 FORMAL SYNTHESIS OF (+)-SCH 351448

Two strategies have been explored in the formation of the monomeric unit. The first was using olefin metathesis between **82** and **92**, while the second strategy adopted Prins cyclization between **84** and **90** (Scheme 5.29).

[166] Refer to chapter 5.5 in this thesis.



94a (Monomeric unit)



Scheme 5.29 Retrosynthesis of the monomeric unit **94**.

5.5.1 The Olefin Metathesis Strategy

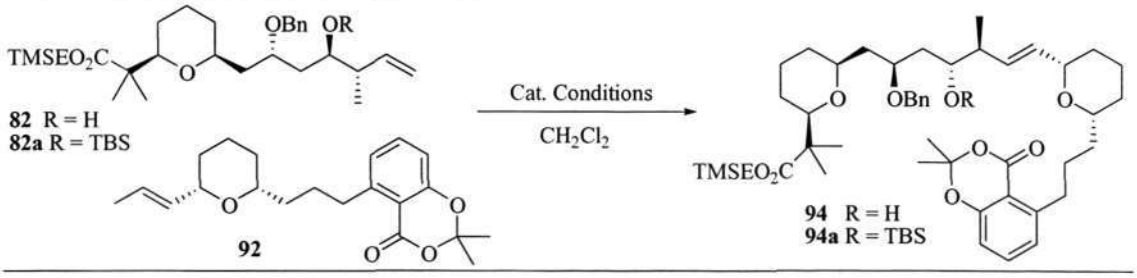
Since the development of ruthenium-carbene complexes, intramolecular ring closing olefin metathesis has exhibited tremendous applicability[167] on total synthesis of complex molecules. On the other hand for larger molecular fragments, intermolecular cross-metathesis may have several limitations such as poor reactivity, steric hindrance, self-coupling and polymerization. Nevertheless, this direct method of forming the monomeric unit is still a worthy attempt because of its ease of use and its elegance in using fewer number of steps to obtain the desired product.

In the attempts to synthesize the monomeric unit, **82** (or **82a**) and **92** was subjected to a series of different reaction conditions and catalysts. Table 5.8 showed that all the conventional reaction conditions failed to afford the desired product. All the catalysts failed except the 2nd generation Hoveyda-Grubbs catalyst which yielded about 10% of the monomeric unit under sealed-tube conditions of 120 ^{o}C for 6 days.

[167] For selected examples and reviews, see (a) Nicolaou, K. C.; King, N. P.; He, Y. *Topics in Organomet. Chem.* **1998**, *1*, 73. (b) Blechats, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (c) Gaich, T.; Mulzer, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1473. (d) Nicolaou, K.C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (e) Ivin, K. J. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1.

Such drastic reaction environment also resulted in self-coupled products and polymerized side products, rendering such a strategy inefficient and tedious.

Table 5.8 Olefin metathesis of **82(a)** and **92**.

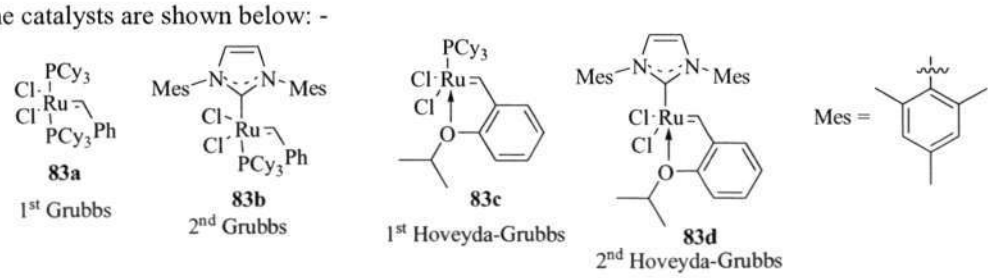


Entry	R	Cat.[168]	Conditions	Product	Yield (%)
1	H	**83b**	Reflux, 48 h	**94**	N.R.
2	H	**83b**	Sealed tube, 120 °C, 48 h	**94**	N.R.
3	H	**83c**	Reflux, 48 h	**94**	N.R.
4	H	**83d**	Sealed tube, 120 °C, 48 h	Self-coupled product of **82**	26
5	TBS	**83a**, followed by **83b**	Reflux, 48 h	**94a**	N.R.
6	TBS	**83b**	Reflux, 48 h	**94a**	N.R
7	TBS	**83c**	Reflux, 48 h	**94a**	N.R.
8	TBS	**83d**	Sealed tube, 120 °C, 6 days	**94a**	13

N.R. denotes no desired product observed, with the recovery of starting material.

There is an interesting phenomenon to note based on the olefin metathesis reactions that had been carried out so far (Table 5.5 and 5.8). The reactivity of the homoallylic alcohol fragment towards olefin metathesis seemed to vary with the

[168] The catalysts are shown below: -



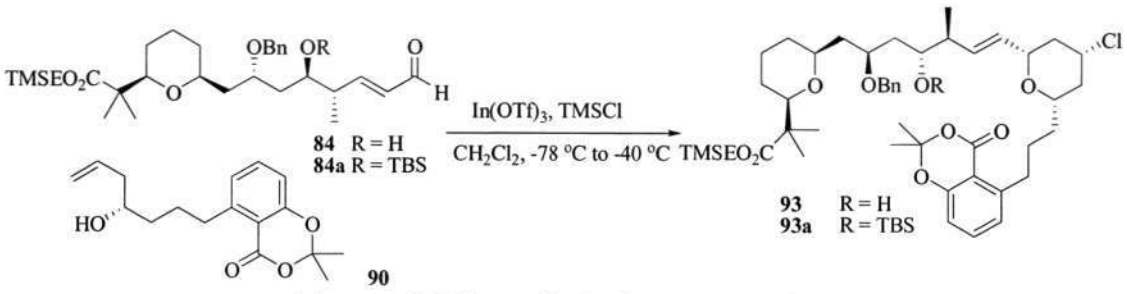
cross-coupled substrate. In the earlier case with the relatively activated acrolein, the reaction proceeded well with unprotected homoallylic alcohol (**82**). On the other hand, the same alcohol had no reaction with **92**. Contrastingly, the more sterically hindered TBS protected alcohol afforded lower yields with acrolein. Such information gives some insight to how the free-alcohol moiety can affect the reactivity of activated alkenes such as acrolein in olefin metathesis.

5.5.2 The Prins Cyclization Strategy

Prins cyclization has been widely established as a convenient method for condensation of aldehydes and homoallylic alcohol. However, application of such methodology on total synthesis has not been commonly utilized, mainly due to several reasons.

1. Racemization of chiral centers in the homoallylic alcohol.
2. Harsh reaction conditions which can affect or deprotect other functional groups.
3. Steric hindrance with larger molecular fragments in assembly of intermediates.

With the development of our indium Lewis acid catalyzed Prins cyclization, we envisaged that some of these potential problems could be overcome. The versatile use of Lewis acids (catalytic amount) and silyl-additives offer very mild reaction conditions for effective suppression of racemization. From the previous experience of acetonide deprotection with TMSBr, we subject **84** and **90** to $InCl_3$ and TMSCl at -78 ^{o}C instead. However, no desired product was observed, with the recovery of **90** and no trace of **84** at all. Despite the risk of racemization, more drastic conditions with $In(OTf)_3$ was used to catalyze the reaction (Scheme 5.30).



Scheme 5.30 Prins cyclization between **84** and **90**.

The reaction failed to proceed at -78 °C after 24 hours. Gradual increment of the temperature to -40 °C initiated the formation of products and the reaction went to completion within 4 hours, with the aldehyde, **84a**, fully consumed. However, the expected TBS-protected THP product **93a** was not isolated. The combination of $In(OTf)_3$ and TMSCl at elevated temperature accelerated the reaction, but at the same time, cleaved the TBS protecting group to form 2,4,6-*syn*-**93** in 42% yield. A portion of unreacted homoallylic alcohol **90** was recovered with 65% *ee*, indicating a reasonable level of selectivity leakage as explained in chapter 5.4.2 earlier.

Apart from the isolation of the *meso*-product **91g**, several unidentified side products were also obtained. The reaction was cleaner and went to completion in a shorter time when carried out at 0 °C, with **91g** being the major product in 46% yield, and less than 15% of the desired product **93** was isolated. Prolonged reaction at -40 °C destroyed the aldehyde **84a**, while subjecting the free hydroxyl-conjugated-aldehyde **84** failed to yield any desired product at all. As mentioned earlier, an increased proportion of either of the substrates and TMSCl had no effects on yield improvement. Nevertheless, a slight excess (1.5 equiv) of the homoallylic alcohol **90** was used to prevent severe racemization. It was noteworthy that only one single isomer was obtained in this reaction. Hence, the optimized condition was, to the best of our knowledge, the first demonstration of convergent Prins cyclization to assemble

marco-molecular fragments to form intermediates of complex molecules. The ^{1}H nmr spectra of **84a**, **90** and purified Prins cyclized product **93** are shown in Figure 5.3[169].

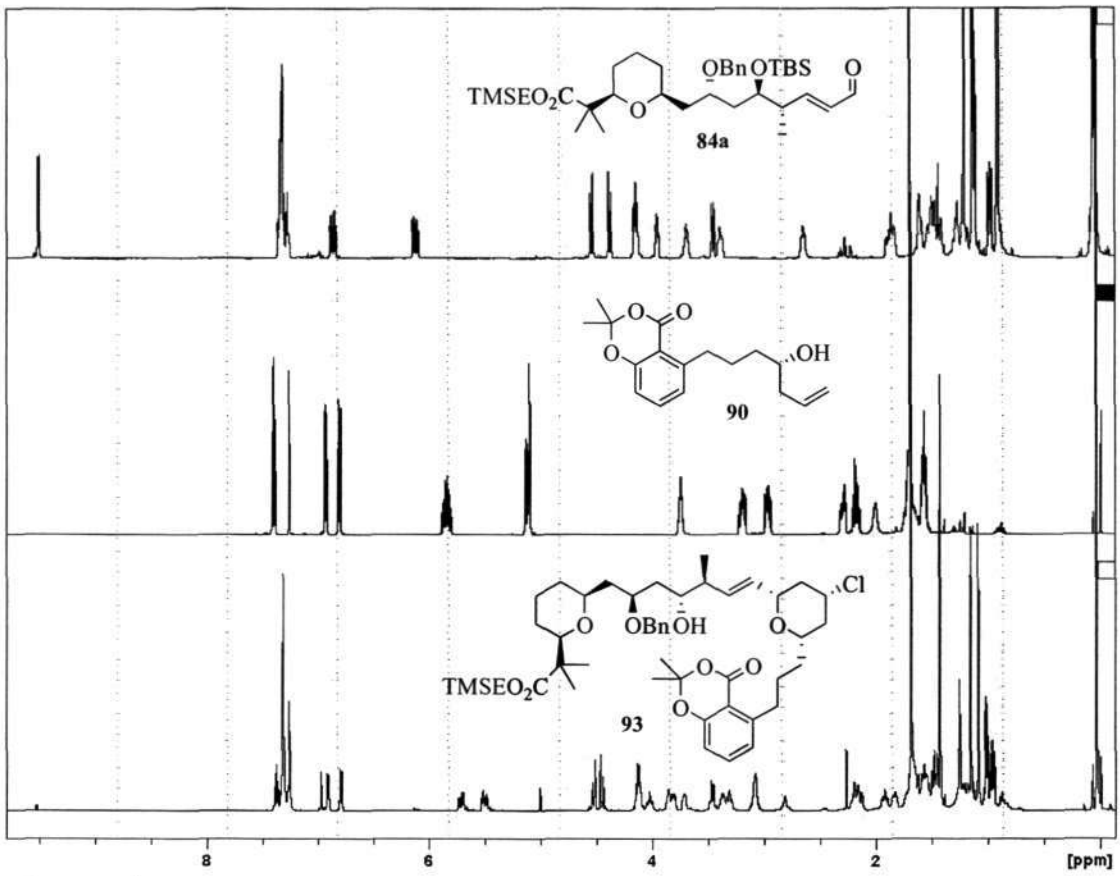
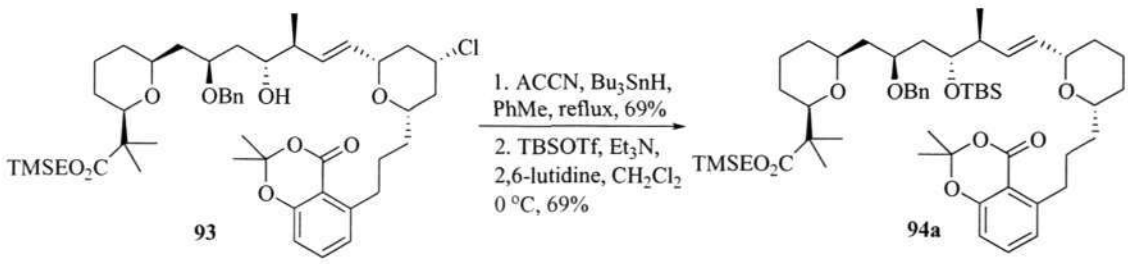


Figure 5.3 ^{1}H nmr spectra of **84a**, **90** and **93**, showing the condensation of the two starting materials.

De-halogenation of **93** using a radical mechanism with ACCN and tributyltinhydride followed by TBS protection furnished **94a**, amounting to a formal synthesis of (+)-SCH 351448[170] (Scheme 5.31).



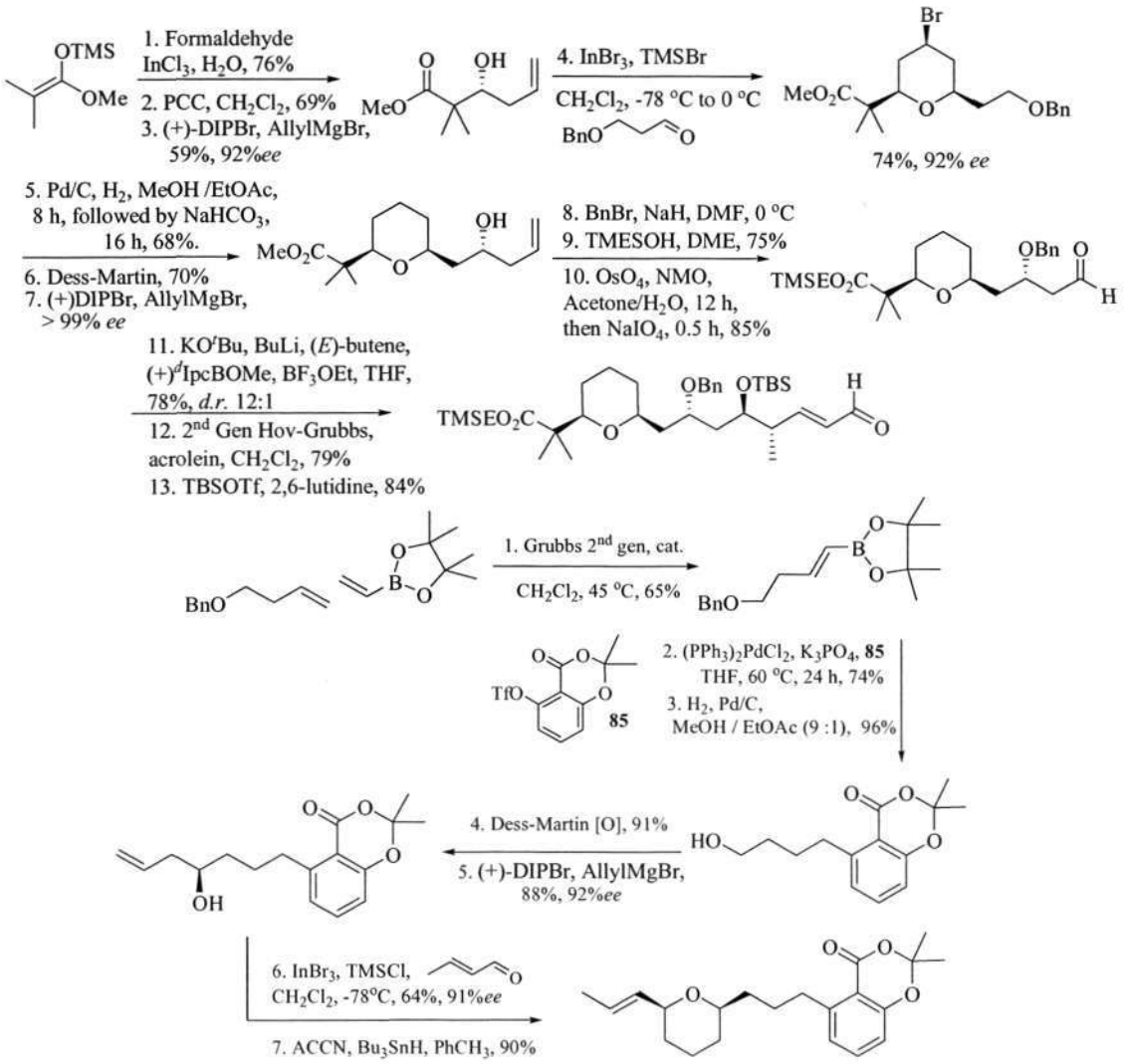
Scheme 5.31 De-halogenation and protection of **93**: Formal synthesis of (+)-SCH 351448.

[169] Note the presence of internal double bonds and the typical 4-chloro-THP proton at δ 4.03 ppm in the product ^{1}H spectrum.
[170] The ^{13}C nmr spectrum of **93a** is the same as the synthetic intermediate obtained by Eun Lee.

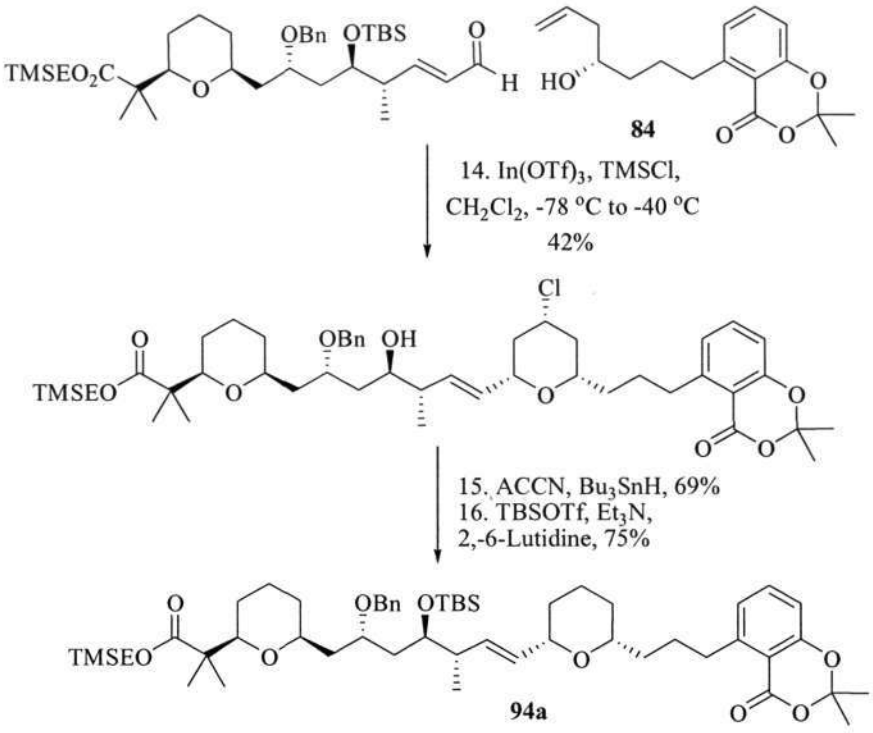
5.6 CONCLUSION

A convergent and elegant route for the formal synthesis of (+)-SCH 351448[171] has been established. This strategy possesses the following features:

- Aqueous Mukaiyama aldol catalyzed by $InCl_3$ to generate the quaternary carbon centers (C-2), and ease of scale-up reactions.
- Catalytic Prins cyclization to form the *syn*-2,6-disubstituted tetrahydropyran backbones while retaining the enantiomeric excess of the precursors.
- First demonstration of convergent synthesis to couple two elaborate molecular fragments *via* Prins cyclization (Scheme 5.32).



[171] Chan, K. P.; Ling, H. Y.; Loh, T. P. *Chem. Commun.* **2007**, *9*, 939.



Scheme 5.32 Formal synthesis of (+)-SCH 351448.

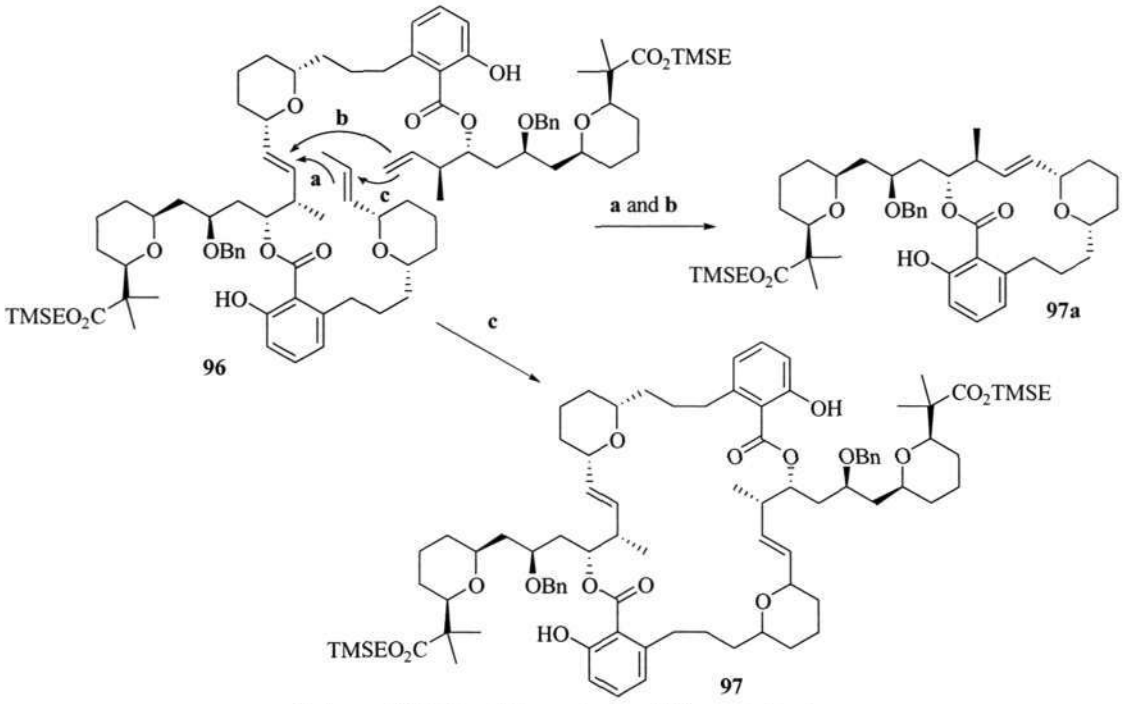
We have successfully demonstrated the use of our novel catalytic Prins cyclization from the building of small molecular fragments to the assembly of more complicated structural motifs in the formal synthesis of biologically active natural products. The syntheses of other natural products containing tetrahydropyran framework such as (+)-Apicularen A are in progress.

5.7 ATTEMPTS ON TOTAL SYNTHESIS OF (+)-SCH 351448: THE SELECTIVE OLEFIN METATHESIS STRATEGY

Upon completion of the formal synthesis, the remaining steps could be exact replication of Eun Lee's total synthesis. However, with our earlier experiences with olefin metathesis of the two fragments (Table 5.8), we found that drastic reaction conditions were required for intermolecular metathesis[172] to overcome the high energy barrier. If the double bond on the monomeric unit was intact in subsequent

[172] Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

transformation, there could be two possible ring closing metathesis[173] routes when forming the 28-membered macrocyclic structure (Scheme 5.33).

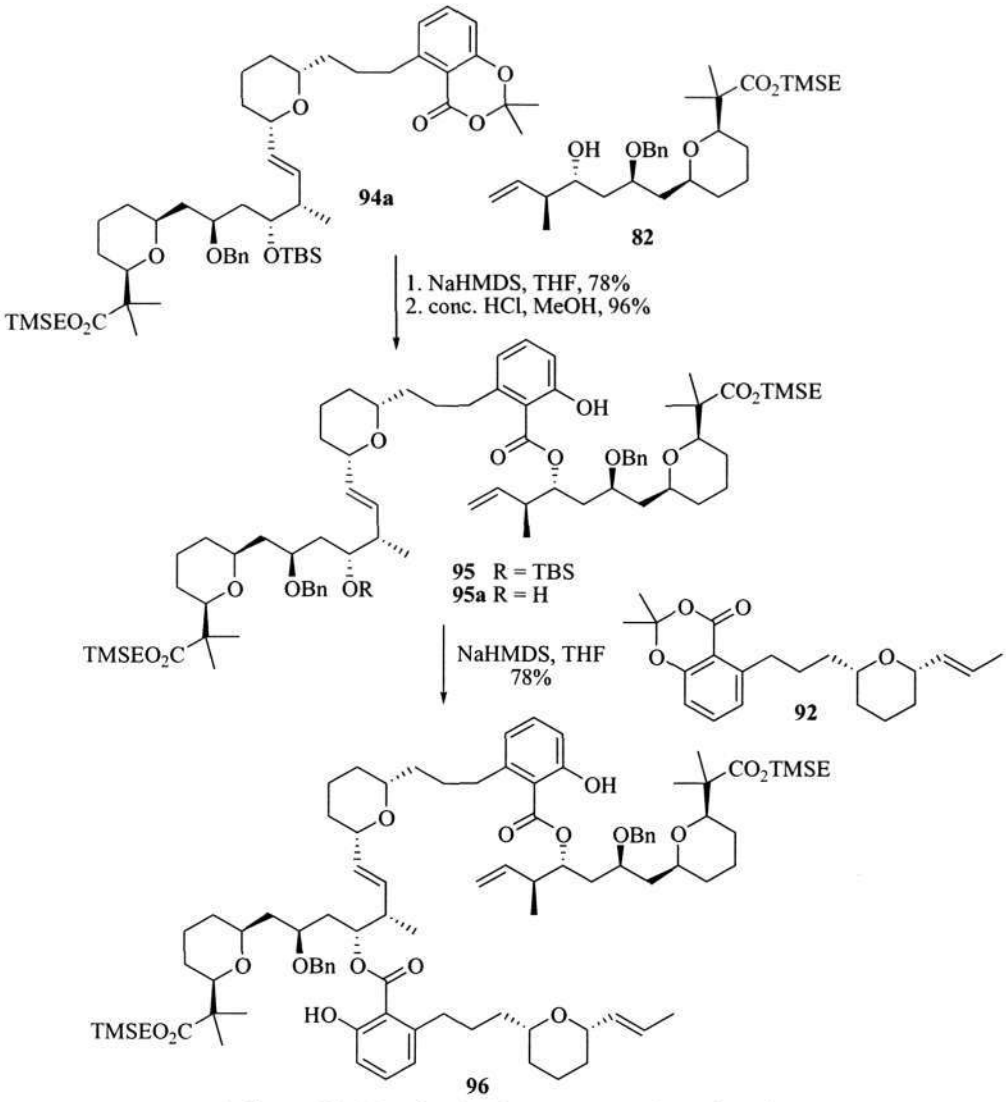


Scheme 5.33 Possible routes in olefin metathesis.

Route **a** and **b** will give the same monomeric 14-membered macrocycle **97a**, while route **c** will give the desired product **97**. Herein present a challenge for selective olefin metathesis towards less hindered double bonds.

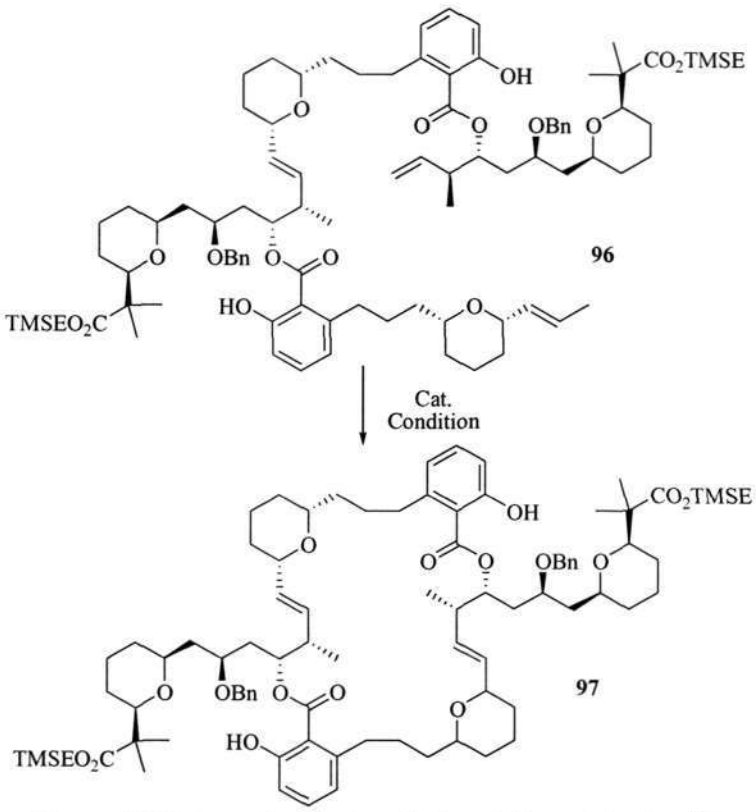
The coupling of free-homoallylic alcohol **82** to the monomeric unit **94a** was mediated by NaHMDS in THF to afford **95** with 78% yield. This was followed by TBS deprotection with concentrated HCl in methanol[174] to give quantitative yield of the free secondary alcohol **95a**. The template of (+)-SCH 351448 was completed with basic coupling of **92** and **95a** using NaHMDS to afford the triene **96** in 78% yield (Scheme 5.34).

[173] For reviews, see (a) Prunet, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1559. (b) Gaich, T.; Mulzer, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1473. (c) Ivin, K. J. *J. Mol. Cat. A* **1998**, *133*, 1.
[174] (a) Wetter, H.; Oertle, K. *Tetrahedron Lett.* **1985**, *26*, 5515. (b) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 1285.



Scheme 5.34 Synthesis of precursor to dimeric unit.

Several conditions were used in the attempts to promote the intramolecular olefin metathesis (Scheme 5.35, Table 5.9).



Scheme 5.35 Intramolecular ring closing olefin metathesis of **96**.

Table 5.9 Results for olefin metathesis of **96**.

Entry	Cat.	Condition[a]	Product	Yield (%)
1	**83b**	Reflux, 48 h	**97**	67[b]
2	**83b**	Sealed tube, 120 °C, 48 h	**97**	51
3	**83a**	Reflux, 48 h	**97**	-
4	**83d**	Sealed tube, 120 °C, 48 h	Unidentified products	-
5	**83c**	Reflux, 48 h	**97**	-

[a] The Grubbs catalyst was dissolved in CH_2Cl_2 and was added into the refluxing solution of **96** in two portions. [b] The yield reported was inclusive of the impurities observed in the ^1H nmr after flash column chromatography.

Due to the disparity in reactivity and steric constraints, intermolecular olefin metathesis seemed very unlikely under conventional reaction conditions. Refluxing dilute solutions of **96** with Grubbs 1st generation catalyst and Hoveyda-Grubbs 1st generation catalyst in separate experiments failed to give any products, with recovery of the starting material. Similar reaction condition with either of Grubbs 2nd

generation catalyst or Hoveyda-Grubbs 2nd generation catalyst gave incomplete reaction after 48 hours. Addition of a dilute solution of Grubbs 2nd generation catalyst in dichloromethane in two parts and refluxing over 48 hours afford reasonable yield of **97**. However, after purification by flash chromatography, the ^{1}H nmr spectrum indicated presence of both the product and unreacted starting material.

Deprotection and reduction of impure **97**[175] using palladium catalyzed hydrogenation afforded carboxylic acid-protected dimeric unit **98**[176] with a crude yield of 71%. Removal of trimethylsilylethanoate protecting group using TBAF[177] followed by acidification with 4*N* HCl saturated with sodium chloride yielded the natural product (+)-SCH 351448[178] (Scheme 5.36).

However, the nmr spectrum of the product indicated a mixture of other impurities which interfered with the nmr signals of the desired product. The desire macrocyclic salt also failed to be separated out from the mixture of open-chained isomer in the attempts on recrystallization. Due to limited material, reverse-phase HPLC purification of (+)-SCH 351448 resulted in drastic yields lost, rendering spectroscopic analysis very tedious. The formation of the sodium salt and its purification seemed to be more difficult than anticipated.

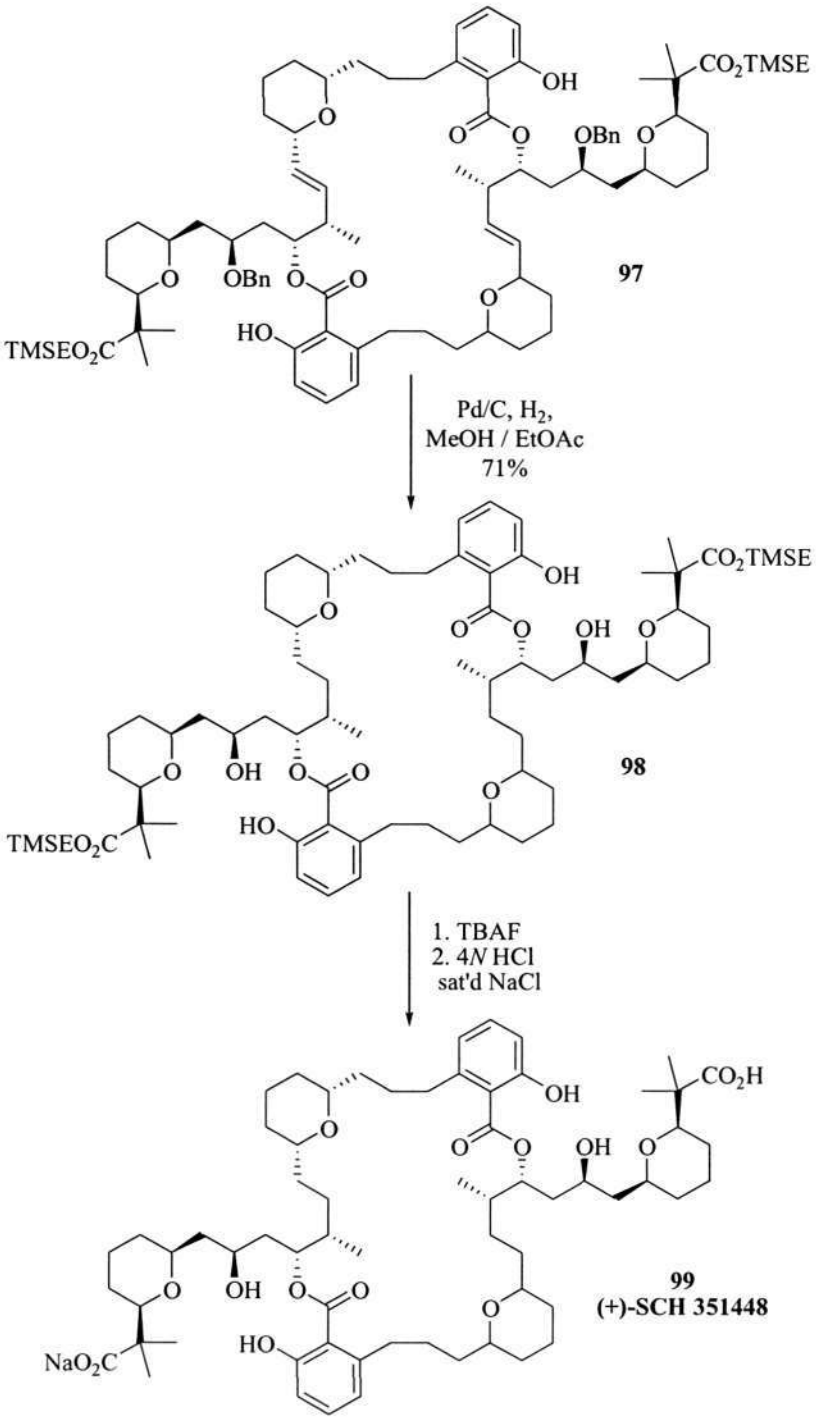
---

[175] The product contained a mixture of **96** (starting material) and **97**. The intention was to proceed with the synthesis and then purify after the deprotection step. Despite the impurities present, mass spectrometry analysis (HRMS FAB) revealed the *m/z* value of 1495.8606 (Calcd for $C_{88}H_{127}O_{16}Si_2$ [M^+-1] = 1495.8657) as the major molecular peak. This indicated the presence of the product **97**.

[176] Mass spectrometry analysis has been done for **98**. HRMS (FAB) *m/z* Calcd for $C_{88}H_{127}O_{16}Si_2$ [M^+-1] = 1495.8657. Found 1495.8606.

[177] Marlowe, C. K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 437.

[178] Mass spectrometry analysis has been done for **99**. HRMS (FAB) *m/z* Calcd for $C_{64}H_{94}NaO_{16}$ [M^+-1] = 1141.6463. Found 1141.6425.



Scheme 5.36 Attempts on the total synthesis of (+)-SCH 351448.

In a concluding note, further works on the synthesis of more natural product for analysis and biological testing are underway.

CHAPTER 6

Experimental Section

6.1 GENERAL INFORMATION

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

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

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego [179]. 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

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

traces of moisture *in vacuo* followed by subsequent purging with nitrogen. Acrolein and crotonylaldehyde were freshly distilled prior to usage.

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

Chromatography

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

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 nm) and freshly distilled solvents. Columns were packed as slurry of silica gel in hexane/CH_2Cl_2 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 & Equipment

Infrared Spectroscopy

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

Optical Rotation

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

Mass Spectroscopy

Mass spectrometry was performed by the staff 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 are 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 Bruker Avance 300, 400 and 500 NMR spectrometers. Boron (^{11}B) nuclear magnetic resonance and fluorine (^{19}F)

nuclear magnetic resonance were performed on a Bruker Avance 300 NMR spectrometer.

Chemical shifts are 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*, $CDCl_3$ (^1H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet).

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

Nomenclature

Systematic nomenclature for the compounds follows the numbering system given by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 8.0 software.

6.2 *Meso*- and Crossed 2,4,6-trisubstituted Tetrahydropyran

General Procedure for Synthesis of *Meso*-4-Chloro-Tetrahydropyrans Mediated by Allyltrichlorosilane

To an oven dried round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (0.225 g, 0.4 mmol) in CH_2Cl_2 (18 mL) to form a suspension. A mixture of allylchlorodimethylsilane (0.323 g, 2.4 mmol) and aldehyde (2 mmol) in CH_2Cl_2 (2 mL) was added to the suspension at room temperature. The mixture was stirred for at least an hour, and subsequently quenched with saturated $NaHCO_3$

solution. After stirring for 15 minutes, the mixture was extracted with ether (3 × 20 mL). The organic phase was successively washed with water (2 × 15 mL), saturated NaCl solution (2 × 10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.

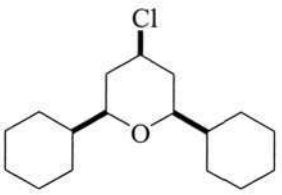
General Procedure for Synthesis of One-pot Crossed 4-Chloro-Tetrahydropyrans

To an oven dried round-bottom flask equipped with a magnetic stirring bar was added allylchlorodimethylsilane (0.336 g, 2.5 mmol) and $InCl_3$ (0.044 g, 0.2 mmol) in CH_2Cl_2 (4 mL) to form a suspension. A solution of hydrocinnamaldehyde (1 mmol) in CH_2Cl_2 (1 mL) was added to the suspension at room temperature. The mixture was stirred for at least an hour, and then cooled to 0 °C. The mixture was diluted with CH_2Cl_2 (4 mL), and then $In(OTf)_3$ (0.112 g, 0.2 mmol) was added followed by addition of a solution of aldehyde (1.0 mmol) in CH_2Cl_2 (1 mL) over a period of 5 minutes. The mixture was allowed to stir at 0 °C for at least 0.5 hour, and was then quenched with saturated $NaHCO_3$ solution. After stirring for 15 min, the mixture was extracted with ether (3 × 20 mL). The organic phase was successively washed with water (2 × 15 mL), saturated NaCl solution (2 × 10 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude product, which was purified by flash column chromatography.

General Procedure for Catalytic Prins Cyclization in Silyl Additives for the Synthesis of 4-halo-2,6-trisubstituted tetrahydropyran

To an oven dried round-bottom flask equipped with a magnetic stirring bar was added 1-phenylhex-5-en-3-ol (0.84 mmol, 148 mg), $In(OTf)_3$ (0.14 mmol, 79 mg) and dichloromethane (7 mL). The mixture was allowed to cool to 0 °C prior to addition of trimethylsilylhalide (0.84 mmol). Aldehyde (0.7 mmol, 0.7 M in dichloromethane) was added over period of 5 minutes. The reaction was allowed to proceed for 2 hours at 0 °C. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and the aqueous layer was extracted with diethylether (3 × 20 mL). The combined organic extracts was washed with water, and saturated NaCl solution, and dried over anhydrous magnesium sulphate, filtered and concentrated in *vacuo*. The residual crude product was purified *via* flash column chromatography to afford the tetrahydropyran.

4-chloro-2,6-dicyclohexyl-tetrahydro-2*H*-pyran



White solid (185 mg, 65%); R_f = 0.70 (8:1 Hex – EtOAc)

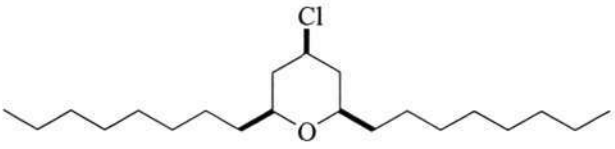
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (tt, *J* = 4.5, 11.8 Hz, 1H), 2.94 (ddd, *J* = 1.0, 6.6, 11.1 Hz, 2H), 1.89-1.91 (m, 2H), 1.77-1.69 (m, 4H), 1.68-1.62 (m, 4H), 1.57-1.53 (m, 1H), 1.47 (q, *J* = 12.2 Hz, 2H), 1.43-1.32 (m, 2H), 1.26-1.13 (m, 6H), 1.05-0.92 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 81.0, 57.7, 42.9, 40.0, 29.1, 28.9, 26.6, 26.2, 26.0.

FTIR (neat) ν_{max}: 2943, 1434, 1266, 737, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{29}ClO$ [M^+] = 284.1907, found 284.1913.

4-chloro-tetrahydro-2,6-dioctyl-2*H*-pyran



Colorless oil (223 mg, 65%); R_f = 0.70 (8:1 Hex – EtOAc)

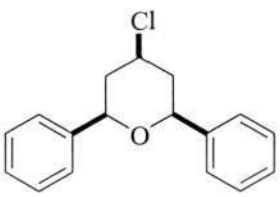
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (tt, *J* = 4.5, 11.8 Hz, 1H), 3.27-3.20 (m, 2H), 2.10 (dd, *J* = 4.5, 12.2 Hz, 2H), 1.55-1.43 (m, 4H), 1.43-1.39 (m, 3H), 1.37-1.34 (m, 1H), 1.32-1.24 (m, 22 H), 0.87 (t, *J* = 6.7 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 76.7, 56.3, 42.7, 35.9, 31.9, 29.6, 29.6, 29.3, 25.6, 22.7, 14.1.

FTIR (neat) ν_{max}: 2929, 1410, 1243, 736, 688 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{41}ClO$ [M^+] = 344.2846, found 344.2852.

4-chloro-tetrahydro-2,6-diphenyl-2*H*-pyran



Colorless oil (122 mg, 45%); R_f = 0.52 (8:1 Hex – EtOAc)

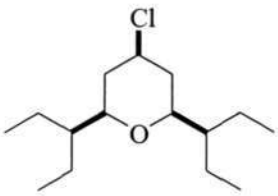
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.36 (m, 8H), 7.33-7.29 (m, 2H), 4.60 (d, *J* = 11.0 Hz, 2H), 4.33 (tt, *J* = 4.1, 11.5 Hz, 1H), 2.49 (dd, *J* = 4.0, 13.1 Hz, 2H), 1.97 (q, *J* = 12.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 128.5, 127.8, 125.8, 79.0, 55.7, 44.3.

FTIR (neat) ν_{max}: 3033, 2958, 1457, 1261, 756, 694 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{17}ClO$ [M^+] = 272.0968, found 272.0960.

4-chloro-tetrahydro-2,6-di(pentan-3-yl)-2*H*-pyran



Colorless oil (244 mg, 94%); R_f = 0.70 (8:1 Hex – EtOAc)

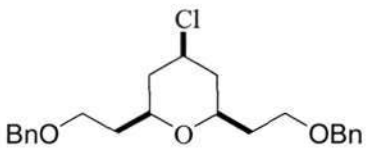
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (tt, *J* = 4.5, 11.6 Hz, 1H), 3.18 (dd, *J* = 5.1, 11.1 Hz, 2H), 2.08 (dd, *J* = 4.1, 12.5 Hz, 2H), 1.57-1.50 (m, 2H), 1.49-1.40 (m, 4H), 1.39 (sextet, *J* = 7.0 Hz, 2H), 1.32-1.23 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 6 H), 0.86 (t, *J* = 7.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 78.4, 57.8, 45.6, 39.9, 21.8, 21.4, 11.4, 11.2,

FTIR (neat) ν_{max}: 3024, 2931, 2858, 1494, 1454, 1118, 1058, 752, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{29}ClO$ [M^+] = 260.1907, found 252.1908.

2,6-bis(2-(benzyloxy)ethyl)-4-chloro-tetrahydro-2*H*-pyran



Colorless oil (175 mg, 45%); R_f = 0.49 (4:1 Hex – EtOAc)

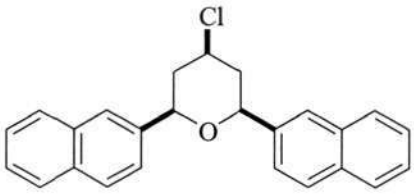
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.27 (m, 10H), 4.49 (s, 4H), 4.02 (tt, *J* = 4.5, 11.6 Hz, 1H), 3.56 (t, *J* = 7.1 Hz, 4H), 3.54-3.46 (m, 2H), 2.13 (dd, *J* = 2.2, 12.8 Hz, 2H), 1.86-1.70 (m, 4H), 1.52 (q, *J* = 11.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.4, 127.6, 127.6, 73.5, 73.1, 66.5, 55.7, 42.6, 36.0.

FTIR (neat) ν_{max}: 3011, 2943, 2849, 1451, 1361, 1158, 910, 737, 692 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{23}H_{29}ClO$ [M^+] = 388.1805, found 388.1801.

4-chloro-tetrahydro-2-(naphthalen-2-yl)-6-(naphthalen-3-yl)-2*H*-pyran



Yellow solid (97 mg, 26%); R_f = 0.43 (8:1 Hex – EtOAc)

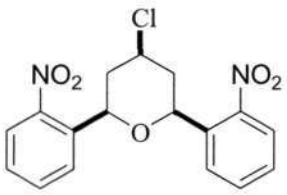
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.83 (m, 8H), 7.59 (dd, *J* = 1.7, 8.3 Hz, 2H), 7.50-7.46 (m, 4H), 4.82 (d, *J* = 11.3 Hz, 2H), 4.45 (tt, *J* = 4.5, 11.8 Hz, 1H), 2.64-2.57 (m, 2H), 2.10 (q, *J* = 12.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 133.3, 132.9, 128.1, 128.0, 127.7, 126.1, 125.8, 124.3, 124.1, 82.1, 56.9, 44.6.

FTIR (neat) ν_{max}: 3055, 2942, 2841, 1491, 1066, 859, 739 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{25}H_{21}ClO$ [M^+] = 372.1281, found 372.1289.

4-chloro-tetrahydro-2,6-bis(2-nitrophenyl)-2*H*-pyran



Yellow solid (91 mg, 25%); R_f = 0.14 (8:1 Hex – EtOAc)

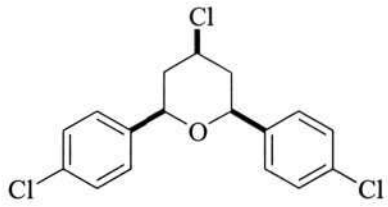
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 0.9, 8.2 Hz, 2H), 7.88 (dd, *J* = 0.9, 7.5 Hz, 2H), 7.70 (dt, *J* 0.9, 7.5 Hz, 2H), 7.47 (dt, *J* = 0.9, 8.2 Hz, 2H), 5.19 (d, *J* = 11.0 Hz, 2H), 4.45 (tt, *J* = 4.5, 11.8 Hz, 1H), 2.77 (dd, *J* = 4.5, 12.8 Hz, 2H), 1.91 (q, *J* = 12.6 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 137.1, 133.5, 128.2, 127.3, 124.4, 81.5, 56.8, 43.6.

FTIR (neat) ν_{max}: 2915, 2869, 1613, 1419, 1323, 1079, 873, 789, 741 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{15}ClN_2O_5$ [M^+] = 362.0669, found 362.0672.

4-chloro-2,6-bis(4-chlorophenyl)-tetrahydro-2*H*-pyran



White solid (122 mg, 36%); R_f = 0.40 (8:1 Hex – EtOAc)

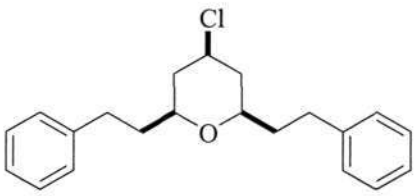
^{1}H NMR (300 MHz, $CDCl_3$) 7.35-7.33 (m, 8H), 4.55 (dd, *J* = 1.7, 11.5 Hz, 2H), 4.30 (tt, *J* = 4.2, 11.7 Hz, 1H), 2.48-2.41 (m, 2H), 1.88 (q, *J* = 11.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 133.6, 128.7, 127.2, 78.3, 55.0, 44.0.

FTIR (neat) ν_{max}: 2929, 2866, 1532, 1273, 1058, 891, 787, 721 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{15}Cl_3O$ [M^+] = 340.0188, found 340.0193.

4-chloro-tetrahydro-2,6-diphenethyl-2*H*-pyran



Colorless oil (60 mg, 74%); R_f = 0.48 (4:1 Hex – EtOAc)

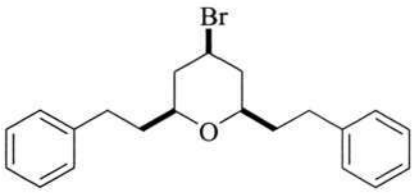
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 4H), 7.22-7.19 (m, 6H), 3.96 (m, *J* = 4.3, 11.3 Hz, 1H), 3.26 (dt, *J* = 3.8, 9.4 Hz, 2H), 2.91-2.82 (m, 2H), 2.79-2.71 (m, 2H), 2.11 (dd, *J* = 4.2, 12.2 Hz, 2H), 1.97-1.87 (m, 2H), 1.81-1.55 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.5, 128.4, 125.9, 75.4, 55.8, 42.6, 37.4, 31.7.

FTIR (neat) ν_{max}: 3025, 2914, 2838, 1599, 1494, 1448, 1353, 1319, 1256, 1149, 1082, 1017, 956, 771, 739, 696 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{25}ClO$ [M^+] = 328.1594, found 328.1596.

4-bromo-tetrahydro-2,6-diphenethyl-2*H*-pyran



Colorless oil (217 mg, 83%); R_f = 0.57 (8:1 Hex – EtOAc)

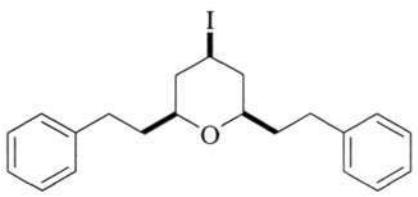
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.25-7.23 (m, 6H), 4.11 (tt, *J* = 4.5, 11.3 Hz, 1H), 3.27 (dt, *J* = 3.8, 9.4 Hz, 2H), 2.93-2.83 (m, 2H), 2.81-2.71 (m, 2H), 2.30 (dd, *J* = 4.2, 12.2 Hz, 2H), 2.02-1.89 (m, 2H), 1.84-1.72 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 128.5, 128.4, 125.8, 76.2, 46.8, 43.4, 37.2, 31.7.

FTIR (neat) ν_{max}: 3025, 2916, 2835, 1598, 1494, 1353, 1319, 1258, 1147, 1076, 1017, 953, 753, 696 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{25}BrO$ [M^+] = 373.1089, found 372.1081.

tetrahydro-4-iodo-2,6-diphenethyl-2*H*-pyran



Colorless oil (253 mg, 86%); R_f = 0.57 (8:1 Hex – EtOAc)

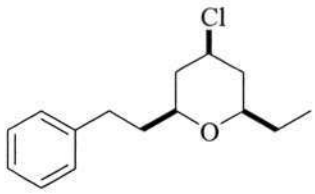
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.26-7.23 (m, 6H), 4.23 (tt, *J* = 4.5, 11.3 Hz, 1H), 3.27 (dt, *J* = 3.8, 9.4 Hz, 2H), 2.92-2.83 (m, 2H), 2.81-2.71 (m, 2H), 2.32 (dd, *J* = 3.5, 12.9 Hz, 2H), 2.04-1.87 (m, 4H), 1.81-1.70 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 128.4, 128.3, 125.8, 77.4, 45.4, 37.2, 31.6, 22.7.

FTIR (neat) ν_{max}: 3025, 2910, 2835, 1556, 1493, 1448, 1352, 1321, 1246, 1141, 1073, 1015, 947, 738, 694, 592 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{25}IO$ [M^+] = 420.0950, found 420.0953.

4-chloro-2-ethyl-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (125 mg, 71%); R_f = 0.54 (8:1 Hex – EtOAc)

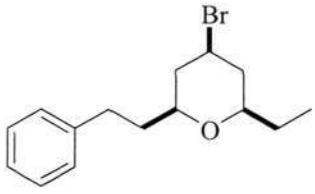
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.22-7.18 (m, 3H), 3.98 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.27-3.13 (m, 2H), 2.82-2.65 (m, 2H), 2.12 (dt, *J* = 4.5, 12.5 Hz, 2H), 1.96-1.84 (m, 1H), 1.78-1.69 (m, 1H), 1.65-1.57 (m, 2H), 1.55-1.48 (m, 2H), 0.95 (t, *J* = 7.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 128.5, 128.4, 125.8, 78.0, 75.3, 56.1, 42.7, 42.3, 37.4, 31.6, 28.9, 10.1.

FTIR (neat) ν_{max}: 3027, 2947, 2848, 1450, 1261, 1147, 1072, 752, 694 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{21}ClO$ [M^+] = 252.1281, found 252.1275.

4-bromo-2-ethyl-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (140 mg, 76%); R_f = 0.62 (8:1 Hex – EtOAc)

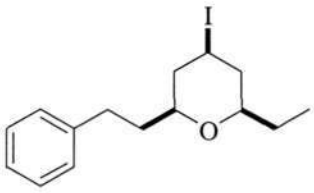
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.17 (m, 3H), 4.12 (tt, J = 4.53, 12.2 Hz, 1H), 3.24-3.13 (m, 2H), 2.84-2.65 (m, 2H), 2.22 (tdd, J = 2.1, 4.5, 12.5 Hz, 2H), 1.96-1.83 (m, 1H), 1.78-1.69 (m, 1H), 1.66-1.57 (m, 2H), 1.55-1.48 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.5, 128.3, 125.8, 78.9, 76.1, 47.2, 43.5, 43.2, 37.4, 31.5, 28.9, 10.1.

FTIR (neat) ν_{max}: 3027, 2958, 2923, 2847, 1604, 1450, 1370, 1329, 1182, 1082, 1005, 748, 699, 546 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{21}BrO$ [M^+] = 297.0776, found 296.0774.

2-ethyl-tetrahydro-4-iodo-6-phenethyl-2*H*-pyran



Colorless oil (199 mg, 82%); R_f = 0.68 (8:1 Hex – EtOAc)

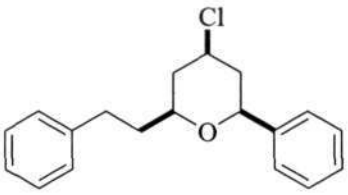
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.24 (tt, J = 4.2, 12.2 Hz, 1H), 3.26-3.14 (m, 2H), 2.84-2.65 (m, 2H), 2.31 (dt, J = 4.2, 12.2 Hz, 2H), 1.99-1.82 (m, 3H), 1.74-1.64 (m, 1H), 1.62-1.46 (m, 2H), 1.00 (t, J = 7.7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.5, 128.3, 125.8, 80.1, 76.6, 45.4, 45.1, 37.2, 31.4, 28.8, 23.2, 10.1.

FTIR (neat) ν_{max}: 3027, 2955, 2845, 1604, 1450, 1368, 1328, 1148, 1078, 749, 700 536 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{21}IO$ [M^+] = 344.0637, found 344.0635.

4-chloro-tetrahydro-2-phenethyl-6-phenyl-2*H*-pyran



Yellowish oil (156 mg, 74%); R_f = 0.50 (8:1 Hex – EtOAc)

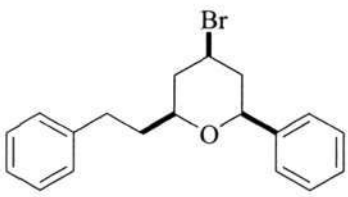
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.40 (m, 4H), 7.35-7.30 (m, 3H), 7.24-7.21 (m, 3H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.23-4.12 (tt, *J* = 4.5, 11.8 Hz, 1H), 3.54-3.46 (m, 1H), 2.94-2.73 (m, 2H), 2.44 (dd, *J* = 2.2, 12.6 Hz, 1H), 2.24 (dd, *J* = 2.2, 12.6 Hz, 1H), 2.08-1.96 (m, 2H), 1.93-1.81 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 141.5, 128.5, 128.4, 128.3, 127.6, 125.8, 125.7, 78.3, 75.8, 55.8, 44.2, 42.2, 37.3, 31.5.

FTIR (neat) ν_{max}: 3028, 2955, 2926, 1641, 1495, 1450, 1266, 1156, 1061, 739, 699 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{21}ClO$ [M^+] = 300.1281, found 300.1278.

4-bromo-tetrahydro-2-phenethyl-6-phenyl-2H-pyran



Colorless oil (199 mg, 82%); R_f = 0.51 (8:1 Hex – EtOAc)

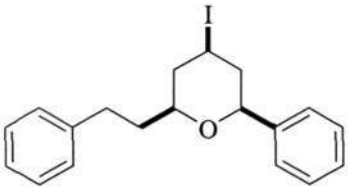
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 4H), 7.37-7.29 (m, 3H), 7.25-7.20 (m, 3H), 4.39 (dd, *J* = 2.1, 11.5 Hz, 1H), 4.30 (tt, *J* = 4.4, 12.0 Hz, 1H), 3.53-3.45 (m, 1H), 2.90-2.72 (m, 2H), 2.53 (tdd, *J* = 2.1, 4.5, 11.2 Hz, 1H), 2.33 (tdd, *J* = 2.1, 4.5, 11.2 Hz, 1H), 2.09-1.96 (m, 2H), 1.92-1.82 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 141.4, 128.5, 128.4, 128.3, 127.6, 125.8, 125.7, 79.1, 76.6, 46.6, 45.1, 42.9, 37.3, 31.4.

FTIR (neat) ν_{max}: 3027, 2951, 2923, 2852, 1600, 1495, 1450, 1351, 1300, 1155, 1059, 753, 699, 554 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{21}BrO$ [M^+] = 345.0776, found 344.0768.

tetrahydro-4-iodo-2-phenethyl-6-phenyl-2*H*-pyran



Colorless oil (226 mg, 82%); R_f = 0.59 (8:1 Hex – EtOAc)

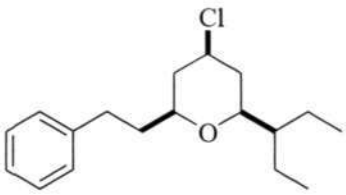
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.42 (m, 4H), 7.40-7.33 (m, 3H), 7.27-7.245 (m, 3H), 4.48-4.40 (m, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.55-3.47 (m, 1H), 2.91-2.78 (m, 2H), 2.64 (tdd, *J* = 1.9, 3.6, 12.8 Hz, 1H), 2.43 (tdd, *J* = 1.9, 3.7, 12.8 Hz, 1H), 2.32-2.11 (m, 2H), 2.07-1.98 (m, 1H), 1.92-1.83 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 141.3, 128.4, 128.4, 128.3, 127.6, 125.8, 125.6, 80.2, 77.7, 47.0, 44.8, 37.1, 31.3, 22.3.

FTIR (neat) ν_{max}: 3027, 2949, 2919, 2850, 1600, 1495, 1448, 1349, 1141, 1063, 985, 753, 699 548 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{21}IO$ [M^+] = 392.0637, found 392.0629.

4-chloro-tetrahydro-2-(pentan-3-yl)-6-phenethyl-2*H*-pyran



Colorless oil (157 mg, 76%); R_f = 0.65 (8:1 Hex – EtOAc)

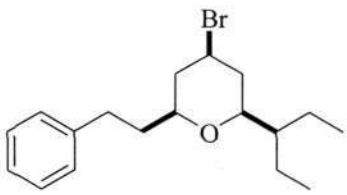
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.00 (tt, *J* = 4.53, 11.5 Hz, 1H), 3.26-3.18 (m, 2H), 2.86-2.77(m, 1H), 2.74-2.64 (m, 1H), 2.11 (tdd, *J* = 2.1, 4.5, 10.8 Hz, 2H), 1.95-1.83 (m, 1H), 1.78-1.67 (m, 1H), 1.63-1.44 (m, 5H), 1.41-1.25 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 128.5, 128.3, 125.8, 78.2, 75.3, 56.8, 45.5, 42.8, 39.7, 37.5, 31.6, 21.5, 21.3, 11.3, 11.2.

FTIR (neat) ν_{max}: 3027, 2955, 2866, 1642, 1454, 1373, 1264, 1072, 745, 699 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{18}H_{27}ClO$ [M^+] = 294.1750, found 294.1747.

4-bromo-tetrahydro-2-(pentan-3-yl)-6-phenethyl-2*H*-pyran



Colorless oil (192 mg, 81%); R_f = 0.733 (8:1 Hex – EtOAc)

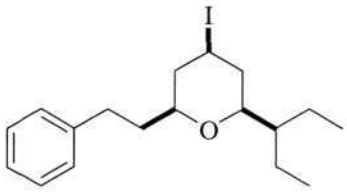
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 2H), 7.24-7.20 (m, 3H), 4.15 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.27-3.20 (m, 2H), 2.87-2.78 (m, 1H), 2.76-2.65 (m, 1H), 2.23 (tdd, *J* = 2.1, 4.5, 10.8 Hz, 2H), 1.96-1.84 (m, 1H), 1.81-1.70 (m, 3H), 1.60-1.46 (m, 3H), 1.41-1.27 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 128.5, 128.3, 125.8, 79.0, 76.2, 48.0, 45.5, 43.6, 40.6, 37.4, 31.6, 21.5, 21.3, 11.3, 11.2.

FTIR (neat) ν_{max}: 3028, 2961, 2872, 1602, 1495, 1455, 1377, 1266, 1157, 1078, 1030, 744, 699, 546 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{18}H_{27}BrO$ [M^+] = 339.1245, found 338.1240.

tetrahydro-4-iodo-2-(pentan-3-yl)-6-phenethyl-2*H*-pyran



Colorless oil (246 mg, 91%); R_f = 0.65 (8:1 Hex – EtOAc)

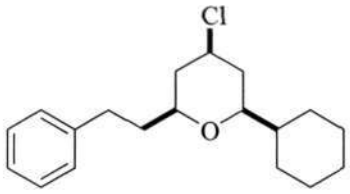
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 4.25 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.24-3.16 (m, 2H), 2.82-2.73 (m, 1H), 2.71-2.61 (m, 1H), 2.29 (tdd, *J* = 2.1, 4.5, 10.8 Hz, 2H), 1.99-1.87 (m, 2H), 1.86-1.76 (m, 1H), 1.73-1.61 (m, 1H), 1.57-1.42 (m, 3H), 1.36-1.22 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 128.5, 128.3, 125.8, 80.4, 77.6, 45.6, 45.5, 42.6, 37.3, 31.5, 24.3, 21.5, 21.2, 11.3, 11.1.

FTIR (neat) ν_{max}: 3026, 2959, 2872, 1602, 1496, 1455, 1377, 1263, 1148, 1075, 1030, 744, 698, 538 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{18}H_{27}BrO$ [M^+] = 386.1107, found 386.1099.

4-chloro-2-cyclohexyl-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (144 mg, 67%); R_f = 0.62 (8:1 Hex – EtOAc)

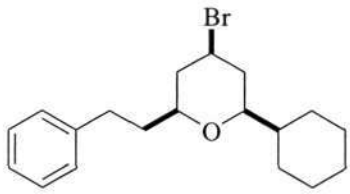
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.21-7.17 (m, 3H), 3.97 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.23-3.15 (m, 1H), 2.98 (ddd, *J* = 1.7, 7.3, 11.1 Hz, 1H), 2.85-2.65 (m, 2H), 2.18 (tdd, *J* = 2.4, 4.5, 12.5 Hz, 1H), 2.10-2.04 (m, 2H), 1.91-1.83 (m, 1H), 1.79-1.64 (m, 5H), 1.59-1.44 (m, 3H), 1.33-1.19 (m, 3H), 1.11-0.97 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 128.5, 128.3, 125.7, 80.9, 75.1, 56.6, 42.8, 39.8, 37.4, 31.6, 29.2, 28.8, 26.5, 26.1, 26.0, 25.9.

FTIR (neat) ν_{max}: 3026, 2925, 2852, 1600, 1495, 1448, 1321, 1263, 1148, 1084, 756, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{27}ClO$ [M^+] = 306.1750, found 306.1743.

4-bromo-2-cyclohexyl-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (210 mg, 86%); R_f = 0.66 (8:1 Hex – EtOAc)

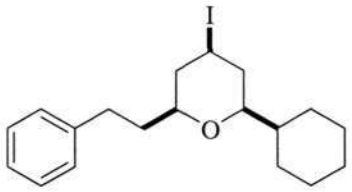
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.23-7.19 (m, 3H), 4.12 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.25-3.17 (m, 1H), 3.00 (ddd, *J* = 1.7, 7.3, 11.1 Hz, 1H), 2.84-2.67 (m, 2H), 2.29 (tdd, *J* = 2.1, 4.5, 12.5 Hz, 1H), 2.18 (tdd, *J* = 2.1, 4.5, 12.5 Hz, 1H), 2.07-1.83 (m, 2H), 1.79-1.64 (m, 5H), 1.59-1.44 (m, 3H), 1.33-1.19 (m, 3H), 1.10-0.93 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.4, 128.2, 125.7, 81.7, 75.9, 47.8, 43.6, 42.8, 40.7, 37.4, 31.5, 29.1, 28.8, 26.4, 26.0, 25.9.

FTIR (neat) ν_{max}: 3027, 2922, 2852, 1704, 1601, 1495, 1448, 1352, 1151, 1084, 746, 699, 544 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{27}BrO$ [M^+] = 351.1245, found 350.1231.

2-cyclohexyl-tetrahydro-4-iodo-6-phenethyl-2*H*-pyran



Colorless oil (249 mg, 89%); R_f = 0.76 (8:1 Hex – EtOAc)

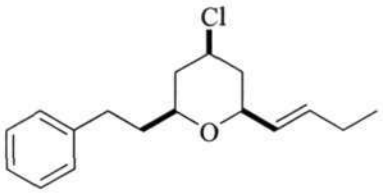
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.23-7.18 (m, 3H), 4.24 (tt, *J* = 4.2, 12.5 Hz, 1H), 3.24-3.17 (m, 1H), 3.00 (ddd, *J* = 1.7, 7.3, 11.1 Hz, 1H), 2.84-2.65 (m, 2H), 2.38 (tdd, *J* = 2.1, 4.2, 12.5 Hz, 1H), 2.27 (tdd, *J* = 2.1, 4.2, 12.5 Hz, 1H), 2.05-1.83 (m, 2H), 1.79-1.64 (m, 5H), 1.59-1.44 (m, 3H), 1.33-1.19 (m, 3H), 1.09-0.87 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.5, 128.3, 125.7, 83.1, 77.2, 45.6, 42.8, 37.3, 31.4, 29.1, 28.8, 26.5, 26.1, 26.0, 25.9, 24.1.

FTIR (neat) ν_{max}: 3026, 2923, 2852, 1600, 1496, 1448, 1266, 1134, 1063, 741, 700, 538 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{27}IO$ [M^+] = 398.1107, found 398.1101.

2-((*E*)-but-1-enyl)-4-chloro-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (152 mg, 77%); R_f = 0.55 (8:1 Hex – EtOAc)

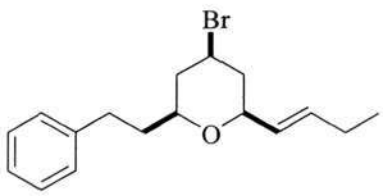
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (m, 2H), 7.25-7.20 (m, 3H) 5.81 (td, *J* = 6.3, 15.3 Hz, 1H), 5.53 (dd, *J* = 5.9, 15.3 Hz, 1H), 4.02 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.79 (ddd, *J* = 1.7, 5.6, 10.5 Hz, 1H), 3.37-3.23, (m, 1H), 2.85-2.68 (m, 4H), 2.22-2.15 (m, 2H), 2.03-1.89 (m, 2H), 1.83-1.53 (m, 2H), 1.05 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 141.7, 134.3, 128.4, 128.3, 125.8, 77.1, 75.4, 55.7, 42.6, 42.1, 37.3, 31.7, 25.2, 13.2.

FTIR (neat) ν_{max}: 2959, 2928, 2852, 1642, 1450, 1315, 1266, 1152, 1058, 968, 739, 700 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{23}ClO$ [M^+] = 278.1437, found 278.1434.

4-bromo-2-((*E*)-but-1-enyl)-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (185 mg, 82%); R_f = 0.66 (8:1 Hex – EtOAc)

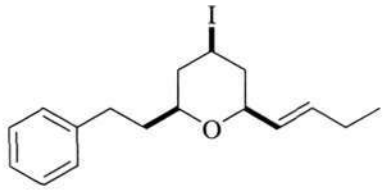
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.24-7.190 (m, 3H), 5.80 (td, *J* = 6.3, 15.3 Hz, 1H), 5.51 (dd, *J* = 5.9, 15.3 Hz, 1H), 4.15 (tt, *J* = 4.5, 12.2 Hz, 1H), 3.79 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.36-3.30, (m, 1H), 2.83-2.71 (m, 2H), 2.23-2.21 (m, 2H), 2.11 (qd, *J* = 7.3, 14.5 Hz, 2H), 2.02-1.91 (m, 2H), 1.83-1.72 (m, 2H), 1.05 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 134.3, 128.5, 128.4, 128.3, 125.8, 77.8, 76.2, 46.6, 43.4, 42.9, 37.4, 31.5, 25.2, 13.2.

FTIR (neat) ν_{max}: 3027, 2959, 2923, 2848, 1603, 1495, 1450, 1312, 1156, 1057, 968, 734, 700, 540 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{23}BrO$ [M^+] = 323.0932, found 322.0930.

2-((*E*)-but-1-enyl)-tetrahydro-4-iodo-6-phenethyl-2*H*-pyran



Brown oil (215 mg, 83%); R_f = 0.61 (8:1 Hex – EtOAc)

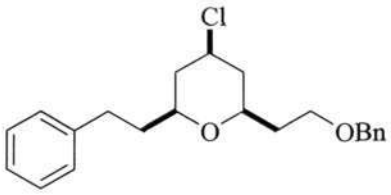
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.23-7.19 (m, 3H), 5.78 (td, *J* = 6.3, 15.3 Hz, 1H), 5.48 (dd, *J* = 5.9, 15.3 Hz, 1H), 4.27 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.78 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.35-3.27, (m, 1H), 2.83-2.65 (m, 2H), 2.40-2.27 (m, 2H), 2.10 (qd, *J* = 7.3, 14.5 Hz, 2H), 2.02-1.84 (m, 2H), 1.79-1.66 (m, 2H), 1.04 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 134.3, 128.7, 128.5, 128.3, 125.8, 79.1, 77.4, 45.4, 44.9, 37.1, 31.5, 25.3, 22.5, 13.3.

FTIR (neat) ν_{max}: 3027, 2959, 2919, 2846, 1604, 1495, 1357, 1266, 1141, 1059, 967, 740, 700, 534 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{23}IO$ [M^+] = 370.794, found 370.0790.

2-(2-(benzyloxy)ethyl)-4-chloro-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (153 mg, 61%); R_f = 0.42 (8:1 Hex – EtOAc)

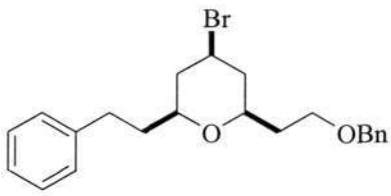
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 10H), 4.53 (s, 2H), 3.98 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.73-3.65 (m, 1H), 3.63-3.56 (m, 1H), 3.54-3.47 (m, 1H), 3.24 (tdd, *J* = 2.1, 3.8, 10.8 Hz, 1H), 2.80-2.61 (m, 2H), 2.11 (tdd, *J* = 2.1, 4.5, 10.8 Hz, 2H), 1.90-1.86 (m, 1H), 1.84-1.78 (m, 2H), 1.75-1.66 (m, 1H), 1.56-1.52 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 138.4, 128.5, 128.4, 128.3, 127.7, 127.6, 125.8, 75.2, 73.4, 73.1, 66.4, 55.8, 42.7, 42.6, 37.4, 36.1, 21.6.

FTIR (neat) ν_{max}: 3028, 2951, 2922, 2859, 2245, 1493, 1450, 1362, 1260, 1158, 1094, 1029, 910, 804, 735, 699 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{22}H_{27}ClO_2$ [M^+] = 358.1700, found 358.1688.

2-(2-(benzyloxy)ethyl)-4-bromo-tetrahydro-6-phenethyl-2*H*-pyran



Colorless oil (186 mg, 66%); R_f = 0.54 (8:1 Hex – EtOAc)

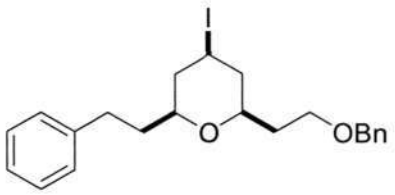
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.17 (m, 10H), 4.55 (s, 2H), 4.13 (tt, *J* = 4.5, 11.9 Hz, 1H), 3.75-3.67 (m, 1H), 3.64-3.59 (m, 1H), 3.54-3.48 (m, 1H), 3.27 (tdd, *J* = 2.1, 3.8, 10.8 Hz, 1H), 2.82-2.63 (m, 2H), 2.22 (tdd, *J* = 2.1, 4.5, 11.5 Hz, 2H), 1.91-1.80 (m, 3H), 1.76-1.67 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 138.4, 128.5, 128.4, 128.3, 127.6, 127.6, 125.8, 76.1, 74.2, 73.1, 66.3, 46.7, 43.5, 43.4, 37.3, 36.0, 31.5.

FTIR (neat) ν_{max}: 3028, 2949, 2922, 2859, 1603, 1062, 1493, 1450, 1362, 1267, 1157, 1098, 1028, 908, 738, 699, 599 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{22}H_{27}BrO_2$ [M^+] = 403.1194, found 402.1194.

2-(2-(benzyloxy)ethyl)-tetrahydro-4-iodo-6-phenethyl-2*H*-pyran



Colorless oil (602 mg, 64%); R_f = 0.51 (8:1 Hex – EtOAc)

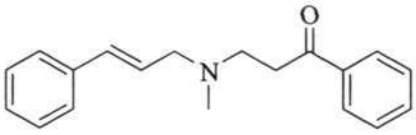
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.16 (m, 10H), 4.55 (s, 2H), 4.24 (tt, *J* = 4.5, 11.3 Hz, 1H), 3.73-3.65 (m, 1H), 3.62-3.57 (m, 1H), 3.52-3.47 (m, 1H), 3.25 (tdd, *J* = 2.1, 3.8, 9.0 Hz, 1H), 2.78-2.63 (m, 2H), 2.30 (tdd, *J* = 1.7, 3.8, 12.5 Hz, 2H), 2.03-1.91 (m, 3H), 1.86-1.76 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 138.4, 128.5, 128.4, 128.3, 127.7, 127.6, 125.8, 77.3, 75.4, 72.9, 66.3, 45.4, 40.8, 37.4, 35.9, 31.5, 21.6.

FTIR (neat) ν_{max}: 3028, 2948, 2918, 2859, 1064, 1493, 1496, 1450, 1362, 1243, 1142, 1079, 1028, 910, 735, 699 527 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{22}H_{27}IO_2$ [M^+] = 450.1056, found 450.1068.

Procedure for Synthesis of 3-(*N*-cinnamyl-N-methylamino)-1-phenylpropan-1-one, 20



3-(*N*-cinnamyl-N-methylamino)-1-phenylpropan-1-one (20): To an oven dried round-bottom flask equipped with a magnetic stirring bar was added *N*-hydroxy-*N*-methyl-1-phenylprop-2-en-1-amine, **19** (0.705 mmol, 0.115 g) and dichloromethane (3 mL). The solution was allowed to cool to 0 °C prior to addition of $In(OTf)_3$ (0.0705 mmol, 40 mg, 0.1 equiv). The reaction mixture was allowed to stir for 48 hours before quenching with $NaHCO_3$ (2 mL). The aqueous layer was extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with water (5 mL) followed by saturated NaCl solution (5 mL), and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford the tertiary amine as colourless oil (94 mg, 48%).

R_f = 0.55 (4:1 Hex – EtOAc)

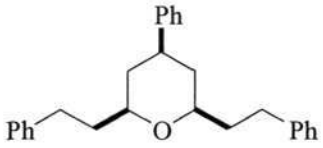
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.0 Hz, 2H), 7.49-7.14 m, 8H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.21 (td, *J* = 6.3, 16.0 Hz, 1H), 4.23 (dd, *J* = 1.0, 6.6 Hz, 2H), 3.22 (t, *J* = 6.7 Hz, 2H), 3.06 (t, *J* = 6.7 Hz, 2H), 2.62 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 136.9, 136.7, 133.3, 133.0, 128.5, 128.5, 128.0, 127.7, 126.5, 125.4, 73.1, 55.6, 46.0, 36.3.

FTIR (neat) ν_{max}: 3059, 3015, 2927, 2865, 1747, 1653, 1332, 1315, 1141, 958, 732 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{21}NO$ [M^+] = 279.1623, found 279.1627.

Procedure for Synthesis of tetrahydro-2,6-diphenethyl-4-phenyl-2*H*-pyran, 1g



tetrahydro-2,6-diphenethyl-4-phenyl-2H-pyran (1g): To a solution of 4-iodo-tetrahydropyran **1c** (0.38 g, 1.0 mmol) dissolved in THF (8 mL) in 25 mL round-bottom flask equipped with a magnetic stirring bar were added phenylmagnesium bromide (1.5 mL, 1M solution in THF, 1.5 mmol) and TMEDA (0.18 mL, 1.2 mmol) at -78 °C. A solution of $FeCl_3$ (8 mg, 0.05 mmol) in THF (0.5 mL) was added to the mixture over a period of 10 minutes. The solution was allowed to stir at 0 °C for another 1 hour prior to quenching with saturated NH_4Cl (3 mL). The aqueous layer was extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with water (5 mL) followed by saturated NaCl solution (5 mL), and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash column chromatography to afford the product as colourless oil (178 mg, 48%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 15H), 3.49-3.40 (m, 2H), 2.93-2.86 (m, 2H), 2.81-2.72 (m, 3H), 2.01-1.92 (m, 2H), 1.83-1.73 (m, 4H), 1.45 (q, J = 12.2 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 142.3, 128.6, 128.5, 128.3, 126.8, 126.3, 125.7, 76.3, 41.8, 39.4, 38.0, 31.9.

FTIR (neat) ν_{max}: 3024, 2932, 2858, 2841, 1495, 1454, 1118, 1076, 1059, 752, 689 cm^{-1}.

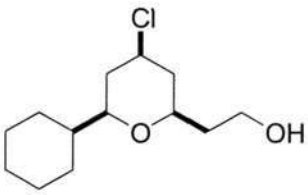
HRMS (EI) *m/z* Calcd for $C_{27}H_{30}O$ [M^+] = 370.2297, found 370.2295.

6.3 Stannane-Free Hydrodehalogenation

General Method for the Synthesis of de-halo-tetrahydropyran

To a 25 ml round-bottom flask equipped with a magnetic stirring bar was charged 10% Pd in carbon (0.122 g, 0.11 mmol, 0.4 equiv) in methanol (2.57 mL). 4-halo-6-cyclohexyl-tetrahydro-2H-pyran (0.28 mmol) in ethyl acetate (0.28ml) was added to the mixture and was allowed to stir under hydrogen atmosphere for 8 h. Sodium bicarbonate (47 mg, 0.56 mmol) was the added to the reaction mixture and was stirred under hydrogen atmosphere for a further 16 h. The mixture was filtered through celite and was then concentrated in *vacuo*. The residue was diluted with ethyl acetate (5 mL) prior to washing with water (2 × 5 mL) followed by saturated NaCl solution (2 × 5 mL). The organic layer was dried with $MgSO_4$ and concentrated in *vacuo*. The residual crude product was purified *via* flash column chromatography to afford the dehalo-tetrahydropyran.

2-(4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)ethanol



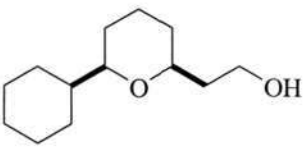
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (tt, J = 4.5, 11.8 Hz, 1H), 3.80-3.75 (m, 2H), 3.58-3.51 (m, 1H), 3.09 (ddd, J = 1.7, 6.3, 11.3 Hz, 1H), 2.68 (br s, 1H), 2.14 (tdd, J = 2.0, 4.2, 12.7 Hz, 1H), 2.08 (tdd, J = 2.4, 4.6, 12.7 Hz , 1H), 1.86-1.77 (m, 1H), 1.76-1.67 (m, 5H), 1.67-1.61 (m, 2H), 1.45-1.34 (m, 1H), 1.27-1.14 (m, 4H), 1.05-0.92 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.4, 76.9, 61.1, 56.0, 42.5, 42.5, 39.3, 37.5, 28.8, 28.8, 26.4, 26.0, 25.9.

FTIR (neat) ν_{max}: 3373, 2924, 2851, 1449, 1080, 1051, 760, 606 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{13}H_{23}ClO_2$ [M^+] = 246.1381, found 246.1338

2-(6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)ethanol



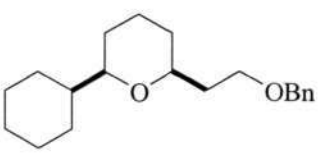
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (t, *J* = 4.8 Hz, 2H), 3.58-3.50 (m, 1H), 3.20 (br s, 1H), 3.07 (ddd, *J* = 1.9, 6.4, 11.2 Hz, 1H), 1.88-1.78 (m, 3H), 1.76-1.66 (m, 5H), 1.65-1.55 (m, 4H), 1.52-1.46 (m, 3H), 1.31-1.23 (m, 2H), 0.97-0.88 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6, 79.2, 62.0, 43.0, 37.8, 31.7, 29.0, 29.0, 28.1, 26.5, 26.2, 26.1, 23.9.

FTIR (neat) ν_{max}: 3370, 2928, 2853, 1449, 1084, 1042, 733 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{13}H_{24}O_2$ [M^+] = 212.1771, found 212.1763

2-(2-(benzyloxy)ethyl)-6-cyclohexyl-tetrahydro-2*H*-pyran



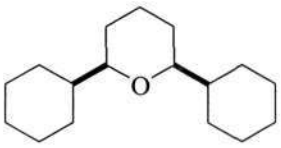
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.31-7.27 (m, 1H), 4.53 and 4.49 (ABq, *J* = 11.8 Hz, 2H), 3.68-3.54 (m, 2H), 3.46-3.37 (m, 1H), 2.94 (ddd, *J* = 1.8, 7.6, 10.7, 1H), 1.98-1.91 (m, 1H), 1.87-1.78 (m, 1H), 1.78-1.71 (m, 3H), 1.70-1.67 (m, 1H), 1.66-1.56 (m, 3H), 1.31-1.25 (m, 2H), 1.24-1.15 (m, 4H), 1.15-1.13 (m, 2H), 1.01-0.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.4, 82.2, 74.6, 73.0, 67.0, 43.2, 36.8, 32.0, 29.3, 28.9, 28.6, 26.7, 26.2, 26.1, 23.8.

FTIR (neat) ν_{max}: 3435, 3107, 3086, 3063, 3028, 2826, 2853, 1494, 1450, 1089, 1043, 733, 696 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{20}H_{30}O_2$ [M^+] = 302.2240, found 302.2243.

2,6-dicyclohexyl-tetrahydro-2*H*-pyran



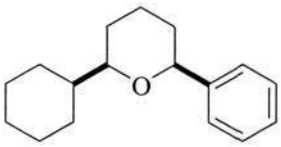
^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (ddd, *J* = 1.4, 7.9, 11.0 Hz, 2H), 2.07-1.96 (m, 2H), 1.88-1.80 (m, 1H), 1.74-1.71 (m, 2H), 1.71-1.66 (m, 3H), 1.66-1.60 (m, 4H), 1.30- 1.22 (m, 6H), 1.22-1.12 (m, 6H), 1.01-0.84 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 82.4, 43.3, 29.4, 29.0, 28.9, 26.7, 26.3, 26.1, 24.0.

FTIR (neat) ν_{max}: 2920, 2849, 1449, 1263, 1084, 1072, 1045, 743 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{30}O$ [M^+]: 250.2297, found 250.2291.

2-cyclohexyl-6-phenyl-tetrahydro-2*H*-pyran



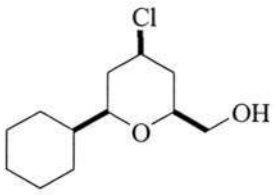
^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 4H), 7.26-7.21 (m, 1H), 4.35 (dd, *J* = 1.8, 11.1 Hz, 1H), 3.24 (ddd, *J* = 1.7, 6.2, 11.1 Hz, 1H), 2.01-1.93 (m, 2H), 1.90-1.82 (m, 1H), 1.79-1.72 (m, 3H), 1.71-1.62 (m, 3H), 1.52-1.42 (m, 2H), 1.351-1.17 (m, 4H), 1.15-1.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 128.1, 126.9, 125.7, 82.5, 79.4, 43.3, 33.9, 29.1, 28.7, 27.8, 26.7, 26.4, 26.3, 24.2.

FTIR (neat) ν_{max}: 3088, 3061, 3028, 2927, 2851, 1497, 1450, 1092, 1043, 749, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{24}O$ [M^+] = 244.1822, found 244.1830.

(4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)methanol



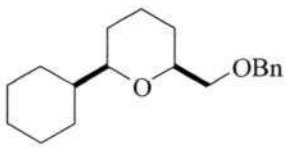
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (tt, *J* = 4.7, 11.9 Hz, 1H), 3.65-3.58 (m, 1H), 3.59-5.51 (m, 1H), 3.48-3.41 (m, 1H), 3.10 (ddd, *J* = 1.6, 6.4, 11.2 Hz, 1H), 2.15 (tdd, *J* = 2.1, 4.5, 12.6 Hz, 1H), 2.08-1.99 (m, 2H), 1.93-1.83 (m, 1H), 1.78-1.64 (m, 4H), 1.57-1.51 (m, 1H) 1.47-1.40 (m, 1H), 1.30-1.13 (m, 4H), 1.08-0.93 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 76.9, 65.7, 56.1, 42.7, 39.4, 38.3, 28.9, 28.6, 26.5, 26.1, 26.0.

FTIR (neat) ν_{max}: 3412, 2926, 2853, 1450, 1087, 1065, 1043, 764, 738, 610 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{21}ClO_2$ [M^+] = 232.1225, found 232.1229.

2-(benzyloxymethyl)-6-cyclohexyl-tetrahydro-2*H*-pyran



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.30-7.24 (m, 1H), 4.61 and 4.56 (ABq, *J* = 12.1 Hz, 2H), 3.54-3.48 (m, 2H), 3.44-3.39 (m, 1H), 3.09-2.99 (m, 1H), 2.01-1.92 (m, 1H), 1.91-1.82 (m, 1H), 1.79-1.72 (m, 1H), 1.72-1.68 (m, 2H), 1.68-

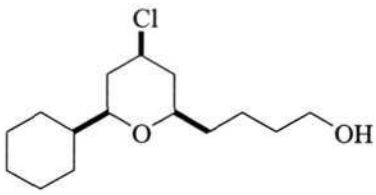
1.65 (m, 1H), 1.46-1.40 (m, 1H), 1.39-1.32 (m, 1H), 1.30-1.18 (m, 5H), 1.18-1.10 (m, 2H), 1.05-0.91 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.3, 127.7, 127.4, 82.3, 77.2, 73.9, 73.3, 43.1, 29.3, 28.7, 28.6, 28.2, 26.7, 26.3, 26.2, 23.5.

FTIR (neat) ν_{max}: 3113, 3088, 3063, 3030, 2926, 2853, 1497, 1450, 1113, 1086, 737, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{28}O_2$ [M^+] = 288.2084, found 288.2082.

4-(4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)butan-1-ol



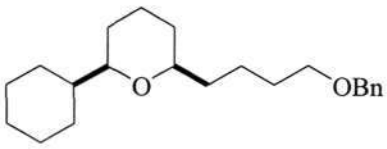
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (tt, *J* = 4.5, 11.7Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.28-3.19 (m, 1H), 2.97 (ddd, *J* = 1.3, 7.1, 11.2 Hz, 1H), 2.15 (tdd, *J* = 2.1, 4.5, 12.3 Hz, 1H), 2.10 (tdd, *J* = 2.2, 4.6, 12.7 Hz, 1H), 1.97-1.87 (m, 1H), 1.78-1.69 (m, 2H), 1.68-1.54 (m, 6H), 1.51-1.35 (m, 7H), 1.27-1.14 (m, 2H), 1.01-0.92 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.1, 76.5, 62.8, 56.8, 42.8, 42.7, 39.7, 35.5, 32.5, 29.2, 28.7, 26.5, 26.1, 26.0, 21.8.

FTIR (neat) ν_{max}: 3418, 2930, 2853, 1450, 1265, 1086, 1065, 738, 704, 608 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{27}ClO_2$ [M^+] = 274.1694, found 274.1698.

2-(4-(benzyloxy)butyl)-6-cyclohexyl-tetrahydro-2*H*-pyran



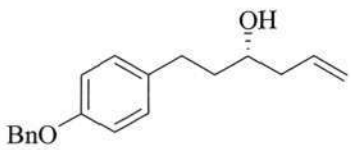
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.30-7.23 (m, 1H), 4.50 (s, 2H), 3.47 (t, J = 6.7 Hz, 2H), 3.24-3.14 (m, 1H), 2.92 (ddd, J = 1.6, 7.8, 11.2 Hz, 1H), 2.04-1.96 (m, 1H), 1.86-1.78 (m, 1H), 1.75-1.67 (m, 2H), 1.55-1.49 (m, 3H), 1.41-1.37 (m, 4H), 1.33-1.22 (m, 7H), 1.18-1.07 (m, 3H), 0.92-0.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.4, 82.4, 77.7, 72.8, 70.5, 43.2, 36.4, 32.0, 29.7, 29.4, 28.9, 28.6, 26.7, 26.2, 26.1, 23.9, 22.3.

FTIR (neat) ν_{max}: 3109, 3088, 3063, 3030, 2910, 2851, 1495, 1092, 1045, 733, 696 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{22}H_{34}O_2$ [M^+] = 330.2553, found 330.2547.

6.4 Total Synthesis of (-)-Centrolobine



(*S*)-1-(4-(benzyloxy)phenyl)hex-5-en-3-ol (34): To an oven dried round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (0.1 mmol, 22 mg). The solid was azeotropically dried with anhydrous tetrahydrofuran (2 × 2 mL) prior to the addition of 1.5 mL of dichloromethane. *(R)*-BINOL (0.11 mmol, 31 mg) and 4Å molecular sieve (15 mg) were added and the mixture was stirred at room temperature for 2 hours to afford a white suspension. Allytributyl stannane (1.0 mmol, 0.31 mL) was added to the resulting suspension and stirred for 10 minutes followed by slow

addition of aldehyde **33** (0.5 mmol, 121 mg in 0.5 mL dichloromethane) at -78°C . The reaction mixture was stirred for 20 hours, warming up to room temperature. The reaction mixture was quenched with 5 mL saturated sodium bicarbonate solution and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts was washed with saturated NaCl solution, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash column chromatography to afford the homoallylic alcohol as oil (96 mg, 68% yield, 84% *ee*).

R_f = 0.24 (4:1 Hex – EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.82 (m, 1H), 5.14 (dd, *J* = 1.7, 13.6 Hz, 2H), 5.04 (s, 2H), 3.72-3.62 (m, 1H), 2.80-2.58 (m, 2H), 2.36-2.28 (m, 1H), 2.23-2.12 (m, 1H), 1.77 (t, *J* = 7.32 Hz, 1H), 1.74 (t, *J* = 7.32 Hz, 1H), 1.59 (d, *J* = 4.17 Hz, 1H)

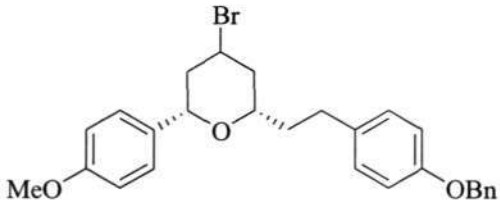
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 137.3, 134.7, 129.3, 129.2, 128.6, 127.9, 127.5, 118.2, 114.9, 70.2, 70.0, 42.1, 38.6, 31.2.

FTIR (neat) ν_{max}: 3236, 2920, 2807, 1639, 1432, 1078, 914, 692, 605, 511 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{22}O_2$ [M^+] = 282.1620, found 282.1614.

$[\alpha]^{23}_D$ = –16.6 (*c* = 2.60 g/100mL, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD–H column (Hexane: *i*-propanol 99:1, 1.0 mL/min: t_1 = 25.71 min for major enantiomer, t_2 = 30.36 min for minor enantiomer).



(2*S*,4*R*,6*S*)-2-(4-(benzyloxy)phenethyl)-4-bromo-tetrahydro-6-(4-methoxyphenyl)-2*H*-pyran (35): To an oven dried round-bottom flask equipped with a magnetic stirring bar was added homoallylic alcohol **34** (0.210 mmol, 59mg), $InBr_3$ (0.018mmol, 6.2 mg) and dichloromethane (1.7 ml). The mixture was allowed to cool to -78 °C prior to addition of trimethylsilylbromide (0.210 mmol, 32 mg). *p*-anisaldehyde (0.175 mmol, 24 mg in 0.25 mL dichloromethane) was added over period of 5 minutes. The reaction was allowed to proceed for 24 hours, warming up to room temperature. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and the aqueous layer was extracted with diethylether (3 × 20 mL). The combined organic extracts was washed with water, saturated NaCl solution, and then dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash column chromatography (1% ether in hexane) to afford the tetrahydropyran as a white solid (70 mg, 83% yield, 84% *ee*).

R_f = 0.47 (4:1 Hex – EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.26 (m, 3H), 7.10-7.06 (m, 2H), 6.92-6.88 (m, 4H), 5.04 (s, 2H), 4.28 (dd, *J* = 1.8, 11.9 Hz, 1H), 4.25 (tt, *J* = 4.4, 11.9 Hz, 1H), 3.81 (s, 3H), 3.47-3.40 (m, 1H), 2.75-2.64 (m, 2H), 2.47-2.43 (m, 1H), 2.31-2.25 (m, 1H), 2.01 (q, *J* = 11.9 Hz, 1H), 1.97-1.89 (m, 1H), 1.84 (q, *J* = 11.8 Hz, 1H), 1.81-1.74 (m, 1H).

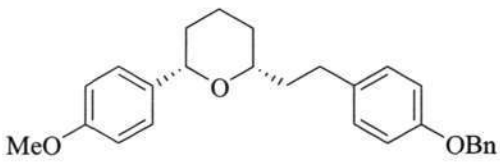
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 157.1, 137.2, 134.2, 133.7, 129.4, 128.6, 127.9, 127.5, 127.1, 114.7, 113.8, 78.9, 76.6, 70.1, 55.3, 46.8, 45.0, 43.0, 37.5, 30.6.

FTIR (neat) ν_{max}: 2929, 2838, 1609, 1512, 1454, 1246, 1175, 1070, 1031, 907, 829, 734, 551 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{27}H_{29}BrO_3$ $[M^+]$ = 481.1300, found 481.1300.

$[\alpha]^{23}_D$ = –33.6 (*c* = 7.50 g / 100 mL, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD–H column (Hexane: *i*-propanol 99:1, 1.0 mL / min: t_1 = 22.95 min for major enantiomer, t_2 = 26.96 min for minor enantiomer).



(2*R*,6*S*)-2-(4-(benzyloxy)phenethyl)-tetrahydro-6-(4-methoxyphenyl)-2*H*-pyran (36): To a solution of the bromide **35** (0.173 mmol, 82 mg) in benzene (17 mL) was added Bu_3SnH (1.73 mmol, 494 mg) and 1,1'-azobis(cyclohexane carbonotrile) (0.034 mmol, 8 mg). The reaction mixture was heated at reflux for 16 hours and allowed to cool to room temperature. The reaction mixture was quenched with saturated KF solution (15 mL) and the aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organic extracts were washed with water, saturated NaCl solution and then dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified *via* flash column chromatography (1% ether in hexane) to afford the tetrahydropyran as a colourless oil (72 mg, 98% yield, 84% *ee*).

R_f = 0.51 (4:1 Hex – EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.40-7.35 (m, 2H), 7.34-7.30 (m, 3H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.91-6.86 (m, 4H), 5.06 (s, 2H), 4.32 (d, *J* = 11.1

Hz, 1H), 3.82 (s, 3H), 3.51-3.43 (m, 1H), 2.82-2.67 (m, 2H), 1.96-1.63 (m, 6H), 1.57-1.44 (m, 1H), 1.38-1.27 (m, 1H).

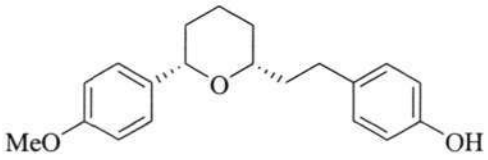
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 157.0, 137.4, 136.0, 135.0, 129.4, 128.5, 127.9, 127.5, 127.1, 114.8, 113.7, 79.1, 77.4, 70.2, 55.3, 38.3, 33.4, 31.3, 30.8, 24.1.

FTIR (neat) ν_{max}: 3061, 2928, 2857, 1614, 1512, 1460, 1244, 1040, 823, 731 cm^{-1}.

HRMS (ESI) *m/z* Calcd for $C_{27}H_{30}NaO_3$ $[M^+ + Na]$ = 425.2195, found 425.2099.

$[\alpha]^{23}_D$ = –45.0 (*c* = 5.1 g / 100 mL, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD–H column (Hexane: *i*-propanol 99:1, 1.0 mL / min: t_1 = 9.79 min for major enantiomer, t_2 = 10.52 min for minor enantiomer).



(-)-Centrolobine (37): A suspension of **36** (0.134 mmol, 82 mg) and Pd/C (10%) (10 mol%, 14.2 mg) in methanol (1.5 mL) and ethyl acetate (0.15 mL) was stirred under H_2 atmosphere at room temperature for 7 hours. The reaction mixture was filtered over celite and concentrated *in vacuo*. The residual crude product was purified *via* flash column chromatography (6% ethyl acetate in hexane) to afford (-)-Centrolobine (30 mg, 71% yield, 84% ee).

R_f = 0.11 (4:1 Hex – EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 4.60 (br. s, 1H), 4.29 (dd, *J* = 2.4, 11.1 Hz, 1H), 3.80 (s, 3H), 3.48-3.37 (m, 1H), 2.78-2.60 (m, 2H), 1.96-1.88 (m, 2H), 1.87-1.79 (m, 2H), 1.79-1.70(m, 1H), 1.69-1.50 (m, 2H), 1.41-1.27 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 153.6, 135.8, 134.5, 129.5, 127.2, 115.1, 113.7, 79.2, 77.4, 55.3, 38.3, 33.2, 31.3, 30.8, 24.1.

FTIR (neat) ν_{max}: 3385, 2938, 1614, 1514, 1246, 1035, 909, 733 cm^{-1}

HRMS (EI) *m/z* Calcd for $C_{20}H_{24}O_3$ [M^+] = 312.1725, found 312.1723.

$[\alpha]^{23}_D$ = –50.8 (*c* = 3.6 g / 100 mL, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD column (Hexane: *i*-propanol 95:5, 1.0 mL / min: t_1 = 21.21 min for major enantiomer, t_2 = 32.12 min for minor enantiomer).

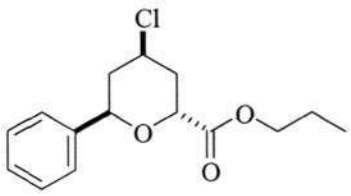
6.5 *Anti* Prins Cyclization

General Procedure for the Preparation of isopropyl 4-chloro-6-cyclohexyl-tetrahydro-2H-pyran-2-carboxylate

To an oven dried 25 mL round-bottom flask equipped with a magnetic stirring bar was added isopropyl 2-hydroxypent-4-enoate (140 mg, 0.88 mmol, 1.1 equiv) dissolved in 9 mL of dichloromethane. The solution was cooled to 0 °C prior to the addition of $In(OTf)_3$ (90 mg, 0.16 mmol, 0.2 equiv) and trimethylsilylchloride (0.12 mL, 0.96 mmol, 1.2 equiv). Cyclohexylcarboxylaldehyde (0.097 mL, 0.80 mmol) dissolved in 1 mL dichloromethane was added slowly over 5 minutes. The reaction mixture was allowed to warm up to room temperature gradually and stirred for 24 hours. The mixture was subsequently quenched with 5 mL saturated sodium bicarbonate solution at room temperature for 15 minutes. The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts washed with water followed by saturated NaCl solution, and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified

via flash column chromatography to afford the 4-chloro-2,6-disubstituted tetrahydropyran.

(2,6-*cis*-2,4-*trans*)-propyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; $R_f = 0.59$ (4:1 Hex – EtOAc)

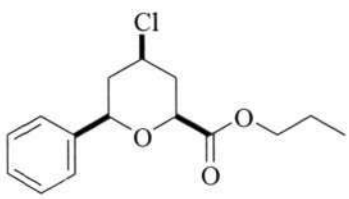
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H), 7.32-7.28 (m, 1H), 4.88 (dd, J = 2.0, 11.8 Hz, 1H), 4.73 (d, J = 5.8 Hz, 1H), 4.19 (tt, J = 4.1, 12.2 Hz, 1H), 4.18 (t, J = 6.8 Hz, 1H), 4.16 (t, J = 6.8 Hz, 1H), 2.70 (tdd, J = 1.8, 4.2, 13.1 Hz, 1H), 2.37 (tdd, J = 2.0, 4.1, 13.1 Hz, 1H), 2.16 (dt, J = 6.5, 12.6 Hz, 1H), 1.93 (q, J = 12.1 Hz, 1H), 1.72 (sextet, J = 7.3 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 140.7, 128.5, 128.1, 126.1, 75.1, 73.6, 67.0, 52.7, 43.5, 36.9, 22.0, 10.4.

FTIR (neat) ν_{max}: 2964, 1758, 1167, 1126, 1051, 711 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{19}ClO_3$ [M^+] = 282.7262, found 282.7265.

(2,4,6-*cis*)-propyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; $R_f = 0.50$ (4:1 Hex – EtOAc)

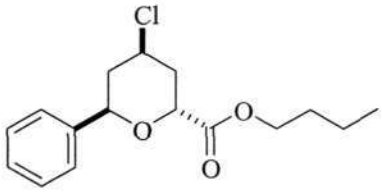
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.30-7.27 (m, 1H), 4.44 (dd, J = 1.1, 11.3 Hz, 1H), 4.21 (tt, J = 4.4, 11.8 Hz, 1H), 4.18 (dd, J = 2.0, 11.9 Hz, 1H), 4.15 (t, J

= 6.7 Hz, 2H), 2.56 (tdd, J = 2.0, 4.3, 12.9 Hz, 1H), 2.41 (tdd, J = 2.0, 4.1, 13.1 Hz, 1H), 1.96 (q, J = 12.4 Hz, 1H), 1.90 (q, J = 12.4 Hz, 1H), 1.70 (sextet, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 140.3, 128.5, 128.0, 125.9, 78.8, 75.8, 66.9, 54.6, 43.8, 38.7, 21.9, 10.3.

FTIR (neat) ν_{max}: 2968, 1749, 1454, 1167, 1124, 1057, 700 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-butyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



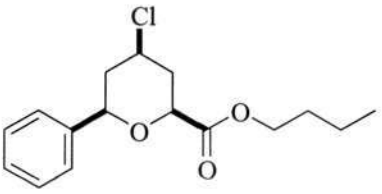
Colorless oil; R_f = 0.66 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H), 7.32-7.28 (m, 1H), 4.87 (dd, J = 2.1, 11.9 Hz, 1H), 4.72 (d, J = 6.4 Hz, 1H), 4.26-4.15 (m, 3H), 2.69 (tdd, J = 2.0, 4.2, 13.3 Hz, 1H), 2.37 (tdd, J = 2.1, 4.1, 13.3 Hz, 1H), 2.15 (dt, J = 6.4, 13.2 Hz, 1H), 1.93 (q, J = 12.5 Hz, 1H), 1.67 (quint, 6.9 Hz, 2H), 1.40 (sextet, J = 7.4 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H),

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 140.7, 128.5, 128.1, 126.1, 75.1, 73.6, 65.2, 52.6, 43.5, 36.9, 30.6, 19.1, 13.7.

FTIR (neat) ν_{max}: 2966, 1755, 1167, 1127, 1057, 704 cm^{-1}.

(2,4,6-*cis*)-butyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.57 (4:1 Hex – EtOAc)

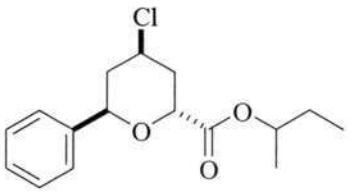
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.31-7.27 (m, 1H), 4.44 (dd, *J* = 1.9, 11.4 Hz, 1H), 4.20 (tt, *J* = 4.5, 11.7 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 2H), 4.18 (dd, *J* = 2.1, 11.6 Hz, 1H), 2.55 (tdd, *J* = 2.2, 4.3, 12.6 Hz, 1H) 2.41 (tdd, *J* = 2.2, 4.3, 12.6 Hz, 1H), 1.95 (q, *J* = 12.3 Hz, 1H), 1.90 (q, *J* = 12.3 Hz, 1H), 1.65 (quint, *J* = 6.9 Hz, 2H), 1.40 (sextet, *J* = 7.6 Hz, 2H), 0.94 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 140.3, 128.5, 128.0, 125.9, 78.8, 75.8, 65.2, 54.5, 43.8, 38.7, 30.5, 19.0, 13.7.

FTIR (neat) ν_{max}: 2961, 1753, 1167, 1124, 1057, 700 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{21}ClO_3$ [M^+] = 296.7891, found 296.7889.

(2,6-*cis*-2,4-*trans*)-*sec*-butyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.63 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H), 7.32-7.29 (m, 1H), 4.97 (sextet, *J* = 5.7 Hz, 1H), 4.87 (d, *J* = 11.3 Hz, 1H), 4.69 (d, *J* = 5.1 Hz, 1H), 4.18 (tt, *J* = 4.3, 11.5 Hz, 1H), 2.69 (tdd, *J* = 2.0, 4.3, 12.7 Hz, 1H), 2.37 (tdd, *J* = 2.0, 4.2, 12.7 Hz, 1H),

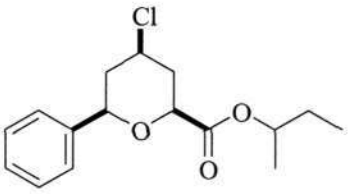
2.15 (dt, J = 6.3, 12.9 Hz, 1H), 1.94 (dt, J = 6.3, 12.9 Hz, 1H), 1.65 (quint, J = 7.0 Hz, 2H), 1.27 (d, J = 6.3 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 140.7, 128.5, 128.1, 126.1, 75.1, 75.0, 73.7, 52.7, 43.5, 36.9, 28.7, 19.5, 9.8.

FTIR (neat) ν_{max}: 2971, 1744, 1439, 1208, 1167, 1112, 700 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{21}ClO_3$ [M^+] = 296.1174, found 296.1183.

(2,4,6-*cis*)-*sec*-butyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



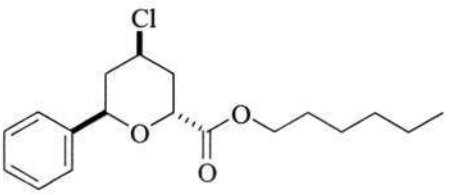
Colorless oil; R_f = 0.57 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.33 (m, 4H), 7.30-7.27 (m, 1H), 4.95 (sextet, J = 6.3 Hz, 1H), 4.44 (d, J = 11.5 Hz, 1H), 4.21 (tt, J = 4.4, 11.8 Hz, 1H) 4.15 (d, J = 11.8 Hz, 1H), 2.55 (tdd, J = 1.7, 4.2, 12.6 Hz, 1H), 2.41 (tdd, J = 1.7, 4.2, 12.7 Hz, 1H), 1.98-1.85 (m, 2H), 1.63 (quint, J = 7.4 Hz, 2H), 1.25 (d, J = 6.5 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 140.4, 128.4, 128.0, 125.8, 78.7, 75.8, 73.5, 54.6, 43.8, 38.8, 28.7, 19.4, 9.6.

FTIR (neat) ν_{max}: 2972, 1747, 1454, 1217, 1167, 1124, 700 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-hexyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.70 (4:1 Hex – EtOAc)

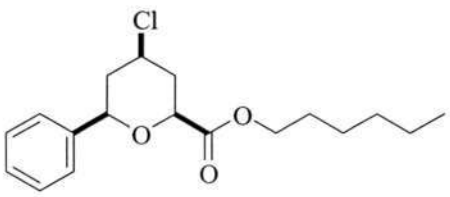
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.32-7.27 (m, 1H), 4.87 (dd, *J* = 2.1, 11.9 Hz, 1H), 4.72 (d, *J* = 4.7 Hz, 1H), 4.24-4.16 (m, 3H), 2.69 (tdd, *J* = 2.0, 4.2, 13.5 Hz, 1H), 2.38 (tdd, *J* = 2.0, 4.3, 13.4 Hz, 1H), 2.15 (dt, *J* = 6.5, 12.5 Hz, 1H), 1.93 (q, *J* = 12.6 Hz, 1H), 1.68 (quint, *J* = 7.1 Hz, 2H), 1.40-1.28 (m, 6H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 140.6, 128.5, 128.0, 126.0, 75.1, 73.6, 65.5, 52.6, 43.5, 36.8, 31.3, 28.5, 25.6, 22.5, 13.9.

FTIR (neat) ν_{max}: 2961, 1743, 1161, 1120, 1044, 701 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{18}H_{25}ClO_3$ [M^+] = 324.1487, found 324.1485.

(2,4,6-*cis*)-hexyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



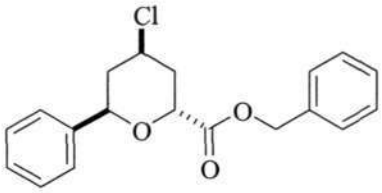
Colorless oil; R_f = 0.59 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.30-7.26 (m, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.20 (tt, *J* = 4.5, 11.7 Hz, 1H), 4.19-4.15 (m, 3H), 2.55 (tdd, *J* = 1.8, 4.2, 12.9 Hz, 1H), 2.40 (tdd, *J* = 1.9, 4.2, 12.9 Hz, 1H), 1.95 (q, *J* = 11.6 Hz, 1H), 1.89 (q, *J* = 11.6 Hz, 1H), 1.66 (quint, *J* = 6.7 Hz, 2H), 1.38-1.29 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 140.3, 128.5, 128.0, 125.8, 78.7, 75.8, 65.5, 54.5, 43.7, 38.7, 31.3, 28.4, 25.4, 22.5, 13.9.

FTIR (neat) ν_{max}: 2965, 1748, 1164, 1127, 1045, 701 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-benzyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.58 (4:1 Hex – EtOAc)

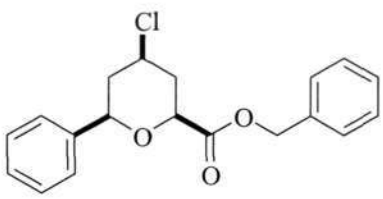
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10H), 5.31 and 5,17 (ABq, *J* = 12.3 Hz, 2H), 4.80 (dd, *J* = 2.0, 11.8 Hz, 1H), 4.76 (dd, *J* = 0.8, 6.2 Hz, 1H), 4.14 (tt, *J* = 4.2, 12.0 Hz, 1H), 2.70 (tdd, *J* = 2.0, 4.1, 13.2 Hz, 1H), 2.33 (tdd, *J* = 2.0, 4.1, 12.9 Hz, 1H), 2.15 (dt, *J* = 6.2, 12.6 Hz, 1H), 1.92 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 140.5, 135.3, 128.7, 128.6, 128.5, 128.4, 128.1, 126.1, 75.2, 73.6, 67.0, 52.5, 43.4, 36.7.

FTIR (neat) ν_{max}: 3425, 2924, 1740, 1456, 1265, 1163, 1117, 739 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{19}ClO_3$ [M^+] = 330.8054, found 330.8054.

(2,4,6-*cis*)-benzyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.51 (4:1 Hex – EtOAc)

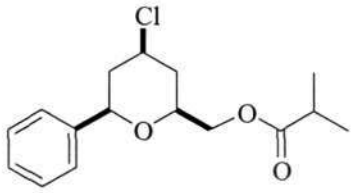
^{1}H NMR (400 MHz, $CDCl_3$) 7.40-7.27 (m, 10H), 5.24 and 5.20 (ABq, *J* = 12.2 Hz, 2H), 4.44 (dd, *J* = 2.0, 11.5 Hz, 1H), 4.22 (dd, *J* = 2.1, 11.9 Hz, 1H), 4.19 (tt, *J* = 4.5,

11.9 Hz, 1H), 2.56 (tdd, J = 1.9, 4.5, 11.9 Hz, 1H), 2.40 (tdd, J = 1.9, 4.2, 12.9 Hz, 1H), 1.97 (q, J = 12.7 Hz, 1H), 1.91 (q, J = 12.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 140.2, 135.3, 128.6, 128.5, 128.5, 128.3, 128.0, 125.9, 78.8, 75.7, 67.7, 54.4, 43.7, 38.6.

FTIR (neat) ν_{max}: 2957, 2928, 1715, 1452, 1273, 1113, 1068, 714 cm^{-1}.

(2,4,6-*cis*)-4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-yl)methyl isobutyrate



Colorless oil; R_f = 0.62 (4:1 Hex – EtOAc)

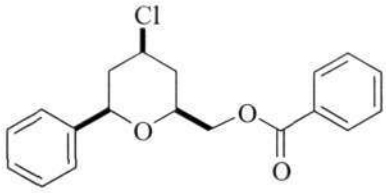
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H), 7.31-7.28 (m, 1H), 4.41 (dd, J = 1.7, 11.4 Hz, 1H), 4.25-4.14 (m, 3H), 3.82-3.75 (m, 1H), 2.59 (hept, J = 7.0 Hz, 1H), 2.40 (tdd, J = 1.9, 4.2, 12.8 Hz, 1H), 2.24 (tdd, J = 1.9, 4.3, 12.8 Hz, 1H), 1.84 (q, J = 12.0 Hz, 1H), 1.73 (q, J = 12.0 Hz, 1H), 1.18 (d, J = 6.8 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 140.9, 128.4, 127.8, 127.7, 78.6, 76.8, 66.0, 55.1, 44.0, 38.5, 33.9, 19.0, 19.0.

FTIR (neat) ν_{max}: 2972, 1732, 1452, 1192, 1159, 733 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{16}H_{21}ClO_3$ [M^+] = 296.1174, found 296.1171.

((2,4,6-*cis*)-4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-yl)methyl benzoate



Yellow solid; R_f = 0.65 (4:1 Hex – EtOAc)

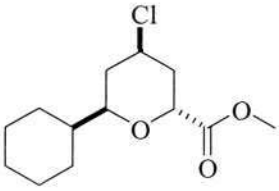
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.59-7.56 (m, 1H), 7.47-7.44 (m, 2H), 7.38-7.35 (m, 4H), 7.32-7.29 (m, 1H), 4.50-4.42 (m, 3H), 4.23 (tt, *J* = 4.4, 11.7 Hz, 1H), 3.95-3.91 (m, 1H), 2.43 (tdd, *J* = 2.0, 4.2, 12.9 Hz, 1H), 2.35 (tdd, *J* = 2.1, 4.2, 12.8 Hz, 1H), 1.90 (q, *J* = 11.9 Hz, 1H), 1.85 (q, *J* = 11.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 140.7, 133.1, 129.8, 129.7, 128.4, 128.4, 127.8, 125.7, 78.6, 74.7, 66.7, 55.0, 44.0, 38.6.

FTIR (neat) ν_{max}: 2966, 2910, 1703, 1431, 1269, 1213, 1120, 1064, 715 cm^{-1}

HRMS (EI) *m/z* Calcd for $C_{19}H_{19}ClO_3$ [M^+] = 330.1017, found 330.1012.

(2,6-*cis*-2,4-*trans*)-methyl 4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.49 (4:1 Hex – EtOAc)

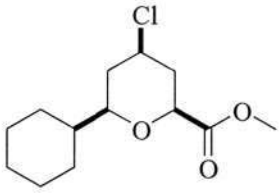
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (dd, *J* = 0.9, 6.3 Hz, 1H), 4.01 (tt, *J* = 4.2, 12.0 Hz, 1H), 3.75 (s, 3H), 3.44 (ddd, *J* = 1.8, 5.9, 11.5 Hz, 1H), 2.59 (tdd, *J* = 2.0, 4.2, 12.9 Hz, 1H), 2.10 (tdd, *J* = 2.1, 4.3, 12.6 Hz, 1H), 1.98 (dt, *J* = 6.3, 12.2 Hz, 1H), 1.90-1.83 (m, 1H), 1.77-1.59 (m, 5H), 1.48-1.37 (m, 1H), 1.30-1.14 (m, 3H), 1.12-0.96 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 77.4, 73.3, 53.5, 52.0, 42.6, 39.1, 31.1, 28.6, 28.3, 26.5, 26.1, 26.0.

FTIR (neat) ν_{max}: 2953, 1711, 1455, 1127, 1125, 700 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{13}H_{21}ClO_3$ [M^+] = 260.1174, found 260.1181.

(2,4,6-*cis*)-methyl 4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-carboxylate



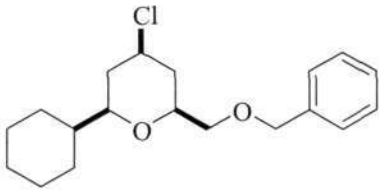
Colorless oil; R_f = 0.45 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (tt, *J* = 4.2, 12.0 Hz, 1H), 4.55 (dd, *J* = 2.1, 11.9 Hz, 1H), 3.74 (s, 3H), 3.06 (ddd, *J* = 1.8, 6.6, 11.1 Hz, 1H), 2.43 (tdd, *J* = 1.8, 4.5, 12.9 Hz, 1H), 2.16 (tdd, *J* = 1.8, 4.4, 12.4 Hz, 1H), 1.97-1.90 (m, 1H), 1.78 (q, *J* = 12.2 Hz, 1H), 1.76-1.64 (m, 4H), 1.55 (q, *J* = 11.7 Hz, 1H), 1.55-1.45 (m, 1H), 1.28-1.08 (m, 3H), 1.05-0.88 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 81.5, 75.6, 55.3, 52.1, 42.3, 39.1, 38.9, 29.1, 28.4, 26.4, 26.0, 25.9.

FTIR (neat) ν_{max}: 2928, 1753, 1448, 1265, 1169, 739 cm^{-1}.

(2,4,6-*cis*)-2-((benzyloxy)methyl)-4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran



Colorless oil; R_f = 0.65 (4:1 Hex – EtOAc)

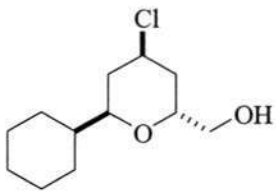
^{1}H NMR (300 MHz, $CDCl_3$) δ δ 7.35-7.32 (m, 4H), 7.31-7.28 (m, 1H), 4.60 and 4.56 (ABq, J = 12.4 Hz, 2H), 4.02, (tt, J = 4.5, 11.8 Hz, 1H), 3.57-3.49 (m, 2H), 3.48-3.42 (m, 1H), 3.07 (ddd, J = 1.8, 6.3, 11.4 Hz, 1H), 2.21-2.11 (m, 2H), 1.94-1.87 (m, 1H), 1.77-1.63 (m, 4H), 1.59-1.53 (m, 2H), 1.48-1.39 (m, 1H), 1.30-1.11 (m, 3H), 1.08-0.92 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.6, 127.6, 81.2, 76.2, 73.4, 72.9, 56.5, 42.7, 39.6, 39.5, 29.0, 28.6, 26.5, 26.2, 26.1.

FTIR (neat) ν_{max}: 2973, 2853, 1450, 1113, 735 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{27}ClO_2$ [M^+] = 332.1694, found 332.169.

((2,6-*cis*-2,4-*trans*)-4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)methanol



Colorless oil; R_f = 0.22 (4:1 Hex – EtOAc)

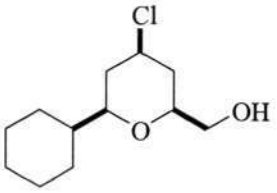
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (tt, J = 4.5 11.8 Hz, 1H), 3.65-3.59 (m, 1H), 3.56-3.52 (m, 1H), 3.47-3.42 (m, 1H), 3.10 (ddd, J = 1.8, 6.4, 11.3 Hz, 1H), 2.16 (tdd, J = 1.8, 4.4, 12.7 Hz, 1H), 2.04 (tdd, J = 2.0, 4.4, 12.5 Hz, 1H), 2.02-1.97 (m, 1H), 1.90-1.85 (m, 1H), 1.77-1.72 (m, 2H), 1.69-1.65 (m, 2H), 1.59-1.52 (m, 2H), 1.47-1.39 (m, 1H), 1.29-1.14 (m, 3H), 1.07-0.97 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 81.0, 76.9, 65.7, 56.1, 42.7, 39.5, 38.4, 28.9, 28.6, 26.5, 26.1, 26.0.

FTIR (neat) ν_{max}: 3406, 2928, 2853, 1450, 1099, 1043, 735 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{21}ClO_2$ [M^+] = 232.1225, found 232.1221.

((2,4,6-*cis*)-4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-yl)methanol



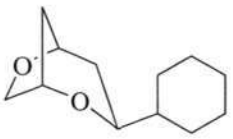
Colorless oil; R_f = 0.38 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17-4.07 (m, 2H), 3.86 (dd, *J* = 10.2, 11.3 Hz, 1H), 3.48-3.42 (m, 1H), 3.33 (ddd, *J* = 2.2, 6.8, 9.8 Hz, 1H), 2.15 (tdd, *J* = 2.2, 4.5 12.6 Hz, 1H), 2.03 (tdd, *J* = 2.1, 4.5, 12.7 Hz, 1H), 2.02-1.96 (m, 1H), 1.94-1.89 (m, 1H), 1.77-1.61 (m, 6H), 1.53-1.47 (m, 1H), 1.27-1.11 (m, 3H), 1.03-0.92 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 74.3, 72.8, 61.2, 53.8, 42.1, 38.7, 36.3, 28.9, 28.7, 26.4, 26.1, 25.9.

FTIR (neat) ν_{max}: 3493, 2954, 1446, 1125, 1028, 733cm^{-1}.

3-cyclohexyl-2,6-dioxa-bicyclo[3.2.1]octane



Colorless oil; R_f = 0.43 (4:1 Hex – EtOAc)

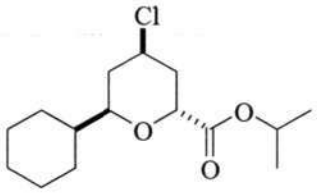
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (t, *J* = 5.2 Hz, 1H), 4.45 (br. s, 1H), 4.14 (d, *J* = 9.8 Hz, 1H), 3.77 (dd, *J* = 3.2, 10.1 Hz, 1H), 3.64 (ddd, *J* = 4.1, 7.0, 10.8 Hz, 1H), 1.90-1.83 (m, 1H), 1.82-1.76 (m, 1H), 1.75-1.67 (m, 4H), 1.65-1.58 (m, 2H), 1.36-1.26 (m, 2H), 1.24-1.12 (m, 3H), 1.00-0.86 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 75.1, 74.3, 74.2, 71.3, 43.0, 38.0, 36.2, 29.1, 28.3, 26.6, 26.2, 26.0.

FTIR (neat) ν_{max}: 2926, 1448, 1205, 1051, 924, 723 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{20}O_2$ [M^+] = 196.1458, found 196.1449.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-carboxylate



White solid; R_f = 0.61 (4:1 Hex – EtOAc)

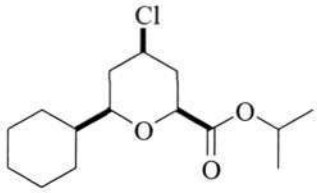
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (hept, *J* = 6.3 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 1H), 4.01 (tt, *J* = 4.9, 12.1 Hz, 1H), 3.42 (ddd, *J* = 1.7, 5.9, 11.5 Hz, 1H), 2.59 (tdd, *J* = 1.8, 4.3, 13.0 Hz, 1H), 2.10 (tdd, *J* = 1.9, 4.2, 12.5 Hz, 1H), 2.01-1.93 (m, 1H), 1.91-1.84 (m, 1H), 1.77-1.69 (m, 2H), 1.66-1.55 (m, 2H), 1.43-1.34 (m, 1H), 1.28 (d, *J* = 2.0 Hz, 3H), 1.27 (d, *J* = 2.0 Hz, 3H), 1.22-1.15 (m, *J* = 6.3 Hz, 3H), 1.11-1.00 (m, *J* = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 77.4, 73.5, 68.9, 53.6, 42.6, 39.2, 37.0, 28.6, 28.5, 26.5, 26.1, 26.0, 21.8, 21.8.

FTIR (neat) ν_{max}: 2928, 1728, 1450, 1227, 1173, 1105, 735 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{25}ClO_3$ [M^+] = 288.1487, found 288.1488.

(2,4,6-*cis*)-isopropyl 4-chloro-6-cyclohexyl-tetrahydro-2*H*-pyran-2-carboxylate



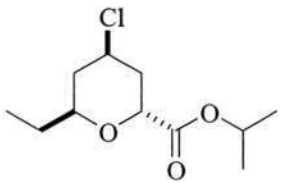
White solid; R_f = 0.55 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (hept, J = 6.2 Hz, 1H), 4.02 (tt, J = 4.6, 11.8 Hz, 1H), 3.87 (dd, J = 2.1, 11.8 Hz, 1H), 3.06 (ddd, J = 1.7, 6.9, 11.3 Hz, 1H), 2.42 (tdd, J = 1.7, 4.4, 12.8 Hz, 1H), 2.17 (tdd, J = 1.9, 4.2, 12.5 Hz, 1H), 2.00-1.93 (m, 1H), 1.76-1.66 (m, 4H), 1.64-1.61 (m, 1H), 1.59-1.49 (m, 2H), 1.26 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 1.21-1.13 (m, 3H), 1.04-0.94, (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 81.4, 75.5, 68.7, 55.5, 42.3, 39.1, 38.8, 28.4, 28.4, 26.4, 26.0, 25.9, 21.7, 21.7.

FTIR (neat) ν_{max}: 2897, 1702, 1415, 1225, 1165, 1103, 736 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-6-ethyl-tetrahydro-2*H*-pyran-2-carboxylate



Yellowish oil; R_f = 0.40 (4:1 Hex – EtOAc)

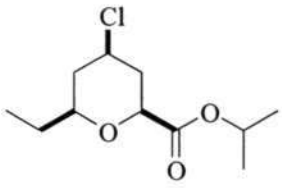
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (hept, J = 6.2 Hz, 1H), 4.50 (dd, J = 1.1, 6.3 Hz, 1H), 4.02 (tt, J = 4.3, 12.0 Hz, 1H), 3.64-3.59 (m, 1H), 2.59 (tdd, J = 1.9, 4.3, 13.0 Hz, 1H), 2.11 (tdd, J = 1.9, 4.4, 12.8 Hz, 1H), 1.98 (dt, J = 6.4, 13.0 Hz, 1H), 1.61-1.53 (m, 2H), 1.51-1.46 (m, 1H), 1.28 (d, J = 6.0 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 74.5, 73.4, 68.9, 53.0, 41.7, 36.9, 28.8, 21.8, 21.8, 9.7.

FTIR (neat) ν_{max}: 2956, 1733, 1481, 1343, 1222, 1172, 1112, 731 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{11}H_{19}ClO_3$ [M^+] = 234.1017, found 234.1026.

(2,4,6-*cis*)-isopropyl 4-chloro-6-ethyl-tetrahydro-2*H*-pyran-2-carboxylate



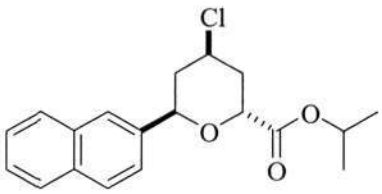
Yellowish oil; R_f = 0.37 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (hept, *J* = 6.2 Hz, 1H), 4.03 (tt, *J* = 4.4, 11.8 Hz, 1H), 3.92 (dd, *J* = 2.0, 11.7 Hz, 1H), 3.29-3.24 (m, 1H), 2.44 (tdd, *J* = 2.1, 4.4, 12.8 Hz, 1H), 2.16 (tdd, *J* = 2.0, 4.4, 12.8 Hz, 1H), 1.74-1.69 (m, 1H), 1.59-1.52 (m, 2H), 1.32-1.29 (m, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 78.5, 75.5, 68.8, 54.9, 41.3, 39.0, 28.5, 21.7, 21.7, 9.8.

FTIR (neat) ν_{max}: 2978, 1751, 1466, 1456, 1375, 1252, 1172, 1107 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-tetrahydro-6-(naphthalen-2-yl)-2*H*-pyran-2-carboxylate



Yellow solid; R_f = 0.60 (4:1 Hex – EtOAc)

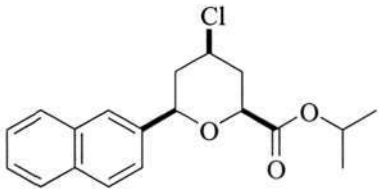
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.84 (m, 4H), 7.51-7.49 (m, 3H), 5.16 (hept, *J* = 6.9 Hz, 1H), 5.06 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 6.1 Hz, 1H), 4.24 (tt, *J* = 4.4, 11.6 Hz, 1H), 2.73 (dt, *J* = 2.1, 13.2 Hz, 1H), 2.48 (dt, *J* = 2.1, 13.2 Hz, 1H), 2.23-2.14 (m, 1H), 2.07-1.98 (m, 1H), 1.33 (d, *J* = 1.3 Hz, 3H), 1.32 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 138.0, 133.2, 133.1, 128.3, 128.1, 127.7, 126.2, 126.0, 124.9, 124.1, 75.1, 73.8, 69.2, 52.7, 43.4, 36.8, 21.8, 21.8.

FTIR (neat) ν_{max}: 2980, 1732, 1375, 1221, 1105, 735 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{21}ClO_3$ [M^+] = 332.1174, found 332.1178.

(2,4,6-*cis*)-isopropyl 4-chloro-tetrahydro-6-(naphthalen-2-yl)-2*H*-pyran-2-carboxylate



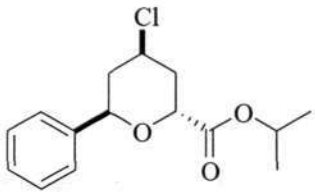
Yellow solid; R_f = 0.54 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.80 (m, 4H), 7.49-7.44 (m, 3H), 5.11 (hept, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.23 (tt, *J* = 4.2, 11.3 Hz, 1H), 4.17 (dd, *J* = 2.2 Hz, 12 Hz, 1H), 2.57 (dt, *J* = 2.1 Hz, 10.4 Hz, 1H), 2.47 (dt, *J* = 2.2 Hz, 13.2 Hz, 1H), 2.23-2.14 (m, 1H), 2.07-1.98 (m, 1H), 1.29 (d, *J* = 1.3 Hz, 3H), 1.28 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 137.7, 133.2, 133.0, 128.2, 128.1, 127.6, 126.1, 126.0, 124.7, 123.9, 78.2, 75.8, 69.8, 54.6, 43.7, 36.8, 21.7, 21.7.

FTIR (neat) ν_{max}: 2956, 1729, 1377, 1201, 1101, 735 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



Yellowish oil; R_f = 0.65 (4:1 Hex – EtOAc)

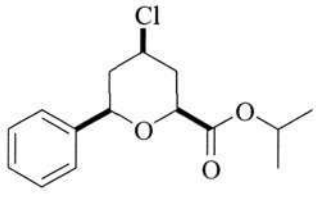
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.34 (m, 4H), 7.32-7.29 (m, 1H), 5.13 (hept, *J* = 6.3 Hz, 1H) 4.87 (dd, *J* = 2.1, 11.8 Hz, 1H), 4.67 (d, *J* = 5.6 Hz, 1H), 4.17 (tt, *J* = 4.4, 12.0 Hz, 1H), 2.69 (tdd, *J* = 1.9, 4.2, 13.2 Hz, 1H), 2.37 (tdd, *J* = 2.1, 4.2, 13.0 Hz, 1H) 2.14 (dt, *J* = 6.5, 13.0 Hz, 1H), 1.94 (q, *J* = 13 Hz, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.30 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 140.6, 128.5, 128.1, 126.2, 75.0, 73.7, 69.1, 52.7, 43.4, 36.8, 21.8, 21.8.

FTIR (neat) ν_{max}: 3410, 2959, 1780, 1722, 1123, 1014, 755, 701 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{19}ClO_3$ [M^+] = 282.1017, found 282.1017.

(2,4,6-*cis*)-isopropyl 4-chloro-tetrahydro-6-phenyl-2*H*-pyran-2-carboxylate



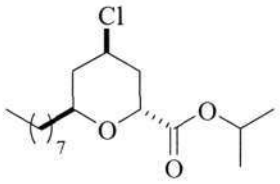
Yellowish oil; R_f = 0.54 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.33 (m, 4H), 7.30-7.27 (m, 1H), 5.10 (hept, *J* = 6.3 Hz, 1H) 4.87 (dd, *J* = 1.7, 11.4 Hz, 1H), 4.20 (tt, *J* = 4.4, 11.8 Hz, 1H), 4.13 (dd, *J* = 2.1, 12.0 Hz, 1H), 2.69 (tdd, *J* = 1.8, 4.6, 12.8 Hz, 1H), 2.37 (tdd, *J* = 1.8, 4.4, 13.0 Hz, 1H) 1.97-1.86 (m, 2H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.27 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 140.3, 128.4, 127.9, 125.8, 78.7, 75.8, 69.0, 54.6, 43.8, 36.6, 21.7, 21.7.

FTIR (neat) ν_{max}: 3380, 2980, 2934, 1747, 1217, 1107, 1055, 756, 700 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-tetrahydro-6-octyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.70 (4:1 Hex – EtOAc)

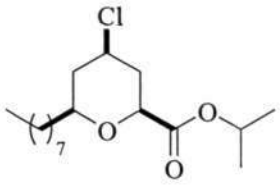
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (hept, *J* = 6.3 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 1H), 4.01 (tt, *J* = 4.4, 11.8 Hz, 1H), 3.71-3.66 (m, 1H), 2.59 (tdd, *J* = 2.1, 4.2, 13.2 Hz, 1H), 2.10 (tdd, *J* = 2.1, 4.2, 13.2 Hz, 1H), 1.98 (dt, *J* = 6.3, 12.6 Hz, 1H), 1.61-1.58 (m, 1H), 1.56-1.51 (m, 2H), 1.46-1.40 (m, 2H), 1.28-1.26 (m, 16H), 0.87 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 73.5, 73.3, 68.9, 52.9, 42.2, 36.2, 35.9, 31.9, 29.5, 29.5, 29.2, 25.3, 22.7, 21.8, 21.8, 14.1.

FTIR (neat) ν_{max}: 2951, 2881, 1715, 1401, 1377, 1253, 1166, 1123, 721 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{31}ClO_3$ [M^+] = 318.1956, found 318.1956.

(2,4,6-*cis*)-isopropyl 4-chloro-tetrahydro-6-octyl-2*H*-pyran-2-carboxylate



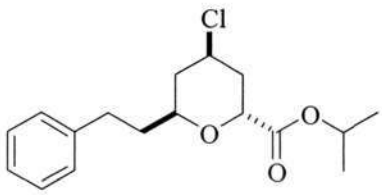
Colorless oil; R_f = 0.65 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (hept, *J* = 6.3 Hz, 1H), 4.02 (tt, *J* = 4.4, 11.8 Hz, 1H), 3.90 (dd, *J* = 2.1, 11.8 Hz, 1H), 3.34-3.29 (m, 1H), 2.42 (tdd, *J* = 2.1, 4.2, 12.8 Hz, 1H), 2.13 (tdd, *J* = 2.1, 4.2, 12.8 Hz, 1H), 1.77 (q, *J* = 11.8 Hz, 1H), 1.72-1.65 (m, 1H), 1.55 (q, *J* = 11.8 Hz, 1H), 1.50-1.38 (m, 2H), 1.32-1.22 (m, 17H), 0.85 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 77.2, 75.5, 68.8, 54.9, 41.7, 39.0, 35.5, 31.8, 29.5, 29.4, 29.2, 25.3, 22.6, 21.7, 21.7, 14.1.

FTIR (neat) ν_{max}: 2926, 2855, 1730, 1465, 1375, 1225, 1167, 1105 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-tetrahydro-6-phenethyl-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.73 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.08 (hept, *J* = 6.3 Hz, 1H), 4.54 (dd, *J* = 1.0, 6.1 Hz, 1H), 4.03 (tt, *J* = 4.4, 12.1 Hz, 1H), 3.81-3.76 (m, 1H), 2.87-2.82 (m, 1H), 2.70-2.64 (m, 1H), 2.61 (ddd, *J* = 1.9, 4.3, 13.0 Hz, 1H), 2.13 (ddd, *J* = 2.0, 4.2, 12.6 Hz, 1H), 2.01 (dt, *J* = 6.3, 12.4 Hz, 1H), 1.92-1.84 (m,

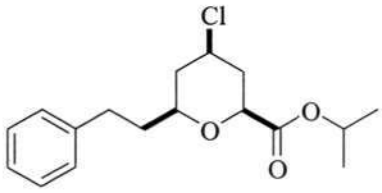
1H), 1.79-1.72 (m, 1H), 1.59-1.56 (m, 1H), 1.28 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 141.9, 128.4, 128.4, 125.9, 73.4, 72.7, 69.0, 52.7, 42.1, 37.8, 36.9, 31.6, 21.8, 21.8.

FTIR (neat) ν_{max}: 2980, 2934, 1728, 1454, 1375, 1227, 1163, 1105, 700 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{23}ClO_3$ [M^+] = 310.1336, found 310.1330.

(2,4,6-*cis*)-isopropyl 4-chloro-tetrahydro-6-phenethyl-2*H*-pyran-2-carboxylate



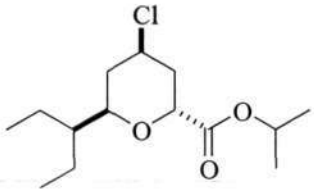
Colorless oil; R_f = 0.68 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.20-7.17 (m, 3H), 5.10 (hept, J = 6.0 Hz, 1H), 4.00 (tt, J = 4.4, 11.6 Hz, 1H), 3.89 (dd, J = 2.1, 11.8 Hz, 1H), 3.32-3.28 (m, 1H), 2.83-2.77 (m, 1H), 2.75-2.69 (m, 1H), 2.45 (ddd, J = 2.1, 4.3, 12.7 Hz, 1H), 2.13 (ddd, J = 2.0, 4.6, 12.9 Hz, 1H), 2.08-2.00 (m, 1H), 1.82-1.76 (m, 2H), 1.69-1.66 (m, 1H), 1.29 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 141.5, 128.5, 128.4, 125.9, 75.9, 75.5, 68.9, 54.7, 41.7, 38.9, 36.8, 31.4, 21.7, 21.7.

FTIR (neat) ν_{max}: 3001, 2921, 1749, 1439, 1377, 1201, 1152, 703 cm^{-1}.

(2,6-*cis*-2,4-*trans*)-isopropyl 4-chloro-tetrahydro-6-(pentan-3-yl)-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.80 (4:1 Hex – EtOAc)

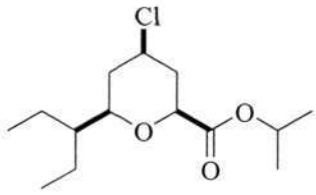
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (hept, *J* = 6.3 Hz, 1H), 4.49 (dd, *J* = 1.0, 6.3 Hz, 1H), 4.02 (tt, *J* = 4.3, 12.0 Hz, 1H), 3.67 (ddd, *J* = 1.7, 4.9, 11.4 Hz, 1H), 2.60 (tdd, *J* = 1.9, 4.2, 13.0 Hz, 1H), 2.06 (tdd, *J* = 1.9, 4.1, 12.8 Hz, 1H), 1.96 (dt, *J* = 6.5, 12.6 Hz, 1H), 1.61 (q, *J* = 12.1 Hz, 1H), 1.53-1.47 (m, 1H), 1.46-1.37 (m, 2H), 1.35-1.27 (m, 1H), 1.27-1.23 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 74.7, 73.5, 68.9, 53.6, 45.8, 39.0, 37.0, 21.8, 21.8, 21.5, 21.2, 11.5, 11.5.

FTIR (neat) ν_{max}: 2933, 1720, 1347, 1220, 1104, 935, 736 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{14}H_{25}ClO_3$ [M^+] = 276.1492, found 276.1487.

(2,4,6-*cis*)-isopropyl 4-chloro-tetrahydro-6-(pentan-3-yl)-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.76 (4:1 Hex – EtOAc)

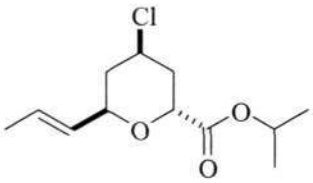
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (hept, *J* = 6.3 Hz, 1H), 4.03 (tt, *J* = 4.2, 11.7 Hz, 1H), 3.29 (dd, *J* = 2.1, 11.3 Hz, 1H), 2.43 (tdd, *J* = 1.9, 4.6, 12.8 Hz, 1H), 2.11 (tdd, *J* = 1.9, 4.4, 12.8 Hz, 1H), 1.77 (q, *J* = 12.1 Hz, 1H), 1.61 (q, *J* = 12.0 Hz, 1H), 1.55-

1.49 (m, 1H), 1.46-1.41 (m, 3H), 1.32-1.29 (m, 1H), 1.26-1.22 (m, 1H), 1.25 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 78.8, 76.5, 68.7, 55.6, 45.1, 39.1, 38.5, 21.7, 21.7, 21.5, 21.4, 11.3, 11.3.

FTIR (neat) ν_{max}: 2965, 1747, 1375, 1219, 1107, 910, 735 cm^{-1}.

(2,6-*cis*-2,4-*trans*)- isopropyl 4-chloro-tetrahydro-6-((*E*)-prop-1-enyl)-2*H*-pyran-2-carboxylate



Colorless oil; R_f = 0.57 (4:1 Hex – EtOAc)

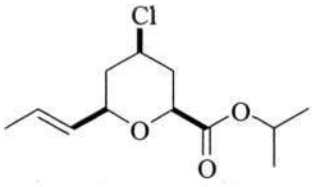
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (dqd, J = 0.75, 6.5, 15.4 Hz, 1H) 5.48 (qdd, J = 1.7, 5.2, 13.7 Hz, 1H) 5.09 (hept, J = 6.3 Hz, 1H), 4.53 (dd, J = 1.4, 6.1 Hz, 1H), 4.27-4.23 (m, 1H), 4.04 (tt, J = 4.2, 12.0 Hz, 1H), 2.58 (tdd, J = 2.1, 4.2, 13.1 Hz, 1H), 2.13 (tdd, J = 2.1, 4.2, 13.1 Hz, 1H), 2.01 (dt, J = 6.4, 12.4 Hz, 1H) 1.74 (dd, J = 1.8, 7.1 Hz, 1H), 1.71 (dd, J = 1.0, 6.5 Hz, 3H), 1.29 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 130.3, 129.2, 73.8, 73.2, 69.0, 52.5, 42.1, 36.7, 21.8, 21.8, 17.8.

FTIR (neat) ν_{max}: 2966, 1752, 1426, 1311, 1131, 1102, 968, 731 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{19}ClO_3$ [M^+] = 246.1017, found 246.1024.

(2,4,6-*cis*)- isopropyl 4-chloro-tetrahydro-6-((*E*)-prop-1-enyl)-2*H*-pyran-2-carboxylate



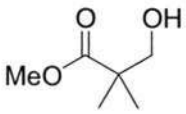
Colorless oil; R_f = 0.57 (4:1 Hex – EtOAc)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (dqd, *J* = 0.75, 6.5, 15.4 Hz, 1H), 5.55 (qdd, *J* = 1.7, 6.7, 15.5 Hz, 1H), 5.08 (hept, *J* = 6.3 Hz, 1H), 4.07 (tt, *J* = 4.2, 12.0 Hz, 1H), 3.97 (dd, *J* = 2.1, 11.9 Hz, 1H), 3.83 (dd, *J* = 6.6, 11.0 Hz, 1H), 2.44 (tdd, *J* = 1.9, 4.5, 12.7 Hz, 1H), 2.17 (tdd, *J* = 2.0, 4.4, 13.0 Hz, 1H), 1.80 (q, *J* = 11.9 Hz, 1H), 1.71 (q, *J* = 11.9 Hz, 1H), 1.69 (d, *J* = 6.0 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 129.9, 128.8, 77.6, 75.3, 68.9, 54.5, 41.8, 38.7, 21.7, 21.7, 17.4.

FTIR (neat) ν_{max}: 2982, 1747, 1454, 1375, 1171, 1107, 966, 737 cm^{-1}.

6.6 Formal Synthesis of (+)-SCH 351448



Methyl 3-hydroxy-2,2-dimethylpropanoate (66): To a 250 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (3.2 g, 14.3 mmol, 0.1 equiv). The compound was cooled to 0 °C prior to addition of formaldehyde (37% in water w/w) (26.7 mL, 0.36 mol, 2.5 equiv). The mixture was allowed to stir for 15 minutes at 0 °C, and (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (25 g, 0.143 mmol) was added to the mixture in a dropping funnel over a period of 1 hour. The reaction

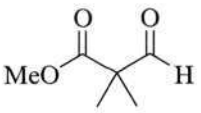
was allowed to proceed at room temperature for another 24 hours before quenching with 1*N* HCl (150 mL) and was allowed to stir for another 2 hours. The aqueous layer was extracted with EtOAc (10 × 50 mL) and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the alcohol as a colourless liquid (16.5 g, 87% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.70 (d, J = 12.1 Hz, 2H), 3.65 (s, 3H), 2.03 (d, J = 12.1 Hz, 1H), 1.17 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 176.9, 74.5, 51.9, 43.3, 22.3.

FTIR (neat) ν_{max}: 3447, 2976, 1724, 1475, 1229, 1047 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_6H_{12}O_3$ [M^+] = 132.1577, found 132.1534.



Methyl 2-formyl-2-methylpropanoate (67): To an oven-dried 250 mL round-bottom flask equipped with a magnetic stirring bar was added pyridinyl-chlorochromate (1.6 g, 7.5 mmol, 1.5 equiv), 4Å molecular sieve (0.3 g), silica gel (0.3 g) and dichloromethane (15 mL). The mixture was allowed to cool to 0 °C and hydroxy-ester (0.66 g, 5 mmol) in dichloromethane (2 mL) was added to the mixture in a dropping funnel. The reaction mixture was gradually warmed up to room temperature and was allowed to stir for another 12 hours. The mixture was filtered through a pad of silica gel and was flushed with 100 mL of diethyl ether. The solution was concentrated *in vacuo* at 0 °C. The crude aldehyde was allowed to stir in oven-dried 4Å molecular sieve under nitrogen atmosphere for a period of 24 hours. The aldehyde was distilled using a short-path distillation set under vacuum to afford a colourless liquid (0.36 g, 56% overall yield).

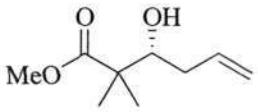
Boiling point at 20 mmHg: 138 °C.

^{1}H NMR (500 MHz, $CDCl_3$) 9.63 (s, 1H), 3.73 (s, 3H), 1.33 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) 199.1, 173.2, 53.8, 52.5, 19.6.

FTIR (neat) ν_{max}: 2988, 2955, 1738, 1714, 1470, 1279, 1151, 1088, 982, 866 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_6H_{10}O_3$ [M^+] = 130.063, found 130.0634.



(*R*)-methyl 3-hydroxy-2,2-dimethylhex-5-enoate (68): To an oven-dried 250 mL round-bottom flask equipped with a magnetic stirring bar was added (+)-DIP-Br (7.3 g, 20 mmol, 2 equiv) and dry THF (65 mL). The solution was cooled to -78 °C prior to addition of allylmagnesium bromide (1.0 M in ether, 15 mL, 1.5 equiv) slowly over 1 hour. The mixture was allowed to stir at -78 °C for 1 hour and was allowed to warm up to room temperature over 1 hour. The mixture was cooled at -78 °C again and was treated with a solution of distilled aldehyde **67** (1.3 g, 10 mmol) in THF (20 mL). The reaction mixture was stirred for 1 hour and was allowed to warm gradually to room temperature and stirred for another 6 hours. The solution was quenched with a pre-formed mixture of 3M NaOH (30 mL) and 30% H_2O_2 (10 mL) for 30 min. The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with water (50 mL) and saturated NaCl solution (50 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 15:1) to afford the homoallylic alcohol as colourless oil (1.22 g, 71% yield, 91% *ee*)

R_f = 0.35 (4:1 Hex – EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (tdd, J = 4.7, 10.4, 17.4 Hz, 1H), 5.13 (d, J = 17.1 Hz, 1H), 5.12 (d, J = 10.1 Hz, 1H), 3.72 (td, J = 2.1, 5.6 Hz, 1H) 3.7 (s, 3H), 3.40 (d, J = 5.6 Hz, 1H), 2.28 (ddd, J = 2.1, 6.3, 13.9 Hz, 1H), 2.06 (ddd, J = 2.1, 6.3, 13.9 Hz, 1H), 1.20 (s, 6H).

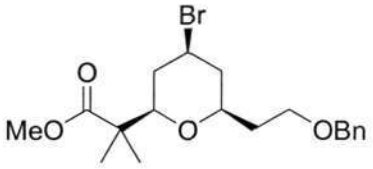
^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 135.6, 117.5, 75.7, 51.9, 46.9, 36.6, 22.0, 20.5.

FTIR (neat) ν_{max}: 3530 (br), 2976, 1732, 1474, 1193, 1153, 993 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_9H_{16}O_3$ [M^+] = 172.1099, found 172.1095.

$[\alpha]^{23}_D$ = +24.0 (c = 4.92 g/100mL, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing 2 Daicel Chiracel OJ column in series (Hexane : *i*-propanol 98:2, 2.0 mL/min) t_1 = 22.0 min (major), t_2 = 32.8 min (minor).



methyl 2-((2*R*,4*S*,6*R*)-6-(2-(benzyloxy)ethyl)-4-bromo-tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (73): To a solution of homoallylic alcohol **68** (0.88 g, 5 mmol) in dichloromethane (50 mL) was added $InBr_3$ (0.18 g, 0.5 mmol, 0.1 equiv) at 0 °C. The solution was allowed to cool to -78 °C and trimethylsilyl bromide (0.78 mL, 6 mmol, 1.2 equiv) was added dropwise. The solution was stirred for 1 minute and was treated with a solution of 3-(benzyloxy)propanal in dichloromethane (1.0 M, 5 mL). The reaction mixture was allowed to stir at -78 °C for 4 hours, and was allowed to warm up gradually to room temperature. The reaction was allowed to proceed for another 12 hours prior to quenching with saturated sodium bicarbonate solution (15 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the

combined organic extracts were washed with water (50 mL) and saturated NaCl solution (50 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the 4-bromo-THP product as colourless oil (1.30 g, 65% yield, 91% *ee*).

R_f = 0.59 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.47, (s, 2H), 4.15, (tt, *J* = 4.4, 12.0 Hz, 1H), 3.64 (s, 3H), 3.55-3.51 (m, 1H) 3.51 (dd, *J* = 4.1, 11.7 Hz, 1H), 3.50 (t, *J* = 5.7 Hz, 2H), 2.19 (tdd, *J* = 2.1, 4.4, 12.4 Hz, 1H), 2.12 (tdd, *J* = 2.1, 4.4, 12.4 Hz, 1H), 1.77-1.67 (m, 4H), 1.17 (s, 3H), 1.12 (s, 3H).

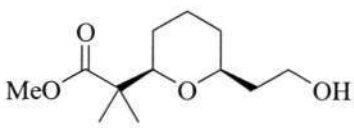
^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 138.4, 128.4, 127.7, 127.6, 81.5, 74.6, 73.1, 66.5, 51.9, 47.0, 46.5, 43.4, 37.6, 35.9, 20.8, 20.6.

FTIR (neat) ν_{max}: 2949, 1732, 1275, 1194, 1070, 737, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{19}H_{27}BrO_4$ [M^+] = 398.1087, found 398.1077.

$[\alpha]^{23}_D$ = +4.2 (c = 1.65 g/100mL, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel OD-H column (Hexane : *i*-propanol 99:1, 1.0 mL/min) t_1 = 8.5 min (minor), t_2 = 14.1 min (major).



methyl 2-((2*R*,6*S*)-tetrahydro-6-(2-hydroxyethyl)-2*H*-pyran-2-yl)-2-methyl-propanoate (75): To an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was added Pd / C (10% w/w, 2.22 g, 0.3 equiv) and was flushed with nitrogen before cooling to 0 °C. Methanol (63 mL) was added slowly to the solid

while stirring at a minimum speed of 500 rpm. The suspension was allowed to warm up to room temperature and was added an EtOAc (7 mL) solution of 4-bromo-THP methyl ester **73** (2.80 g, 7 mmol). The mixture was allowed to proceed under a H_2 atmosphere introduced through a balloon for 8 hours. The reaction mixture was subsequently treated with $NaHCO_3$ (1.76 g, 21 mmol, 3 equiv) and was allowed to stir under H_2 atmosphere for another 16 hours. The mixture was filtered through a pad of Celite and flushed with 300 mL of dichloromethane. The solution was concentrated *in vacuo* and was dissolved in 50 mL diethyl ether. The organic layer was washed with H_2O (3 × 20 mL) and saturated NaCl solution (20 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – EtOAc, 8:1) to afford the debromo THP-alcohol as colourless oil (1.10 g, 68% yield).

R_f = 0.13 (4:1 Hex – EtOAc).

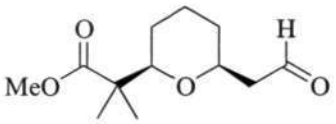
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73-3.69 (m, 2H), 3.68 (s, 3H), 3.58-3.52 (m, 2H), 2.80 (br s, 1H), 1.90-1.84 m, 2H), 1.71-1.67 (m, 2H), 1.53-1.47 (m, 2H), 1.31-1.23 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H).

13C-NMR (125 MHz, CDCl3) δ 177.5, 83.0, 79.3, 61.6, 51.9, 46.6, 38.0, 31.5, 24.8, 23.4, 21.9, 19.7.

FTIR (neat) ν_{max}: 3446, 2943, 2860, 1732, 1437, 1271, 1088, 1047 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{22}O_4$ [M^+] = 230.1513, found 230.1507.

$[\alpha]^{23}_D$ = +8.8 (c = 1.55 g/100mL, CH_2Cl_2)



methyl 2-((2*R*,6*S*)-6-(formylmethyl)-tetrahydro-2*H*-pyran-2-yl)-2-methyl-propanoate (76): To a solution of THP methyl ester alcohol **75** (1.15 g, 5 mmol) in dichloromethane (20 mL) was added Dess-Martin periodinane (3.18 g, 7.5 mmol, 1.5 equiv) at 0 °C. The reaction was allowed to proceed for 0.5 hour before quenching with a pre-formed mixture of saturated $Na_2S_2O_3$ solution (10 mL) and saturated $NaHCO_3$ solution (10 mL) at 0 °C. Upon turning to a colourless solution, the aqueous layer was extracted with diethyl ether (3 × 30 mL). The organic layer was washed with H_2O (20 mL) and saturated NaCl solution (20 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – EtOAc, 12:1) and the THP-aldehyde was obtained as colourless oil (0.86 g, 75% yield).

R_f = 0.40 (4:1 Hex – EtOAc).

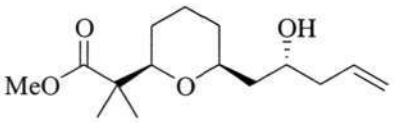
^{1}H NMR (500 MHz, $CDCl_3$) δ δ 9.71 (t, J = 2.3 Hz, 1H), 3.85 (dddd, J = 1.5, 4.0, 6.5, 12.7 Hz, 1H), 3.64 (s, 3H), 3.58 (dd, J = 1.8, 11.7Hz, 1H), 2.51 and 2.38 (ABXY, J_{AB} = 16.0, J_{AX} = 8.6, J_{BX} = 4.0, J_{AY} = 2.9, J_{BY} = 2.1 Hz, 2H), 1.91-1.87 (m, 1H), 1.60-1.53 (m, 2H), 1.52-1.46 (m, 1H), 1.30-1.17 (m, 2H),1.15 (s, 3H), 1.09 (s, 3H).

^{13}C-NMR (125 MHz, CDCl3) δ 201.8, 177.3, 82.4, 73.7, 51.8, 49.7, 46.6, 31.3, 24.7, 23.4, 21.1, 20.2.

FTIR (neat) ν_{max}: 2945, 2860, 1728, 1435, 1390, 1271, 1139, 1086, 1047 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{12}H_{21}O_4$ [M^++1] = 229.1434, found 229.1431.

$[\alpha]^{23}_D$ = +6.8 (c = 1.5 g/100mL, CH_2Cl_2)



methyl 2-((2*R*,6*S*)-tetrahydro-6-((*R*)-2-hydroxypent-4-enyl)-2*H*-pyran-2-yl)-2-methylpropanoate (77): A stirred solution of (+)-DIPBr (2.1 g, 5.82 mmol, 2 equiv) in dry THF (21 mL) was cooled to -78 °C. Allylmagnesium bromide (1.0 M in diethyl ether, 4.4 mL, 1.5 equiv) was added slowly over 45 minutes under nitrogen. The reaction mixture was allowed to stir for 1 hour before warming up to room temperature over an hour. The solution was cooled back to -78 °C before addition of a solution of the aldehyde **76** (0.66 g, 2.91 mmol) in dry THF (6 mL) dropwise. The reaction mixture was stirred for 1 hour and allowed to warm gradually to room temperature over 1 hour. The solution was quenched with a pre-formed mixture of 3M NaOH (3 mL) and 30% H_2O_2 (1 mL) for 30 min. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with water (10 mL) and saturated NaCl solution (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 12:1) and the homoallylic alcohol was obtained as colourless oil (0.71 g, 90% yield, 88% *de*, 98% *ee*).

R_f = 0.51 (4:1 Hex – EtOAc).

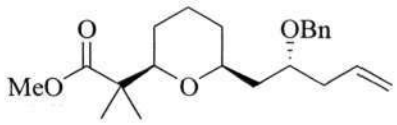
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (tdd, *J* = 7.0, 9.9, 17.0 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 5.05 (d, *J* = 10.1 Hz, 1H), 3.86-3.79 (m, 1H), 3.69 (s, 3H), 3.59-3.54 (m, 3H), 2.28-2.14 (m, 2H), 1.88-1.84 (m, 1H), 1.58-1.43 (m, 5H), 1.31-1.20 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.2, 135.1, 116.8, 82.8, 79.7, 71.2, 52.0, 46.4, 42.0, 41.6, 31.9, 24.7, 23.1, 21.6, 19.7.

FTIR (neat) ν_{max}: 3527, 2935, 2860, 1732, 1264, 1145, 1086, 915, 737 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{15}H_{26}O_4$ [M^+] = 270.1826, found 270.1821.

$[\alpha]^{23}_D$ = +11.7 (*c* = 1.35 g/100mL, CH_2Cl_2).



methyl 2-((2*R*,6*S*)-6-((*R*)-2-(benzyloxy)pent-4-enyl)-tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (78): To a solution of homoallylic alcohol **77** (1.08 g, 4.0 mmol) and benzyl bromide (0.57 mL, 4.8 mmol, 1.2 equiv) in dry DMF (12 mL) was added sodium hydride (60% in mineral oil, 0.32 g, 8 mmol, 2 equiv) at 0 °C. The reaction mixture was allowed to stir for 15 minutes before addition of another aliquot of sodium hydride (0.16 g, 4 mmol, 1 equiv). The reaction was allowed to proceed for another 15 minutes prior to quenching with cold 1M HCl (20 mL) at 0 °C and was stirred for 10 minutes. The aqueous layer was extracted with hexane (5 × 15 mL), and the combined organic extracts were washed with water (30 mL) and saturated NaCl solution (30 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the benzyl ether as colourless oil (1.29 g, 89% yield).

R_f = 0.70 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 5.87 (tdd, , *J* = 7.0, 10.2, 17.2 Hz, 1H), 5.09 (dd, *J* = 1.9, 15.7 Hz, 1H), 5.09 (d, *J* = 8.8 Hz, 1H), 4.52 and 4.48 (ABq, J_{AB} = 11.7 Hz, 2H), 3.62 (s, 3H), 3.61-3.54 (m, 1H), 3.49 (dd, *J* = 1.8, 11.4 Hz, 1H), 3.45-3.36 (m, 1H), 2.42-2.22 (m, 2H), 1.87-1.78 (m, 2H), 1.58-1.42 (m, 4H), 1.30-1.13 (m, 2H), 1.16 (s, 3H), 1.10 (s, 3H).

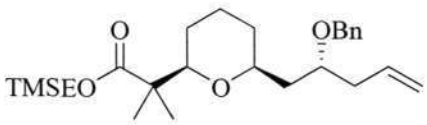
^{13}C-NMR (125 MHz, CDCl3) δ 177.5, 138.9, 135.2, 128.3, 127.7, 127.4, 116.8, 82.2, 75.4, 74.9, 70.7, 51.7, 46.7, 40.2, 37.9, 31.8, 25.1, 23.7, 21.2, 20.3.

FTIR (neat) ν_{max}: 2943, 2860, 1736, 1454, 1269, 1087, 914, 735, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{22}H_{32}O_4$ [M^+] = 360.2295, found 360.2281.

$[\alpha]^{23}_D$ = -8.2 (*c* = 1.42 g/100mL, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column and AD-H column in series (Hexane : *i*-propanol 99:1, 1.0 mL/min): t_1 = 7.5 min (major), t_2 = 8.1 min (minor).



2-(trimethylsilyl)ethyl 2-((2*R*,6*S*)-6-((*R*)-2-(benzyloxy)pent-4-enyl)-tetrahydro-2H-pyran-2-yl)-2-methylpropanoate (80): To a solution of benzyl ether **78** (0.91 g, 2.52 mmol) in dimethoxyethane (10 mL) and trimethylsilylethanol (10 mL) was added titanium(IV) tetraisopropoxide (0.22 mL, 0.76 mmol, 0.3 equiv). The reaction mixture was allowed to reflux for 48 hours and was cooled to approximately 30 °C prior to quenching with 1 M HCl solution (10 mL). The aqueous layer was extracted with hexane (5 × 5 mL), and the combined organic extracts were washed with water (10 mL) and saturated NaCl solution (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the transesterified product as colourless oil (0.94 g, 83% yield).

R_f = 0.77 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 5.87 (tdd, *J* = 7.0, 10.2, 17.2 Hz, 1H), 5.09 (dd, *J* = 1.8, 15.7 Hz, 1H), 5.05 (d, *J* = 8.9 Hz, 1H), 4.52 and 4.47 (ABq,

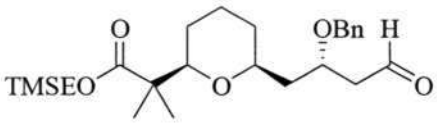
J_{AB} = 11.6 Hz, 2H), 4.15-4.09 (m, 2H), 3.65-3.57 (m, 1H), 3.49 (dd, J = 1.5, 11.1 Hz, 1H), 3.47-3.37 (m, 1H), 2.42-2.24 (m, 2H), 1.88-1.79 (m, 2H), 1.56-1.41 (m, 4H), 1.29-1.16 (m, 2H), 1.16 (s, 3H), 1.09 (s, 3H), 1.00-0.94 (m, 2H), 0.04 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.2, 138.9, 135.1, 128.3, 127.7, 127.4, 116.8, 82.1, 75.5, 74.9, 70.7, 62.6, 46.5, 40.2, 38.0, 31.8, 25.2, 23.7, 20.9, 20.7, 17.3, −1.5.

FTIR (neat) ν_{max}: 3046, 2978, 1730, 1455, 1183, 1153, 993, 739 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{26}H_{42}O_4Si$ [M^+] = 446.2847, found 446.2835.

$[\alpha]^{23}_D$ = -10.8 (*c* = 1.4 g/100mL, CH_2Cl_2).



2-(trimethylsilyl)ethyl 2-((2*R*,6*S*)-6-((*S*)-2-(benzyloxy)-3-formylpropyl)-tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (81): To a solution of alkene **80** (0.92 g, 2.05 mmol) and 4-methylmorpholine *N*-oxide (0.72 g, 6.15 mmol, 3.0 equiv) in acetone-water mixture (3 : 1; 20 mL) was treated OsO_4 (4% w/w in water, 0.095 mL) at room temperature. The reaction was allowed to proceed for 12 hours, and was subsequently treated with $NaIO_4$ (1.32 g, 6.15 mmol, 3.0 equiv). The mixture was stirred for 30 minutes and was quenched with saturated NH_4Cl solution (40 mL). The aqueous layer was extracted with (3 × 30 mL) diethyl ether and the combined organic extracts were washed with water (50 mL) and saturated NaCl solution (50 mL), dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the aldehyde as colourless oil (0.83 g, 90% yield).

R_f = 0.59 (4:1 Hex – EtOAc).

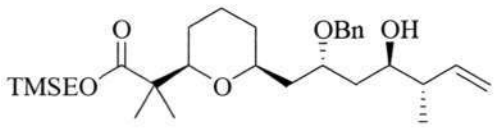
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, J = 2.6 Hz, 1H), 7.36-7.24 (m, 5H), 4.55 and 4.47 (ABq, J_{AB} = 11.5 Hz, 2H), 4.18-4.04 (m, 3H), 3.51 (dd, J = 1.7, 11.4 Hz, 1H), 3.42 (dt, J = 2.9, 11.4 Hz, 1H), 2.64-2.59 (m, 2H), 1.93 and 1.62 (ABXY, J_{AB} = 13.9, J_{AX} = 9.4, J_{BX} = 8.3, J_{AY} = 4.3, J_{BY} = 3.4 Hz, 2H), 1.88-1.83 (m, 1H), 1.54 - 1.45 (m, 3H), 1.31-1.17 (m, 2H), 1.15 (s, 3H), 1.09 (s, 3H), 0.99-0.93 (m, 2H), 0.04 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 201.9, 177.0, 138.2, 128.4, 127.8, 127.6, 82.1, 74.3, 71.7, 71.0, 62.6, 48.0, 46.5, 39.9, 31.9, 25.0, 23.6, 21.2, 20.4, 17.3, −1.5.

FTIR (neat) ν_{max}: 2949, 2862, 1728, 1265, 1252, 1165, 1142, 1088, 1049, 860, 837 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{25}H_{40}O_5Si$ [M^+] = 448.2640, found 448.2616.

$[\alpha]^{23}_D$ = +6.94 (*c* = 1.1 g/100mL, CH_2Cl_2).



2-(trimethylsilyl)ethyl 2-((2*R*,6*S*)-6-((2*R*,4*R*,5*S*)-2-(benzyloxy)-4-hydroxy-5-methylhept-6-enyl)-tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (82): To an oven-dried 100 mL round-bottom flask flushed with nitrogen was added KO*t*-Bu (1.0 M solution in THF, 2.86 mL, 1.5 equiv) and dry THF (23 mL) and was allowed to cool to –78 °C. *Trans*-2-butene (32.2 mg, 0.486 mmol, 3 equiv) was condensed from a gas lecture bottle into the mixture at –78 °C. *n*-BuLi (1.6 M in hexane, 1.79 mL, 1.5 equiv) was then added dropwise at a rate such that the internal temperature does not rise above –65 °C. After complete addition of *n*-BuLi (for 90 min), the mixture was stirred at –45 °C for 15 min. The resulting solution was cooled back to –78 °C, and to it was added B(^{d}Ipc)$_2$OMe (1 M in ether, 5.73 mL, 3 equiv, derived from (+)-α-pinene). The reaction mixture was allowed to stir at –78 °C for 30 min, and to it was

added $BF_3{\cdot}OEt_2$ (2.86 mL, 21.4 mmol, 11.2 equiv), followed by addition of the aldehyde **81** (0.86 g, 1.91 mmol) at –78 °C in THF (2 mL) over a period of 15 minutes. After 4 h, the reaction mixture was quenched by addition of a preformed solution of 3 N NaOH (12 mL) and 30% H_2O_2 (12 mL) at -78 °C, and was allowed to warm to room temperature for 1 h. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were with water (20 mL) and saturated NaCl solution (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 20:1) to afford the alcohol as pale yellowish oil (0.75 g, 78% yield, 84% *de*).

R_f = 0.58 (4:1 Hex – EtOAc).

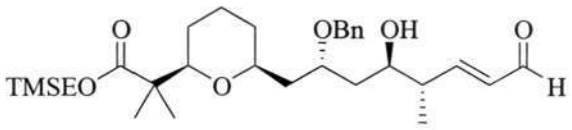
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 4H), 7.28-7.26 (m, 1H), 5.84 (ddd, , *J* = 7.8, 10.8, 17.7 Hz, 1H), 5.07 (d, *J* = 9.8 Hz, 1H), 5.06 (d, *J* = 18.5 Hz, 1H), 4.55 and 4.47 (ABq, J_{AB} = 11.6 Hz, 2H), 4.13 (qd, *J* = 8.4, 10.9 Hz, 2H), 3.90-3.86 (m, 1H), 3.75-3.73 (m, 1H), 3.48 (dd, *J* = 1.4, 11.3 Hz, 1H), 3.35-3.32 (m, 1H), 2.79 (d, *J* = 3.4 Hz, 1H), 2.23-2.17 (m, 1H), 1.93 (ddd, , *J* = 4.3, 9.4, 13.9 Hz, 1H), 1.87-1.83 (m, 1H), 1.73-1.68 (m, 1H), 1.62-1.58 (m, 2H), 1.52-1.43 (m, 3H), 1.26-1.15 (m, 2H), 1.16 (s, 3H), 1.09 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.98-0.95 (m, 2H), 0.04 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 177.2, 140.7, 138.5, 128.4, 127.9, 127.6, 115.1, 82.1, 74.9, 74.2, 71.5, 71.0, 62.6, 46.4, 44.1, 39.7, 37.0, 32.0, 25.2, 23.7, 20.9, 20.8, 17.3, 16.0, –1.4.

FTIR (neat) ν_{max}: 3496, 2945, 2860, 1728, 1454, 1269, 1141, 1088, 1049, 914, 737, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{29}H_{48}O_5Si$ [M^+] = 505.3256, found 505.3266.

$[\alpha]^{23}_D$ = +13.6 (*c* = 1.12 g/100mL, CH_2Cl_2).



2-(trimethylsilyl)ethyl 2-((2*R*,6*S*)-6-((*E*,2*R*,4*R*,5*S*)-2-(benzyloxy)-7-formyl-4-hydroxy-5-methylhept-6-enyl)-tetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (84): To a solution of alcohol **82** (0.2 g, 0.5 mmol) and acrolein (0.07 mL, 1.0 mmol, 2 equiv) in degassed dichloromethane (10 mL) was added 2nd generation Hoveyda-Grubbs catalyst (31 mg, 0.05 mmol, 0.1 equiv) under argon atmosphere. The reaction was refluxed for 12 hours and was allowed to stir at room temperature for another 2 hours under air. The mixture was filtered through celite and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 8:1) and the hydroxyl aldehyde was obtained as pale yellowish oil (0.21 g, 79% yield).

R_f = 0.30 (4:1 Hex – EtOAc).

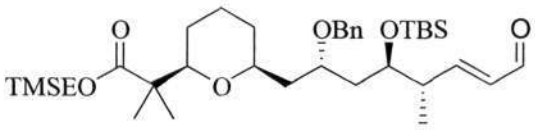
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, J = 7.8 Hz, 1H), 7.35-7.27 (m, 5H), 6.96 (dd, J = 7.8, 15.8 Hz, 1H), 6.11 (ddd, J = 1.0, 7.9, 15.8 Hz, 1H), 4.55 and 4.43 (ABq, J_{AB} = 11.6 Hz, 2H), 4.14-4.09 (m, 2H), 3.88-3.84 (m, 1H), 3.84-3.80 (m, 1H), 3.48 (dd, J = 1.7, 10.8 Hz, 1H), 3.36-3.30 (m, 1H), 3.14 (d, J = 3.8 Hz, 1H), 2.45 (sextet, J = 6.5 Hz, 1H), 1.95 (ddd, J = 3.9, 9.6, 13.8 Hz, 1H), 1.89-1.83 (m, 1H), 1.75-1.72 (m, 1H), 1.62-1.56 (m, 2H), 1.51-1.43 (m, 3H), 1.28-1.18 (m, 2H), 1.15 (s, 3H), 1.12 (J = 6.8 Hz, 3H), 1.08 (s, 3H), 0.97-0.94 (m, 2H), 0.03 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.3, 177.2, 160.8, 138.2, 132.9, 128.5, 127.9, 127.8, 82.2, 74.8, 73.9, 71.5, 71.0, 62.7, 46.5, 43.3, 39.2, 37.5, 31.9, 25.0, 23.6, 21.3, 20.3, 17.3, 15.9, -1.5.

FTIR (neat) ν_{max}: 3487, 2947, 2862, 1720, 1693, 1454, 1391, 1265, 1250, 1165, 1146, 1088, 1049, 858, 837, 698 cm^{-1}.

HRMS (FAB) *m/z* Calcd for $C_{30}H_{48}O_6Si$ [M^+] = 532.3215, found 532.3212.

$[\alpha]^{23}_D$ = +10.5 (*c* = 1.17 g/100mL, CH_2Cl_2).



αβ-unsaturated aldehyde (84a): To a solution of hydroxyl-aldehyde **84** (0.64 g, 1.19 mmol) in dichloromethane (20 mL) was treated with 2,6-lutidine (0.55 mL, 4.76 mmol, 4 equiv) and triethylamine (1.0 mL, 7.14 mmol, 6 equiv). The mixture was allowed to cool to 0 °C and was added TBSOTf (0.82 mL, 3.57 mmol, 3 equiv) over a period of 15 minutes. The reaction mixture was allowed to stir at 0 °C for 15 minutes and was quenched with saturated NH_4Cl solution (20 mL). The mixture was extracted with diethyl ether (3 × 15 mL), and the combined organic extracts were washed with water (20 mL) and saturated NaCl solution (20 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated in vacuo. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the OTBS-αβ-unsaturated aldehyde as pale yellowish oil (0.64 g, 84% yield).

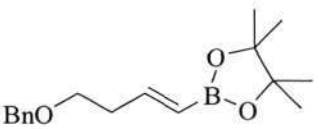
R_f = 0.65 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.5 (d, *J* = 7.8 Hz, 1H), 7.36-7.27 (m, 5H), 6.86 (dd, *J* = 7.0, 15.6 Hz, 1H), 6.12 (dd, *J* = 7.9, 15.8 Hz, 1H), 4.54 and 4.38 (ABq, *J* = 11.6 Hz, 2H), 4.17-4.12 (m, 2H), 3.97-3.94 (m, 1H), 3.72-3.67 (m, 1H), 3.45 (d, *J* = 10.8 Hz, 1H), 3.41-3.36 (m, 1H), 2.68-2.62 (m, 1H), 1.91-1.82 (m, 2H), 1.64-1.58 (m, 2H), 1.55-1.41 (m, 4H), 1.30-1.25 (m, 2H), 1.21 (s, 3H), 1.13 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.00-0.96 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H), 0.05 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 194.0, 176.7, 160.0, 138.8, 133.0, 128.3, 127.5, 127.4, 82.0, 74.8, 73.3, 72.4, 69.9, 62.5, 46.5, 42.9, 40.8, 40.2, 31.8, 25.9, 25.6, 23.6, 22.4, 19.9, 18.1, 17.3, 14.6, -1.5, -4.2, -4.5.

FTIR (neat) ν_{max}: 2951, 2856, 1726, 1693, 1456, 1252, 1142, 1088, 1047, 860, 837, 775, 736, 698 cm^{-1}.

HRMS (FAB) *m/z* Calcd for $C_{36}H_{62}O_6Si_2$ [M^+] = 646.4079, found 646.4097.



2-((*E*)-4-(benzyloxy)but-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (86): To a solution of 1-benzyloxy-but-3-ene (8.1 g, 50 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (8.5 mL, 50 mmol) in degassed dichloromethane (1 L) was added 2nd generation Grubbs catalyst (2.1 g, 2.5 mmol, 0.05 equiv) under argon atmosphere. The reaction was refluxed for 8 hours and was allowed to stir at room temperature for another 2 hours under air. The mixture was filtered through celite and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 8:1) to afford the benzyloxy-dioxoborolane as brown oil (10.2 g, 71% yield).

R_f = 0.73 (4:1 Hex – EtOAc).

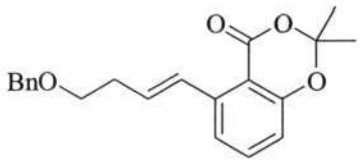
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.33 (m, 4H), 7.29-7.26 (m, 1H), 6.63 (td, *J* = 6.3, 17.9 Hz, 1H), 5.53 (d, *J* = 18.0, 1H), 4.51 (s, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 2.49 (dq, *J* = 1.5, 6.8 Hz, 2H), 1.26 (s, 12H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 150.4, 138.4, 128.3, 127.7, 127.6, 127.5, 83.1, 72.8, 68.9, 36.1, 24.8.

^{11}B NMR (32 MHz, $CDCl_3$) δ 29.5 ($BF_3{\cdot}OEt_2$ as reference standard).

FTIR (neat) ν_{max}: 2978, 1639, 1360, 1146, 1103, 997, 851, 737, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{25}BO_3$ [M^+] = 288.1891, found 288.1886.



Acetonide alkene (87): To a solution of dioxaborolane **86** (3.36 g, 11.7 mmol) and triflate **85** (4.2 g, 12 mmol, 1.03 equiv) in THF (120 mL) was added K_3PO_4 (3.73 g, 17.6 mmol, 1.5 equiv) and $PdCl_2$(dppf) (0.95 g, 1.17 mmol, 0.1 equiv). The reaction mixture was refluxed for 12 hours and was quenched with a preformed solution of 3M NaOH (20 mL) and 30% H_2O_2 (20 mL) at 0 °C. The mixture was allowed to stir for 1 hour and was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 10:1) to afford the benzyloxy acetonide as pale yellowish oil (2.97 g, 75% yield).

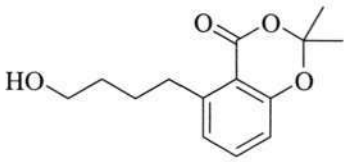
R_f = 0.50 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 15.8 Hz, 1H), 7.41 (t, 7.9 Hz, 1H), 7.35-7.31 (m, 4H), 7.29-7.25 (m, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 1.0, 8.1 Hz, 1H), 6.27 (td, *J* = 6.9, 15.8 Hz, 1H), 4.55 (s, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.60 (dq, *J* = 1.5, 6.7 Hz, 2H), 1.70 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.3, 156.7, 142.2, 138.4, 135.0, 131.6, 129.7, 128.3, 127.7, 127.5, 121.3, 115.7, 110.6, 105.1, 72.9, 69.6, 33.5, 25.6.

FTIR (neat) ν_{max}: 2997, 2856, 1732, 1599, 1576, 1475, 1317, 1269, 1209, 1080, 1045, 737, 698 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{22}O_4$ [M^+] = 338.1513, found 338.1516.



Acetonide alcohol (88): To a solution of acetonide alkene **87** (3.78 g, 11.2 mmol) in MeOH (80 mL) and EtOAc (10 mL) was added Pd / C (1.20 g, 10% w/w, 0.1 equiv). The solution was allowed to stir under H_2 atmosphere for 4 hours. The mixture was filtered through celite and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (4:1 Hex – EtOAc) and the acetonide alcohol was obtained as pale yellowish oil (2.80 g, >99% yield).

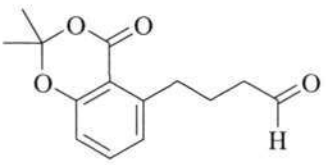
R_f = 0.12 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 6.93 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.70 (t, *J* = 5.5 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.02 (br s, 1H), 1.68 (s, 6H), 1.67 (quint, *J* = 5.5 Hz, 2H), 1.66 (quint, *J* = 7.4 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.5, 157.2, 148.0, 135.3, 125.2, 115.3, 111.9, 105.1, 62.0, 33.7, 32.3, 27.1, 25.6.

FTIR (neat) ν_{max}: 3412, 2939, 2864, 1736, 1607, 1582, 1477, 1389, 1379, 1315, 1269, 1209, 1070, 1041, 926 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{14}H_{18}O_4$ [M^+] = 250.1200, found 250.1195.



Acetonide aldehyde (89): To a solution of acetonide alcohol **88** (2.52 g, 10.1 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (6.4 g, 15.2 mmol, 1.5 equiv) at 0 °C. The reaction mixture was allowed to stir for 30 minutes and was quenched

with a pre-formed solution of $Na_2S_2O_3$ (20 mL) and $NaHCO_3$ (10 mL). The mixture was stirred at 0 °C until a clear solution was obtained, which was then extracted with ether (3 × 40 mL). The combined organic layer was washed with water (50 mL) and saturated NaCl solution (50 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – EtOAc, 8:1) to afford the alcohol as pale yellowish oil (2.0 g, 80% yield).

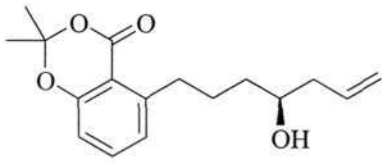
R_f = 0.36 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.80 Hz, 1H), 3.10 (t, *J* = 7.6 Hz, 2H), 2.52 (dt, *J* = 1.4, 7.3 Hz, 2H), 1.94 (quint, *J* = 7.6 Hz, 2H), 1.68 (s, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 202.5, 160.3, 157.2, 146.7, 135.3, 125.2, 115.7, 112.0, 105.2, 43.6, 33.5, 25.6, 23.5.

FTIR (neat) ν_{max}: 2997, 1732, 1714, 1605, 1582, 1479, 1447, 1391, 1315, 1271, 1209, 1070, 1042, 925, 810 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{14}H_{16}O_4$ [M^+] = 248.1043, found 248.1045.



Acetonide homoallylic alcohol (90): A stirred solution of (+)-DIPBr (3.65 g, 10.0 mmol, 2 equiv) in dry THF (35 mL) was cooled to -78 °C. Allylmagnesium bromide (1.0 M in diethyl ether, 7.5 mL, 1.5 equiv) was added slowly over 45 minutes under nitrogen. The reaction mixture was allowed to stir for 1 hour before warming up to room temperature over an hour. The solution was cooled back to -78 °C before

addition of a solution of the aldehyde **89** (1.24 g, 5.0 mmol) in dry THF (10 mL) dropwise. The reaction mixture was stirred for 1 hour and allowed to warm gradually to room temperature over 1 hour. The mixture was quenched with a pre-formed mixture of 3M NaOH (15 mL) and 30% H_2O_2 (5 mL) solution and was stirred for 30 min. The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with water (20 mL) and saturated NaCl solution (20 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 6:1) to afford the homoallylic alcohol as colourless oil (1.28 g, 88% yield, 92% *ee*).

R_f = 0.27 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 1.0, 8.1 Hz, 1H), 5.88-5.80 (m, 1H), 5.12 (d, *J* = 8.3 Hz, 1H), 5.11 (d, *J* = 17.9 Hz, 1H), 3.77-3.72 (m, 1H), 3.22-3.17 (m, 1H), 2.99-2.94 (m, 1H), 2.32-2.27 (m, 1H), 2.20-2.14 (m, 1H), 2.00 (br. s, 1H), 1.76-1.71 (m, 2H), 1.70 (s, 3H), 1.69 (s, 3H), 1.59-1.53 (m, 2H).

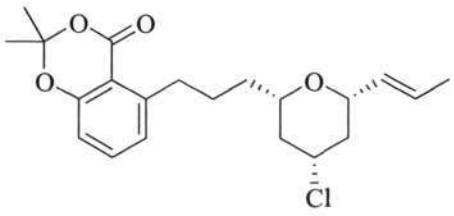
^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.4, 157.2, 148.0, 135.3, 135.0, 125.2, 117.8, 115.3, 111.9, 105.1, 70.1, 41.9, 36.5, 34.1, 27.4, 25.7, 25.6.

FTIR (neat) ν_{max}: 3447 (br), 2934, 1736, 1607, 1582, 1477, 1389, 1315, 1271, 1209, 1072, 922 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{17}H_{22}O_4$ [M^+] = 290.1513, found 290.1509.

$[\alpha]^{23}_D$ = -25.5 (*c* = 1.48 g/100mL, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AD and OJ column in series (Hexane : *i*-propanol 99.6:0.4, 3.7 mL/min): t_1 = 83.7 min (major), t_2 = 92.0 min (minor).



Acetonide-chloro-THP (91): To a solution of acetonide homoallylic alcohol **90** (0.29 g, 1 mmol) in dichloromethane (30 mL) was added $InCl_3$ (44 mg, 0.2 mmol, 0.2 equiv) at -78 °C. Trimethylsilyl chloride (0.38 mL, 3 mmol, 3 equiv) was added dropwise. The solution was stirred for 1 minute and was treated with a solution of crotonylaldehyde (0.1 mL, 1.2 mmol, 1.2 equiv) in dichloromethane (5 mL). The reaction mixture was allowed to stir at -78 °C for 2 hours, and was allowed to warm up gradually to -40 °C. The reaction was allowed to proceed for another 4 hours at -40 °C prior to quenching with saturated sodium bicarbonate solution (15 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organic extracts were washed with water (10 mL) and saturated NaCl solution (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) and the chloro-THP product was obtained as colourless oil (0.24 g, 62% yield).

R_f = 0.71 (4:1 Hex – EtOAc).

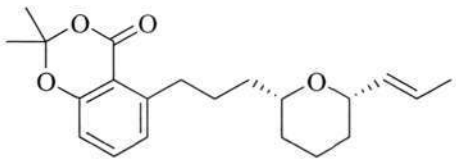
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.80 (dd, *J* = 0.9, 8.2 Hz, 1H), 5.69 (dqd, *J* = 1.0, 6.6, 15.5 Hz, 1H), 5.46 (qdd, *J* = 1.5, 6.3, 15.5 Hz, 1H), 4.02 (tt, *J* = 4.5, 11.7 Hz, 1H), 3.76 (dd, *J* = 6.3, 11.1 Hz, 1H), 3.40-3.34 (m, 1H), 3.14-3.02 (m, 1H), 2.13 (dd, *J* = 4.3, 12.2 Hz, 2H), 1.69 (s, 3H), 1.68 (s, 3H), 1.67 (d, *J* = 6.1 Hz, 3H), 1.77-1.71 (m, 1H), 1.61-1.58 (m, 2H), 1.56-1.53 (m, 2H), 1.29-1.22 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.2, 157.1, 147.7, 135.1, 130.8, 127.7, 125.2, 115.3, 112.0, 105.0, 77.0, 76.4, 55.8, 42.4, 42.1, 35.6, 34.1, 26.9, 25.7, 25.6, 17.8.

FTIR (neat) ν_{max}: 2930, 2853, 1736, 1605, 1582, 1477, 1447, 1377, 1313, 1269, 1072, 1043, 964, 736 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{27}ClO_4$ $[M^+]$ = 378.1592, found 378.1597.

$[\alpha]^{23}_D$ = -6.2 (*c* = 0.95 g/100mL, CH_2Cl_2)



Fragment B (92): To a solution of chloro-THP **91** (50 mg, 0.13 mmol) in toluene (2 mL) was added tributyltinhydride (0.14 mL, 0.52 mmol, 4.0 equiv) and ACCN (3.2 mg, 0.013 mmol, 0.1 equiv). The mixture was allowed to reflux for 12 hours before quenching with saturated KF solution (2 mL), stirring for 2 hours. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with water (10 mL) and saturated NaCl solution (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the de-chloro THP product as colourless oil (34 mg, 77% yield).

R_f 0.71 (4:1 Hex – EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.78 (dd, *J* = 0.7, 8.2 Hz, 1H), 5.64 (dqd, *J* = 1.0, 6.7, 15.3 Hz, 1H), 5.48 (qdd, *J* = 1.5, 6.1, 15.3 Hz, 1H), 3.73 (dd, *J* = 6.5, 10.9 Hz, 1H), 3.36-3.31 (m, 1H), 3.14-3.02 (m, 2H), 1.83-1.78 (m, 1H), 1.75-1.70 (m, 1H), 1.68 (s, 3H), 1.68 (s, 3H), 1.66 (d, *J* = 6.1 Hz,

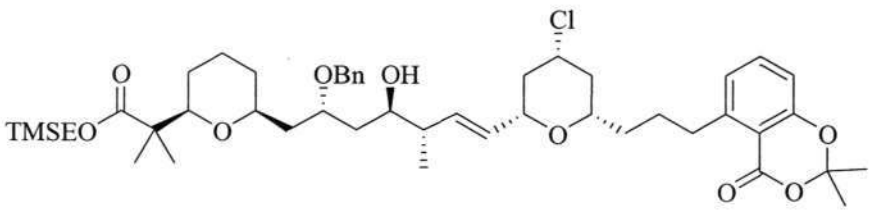
1H), 1.65-1.61 (m, 5H), 1.60-1.54 (m, 2H), 1.31-1.28 (m, 1H),1.25-1.23 (m, 1H), 1.16-1.14 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 160.2, 157.1, 148.1, 135.1, 132.8, 126.2, 125.3, 115.1, 112.0, 104.9, 78.1, 77.6, 36.4, 34.3, 31.1, 27.8, 27.0, 25.7, 25.6, 23.6, 17.8.

FTIR (neat) ν_{max}: 2934, 2857, 1736, 1605, 1582, 1477, 1447, 1377, 1313, 1269, 1209, 1074, 1043, 966, 737 cm^{-1}.

HRMS (EI) *m/z* Calcd for $C_{21}H_{28}O_4$ $[M^+]$ = 344.1982, found 344.1975.

$[\alpha]^{23}_D$ = -5.5 (*c* = 1.05 g/100mL, CH_2Cl_2).



Chloro-Monomeric unit (93): To a solution of acetonide homoallylic alcohol **90** (0.19 g, 0.64 mmol, 1.5 equiv) in dichloromethane (8 mL) was added $In(OTf)_3$ (5 mg, 0.086 mmol, 0.2 equiv) at -78 °C, followed by dropwise addition of trimethylsilyl chloride (0.081 mL, 0.64 mmol, 1.5 equiv). The solution was stirred for 1 minute and was treated with a solution of αβ-unsaturated aldehyde **84a** (0.28 g, 0.43 mmol) in dichloromethane (2 mL). The reaction mixture was allowed to stir at -78 °C for 2 hours, and was allowed to warm up gradually to -40 °C. The reaction was allowed to proceed for another 4 hours at -40 °C prior to quenching with saturated sodium bicarbonate solution (5 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic extracts were washed with water (5 mL) and saturated NaCl solution (5 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash

column chromatography (Hex – ether, 8:1) to afford the chloro-monomer unit as colourless oil (0.15 g, 42% yield).

R_f = 0.32 (4:1 Hex – EtOAc).

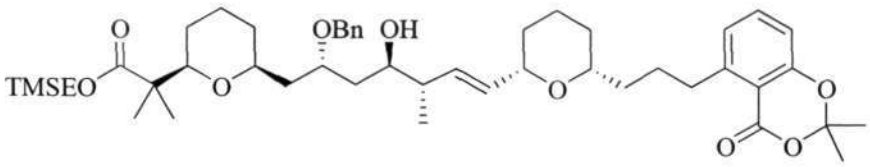
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.9 Hz, 1H), 7.34-7.31 (m, 4H), 7.27-7.25 (m, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.72 (dd, *J* = 7.5, 15.3 Hz, 1H), 5.51 (dd, *J* = 5.9, 15.5 Hz, 1H), 4.53 and 4.46 (ABq, *J* = 11.6 Hz, 2H), 4.17-4.08 (m, 2H), 4.03 (tt, *J* = 4.6, 11.7 Hz, 1H), 3.88-3.84 (m, 1H), 3.81 (dd, *J* = 6.2, 11.2 Hz, 1H), 3.73-3.70 (m, 1H), 3.46 (d, *J* = 10.5 Hz, 1H), 3.37 (td, *J* = 4.9, 10.5 Hz, 1H), 3.13 (dt, *J* = 2.1, 9.1 Hz, 1H), 3.12-3.05 (m, 2H), 2.82 (br s, 1H), 2.23-2.13 (m, 2H), 1.95-1.90 (m, 1H), 1.86-1.82 (m, 1H), 1.69 (s, 6H), 1.71-1.63 (m, 6H), 1.60-1.55 (m, 4H), 1.51-1.46 (m, 3H), 1.23-1.18 (m, 2H), 1.15 (s, 3H), 1.09 (s, 3H), 1.03-0.95 (m, 4H), 0.91-0.83 (m, 1H), 0.04 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) 177.1, 160.2, 157.2, 147.7, 138.5, 135.2, 134.0, 130.4, 128.4, 127.8, 127.6, 125.2, 115.3, 112.0, 105.1, 82.1, 77.0, 76.5, 74.9, 74.2, 71.6, 71.0, 62.6, 55.8, 46.5, 42.7, 42.4, 42.2, 39.7, 36.9, 35.7, 34.1, 32.0, 30.3, 26.9, 25.7, 25.2, 23.7, 20.9, 20.8, 17.3, 15.8, -1.4.

FTIR (neat) ν_{max}: 3489, 2949, 1734, 1607, 1477, 1389, 1269, 1047, 733 cm^{-1}

HRMS (FAB) *m/z* Calcd for $C_{47}H_{69}ClO_9Si$ [M^+-1] = 839.4316, found 839.4296.

$[\alpha]^{23}_D$ = -4.4 (*c* = 1.05 g/100mL, CH_2Cl_2)



de-chloro-monomeric unit (94): To a solution of chloro-monomeric unit **93** (43 mg, 0.051 mmol) in toluene (1.5 mL) was added tributyltinhydride (0.06 mL, 0.20 mmol, 4.0 equiv) and ACCN (1.2 mg, 5 μmol, 0.1 equiv) under nitrogen. The mixture was allowed to reflux for 12 hours before stirring for 2 hours in the atmosphere. The mixture was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 8:1) and the de-chloro-monomeric unit was obtained as colourless oil (28 mg, 69% yield).

R_f = 0.30 (4:1 Hex – EtOAc).

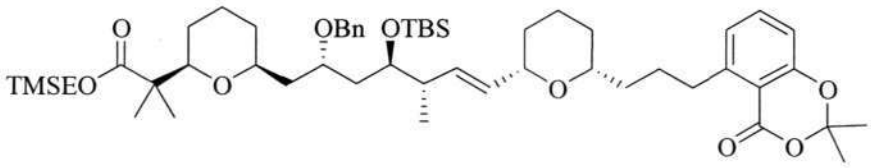
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.9 Hz, 1H), 7.33-7.30 (m, 4H), 7.27-7.25 (m, 1H), 6.93 (dd, *J* = 0.8, 7.6 Hz, 1H), 6.79 (dd, *J* = 0.9, 8.1 Hz, 1H), 5.66 (dd, *J* = 7.6, 16.2 Hz, 1H), 5.54 (dd, *J* = 5.8, 15.8 Hz, 1H), 4.53 and 4.46 (ABq, *J* = 11.5 Hz, 2H), 4.16-4.09 (m, 2H), 3.89-3.83 (m, 1H), 3.82-3.77 (m, 1H), 3.74-3.70 (m, 1H), 3.45 (dd, *J* = 1.3, 11.3 Hz, 1H), 3.37-3.28 (m, 2H), 3.15-3.03 (m, 2H), 2.76 (br s, 1H), 2.24-2.14 (m, 1H), 1.95-1.88 (m, 1H), 1.85-1.79 (m, 2H), 1.69 (s, 6H), 1.70-1.62 (m, 6H), 1.61-1.53 (m, 4H), 1.53-1.47 (m, 3H), 1.45-1.35 (m, 3H), 1.32-1.25 (m, 2H), 1.15 (s, 3H), 1.08 (s, 3H), 1.03-0.99 (m, 3H), 0.97-0.95 (m, 1H), 0.03 (m, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$) 177.1, 160.3, 157.1, 148.2, 138.6, 135.1. 132.6, 132.6, 128.4, 127.9, 127.6, 125.3, 115.2, 112.0, 105.0, 82.1, 78.2, 77.7, 74.9, 74.3, 71.6, 71.1, 62.6, 46.5, 42.5, 39.8, 36.4, 34.3, 31.9, 31.2, 27.9, 27.1, 26.9, 25.7, 25.3, 23.7, 23.6, 21.0, 17.5, 17.3, 15.8, 13.6, -1.4.

FTIR (neat) ν_{max}: 3489, 2949, 1734, 1607, 1477, 1389, 1269, 1047, 733 cm^{-1}

HRMS (FAB) *m/z* Calcd for $C_{47}H_{70}O_9Si$ [M^+-1] = 805.4705, found 805.4740.

$[\alpha]^{23}_{D}$ = -2.6 (*c* = 0.70 g/100mL, CH_2Cl_2)



OTBS-monomeric unit (94a): To a solution of de-chloro-monomeric unit **94** (26.4 mg, 0.033 mmol) in dichloromethane (1.5 mL) was treated with 2,6-lutidine (0.015 mL, 0.13 mmol, 4 equiv) and triethylamine (0.027 mL, 0.20 mmol, 6 equiv). The mixture was allowed to cool to 0 °C and was added TBSOTf (0.022 mL, 0.10 mmol, 3 equiv) over a period of 15 minutes. The reaction mixture was allowed to stir at 0 °C for 15 minutes and was quenched with saturated NH_4Cl solution (5 mL). The mixture was extracted with diethyl ether (3 × 5 mL), and the combined organic extracts were washed with water (5 mL) and saturated NaCl solution (5 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 20:1) to afford the OTBS-monomeric unit as pale yellowish oil (21 mg, 69% yield).

R_f = 0.62 (4:1 Hex – EtOAc).

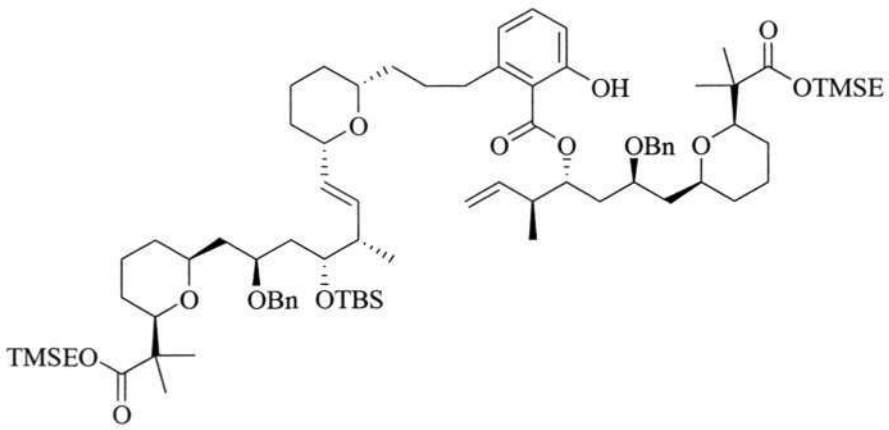
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 5H), 7.25-7.22 (m, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.77 (dd, *J* = 1.0, 8.2 Hz, 1H), 5.60 (dd, *J* = 6.3, 15.5 Hz, 1H), 5.50 (dd, *J* = 6.1, 15.5 Hz, 1H), 4.49 and 4.40 (ABq, J_{AB} = 11.7 Hz, 2H), 4.16-4.11 (m, 2H), 3.87 (td, *J* = 3.5, 8.0 Hz, 1H), 3.78-3.75 (m, 1H), 3.68-3.65 (m, 1H), 3.43 (d, *J* = 11.2 Hz, 1H), 3.40-3.37 (m, 1H), 3.34-3.31 (m, 1H), 3.09-3.04 (m, 2H), 2.36-2.33 (m, 1H), 1.89-1.85 (m, 1H), 1.83-1.79 (m, 2H), 1.68 (s, 6H), 1.65-1.56 (m, 6H), 1.52-1.45 (m, 6H), 1.41-1.36 (m, 1H), 1.32-1.21 (m, 2H), 1.20 (s, 3H), 1.16-1.13 (m, 2H), 1.11 (s, 3H), 0.99-0.96 (m, 5H), 0.87 (s, 9H), 0.03 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) 177.0, 160.2, 157.1, 148.2, 139.2, 135.1, 132.9, 131.8, 128.2, 127.5, 127.2, 125.3, 115.1, 112.0, 104.9, 82.0, 78.5, 77.7, 75.1, 73.2, 72.4, 69.7, 62.5, 46.6, 41.9, 41.2, 38.3, 36.4, 34.3, 31.9, 31.6, 31.2, 27.0, 26.0, 25.8, 25.7, 25.6, 23.7, 23.6, 22.7, 19.7, 18.1, 17.3, 13.9, -1.4, -4.2, -4.3.

FTIR (neat) ν_{max}: 2949, 2859, 1724, 1452, 1265, 1250, 1088, 1047, 837, 739 cm^{-1}

HRMS (FAB) *m/z* Calcd for $C_{53}H_{84}O_9Si_2$ [M^+-1] = 919.5570, found 919.5597.

$[\alpha]^{23}_D$ = -14.8 (*c* = 0.91 g/100mL, CH_2Cl_2)



OTBS-unsaturated ester (95): To a solution of homoallyllic alcohol **82** (9.1 mg, 0.018 mmol) in THF (0.4 mL) was slowly added NaHMDS solution (0.045 mL, 1.0 M solution in THF, 2.5 equiv) at 0°C. The reaction was allowed to proceed for 1 hour, and was added a solution of OTBS-monomeric unit **94a** (18.3 mg, 0.02 mmol) in THF (0.2 mL) dropwise at 0 °C. The mixture was allowed to stir for 2 hours at room temperature. The reaction was quenched with saturated NH_4Cl solution (1 mL) and was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and saturated NaCl solution (5 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hex – ether, 25:1) to afford the OTBS-diene as pale yellowish oil (19 mg, 78% yield).

R_f = 0.49 (Hex – EtOAc, 8:1).

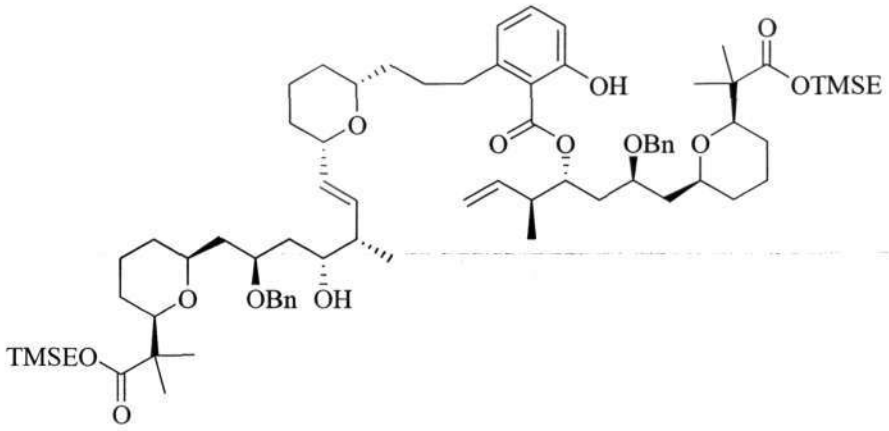
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.16 (s, 1H), 7.35-7.29 (m, 8H), 7.25-7.22 (m, 3H), 6.80 (dd, J = 1.0, 8.4 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 5.81 (ddd, J = 7.4, 10.3, 17.4 Hz, 1H), 5.63-6.60 (m, 1H), 5.60 (dd, J = 6.1, 15.8 Hz, 1H), 5.50 (dd, J = 6.1, 15.9 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 10.3 Hz, 1H), 4.49 and 4.39 (ABq, J_{AB} = 11.7 Hz, 2H), 4.47 and 4.33 (ABq, J_{AB} = 11.0 Hz, 2H), 4.15-4.11 (m, 2H), 4.11-4.07 (m, 2H), 3.88 (td, J = 3.5, 8.2 Hz, 1H), 3.78-3.74 (m, 1H), 3.69-3.64 (m, 1H), 3.60-3.55 (m,1H), 3.43 (dd, J = 1.6, 11.1 Hz, 1H), 3.40-3.35 (m, 3H), 3.32-3.27 (m, 1H), 2.94-2.80 (m, 2H), 2.57-2.50 (m, 1H), 2.38-2.31 (m, 1H), 1.90-1.78 (m, 7H), 1.62-1.55 (m, 11H), 1.51-1.44 (m, 10H), 1.20 (s, 3H), 1.11 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.87 (m, 12H), 0.03 (s, 9H), 0.02 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$) 177.0, 176.9, 170.9, 162.3, 145.5, 139.2, 139.1, 138.5, 133.8, 133.0, 131.7, 128.3, 128.2, 128.1, 127.5, 127.3, 125.5, 122.1, 116.3, 115.6, 112.6, 82.0, 81.9, 78.6, 77.8, 76.0, 75.1, 74.5, 73.3, 72.9, 72.4, 71.2, 69.7, 62.6, 62.5, 46.6, 46.4, 42.1, 41.9, 41.2, 40.6, 38.4, 37.5, 36.8, 36.6, 36.1, 34.2, 32.1, 31.8, 31.7, 31.3, 30.3, 28.1, 26.0, 25.8, 25.6, 23.7, 22.8, 22.4, 19.7, 19.6, 18.2, 17.3, 15.2, 13.7, -1.4, -4.3, -4.3.

FTIR (neat) ν_{max}: 2949, 2858, 1724, 1653, 1607, 1452, 1265, 1250, 1088, 1047, 837, 739, 698 cm^{-1}.

HRMS (FAB) *m/z* Calcd for $C_{79}H_{125}O_{13}Si_3$ [M^+-1] = 1365.8423, found 1365.8849.

$[\alpha]^{23}_D$ = +15.1 (c = 0.69 g/100mL, CH_2Cl_2)



Hydroxy ester (95a): To a solution of OTBS-unsaturated ester **95** (14 mg, 0.010 mmol) in MeOH (1.0 mL) was conc. HCl (2 drops) at 0 °C. The mixture was allowed to stir at room temperature for 2 hours before triethylamine (0.8 mL) was added at 0 °C. The mixture was concentrated *in vacuo* and the residual crude product was purified by flash column chromatography (Hex – EtOAc, 10:1) to afford the hydroxy ester as colourless oil (12 mg, 96% yield).

R_f = 0.46 (4:1 Hex – EtOAc).

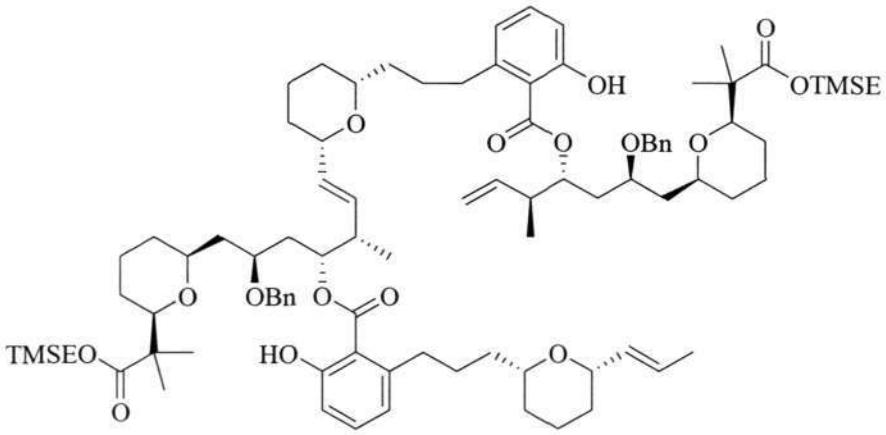
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.15 (s, 1H), 7.35-7.30 (m, 8H), 7.29-7.22 (m, 3H), 6.81 (dd, J = 0.9, 8.2 Hz, 1H), 6.71 (dd, J = 0.8, 7.6 Hz, 1H), 5.82 (ddd, J = 7.8, 10.3, 17.7 Hz, 1H), 5.67 (dd, J = 7.4, 16.3 Hz, 1H), 5.66-5.60 (m, 1H), 5.54 (dd, J = 5.9, 15.8 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 5.08 (d, J = 10.1 Hz, 1H), 4.53 and 4.46 (ABq, J_{AB} = 11.4 Hz, 2H), 4.47 and 4.34 (ABq, J_{AB} = 11.0 Hz, 2H), 4.15-4.11 (m, 2H), 4.11-4.07 (m, 2H), 3.88-3.84 (m, 1H), 3.80 (dd, J = 4.8, 9.7 Hz, 1H), 3.73-3.69 (m, 1H), 3.61-3.57 (m,1H), 3.46 (dd, J = 1.6, 11.5 Hz, 1H), 3.40-3.35 (m, 2H), 3.34-3.28 (m, 2H), 2.95-2.84 (m, 2H), 2.78 (br s, 1H), 2.58-2.51 (m, 1H), 2.22-2.17 (m, 1H), 1.95-1.89 (m, 1H), 1.87-1.79 (m, 6H), 1.67-1.55 (m, 14H), 1.52-1.41 (m, 8H), 1.27-1.24 (m, 2H), 1.15 (s, 3H), 1.09 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.98-0.91 (m, 3H), 0.03 (s, 9H), 0.02 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) 177.1, 176.9, 170.9, 162.3, 145.4, 139.2, 138.6, 138.5, 133.8, 132.7, 132.4, 128.4, 128.3, 128.1, 127.9, 127.6, 127.6, 122.2, 116.3, 115.7, 112.6, 82.1, 81.9, 78.3, 77.8, 76.0, 75.0, 74.5, 74.2, 72.9, 71.6, 71.2, 71.1, 62.7, 62.6, 46.5, 46.4, 42.5, 42.2, 40.6, 38.8, 37.5, 37.0, 36.7, 36.1, 32.1, 31.9, 31.8, 31.3, 28.1, 25.6, 25.3, 23.7, 23.7, 23.6, 22.4, 21.0, 20.8, 19.6, 17.3, 17.3, 16.2, 15.8, -1.4, -1.5.

FTIR (neat) ν_{max}: 3485 (br), 2943, 2860, 1720, 1653, 1452, 1250, 1165, 1088, 1047, 912, 837, 733 cm^{-1}.

HRMS (FAB) *m/z* Calcd for $C_{73}H_{111}O_{13}Si_2$ $[M^+-1]$ = 1251.7558, found 1251.7575.

$[\alpha]^{23}_D$ = +21.0 (c = 0.56 g/100mL, CH_2Cl_2)



Diester triene (96): To a solution of hydroxyl ester **95a** (12.2 μg, 9.7 μmol) in THF (0.5 mL) was slowly added NaHMDS solution (0.04 mL, 1.0 M solution in THF, 4 equiv) at 0°C. The reaction was allowed to proceed for 1 hour, and was added a solution of Fragment **B**, **92** (5 mg, 14.6 μmol) in THF (0.15 mL) dropwise at 0 °C. The mixture was allowed to stir for 2 hours at room temperature. The reaction was quenched with saturated NH_4Cl solution (1 mL) and was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with water (5 mL) and saturated NaCl solution (5 mL). The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. The residual crude product

was purified by flash column chromatography (Hex – ether, 25:1) and the triene was obtained as pale yellowish oil (12 mg, 78% yield).

R_f = 0.27 (Hex – EtOAc, 8:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.16 (s, 1H), 11.13 (s, 1H), 7.35-7.21 (m, 12 H), 6.81 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 5.86-5.78 (m, 1H), 5.68-5.64 (m, 1H), 5.64-5.60 (m, 2H), 5.60-5.53 (m, 2H), 5.52-5.46 (m, 1H), 5.09 (d, J = 17.1 Hz, 1H), 5.07 (d, J = 9.7 Hz, 1H), 4.47 and 4.34 (ABq, J_{AB} = 11.1 Hz, 4H), 4.09 (t, J = 8.5 Hz, 4H), 3.75-3.70 (m, 2H), 3.62-3.56 (m, 2H), 3.41-3.33 (m, 4H), 3.32-3.24 (m, 2H), 2.95-2.82 (m, 4H), 2.58-2.51 (m, 2H), 1.87-1.77 (10H), 1.74-1.67 (m, 1H), 1.67 (d, J = 6.5 Hz, 3H), 1.64-1.52 (m, 10H), 1.50-1.42 (m, 7H)1.33-1.12 (m, 10H), 1.08 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.04-1.01 (m, 12H), 0.95-0.91 (m, 4H), 0.90-0.86 (m, 2H), 0.02 (s, 9H), 0.02 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) 176.9, 176.9, 170.9, 162.3, 145.5, 145.4, 139.2, 138.5, 135.8, 133.8, 133.7, 133.3, 132.8, 131.0, 128.3, 128.3, 128.1, 128.1, 127.6, 127.5, 126.2, 125.6, 122.2, 122.1, 116.4, 115.7, 112.6, 112.6, 81.9, 81.5, 78.2, 77.8, 77.7, 77.6, 77.6, 76.1, 76.0, 74.5, 74.5, 72.9, 72.9, 71.2, 62.6, 62.6, 46.5, 42.2, 40.8, 40.6, 37.5, 36.8, 36.7, 36.2, 36.1, 34.3, 32.1, 32.1, 31.7, 31.5, 31.4, 31.3, 30.3, 29.7, 25.7, 25.6, 23.7, 23.6, 23.5, 22.7, 22.5, 22.4, 19.7, 19.6, 17.9, 17.3, 16.2, -1.5, -1.5.

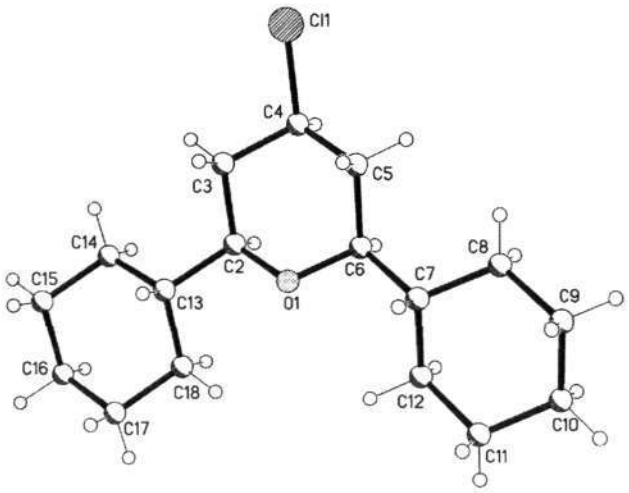
FTIR (neat) ν_{max}: 3400, 2934, 1724, 1653, 1607, 1450, 1250, 1088, 1047, 837, 735 cm^{-1}.

HRMS (FAB) *m/z* Calcd for $C_{91}H_{133}O_{16}Si_2$ [M^+-1] = 1537.9127, found 1537.9153.

$[\alpha]^{23}_D$ = +22.4 (c = 0.40 g/100mL, CH_2Cl_2)

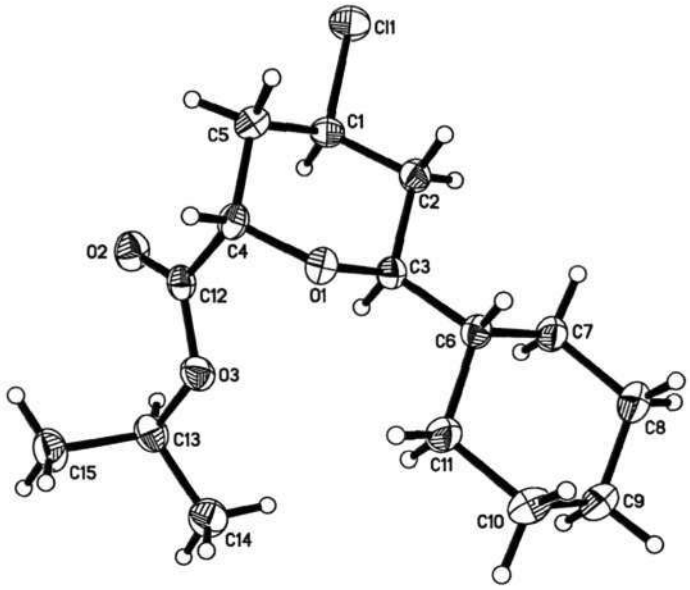
Appendix

Single crystal X-ray diffraction analysis of **4**



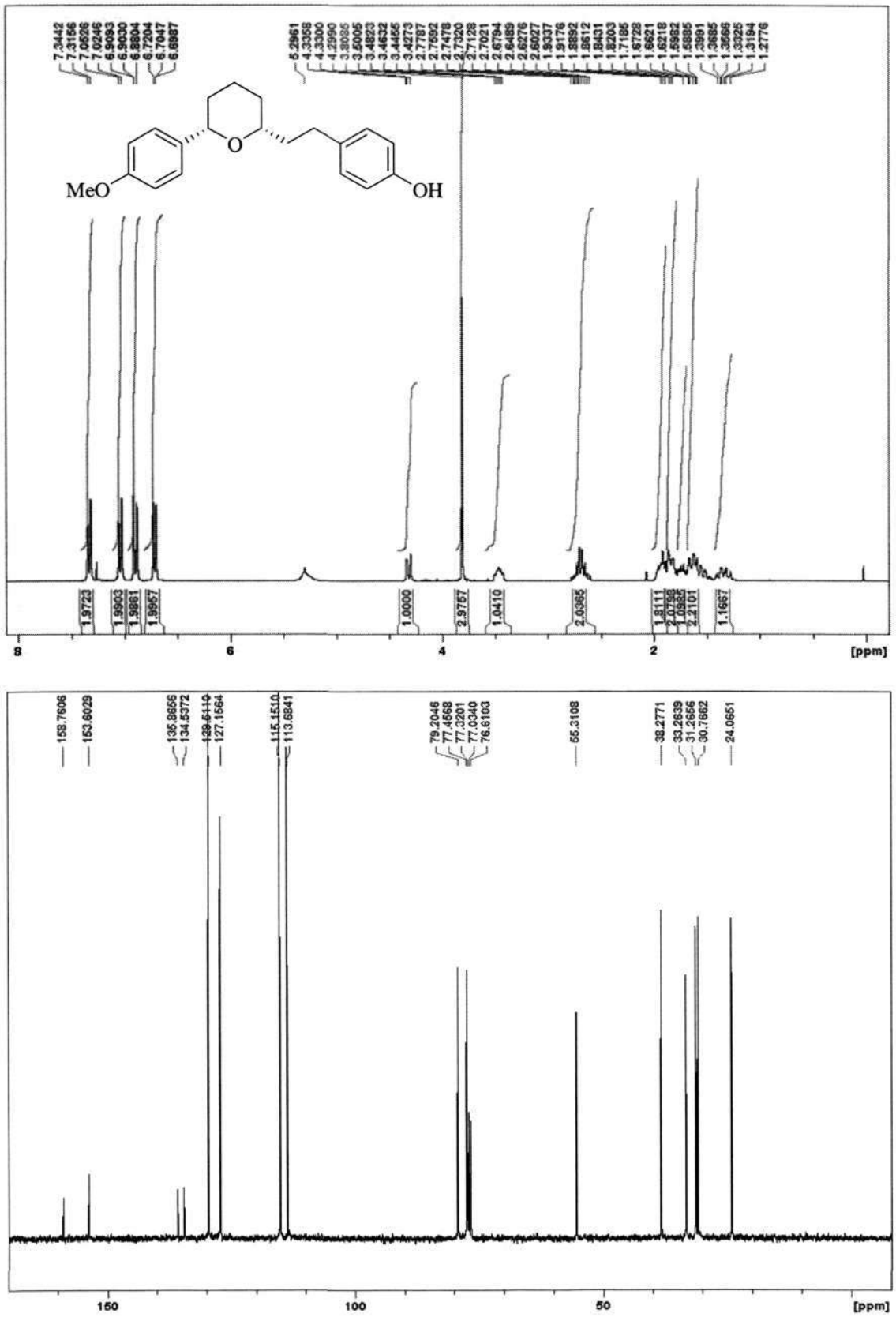
Empirical formula	C17 H29 Cl O
Formula weight	284.85
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 14.8795(11) Å α= 90°.
	b = 10.4911(8) Å β= 91.203(2)°.
	c = 10.5150(8) Å γ = 90°.
Volume	1641.1(2) Å^3
Z	4
Density (calculated)	1.153 Mg/m^3
Absorption coefficient	0.225 mm^{-1}
F(000)	624
Crystal size	0.38 x 0.30 x 0.26 mm^3
Theta range for data collection	1.37 to 27.50°.
Index ranges	-19<=h<=12, -13<=k<=13, -12<=l<=13
Reflections collected	11370
Independent reflections	3773 [R(int) = 0.0275]
Completeness to theta = 27.50°	100.0 %
Absorption correction	Sadabs, (Sheldrick 2001)
Max. and min. transmission	0.9438 and 0.9193
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3773 / 0 / 172
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0501, wR2 = 0.1334
R indices (all data)	R1 = 0.0660, wR2 = 0.1464
Largest diff. peak and hole	0.388 and -0.175 e.Å^{-3}

Single crystal X-ray diffraction analysis of **58b**

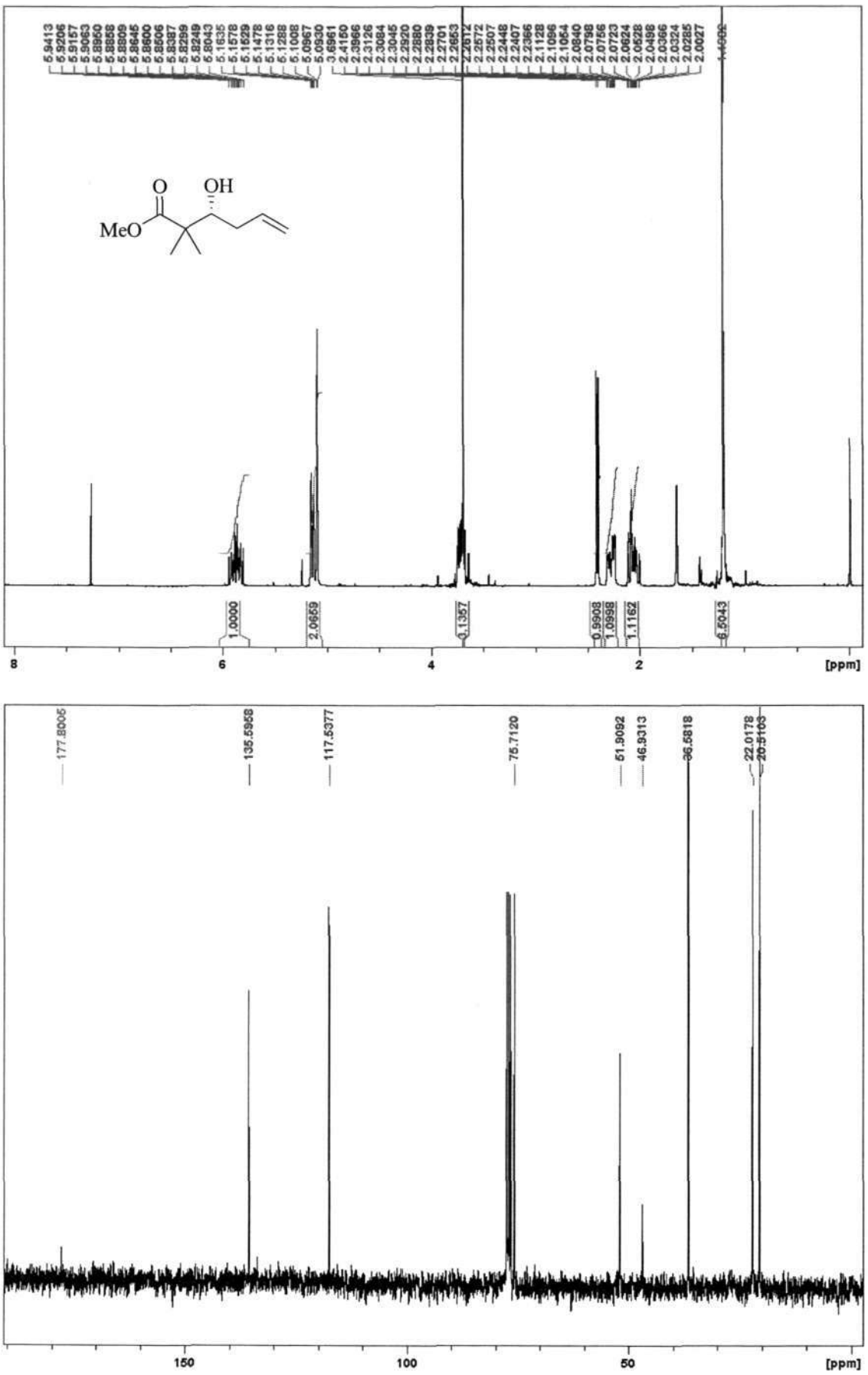


Empirical formula	C15 H25 Cl O3	
Formula weight	288.80	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.0151(4) Å	α= 104.439(2)°.
	b = 10.1848(4) Å	β= 91.767(2)°.
	c = 16.0540(7) Å	γ = 99.055(2)°.
Volume	1561.84(11) Å^3	
Z	4	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.247 mm^{-1}	
F(000)	624	
Crystal size	0.30 x 0.30 x 0.30 mm^3	
Theta range for data collection	1.31 to 30.56°.	
Index ranges	-14<=h<=14, -14<=k<=14, -22<=l<=22	
Reflections collected	22845	
Independent reflections	9489 [R(int) = 0.0237]	
Completeness to theta = 30.56°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9296 and 0.9296	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9489 / 0 / 543	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0368, wR2 = 0.0994	
R indices (all data)	R1 = 0.0509, wR2 = 0.1133	
Largest diff. peak and hole	0.339 and -0.246 e.Å^{-3}	

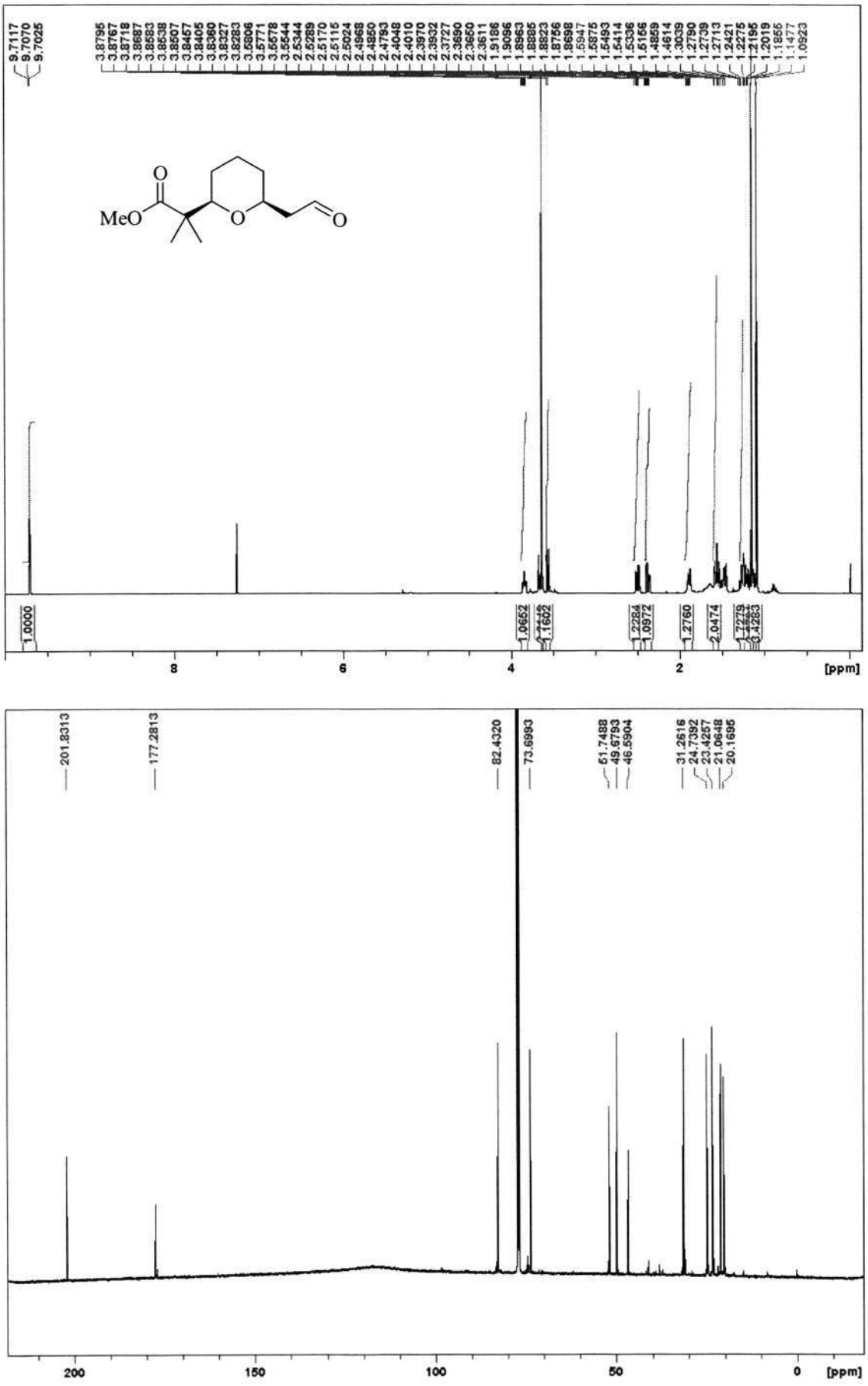
NMR spectra of selected compounds



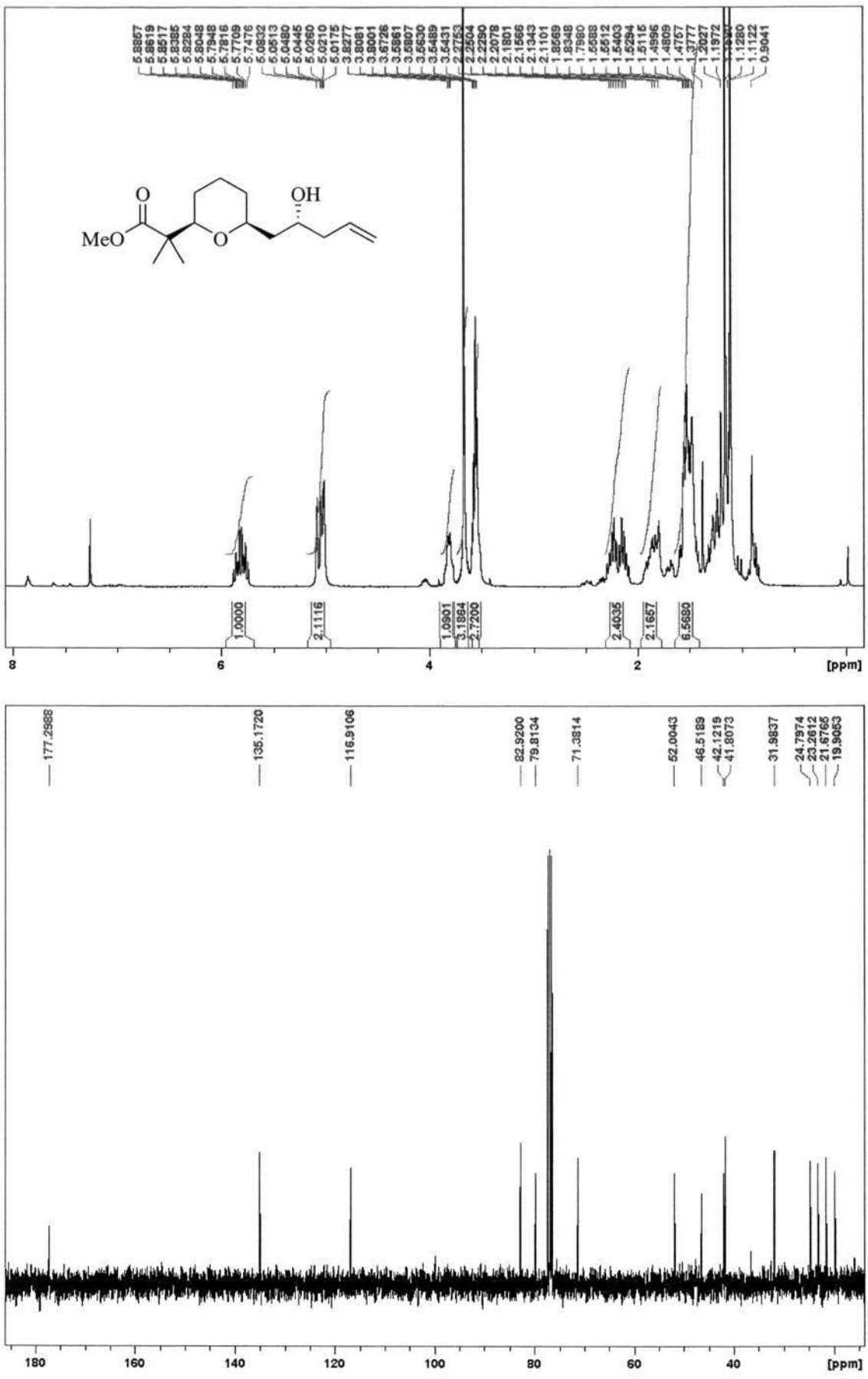
^{1}H and ^{13}C NMR of (-)-Centrolobine **37**



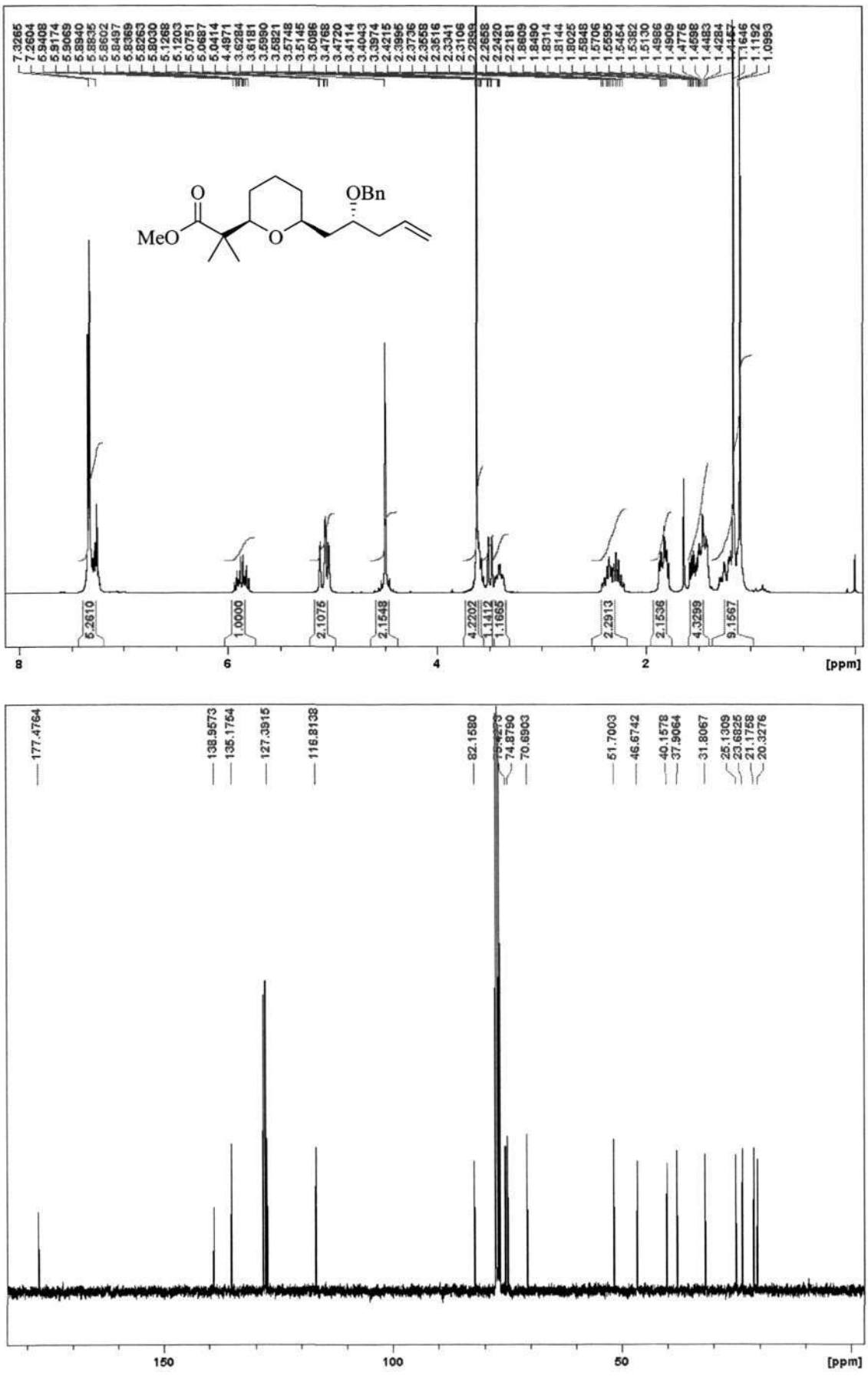
^{1}H and ^{13}C NMR of (*R*)-methyl 3-hydroxy-2,2-dimethylhex-5-enoate **68**



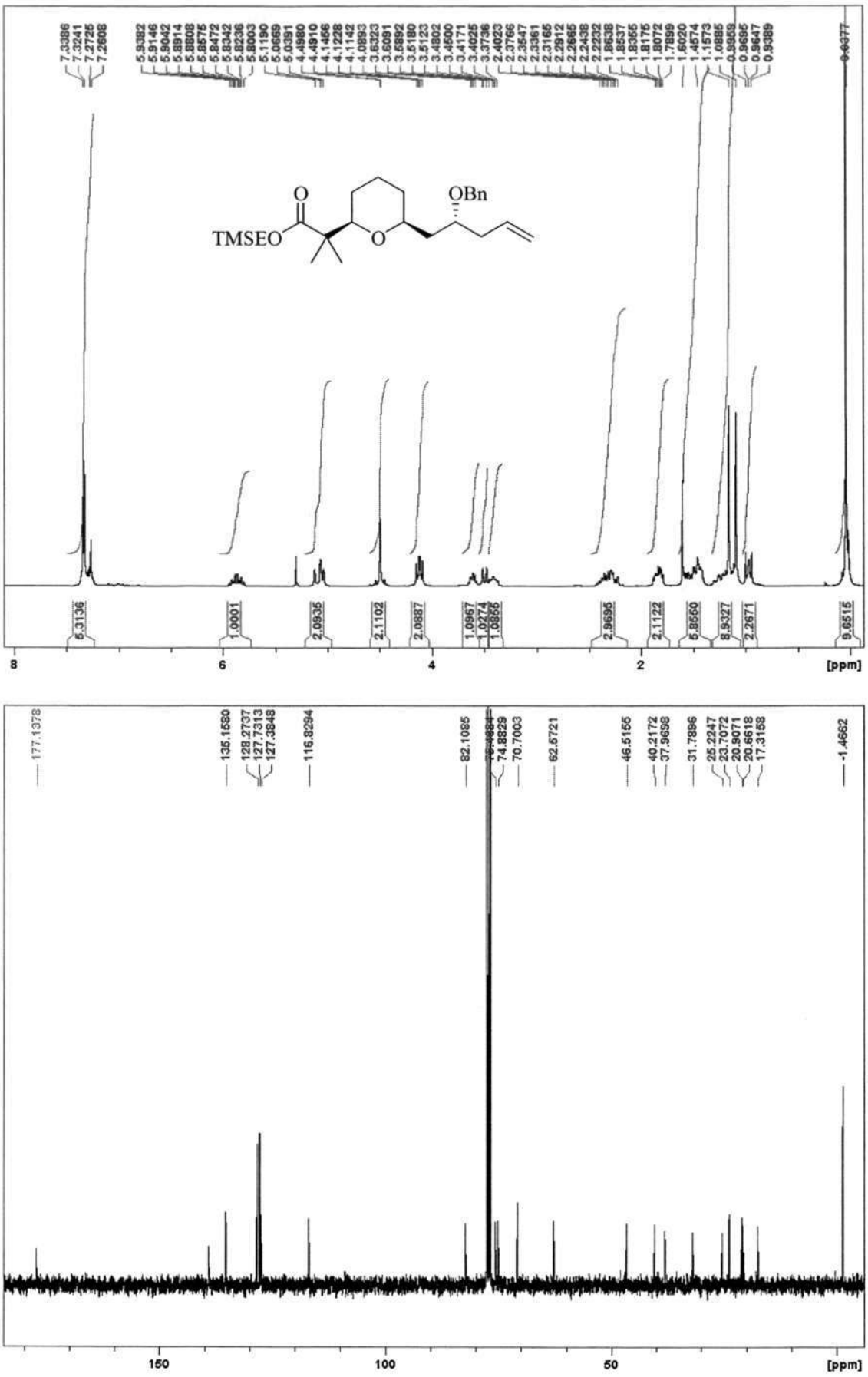
^{1}H and ^{13}C NMR of methyl ester aldehyde **76**



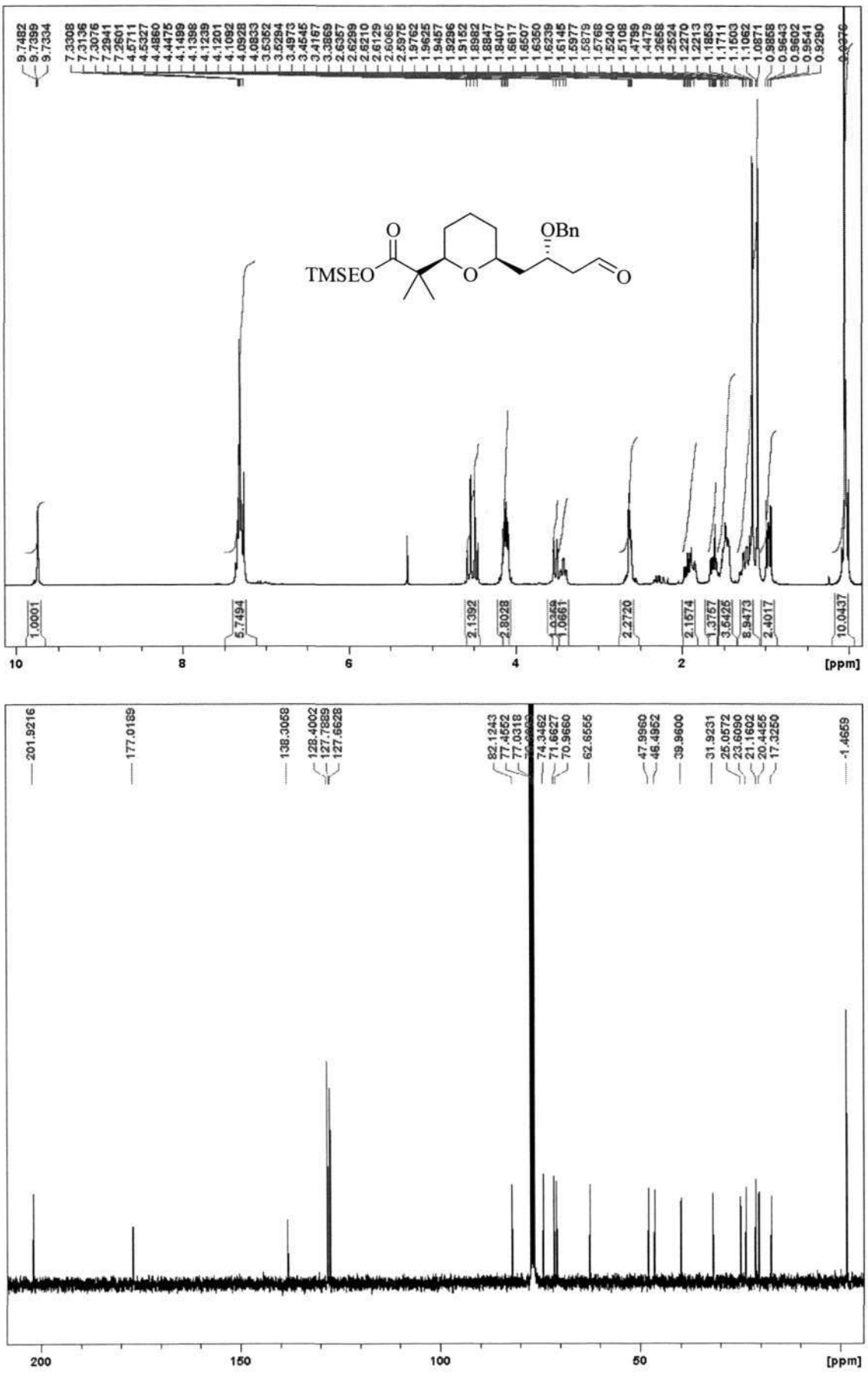
^{1}H and ^{13}C NMR of methyl ester THP homoallylic alcohol **77**



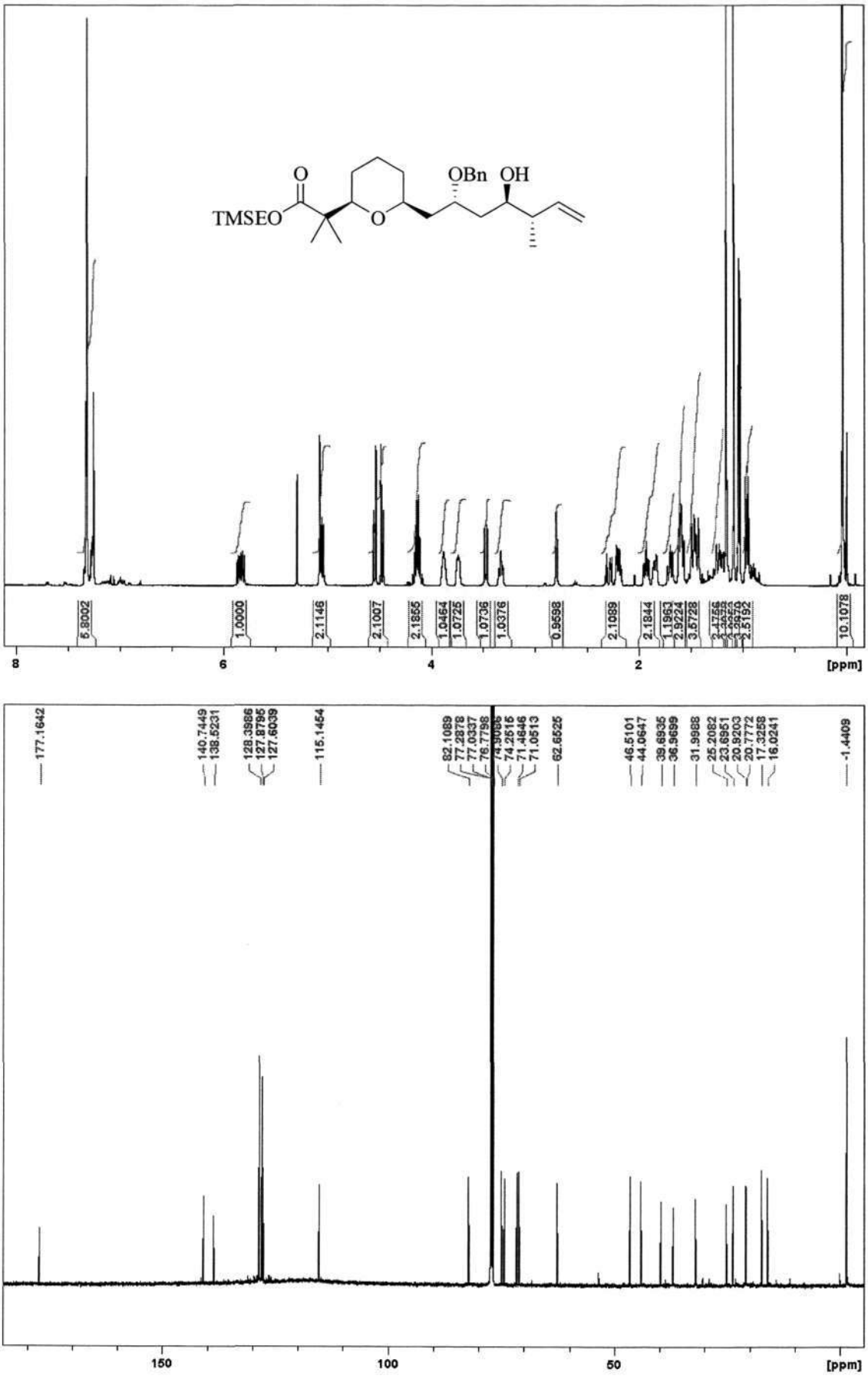
^{1}H and ^{13}C NMR of THP homoallylic benzylether **78**



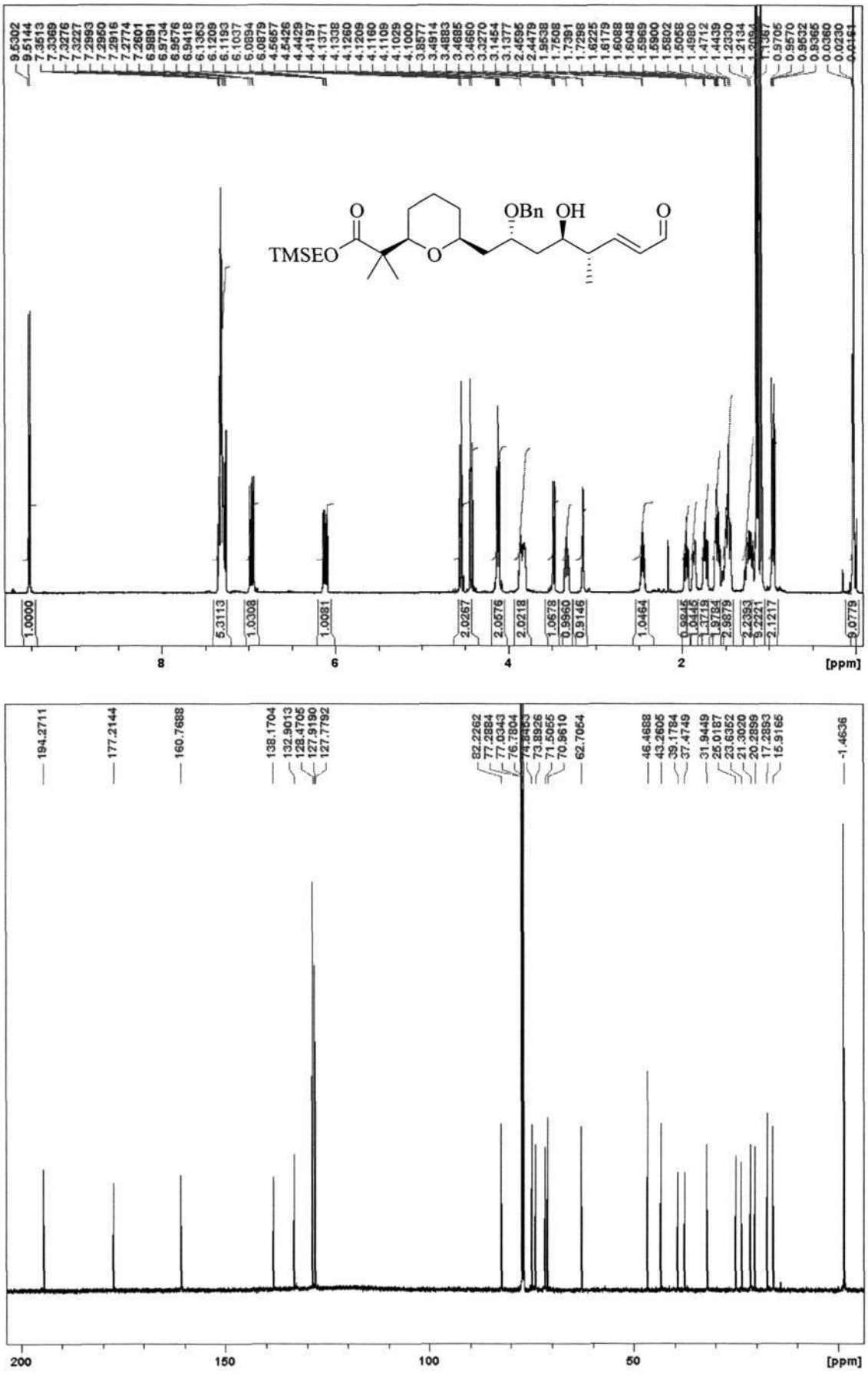
^{1}H and ^{13}C NMR of TMES-protected benzylether **80**



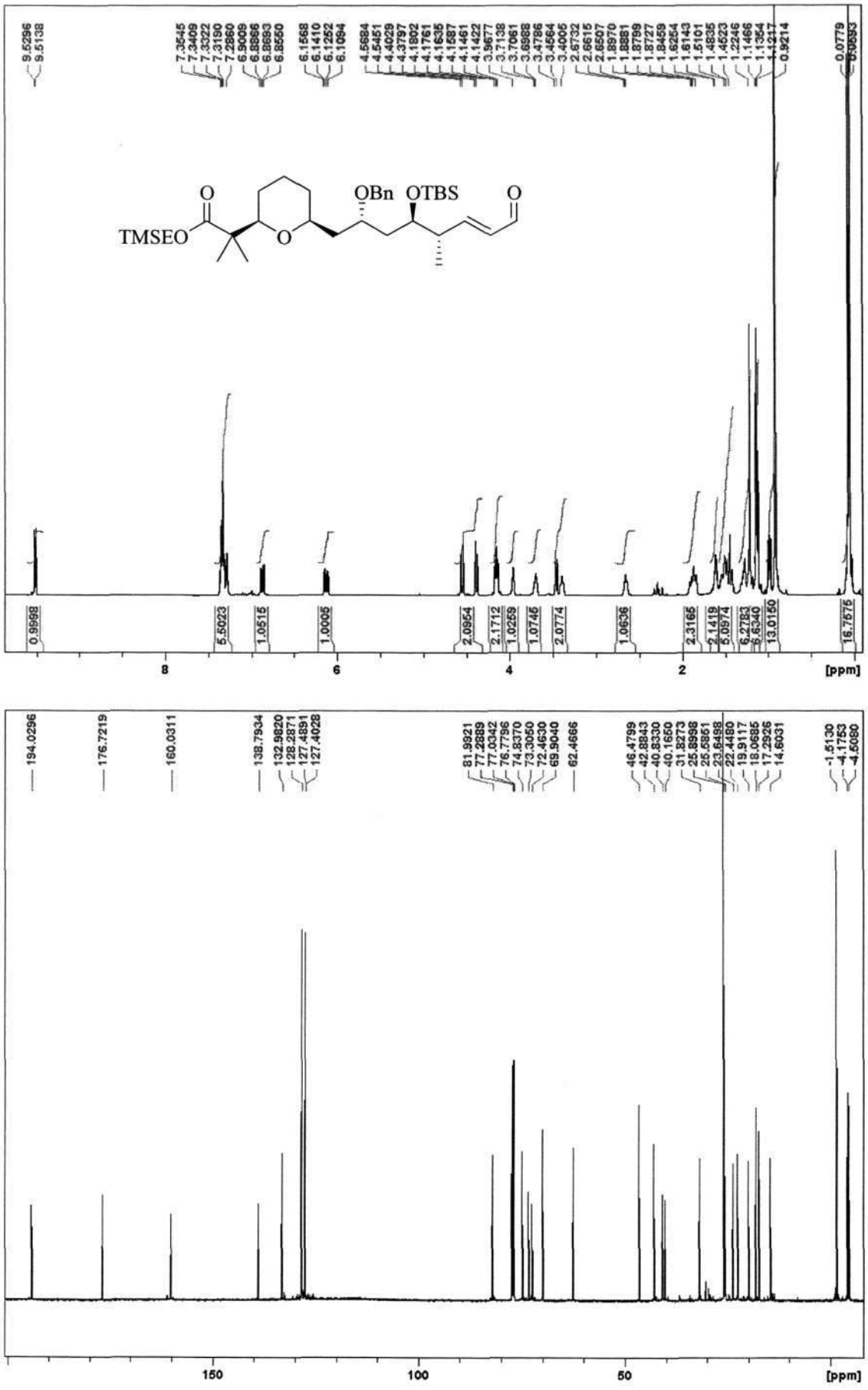
^{1}H and ^{13}C NMR of benzylether aldehyde **81**



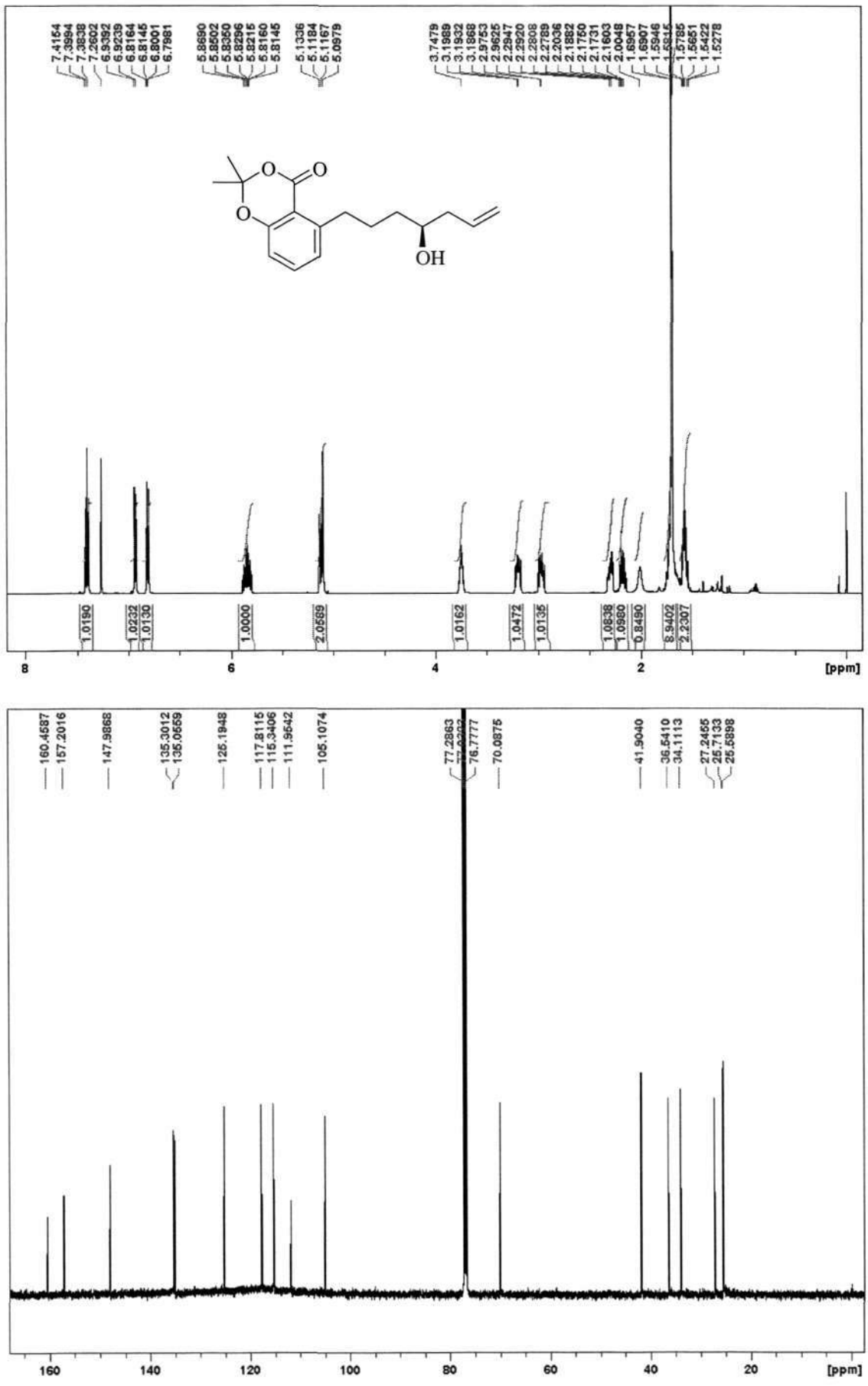
^{1}H and ^{13}C NMR of homoallylic alcohol **82**



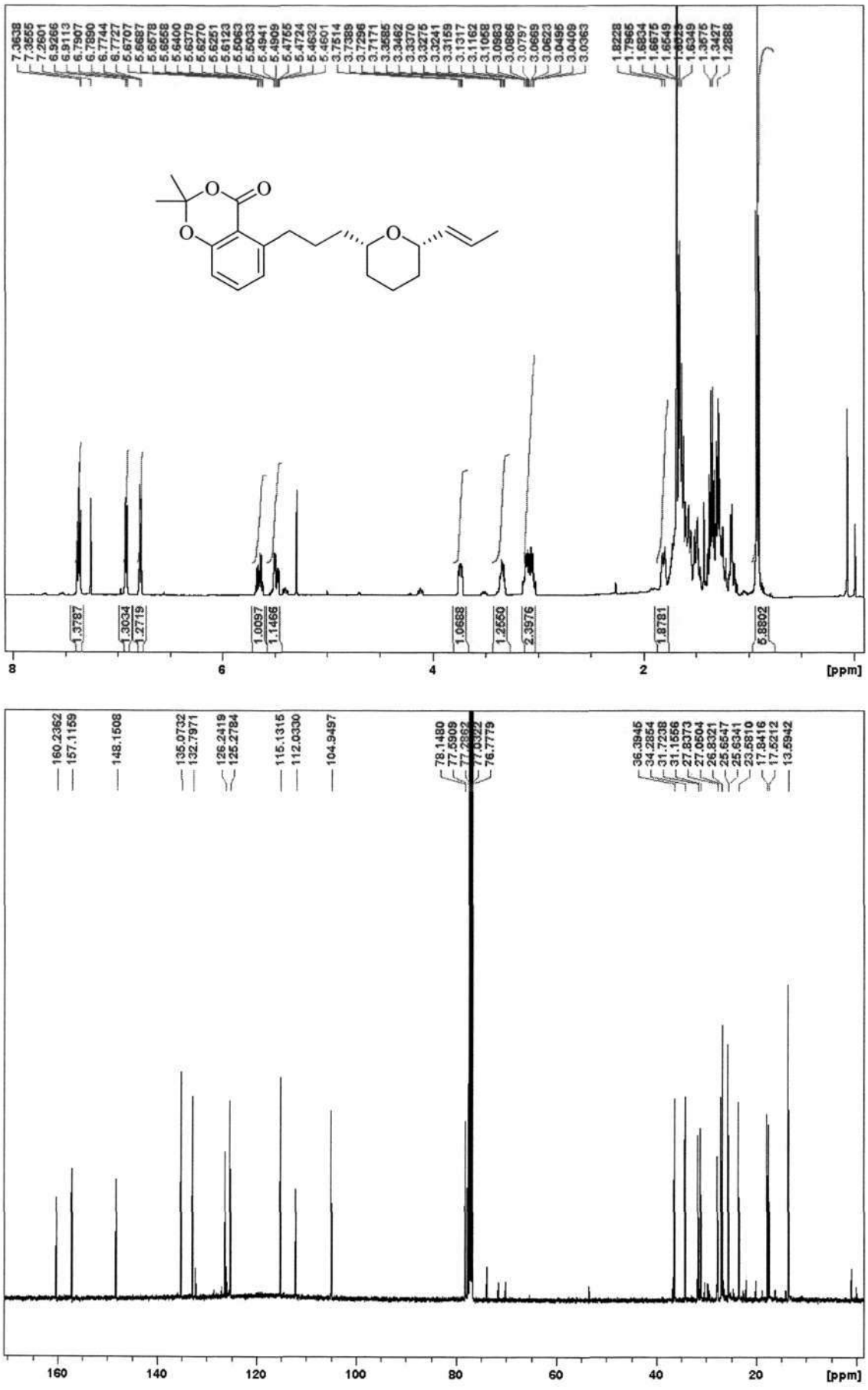
^{1}H and ^{13}C NMR of hydroxyl aldehyde **84**



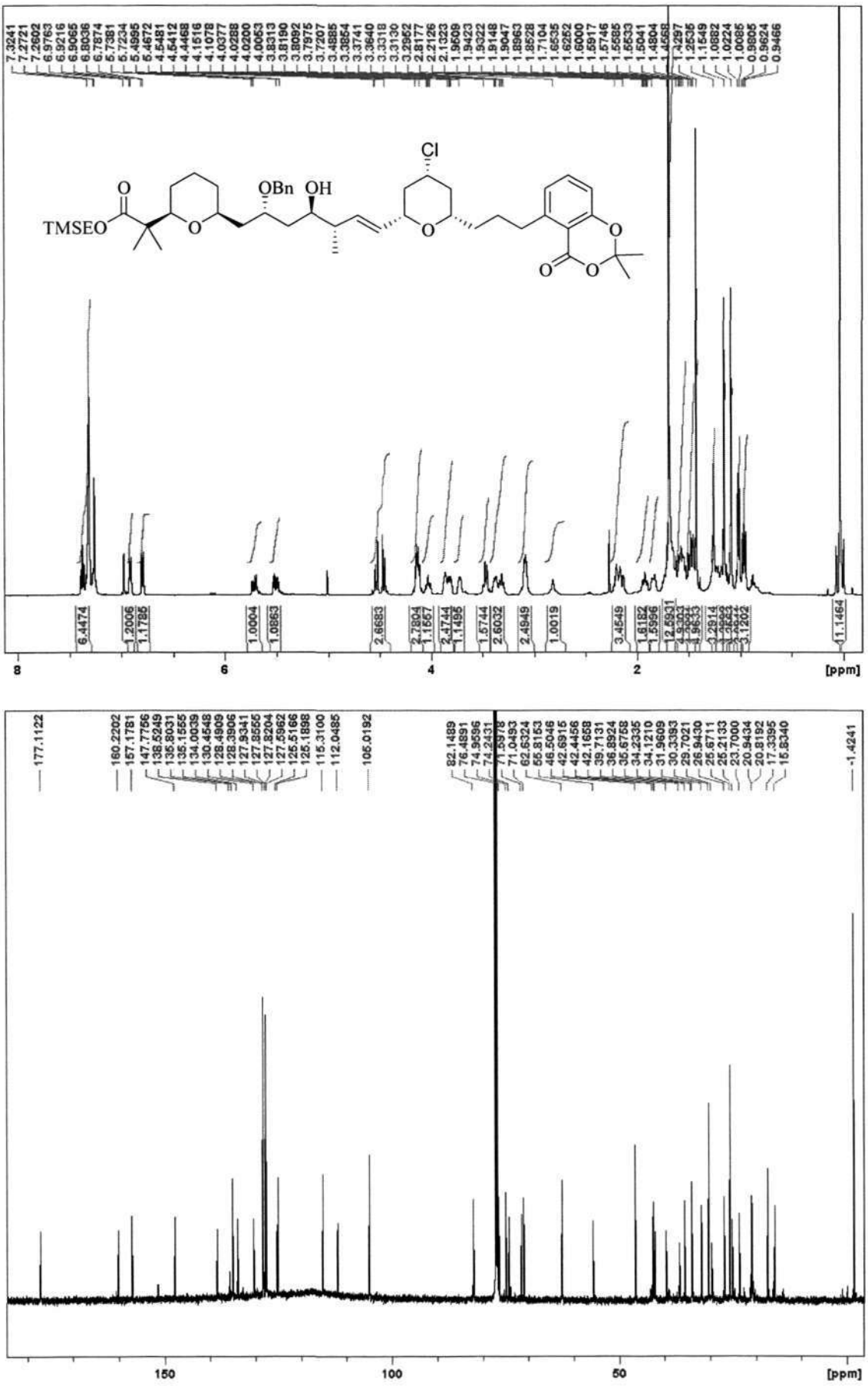
^{1}H and ^{13}C NMR of OTBS-proctected aldehyde **84a**



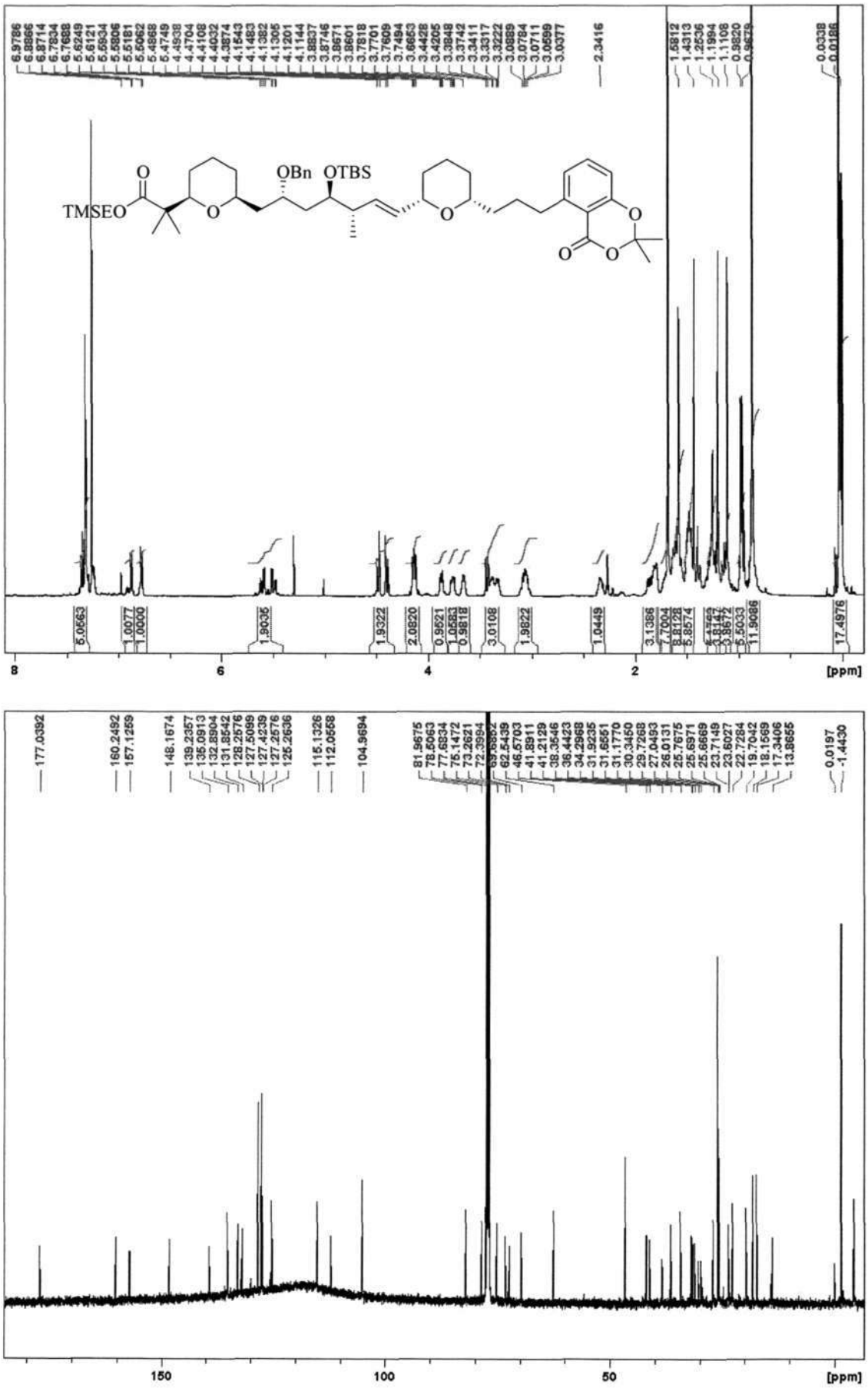
^{1}H and ^{13}C NMR acetonide homoallylic alcohol **90**



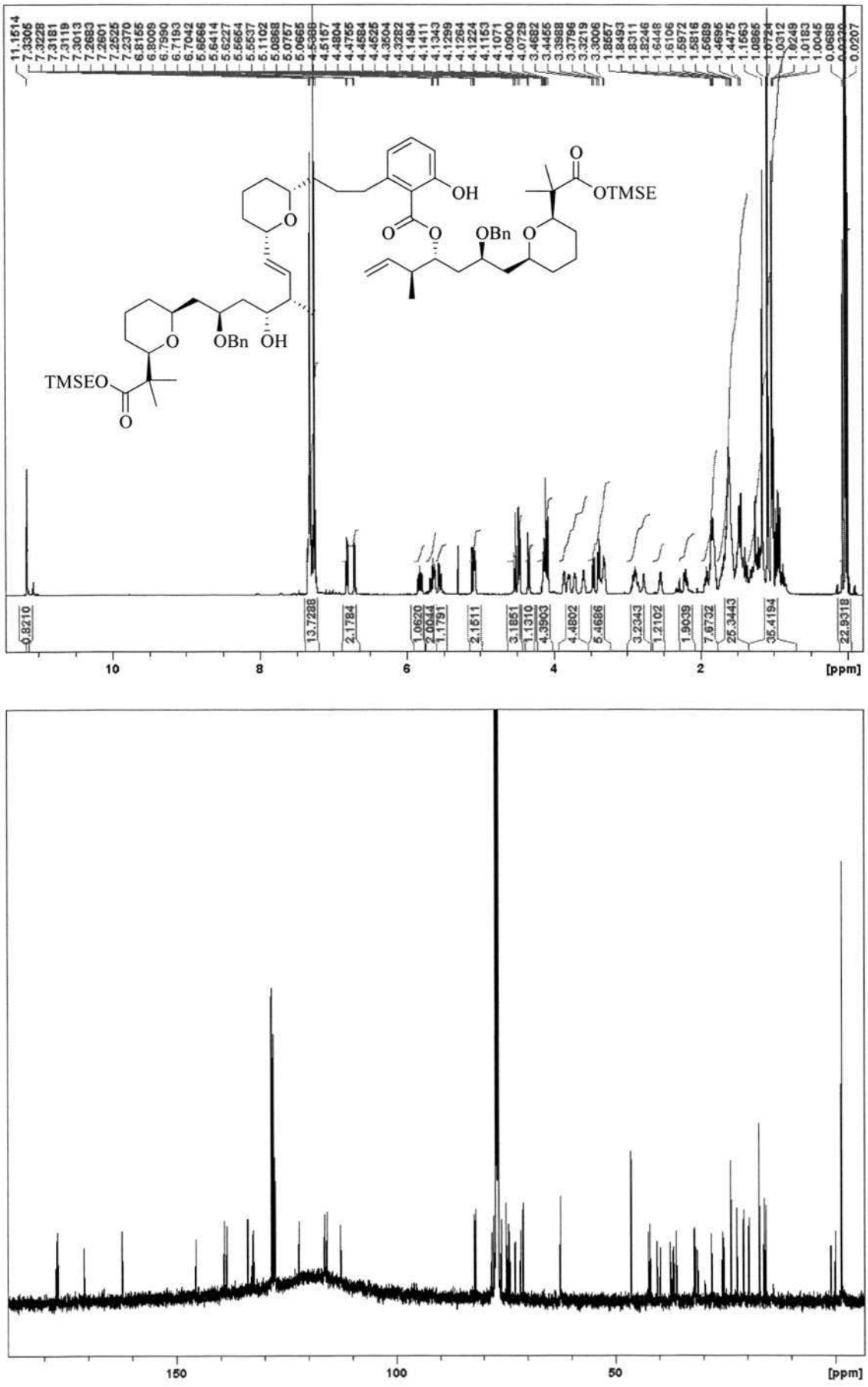
^{1}H and ^{13}C NMR acetonide THP **92**



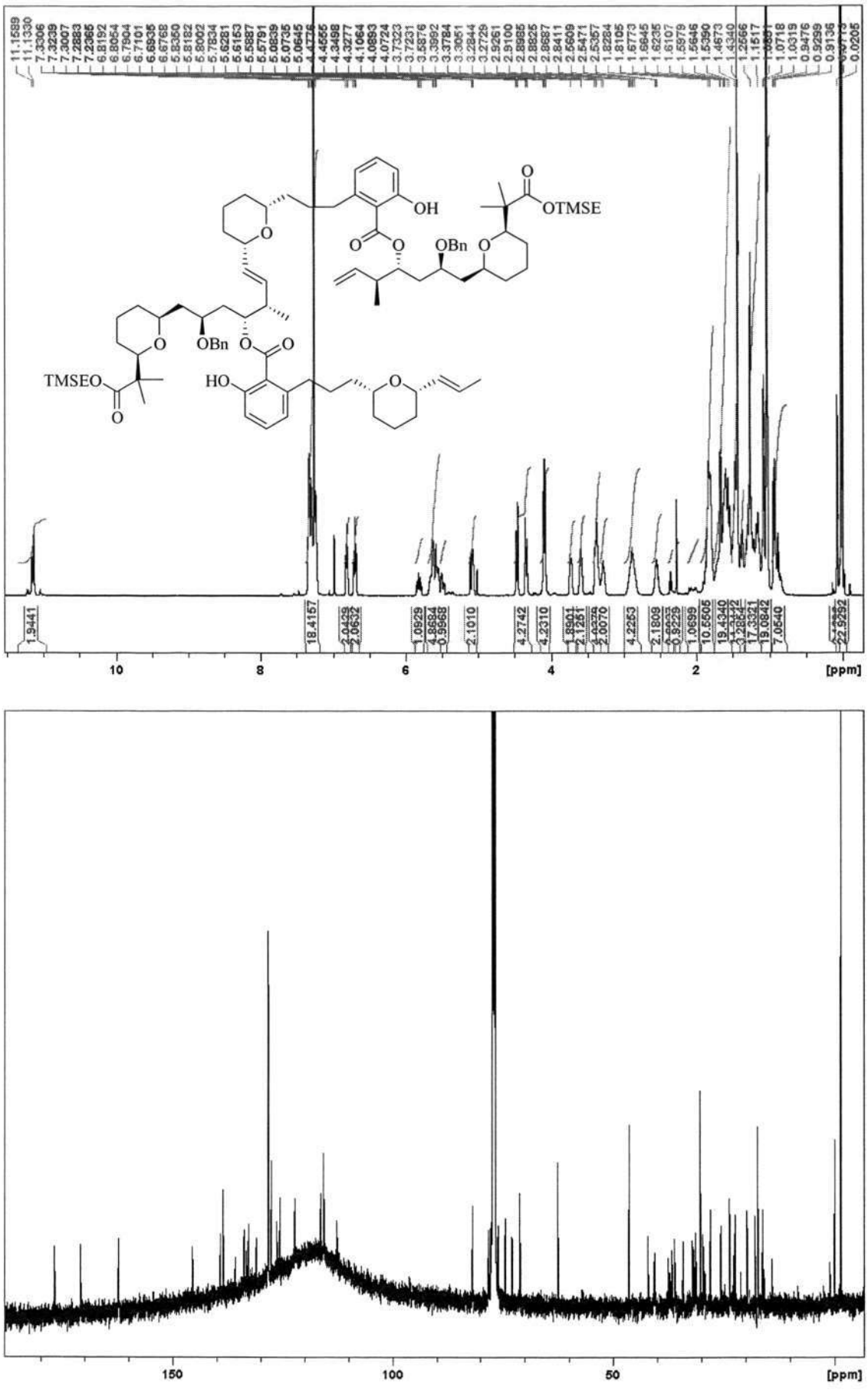
^{1}H and ^{13}C NMR chloro-monomeric unit **93**



^{1}H and ^{13}C NMR OTBS protected monomeric unit **94a** (Formal synthesis)



^{1}H and ^{13}C NMR hydroxyl ester **95a**



^{1}H and ^{13}C NMR hydroxyl ester **96**

List of Publication

1. Chan, K. P.; Ling, H. Y.; Loh, T. P. Formal Synthesis of (+)-SCH 351448: The Prins Cyclization Approach. *Chem. Commun.* **2007**, *9*, 939-941.

2. Chan, K. P.; Ling, H. Y.; Chan, L. –T. J.; Loh, T. P. Stannane-Free Chemoselective Hydrodehalogenation of 4-Halotetrahydropyrans: Scope and Application to Natural Product Synthesis. *J. Org. Chem.* **2007**, *6*, 2127-2132.

3. Chan, K. P.; Seow A. –H.; Loh, T. P. Stereochemical Prins Cyclization: Electronic versus Steric Effects in the Synthesis of 2,4,6-Trisubstituted Tetrahydropyran Rings. *Tetrahedron Lett.* **2007**, *48*, 37-41.

4. Chan, K. P.; Loh, T. P. Prins Cyclization in Silyl Additives with Suppression of Epimerization: Versatile Tool in the Synthesis of Tetrahydropyran Backbone of Natural Products. *Org. Lett.* **2005**, *7(20)*, 4491-4494.

5. Chan, K. P.; Loh, T. P. Lewis Acid-Catalyzed One-pot Crossed Prins Cyclization using Allylchlorosilane as Allylating Agent. *Tetrahedron Lett.* **2004**, *45(45)*, 8387-8390.

6. Lee, C. L.; Chan, K. P.; Lam, Y.; Lee, S. Y. Solid-phase Combinatorial Synthesis of 1,4-Benzoxazin-3(4*H*)-one Derivatives. *Tetrahedron Lett.* **2001**, *42(6)*, 1167-1170.

Conferences

1. Chan, K. P.; Loh, T. P. *Epimerization Suppression in Catalytic Prins Cyclization: Application to Total Synthesis of (-)-Centrolobine and (+)-SCH 351448.* 1st European Chemistry Congress, Budapest, Hungary, August 27-31, 2006.

2. Chan, K. P.; Loh, T. P. *Synthetic Studies Towards Total Synthesis of (+)-SCH 351448.* 4th Singapore International Chemistry Conference. Singapore, December 8-10, 2005.

3. Chan, K. P.; Loh, T. P. *Indium-mediated Prins Cyclization using Allylic Silicon as Allylating Reagent.* Abstract of Papers, 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26 2004.