I. SYNTHESIS OF ETHER LINKED ANALOGS AND SAR STUDIES OF *ANNONACEOUS* ACETOGENINS
II. ASYMMETRIC ELECTROPHILIC HALOCYCLIZATION REACTIONS

By

Atefeh Garzan

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ABSTRACT

I. SYNTHESIS OF ETHER LINKED ANALOGS AND SAR STUDIES OF *ANNONACEOUS* ACETOGENINS
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This dissertation discusses the synthesis of ether linked analogs of *annonaceous* acetogenins. Utilization of ether linkages will enable rapid synthesis of a library of acetogenins with a variety of groups flanking the right and left side of the bis-adjacent THF core, which will be used for future SAR studies of acetogenins. An efficient method for regio- and stereoselective double cyclization of polyhydroxylated systems to form bis-adjacent THF rings with ether linked is developed.

Several elegant reports of asymmetric halogenation of alkenes and alkynes followed by intra or inter molecular attack of a nucleophile have appeared in the literature in the last decade. We have recently disclosed catalytic asymmetric routes to chlorolactones, chlorooxazolines, and chlorooxazines. Further studies have shown the feasibility for the cyclization of carbamates to yield chlorooxazolidinone. We have observed a remarkable solvent effect that essentially reverses the chirality of the product chlorooxazolidinone with the same chiral catalyst. The results of this study along with kinetic investigations that suggest enthalpy-entropy compensation as the origin of the chirality switch are discussed in this dissertation.

To My Beloved Parents

ACKNOWLEDGEMENTS

An undertaking such as a dissertation is not completed with out the support of many people. My first debt of gratitude must go to my advisor, Prof. Babak Borhan. I would like to gratefully and sincerely thank him for his guidance, understanding, patience, and most importantly, his friendship during my graduate studies. His mentorship was paramount in providing a well rounded experience consistent my long-term career goals. He encouraged me to not only grow as an experimentalist and a chemist but also as an instructor and an independent thinker. For everything you have done for me, Babak, I thank you. I would also like to thank Profs. Wulff, Jackson, and Smith for serving on my committee at various times along with the advice they have provided over the years.

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KEY TO SYMBOLS AND ABBREVIATIONS

Å	angstrom
Ac	acetyl
AcOH	acetic acid
acac	acetoacetate
Ar	aryl
aq.	aqueous
Bn	benzyl
CH_2Cl_2	dichloromethane
CI	chemical ionization
CSA	camphorsulfonic acid
Cy	cyclohexyl
δ	chemical shift (parts per million)
D	dextro (denotes configurational relationship with (*R*)-(+)-glyceraldehyde)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diasteromeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DI	deionized
DIAD	diisopropyl azodicarboxylate

DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyl dioxirane
DMF	N,N-dimethylformamide
DMP	dess-martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ECCD	exciton coupled circular dichroim
ED_{50}	Effective Dose to 50 percent
ee	enantiomeric excess
EI	electric ionization
equiv.	equivalent(s)
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
HMPA	hexamethyl phosphoramide

HRMS	high resolution mass spectrometry
HWE	Horners-Wadsworth-Emmons reaction
Hz	Hertz
^{i}PrOH	isopropyl alcohol
IR	infrared spectrum
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	levo (denotes configurational relationship with (*S*)-(-)-glyceraldehyde)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar (concentration)
*m*CPBA	4-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl
mL	milliliter
mmol	millimole
Ms	methane sulfonate
MS	mass spectrometry

NaHMDS	sodium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
OAc	acetate
OTf	trifluoromethanesulfonate
OsO_4	osmium tetroxide
PCC	pyridinium *p*-toluenesulfonic acid
Ph	phenyl
PMB	p-methoxybenzyl
PPTS	pyridinium para-toluenesulfonate
pTSA	*p*-toluenesulfonic acid
R	rectus (Cahn-Ingold-Prelog system)
RT	room temperature
S	sinister (Cahn-Ingold-Prelog system)
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBA-OX	tetra-*n*-butylammonium peroxymonosulfate
TBHP	*t*-butyl hydroperoxide

TBS	*t*-butyldimethylsilyl
TBSOTf	*t*-butyldimethylsilyl trifluoromethanesulfonate
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMEDA	tetramethylethylenediamine
TsOH	*p*-toluenesulfonic acid

CHAPTER I

Development of an Efficient Method to Synthesize a Library of Ether Linked Analogs of *Annonaceous* Acetogenins

I.1 Introduction

Annonaceous acetogenins are a series of natural products isolated from the plant family *Annonaceae*, whose members include edible fruits such as cherimoya and custard apple that are widely distributed in tropical and sub-tropical regions.[1-9] *Annonaceous* acetogenins can be found in the seeds, leaves, twigs, barks, and root of the plants. They are found to have potent and diverse biological effects such as cytotoxic, antitumor, antimalarial, pesticidal, and insecticidal activities.[1-8]

Before the early 1980's, phytochemical studies of the plant family *Annonaceae* mainly focused on the isolation of numerous secondary metabolites including isoquinoline alkaloids, polyphenols, carbohydrates, lipids, proteins, aromatic compounds, essential oils and terpenes.[10] In 1982, Cole and coworkers isolated and characterized the first acetogenin, uvaricin, from the roots of *Uvaria accuminata* (a member of the

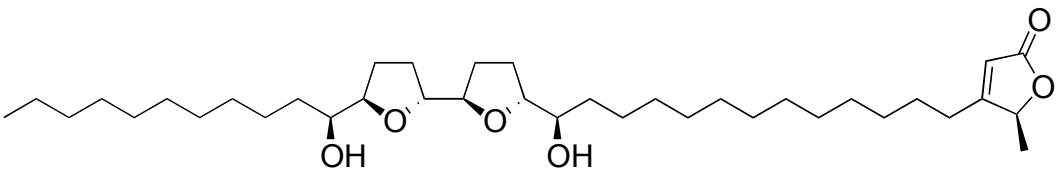


Figure I-1: The first isolated acetogenin, uvaricin

Annonaceae family) (Figure I-1).[11] It contains a set of bis-adjacent tetrahydrofuran (THF) rings flanked by two hydroxyl groups and a terminal unsaturated lactone ring, which is connected to the THF moiety through an unbranched alkyl chain. Uvaricin was demonstrated to have antitumor properties with *in vivo* PS system (P-338 lymphocytic leukemia in mice).[11, 12] It exhibited an activity of 157% test/control (T/C) at 1.4 mg/kg in the PS test system. Activity in the PS system is defined as an increase in the survival of treated animals over that of controls resulting in a T/C ≥ 125%.[12]

Since uvaricin, during the past quarter century, more than 400 related compounds have been isolated by preparative HPLC, countercurrent chromatography, or chromatography on silica gel. Research in the field of *Annonaceous* acetogenins dealing with the isolation, structural elucidation, semi-synthesis or total synthesis, mechanism of the cytotoxic action, and structure-activity relationship studies has been growing rapidly.[5, 7, 9]

I.1.1 Structure and Classification

Annonaceous acetogenins share a common skeleton characterized by an unbranched C32 or C34 fatty acid ending in an α,β-unsaturated γ-lactone (Figure I-2).[2, 7, 9] Several oxygenated functional groups, such as tetrahydrofuran (THF), tetrahydropyran (THP),

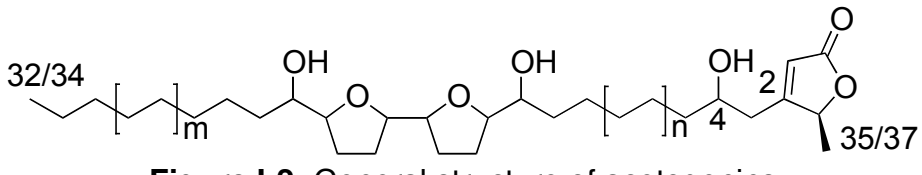


Figure I-2: General structure of acetogenins

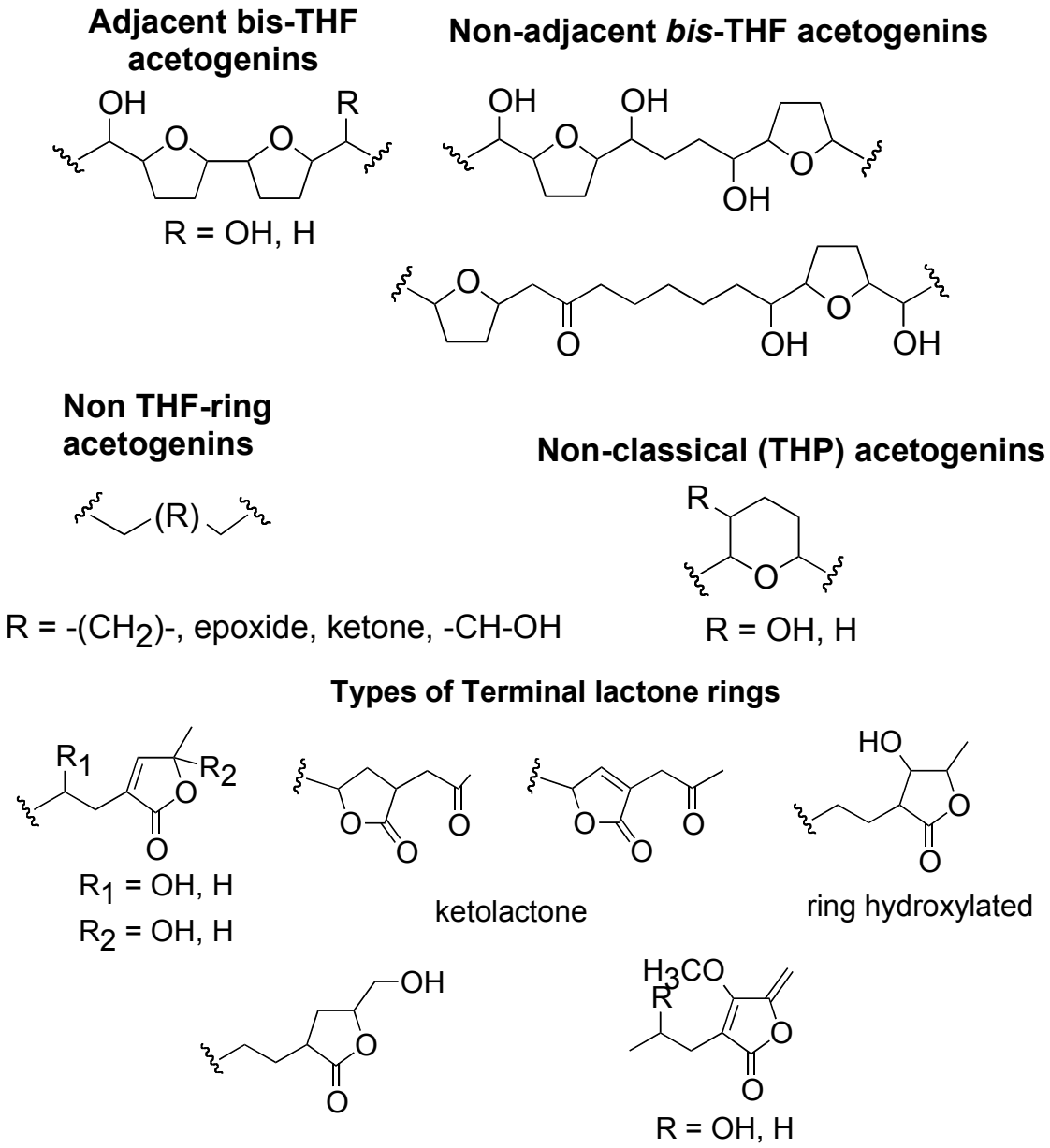


Figure I-3: Core units for classification of *Annonaceous* acetogenins

epoxide, hydroxyl, and ketone could be present in the structure, as well as double and triple bonds. There is a variety of stereoisomers of the center THF cores, however, all the isolated compounds have *S* configuration of the chiral center in the γ-lactone ring. The classification of acetogenins is based on the structural characteristics shown in Figure

I-3.[2, 5, 7] McLaughlin classified all these congeners based on the number and the arrangement of the THF rings including mono-THF, adjacent bis-THF, non-adjacent

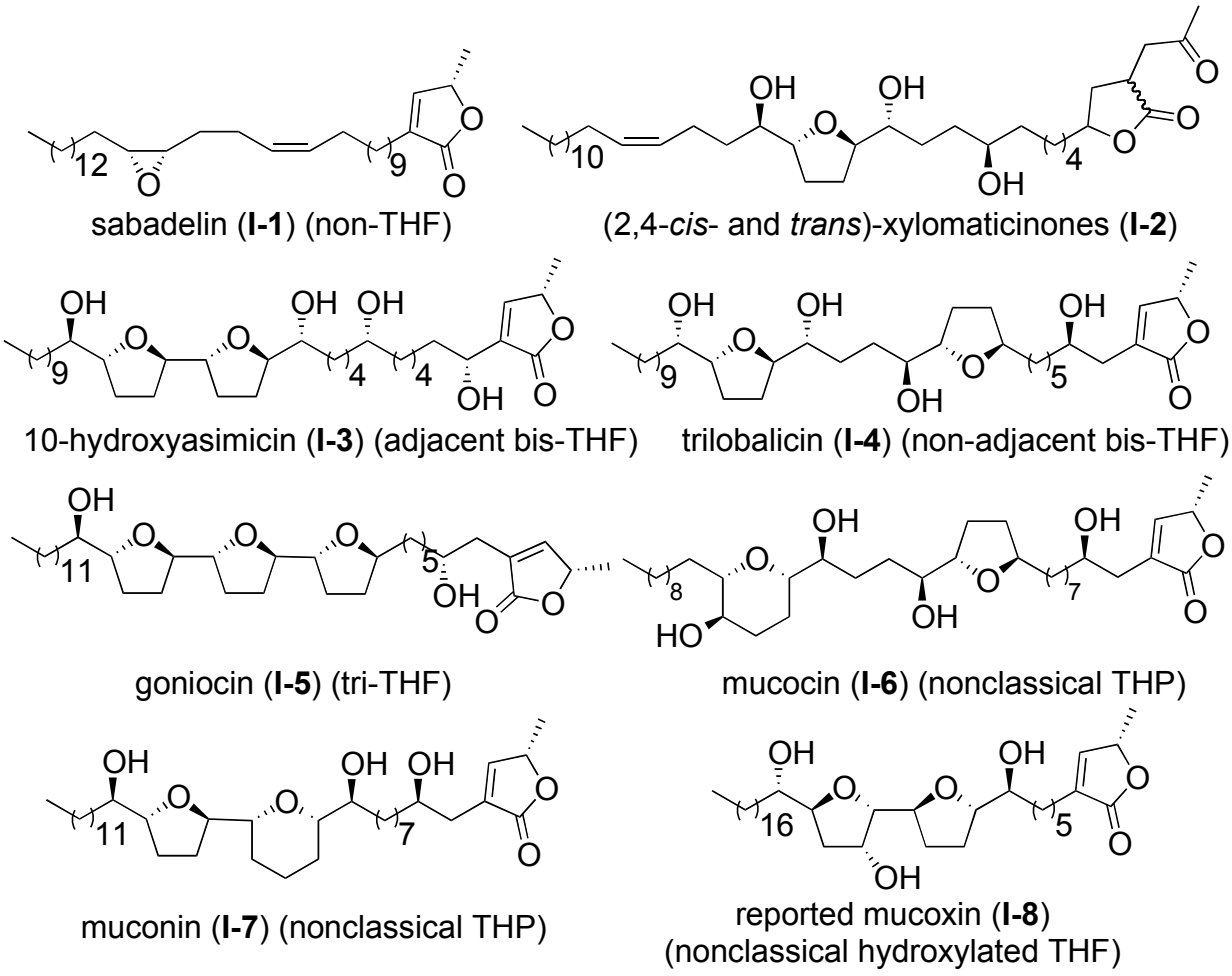


Figure I-4: Examples of both classical and nonclassical acetogenins

bis-THF, tri-THF, non-THF ring, THP ring, and hydroxylated THF ring, followed by sub-classification of the γ-lactone, substituted γ-lactone, or ketolactone variations.[5, 7] Generally, all acetogenins belong to two broad groups: 1) Classical acetogenins, which involve acetogenins comprising none to three THF units along with a terminal γ-lactone; 2) Nonclassical acetogenins, which include acetogenins containing a THP ring or

hydroxylated THF ring along with a terminal γ-lactone. Figure I-4 shows some examples of both classical and nonclassical acetogenins. Compounds **I-1** to **I-5** are classical acetogenins with none to three THF units.[1, 13-16]

If there are no THF units in the structure, epoxide or double bonds are the most common sub-units such as sababelin **I-1**, which is a mono-epoxy olefinic acetogenin.[13] Mucocin **I-6** is the first nonclassical acetogenin to be reported that bears a hydroxylated THP ring along with a non-adjacent THF ring.[17] More examples of this class are muconin **I-7**,[18] which contains a nonhydroxylated THP ring adjacent to another THF ring, pyranicin,[19] the first mono-THP ring acetogenin, and jimenezin,[20] containing a hydroxylated THP ring adjacent to a THF ring. Mucoxin **I-8** is the first nonclassical acetogenin containing a hydroxylated THF ring.[18] Two other examples are goniotriocin[14] and donnaienin.[21]

I.1.2 Biological Activity

Annonaceous acetogenins have several interesting and potent biological activities, including antibacterial, antimalarial, *in vivo* antitumor, parasiticidal, and pesticidal effects.[1-6] In addition, in recent studies, acetogenins are found to show promising cytotoxic properties against multi drug resistant (MDR) tumor cells and pesticide-resistant insects.

I.1.2.1 *In Vitro* and *In Vivo* Cytotoxicity Results

Annonaceous acetogenins have been always judged as promising candidates for future generation of drugs against the current chemotherapy-resistant tumors. The first

isolated acetogenin, uvaricin, was announced as a new antitumor compound.[11] Many studies have established the cytotoxic potency of acetogenins for several human tumor cell lines. For example, asimocin and bullanin have shown ED_{50} values of ~10^{-12} μg/mL against A-549 (lung), MCF-7 (breast), and HT-29 (colon) human cancer cell lines, much lower than adriamycin (~10^{-4} to ~10^{-2} μg/mL), an anticancer drug currently in clinical use.[22] Moreover, a series of acetogenins show greater cytotoxic effects against cancerous over noncancerous cells.[23]

Although extensive and comprehensive animal testing has not been conducted, acetogenins have shown promising *in vivo* results. Uvaricin showed *in vivo* activity against 3PS (murine lymphocytic leukemia) (157% T/C at 1.4 mg/kg),[11] and the rollinones (147% T/C at 1.4 mg/kg) and asimicin (124% T/C at 25 μg/kg) were active in the same assay.[8] Bullatacin was 300 times more potent than paclitaxel against L1210 (murine leukemia) in normal mice (effective at only 50 μg/kg)[24] and against X-5563 plasma cell myeloma grafts in normal mice (67% tumor inhibition at 50 μg/kg).[5] The latter data has led to further research to elucidate structure-activity relationships.

I.1.2.2 Cytotoxic and Antitumor Mechanisms

Members of *Annonaceous* acetogenins family are the most potent inhibitors of nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase that reside in complex I, which is a membrane-bound protein of the mitochondrial electron transport system and the ubiquinono-linked NADH oxidase in the plasma membranes of cancerous

cells.[1, 5, 7, 24, 25-27] In 1991, Weiss and coworkers reported that the mitochondrial complex I was the target enzyme for acetogenins. Nowadays, they are considered to be one of the most powerful groups of complex I inhibitors.[28-30]

NADH:ubiquinone oxidoreductase is the largest and most complicated of the protein complexes in the inner mitochondrial membrane.[1] Complex I plays an important role in the electron-transfer from NADH to ubiquinone and in the maintenance of the bioenergetic function of the cell by driving the ATP synthesis from the mitochondrial reduced equivalents produced in the central metabolic oxidative pathways.[1, 7] As part of the respiratory chain, as well as in the cytoplasmic membrane bacteria, complex I has been implicated in a variety of neurodegenerative diseases such as Parkinson's disease, maturity onset diabetes, stroke-like episodes and Huntington's disease.[31-33] Further

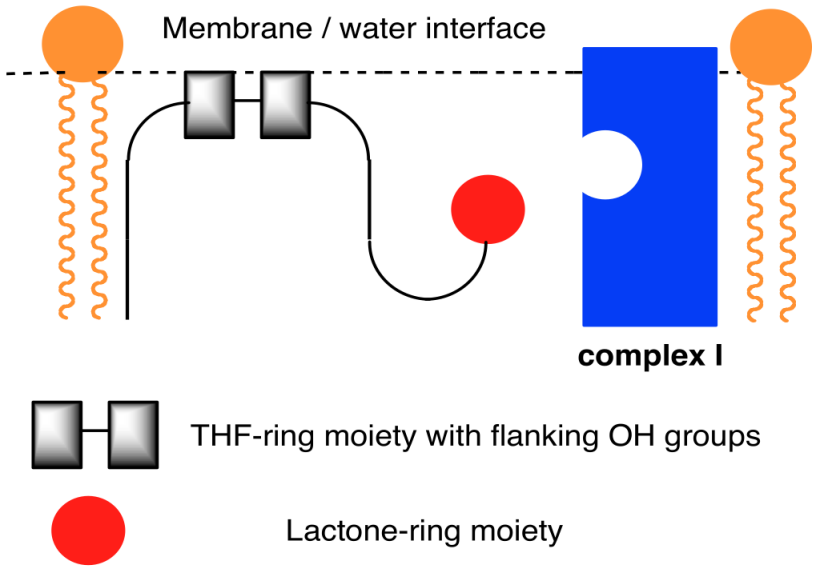


Figure I-5: Model for the active conformation of acetogenins interacting with complex I in the mitochondrial membrane proposed by McLaughlin, Shimada, and coworkers
For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation

study of these diseases and their medical treatment requires a deeper understanding of the genetics, the structure and the function of this enzyme. Inhibitors of complex I such as acetogenins are important and useful for the elucidation of the structure and mechanism of this enzyme.

Although the precise mode of complexation of acetogenins and complex I, as well as their mechanism of selective cytotoxicity, and the factors that modulate the efficacy against cancer cells are not known, some generally accepted suggestions are summarized below. One popular hypothesis, proposed by McLaughlin, Shimada, and coworkers, suggests that the conformation of acetogenins in membranes is strongly related to cytotoxicity.[5, 31] They determined positions of both the THF and lactone ring within liposomal membranes by ^{1}H NMR and nOe spectroscopy and found that an asimicin-type acetogenin can be in either a sickle-shaped or a U-shaped conformations, depending on the length of the alkyl chain between the THF rings and the lactone ring. The model of this hypothesis is shown in Figure I-5.[34-36] Here the THF rings with flanking hydroxyl group work as a hydrophilic anchor on the mitochondrial membrane. The position of the THF ring-anchor along the acetogenin chain determines the depth of the lactone functional group, which then directly acts with the protein receptor site, perhaps, mimicking the quinone ring of ubiquinone. The functional lactone group reaches complex I by lateral diffusion in the membrane. The THF rings, acting as an anchor in the lipid bilayer, may enhance the bioactivity by restricting the location, conformation, and orientation of the functional lactone moiety by interacting with the head group of the

phospholipids.

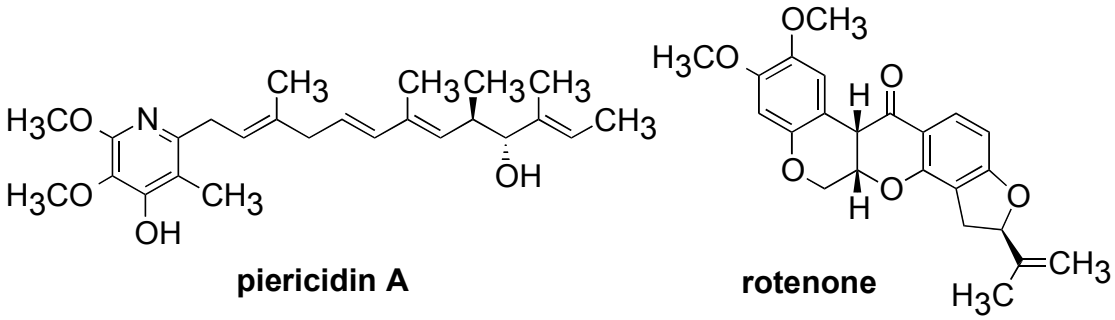
In addition, Miyoshi and coworkers did a mechanistic and structure activity study against submitochondrial particles by using 22 representative acetogenins.[34] They also studied the three-dimensional structure of the bis-THF rings of the different possible stereoisomers optimized by quantum chemical calculations (MNDO-AM1).[34] Their results helped them to propose that the stereochemistry surrounding the THF rings is much less important for activity at the enzymatic level than previously believed, while acetogenins act as potent inhibitors only when the γ-lactone and the THF rings are directly linked by an alkyl spacer with optimal length.

Moreover, even though acetogenins are not ionophoric in living cells, the ion complexation ability studies of acetogenins showed that they could form complexes with Ca^{2+} or Mg^{2+}, which adopted different structures from the free molecules.[37, 38] These secondary structures may be seen as the active conformations of the molecules when they interact with the binding sites on the cell membranes. Binding affinity, metal cation selectivity, and ligand assembly highly depend on the stereochemistry of the coordination sites and the nature of the alkyl side chains. Although the relationship between binding properties of acetogenins and their biological activity is not clear, these ion complexation ability studies could help to investigate the details of the mode of action as well as the application of developing new antitumor agents. Since NADH:ubiquinone oxidoreductase is an iron dependent cluster enzyme, the investigation of Fe^{2+} and FeS-acetogenin complexation in aqueous media are suggested by Mclaughlin and

coworkers.[5]

I.1.3 Structure-Activity Relationship Studies

Although *Annonaceous* acetogenins are thought to inhibit complex I in mitochondrial electron transport systems, there is no direct experimental evidence to verify the exact mode of action with the target proteins. In addition, acetogenins have few structural similarities as compared to ordinary complex I inhibitors such as piericidin A and rotenone (Figure I-6).[39] Thus, there is interest in studying their unusual structural characteristics as well as the strong inhibitory properties of acetogenins.



piericidin A **rotenone**

Figure I-6: Two common complex I inhibitors piericidin A and rotenone

Structure-activity relationship (SAR) studies are also important to elucidate the mode of inhibition of complex I.

Even though there is no comprehensive SAR study of acetogenins, several groups have initiated some systematic studies based on their specific interest on particular structures. In 1999, Mclaughlin, Alali, and Liu summarized the previous SAR study based on naturally isolated acetogenins in their review,[5] which suggested the following generalizations: 1) Comparing the potent activity, the general order of different acetogenin classes in order of decreasing inhibitory activity is: adjacent bis-THF >

non-adjacent bis-THF > mono-THF > non-THF acetogenins. The THP ring has no effect on activity. The C-35 acetogenins are more potent than the C-37 compounds when their structural features are identical. 2) The terminal γ-lactone ring is crucial for activity. Ketolactone acetogenins are usually less active than those having an α, β-unsaturated γ-lactone. 3) The alkyl chain between the OH-flanked THF and the γ-lactone is critical to potency. 4) Neither the 4-OH group nor the 10-OH group is essential for activity. 5) Three hydroxyl groups (two flanking the THF units and one in the hydrocarbon chain) are important for the potency. A ketone instead of a hydroxyl group normally reduced the activity.

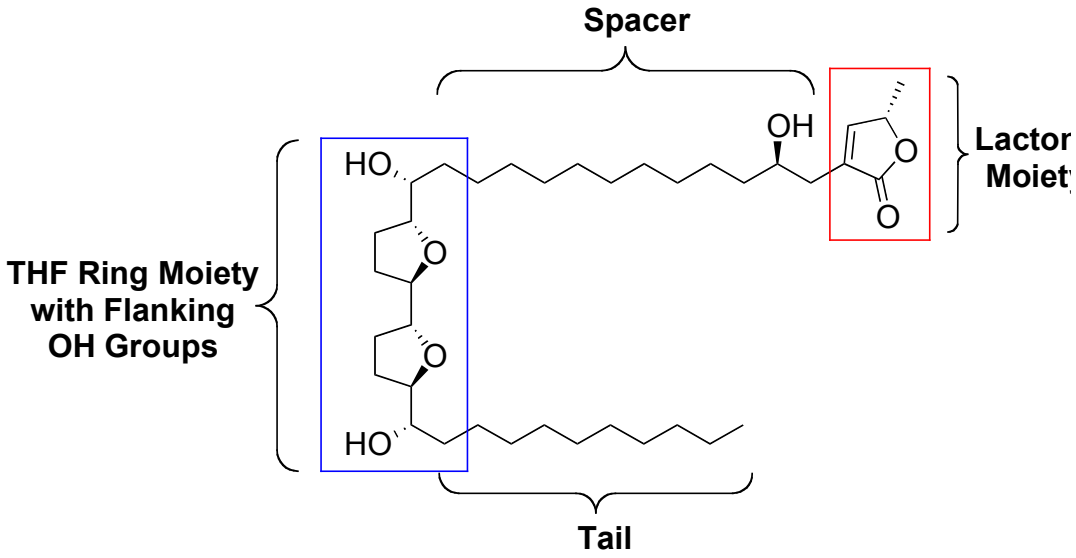
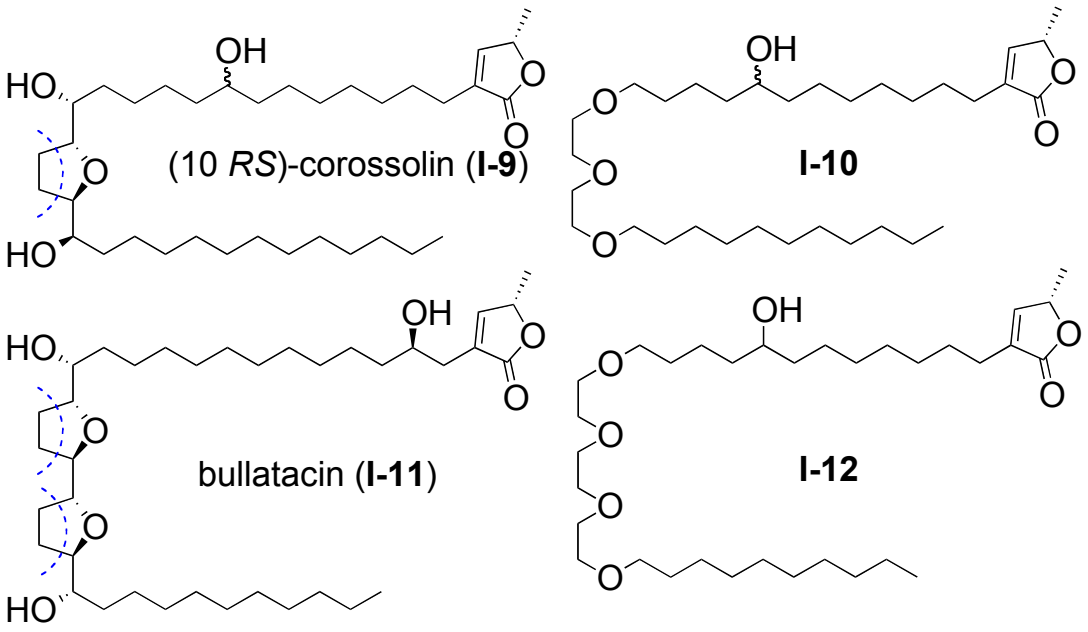


Figure I-7: Structure of bullatacin

Since then, Miyoshi et al.,[35, 36, 40-46] Yao and Wu et al.,[47-54] Cortes et al.,[30, 55, 56] Figadère, et al.,[57, 58] Poupon et al.,[59, 61] Duval and Lewin et al.,[62, 63] and Koert et al.[64] have published different SAR studies of acetogenins. Some of their results are in accordance with the previous observation while some are in conflict with it.

Table I-1: Cytotoxicity against two human cancer cell lines of acetogenins and their polyether mimics



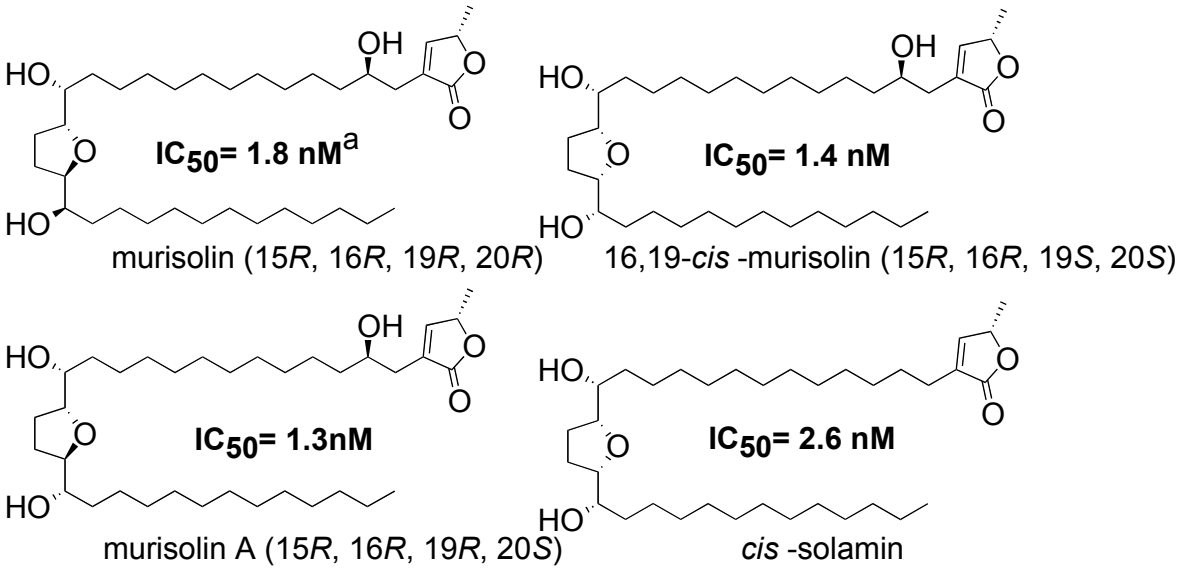
	IG[a] %					
	for HL-60			for K562		
concentration (μM)	100	10	1	100	10	1
(10 *RS*)-corossolin **I-9**	63	56	5	10	2	0
compound **I-10**	100	50	0	31	18	0
bullatacin **I-11**	73	7	0	53	39	27
compound **I-12**	100	65	21	55	25	22

Generally, for a SAR study, there are four parts of the acetogenin structure which need to be considered: the lactone moiety, the spacer (the alkyl chain connect lactone moiety to the THF cores), the THF ring moiety with flanking hydroxyl groups, and the tail (the long alkyl chain in the end). Figure I-7 shows one example, bis-THF acetogenin isolated from *Annona bullata*, bullatacin, which is one of the most potent inhibitors of

complex I.[35] All the SAR studies are focused on the relationship of activities and variation of these four domains of the structures.

The conclusion based on the most recent SAR studies could be summarized as following:

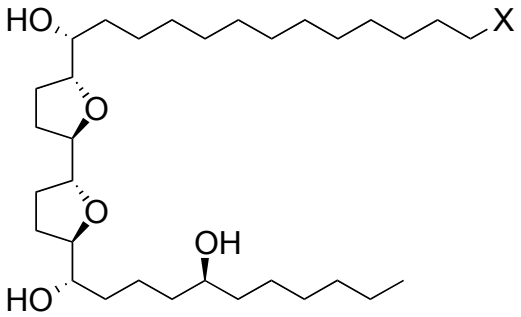
1) The number of THF rings, the hydroxyl groups in the hydrocarbon chains and the stereochemistry around the THF rings as well as the flanking hydroxyl groups are not essential structural factors for potent activity. Miyoshi, Makabe, and coworkers synthesized a series of diastereomers of natural products and test their bioactivities.[44-46] The inhibitory activity of these acetogenins on complex I shows the comparable IC_{50}

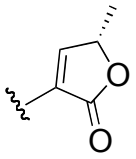
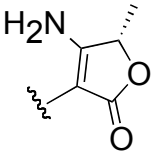
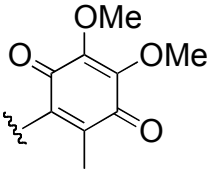
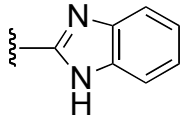
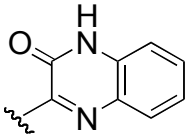
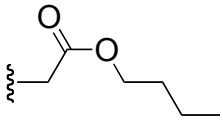


[a] IC_{50} value (nM); bullatacin IC_{50} = 0.8 nM.

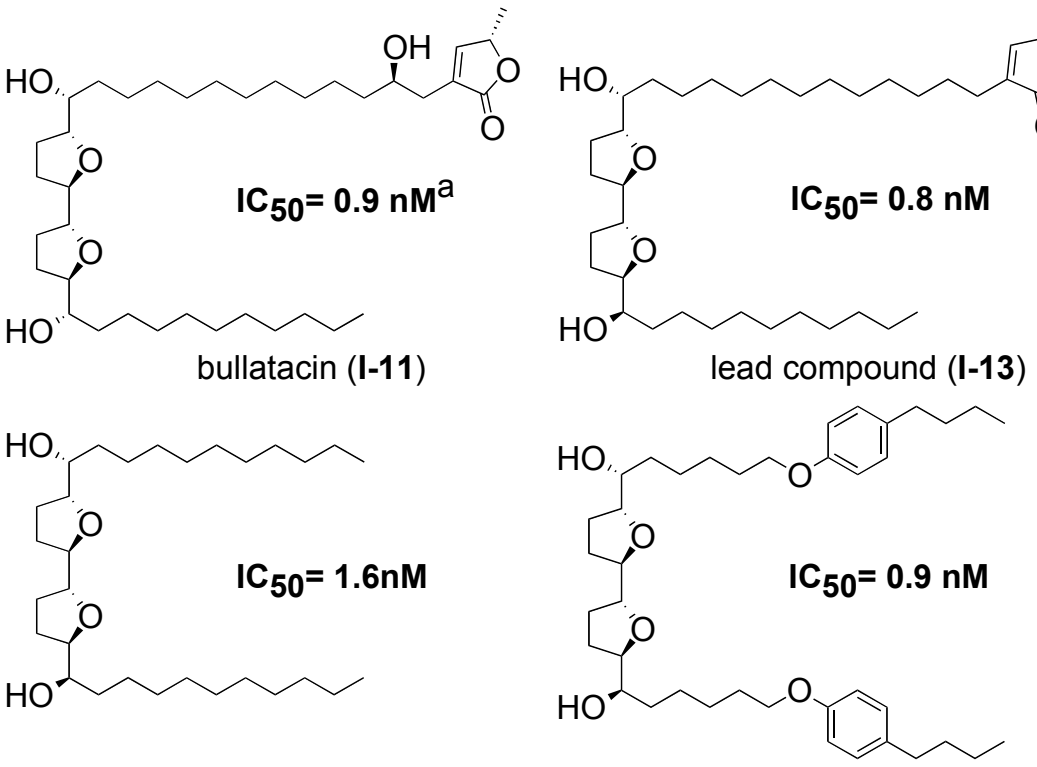
Figure I-8: Mitochondrial complex I inhibitory activity of various acetogenins

Table I-2: Inhibition of mitochondrial complex I by natural acetogenins and synthetic analogs with various terminal functional groups



Compound	Group X	Complex I Inhibition IC_{50} (nM)	
		NADH oxidase	NADH-DB oxidoreductase
squamocin		0.9	1.3
β-aminosquamocin		---	8.0
quinone analog of squamocin		---	1.7
benzimidazole squamocin		0.9	3.3
quinoxalinone squamocin		2.0	3.3
n-butylester squamocin		2.3	9.2

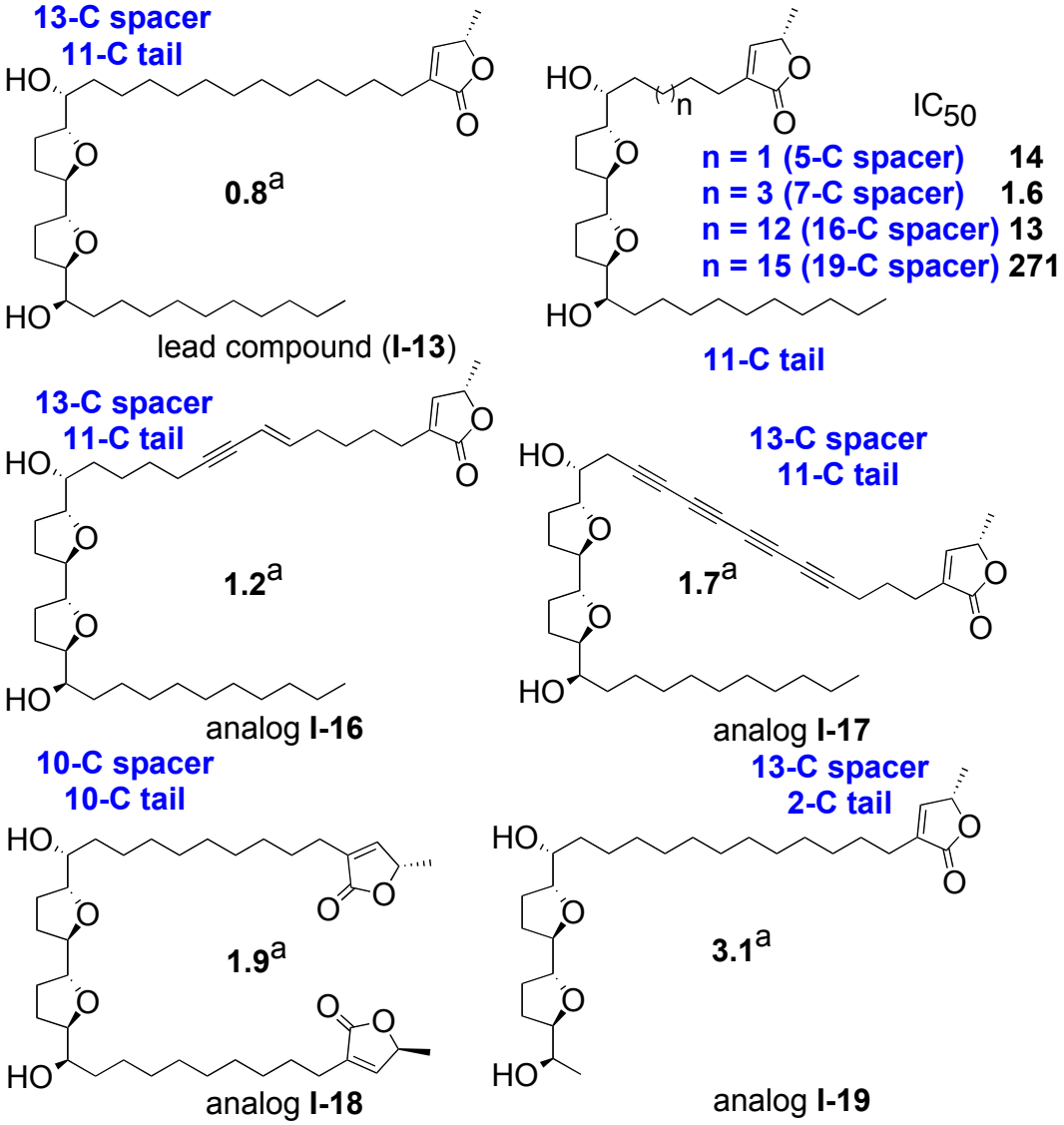
value (examples shows in Figure I-8 [46]). In addition, Yao, Wu, and coworkers found that polyether mimics of acetogenins can lead to remarkable cytotoxicity against human tumor cells (Table I-1).[40-52, 54] Both of the synthetic polyether mimics **I-10** and **I-12** have comparable cytotoxicity with similar-size natural acetogenins. These experiments indicate that the THF moiety is not a necessary structural feature for bioactivity.



[a] The IC_{50} value (nM) is the molar concentration

Figure I-9: Examples of natural and Δlac-acetogenins and their IC_{50} values

2) The terminal γ-lactone ring could be helpful for the high activity of acetogenins, but it is not a necessary functionality. There are reports of acetogenins with other terminal functional groups such as quinones,[64] heterocycles,[61, 63] substituted benzenes,[45] or photoaffinity groups[59] that are still potent inhibitors of complex I. Table



[a] The IC_{50} value (nM) of inhibition for mitochondrial complex I.

Figure I-10: Variation of the length of spacer and tail of acetogenin analogs

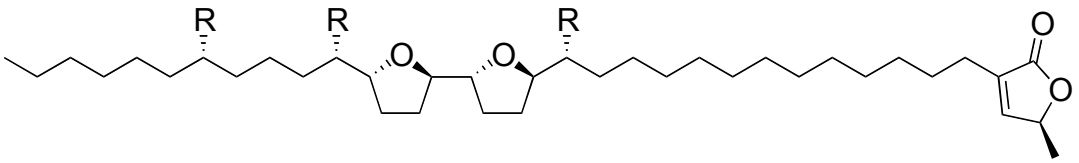
I-2 shows that both natural acetogenins and synthetic analogs with various terminal functional groups have comparable value for complex I inhibition.

Miyoshi and coworkers also reported that acetogenin analogs possessing two alkyl or aryl chains without a γ-lactone ring, named Δlac-acetogenins; could still retain similar

bioactivity (Figure I-9).[41, 43, 45]

3) The lengths of both spacer and tail are important structural factors for obtaining high activity. Generally, acetogenins act as potent inhibitors only when the THF moiety and the γ-lactone ring are directly linked by an appropriate alkyl spacer (the optimal length of the spacer for inhibition is approximately 13 carbon atoms).[64, 65-67, 45] However, the spacer portion is not affected by steric congestion when multiple bonds are introduced into different regions of the spacer (Figure I-10, analog **I-16** and **I-17**).[42] The appropriate length of the hydrophobic tail is preferable for activity, but is not as important as the spacer (Figure I-10, analog **I-18** and **I-19**).

Table I-3: Cytotoxic activity of squamocin and its derivatives

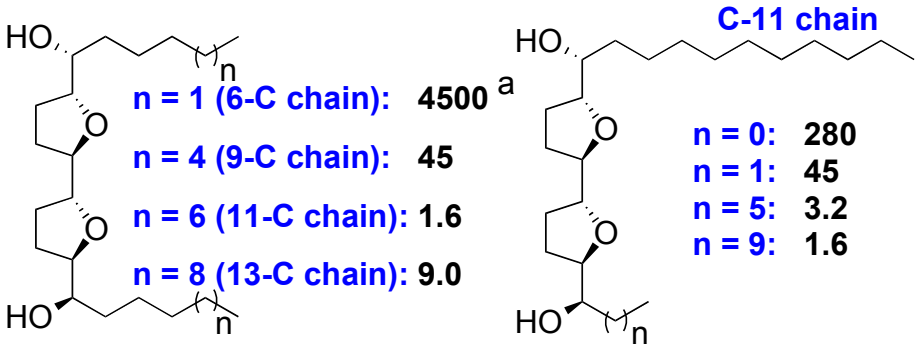


Compound	Group R	KB[a] EC_{50} (μM)
squamocin	-OH	1.6×10^{-5}
tritosyl squamocin	-OTs	$< 1.3 \times 10^{-1}$
trimesyl squamocin	-OMs	1.5×10^{-2}
triazido squamocin	$-N_3$	$< 1.4 \times 10^{-1}$
triamino squamocin	$-NH_2$	2.4×10^{-2}

[a] Human epidermoid carcinoma cell lines.

These effects are more significant in Δlac-acetogenin analogs (Figure I-11).[41-43, 45]

4) The presence of free hydroxyl groups flanking the THF moiety is important t elicit



[a] The IC_{50} value (nM) of inhibition for mitochondrial complex I.

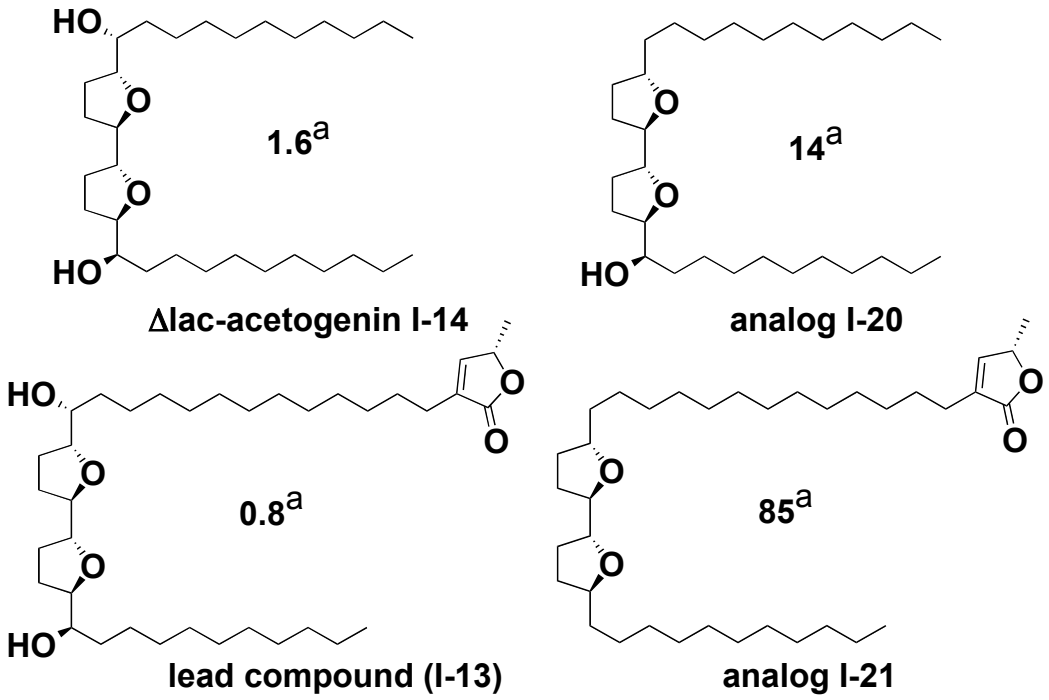
Figure I-11: Variation of the length of alkyl chains in Δlac-acetogenins

potent activity. Generally, protection of the free hydroxyl groups such as the transformation of the secondary alcohols into acetates or mesylates could lead to

Table I-4: Inhibitory potency of squamocin and its derivatives

Compound	Group R	IC_{50} (nM)	
		NADH oxidase	NADH:DB oxidoreductase
squamocin	-OH	0.59 ± 0.07	0.77 ± 0.15
trimesyl squamocin	-OMs	14.1 ± 1.6	2037 ± 28
triacyl squamocin	-OAc	5.0 ± 1.3	2936 ± 564

significant loss of cytotoxicity (>1000 times, examples in Table I-3) as well as inhibitory potency (Table I-4),[57, 62] while some of these derivatives could retain comparable enzymatic inhibition (such as acetate, examples in Table I-4).[55, 62] Removal of one of the two hydroxyl groups around the THF moiety resulted in a slight, but noticable, loss of activity (Figure I-12, analog **I-20**). Removal of both hydroxyl groups led to further decreased inhibitory potency of complex I (Figure I-12, analog **I-21**).[41]



[a] The IC_{50} value (nM) of inhibition for mitochondrial complex I.

Figure I-12: Comparison of inhibition

In summary, some of the previous results of SAR studies match with the proposed model of active conformation of acetogenins interacting with complex I. Since THF rings with flanking hydroxyl groups only work as a hydrophilic anchor, the stereochemistry in this region should have no effect. The presence of free hydroxyl groups in this region could help to interact with mitochondrial membrane, thus it is important to the activity. Moreover, in the proposed model, the length of spacer is very important because it leads the lactone ring to complex I. The SAR studies also showed that the length of the spacers had effect on the activity. However, some of the results conflict with the proposed model. Since lactone ring acts with the protein receptor site, the presence of lactone ring should be important. In SAR studies, Δlac-acetogenins without terminal functional groups were found to maintain good activity. In addition, besides the length of spacer, the length of

tail also has effect on the activity, which suggests that the shape of the whole molecule requires considaration.

The SAR studies provide some useful information in helping to understand the inhibitory mechanism of acetogenins against their protein targets, mitochondrial NADH ubiquinone oxidoreductase and plasma membrane NADH oxidase. It would also be helpful to explore acetogenins and their analogs as chemotherapeutic, pesticidal, and antimicrobial agents. However, since there are some conflicts between the SAR studies and the proposed mode of action, further SAR studies of acetogenins need to be carried.

I.1.4 Mucoxin

As described before, generally, *Annonaceous* acetogenins belong to two broad groups. Classical acetogenins contain none to three 2,5-disubstitued tetrahydrofuran (THF) units along with a terminal γ-lactone, such as uvaricin[64] and bullatacin.[65] Nonclassical acetogenins contain tetrahydropyran (THP) or hydroxylated THF rings and/or the normal 2,5-disubstituted THF rings along with a terminal γ-lactone. Examples of such are mucocin, which is the first reported nonclassical acetogenin that bears a hydroxylated THP ring with a non-adjacent THF ring,[66] and muconin, which contains a THP ring adjacent to another THF ring.[67] More recently, these THP-containing nonclassical acetogenins have drawn the attention of synthetic chemists due to their novel structural features and biological activities.[68-73]

Until 2006, however, there were no synthetic studies on the hydroxylated THF-containing nonclassical acetogenins. Mucoxin (Figure I-13), the first hydroxylated

THF-containing nonclassical acetogenin was isolated by McLaughlin and coworkers in 1996 from the bioactive leaf extracts of *Rollinia mucosa*.[67] [Four acetogenins were previously reported to possess hydroxylated THF rings,[74] however their structures were

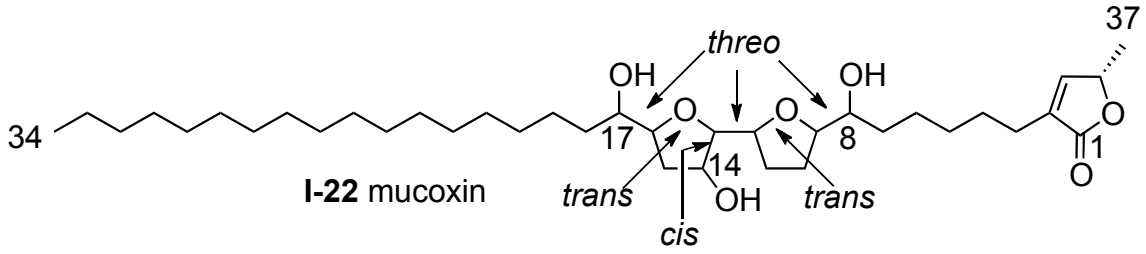


Figure I-13: Proposed structure of mucoxin

proved erroneous and have been corrected.[75]] Mucoxin exhibited potent and selective *in vitro* cytotoxicity against MCF-7 cells (breast cancer) in a panel of six human solid tumor cell lines.[67] It has an ED_{50} value of 3.7×10^{-3} μg/mL, which is more potent than adriamycin ($ED_{50} = 1.0 \times 10^{-2}$ μg/mL). However, further biological studies were limited because only 1.8 mg of mucoxin was isolated from the natural sources. For the same reason, the absolute stereochemistry of mucoxin was not determined. Its novel structural features as well as its interesting bioactivity led us to study the total synthesis of mucoxin.

I.1. 4.1 Previous Total Synthesis of the Proposed Structure of Mucoxin

Structurally, mucoxin contains a 3-hydroxylated-2,3,5-trisubstituted THF ring adjacent to a 2,5-disubstituted THF ring along with a γ-lactone moiety bound through a 6-carbon linker (Figure I-14). There are eight chiral centers in the molecule. Although no attempts were made to determine the absolute stereochemistry of the C8-C17 region,

the absolute configuration at C36 was assigned as *S* based on the observation that over 400 natural isolated acetogenins possess *S* configuration in the butenolide moiety.[76, 77]

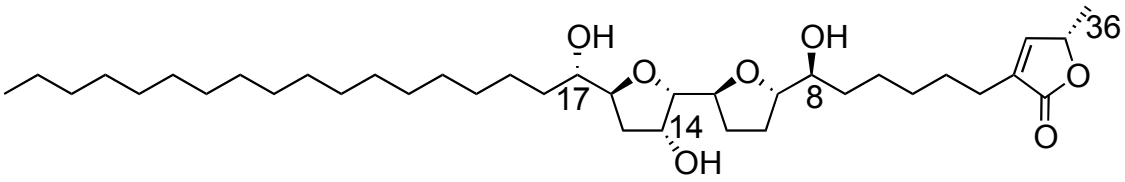


Figure I-14: Synthetic target (mucoxin)

Therefore, we chose the enantiomer represented in Figure I-14 as the synthetic target and completed the first total synthesis of the proposed structure of mucoxin in 2006.[78]

I.1.4.2 Retrosynthetic Analysis

The general scheme involves the construction of the polycyclic ether moiety bearing some functional group handles, as well as the terminal butenolide group, followed by the coupling of these two parts via the appropriate linker. Our retrosynthesis for mucoxin was also based on this sequence and is outlined in Figure I-15.[78] We planned to connect the terminal γ-lactone ring **I-25**, which could be prepared from the commercially available chiral epoxide **I-26**, with the bis-THF moiety **I-24** via an alkylation reaction. The 2,5-disubstituted THF ring was formed using our 1,2,*n*-triol cyclization methodology from intermediate **I-27**.[79] The two adjacent THF cores were coupled via a 1,2-chelation-controlled addition of the Grignard reagent derived from iodide **I-29**, with THF aldehyde **I-28**. The 2,3,5-trisubstituted THF **I-28** would be accessed using our Lewis acid-catalyzed, thiophenyl group-directed epoxide ring-opening of bis-protected epoxydiol **I-30**,[80, 81] which could be derived from the commercially available alkynyl

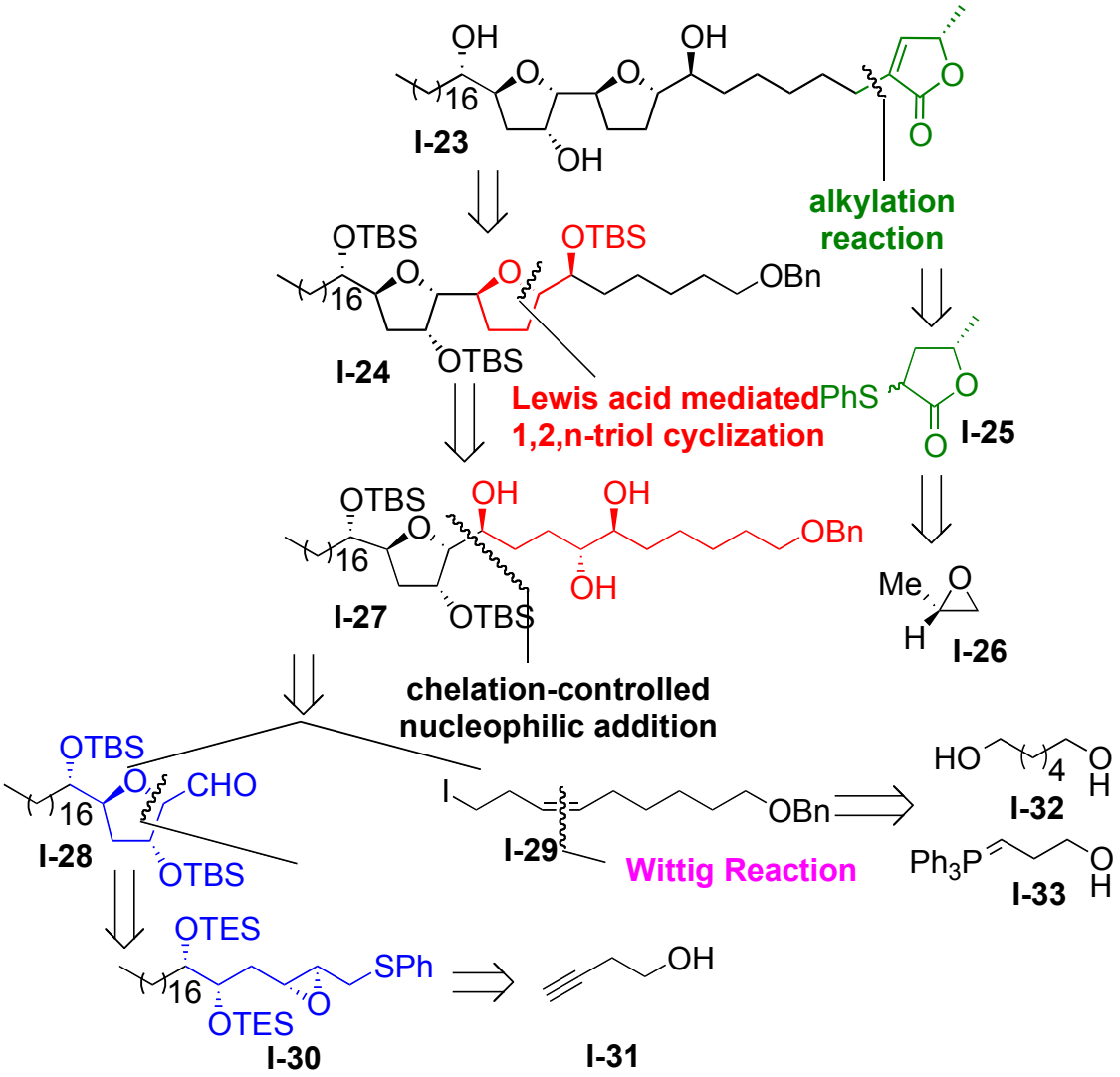


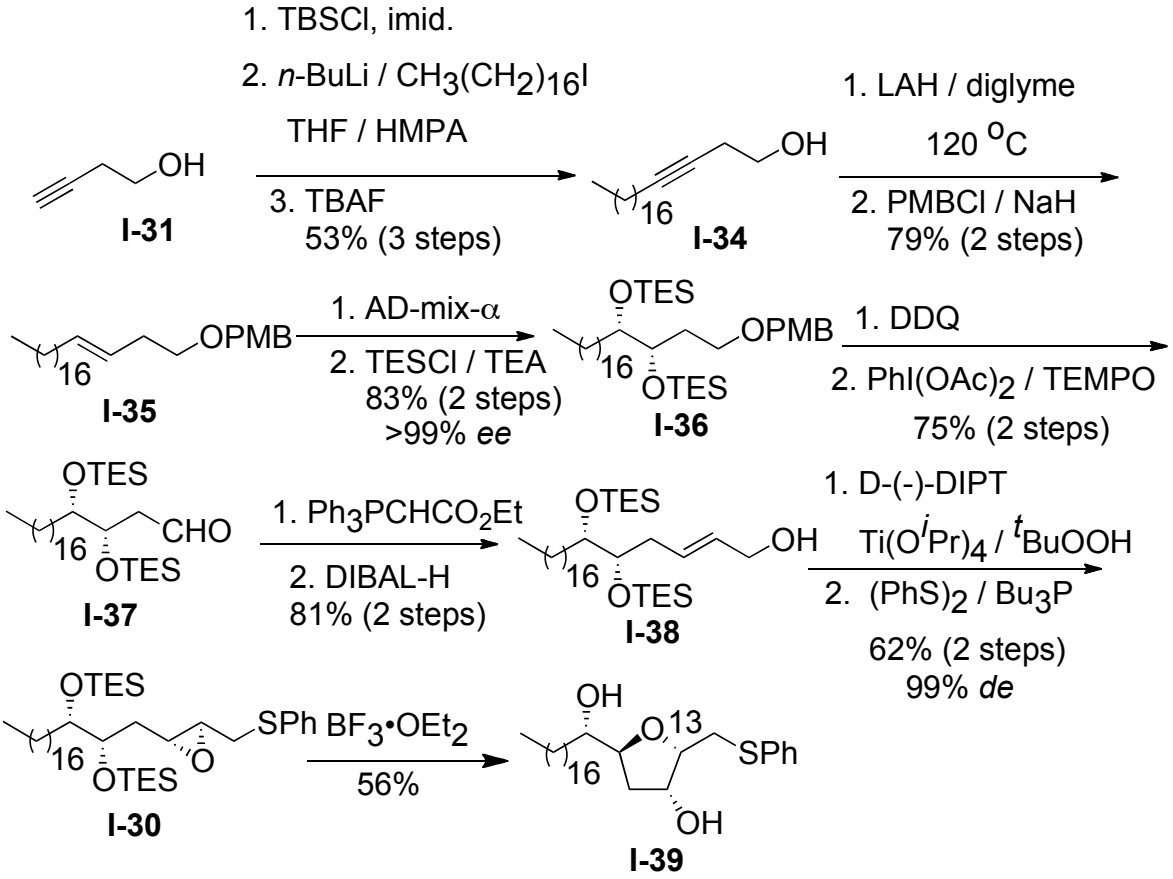
Figure I-15: Retrosynthetic analysis for preparation of mucoxin

alcohol **I-31**. Homoallylic iodide **I-29** could also be derived from diol **I-32** and ylide **I-33** via the Wittig reaction.

I.1.4.3 Total Synthesis of the Proposed Structure of Mucoxin

The total synthesis of the proposed structure of mucoxin was completed by our group in 2006,[78] utilizing the previously described methodology. The synthesis of the

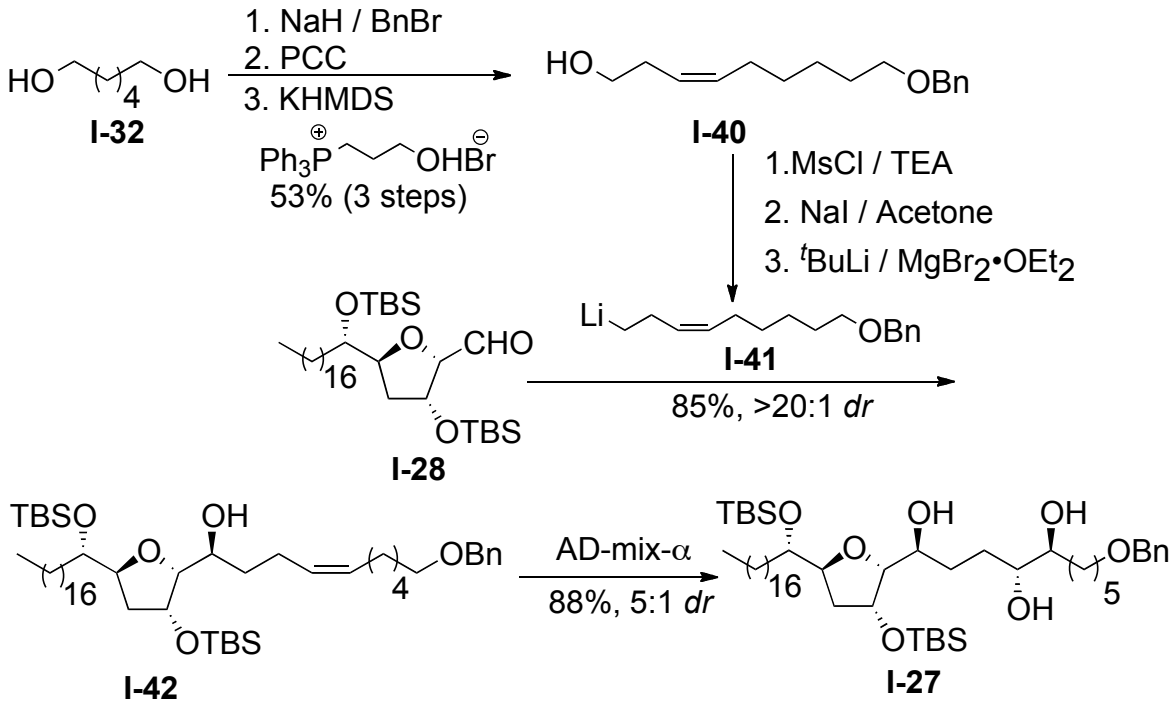
2,3,5-trisubstitued THF core of mucoxin is shown in Scheme I-1. Alkylation of the lithium acetylide derived from TBS-protected commercially available 3-butynol **I-31**



Scheme I-1: Synthesis of 2,3,5-trisubstituted THF **I-39**

gave the homopropargylic TBS ether, which after TBS deprotection forms homopropargylic alcohol **I-34**. LAH reduction of the triple bond and PMB protection of the alcohol provided the *E*-homoallylic PMB ether **I-35**. Sharpless asymmetric dihydroxylation[82] of **I-35** afforded the corresponding diol in excellent yield and enantioselectivity (92% yield and >99% *ee*). Silyl protection of the diol and PMB

deprotection of the terminal alcohol followed by TEMPO catalyzed oxidation gave aldehyde **I-37**, which could undergo Wittig olefination and subsequent DIBAL-H reduction to form the allylic alcohol **I-38**. Sharpless asymmetric epoxidation[83] of the allylic alcohol **V-31** provided the desired epoxy diol in excellent diastereoselectivity (>99:1, by ^{1}H NMR) and good yield (73%) under optimized conditions. After converting

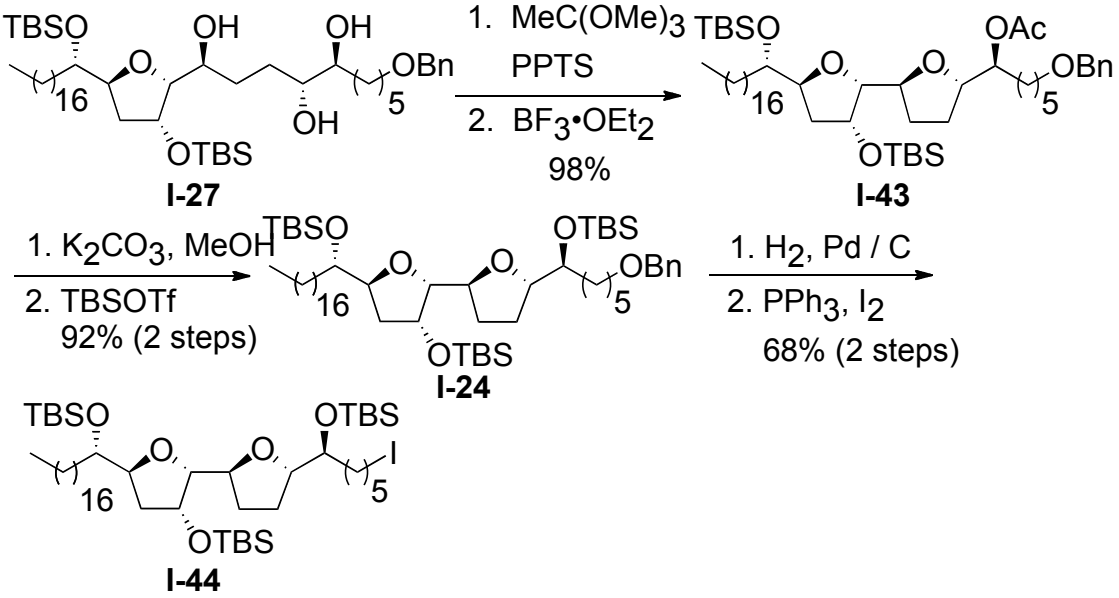


Scheme I-2: Synthesis of triol intermediate **I-27**

the epoxy alcohol to the required epoxysulfide precursor **I-30**, the neighboring group-assisted cyclization reaction under our standard conditions led to the formation of the desired 2,3,5-trisubstituted THF diol **I-39** in 56% yield, which could be cleanly separated from a 20% yield of an inseparable mixture of other isomeric cyclic diols. Optimization attempts by changing solvents, concentration, temperature, and acid

promoters were unsuccessful. However, this was still a good method to form intermediate **I-39** because of the efficient separation of the byproducts and the ability to scale-up the reaction. To obtain a matched SAE product, D-(-)-DIPT needed to be used to set the stereochemistry of the epoxide **I-30**. Compared with the required stereochemistry of the THF product **I-39**, the stereochemistry of C13 had to be retained, which led to the choice for the thiophenyl group as the neighboring directing-group.

The following step was to couple the trisubstituted THF ring with the functional group before constructing the disubstituted THF ring (Scheme I-2). The free hydroxyl



Scheme I-3: Synthesis of bis-THF iodide **I-44**

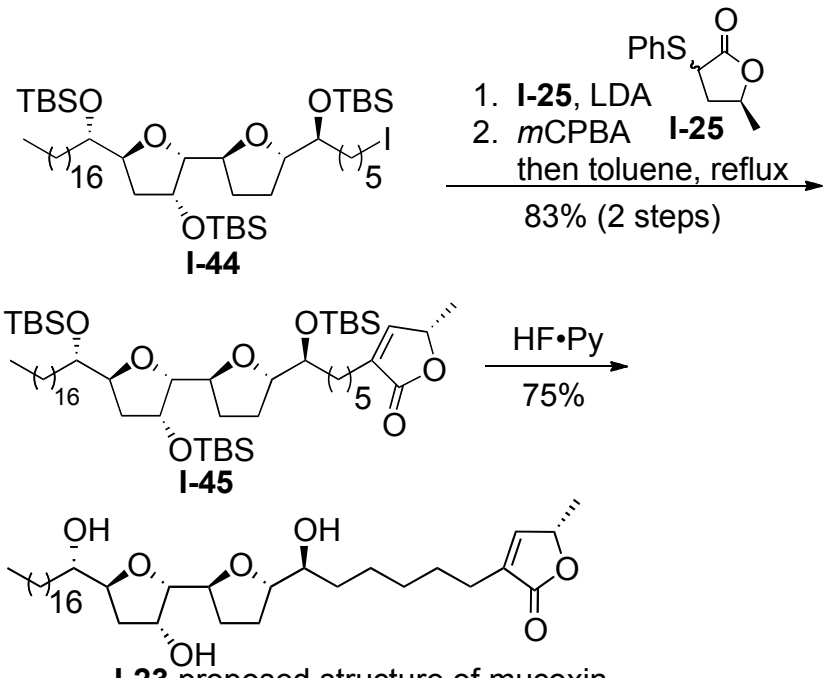
groups of compound **I-39** were protected as TBS ethers, and the product was subjected to Pummerer rearrangement[84, 85] conditions, providing the desired aldehyde **I-28** in good yield. Synthesis of the organolithium reagent **I-41** was accomplished in a concise process, which involved the monobenzylation of commercially available 1,6-hexanediol **I-32**,

PCC oxidation, the *Z*-selective Wittig olefination by *in situ* TMS protection / deprotection of the ylide's hydroxyl group,[86, 87] iodination via S_N2 displacement, and a lithium-halogen exchange with ^{t}BuLi. After transmetalation with freshly prepared $MgBr_2 \bullet OEt_2$ at -95 °C,[88, 89] the Grignard reagent was formed and treated with aldehyde **I-28,** which was precoordinated with freshly prepared $MgBr_2 \bullet OEt_2$ at -40 °C. This optimized procedure gave the desired chelation-controlled addition product **I-42** in good yield and excellent diastereoselectivity. The subsequent Sharpless asymmetric dihydroxylation[82] using AD-mix-α proceeded through attacking the olefin from the *si* face to form isomer **I-27**. Generally, during the SAD reaction, the stereoselctivity for *Z*-olefins is lower than for *E*-olefins, yielding the desired triol in a 5:1 diastereomeric ratio.

Next, we focused on constructing the disubstituted THF ring (Scheme I-3). Treatment of **I-27** with trimethyl orthoacetate and 10 mol% PPTS followed by addition of catalytic amount of $BF_3 \bullet OEt_2$ led to the desired 2,5-disubsituted THF ring in 98% yield as a single diastereomer via our 1,2,*n*-triol cyclization pathway. After converting the acyl group to the silyl group, benzyl-deprotection of **I-24** via hydrogenation was followed by iodination to afford the bis-THF iodide **I-44**.

The final stages of the total synthesis are shown in Scheme I-4. α-Phenylthio-γ-lactone **I-25** was prepared by White's procedure from commercially available thiophenyl acetic acid and chiral epoxide.[90] The coupling of iodide **I-44** and α-phenylthio-γ-lactone **I-25** was achieved by LDA-mediated α-alkylation in a THF/HMPA (4:1) mixture.

Treatment with *m*CPBA followed by the thermal *syn*-elimination of the sulfoxide gave the terminal γ-lactone **I-45**, which upon global deprotection using HF•py furnished the target molecule **I-23**, in high purity after HPLC isolation.



Scheme I-4: Completion of the total synthesis of the proposed structure of mucoxin

The proposed structure of the natural acetogenin, mucoxin, was synthesized in 32 steps and 26 steps along the longest linear sequence. The synthesis contains two regio- and stereoselective THF ring-forming methods developed by our group. The 2,3,5-trisubstituted THF ring (C13-C17) was constructed using neighboring group-assisted epoxydiol cyclization,[80, 81] and the 2,5-disubstituted THF ring (C8-C12) was constructed using a one-pot 1,2,*n*-triol cyclization strategy.[79] The absolute stereochemistries in **I-23** were established via Sharpless asymmetric epoxidation[83] and

dihydroxylation,[82] as well as the chelation-controlled addition.

I.1.4.4 Comparison of Spectral Data of the Synthetic and Natural Mucoxin

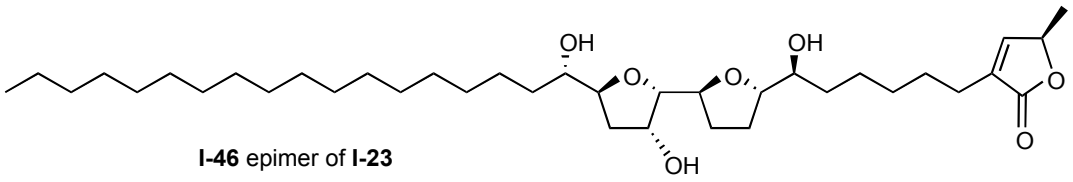


Figure I-16: C36 Epimer of synthesized mucoxin **I-23**

Although the synthesis of the proposed structure of mucoxin was accomplished, both the ^{1}H and the ^{13}C NMR spectra of the synthetic material did not match the published spectra of the natural sample. The major differences were in the adjacent bis-THF region

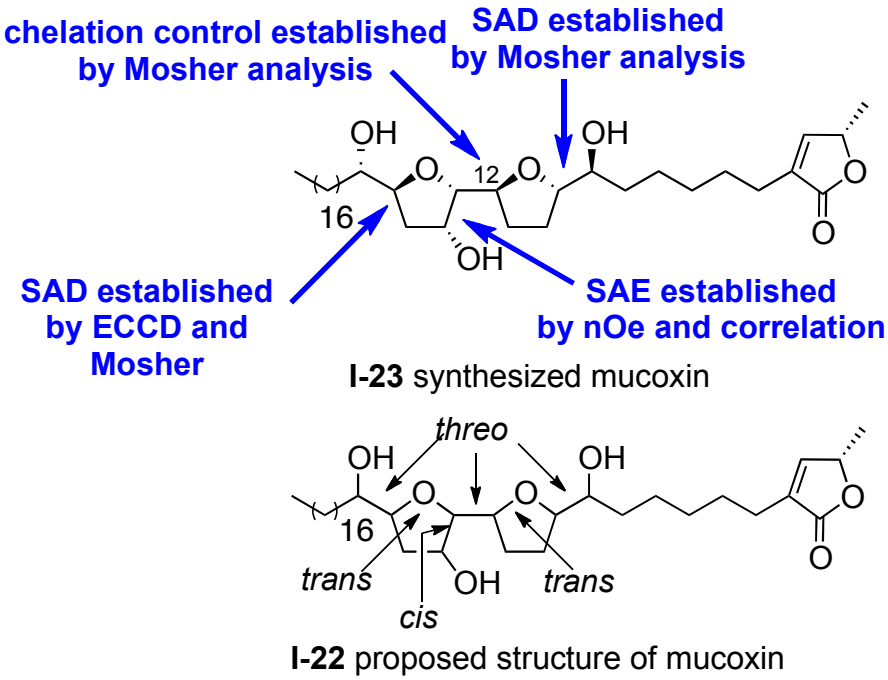
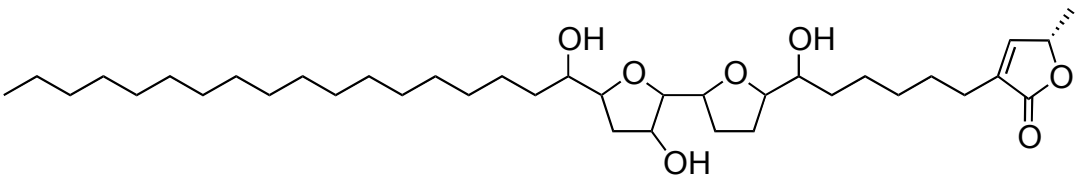


Figure I-17: Structure of synthetic mucoxin and proposed structure of mucoxin

(C8-C17) (Table I-16).[67, 78] In particular, H10, H11, H14, H15, and H17 exhibited differences of greater than 0.1 ppm as compared to the published spectra of the natural

Table I-5: Comparison of NMR resonances between natural and synthetic mucoxin



Proton / Carbon	**I-23**	Natural Mucoxin	Δδ (**I-23**–natural) (ppm)
H8	3.41	3.42	-0.01
H9	3.96	3.95	+0.01
H10	1.69, 2.02	1.91, 2.05	**-0.22**, -0.03
H11	2.02, 2.13	1.91, 2.05	**+0.11**, +0.08
H12	4.35	4.31	+0.04
H13	3.80	3.71	+0.09
H14	4.44	4.32	**+0.12**
H15	1.84, 2.02	1.91, 2.35	+0.07, **-0.33**
H16	4.09	4.04	+0.05
H17	3.41	3.53	**-0.12**
C8	73.6	73.6	0.0
C9	84.1	83.4	+0.7
C12	79.3	78.9	+0.4
C13	83.3	83.5	-0.2
C14	74.7	72.8	**+1.9**
C15	39.0	38.0	**+1.0**
C16	81.6	79.9	**+1.7**

mucoxin, while C14, C15, and C16 exhibited differences of greater than 1.0 ppm. In order to determine whether or not chiral carbon C36 has any effect on the spectra, the epimer **I-46** (Figure I-16) was synthesized using the epimer of α-phenylthio-γ-lactone

I-25. ^{1}H and ^{13}C NMR spectra of epimer **I-46** were found to be identical with those of **I-23**, which supported our hypothesis that configuration of C36 is not the reason for the difference between the synthetic and natural mucoxin. Based on what was previously mentioned, we still believed that C36 should have the *S* configuration.

Based on the latter description, a summary of the stereochemical assignments is shown in Figure I-17. We reason that all the configurations in the C8-C17 region of the synthesized mucoxin **I-23** are identical to the proposed relative stereochemistry of natural mucoxin.[67] Therefore, the disagreement in both ^{1}H and ^{13}C NMR must be due to the misassignments of the natural sample.

I.1.4.5 The Strategy towards Structure Elucidation of Mucoxin

We re-examined McLaughlin's structural assignment of mucoxin[67] in order to find the possible reasons for the discrepancies in the NMR spectra between our synthetic and the natural mucoxin. The published 2D-COSY and HRMS fragmentation of the tri-TMS

cccEEE	cccTEE	tccEEE	ttcTTE	ctcTEE	**cctTTE**	**cctTET**	cccTET
ctcETE	ttcEEE	tctETE	tctEET	tccEET	tccTTE	tttTEE	***tttTTT***
ttcTTT	cttTTE	cttTET	ctcTET	*cccTTT*	***cctTTT***	cctTEE	cccETE
cttEEE	cttETT	ctcETT	tttETE	tttEET	tccETT	**tctETT**	ttcEET
tctTEE	tccTTT	ttcTET	**tttTET**	tttTTE	ctcTTT	**cttTTT**	cttTEE
cccTTE	cctEEE	**cctETT**	cccETT	ctcEET	cttEET	cttETE	ttcETT
tttETT	tttEEE	tccETE	**tccTET**	**tctTET**	**tctTTE**	ttcTEE	ctcTTE
cccEET	cctEET	cctETE	tccTEE	ttcETE	ctcEEE	**tctTTT**	tctEEE

Figure I-18: 64 possible diastereomers of mucoxin

derivative of the natural mucoxin suggested that the proposed structure of mucoxin is constitutionally correct. Therefore, the differences in NMR spectra are most likely due to the misassignments of the stereochemistry of the natural sample. We have performed

modeling studies which indicated other possibilities for the stereochemical assignments.[91] Using molecular mechanics (MMFF94 force field), conformational searches and energy minimizations of different diastereomers were carried out. It was found that a 3 Hz coupling constant may be maintained for H13 in both H12-H13 *threo* and *erythro* relationship. Thus, the possibility of the *erythro* relationship between two THF rings could not be ruled out only based on the observed coupling constant for H13 in McLaughlin's assignment.[91]

Previous studies demonstrated that the configuration at C36 does not influence the NMR spectra of the molecule. Hence we took into account the remaining seven stereogenic centers (C8, C9, C12, C13, C14, C16, and C17) in calculating the total number of possible diastereomers of mucoxin. There are in all 128 (2^7) possible stereoisomers including all the enantiomers. Since a pair of enantiomers has identical NMR spectra, we only considered the diastereomers for spectral comparison. Figure I-18 indicates all the possible 64 diastereomers of mucoxin, which were encoded in the

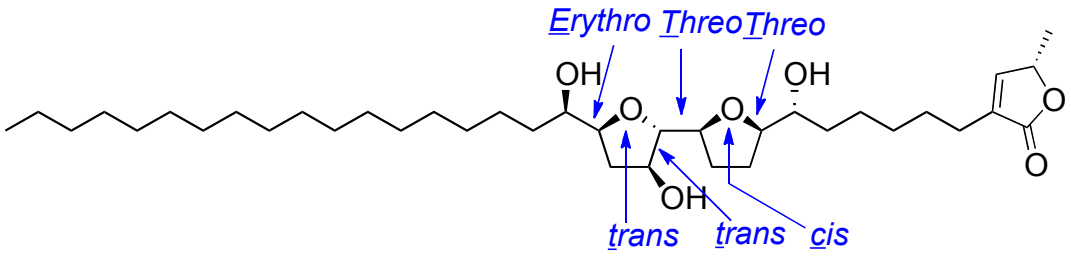
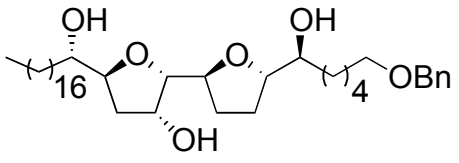


Figure I-19: *ttcETT* Diastereomer of mucoxin

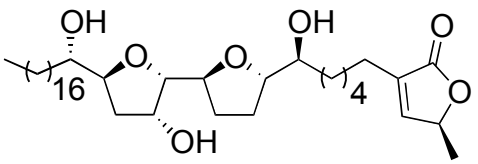
following manner: *c* or *t* is used to denote *cis* or *trans* relationship between C16-C13, C14-C13, and C12-C9; *E* or *T* is used to denote *erythro* or *threo* relationship between

C17-C16, C13-C12, and C9-C8. For example, *ttcETT* diastereomer of mucoxin refers to *trans*-relationship between C16-C13 and C14-C13, *cis*-relationship between C12-C9, *erythro*-relationship between C17-C16, and *threo*- relationship between C13-C12 and C9-C8 (Figure I-19).

Table I-6: ^{1}H NMR comparison of truncated structure **V-47** and synthesized mucoxin **V-2**



I-47



I-23

Proton	**I-47**	**I-23**	Δδ (**I-47** – **I-23**) (ppm)
8	3.41	3.41	0.00
9	3.95	3.96	-0.01
10	1.71, 2.01	1.69, 2.02	+0.02, -0.01
11	2.01, 2.12	2.02, 2.13	-0.01, -0.01
12	4.33	4.35	-0.02
13	3.80	3.80	0.00
14	4.43	4.44	-0.01
15	1.83, 2.01	1.84, 2.02	-0.01, -0.01
16	4.09	4.09	0.00
17	3.41	3.41	0.00

Of all the 64 diastereomers, we synthesized a focused library of a few representative molecules to construct a database of their NMR spectra.

Because C36 chiral center in the terminal γ-lactone ring has no effect on the NMR spectra of the bis-THF region (C8-C17) of mucoxin, it is possible to evaluate truncated structures containing only the bis-THF core and the hydrocarbon tail without the terminal lactone ring instead of preparing the fully assembled molecule for NMR evaluation. Thus prior to the library synthesis of the representative diastereomers of mucoxin we synthesized compound **I-47**, the truncated structure of the synthesized mucoxin **I-23**, and compared their ^{1}H NMR spectra (Table I-6). The ^{1}H NMR chemical shifts in the C8-C17

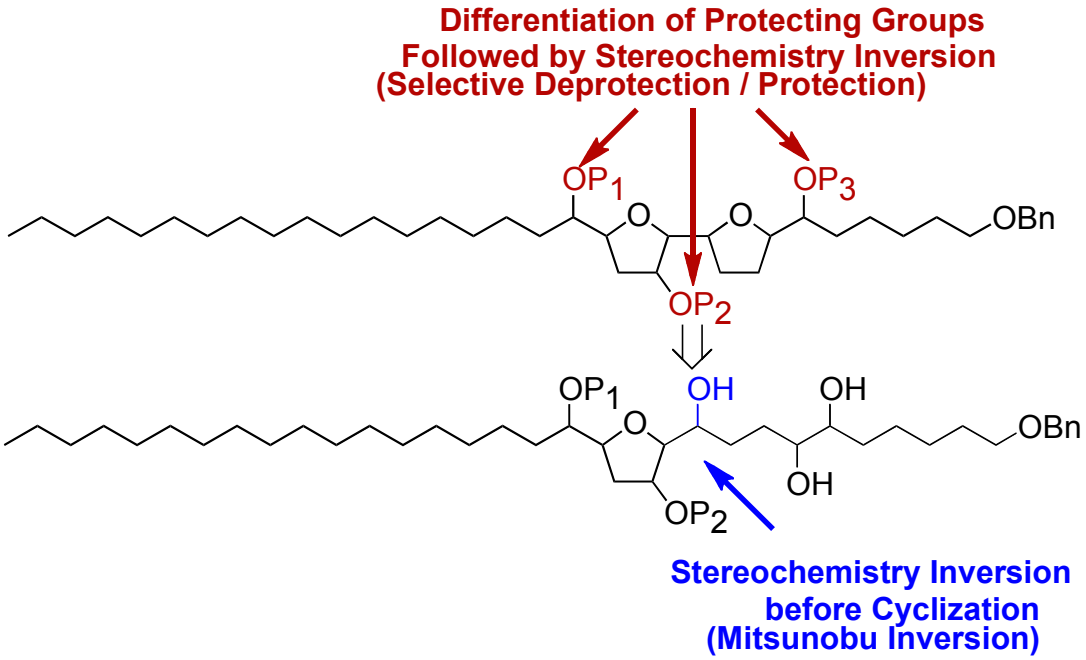


Figure I-20: New synthetic strategy to construct different diastereomers of mucoxin

region of mucoxin analogs **I-47** and **I-23** differ only by 0.02 ppm or less, which shows that both of these molecules have identical NMR spectra in the bis-THF (C8-C17) region.

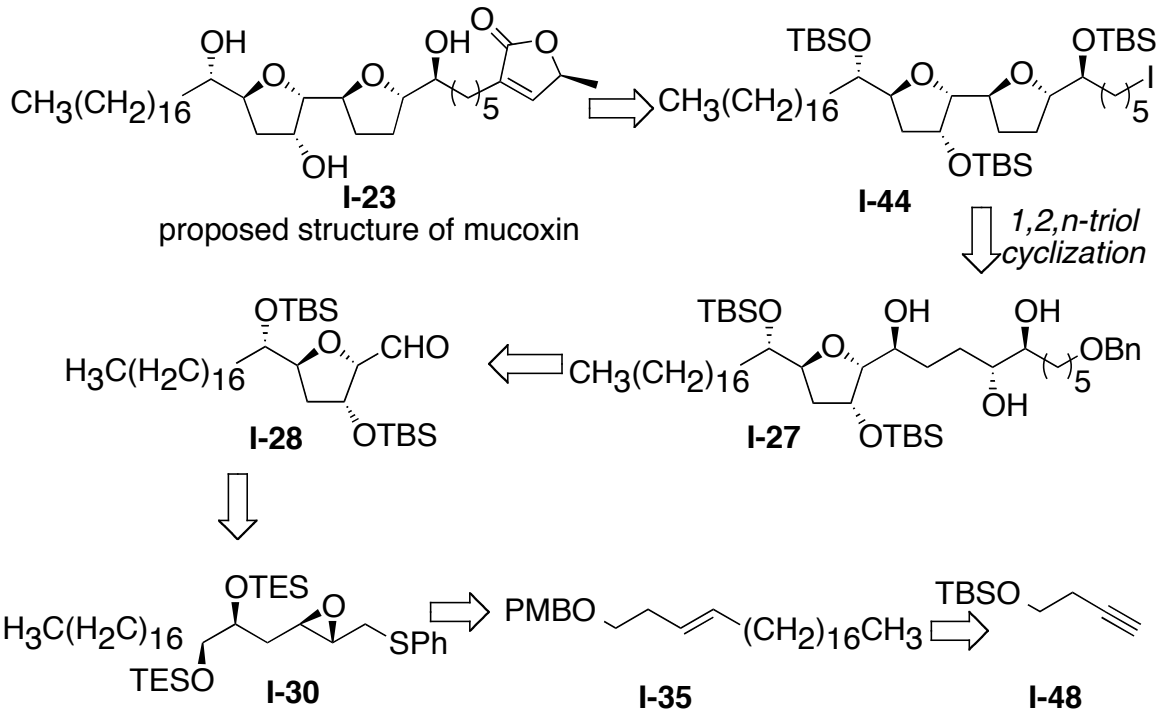
This enabled us to use the simpler truncated structures instead of the fully assembled molecule in the studies to determine the real structure of mucoxin, which could expedite the library synthesis of representative diastereomers.

The methods utilized in the total synthesis of the proposed structure of mucoxin[78] were designed so that its stereoisomers could be prepared in a straightforward pathway. Since the absolute stereochemistries in both the THF rings and the flanking hydroxyl groups, except C12, were set from SAD and SAE reactions with the appropriate olefin precursors, the complementary diastereomers could be accessed simply by the choice of the opposite olefin geometry and chiral reagents. Thus the regio- and stereoselective cyclization methods could prepare several isomeric hydroxylated THF rings from a common epoxydiol or triol intermediate. In addition, the stereochemistry of C12 could be varied using Mitsunobu inversion following the chelation-controlled nucleophilic addition. Finally, once the adjacent bis-THF core was constructed, three hydroxyl groups (hydroxyl groups in C8, C14, and C17) could be distinguished via a selective deprotection / protection strategy. Each of these chiral centers (C8, C14, or C17) could then be inverted by simple techniques such as oxidation/reduction or Mitsunobu inversion (Figure I-20).

I.1.4.6 Synthetic Pathway and Library Synthesis of Representative Truncated Structures of Mucoxin

Scheme I-5 summarizes the strategies utilized to establish the stereogenic centers in **I-23**. The stereochemistries of C17-C16 and C9-C8 were established via Sharpless

asymmetric dihydroxylation, while the stereochemistry of C14-C13 originates from Sharpless asymmetric epoxidation.[78] The stereochemistry at C12 was arrived at via chelation controlled addition of an organometallic reagent with an incipient aldehyde. The trisubstituted tetrahydrofuran ring in **I-28** was closed regioselectively with the aid of



Scheme I-5: Retrosynthetic strategy used to synthesize the proposed structure of mucoxin.

the thiophenyl directed epoxydiol cyclization,[80] while the disubstituted ring in **I-44** was furnished through the 1,2,n-triol cyclization.[79] Inspection of the synthetic strategy indicates the ease by which stereogenic changes to the molecule can be accomplished. These could be either through changes in the ligands used for symmetric induction or by inversion of stereochemistry of the three hydroxyl groups present in the target molecule. It should be noted, however, that the stereochemistry of each diastereomer was rigorously

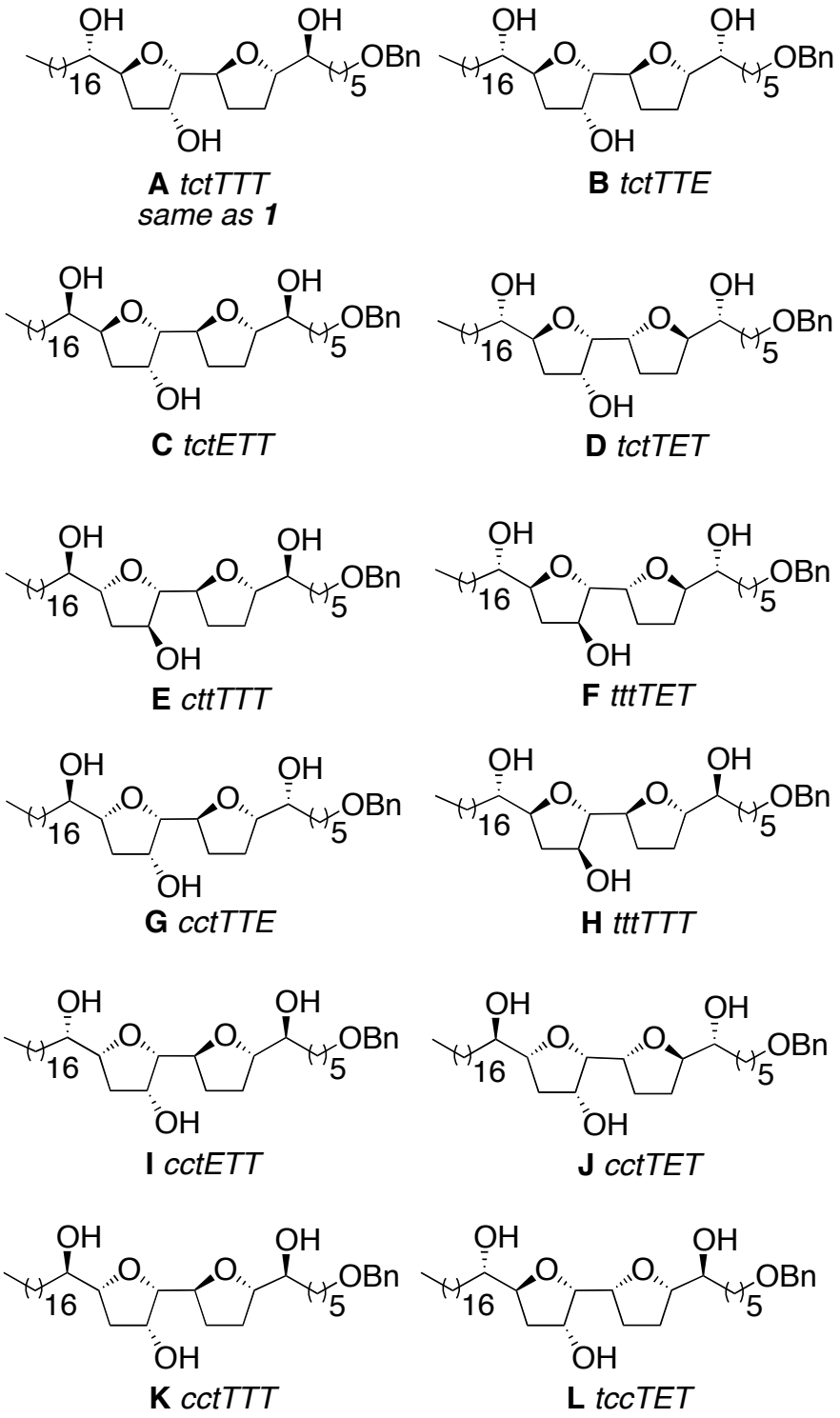


Figure I-21: Structure of synthesized truncated diastereomers of

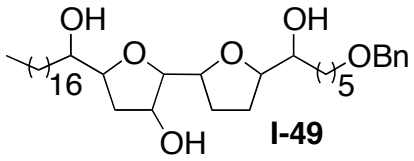
confirmed by a battery of 1D and 2D NMR experiments.[92]

Upon completion of the syntheses and inspection of the 1H and 13C NMR data, none

of the spectra from 12 isomers **A**-**L** (Figure I-21) fully matched the spectra obtained for natural mucoxin.[92] In order to efficiently compare the data for each of the isomers with natural mucoxin, the deviations of 1H and 13C NMR chemical shift between the truncated structures and the reported natural mucoxin are tabulated in Table I-7. Considering the analysis of the truncated analogues of mucoxin: C8-C9 threo, C16-C17 threo, C14-C16 cis, C12-C13 threo, the field of isomeric possibilities is narrowed from 64 total diastereomeric choices to only 4. These isomers are highlighted in blue in Figure I-18. As luck would have it, two of the four possibilities (**H** and **K**) were synthesized as part of the 12 diastereomers chosen for spectral analysis, thus further narrowing the field to the remaining 2 isomers (ttcTTT **M** and cccTTT **N**, see Figure I-18, bold and italicized). Both of the latter truncated isomers were synthesized, and gratifyingly, the cccTTT analogue N was found to be a perfect match (Table I-8). Further verification of this was obtained via the synthesis of the full-length cccTTT molecule, which produced identical 1H and 13C NMR spectra as compared to reported mucoxin. It is noteworthy that upon spectroscopic analysis of the additional two truncated structures ttcTTT (**M**) and cccTTT (**N**), the four trends derived from the original 12 diastereomers also fit these structures. In the final analysis, our results indicate that the original *trans* stereochemical relationship for both rings (C9-C12 and C13-C16) is the source of error in the structure determination (*trans* stereochemistry of the ring substituents was assumed from lack of NOE). This clearly demonstrates the fallibility of using negative NOE results to assign relative stereochemistries, especially in five membered rings (pseudo axial and pseudo

equatorial disposition of substituents) if both *cis* and *trans* isomers are not available for comparative analysis. These problems are not isolated in structure determination, but also

Table I-7: Chemical shift differences between the truncated analogues and the reported chemical shifts for mucoxin (NMR spectra recorded in $CDCl_3$)



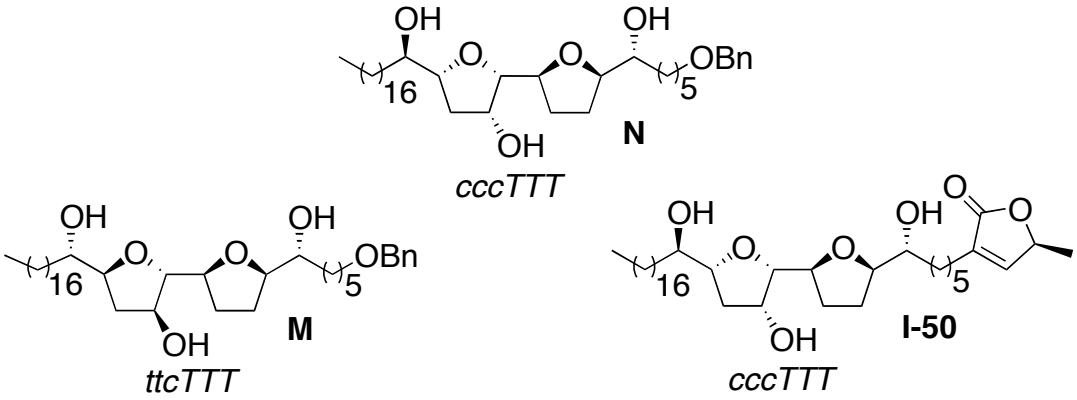
I-49

$\Delta\delta$ = δ (ppm) truncated analog – δ (ppm) reported mucoxin

H/C		A	B	C	D	E	F	G	H	I	J	K	L
8	H	-0.01	+0.40	-0.01	-0.02	-0.03	-0.05	+0.44	-0.05	-0.01	-0.02	+0.03	-0.02
	C	-0.2	-2.1	0.0	+0.2	0.0	+0.3	-2.3	+0.3	+0.3	---	+0.1	---
9	H	0.00	+0.05	-0.03	-0.10	-0.11	-0.12	+0.02	-0.18	-0.09	-0.12	-0.01	-0.16
	C	+0.5	+0.4	+0.5	-0.2	0.0	-0.3	-0.2	-0.1	+0.1	---	+0.2	---
10	H	-0.20	-0.10	-0.27	-0.2	-0.20	-0.25	-0.04	-0.27	-0.28	-0.21	-0.20	-0.17
	H	-0.05	-0.15	-0.04	-0.02	-0.06	-0.06	-0.18	-0.09	-0.11	-0.04	-0.02	-0.12
11	H	+0.10	-0.01	+0.02	-0.07	+0.08	-0.09	-0.09	+0.05	+0.05	-0.01	-0.05	+0.02
	H	+0.07	+0.08	+0.07	+0.16	-0.06	+0.03	+0.15	-0.09	+0.14	+0.12	+0.16	+0.08
12	H	+0.02	+0.09	-0.02	-0.09	-0.24	-0.48	-0.02	-0.36	-0.19	-0.08	-0.05	-0.13
	C	+0.1	+0.2	+0.2	-1.1	+0.3	+1.3	+0.3	+0.8	-0.2	---	-0.2	---
13	H	+0.09	+0.06	+0.16	0.00	+0.05	+0.02	-0.05	+0.15	-0.14	-0.12	0.00	-0.02
	C	-0.4	-0.2	+0.6	+0.5	+3.5	+4.6	+2.3	+5.7	+2.6	---	+2.1	---

pose a challenge to synthetic organic chemists in assigning stereochemistry of synthetic products. The data also point to the fact that empirical results can be of great value in

Table I-8: ^{1}H- and ^{13}C-NMR comparison of *ttcTTT* and *cccTTT* truncated analogs and *cccTTT* full length acetogenin with naturally isolated mucoxin



	*ttc*TTT **M** (truncated)		*ccc*TTT **N**		*ccc*TTT (I-50)	
C/H	Δδ H	Δδ C	Δδ H	Δδ C	Δδ H	Δδ C
8	-0.05	+0.9	0.00	-0.1	0.00	+0.1
9	-0.09	-0.8	-0.02	+0.1	0.00	+0.1
10	-0.07, -0.10	---	0.00, 0.00	---	+0.02,	---
11	0.04, -0.10	---	0.00, 0.00	---	+0.02,	---
12	-0.31	+0.8	0.00	0.0	0.00	0.0
13	+0.17	+5.1	+0.03	+0.2	+0.04	+0.2
14	-0.05	+1.2	-0.01	+0.1	0.00	+0.1
15	-0.07, +0.09	-0.1	0.00, 0.00	+0.8a	+0.02, 0.00	+0.8a
16	+0.04	+1.7	0.00	+0.2	+0.01	+0.2
17	-0.01	+1.0	0.00	+0.1	+0.01	-0.2

[a]The reported deviation is based on tabulated data from the original isolation and characterization report, however, close inspection of the original NMR spectrum suggests that the listed data for C15 was transcribed incorrectly by ~1 ppm, and in actuality the deviation between the NMR of *cccTTT* and the original data is less than 0.2 ppm.

stereochemical assignments since they can be used as a guide and/or secondary verification for structural elucidations.[92]

I.1.4.7 Biological Evaluation of Mucoxin and Analogs

In the original report of mucoxin's discovery and structural elucidation, biological activity against a panel of six cancer cell lines was reported. As tabulated in Table I-9, mucoxin appeared to have significant activity against a number of cancer cell lines, however most significantly, MCF-7 breast carcinoma and A-549 lung cancer showed the best responses intoxicity assays.[18] We have tested the cytotoxicity of both the compound with the proposed structure of mucoxin (**I-23**) and the corrected structure (**I-50**) against a large panel of cancer cell lines (Table I-9). In comparison with the data obtained from the initial report of mucoxin's discovery, our assays do not replicate the high activity observed for A-549 and MCF-7 cell lines, although both **I-23** and **I-50** retain higher activity in comparison to adriamycin. The synthesis of the enantiomer of **I-50** (*ent*-**I-50**) was pursued, since the original disclosure did not propose the absolute stereochemistry of mucoxin, nor did it report chiroptical spectroscopic data (such as CD or $[\alpha]_D$ values). It should be noted that *ent*-**I-50** is in fact a diastereomer of **I-50** since the absolute stereochemistry at C35 was retained as *S* (common to all acetogenins). Although we had hoped that comparison of the biological data obtained for *ent*- **I-50** and **I-50** might lead to the prediction for the correct absolute stereochemistry, as evident from the data in Table I-9, this was not possible. Both **I-50** and *ent*-**I-50** lead to similar cytotoxic activities across the panel of cancer cells. Mucoxin analogs do display a reasonably potent cytotoxic activity against all of the nine cancer cell lines tested in Table 10. Most importantly, they retain their potency against the adriamycin resistant cell line

(NCI-Adr). The C35 epimer of **I-23** (*epi*-**I-23**) was also synthesized to investigate its effect, however, in comparison to **I-23**, one must conclude that the absolute stereochemistry of C35 does not influence cytotoxicity to a large extent. As discussed above, the inhibition of mitochondrial complex I is the generally accepted mode of action for acetogenins. Nonetheless, few studies of acetogenins compare the cytotoxic activity of the molecules with Complex I inhibition potency. Examining the cytotoxicity of **I-23**, *epi*-**I-23**, **I-50**, and *ent*-**I-50**, it is clear that for each cell line the variation in activity is no greater than 4 fold and in most cases is within 50% of each other. Surprisingly, complex I inhibition results tabulated in Table I-9 suggest that **I-23** and *epi*-**I-23** with minimal activity (compared to rotenone, a standard complex I inhibitor) must follow a different mode of action as compared to **I-50** and *ent*-**I-50**, which exhibit potent complex I inhibition (more than rotenone). This is a surprising result since it indicates a clear structure/activity relationship, which is not realized through cytotoxic analyses, but is clearly evident via enzymatic activity assays. It points to the fact that acetogenin bioactivity must be analyzed through targeted biological assays, and might suggest a reason for some of the reported discrepancies in the literature with respect to the levels of apoptotic and necrotic activity of acetogenins. Although we are in no position at this time to suggest alternate targets besides complex I, it clearly points to the need for supplementing cytotoxicity data with complex I inhibition to investigate the relationship (or lack thereof) between the two. Currently, we are investigating other targets besides complex I for the observed cytotoxicity of **I-23** and *epi*-**I-23**.

I.1.4.7.1 Red Blood Cell Hemolysis

The red blood cell (RBC) is one of the most studied membrane systems and is therefore used as a model to describe many membrane-solvent-solute interactions. A red blood cell placed into a hypotonic solution of nonpenetrating molecules (i.e., a solution with lower concentration of solute and a higher concentration of solvent than the cell, for example, water) will rapidly swell and hemolyse, as the water molecules influx by osmosis from higher to lower concentration. Conversely, a red blood cell placed into a hypertonic solution of nonpenetrating molecules (i.e., a solution with higher concentration of solute and lower concentration of solvent than the cell, for example, salt water) will rapidly shrink and crenate, as water molecules efflux by osmosis from a

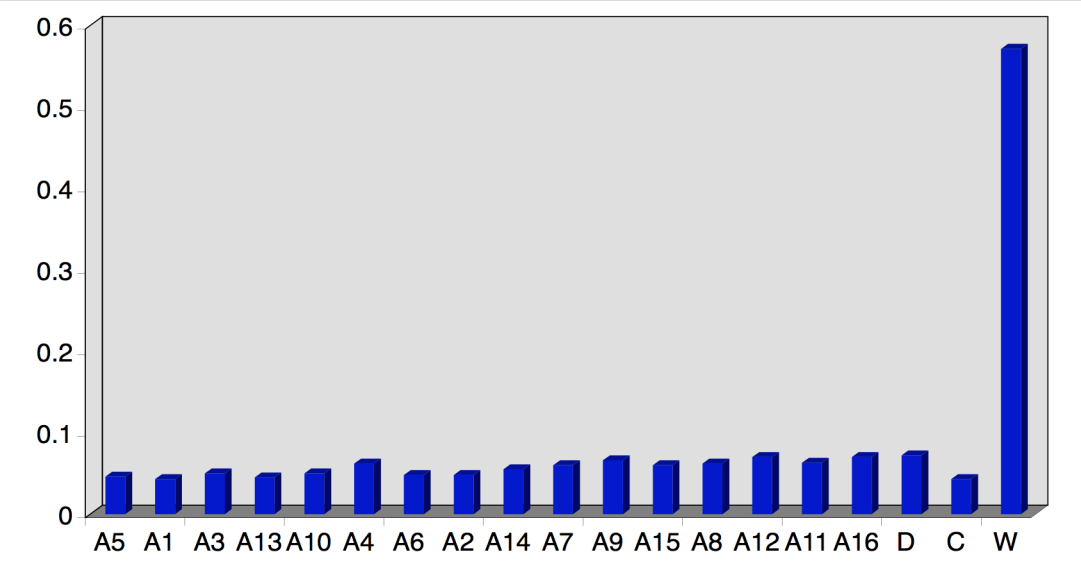


Figure I-22: RBC Hemolysis for mucoxin and its analogs (D: DMSO, C: Cell, W: Water)

higher to a lower concentration. Further, a red blood cell placed into an isotonic solution of nonpenetrating molecules (i.e., a solution with the same concentration of solute and

solvent as the cell, for example, saline solution) will neither swell nor shrink because the osmotic influx and efflux of water is in equilibrium in the absence of a concentration gradient. The amount of time that it takes for hemolysis or crenation to occur is directly related to the rate of osmosis across the cellmembrane. Therefore, hemolysis can be used to determine the hypertonic, hypotonic and isotonic concentrations of particular nonpenetrating solutes and the hemolysis time can be used as an index of the rate of osmosis.[93] The Red Blood Cell (RBC) hemolysis for all molecules that is shown in Table I-9 was studied and no significant hemolytic activity was detected, suggesting a target based mode of action and not cellular membrane disruption as the cause for biological activity (Figure I-22).

I.1.5 Library Design of Ether-Linkage Analogs of Acetogenins

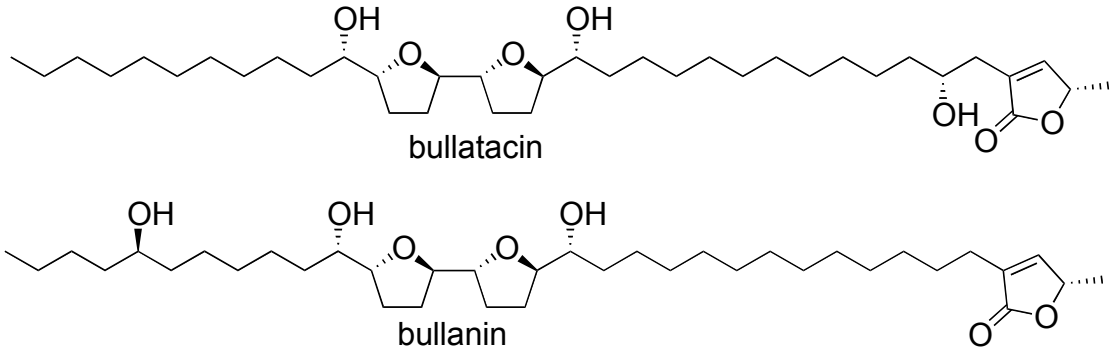


Figure I-23: Ether linked analogs of bis-adjacent THF acetogenins

Encouraged by the results of the initial structure-activity relationship (SAR) studies on mucoxin and its analogs, and in order to further understand the mechanism and the exact mode of action of acetogenins, more SAR studies were necessary. Since the

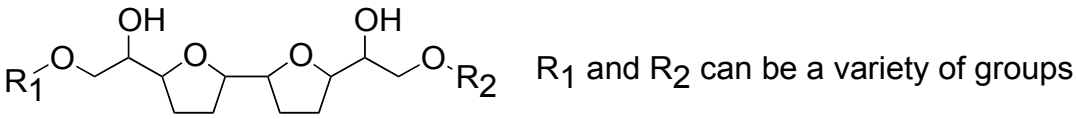


Figure I-24: Ether linked analogs of bis-adjacent THF acetogenins

bis-adjacent THF acetogenins are the most active members of the acetogenin family such as bullatacin (one of the most potent inhibitors of complex I)[35] and bullanin (having much lower ED_{50} values against a panel of some human cancer cell lines than

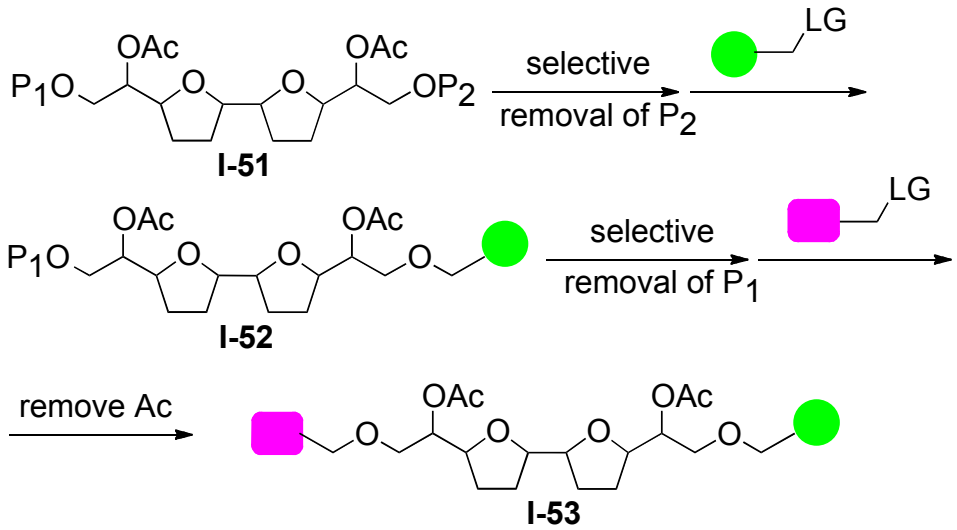


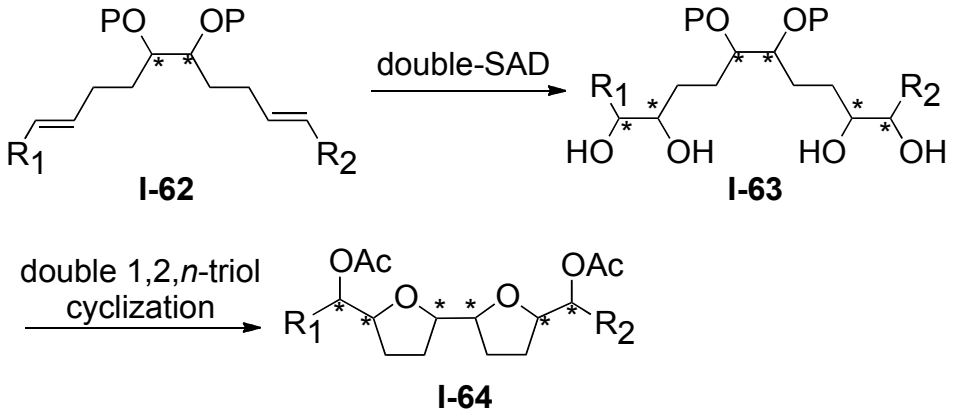
Figure I-25: Modular synthesis of acetogenin analogs with bis-adjacent THF core

adriamycin, an anticancer drug currently in clinical use)[22] (Figure I-23), we decided to use the bis-THF motif as the core for further SARs. In order to obtain a large library of acetogenin analogs in the SAR studies, an established methodology on how to quickly and efficiently assemble a series of compounds is very important.

Our new plan for SAR investigations is focused on the use of ether linked analogs of acetogenins (Figure I-24). Utilization of ether linkages will enable rapid synthesis of a large library of acetogenins with a variety of groups flanking the right and left side of the

bis-THF core. After constructing bis-adjacent THF core **I-51**, each protecting group (P_1 and P_2) can be removed selectively and the desired side chain can be installed through a simple Williamson etherification to afford compound **I-52** and **I-53** (Figure I-25). In theory, there is no limitation for the choice of the side chains, which could lead to a large library of bis-adjacent THF acetogenin analogs that can be evaluated rapidly for their bioactivities. For example, a variety of hydrophobic tails as well as the spacers with terminal butenolide moiety can be installed with different lengths by using electrophiles **I-54** and **I-55** (Figure I-25). The butenolide functionality can be changed to other groups that could interfere with electron transport in complex I, such as substituted benzenes (**I-56**) and quinones. Membrane-binding elements such as phosphate esters (**I-57**) and steroidal compounds (**I-58**) can also be attached to the tail or instead of the butenolide moiety. Also, by coupling two or more acetogenin skeletons, dimer, trimer or oligomeric acetogenins can be formed (**I-59**). In addition, fluorescent molecules can be attached for sub-cellular localization experiments (**I-60**) and photoaffinity groups can be attached for photoaffinity labeling experiements (**I-61**). The attractive feature of this strategy is that all these compounds can be synthesized easily, and therefore SAR information can be obtained quickly. To implement the latter strategy, the development of the methodology to synthesize bis-adjacent THF segments needs considerable attention. Several stereospecific synthetic approaches to bis-adjacent THF segments have been developed successfully. Our alternative methodology is based on the Lewis acid mediated one-pot

regio- and stereoselective cyclization of 1,2,*n*-triols developed in our group in 2005.[79] Using Sharpless asymmetric dihydroxylation (SAD)[82] to control the absolute stereochemistry, 2,5-disubstituted THF rings could be formed in excellent yield. This

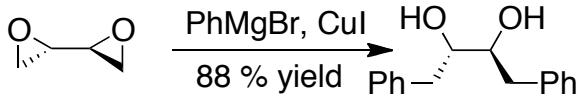


Scheme I-6: Proposed synthetic plan to form bis-adjacent THF segments

methodology was successfully used in the total synthesis of mucoxin and its analogs.[78, 92] The advantages of the 1,2,*n*-triol cyclization are that reaction conditions are mild and the reaction is fast. Generally the reaction is complete within 30 min at room temperature. Also the experimental procedure is operationally facile as compared to other methodologies such as metal-mediated oxidative cyclizations. The question was whether or not this transformation could lead to the formation of a bis-THF moiety in one step. Our proposed synthetic plan is shown in Scheme I-6. After preparing intermediate **I-62** containing two double bonds, double SAD reactions can provide tetra-ol **I-63** stereospecifically in one step. The following double 1,2,*n*-triol cyclization mediated by a Lewis acid can afford the desired bis-adjacent THF segment **I-64** in one simple step. By varying the stereochemistry of the two double bonds and using different SAD chiral

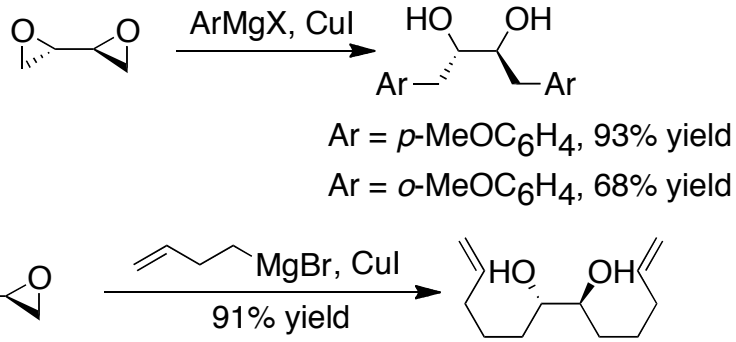
reagents, different diastereomers can be formed efficiently. This one-pot regio- and stereoselective double cyclization of polyhydroxylated systems provides a good alternative pathway to form bis-adjacent THF segments.

I.2 Bis-Epoxide Ring-Opening Pathway



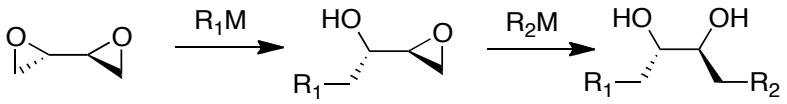
Scheme I-7: Robbins synthesis of chiral non-racemic vicinal diol

Epoxide ring-opening reaction is an efficient route to prepare chiral secondary alcohols since many good methodologies to prepare chiral epoxides such as Sharpless



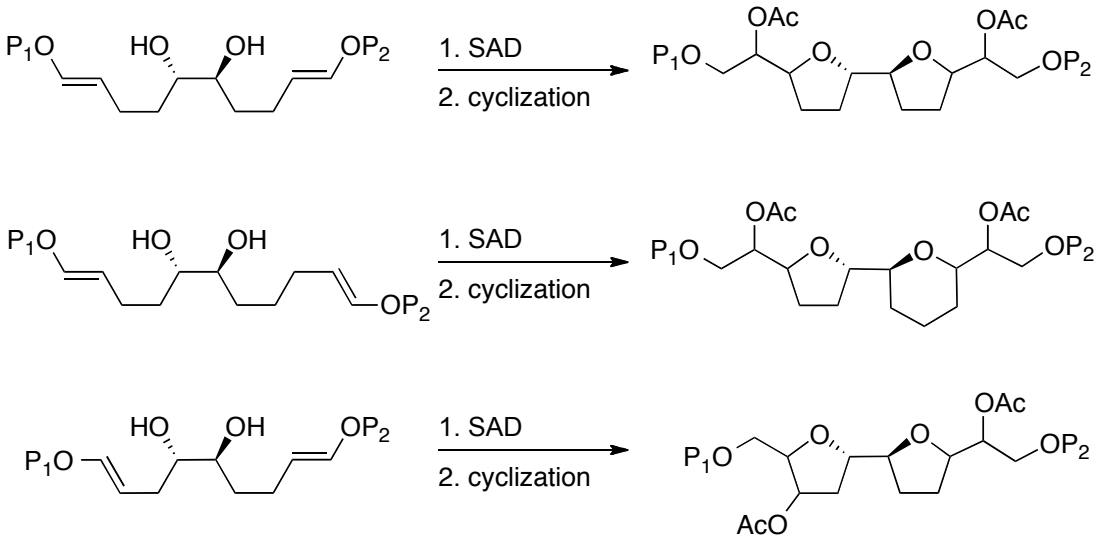
Scheme I-8: Aromatic and aliphatic Grignard reagent in bis-epoxide

asymmetric epoxidation,[83] Jacobsen's epoxidation,[9a] and Shi epoxidation [94b] are already well developed. Different organometallic reagents such as organolithium,[95] Grignard,[96] organocuprate,[97] and organoaluminum reagents [96] were successfully used in the ring-opening reaction of chiral epoxides to form secondary alcohols.



. **Scheme I-9:** Synthesis of non-C2-symmetirc adjacent diols reactions

In 1999, Robbins and coworkers reported the synthesis of chiral non-racemic vicinal diols (Scheme I-7), which provided an efficient route to prepare chiral vicinal diols.[99, 100] Later on, different nucleophilic reagents were used, following the same strategy, to open the chiral bis-epoxide. For example, de March and coworkers reported the synthesis



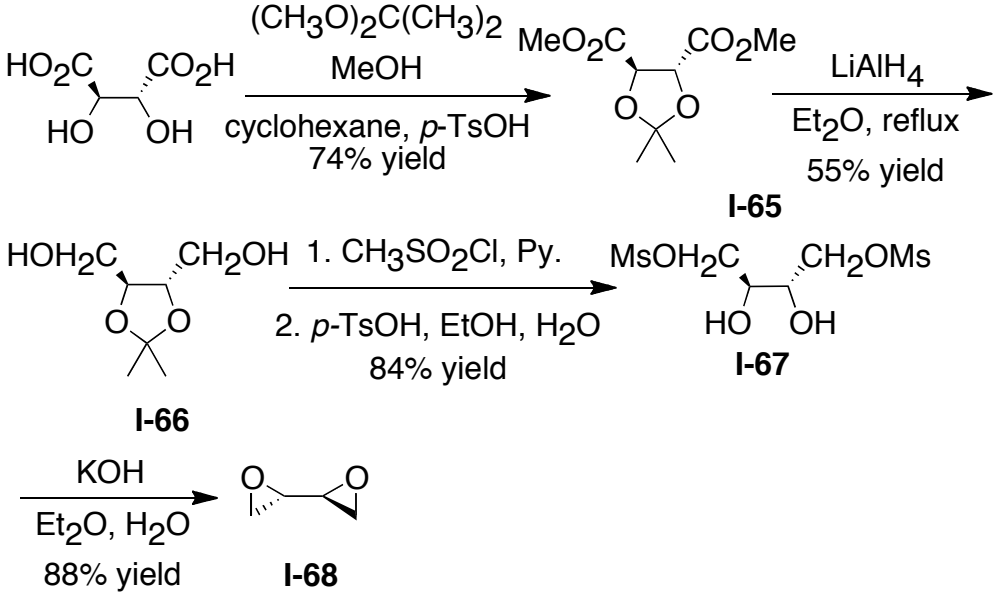
Scheme I-10: Preparation of different classes of acetogenins

of enantiomerically pure monoketals of *p*-benzoquinone[101] and Clive and coworkers found that aliphatic Grignard reagents could undergo the same ring-opening reaction to give the desired chiral vicinal diols[102] (Scheme I-8).

The bis-epoxide ring-opening pathway provides an efficient method to prepare chiral vicinal diols with a variety of side functional groups. Thus, in order to prepare our

diene precursors, we just need to prepare the corresponding organometallic reagents. If only 1 equiv. of organometallic nucleophile (R_1M) is used epoxyalcohol could be formed, which could be subjected to a second ring-opening reaction using a different organometallic nucleophile (R_2M) to afford the non-C_2-symmetric adjacent diol (Scheme I-9).

The ability to change R_1 and R_2 groups leads to quick access to different classes of acetogenins (Scheme I-10). For example, if both R_1 and R_2 are allylic organometallic nucleophiles, diol **53** would be formed after the two-step ring-opening reactions, which then leads to the formation of the bis-adjacent THF acetogenins with two different

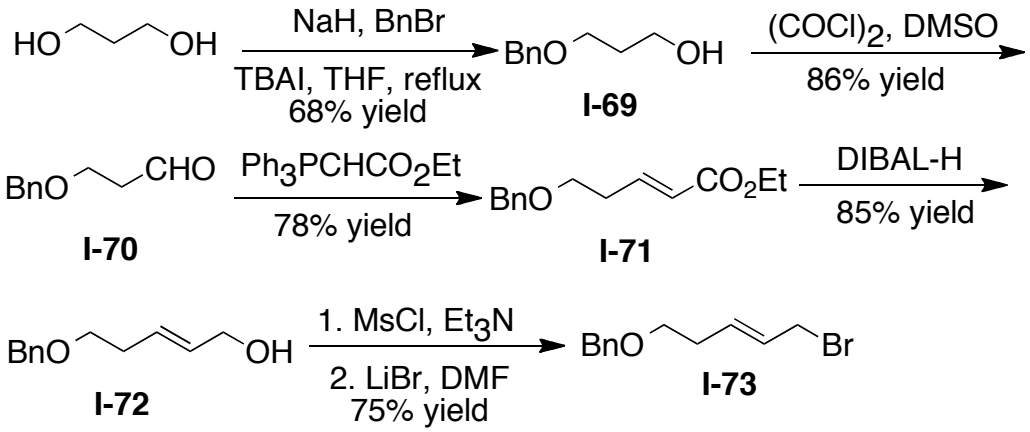


Scheme I-11: Synthesis of chiral bis-epoxide **62**

terminal protecting groups. If R_1 is allylic and R_2 is a homoallylic organometallic nucleophile, diol would be formed from which the non-classical THF-THP acetogenin

would be obtained. If R_1 is vinyl and R_2 is an allylic organometallic nucleophile, diol is anticipated and the hydroxylated THF acetogenin would be accessed.

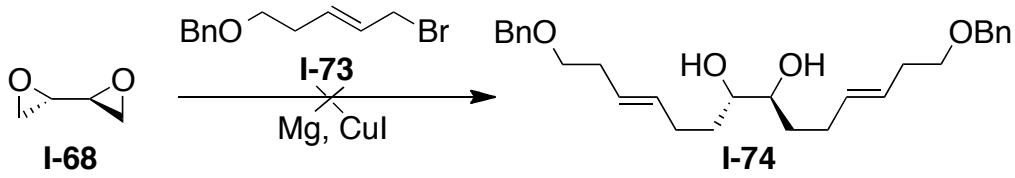
Synthesis of chiral bis-epoxide **I-68** was carried out from the commercially available L-tartaric acid. L-tartaric acid was protected by 2,2-dimethoxylpropane in methanol to give **I-65** in 74% yield. Reduction of the dimethyl ester with $LiAlH_4$, followed by mesyl protection and acetonide group deprotection afforded diol **I-67**. Base-mediated cyclization furnished the (*S*,*S*)-1,2,3,4-diepoxybutane **I-68** (Scheme I-11).



Scheme I-12: Synthesis of allylic bromide **I-73**

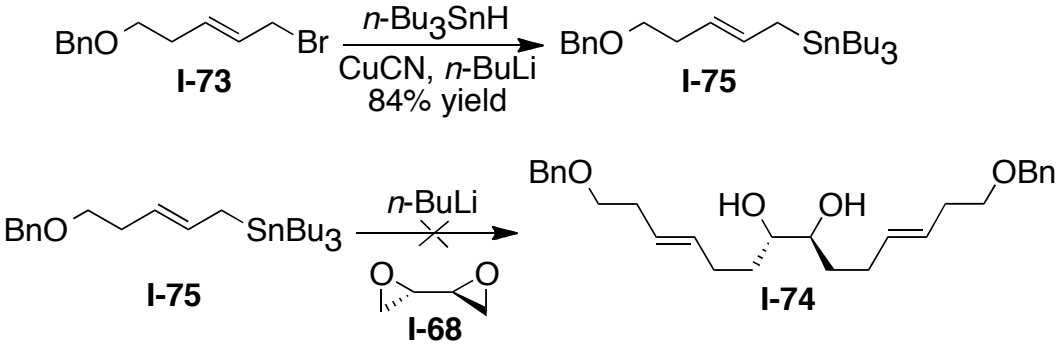
In order to synthesize bis-adjacent THF acetogenin analogs, allylic organometallic reagents are used in the epoxide ring-opening reactions. The following study was to prepare the desired allyl bromide containing a *trans*-olefin. Mono-benzylation of 1,3-propanediol with NaH and benzyl bromide at refluxing conditions provided the desired alcohol **I-69** in 68% yield. Swern oxidation followed by Wittig reaction provided *trans*-olefin **I-71** as a single isomer, which was subjected to DIBAL-H reduction to give

allylic alcohol **I-72**. The terminal hydroxyl group was converted to a good leaving group followed by S_N2 displacement with lithium bromide to provide allylic bromide **I-73** (Scheme I-12).



Scheme I-13: Bis-epoxide ring-opening reaction by using Grignard reagent

Attempts to perform the bis-epoxide ring-opening reaction with Grignard reagent generated *in situ* in different solvents such as THF and Et_2O under reflux condition did not give any desired diol product **I-74**. The starting material was recovered based on the crude NMR of the reaction (Scheme I-13).



Scheme I-14: Different method for bis-epoxide ring-opening reaction

With the failure of the Grignard approach, we next turned to organolithium reagents. Since allylic bromide is not as efficient in the halogen-lithium exchange, the corresponding allyltin was prepared by using *tri*-butyltin hydride. The reaction proceeded

smoothly in good yield. Treatment of compound **I-75** with *n*-butyl lithium should provide the desired organolithium reagent, which could then be coupled with the diepoxide. But, even after more than 24 h, there was still no desired product. After failing i*n situ* generation of lithium reagent, we tried to first prepare the organolithium reagent. Allyltin **I-75** was treated with *n*-butyl lithium and after 24 h no desired product was obtained. Considering that this reaction failed, it seemed that the problem was due to the generation of the organolithium reagent (Scheme I-14).

I.3 Sp^3-Sp^2 Cross Coupling Reactions to Synthesize Triene Intermediate

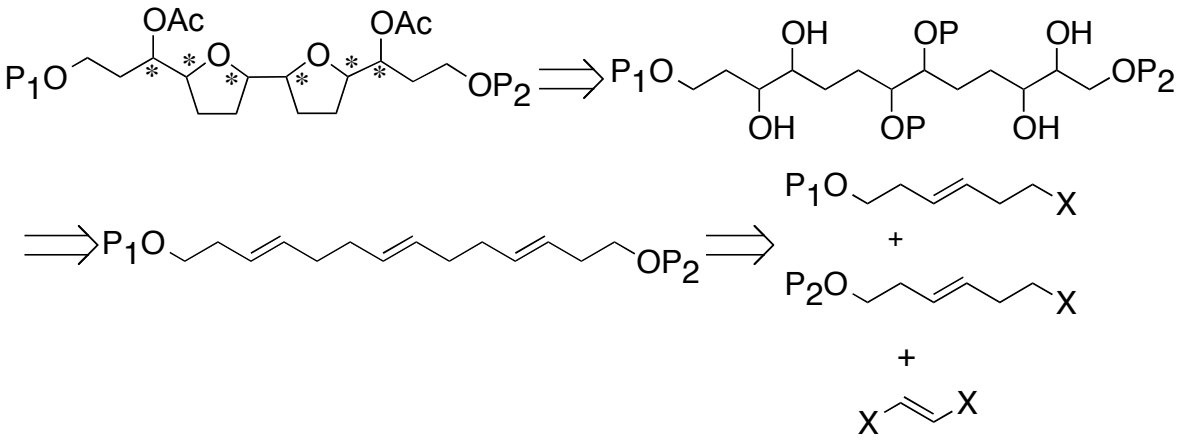
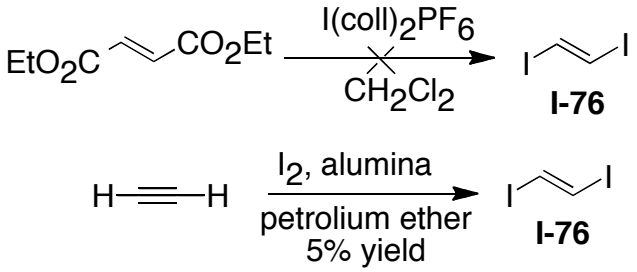


Figure I-26: Retro-synthesis of triene

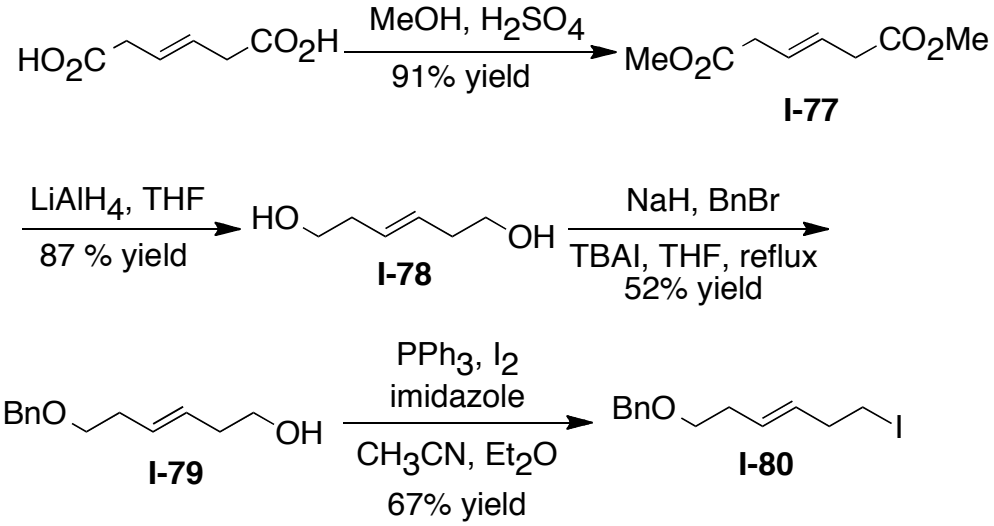
With the failure of the bis epoxide opening, we next turned to develop another simple and efficient method to achieve the bis-THF core in a stereocontrolled fashion (Figure I-26). We had seen an example in the literature where the exact same substrate was used (where the terminal carbons are the ethyl esters) and the Sharpless Asymmetric Dihydroxylation (SAD) was achieved selectively at the central double bond.[103] Our goal was to synthesize the triene and vary the oxidation state of the terminal carbons (free

hydroxyls, protected hydroxyls, or esters) and see if we could get selective dihydroxylation of the central double bond (using SAD). If we could get selective dihydroxylation, then the next step would be to develop an efficient methodology to synthesize the triene.



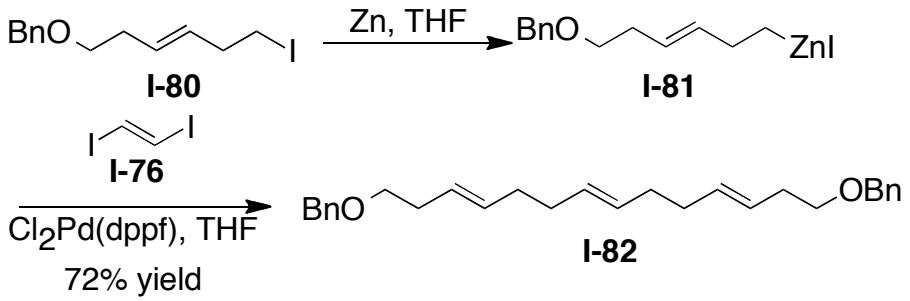
Scheme I-15: Attempts for synthesis of diiodoethylene

The synthesis of the central fragment was started using two different approaches. The first approach began by iodination of ethylene dicarboxylic acid that is failed. The second method was bubbling acetylene gas into a solution of alumina and iodine (Scheme I-15).



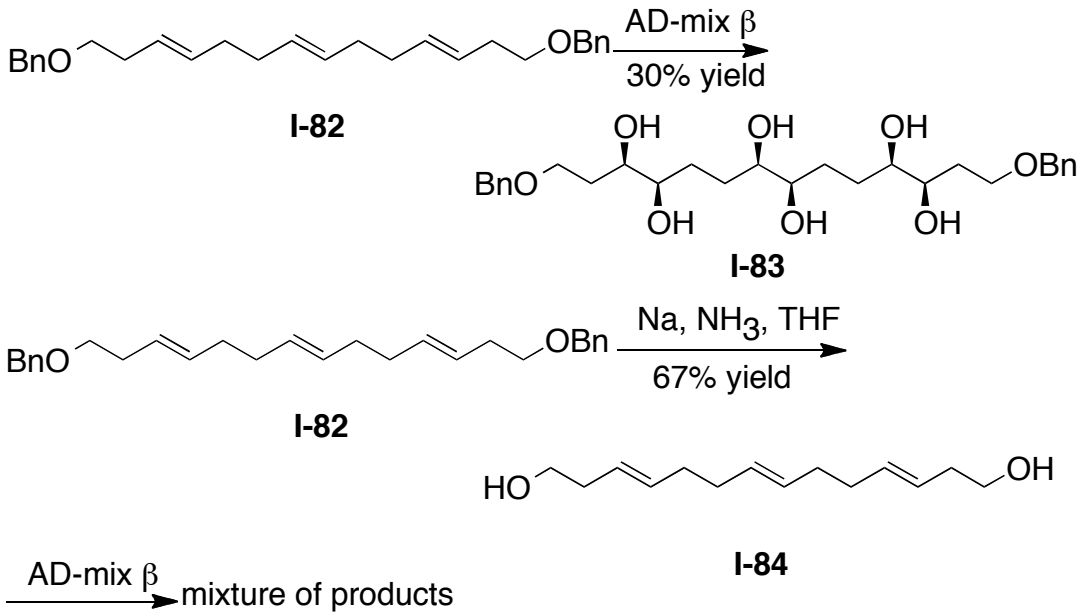
Scheme I-16: Synthesis of homo-allylic iodide **I-80**

The synthesis of side chain started by esterification of *trans*-hydromuconic acid followed by LAH reduction. Mono-benzylation of **I-78** with NaH and benzyl bromide at refluxing conditions provided the desired alcohol **I-79** in 52% yield. Iodination reaction of **I-79** afforded **I-80** in good yield (Scheme I-16).



Scheme I-17: Synthesis of triene

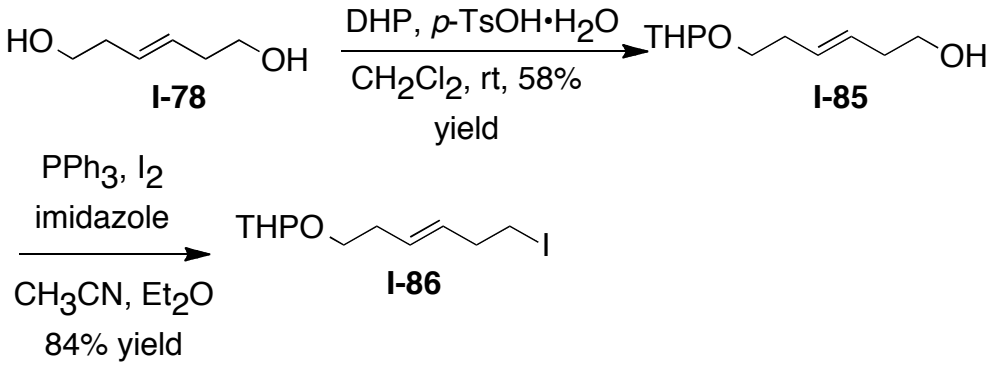
The next attempt to synthesize the triene required zinc activation of the iodinated side fragment **I-81** to couple with diiodoethylene and two side fragments together using



Scheme I-18: SAD reaction of triene

palladium (Scheme I-17).

The subsequent Sharpless Asymmetric Dihydroxylation (SAD) using AD-mix-β proceeded **I-83** in 30% yield as the major product without showing any regio- and enantio-selectively. With the failure of the selective SAD reaction, we next deprotected benzyl group of **I-82** to afford diol **I-84**. SAD reaction of diol **I-84** gave a mixture of different products (Scheme I-18).

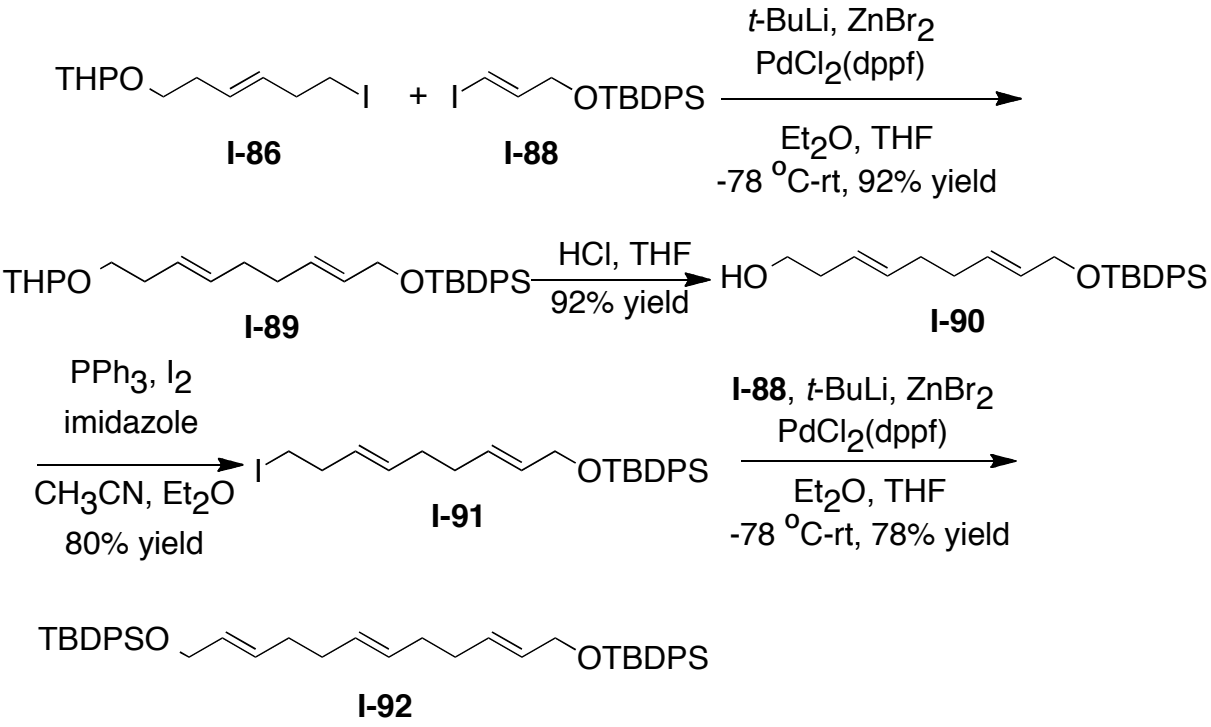


Scheme I-19: Synthesis of homo-allylic iodide **I-86**

With the failure of selective SAD reaction, we next turned to change the alcohol protective group to a bulkier one such as TBDPS and closer to the sides of the double bond (by removing one methylene) to see if a selective SAD reaction of middle double bond. For this purpose we change our pathway to avoid the low yield in synthesis of diiodoethylene **I-76**. Our methodology for this synthesis is described in the following. We started with mono-THP protection and iodination of diol **I-78** to provide the desired central fragment **I-86**, which was then coupled with vinyl iodide **I-88** (Scheme I-19).

Hydrozirconation of propargyl alcohol with Cp_2ZrCl_2/DIBAL-H and iodination provided the desired product **I-87** in 85% yield. TBDPS protection of the free alcohol **I-87** gave the desired vinyliodide **I-88** in excellent yield (Scheme I-20).

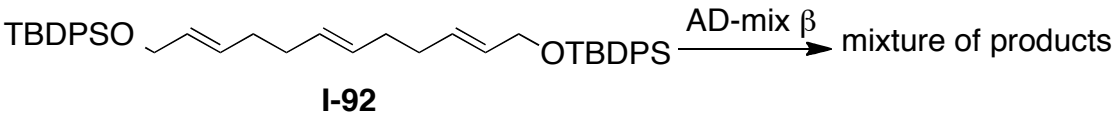
Then, synthesis of the desired triene by sp^3-sp^2 cross-coupling reaction was considered. For this purpose, Negishi coupling could be used to form the desired carbon-carbon bond. Thus, homoallylic iodide **I-86** and vinyliodide **I-88** was converted to the corresponding diene **I-89** under Negishi condition followed by THP deprotection, iodination and another Negishi coupling with **I-88** (Scheme I-21).



Scheme I-21: Synthesis of di-TBDPS protected of triene

At this point, Sharpless Asymmetric Dihydroxylation (SAD)[82] of the middle double bond, with TBDPS protected alcohols also failed (Scheme 22). However, Sharpless

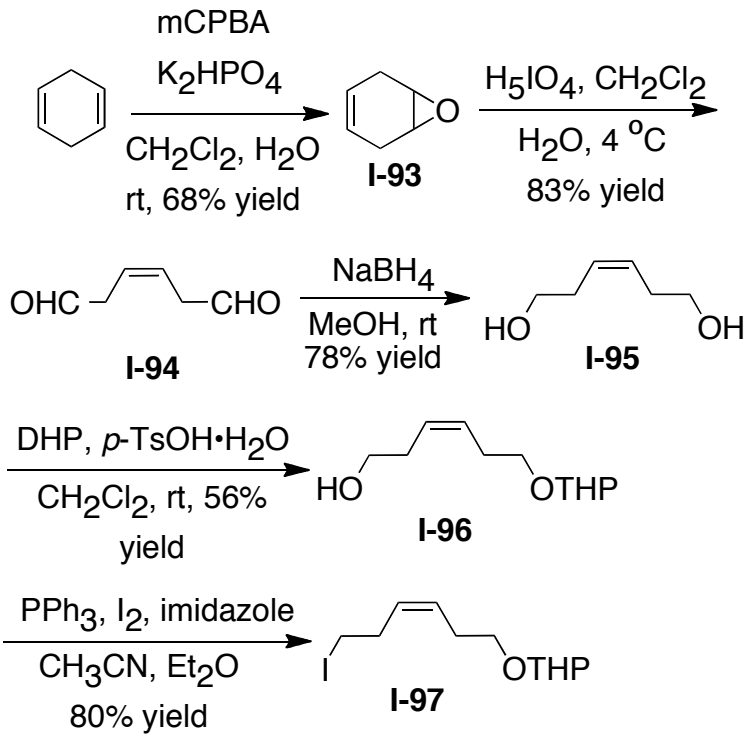
Asymmetric Dihydroxylation (SAD)[82] was achieved selectively at the central double bond where there is an ester on both ends of triene.[103]



I-92

Scheme I-22: SAD reaction of **I-92**

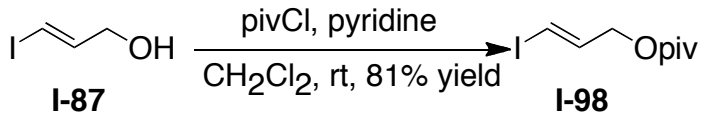
Therefore, the future work for the synthesis of the triene can be based on having two different esters on both ends of the triene. To accomplish this, we tried to make the



Scheme I-23: Synthesis of homo-allylic iodide **I-97**

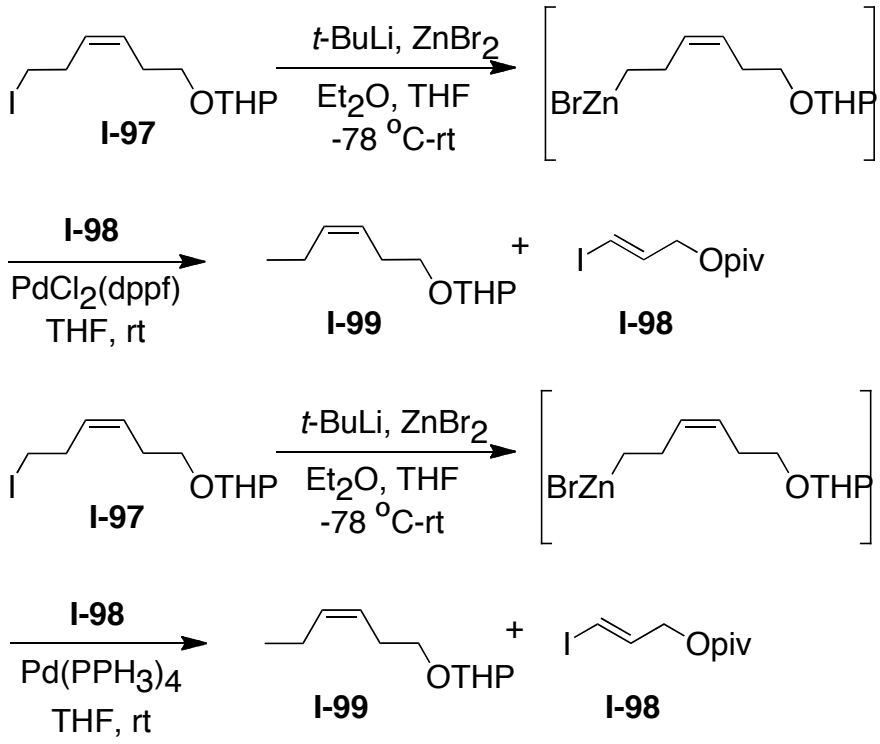
cis-isomer of **I-86** by the following method. Mono-epoxidation of 1,4-cyclohexadiene provided 68% yield of the desired product **I-93**. Next, oxidation of epoxide to dialdehyde was considered followed by reduction with $NaBH_4$. After reducing the dialdehyde to the

diol, mono-protection of diol **I-95** proceeded smoothly. Iodination of alcohol led to the homo-allylic alcohol **I-97** (Scheme I-23).



Scheme I-23: Piv protection of **I-87**

For synthesis of desired vinyl iodide, Piv protection of **I-87** was applied (Scheme I-23). Negishi conditions were applied for coupling of homo-allylic iodide **I-97** and vinyl

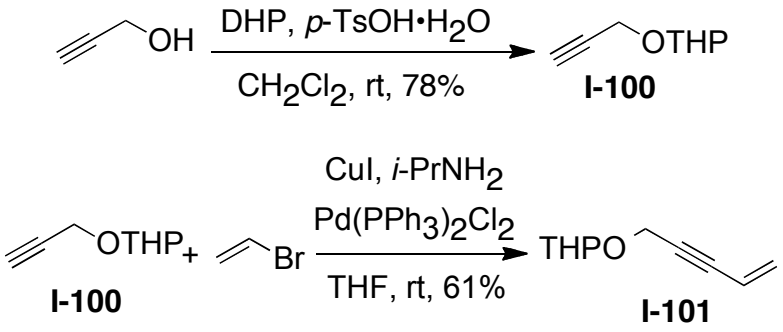


Scheme I-24: Attempts for Negishi reaction of **I-97** with vinyl iodide **I-98**

iodide **I-98** in the presence of $PdCl_2$(dppf) as a catalyst. The result did not show any desired coupling product and gave compound **I-99** that was the result of protonation of alkyl zinc bromide which presumably occurred in the work up. Changing of the catalyst

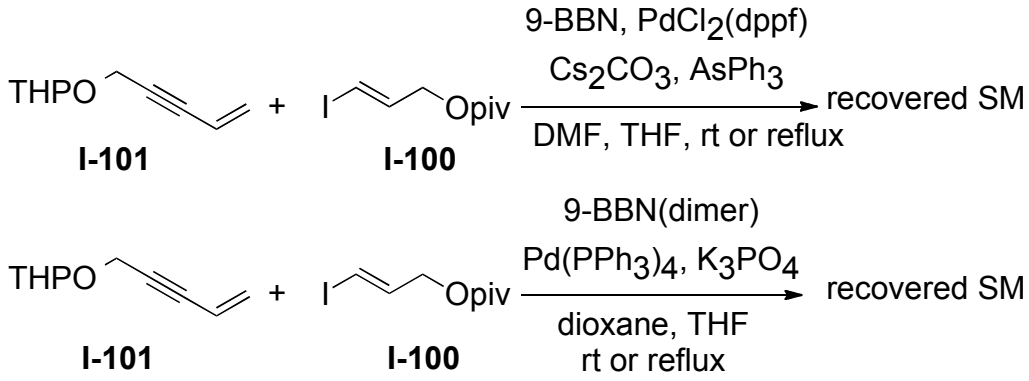
to $Pd(PPh_3)_4$ did not change the results, yielding **I-99** again as the product (Scheme I-24).

With the failure of above Negishi coupling, we next turned to the Suzuki coupling of vinyl iodide **I-98**. Sp^2-Sp coupling of THP protected propargyl alcohol **I-100** and vinyl bromide should provide the desired central fragment **I-101**, which could then be coupled with vinyl iodide **I-98** (Scheme I-25).



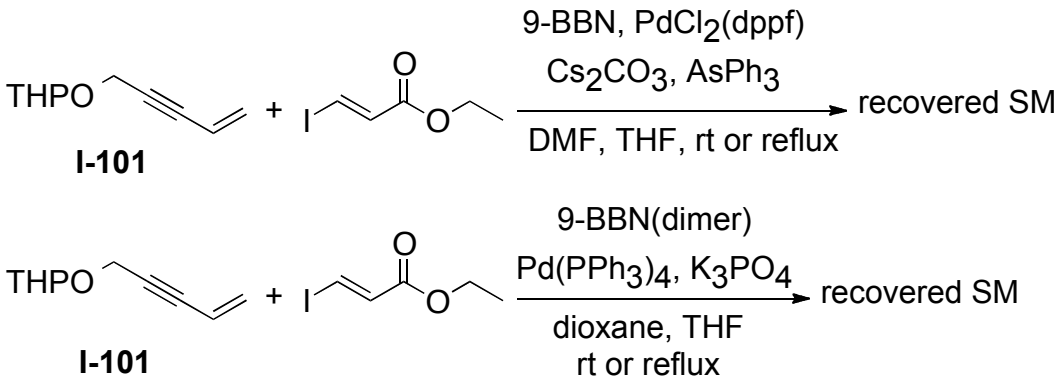
Scheme I-25: Synthesis of **I-101**

As shown in Scheme I-26, Suzuki coupling of vinyl iodide **I-100** and **I-101** in the presence of 9-BBN and $PdCl_2(dppf)$ as a catalyst failed and starting material was



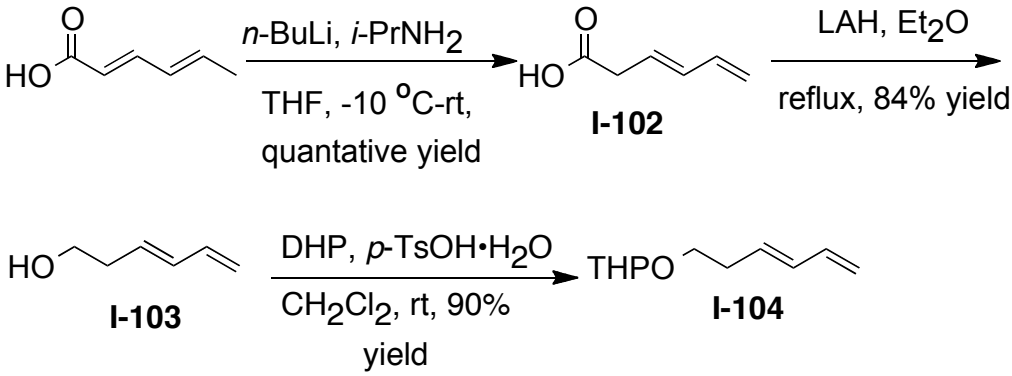
Scheme I-26: Attempts for Suzuki reaction

recovered. Changing the boron source to 9-BBN (dimer) and $Pd(PPh_3)_4$ as a catalyst, also failed and starting material was again recovered (Scheme I-26).



Scheme I-27: Attempts for Suzuki reaction

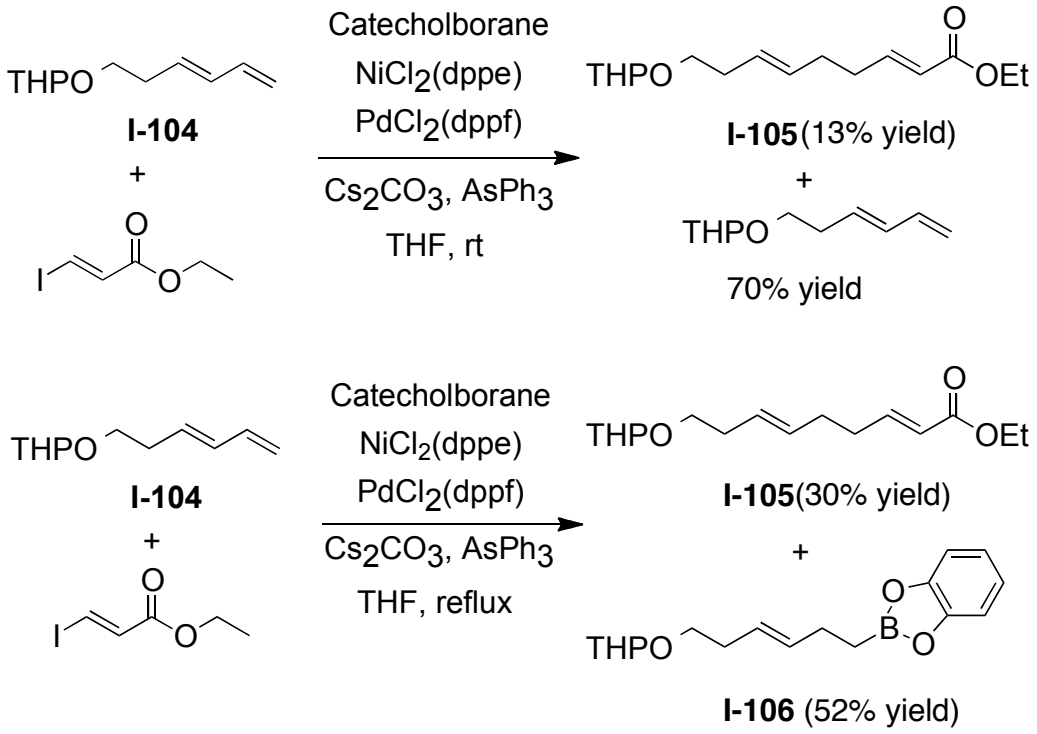
The piv protecting group in vinyl iodide **I-100** was changed to other groups to further explores the Suzuki reaction. We used commercially available (*E*)-ethyl 3-iodoacrylate to have an ester vinyl iodide instead of a reverse ester. Suzuki coupling reaction was attempted under different conditions (Scheme I-27). Neither 9-BBN with $PdCl_2(dppf)$ nor 9-BBN (dimer) with $Pd(PPh_3)_4$ gave any product. In 1997, Zaidlewics and coworker



Scheme I-28: Synthesis of diene **I-104**

reported the monohydroboration of conjugated dienes with catecholborane catalyzed by nickel(II) chloride with good selectivity and yield.[104]

To use the same conditions, conjugated diene **I-104** was prepared in three steps starting with a conjugated acid ((2*E*,4*E*)-hexa-2,4-dienoic acid) which was deconjugated by kinetic protonation of its extended enolate. LAH reduction of acid **I-102** and THP



Scheme I-29: Synthesis of Suzuki coupling

protection provided diene **I-104** in 90% yield (Scheme I-28). The coupling reaction was attempted under the same reported condition. The reaction at room temparature was attempted and we isolated the desired coupled product in 13% yield, with 70% of diene **I-104** isolated as well. Isolation of starting material, suggests that the problem of low yield resides with hydroboration step. This reaction under reflux condition proceeded to

yield 30% of desired product **I-105** and 52% of hyroboration product **I-106** was isolated without any trace of diene **I-104** (Scheme I-29). The latter result indicates that the hydroboration problem was solved by refluxing the reaction, however, the coupling step is still problematic.

I.4 Sulfone Coupling

The sulfone-stabilized carbanion is an efficient nucleophile to couple with alkyl or allyl halides in carbon-carbon bond forming reactions.[105] Since, attempts to perform the

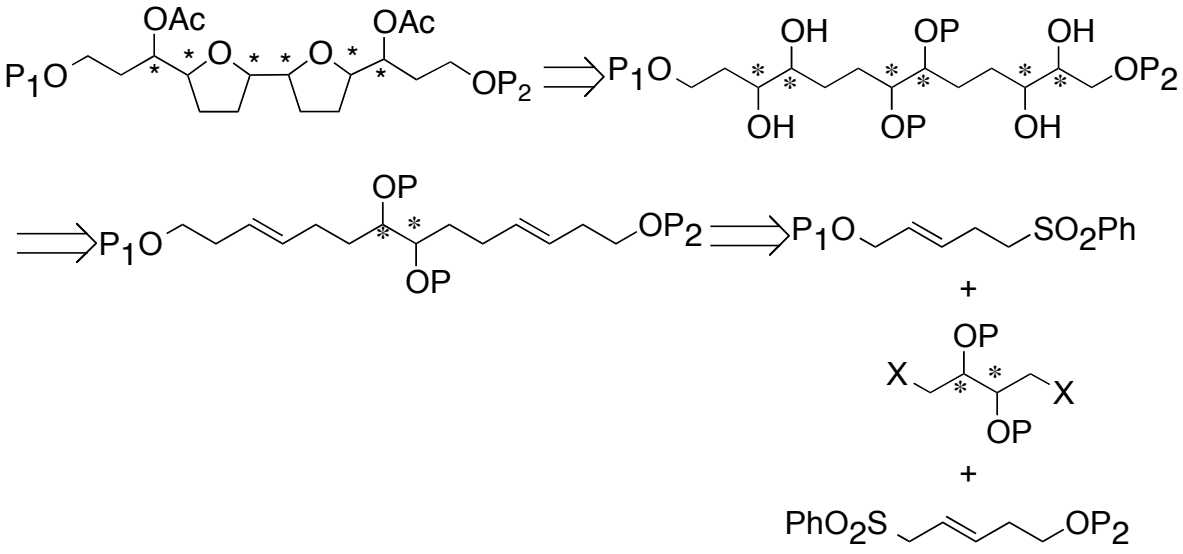
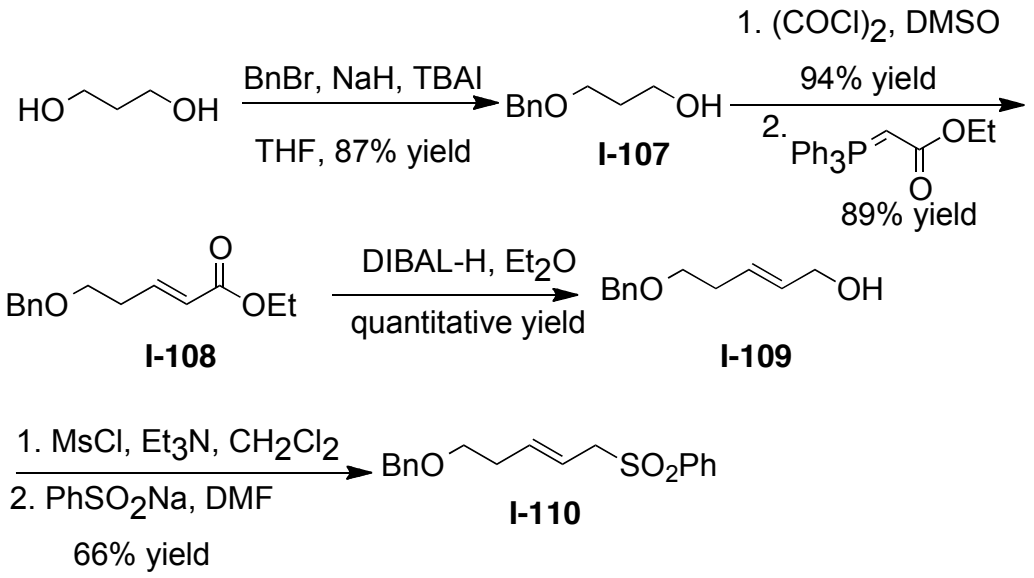


Figure I-27: Retro-synthesis of sulfone coupling

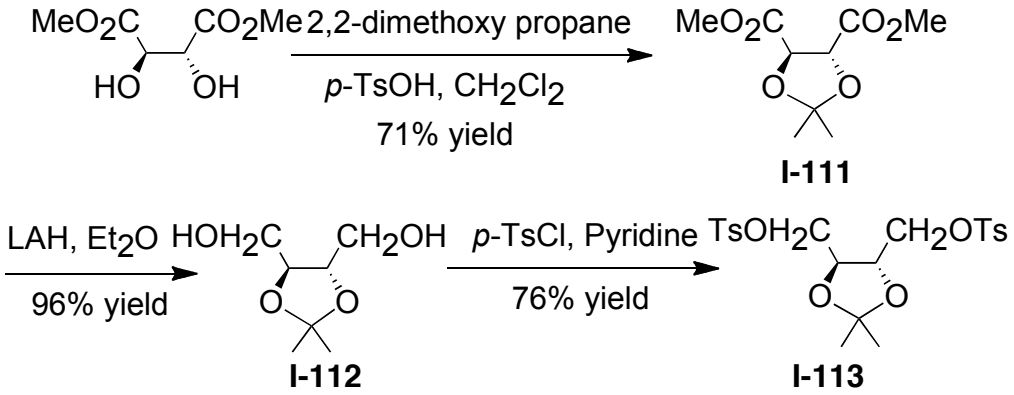
carbon-carbon bond formation by sp^3-sp^2 coupling failed, we next turned to coupling of sulfone with alkyl halide. Our retro-synthesis is outlined in Figure I-27. The protected alcohol was established in the middle before coupling, since we knew the SAD reaction of the triene is not selective for the center double bond.

Our studies began with the synthesis of sulfone **I-110**. 1,3-Propandiol was treated with sodium hydride and benzyl bromide to give mono-protected alcohol **I-107** in 87%



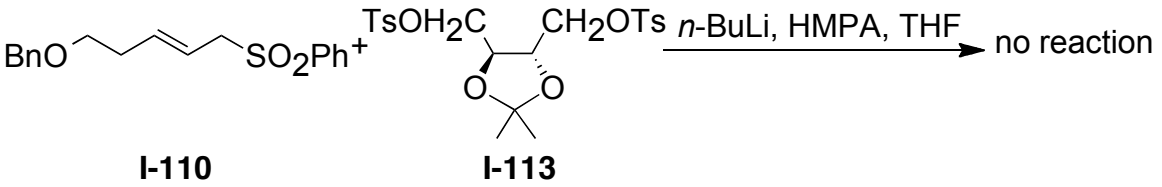
Scheme I-30: Synthesis of sulfone **I-110**

yield. The following Swern oxidation and Wittig olefination afford compound **I-108**. The ester group was successfully reduced under DIBAL-H condition and the sulfonation of alcohol **I-109** occurred uneventually (Scheme I-30).



Scheme I-31: Synthesis of **I-113**

Next, the synthesis of the mid-section was carried out. Since selective SAD reaction of triene failed, we started our synthesis with L-dimethyl tartrate with the stereochemistry of the center diol in place. Acetonide protection of L-dimethyl tartrate under acidic condition followed by LAH reduction gave **I-112** in 96% yield. The corresponding diol was activated as a tosyl group as it is a good leaving group for sulfone coupling (Scheme I-31).

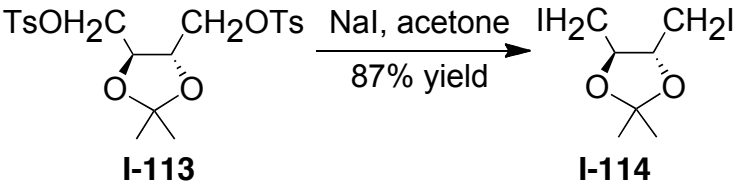


I-110 **I-113**

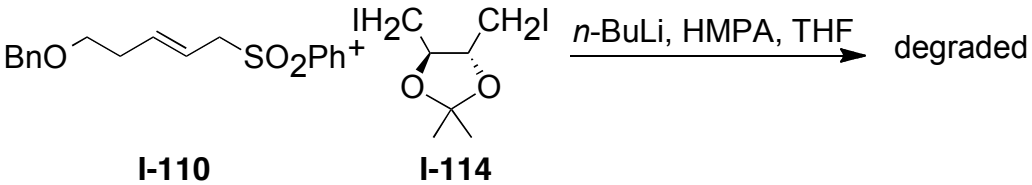
Scheme I-32: Attempts for sulfone coupling

The coupling between sulfone **I-110** and **I-113** was tried in basic condition by using *n*-BuLi as the base in the presence of HMPA. There was no reaction even after 24 h, both starting materials were recovered (Scheme I-32).

The major problem in the failed sulfone coupling reaction is due to the tosyl



I-113 **I-114**

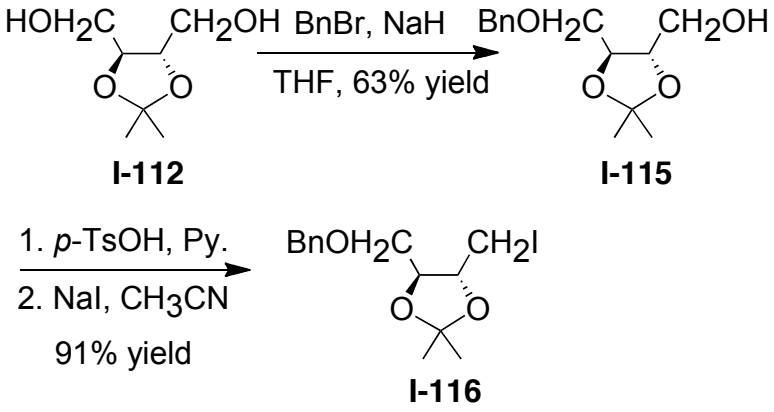


I-110 **I-114**

Scheme I-33: Synthesis of diiodide **I-114** and attempts for sulfone coupling

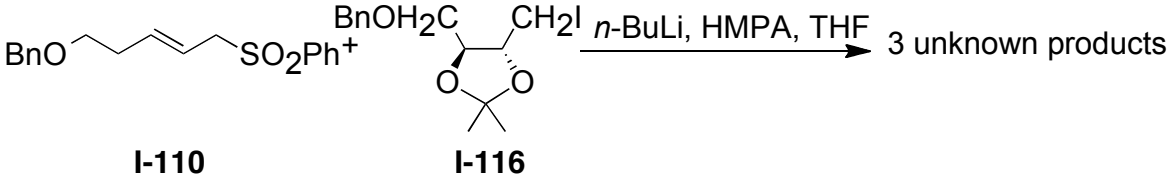
protecting groups of **I-113**. So, to solve this problem, we converted the tosyl protected alcohols in **I-113** to the corresponding diiodide to have a better leaving group for the coupling (Scheme I-33). After treating sulfone **I-110** with diiodide **I-114**, the reaction is degraded and none of the starting materials were isolated (Scheme I-33).

The failure of the coupling reaction might be the result of having two iodides in **I-114**. We synthesized mono iodide compound to be sure that the substrate has just one reactive



Scheme I-34: Synthesis of alkyl iodide **I-116**

site. Diol **I-112** was monobenzylated, followed by iodination of the tosyl protected alcohol to provide the desired iodide **I-116** in 91% yield (Scheme I-34).

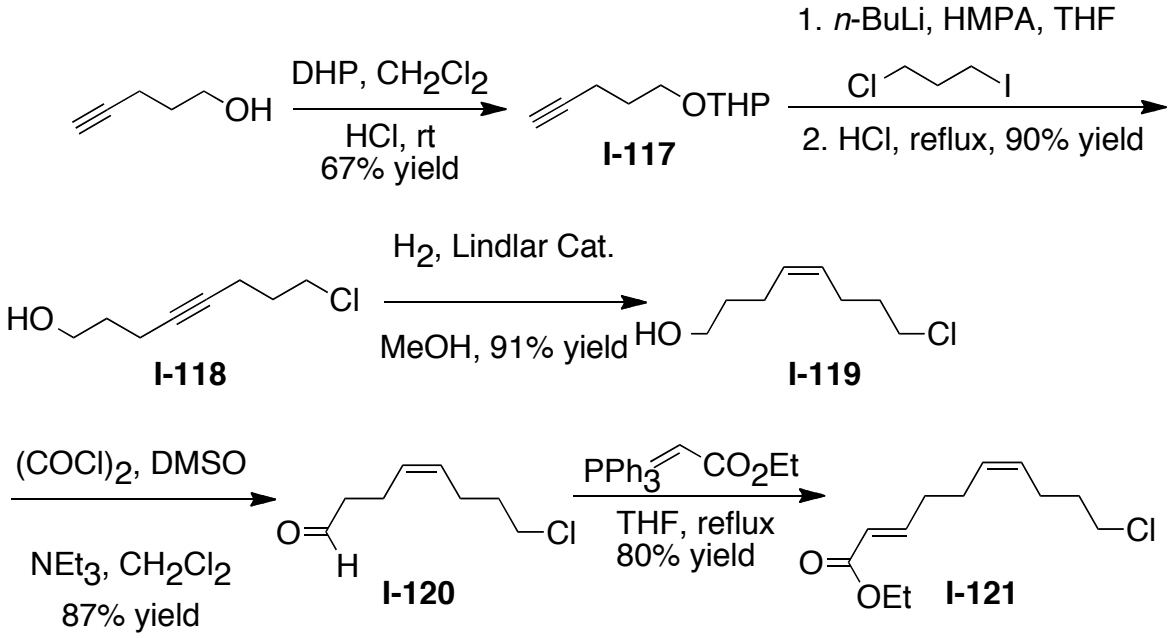


Scheme I-35: Attempts for sulfone coupling

The coupling reaction of sulfone **I-110** with **I-116** led to the production of three unknown products (Scheme I-35).

I.5 Total Synthesis of the Center THF Core

At this point, we decided to synthesze one of the center THF cores with two different alcohol protecting group on the two ends of the core to minimized problems with etherification in future steps. For this purpose, we started our synthesis with



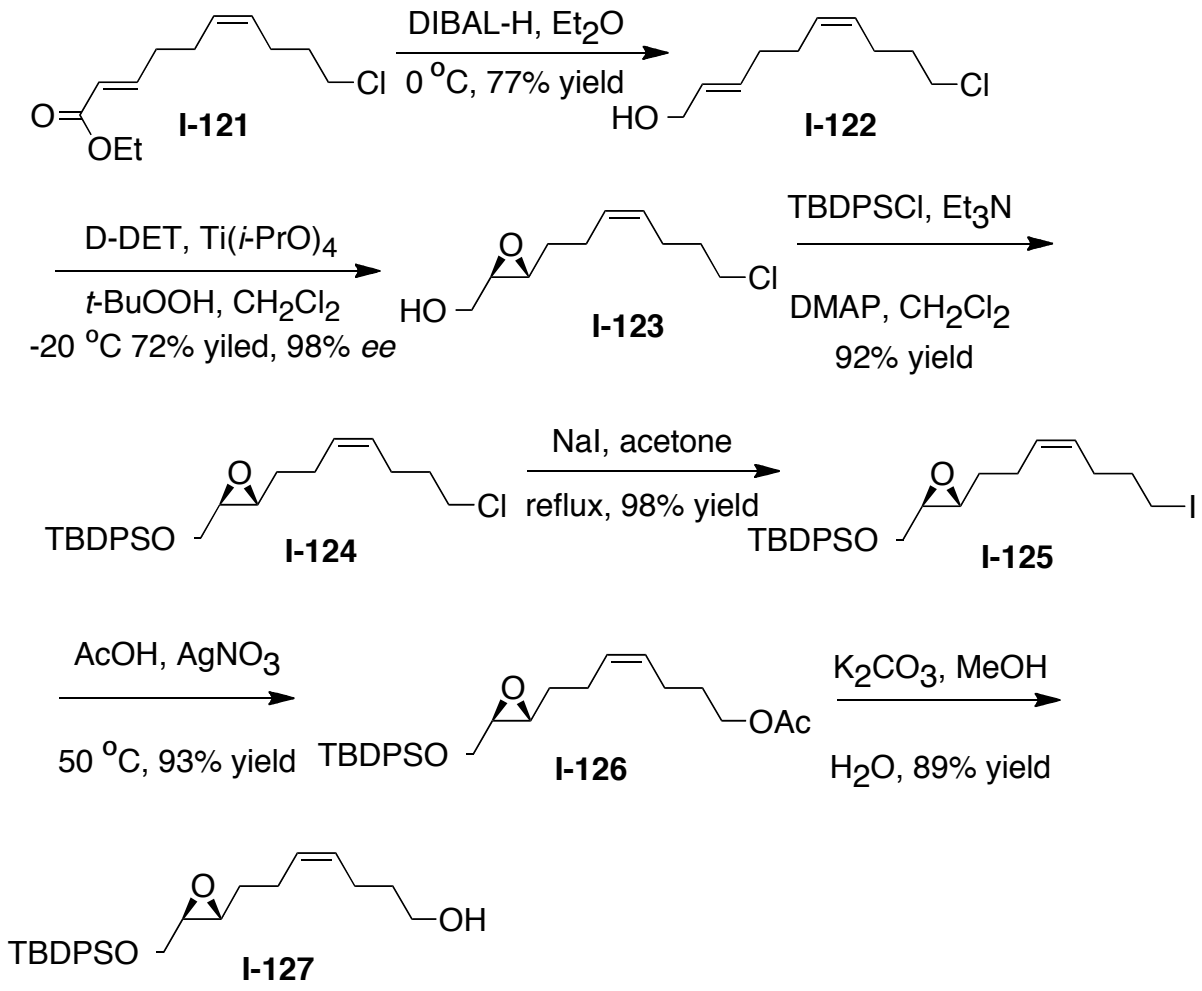
Scheme I-36: Synthesis of α,β–unsaturated ester **I-121**

4-pentyn-1-ol shown in Scheme I-36. THP protection of 4-pentyn-1-ol gave the THP ether **I-117**, which after coupling with commercially available 1-chloro-3-iodopropane, and subsequent THP deprotection yielded alcohol **I-118**. Lindlar hydrogenation of the triple bond and Swern oxidation of the alcohol provided the *cis*-aldehyde **I-120**. Wittig olefination of **I-120** afforded the corresponding α,β–unsaturated ester **I-121** in good yield (80% yield).

DIBAL reduction of the ester and Sharpless Asymmetric Epoxidation (SAE)[83] of the side double bond provided the desired epoxide in excellent enantioselectivity (98% *ee*).

TBDPS protection of alcohol **I-123** gave **I-124**, which upon Finkelstein reaction, subsequent, nucleophilic attack of acetate, and hydrolysis provided **I-127** (Scheme I-37).

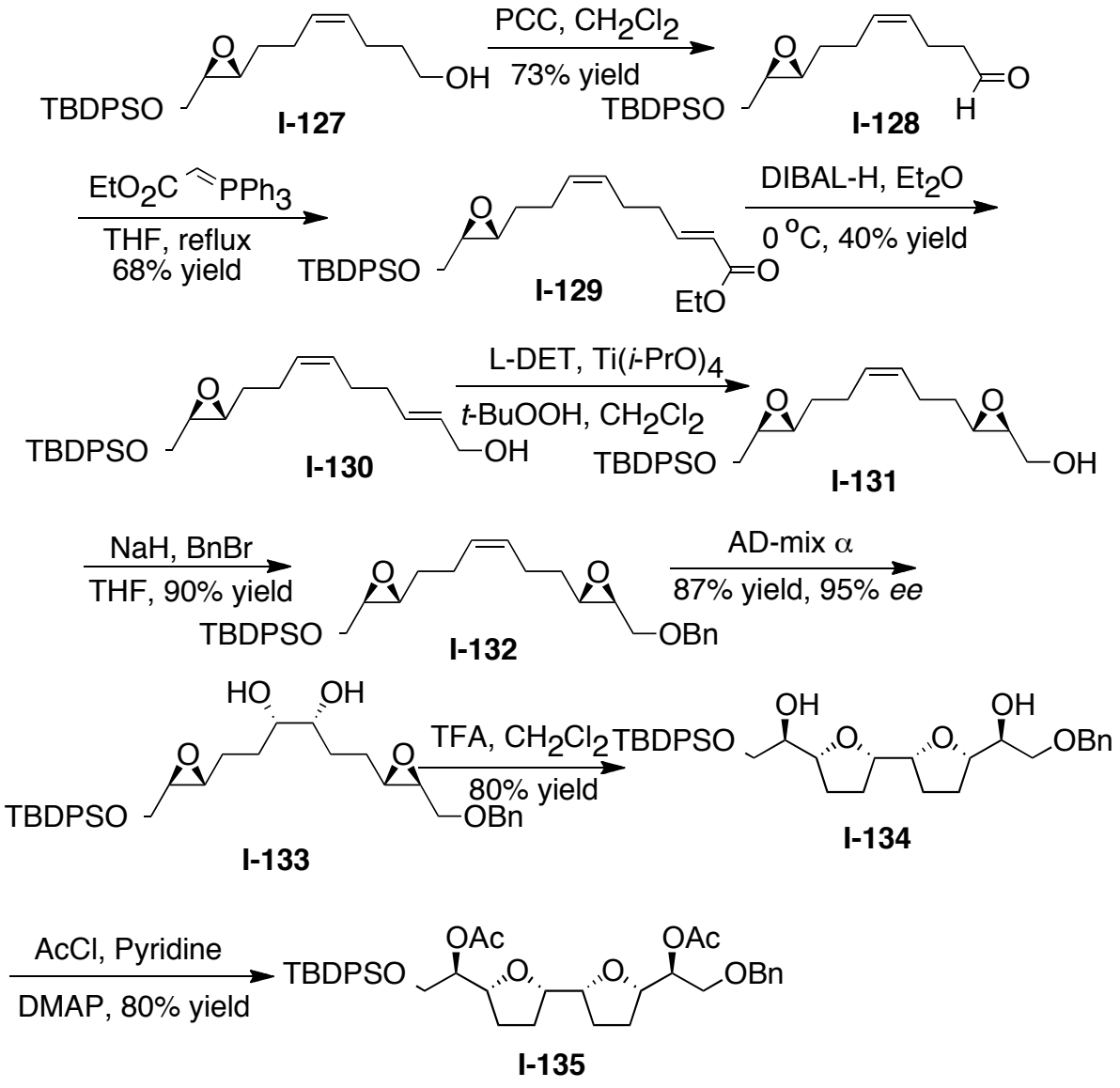
PCC reduction and Wittig olefination of alcohol **I-127** provided the desired



Scheme I-37: Synthesis of alcohol **I-127**

α,β−unsaturated ester **I-129** in moderate yield (68%). After converting the ester **I-129** to the required allyl alcohol **I-130**, the SAE reaction[83] led to the formation of the desired diepoxide **I-131** in 75% yield (97% *ee*), which could be cleanly separated from a 10% recovery of starting material. Benzylation of the alcohol and Sharpless Asymmetric

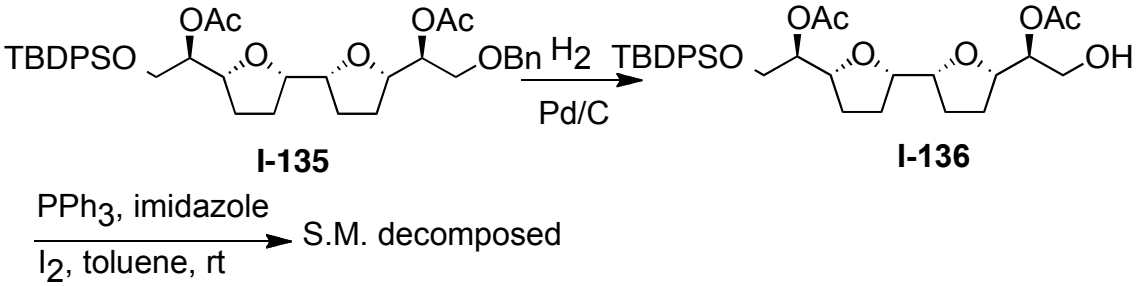
Dihydroxylation (SAD)[82] gave **I-133**, which was treated with trifluoroacetic acid[106] to produce the THF core **I-134** (Scheme I-38). Next, we protected the free diol with an acetate group to have the desired THF core for the etherification reactions.



Scheme I-38: Synthesis of desired THF core **I-135**

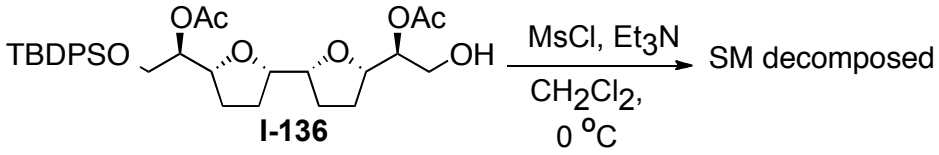
I.6 Etherification of Bis-Adjacent THF Core

Our goal is to develop a quick and efficient pathway to synthesize the bis-adjacent THF core with different stereochemistries for providing a possibility for the library synthesis of ether linked analogs of acetogenins. However, before we run the library



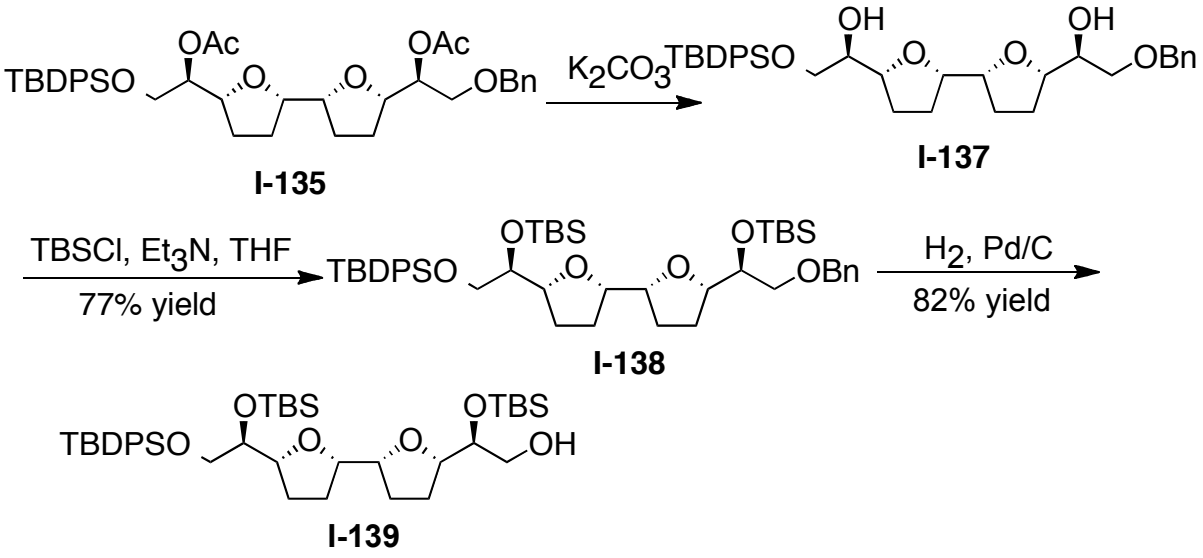
Scheme I-39: Conversion of primary alcohol to iodide

synthesis and install different functional groups to either side of the bis-adjacent THF core, it is important to optimize the conditions for the etherification reaction. For this purpose, we made bis THF ring **I-135** to optimize the etherification reaction. The first



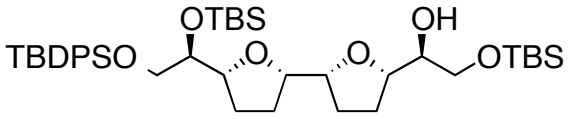
Scheme I-40: Attempts for conversion of primary alcohol **I-136** to mesylate

idea for the etherification reaction was to convert the terminal hydroxyl group after deprotection in the bis-adjacent THF core to a good leaving group such as an iodide. Then the subsequent S_N2 displacement using different nucleophiles could install different functional groups in both sides of the bis-THF core. However, the conversion of hydroxyl



Scheme I-41: Synthesis of alcohol **I-139**

groups to iodides in substrate **I-136**, which was formed via hydrogenolysis of the benzyl groups in intermediate **I-135**, was not successful and the messy crude NMR showed that the starting material decomposed under these conditions (Scheme I-39). The mesylation of alcohol **I-136** using triethylamine and mesyl chloride in dichloromethane was not successful also and the starting material decomposed. The reason can be the instability of the acyl groups under basic condition (Scheme I-40). An alternate way for the etherification was to use the bis-adjacent THF core as the nucleophile in the etherification reaction. Since acyl groups are not stable under basic conditions, the protecting groups were changed and the alcohols were protected as TBS ethers (Scheme I-41). Some of the experiments and the results for the etherification reactions are summarized in Table I-10.

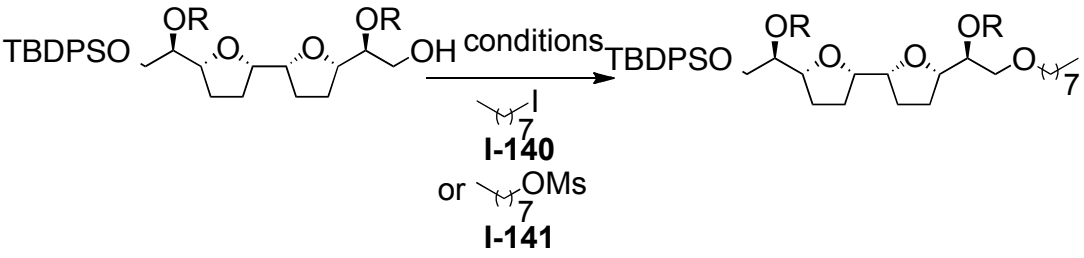


I-142

Figure I-28: Silyl migration product under basic conditions

With sodium hydride as the base, for the substrates **I-140** and **I-141** no desired products were obtained (Table I-10, entries 1 and 3). Instead, silyl migration of 1,2-diols under basic conditions occurred, which gave the secondary free alcohols as the product

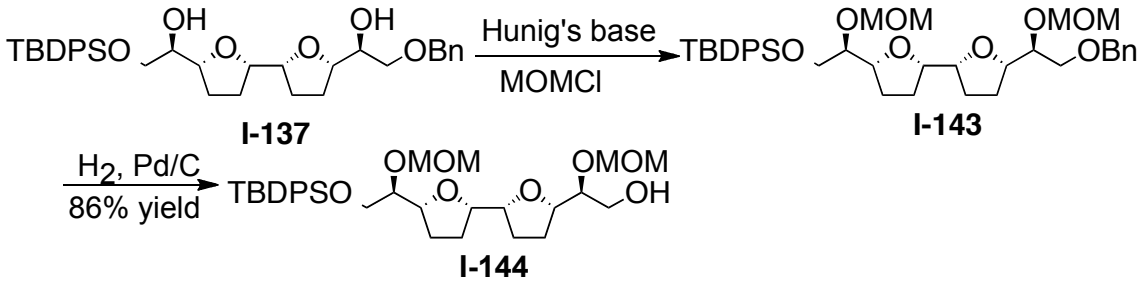
Table I-10: Experiments for etherification reactions



Entry	R	Reagents		Temperature	Solvent	Results
1	TBS	**I-140**	NaH	0 °C to RT	THF	**I-142**
2	TBS	**I-140**	K_2CO_3	reflux	acetone	**I-142** + SM
3	TBS	**I-141**	NaH	0 °C to RT	THF	**I-142**
4	Ac	**I-140**	NaH	0 °C to RT	THF	S.M. decomposed
5	Ac	**I-141**	NaH	0 °C to RT	THF	S.M. decomposed

(Figure I-28). However, after changing the TBS groups to acyl groups, the same conditions decomposed the starting material (Table I-10, entries 4 and 5). Potassium

carbonate in refluxing acetone could not promote the reaction; after overnight stirring only **I-142** along with some starting material were isolated (Table I-10, entry 2). It seems that the major problem in the failed etherification reactions is due to the protecting groups on the secondary alcohols. It is possible that the steric bulk of the protecting group on the secondary alcohols can hinder the etherification of the neighboring primary alcohol. In addition, silyl groups are not good under basic etherification conditions because they preferred to migrate from the secondary alcohols to primary alcohols. Therefore, a less hindered protecting group such as methoxy methyl (MOM) was chosen to prevent these problems. The synthesis of new bis-adjacent THF substrate **I-144** was achieved via MOM protection of intermediate **I-137**, followed by debenzylation via hydrogenolysis in excellent yield over two steps (Scheme I-42).

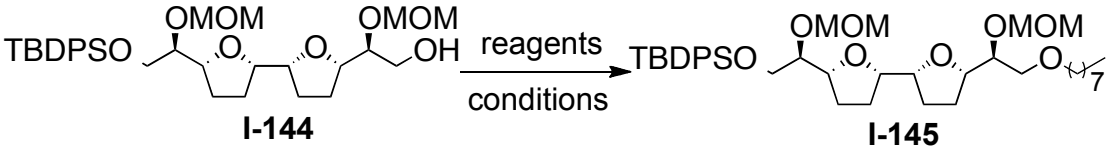


Scheme I-42: Synthesis of MOM-protected bis-adjacent THF core **I-144**

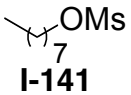
Treatment of intermediate **I-144** under etherification conditions provided the desired product in low yield (Table I-11). Increasing the amount of sodium hydride and mesylate improved the yield of the etherification (Table I-11, entry 2). DMF was a better solvent under the same conditions. By changing the reactant from mesylate to iodide the yield dropped to 28% (Table I-11, entry 4).

At this point, it seemed that the major problem in the etherification reactions was having the protected secondary alcohols neighboring the primary alcohols (the reaction side). For solving this problem, we thought it is better to have primary alcohol one carbon further away from the protected secondary alcohol to avoid any silyl migration and low conversions.

Table I-11: Etherification reactions of **I-144**



I-144 **I-145**

Entry	NaH	Mesylate or Iodide	Solvent	Temperature	Yield (%)
1	3.0 equiv	3.0 equiv	THF	0 °C to reflux	32
2	8.0 equiv	 **I-141**	4.0 equiv	THF	0 °C to reflux	36
3	8.0 equiv	4.0 equiv	DMF	0 °C to 50 °C	40

I.7 General Pathway for the Synthesis of Different Analog of Center THF Core

The general pathway for the synthesis of the ether linked analog of the central THF core is outlined in Figure I-29. We planned to connect the two sides with the center moiety via alkyne coupling. The bis THF rings would be formed using our 1,2,*n*-triol cyclization methodology from intermediate **I-147**.[79] The tetraol **I-147** could be derived from the SAD reaction[82] of **I-148** after reducing the triple bonds to *cis* or *trans* double

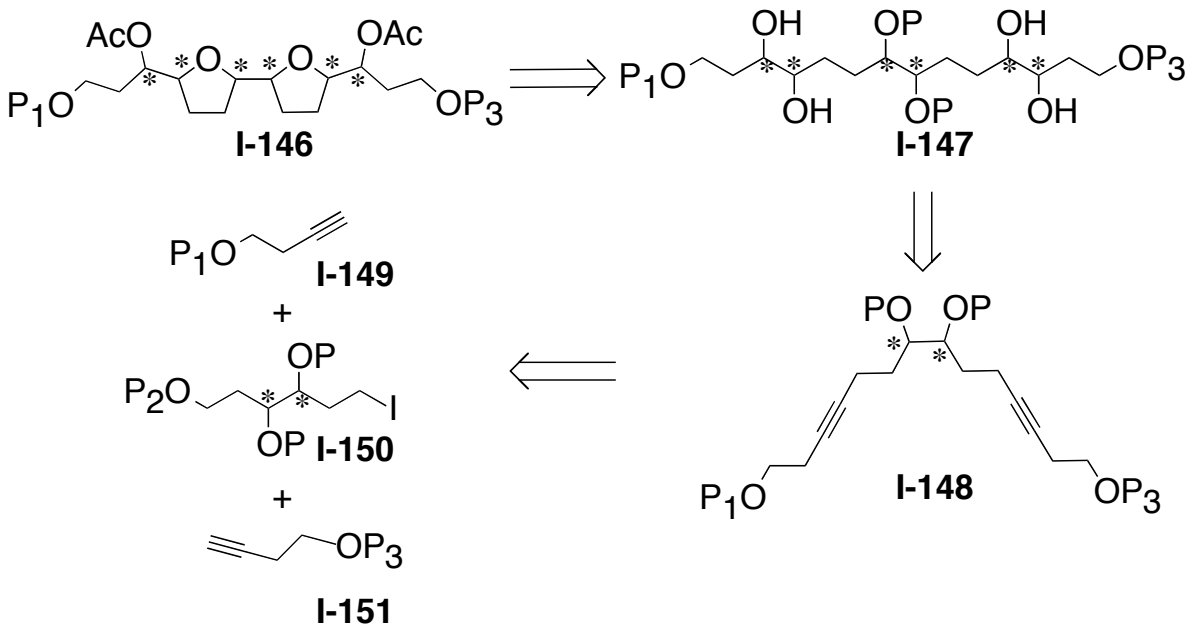
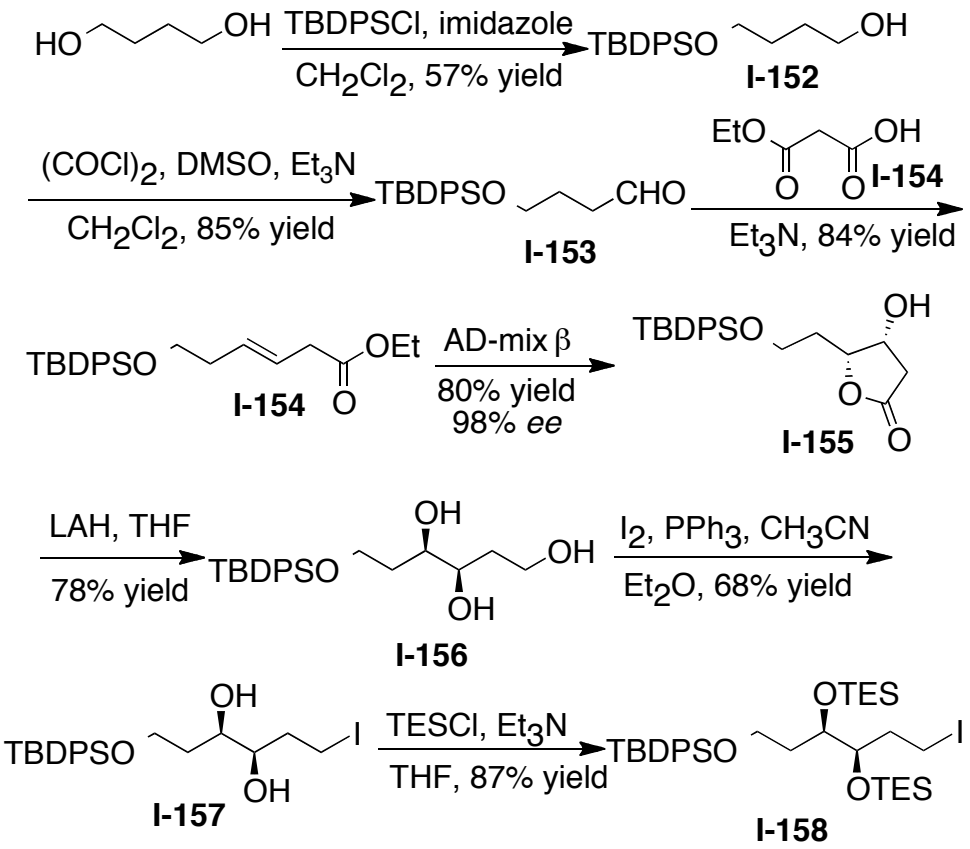


Figure I-29: Retro-synthetic analysis for eher linkage analog of bis-adjacent THF core **I-146**

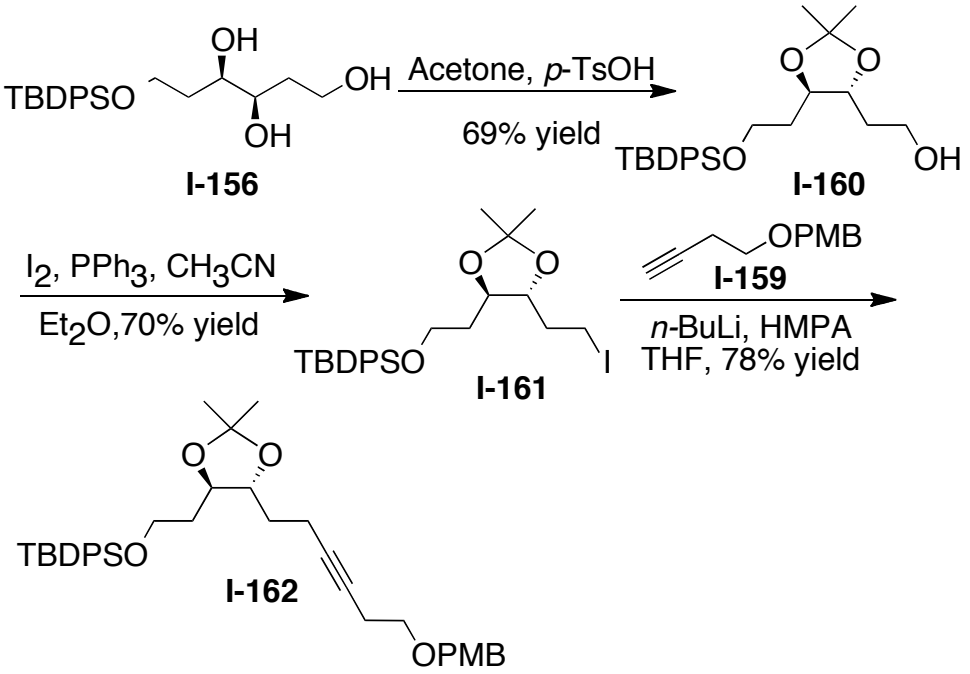
bonds. The dialkyne **I-148** would be accessed by alkyne coupling with alkyl iodide **I-150** derived from the commercially available 1,4-butanediol. Homoallylic protected alcohols **I-149** and **I-151** could also be derived from protection of 3-butyn-1-ol.

The synthesis of one derivative of alkyl iodide **I-150** is shown in Scheme I-43. Mono TBDPS-protection of commercially available 1,4-butanediol gave the alcohol **I-152**, which after Swern oxidation yielded the aldehyde **I-153**. Reaction of **I-153** with monoethyl malonate under basic condition provided the *trans* ester **I-154**. Sharpless asymmetric dihydroxylation[82] of **I-154** afforded the corresponding lactone in excellent yield and enantioselectivity (80% yield and >99% *ee*). LAH reduction and iodination of the primary alcohol gave **I-157**, which was protected as TES ethers to form iodide **I-158**. PMB protected homopropargyl alcohol **I-159** was synthesized and subjected to iodide



Scheme I-43: Synthesis of alkyl iodide **I-158**

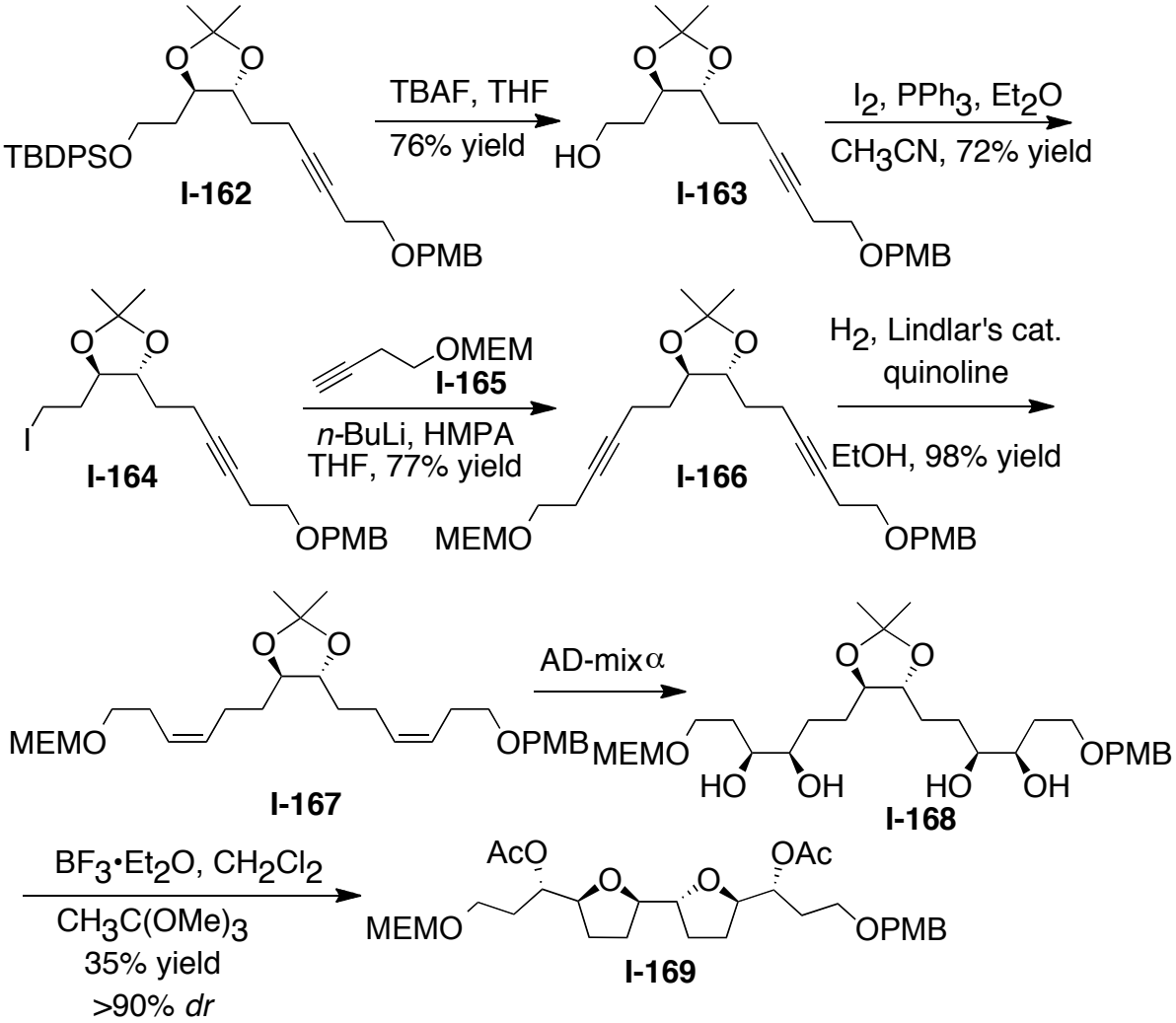
I-158 in a coupling reaction. Iodide **I-158** decomposed under coupling conditions and no desired product was obtained. The lack of success was probably due to the instability of the TES groups under basic conditions. After converting the TES protecting groups to acetonide **I-160**, followed by iodination, the coupling reaction provided the desired product in 78% yield (Scheme I-44). The final stages of the synthesis of the bis THF core are shown in Scheme I-45. Deprotection of the TBDPS group followed by iodination of free alcohol provided iodide **I-164**. The coupling of iodide **I-164** and MEM protected homopropargyl alcohol **I-165** was promoted with *n*-butyllithium in a THF/HMPA mixture. Hydrogenation with Lindlar catalyst followed by the Sharpless asymmetric



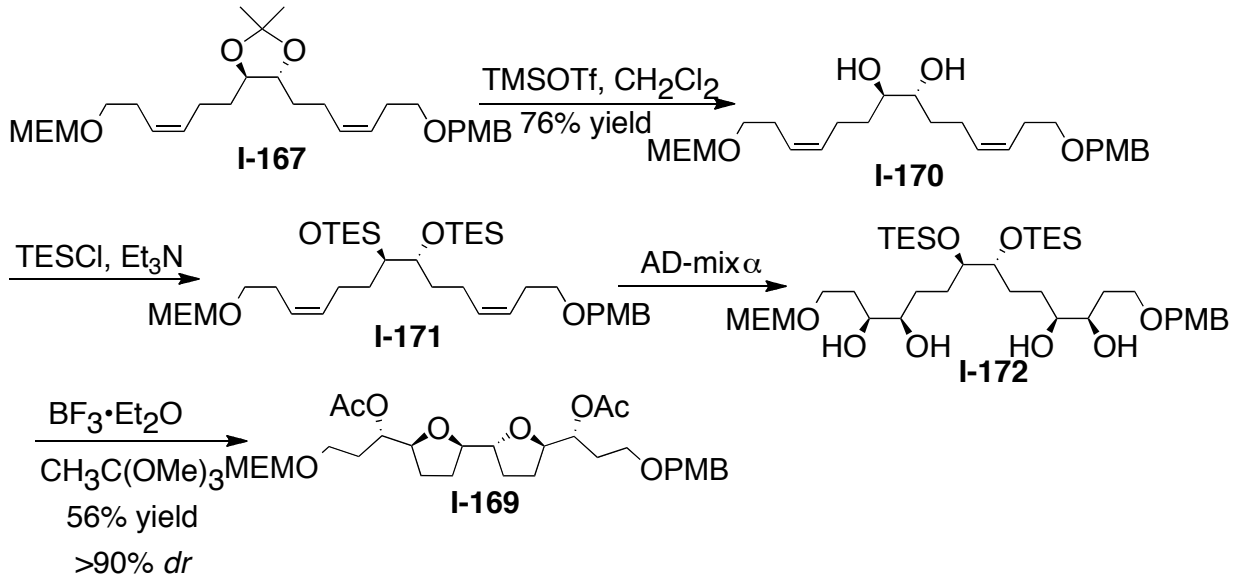
Scheme I-44: Coupling of iodide **I-161** with **I-159**

dihydroxylation[82] gave the desired tetraol **I-168**. Construction of the bis THF unit was achieved via the 1,2,*n*-triol cyclization mediated with BF_3•OEt_2[79] (Scheme I-45) in low yield (35% and >90% *dr*), producing three other undetermined products as well.

One hypothesis for why this reaction only affords low yield was that the acetonide protecting group could not be successfully deprotected before cyclization in the presence of BF_3•Et_2O as a Lewis acid, thus cyclization of **I-168** did not occur. In order to solve this problem, we changed the acetonide protecting group to TES. The newly formed compound **I-171** was subjected to the Sharpless asymmetric dihydroxylation[82] and 1,2,*n*-triol cyclization[79] to provide the desired bis THF rings in 56% yield, along with two other undetermined products (Scheme I-46).



Scheme I-45: Synthesis of bis-THF core **I-169**



Scheme I-46: Synthesis of bis-THF core **I-169**

I.8 Summary

In conclusion, desymmetrization and etherification of the bis-adjacent THF core can be used to make ether linked analogs of acetogenins. Scheme I-46 depicts our strategy towards the synthesis of THF core. Utilization of ether linkages will enable the rapid synthesis of a library of acetogenin analogs with a variety of groups flanking the left and right side of the bis-adjacent THF core, which is very useful for the SAR study of acetogenins.

I.9 Experimental Section

Commercially available starting materials were obtained from Aldrich or Fluka and were used without further purification. Unless otherwise mentioned, solvents were purified as follows: tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone; methylene chloride (CH_2Cl_2) and toluene ($PhCH_3$) was dried over calcium hydride (CaH_2) and freshly distilled prior to use; DMF, DMSO, Et_3N, and HMPA were distilled from CaH_2 and stored over 4 Å molecular sieves. 4 Å molecular sieves were dried at 160 ^{o}C under vacuum prior to use. All of the spectral data for known compounds either match those reported by Aldrich or by comparison to the literature report.

^{1}H NMR spectra were measured at 300, 500 or 600 MHz on a Varian Gemini-300, a Varian VXR-500 or Varian Inova-600 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for $CDCl_3$). ^{13}C NMR spectra were measured at 75 MHz on a Varian Gemini-300, at 125 MHz on a Varian VXR-500 or 150 MHz on a Varian Inova-600 instrument. Chemical shifts are reported relative to the central line of $CDCl_3$ (δ 77.0 ppm). High resolution mass spectra were measured at the Michigan State University, Mass Spectrometry Laboratory. Optical rotations were measured on a Perkin-Elmer polarimeter (model 341) using a 1 mL capacity quartz cell with a 10 cm path length.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica

gel 60 F_{254} plates. Compounds were visualized with UV light, potassium permanganate stain, *p*-anisaldehyde stain or phosphomolybdic acid in EtOH. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 μm silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments. GC analysis was performed using HP (6890 series) GC system equipped with an Altech SE-54, 30 m × 320 μm × 0.25 μm column.

(4*R*,5*R*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate[107]

In a 1-L, one-necked, round-bottomed flask fitted with a reflux condenser and a large magnetic stirring bar under argon, a mixture of L-tartaric acid (101 g, 0.673 mol), 2,2-dimethoxypropane (190 mL, 161 g, 1.54 mol), methanol (40 mL), and *p*-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) is warmed on a steam bath with occasional swirling until a dark-red homogeneous solution is obtained. Additional 2,2-dimethoxypropane (95 mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) are added and the flask is fitted with a 30-cm Vigreux column and a variable reflux distilling head. The mixture is heated to reflux with internal stirring and the acetone–cyclohexane and methanol–cyclohexane azeotropes are slowly removed. Additional 2,2-dimethoxypropane (6 mL, 5.1 g, 49 mmol) is then added and the mixture heated under reflux for 15 min. After the mixture has cooled to room temperature, anhydrous potassium carbonate (1 g, 7.2 mmol) is added and the mixture is stirred until the reddish color has abated. Volatile material is removed under reduced pressure (water aspirator) and the residue is

fractionally distilled under vacuum to afford the product **I-65** as pale-yellow oil, (108 g, 74% yield).

Data for **I-65**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (2H, s), 4.20 (6H, s), 1.32 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.0, 113.8, 76.9, 52.7, 26.2.

((4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol[108]

In a dry, 2-L, three-necked, round-bottomed flask equipped with a 500-mL pressure-equalized addition funnel, a reflux condenser, a thermometer, and a large magnetic stirring bar is suspended lithium aluminum hydride (36 g, 0.95 mol) in diethyl ether (600 mL) under argon. The mixture is stirred and heated to reflux for 30 min. Heating is discontinued while a solution of **I-65** (123 g, 0.564 mol) in diethyl ether (300 mL) is added dropwise over 2 h. Heating is then resumed and the mixture is refluxed for an additional 3 h. The mixture is cooled to 0–5 ^{o}C and cautiously treated with water (36 mL), 4 *N* sodium hydroxide solution (36 mL), and water (112 mL). The mixture is then stirred at room temperature until the gray color of unquenched lithium aluminum hydride has completely disappeared. The mixture is filtered on a Büchner funnel and the inorganic precipitate is extracted with ether in a Soxhlet apparatus. The combined ethereal extracts are dried over anhydrous magnesium sulfate and filtered, and volatile material is removed under reduced pressure (water aspirator). The residue is fractionally distilled under vacuum to afford the product **I-66** as colorless oil (50 g, 55% yield).

Data for **I-66**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42-4.48 (2H, m), 3.80-3.83 (4H, m), 2.10

(2H, br.), 1.35 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ109.3, 78.3, 62.1, 27.0.

(2*S*,3*S*)-2,3-Dihydroxybutane-1,4-diyl dimethanesulfonate[109]

1. A dry, 1-L, round-bottomed flask equipped with a magnetic stirring bar, vacuum adapter, rubber septum, and a nitrogen line is charged with 2,3-*o*-isopropylidene -L-threitol (25.0 g, 0.154 mol), pumped under high vacuum for 10 min, and a nitrogen atmosphere is introduced. Methylene chloride (308 mL) and pyridine (37.4 mL, 0.462 mol) are added, and the stirred solution is cooled to 0 ^{o}C with an ice-water bath. methanesulfonyl chloride (29.8 mL, 0.385 mol) is added dropwise via a 50-mL glass syringe over a period of 10 min. After an additional 30 min, the ice-water bath is removed, and the stirred solution is allowed to warm to room temperature. After an additional 6 h a precipitate forms (pyridinium chloride); 300 mL of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$) is added slowly, dissolving the precipitate. The solution is stirred for an additional 30 min and then transferred to a 1-L separatory funnel. The layers are separated, and the aqueous layer is extracted with methylene chloride (3 × 100 mL). The organic layers are combined, dried with anhydrous sodium sulfate, and the drying agent is removed by filtration. The solvent is removed by rotary evaporation to give a tan solid that can be used as such or recrystallized from 1:1 chloroform-diethyl ether to give the product as a crystalline white solid,

2. A 1-L, one-necked, round-bottomed flask equipped with a heating mantle, magnetic stirring bar, and a reflux condenser is charged with 2,3-*o*-isopropylidene-L-threitol 1,4-bismethanesulfonate (40 g, 0.126 mol), 95% ethanol (250 mL) and methanesulfonic

acid (0.204 mL, 3.14 mmol), and brought to a gentle reflux. The solution is refluxed for 10 h and then cooled to 0 °C with an icewater bath resulting in the formation of crystals. The crystals are collected by suction filtration, washed with cold ethanol (2 x 50 mL) and diethyl ether (2 x 50 mL), and dried in a vacuum desiccator at 60 ºC under full vacuum for 4 h to give the product as white crystals (36.0 g, 84% yield).

Data for **I-67**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25-4.20 (4H, m), 3.85-3.83 (2H, m), 3.25 (6H, s), 2.08 (2H, br.); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.9, 68.4, 36.4.

(2*S*,2'*S*)-2,2'-Bioxirane[110]

A 250-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen line, and a 125-mL pressure-equalizing addition funnel is charged with L-threitol 1,4-bismethanesulfonate (25.0 g, 0.0898 moles) and diethyl ether (180 mL). The mixture is stirred vigorously to form a suspension, and a solution of potassium hydroxide (11.6 g, 0.207 mol) in water (35 mL) is added dropwise via the addition funnel over a period of 15 min. The clear mixture is stirred for an additional 45 min at room temperature, and the ether layer is decanted. The aqueous layer is transferred to a 500-mL separatory funnel and extracted with methylene chloride (3 x 50 mL). The combined ether and methylene chloride extracts are dried with anhydrous sodium sulfate, the sodium sulfate is removed by filtration, and the solution is concentrated to approximately 50 mL total volume by rotary evaporation. The concentrate is fractionally distilled through a 13-cm Vigreux distillation column at atmospheric pressure to give the product as a clear oil (6.8 g, 88% yield).

Data for **I-68**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90-2.85 (2H, m), 2.42-2.39 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5, 50.42.

3-(Benzyloxy)propan-1-ol[111]

To a slurry of NaH (6.1 g, 152.4 mmol) in THF (277 mL), propane-1,3-diol (10 mL, 138.55 mmol) was added at 0 ^{o}C and stirred for 1 h while warming to rt. Benzyl bromide (17.3 mL, 145.48 mmol) was the added drop wise followed by TBAI (2.56 g, 6.93 mmol). The reaction was heated to 60 ^{o}C for 15 h. After cooling to room temperature H_2O (100 mL) was carefully added. The layers were separated, aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Monobenzyl ether **I-69** was obtained as pale yellow oil (15.6, 68% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for monobenzyl ether **I-69**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (5H, m), 4.53 (2H, s), 3.77 (2H, t, *J* = 6.0 Hz), 3.66 (2H, t, *J* = 6.0 Hz), 2.05 (1H, br), 1.89-1.86 (2H, quin, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 127.6, 73.2, 69.0, 61.5, 31.9.

3-(Benzyloxy)propanal[112]

To a slurry of Oxalyl dichloride (8.7 mL, 99.9 mmol) in CH_2Cl_2 (250 mL) at -78 ^{o}C, a solution of DMSO (14.2 mL, 199.8 mmol) in CH_2Cl_2 (83 mL) was added drop wise. After 5 min. alcohol **I-69** (13.82 g, 83.25 mmol) in CH_2Cl_2 (83 mL) was added drop wise and after 15 min. triethyl amine (58 mL, 416.25 mmol) was added. The solution

stirred for 5 min and then at rt H_2O (100 mL) were added. The layers were separated, aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. The product was concentrated and the crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde **I-70** as a pale yellow oil (11.74 g, 86% yield).

Data for aldehyde **I-70**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (1H, t, *J* = 1.7 Hz), 7.38-7.27 (5H, m), 4.55 (2H, s), 3.83 (2H, t, *J* = 6.0 Hz), 2.73-2.71 (2H, td, *J* = 6.0, 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 137.8, 128.4, 127.8, 127.7, 73.2, 63.8, 43.8.

(*E*)-Ethyl 5-(benzyloxy)pent-2-enoate[113]

A solution of aldehyde **I-70** (6.45 g, 39.33 mmol) and (carbethoxymethylene) triphenylphosphorane (27.37 g, 78.66 mmol) in THF (450 mL) was heated to reflux for 16 h. After cooling the solution to rt, the solvent was evaporated and the crude product was purified by column chromatography (5% EtOAc in hexanes) to afford α, β-unsaturated *trans*-ester **I-71** as a colorless oil (7.18 g, 78% yield).

Data for **I-71**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (5H, m), 7.00-6.90 (1H, m), 5.96 (1H, dd, *J* = 15.6, 1.3 Hz), 4.46 (2H, s), 4.24-4.19 (2H, q, *J* = 7.1 Hz), 3.64-3.60 (2H, m), 2.54-2.56 (2H, q, *J* = 6.6 Hz), 1.32 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 145.5, 138.0, 128.3, 127.8, 127.6, 122.8, 72.9, 68.2, 60.1, 32.5, 14.2.

(*E*)-5-(Benzyloxy)pent-2-en-1-ol[114]

To a cold (0 ^{o}C) solution of ester **I-71** (3.63 g, 15.51 mmol) in diethyl ether (135 mL),

DIBAL-H (46.54 mmol, 18.61 mL of 2.5 M solution in toluene) was added under N_2. After stirring for 1 h. at the same temperature, saturated potassium-sodium tartrate solution (157 mL) was added and the mixture was brought to rt. Et_2O (162 mL), H_2O (32.5 mL) and glycerol (7.5 mL) were added and the resultant heterogeneous mixture was stirred overnight. The two layers were then separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the crude product after chromatographic purification (30% EtOAc in hexanes) afforded allylic alcohol **I-72** as a colorless oil (2.53 g, 85% yield).

Data for allylic alcohol **I-72**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.37 (5H, m), 5.74 (2H, m), 4.55 (2H, s), 4.10-4.11 (2H, m), 3.56 (2H, t, *J* = 6.6 Hz), 2.40 (2H, m), 2.00(1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 130.8, 129.0, 128.2, 127.5, 127.4, 72.9, 69.6, 63.5, 32.7.

(*E*)-(((5-Bromopent-3-en-1-yl)oxy)methyl)benzene[115]

A solution of allylic alcohol **I-72** (2.31 g, 12.03 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 ^{o}C. To this, mesyl chloride (2.8 mL, 36.09 mmol) and triethyl amine (5.9 mL) were added and stirring was continued at the same temperature for 30 min. The reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and combined organic layers were concentrated. The residue was taken up in DMF (50 mL) and cooled to 0 ^{o}C. Lithium bromide (0.9 mL, 36.09 mmol) was added dropwise and allowed to stir at room temperature for 5 h. The reaction was treated with 1 M HCl

solution. The organic layer was separated. The aqueous layer was extracted with EtOAc (3×50 mL). Chromatographic purification (5% EtOAc in hexanes) of the crude product obtained by concentration of the organic portion afforded **I-73** (2.29 g, 75% yield).

Data for **I-73**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.37 (5H, m), 5.82-5.65 (2H, m), 4.55 (2H, s), 4.09-4.06 (2H, m), 3.58-3.54 (2H, t, *J* = 6.6 Hz), 2.44-2.42 (2H, q, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 132.7, 128.4, 128.1, 127.6, 127.5, 72.9, 69.1, 33.1, 32.5.

(*E*)-(5-(Benzyloxy)pent-2-en-1-yl)tributylstannane

To a cooled (−78 ^{o}C) and stirred suspension of CuCN (40 mg, 0.451 mmol) in dry THF (1 mL) a solution of butyllithium in hexane (0.361 mL, 0.902 mmol) was added and the mixture was stirred for 10 min. To a slightly yellow solution of resulting organocuprate, tri-*n*-butyltin hydride (0.239 mL, 0.902 mmol) was added by a syringe at −78 ^{o}C and stirred for more 10 min. A solution of allyl bromide (0.1 g, 0.392 mmol) in 0.5 mL of dry THF was added by a syringe to a solution of tributyltin cuprate in THF and the mixture was stirred at -78 ^{o}C for 5 min. The mixture was diluted with ether (15 mL), aqueous saturated ammonium chloride (5 mL) was added and the mixture was stirred for 30 min at rt. Organic layer was separated, washed with water, dried and concentrated and the crude product was isolated by column chromatography (hexane–diethyl ether, 95:5 and then hexane–ethyl acetate, 15:1) to yield **I-75** in 80% yield (0.15 g).

Data for **I-75**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.38 (5H, m), 5.82-5.65 (2H, m), 4.56 (2H, s), 3.54-3.49 (2H, t, *J* = 6.5 Hz), 2.44-2.42 (2H, q, *J* = 6.3 Hz), 2.22-2.19 (2H, m),

1.65-1.63 (6H, m), 1.52-1.50 (6H, m), 1.35-1.32 (6H, m), 0.94-0.91 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 129.3, 128.5, 128.1, 127.7, 127.6, 76.2, 73.1, 29.3, 27.5, 32.3, 17.9, 14.5, 9.3.

(*E*)-1,2-Diiodoethene[116]

Petroleum ether (40 mL of 35-60 ^{o}C), iodine (7.40 g, 29.2 mmol), and alumina (25 g of Brockman I, basic) were combined. In a separate flask, calcium carbide (excess) and distilled water (excess) were added to liberate acetylene gas which was cooled in a trap filled with dry ice/acetone, and then bubbled into the reaction flask. The gas was bubbled for 120 minutes (30 minutes extra time). The reaction was then capped and stirred at room temperature overnight. In the morning, chloroform (50 mL) was added and the rxn contents were extracted using sodium metabisulfite (2 x 50 mL of a 10% aqueous solution), dried using brine (2 x 20 mL), and dried over anhydrous potassium carbonate. The solution was then filtered and concentrated (0.40 g, 5% yield).

Data for diiodoethylene **I-76**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, m).

(*E*)-Dimethyl hex-3-enedioate[117]

Concentrated sulfuric acid (5.0 mL, 94 mmol) was added to a stirred suspension of *trans*-hydromuconic acid (30.0 g, 208 mmol) in MeOH (150 mL) and the reaction mixture refluxed under a nitrogen atmosphere for 21 h. The mixture was then allowed to cool to room temperature, and the solvent was evaporated *in vacuo*. The resulting residue was diluted with Et_2O (80 mL) and washed successively with a saturated aqueous

solution of NH_4Cl (2 x 33 mL), a saturated aqueous solution of $NaHCO_3$ (2 x 33 mL), and brine (1 x 33 mL). The combined aqueous washings were extracted with Et_2O (33 mL), and the combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title diester (32.5 g, 91% yield).

Data for diester **I-77**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (2H, m), 3.71 (6H, s), 3.12 (4H, d, *J*= 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 125.9, 51.8.

(*E*)-Hex-3-ene-1,6-diol[118]

To a stirred solution of **3** (15.9 g, 92.4 mmol) in anhydrous THF (60 mL) was added $LiAlH_4$ in THF (2.0 M, 60.0 mL, 120.1 mmol) dropwise at 0 ^{o}C. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 19 h. The reaction was quenched at 0 ^{o}C by the successive dropwise addition of H_2O (4 mL), aqueous solution of NaOH (4 M, 4 mL) and H_2O (12 mL). The salt formed was filtered and washed thoroughly with THF, and the filtrate dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the title diol (9.3 g, 87% yield).

Data for diol **I-78**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (2H, m), 3.68 (4H, m), 2.33 (4H, m), 1.68 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6, 61.7, 36.0.

(*E*)-6-(Benzyloxy)hex-3-en-1-ol[119]

To a suspension of NaH (416 mg, 10.4 mmol, 1.1 equiv) in THF (200 mL) and DMSO (44 mL), diol **4** (4.33 g, 9.45 mmol, 1.0 equiv) in THF (120 mL) was added and stirred for 0.5 h. Benzyl bromide (1.25 mL, 10.4 mmol) in THF (120 mL) was added drop wise followed by TBAI (1.75 g, 4.73 mmol). The reaction was refluxed for 15 h.

After cooling to room temperature H_2O (200 mL) was carefully added. The layers were separated, aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Mono-benzyl ether **I-79** was obtained (1.01 g, 52% yield).

Data for mono-benzyl ether **I-79**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.41 (5H, m), 5.74-5.59 (2H, m), 4.54 (2H, s), 4.16-4.14 (4H, m), 3.63 (2H, m), 3.53 (2H, m), 2.28-2.32 (4H, m), 2.07 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 130.0, 128.3, 128.1, 127.6, 127.5, 72.8, 69.8, 61.8, 36.0, 33.0.

(*E*)-(((6-Iodohex-3-en-1-yl)oxy)methyl)benzene

To a stirred solution of **I-79** (2.0 g, 9.4 mmol), triphenylphosphine (5.0 g, 19.0 mmol) and imidazole (1.3 g, 19.0 mmol) in dry CH_3CN/Et_2O 1:2 (16.7:33.3 mL) at 0 ^oC was added I_2 (4.8 g, 19.0 mmol) in portions. The reaction mixture was left to stir at room temperature for 1 h. The mixture was diluted with pentane/ether (4:1) and filtered through a silica plug. The colorless filtrate was dried and concentrated in vacuo and the residue was chromatographed on silica eluting with hexanes, then 20% EtOAc–hexanes to give **I-80** (2.0 g, 67% yield).

Data for **I-80**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.39 (5H, m), 5.74-5.59 (2H, m), 4.56 (2H, s), 3.56 (2H, m), 3.20 (2H, m), 2.62 (2H, m), 2.38 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ138.3, 130.1, 128.2, 128.1, 127.8, 127.6, 72.8, 69.9, 36.2, 33.1, 5.5.

(3*E*,7*E*,11*E*)-1,14-Bis(benzyloxy)tetradeca-3,7,11-triene

1,2-Dibromoethane (10 μL, 5 mol%) in THF (1 mL) was added to zinc dust (200 mg, 1.17 mmol) and the suspension was refluxed for 30 min. Upon cooling the mixture to rt, TMSCl (8.5 μL, 3 mol%) and **I-80** (0.2 g, 0.56 mmol) in THF (2 mL) were added and the mixture was heated at 40 ^{o}C for 20 h after which CG analysis indicated complete consumption of **I-80**. The suspension was then allowed to settle at room temperature. A solution of **I-78** (78 mg, 0.28 mmol) and $Cl_2Pd(dppf)(CH_2Cl_2)$ (11 mg, 0.015 mmol) in THF (1 mL) were added and the reaction was completed within 2 h at rt. The reaction mixture was quenched with H_2O (1 mL) and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and evaporated. The crude oil was purified by flash chromatography (hexane) to give the title compound (0.16 g, 72% yield).

Data for **I-82**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.33 (10H, m), 5.34-5.58 (6H, m), 4.48 (4H, s), 3.00-3.50 (4H, m), 2.23-2.33 (4H, m), 1.96-2.02 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 134.9, 128.3, 127.8, 127.7, 127.5, 126.8, 126.3, 71.9, 71.0, 29.9, 29.5.

(3*R*,4*R*,7*R*,8*R*,11*R*,12*R*)-1,14-Bis(benzyloxy)tetradecane-3,4,7,8,11,12-hexaol

AD-mix-β (89 mg) was dissolved in 1:1 *t*BuOH:H_2O (1 mL). To this clear, orange solution, methane sulfonamide (6 mg, 0.064 mmol) and potassium osmate (0.2 mg, 0.00064 mmol) was added and stirred until all the solids dissolved. The solution was then cooled to 0 ^{o}C upon which triene **I-82** (26 mg, 0.64 mmol) was added in one portion. The reaction was vigorously stirred for 24 h after which solid sodium sulfite (95 mg) was

added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4×10 mL), combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude product was purified by column chromatography (50% EtOAc in hexanes to pure EtOAc) to yield **I-83** (97 mg, 30% yield).

Data for tetraol **I-83**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.34 (10H, m), 4.51 (4H, s), 3.63-3.71 (6H, m), 3.23 (2H, m), 3.15 (2H, m), 1.77-1.78 (4H, m), 1.45-1.57 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 128.5, 127.9, 127.7, 75.7, 73.7, 72.8, 72.6, 72.3, 31.5, 30.8, 26.6.

(3*E*,7*E*,11*E*)-Tetradeca-3,7,11-triene-1,14-diol

A solution of **I-82** (0.36 g, 0.90 mmol) in THF (4 mL) was cooled to -78 ^{o}C and liquid ammonia (10 mL) was added. An adequate amount of sodium was added in small pieces. After stirring for 45 min at 33 ^{o}C, excess metal was consumed by careful addition of aq. NH_4Cl (sat.). The resulting mixture was allowed to warm to room temperature, stirred for 2 h and then extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$. Filtration and concentration in *vacuo* afforded the crude product, which was purified by a flash column chromatography (30% EtOAc in hexane) to give **I-84** (0.13 g, 67% yield).

Data for diol **I-84**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36-5.60 (6H, m), 3.41-3.55 (4H, m),

2.25-2.36 (4H, m), 1.95-2.01 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 128.9, 127.5, 63.8, 31.3, 29.9, 29.3.

(*E*)-6-((Tetrahydro-2*H*-pyran-2-yl)oxy)hex-3-en-1-ol[120]

To a solution of DHP (0.53 mL, 5.85 mmol) and diol **I-78** (0.68 g, 5.85 mmol) in CH_2Cl_2 (3 mL), *p*-TsOH.H_2O (0.011 g, 0.058 mmol) was added and stirred for 4 h. H_2O (100 mL) was added. The layers were separated, aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Mono-THP ether **I-85** was obtained as pale yellow oil (0.67 g, 58% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-85**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47-5.54 (2H, m), 4.54-4.56 (1H, m), 3.85-3.70-3.75 (2H, m), 3.57-3.63 (2H, m), 3.38-3.49 (2H, m), 2.22-2.34 (4H, m), 1.51-1.72 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.1, 128.1, 98.8, 66.9, 62.4, 61.7, 35.9, 33.0, 30.6, 25.4, 19.6.

(*E*)-2-((6-Iodohex-3-en-1-yl)oxy)tetrahydro-2*H*-pyran[120]

To a stirred solution of **I-85** (0.37 g, 1.85 mmol), triphenylphosphine (0.97 g, 3.70 mmol) and imidazole (0.25 g, 3.70 mmol) in dry CH_3CN/Et_2O 1:2 (5:8 mL) at 0 ^{o}C was added I_2 (0.47 g, 1.85 mmol) in portions. The reaction mixture was left to stir at room temperature for 12 h. The mixture was diluted with pentane/ether (4:1) and filtered through a silica plug. The colorless filtrate was dried and concentrated in *vacuo* and the residue was chromatographed on silica eluting with hexanes, then 2% EtOAc–hexanes to give **I-86** (0.48 g, 84% yield).

Data for **I-86**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45-5.52 (2H, m), 4.56-4.57 (1H, m), 3.72-3.75 (2H, m), 3.40-3.45 (2H, m), 3.09-3.14 (2H, m), 2.52-2.55 (2H, m), 2.28-2.30 (2H, m), 1.49-1.72 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.3, 129.6, 98.7, 66.9, 62.3, 36.7, 32.9, 30.7, 25.4, 19.6, 5.7.

(*E*)-3-Iodoprop-2-en-1-ol[121]

To a solution of Cp_2ZrCl_2 (5.90 g, 20.31 mmol) in THF (76 mL) at 0 ^{o}C, DIBAL-H (7.45 mL, 18.62 mmol) was added in dark and let to stir for 30 min. at 0 ^{o}C. In another flask, propargyl alcohol (1.00 mL, 16.93 mmol) was added to DIBAL-H (8.10 mL, 20.31 mmol) solution and stir at 0 ºC for 30 min. This solution was transferred to a zirconium hydride solution by cannula. After stiring 2 h. at rt, a solution of iodine (6.50 g, 25.39 mmol) in THF (16 mL) was added drop wise to the reaction at -78 ^{o}C. After 30 min. HCl (1 mL) was added and the aqueous layer was extracted with Et_2O (3×100 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. The product was concentrated and the crude brown oily material was purified by flash column chromatography (20% EtOAc in hexanes) to afford **I-87** as a pale yellow oil (2.63 g, 85% yield).

Data for **I-87**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70-6.77 (1H, m), 6.41-6.47 (1H, m), 4.13-4.17 (2H, m), 2.39 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 77.8, 65.1.

(*E*)-*tert*-Butyl((3-iodoallyl)oxy)diphenylsilane[122]

To a solution of the alcohol **I-87** (2.25 g, 12.23 mmol) in DMF (34 mL), imidazole (4.16 g, 61.15 mmol) was added followed by *t*-butyl diphenylsilyl chloride (3.18 mL,

12.23 mmol) at room temperature. The reaction was stirred under N_2 for 14 h after which time it was quenched by adding water (100 mL). The aqueous layer was extracted with EtOAc (3×100 mL) to afford a crude oil which was purified by column chromatography (2% EtOAc in hexanes) providing the protected **I-88** (4.12 g, 80% yield).

Data for **I-88**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.7 (4H, m), 7.42-7.48 (6H, m), 6.61 (1H, m), 6.40 (1H, m), 4.15 (2H, m), 1.1 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 135.8, 133.6, 130.0, 128.0, 77.9, 65.6, 28.3, 19.4.

tert-Butyldiphenyl(((2*E*,6*E*)-9-((tetrahydro-2*H*-pyran-2-yl)oxy)nona-2,6-dien-1-yl)oxy)silane

To a solution of **I-88** (12.7 g, 30.0 mmol) in Et_2O (30 mL) was added dropwise at -78 ^{o}C a 1.7 M solution of *t*-BuLi (18.8 mL, 32.0 mmol) in pentane via syringe. After stirring for 30 min at -78 ^{o}C, a solution of flame dried $ZnBr_2$ (6.8 g, 30.0 mmol) in THF was transferred via cannula into the reaction mixture which was then warm to 0 ºC. A solution of **I-86** (6.2 g, 20.0 mmol) and $PdCl_2(dppf)(CH_2Cl_2)$ (326 mg, 0.4 mmol) in THF (30 mL) were added and the reaction was completed in 2 h at rt. The reaction mixture was quenched with H_2O (50 mL) and extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated, the crude oil was purified by flash column chromatography (hexanes) to give the title **I-89** (8.8 g, 92% yield).

Data for **I-89**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.68 (4H, m), 7.32-7.45 (6H, m), 5.65-5.82 (4H, m), 4.57 (1H, m), 4.18-4.21 (2H, m), 3.73-3.76 (2H, m), 3.40-3.45 (2H, m), 2.06-2.10 (6H, m), 1.49-1.72 (6H, m), 1.04 (9H, m).

(3*E*,7*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)nona-3,7-dien-1-ol

A solution of **I-89** (16.2 g, 33.9 mmol) and 3M aq. HCI (22.6 mL, 67.8 mrnol) in THF (125 mL) was stirred at room temperature for 15 h. The mixture was concentrated in *vacuo* and basified with 2M aq. KOH (until pH=10). The aq. solution was extracted with EtOAc (3x50 rnL) and the organic phases were combined, dried over K_2CO_3, filtered and concentrated in *vacuo* to afford a yellow oil which slowly crystallised. Flash chromatography (30% EtOAc in hexanes) yielded **I-90** (12.3 g, 92% yield).

Data for **I-90**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.68 (4H, m), 7.33-7.45 (6H, m), 5.65-5.82 (4H, m), 4.26-4.28 (2H, m), 3.72-3.75 (2H, m), 2.05-2.13 (6H, m), 1.51 (1H, br. s), 1.04 (9H, m).

***tert*-Butyl(((2*E*,6*E*)-9-iodonona-2,6-dien-1-yl)oxy)diphenylsilane**

To a stirred solution of **I-90** (0.73 g, 1.85 mmol), triphenylphosphine (0.97 g, 3.70 mmol) and imidazole (0.25 g, 3.70 mmol) in dry CH_3CN/Et_2O 1:2 (5:8 mL) at 0 ^{o}C was added I_2 (0.47 g, 1.85 mmol) in portions. The reaction mixture was left to stir at room temperature for 12 h. The mixture was diluted with pentane/ether (4:1) and filtered through a silica plug. The colorless filtrate was dried and concentrated in *vacuo* and the residue was chromatographed on silica eluting with hexanes, then 2% EtOAc–hexanes to give **I-91** (0.74 g, 80% yield).

Data for **I-91**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.68 (4H, m), 7.33-7.45 (6H, m), 5.66-5.80 (4H, m), 4.26-4.28 (2H, m), 3.16-3.20 (2H, m), 2.05-2.20 (6H, m), 1.03 (9H, m).

(6*E*,10*E*,14*E*)-2,2,19,19-Tetramethyl-3,3,18,18-tetraphenyl-4,17-dioxa-3,18-disilaicosa-6,10,14-triene

To a solution of **I-88** (1.5 g, 3.0 mmol) in Et_2O (3 mL) was added dropwise at -78 ^oC a 1.7 M solution of *t*-BuLi (1.9 mL, 3.2 mmol) in pentane via syringe. After stirring for 30 min at -78 ^oC, a solution of flame dried $ZnBr_2$ (0.7 g, 3.0 mmol) in THF was transferred via cannula into the reaction mixture which was then warm to 0 ^oC. A sulution of **I-91** (0.6 g, 2.0 mmol) and $PdCl_2(dppf)(CH_2Cl_2)$ (3.26 mg, 0.04 mmol) in THF (3 mL) were added and the reaction was completed in 2 h at rt. The reaction mixture was quenched with H_2O (5 mL) and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated, the crude oil was purified by flash column chromatography (hexanes) to give the title **I-92** (0.10 g, 78% yield).

Data for **I-92**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (8H, m), 7.44-7.45 (12H, m), 5.48-5.79 (6H, m), 4.20 (4H, m), 2.02-2.12 (8H, m), 1.10 (18H, m).

7-Oxabicyclo[4.1.0]hept-3-ene[117]

To a solution of 1,4-cyclohexadiene (5.00 g, 62.40 mmol) in H_2O (3 mL) and CH_2Cl_2 (450 mL) was added mCPBA (10.55 g, 61.15 mmol) and K_2HPO_4 (13.95 g, 61.15 mmol) and stirring was continued at rt for 18 h. The reaction was quenched with H_2O (50 mL) and washed with $NaHCO_3$ (sat.), Na_2SO_3 (5%), $NaHCO_3$ (sat.), H_2O and brine. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and combined organic layers were concentrated to afforded **I-93** (4.07 g, 68% yield).

Data for **I-93**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (2H, m), 3.22 (2H, m) , 2.45-2.52 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.5, 50.8, 24.9.

(*Z*)-Hex-3-enedial[123]

Into CH_2Cl_2 (10 mL) and H_2O (50 mL) were added under stirring sequentially **I-93** (2.50 g, 26.00 mmol), followed by H_5IO_6 (5.87 g, 25.74 mmol). After stirring for 3.5 h. at 0 ^{o}C, brine (50 mL) was added to the residue. The aqueous layer was extracted with EtOAc (3 x 50 mL) and washed with Na_2SO_3 (sat.). to afford crude oil which was purified by column chromatography (5% EtOAc in hexanes) providing **I-94** (2.41 g, 83% yield).

Data for **I-94**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (2H, s), 5.89 (2H, m), 3.18-3.21 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 123.5, 42.4.

(*Z*)-Hex-3-ene-1,6-diol[117]

To a solution of **I-94** (2.41 mL, 21.49 mmol) in MeOH (107 mL) at 0 ^{o}C, $NaBH_4$ (2.44 g, 64.48 mmol) was added and stirred for 4 h. at rt. NH_4Cl (sat.) (100 mL) was added. The layers were separated, aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Diol **I-95** was obtained (1.94 g, 78% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-95**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (2H, m), 3.69-3.71 (4H, m), 2.38-2.39 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.7, 61.5, 30.4.

(*Z*)-6-((Tetrahydro-2*H*-pyran-2-yl)oxy)hex-3-en-1-ol[120]

To a solution of DHP (0.53 mL, 5.85 mmol) and diol (0.68 g, 5.85 mmol) in CH_2Cl_2 (3 mL), *p*-TsOH.H_2O (0.011 g, 0.058 mmol) was added and stirred for 4 h. H_2O (100 mL) was added. The layers were separated, aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Mono-THP ether **I-96** was obtained as pale yellow oil (0.65 g, 56% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-96**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50-5.57 (2H, m), 4.56-4.57 (1H, m), 3.77-3.83 (2H, m), 3.59-3.65 (2H, m), 3.39-3.49 (2H, m), 2.30-2.39 (2H, m), 2.34-2.36 (2H, m), 1.95-1.99 (1H, s), 1.49-1.67 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.5, 127.5, 98.8, 66.7, 62.2, 61.9, 30.6, 30.5, 27.9, 25.3, 19.5.

(*Z*)-2-((6-Iodohex-3-en-1-yl)oxy)tetrahydro-2*H*-pyran[124]

To a stirred solution of **I-96** (0.37 g, 1.85 mmol), triphenylphosphine (0.97 g, 3.70 mmol) and imidazole (0.25 g, 3.70 mmol) in dry CH_3CN/Et_2O 1:2 (5:8 mL) at 0 ^oC was added I_2 (0.47 g, 1.85 mmol) in portions. The reaction mixture was left to stir at room temperature for 12 h. The mixture was diluted with pentane/ether (4:1) and filtered through a silica plug. The colorless filtrate was dried and concentrated in *vacuo* and the residue was chromatographed on silica eluting with hexanes, then 2% EtOAc–hexanes to give **I-97** (0.46 g, 80% yield).

Data for **I-97**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51-5.58 (2H, m), 4.62-4.63 (1H, m), 3.78-3.90 (2H, m), 3.46-3.51 (2H, m), 3.16-3.20 (2H, d, *J*= 14.4 Hz), 2.59-2.61 (2H, m), 2.34-2.36 (2H, m), 1.55-1.74 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.3, 127.6, 98.7, 66.8, 62.1, 36.0, 32.1, 30.7, 25.4, 19.6, 5.6.

2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran[125]

To a solution of DHP (0.53 mL, 5.85 mmol) and propargyl alcohol (0.33 g, 5.85 mmol) in CH_2Cl_2 (3 mL), *p*-TsOH.H_2O (0.011 g, 0.058 mmol) was added and stirred for 4 h. H_2O (100 mL) was added. The layers were separated, aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. THP ether **I-100** was obtained as pale yellow oil (0.64 g, 78% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-100**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85-4.87 (1H, t, *J*= 3.3 Hz), 4.28-4.31 (2H, dd, *J*= 4.5 Hz, 2.4), 3.87 (1H, m), 3.59 (1H, m), 2.45 (1H, t, *J*= 2.4 Hz), 1.57-1.81 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.7, 79.7, 73.9, 61.9, 53.9, 30.1, 25.2, 18.9.

2-(Pent-4-en-2-yn-1-yloxy)tetrahydro-2*H*-pyran

A mixture of $Pd(PPh_3)_2Cl_2$ (34 mg, 0.048 mmol) and CuI (57 mg, 0.3 mmol) were dissolved in *i*-$PrNH_2$:THF (7.5 mL) under argon. After cooling to –10 ^{o}C, **I-100** (2.1 g, 15 mmol) and vinyl bromide (20 mL, 1.0 M in THF, 20 mmol) were added. The reaction mixture was kept stirring at rt for 20 h. The reaction mixture was poured into H_2O, and extracted with Et_2O. The organic phase was washed with HCl (1 M), dried with $MgSO_4$ and concentrated to give crude compound. The crude was purified by column

chromatography (hexanes) over silica gel to give pure product **I-101** as colorless oil (1.5 g, 61%yield).

Data for **I-101**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81-5.90 (1H, m), 5.66-5.71 (1H, m), 5.51-5.54 (1H, m), 4.86 (1H, m), 4.48, (2H, m), 3.84-3.91 (1H, m), 3.54-3.59 (1H, m), 1.43-1.91 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ127.5, 116.5, 96.8, 87.8, 84.4, 60.2, 51.5. 30.2, 25.5, 18.9.

(*E*)-3-Iodoallyl pivalate[125]

To a solution of the alcohol **I-87** (0.50 g, 2.71 mmol) in CH_2Cl_2 (25 mL) at 0 ^{o}C, pyridine (0.88 mL, 10.84 mmol) was added followed by PivCl (0.67 mL, 5.43 mmol). The reaction was stirred under N_2 for 3 h at rt and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes) providing **I-98** (0.58 g, 81% yield).

Data for **I-98**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59-6.64 (1H, m), 6.41-6.45 (1H, m), 4.44-4.46 (2H, d, *J*= 4.5 Hz), 1.19 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 135.1, 76.5, 61.0, 38.9, 27.3.

(*E*)-Hexa-3,5-dienoic acid[126]

Isopropylamine (2.26 g, 38.3 mmol) in THF (40 mL) was stirred under N_2 in a dry ice-acetone bath. Added dropwise was *n*-butyllithium in hexanes (20.1 mL, 38.3 mmol, 1.9 M in hexanes). The resulting slightly yellow solution was stirred at this temperature for 40 min. The conjugated acid (3.6 g, 32.14 mmol) in THF (15 mL) was added

dropwise over 1 h. The temperature did not rise past -10 ^{o}C during addition. Stirring was continued for 3 h. The orange enolate solution was warmed to rt and poured into H_2O (75 mL) and separated. The aqueous layer was washed with (1 x 50 mL) of ether, and the aqueous layer was then acidified to pH 3 with 3 M HCl. Extraction with ether (4 x 50 mL) and drying ($MgSO_4$) gave after removal of solvent in *vacuo* (3.6 g, quantitative yield) of the deconjugated acid. Data for **I-102**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6 6.46 (1H, dd, *J* = 10.7, 14.9 Hz), 6.14 (1H, d, *J* = 6.3 Hz), 5.63 (1H, dd, *J* = 7.2, 14.9 Hz), 5.19 (1H, dd, *J* = 6.3, 10.7 Hz), 4.92 (2H, s), 3.73 (2H, m) 3.55 (2H, m), 3.38 (3H, s), 3.15 (2H, d, *J* = 7.2 Hz); ^{13}CNMR (75 MHz, $CDCl_3$) δ 177.44, 143.58, 127.03, 121.71,108.09, 95.86, 71.81, 67.74, 59.25, 38.29.

(*E*)-Hexa-3,5-dien-1-ol[127]

A solution of **I-102** (0.63 g, 5.64 mmol) in diethyl ether (3 mL) is added dropwise over 2 h to a suspended lithium aluminum hydride (0.36 g, 9.50 mmol) in diethyl ether (6 mL) under argon. The mixture is refluxed for an additional 3 h. The mixture is cooled to 0–5 ^{o}C and cautiously treated with water (0.4 mL), 4 *N* sodium hydroxide solution (0.4 mL), and water (1 mL). The mixture is then stirred at room temperature until the gray color of unquenched lithium aluminum hydride has completely disappeared. The mixture is filtered on a Büchner funnel and the inorganic precipitate is extracted with ether in a Soxhlet apparatus. The combined ethereal extracts are dried over anhydrous magnesium sulfate and filtered, and volatile material is removed under reduced pressure (water aspirator). The residue is fractionally distilled under vacuum to afford the product **I-103**

as colorless oil (0.46 g, 84% yield).

Data for **I-103**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (1H, ddd, *J* = 16.8, 10.4, 10.4 Hz), 6.16 (1H, dd, *J* = 15.2, 10.4 Hz), 5.68 (1H, dt, *J* = 15.2, 7.2 Hz), 5.14 (1H, d, *J* =16.8 Hz), 5.02 (1H, d, *J* = 10.0 Hz), 3.69 (2H, t, *J* = 6.4 Hz), 2.36 (2H, dt, *J* = 6.4, 6.4 Hz), 1.50 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 133.7, 130.6, 115.9, 61.9, 35.9.

(*E*)-2-(Hexa-3,5-dien-1-yloxy)tetrahydro-2*H*-pyran

To a solution of DHP (0.53 mL, 5.85 mmol) and alcohol **I-103** (0.57 g, 5.85 mmol) in CH_2Cl_2 (3 mL), *p*-TsOH•H_2O (0.011 g, 0.058 mmol) was added and stirred for 4 h. H_2O (100 mL) was added. The layers were separated, aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. THP ether **I-104** was obtained as pale yellow oil (0.95 g, 90% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-104**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (1H, ddd, *J* = 16.8, 10.4, 10.4 Hz), 6.17 (1H, dd, *J* = 15.2, 10.4 Hz), 5.66 (1H, dt, *J* = 15.2, 7.2 Hz), 5.14 (1H, d, *J* =16.8 Hz), 5.02 (1H, d, *J* = 10.0 Hz), 4.85-4.86 (1H, t, *J*= 3.3 Hz), 3.85 (2H, m), 3.75 (2H, t, *J* = 6.4 Hz), 2.37 (2H, dt, *J* = 6.4, 6.4 Hz), 1.57-1.81 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 133.7, 130.6, 115.9, 97.1, 61.9, 54.1, 35.9, 30.2, 25.3, 19.0.

3-(Benzyloxy)propan-1-ol[111]

To a slurry of NaH (6.1 g, 152.4 mmol) in THF (277 mL), propane-1,3-diol (10 mL, 138.55 mmol) was added at 0 ^{o}C and stirred for 1 h while warming to rt. Benzyl bromide (17.3 mL, 145.48 mmol) was the added drop wise followed by TBAI (2.56 g, 6.93 mmol).

The reaction was heated to 60 ^{o}C for 15 h. After cooling to room temperature H_2O (100 mL) was carefully added. The layers were separated, aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Monobenzyl ether **6** was obtained as pale yellow oil (20 g, 87% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for monobenzyl ether **I-107**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.30 (5H, m), 4.53 (2H, s), 3.77 (2H, t, *J* = 6.0 Hz), 3.66 (2H, t, *J* = 6.0 Hz), 2.05 (1H, br), 1.89-1.86 (2H, quin, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.0, 127.5, 127.4, 72.9, 68.8, 61.1, 32.1.

(*E*)-Ethyl 5-(benzyloxy)pent-2-enoate[113]

1. To a slurry of oxalyl chloride (8.7 mL, 99.9 mmol) in CH_2Cl_2 (250 mL) at -78 ^{o}C, a solution of DMSO (14.2 mL, 199.8 mmol) in CH_2Cl_2 (83 mL) was added drop wise. After 5 min alcohol **I-107** (13.82 g, 83.25 mmol) in CH_2Cl_2 (83 mL) was added drop wise and after 15 min triethyl amine (58 mL, 416.25 mmol) was added. The solution stirred for 5 min and then at rt H_2O (100 mL) was added. The layers were separated, aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. The crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde (94% yield) as a pale yellow oil.

2. A solution of aldehyde (6.45 g, 39.33 mmol) and (carbethoxymetylene) triphenylphosphorane (27.37 g, 78.66 mmol) in THF (450 mL) was heated to reflux for

16 h. After cooling the solution to rt, the solvent was evaporated and the crude product was purified by column chromatography (5% EtOAc in hexanes) to afford α, β-unsaturated *trans*-ester **I-108** as a colorless oil (17.33 g, 89% yield).

Data for α, β-unsaturated *trans*-ester **I-108**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (5H, m), 7.00-6.90 (1H, m), 5.96 (1H, dd, J = 15.6, 1.3 Hz), 4.46 (2H, s), 4.24-4.19 (2H, q, J = 7.1 Hz), 3.64-3.60 (2H, m), 2.54-2.56 (2H, q, J = 6.6 Hz), 1.32 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 145.5, 138.0, 128.3, 127.8, 127.6, 122.8, 72.9, 68.2, 60.1, 32.5, 14.2.

(*E*)-5-(Benzyloxy)pent-2-en-1-ol[114]

To a cold (0 ^{o}C) solution of ester **I-108** (3.63 g, 15.51 mmol) in diethyl ether (135 mL), DIBAL-H (46.54 mmol, 18.61 mL of 2.5 M solution in toluene) was added under N_2. After stirring for 1 h. at the same temperature, saturated potassium-sodium tartrate solution (157 mL) was added and the mixture was brought to rt. Et_2O (162 mL), H_2O (32.5 mL) and glycerol (7.5 mL) were added and the resultant heterogeneous mixture was stirred overnight. The two layers were then separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the crude product after chromatographic purification (30% EtOAc in hexanes) afforded allylic alcohol **I-109** as a colorless oil (2.97 g, quantitative yield).

Data for allylic alcohol **I-109**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.37 (5H, m), 5.74

(2H, m), 4.55 (2H, s), 4.10-4.11 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 2.40 (2H, m), 2.00 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 131.0, 129.1, 128.3, 127.6, 127.5, 72.9, 69.6, 63.5, 32.6.

(*E*)-((5-(Benzyloxy)pent-2-en-1-yl)sulfonyl)benzene

1. A solution of allylic alcohol **I-109** (2.31 g, 12.03 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 ^{o}C. To this, mesyl chloride (2.8 mL, 36.09 mmol) and triethyl amine (5.9 mL) were added and stirring was continued at the same temperature for 30 min. The reaction was quenched with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and combined organic layers were concentrated. The residue was taken up in DMF (50 mL) and cooled to 0 ^{o}C. Lithium bromide (0.9 mL, 36.09 mmol) was added dropwise and allowed to stir at room temperature for 5 h. The reaction was treated with 1 M HCl solution. The organic layer was separated. The aqueous layer was extracted with EtOAc (3×50 mL). Chromatographic purification (5% EtOAc in hexanes) of the crude product obtained by concentration of the organic portion afforded the desired product.

2. Into anhydrous DMF (24 mL) were added under stirring sequentially (2.89 g, 17.02 mmol) of mesylated alcohol, followed by sodium benzenesufinate (4.19 g, 25.53 mmol). After stirring for 1 h at 0 ^{o}C, brine (100 mL) was added to the residue. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) to afford crude oil which was purified by column chromatography (3% EtOAc in hexanes) providing **I-110** (2.50 g, 66% yield).

Data for **I-110**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.84 (2H, m), 7.22-7.62 (7H, m), 7.05-7.07 (1H, m), 5.45-5.58 (2H, m), 4.29 (2H, s), 3.73-3.75 (2H, d, J = 6 Hz), 3.37-3.41 (2H, t, J = 6.3 Hz), 2.27-2.33 (2H, m).

(4*R*,5*R*)-Dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate[107]

In a 1-L, one-necked, round-bottomed flask fitted with a reflux condenser and a large magnetic stirring bar under argon, a mixture of L-tartaric acid (101 g, 0.673 mol), 2,2-dimethoxypropane (190 mL, 161 g, 1.54 mol), methanol (40 mL), and *p*-toluenesulfonic acid monohydrate (0.4 g, 2.1 mmol) is warmed on a steam bath with occasional swirling until a dark-red homogeneous solution is obtained. Additional 2,2-dimethoxypropane (95 mL, 80.5 g, 0.77 mol) and cyclohexane (450 mL) are added and the flask is fitted with a 30-cm Vigreux column and a variable reflux distilling head. The mixture is heated to reflux with internal stirring and the acetone–cyclohexane and methanol–cyclohexane azeotropes are slowly removed. Additional 2,2-dimethoxypropane (6 mL, 5.1 g, 49 mmol) is then added and the mixture is heated under reflux for 15 min. After the mixture has cooled to room temperature, anhydrous potassium carbonate (1 g, 7.2 mmol) is added and the mixture is stirred until the reddish color has abated. Volatile material is removed under reduced pressure (water aspirator) and the residue is fractionally distilled under vacuum to afford the product **I-111** as pale-yellow oil, (104 g, 71% yield).

Data for **I-111**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42 (2H, s), 4.20 (6H, s), 1.32 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 113.8, 76.9, 52.7, 26.2.

((4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol[108]

In a dry, 2-L, three-necked, round-bottomed flask equipped with a 500-mL pressure-equalized addition funnel, a reflux condenser, a thermometer, and a large magnetic stirring bar is suspended lithium aluminum hydride (36 g, 0.95 mol) in diethyl ether (600 mL) under argon. The mixture is stirred and heated to reflux for 30 min. Heating is discontinued while a solution of **I-111** (123 g, 0.564 mol) in diethyl ether (300 mL) is added dropwise over 2 h. Heating is then resumed and the mixture is refluxed for an additional 3 h. The mixture is cooled to 0–5 ^{o}C and cautiously treated with water (36 mL), 4 *N* sodium hydroxide solution (36 mL), and water (112 mL). The mixture is then stirred at room temperature until the gray color of unquenched lithium aluminum hydride has completely disappeared. The mixture is filtered on a Büchner funnel and the inorganic precipitate is extracted with ether in a Soxhlet apparatus. The combined ethereal extracts are dried over anhydrous magnesium sulfate and filtered, and volatile material is removed under reduced pressure (water aspirator). The residue is fractionally distilled under vacuum to afford the product **I-112** as colorless oil (87 g, 96% yield).

Data for **I-112**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42-4.48 (2H, m), 3.80-3.83 (4H, m), 2.10 (2H, br.), 1.35 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.3, 78.3, 62.1, 27.0.

((4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)-bis(4-methylbenzenesulfonate)[128]

A dry, 1-L, round-bottomed flask equipped with a magnetic stirring bar, vacuum adapter, rubber septum, and a nitrogen line is charged with 2,3-*o*-isopropylidene

-L-threitol (25.0 g, 0.154 mol), pumped under high vacuum for 10 min, and a nitrogen atmosphere is introduced. Methylene chloride (308 mL) and pyridine (37.4 mL, 0.462 mol) are added, and the stirred solution is cooled to 0 ^{o}C with an ice-water bath. *p*-Tosyl chloride (73.1 g, 0.385 mol) is added dropwise via a 50-mL glass syringe over a period of 10 min. After an additional 30 min, the ice-water bath is removed, and the stirred solution is allowed to warm to room temperature. After an additional 6 h a precipitate forms (pyridinium chloride); 300 mL of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$) is added slowly, dissolving the precipitate. The solution is stirred for a further 30 min and then transferred to a 1-L separatory funnel. The layers are separated, and the aqueous layer is extracted with methylene chloride (3 x 100 mL). The organic layers are combined, dried with anhydrous sodium sulfate, and the drying agent is removed by filtration. The solvent is removed by rotary evaporation to give a tan solid that can be used as such or recrystallized from 1:1 chloroform-diethyl ether to give the product as a crystalline white solid (55.0 g, 76% yield).

Data for **I-113**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.81 (8H, m), 4.10 (4H, m), 4.01 (2H, m), 2.46 (6H, s), 1.29 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 132.1, 130.1, 128.1, 110.9, 75.1, 68.5, 26.8, 22.8.

(4*R*,5*R*)-4,5-Bis(iodomethyl)-2,2-dimethyl-1,3-dioxolane[129]

To a stirred solution of **I-113** (5.95 g, 12.67 mol), in acetone (30 mL) was added NaI (11.40 g, 76.05 mol). The reaction mixture was left to stir at room temperature for 12 h.

The mixture was diluted with water and Et_2O. The aqueous layer was extracted with Et_2O (3 x 50 mL) to afford **I-114** (4.20 g, 87% yield).

Data for **I-114**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (2H, m), 3.36 (4H, s), 1.44 (6H, s); ^{13}CNMR (CDCl3) δ 109.8, 79.7, 27.4, 6.2.

((4*S*,5*S*)-5-((Benzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol[130]

To a slurry of NaH (6.1 g, 152.4 mmol) in THF (277 mL), diol **I-112** (22.44 g, 138.55 mmol) was added at 0 ^{o}C and stirred for 1 h while warming to rt. Benzyl bromide (17.3 mL, 145.48 mmol) was the added drop wise followed by TBAI (2.56 g, 6.93 mmol). The reaction was heated to 60 ^{o}C for 15 h. After cooling to room temperature H_2O (100 mL) was carefully added. The layers were separated, aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Monobenzyl ether **I-115** was obtained as pale yellow oil (22.0 g, 63% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-115**: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.25 (5H, m), 4.52 (2H, s), 3.99 (1H, m), 3.88 (1H, m), 3.63 (3H, m), 3.49 (1H, dd, *J* = 9.9, 5.5 Hz), 2.15 (1H, br s), 1.35 (6H, s); ^{13}C NMR (75 MHz, CDCl3) δ 27.1, 62.6, 70.6, 73.9, 76.8, 79.9, 109.5, 128.0, 128.1, 128.7, 137.8.

(4*S*,5*R*)-4-((Benzyloxy)methyl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolane[131]

1. A dry, 1-L, round-bottomed flask equipped with a magnetic stirring bar, vacuum adapter, rubber septum, and a nitrogen line is charged with **I-115** (38.9 g, 0.154 mol),

pumped under high vacuum for 10 min, and a nitrogen atmosphere is introduced. CH_2Cl_2 (308 mL) and pyridine (37.4 mL, 0.462 mol) are added, and the stirred solution is cooled to 0 ^oC with an ice-water bath. *p*-Tosyl chloride (73.1 g, 0.385 mol) is added dropwise via a 50-mL glass syringe over a period of 10 min. After an additional 30 min, the ice-water bath is removed, and the stirred solution is allowed to warm to room temperature. After an additional 6 h a precipitate forms (pyridinium chloride); 300 mL of an aqueous saturated solution of sodium bicarbonate ($NaHCO_3$) is added slowly, dissolving the precipitate. The solution is stirred for a further 30 min and then transferred to a 1-L separatory funnel. The layers are separated, and the aqueous layer is extracted with methylene chloride (3 x 100 mL). The organic layers are combined, dried with anhydrous sodium sulfate, and the drying agent is removed by filtration. The solvent is removed by rotary evaporation to give the product.

2. To a stirred solution of tosylated alcohol (5.14 g, 12.67 mol), in acetonitrile (30 mL) was added NaI (11.40 g, 76.05 mol). The reaction mixture was left to stir at room temperature for 12 h. The mixture was diluted with water and Et_2O. The aqueous layer was extracted with Et_2O (3 x 50 mL). **I-116** (50.7 g, 91% yield) was obtained after chromatographic purification (10% EtOAc in hexanes).

Data for **I-116**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.25 (5H, m), 4.58 (2H, s), 3.96 (1H, dt, *J* = 7.2, 4.8 Hz), 3.86 (1H, dt, *J* = 7.5, 5.4 Hz), 3.65 (1H, d, *J* = 1.8 Hz), 3.64 (1H, d, *J* = 1.5 Hz), 3.34 (1H, dd, *J* = 10.8, 5.1 Hz), 3.24 (1H, dd, *J* = 10.8, 5.1 Hz), 1.46 (3H, s), 1.41 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 128.3, 127.6, 127.5, 109.6, 79.9, 73.4,

70.3, 30.8, 27.2, 27.1, 6.3.

2-(Pent-4-yn-1-yloxy)tetrahydro-2*H*-pyran[13]

To a stirred solution of 5-hydroxypentynol (4.5 g, 53.5 mmol) in CH_2Cl_2 (100 mL) at 0 ^oC under an argon atmosphere was added DHP (4.9 mL, 53.6 mmol). A few drops of concentrated HCl were added to catalyze the reaction. The reaction was allowed to slowly return to rt and stir overnight. Water was added and the organic layer was separated from the aqueous fraction. The aqueous fraction was extracted three times with CH_2Cl_2. The combined organic material was washed with saturated brine then dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation to give the product in 67% yield (6.0 g).

Data for **I-117**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.52-4.58 (1H, m), 3.72-3.85 (2H, m), 3.35-3.48 (2H, m), 2.20-2.28 (2H, m), 1.87 (1H, s), 1.68-1.78 (2H, t), 1.40-1.65 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.7, 83.8, 68.3, 65.7, 62.0, 30.6, 28.6, 25.4, 19.4, 15.2.

8-Chlorooct-4-yn-1-ol[133]

A solution composed of 5-tetrahydropyranyl-l-pentyne **I-117** (7.9 g, 47.0 mmol) in THF (80 mL) was placed under an argon atmosphere at 0 ^oC. To this solution *n*-BuLi (24.7 mL, 47.0 mmol, 1.9 M in hexanes) were added dropwise. The mixture was stirred for five minutes, followed by addition of HMPA (7.8 mL). The temperature was allowed to slowly warm to rt and stirring was continued for 30 min. The reaction was chilled to -78 ^oC and 1,3-chloroiodopropane (5.5 mL, 51.2 mmol) was added. The reaction was allowed to slowly reach rt and to stir for 24 hours. Water was used to quench the reaction,

followed by extraction of the aqueous layer three times with hexane. The combined organic extracts were washed with saturated brine and then saturated sodium bicarbonate. The organic extracts were dried over $MgSO_4$ and solvent was removed via rotary evaporation to give the crude product. The crude product was placed in THF / HCl (1:l, 25 mL, 5% aq.). solution and heated to reflux for 8 hours. After the reaction had cooled to rt, the THF was removed by rotary evaporation, and the water solution was extracted three times with diethyl ether. The extracts were dried over $MgSO_4$, and the solvent was removed via rotary evaporation to give product **I-118** in 90% yield (6.7 g).

Data for **I-118**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70-3.76 (2H, m), 3.60-3.64 (2H, m), 2.23-2.35 (4H, m), 1.86-1.93 (2H, m), 1.70-1.76 (2H, m), 1.42-1.51 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.5, 78.9, 62.0, 43.7, 31.8, 31.7, 16.2, 15.4.

(*Z*)-8-Chlorooct-4-en-1-ol

The titled compound **I-119** was prepared by hydrogenation of **I-118** (9.6 g, 60 mmol) in dry methanol (30 mL) in the presence of Lindlar catalyst (1.03 g) under 1 atm of H_2 at room temperature. The reaction mixture was filtered with suction through a pad of celite. The filter cake was washed several times with diethyl ether. This mixture was concentrated and alcohol **I-119** was obtained as a pale yellow oil (8.8 g, 91% yield) after chromatographic purification (30% EtOAc in hexanes).

Data for **I-119**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34-5.41 (2H, m), 3.60-3.63 (2H, m), 3.48-3.53 (2H, d, J = 6.6 Hz), 2.08-2.19 (4H, m), 1.79-1.87 (2H, m), 1.58-1.65 (2H, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 131.0, 128.8, 62.8, 44.9, 32.9, 32.7, 24.7, 23.9.

(*Z*)-8-Chlorooct-4-enal

To a slurry of oxalyl chloride (8.7 mL, 99.9 mmol) in CH_2Cl_2 (250 mL) at -78 ^{o}C, a solution of DMSO (14.2 mL, 199.8 mmol) in CH_2Cl_2 (83 mL) was added drop wise. After 5 min alcohol **I-119** (13.49 g, 83.25 mmol) in CH_2Cl_2 (83 mL) was added drop wise and after 15 min triethyl amine (58 mL, 416.25 mmol) was added. The solution stirred for 5 min and then at rt H_2O (100 mL) were added. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. The product was concentrated and the crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde (11.59 g, 87% yield).

Data for **I-120**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (1H, s), 5.32-5.42 (2H, m), 3.48-3.52 (2H, t, *J* = 6.6 Hz), 1.78-2-51 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 129.7, 129.3, 44.8, 44.1, 32.5, 24.6, 20.4.

(2*E*,6*Z*)-Ethyl 10-chlorodeca-2,6-dienoate

A solution of aldehyde (6.29 g, 39.33 mmol) and (carbethoxymethylene) triphenylphosphorane (27.37 g, 78.66 mmol) in THF (450 mL) was heated to reflux for 16 h. After cooling the solution to rt, the solvent was evaporated and the crude product was purified by column chromatography (5% EtOAc in hexanes) to afford **I-121** as a colorless oil (7.23 g, 80% yield).

Data for **I-121**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89-6.95 (1H, m), 5.77-5.83 (1H, d, *J* = 14.1 Hz), 5.33-5.40 (2H, m), 4.12-4.19 (2H, m), 3.48-3.52 (2H, m), 2.12-2.24 (6H, m), 1.77-1.84 (2H, m), 1.23-1.28 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 148.3, 129.5, 128.9, 121.7, 60.1, 44.3, 32.2, 32.1, 25.7, 24.3, 14.2.

(2*E*,6*Z*)-10-Chlorodeca-2,6-dien-1-ol

To a cold (0 ^{o}C) solution of ester **I-121** (3.57 g, 15.51 mmol) in diethyl ether (135 mL), DIBAL-H (46.54 mmol, 18.61 mL of 2.5 M solution in toluene) was added under N_2. After stirring for 1 h. at the same temperature, saturated potassium-sodium tartrate solution (157 mL) was added and the mixture was brought to rt. Et_2O (162 mL), H_2O (32.5 mL) and glycerol (7.5 mL) were added and the resultant heterogeneous mixture was stirred overnight. The two layers were then separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the crude product after chromatographic purification (30% EtOAc in hexanes) afforded allylic alcohol **I-122** as a colorless oil (2.24 g, 77% yield).

Data for **I-122**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62-5.71 (2H, m), 5.31-5.42 (2H, m), 4.06-4.10 (2H, m), 3.50-3.53 (2H, m), 2.09-2.20 (6H, m), 1.78-1.83 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.5, 128.9, 122.2, 121.7, 64.9, 44.3, 32.2, 32.1, 25.7, 24.3.

((2*R*,3*R*)-3-((*Z*)-7-Chlorohept-3-en-1-yl)oxiran-2-yl)methanol

A two necked round bottom flask charged with 4 Å mol. sieves (0.8 g) and CH_2Cl_2 (7 mL) was cooled to -20 ^{o}C. To this, $Ti(O^{i}Pr)_4$ (0.38 mL, 1.29 mmol) and a CH_2Cl_2

soltution of D-(-)-DET (0.27 ml, 1.55 mmol in 6 mL CH_2Cl_2) were added in that order and stirred at the same temperature under N_2 for 30 min. After cooling the complex to -30 ^oC, *t*BuOOH (0.6 mL of 3.1 M solution in toluene, 2.19 mmol) was added dropwise and the mixture was stirred for another 45 min. A solution of allylic alcohol **I-122** (0.24 g, 1.29 mmol) in CH_2Cl_2 (5 mL) was added via a syringe pump over 45 min. The reaction was warmed to -20 ^oC, stirred for 2 h and then quenched by adding saturated Na_2SO_4 and Na_2SO_3 solutions (1.2 mL each). Et_2O (5 mL) was added and the resultant yellow mixture was vigorously stirred at rt for 4 h. The yellow gelatinous mass was further diluted with Et_2O (30 mL), celite was added and the mixture was filtered through a pad of celite. The filter cake was washed with Et_2O (ca. 60 mL) until it turned dry and granular. The filtrate was concentrated and epoxy alcohol **I-123** was isolated in 72% yield (0.19 g) after purification by column chromatography (5% EtOAc in hexanes).

Data for epoxy alcohol **I-123**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.32-5.45 (2H, m), 3.86-3.88 (1H, m), 3.56-3.60 (1H, m), 3.48-3.50 (2H, m), 2.91-2.95 (2H, m), 2.17-2.21 (4H, m), 1.77-1.83 (2H, m), 1.59-1.63 (2H, m).

***tert*-Butyl(((2*R*,3*R*)-3-((*Z*)-7-chlorohept-3-en-1-yl)oxiran-2-yl)methoxy)diphenylsilan e**

To a solution of the alcohol **I-23** (2.52 g, 12.23 mmol) in CH_2Cl_2 (34 mL), triethyl amine (2.06 mL, 14.68 mmol) and DMAP (0.6 g, 4.89 mmol) was added followed by *t*-butyl diphenylsilyl chloride (3.18 mL, 12.23 mmol) at room temperature. The reaction

was stirred under N_2 for 14 h after which time was quenched by adding water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) to afford crude oil which was purified by column chromatography (2% EtOAc in hexanes) providing the protected **I-124** (4.97 g, 92% yield).

Data for **I-124**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.68 (4H, m), 7.34-7.42 (6H, m), 5.35-5.41 (2H, m), 3.72-3.76 (2H, dd, *J* = 4.5, 3.6), 3.48-3.52 (2H, t, *J* = 6.6 Hz), 2.89-2.90 (1H, m), 2.79-2.80 (1H, m), 2.14-2.20 (4H, m), 1.78-1.82 (2H, m), 1.57-1.61 (2H, m), 1.04 (9H, s).

***tert*-Butyl(((2*R*,3*R*)-3-((*Z*)-7-iodohept-3-en-1-yl)oxiran-2-yl)methoxy)diphenylsilane**

To a stirred solution of **I-124** (5.60 g, 12.67 mol), in acetone (30 mL) was added NaI (11.40 g, 76.05 mol). The reaction mixture was reflux for 12 h. The mixture was diluted with water and Et_2O. The aqueous layer was extracted with Et_2O (3×50 mL). to afford **I-125** was obtained (6.63 g, 87% yield) after chromatographic purification (10% EtOAc in hexanes).

Data for **I-125**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.67 (4H, m), 7.35-7.42 (6H, m), 5.33-5.41 (2H, m), 3.72-3.76 (2H, dd, *J* = 4.5, 3.6), 3.13-3.18 (2H, t, *J* = 6.9 Hz), 2.88-2.91 (1H, m), 2.77-2.82 (1H, m), 2.10-2.22 (4H, m), 1.80-1.89 (2H, m), 1.54-1.61 (2H, m), 1.03 (9H, s).

(*Z*)-7-((2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)hept-4-en-1-yl acetate

To a stirred solution of **I-125** (6.76 g, 12.67 mol), in acetic acid (30 mL) was added

$AgNO_3$ (6.46 g, 38.01 mol). The reaction mixture was heated to 50 ^oC for 4 h. The mixture was filtered through a celite pad and the solventwas removed under reduced pressure. The crude product after chromatographic purification (5% EtOAc in hexanes) afforded **I-126** as a colorless oil (5.49 g, 93% yield).

Data for **I-126**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66-7.67 (4H, m), 7.34-7.43 (6H, m), 5.35-5.39 (2H, m), 4.01-4.05 (2H, t, *J* = 6.6 Hz), 3.71-3.76 (2H, dd, *J* = 4.5, 3.6), 2.88-2.89 (1H, m), 2.77-2.79 (1H, m), 2.11-2.16 (4H, m), 2.02 (3H, s), 1.53-1.68 (4H, m), 1.03 (9H, s).

(*Z*)-7-((2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)hept-4-en-1-ol

To a stirred solution of **I-126** (11.05 g, 23.70 mol), in MeOH (258 mL) and water (24 mL) was added K_2CO_3 (6.88 g, 29.77 mol). The reaction mixture was stirred at rt for 12 h. The mixture was diluted with water. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the solvent was removed under reduced pressure. The crude product after chromatographic purification (30% EtOAc in hexanes) afforded **I-127** as a colorless oil (8.94 g, 89% yield).

Data for **I-127**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.64-7.70 (4H, m), 7.34-7.41 (6H, m), 5.37-5.41 (2H, m), 3.71-3.75 (2H, dd, *J* = 4.5, 3.6), 3.58-3.63 (2H, m), 2.88-2.89 (1H, m), 2.78-2.80 (1H, m), 2.09-2.19 (4H, m), 1.56-1.64 (4H, m), 1.03 (9H, s).

(*Z*)-7-((2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)hept-4-enal

To a slurry of PCC (1.99 g, 9.23 mmol) in CH_2Cl_2 (20 mL), a solution of alcohol

I-127 (2.61 g, 6.16 mmol) in CH_2Cl_2 (5 mL) was added at room temperature under N_2 with vigorous stirring. After 2 h, anhydrous Et_2O (30 mL) was added and the reaction mixture was filtered through a pad of celite. The filtrate was concentrated and the crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde **I-128** as a pale yellow oil (1.90 g, 73% yield).

Data for aldehyde **I-128**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.64-7.67 (4H, m), 7.37-7.42 (6H, m), 5.37-5.40 (2H, m), 3.71-3.76 (2H, dd, *J* = 4.5, 3.6), 2.88-2.89 (1H, m), 2.78-2.79 (1H, m), 2.14-2.49 (6H, m), 1.56-1.58 (2H, m), 1.03 (9H, s).

(2*E*,6*Z*)-Ethyl-9-((2*R*,3*R*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)nona-2, 6-dienoate

A solution of aldehyde **I-128** (16.60 g, 39.33 mmol) and (carbethoxymethylene) triphenylphosphorane (27.37 g, 78.66 mmol) in THF (450 mL) was heated to reflux for 16 h. After cooling the solution to rt, the solvent was evaporated and the crude product was purified by column chromatography (5% EtOAc in hexanes) to afford **I-129** as a colorless oil (13.16 g, 68% yield).

Data for **I-129**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.70 (4H, m), 7.36-7.40 (6H, m), 6.91-6.94 (1H, m), 5.79-5.82 (1H, d, *J* = 15.5 Hz), 5.36-5.40 (2H, m), 4.14-4.18 (2H, m), 3.69-3.77 (2H, m), 2.88-2.89 (1H, m), 2.77-2.79 (1H, m), 2.14-2.23 (6H, m), 1.56-1.59 (2H, m), 1.25-1.27 (3H, t, *J* = 7.0 Hz), 1.03 (9H, s).

(2*E*,6*Z*)-9-((2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)nona-2,6-dien-1-ol

To a cold (0 ^{o}C) solution of ester **I-129** (7.63 g, 15.51 mmol) in diethyl ether (135 mL), DIBAL-H (46.54 mmol, 18.61 mL of 2.5 M solution in toluene) was added under N_2. After stirring for 1 h. at the same temperature, saturated potassium-sodium tartrate solution (157 mL) was added and the mixture was brought to rt. Et_2O (162 mL), H_2O (32.5 mL) and glycerol (7.5 mL) were added and the resultant heterogeneous mixture was stirred overnight. The two layers were then separated and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated and the crude product after chromatographic purification (30% EtOAc in hexanes) afforded allylic alcohol **I-130** as a colorless oil (2.79 g, 40% yield).

Data for allylic alcohol **I-130**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.68 (4H, m), 7.35-7.42 (6H, m), 6.63-6.65 (2H, m), 5.36-5.90 (2H, m), 4.09-4.12 (2H, m), 3.72-3.76 (2H, dd, J = 4.5, 3.6), 2.88-2.89 (1H, m), 2.78-2.79 (1H, m), 2.10-2.19 (6H, m), 1.52-1.56 (2H, m), 1.03 (9H, s).

((2*S*,3*S*)-3-((*Z*)-6-((2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)hex-3-en-1-yl)oxiran-2-yl)methanol

A two necked round bottom flask charged with 4 Å mol. sieves (0.8 g) and CH_2Cl_2 (7 mL) was cooled to -20 ^{o}C. To this, Ti(O^{i}Pr)$_4$ (0.38 mL, 1.29 mmol) and a CH_2Cl_2 soltution of L-(-)-DET (0.27 ml, 1.55 mmol in 6 mL CH_2Cl_2) were added in that order

and stirred at the same temperature under N_2 for 30 min. After cooling the complex to -30 ^oC, *t*BuOOH (0.6 mL, 3.1 M solution in toluene, 2.19 mmol) was added dropwise and the mixture was stirred for another 45 min. A solution of allylic alcohol **I-130** (0.58 g, 1.29 mmol) in CH_2Cl_2 (5 mL) was added via a syringe pump over 45 min. The reaction was warmed to -20 ^oC, stirred for 2 h and then quenched by adding saturated Na_2SO_4 and Na_2SO_3 solutions (1.2 mL each). Et_2O (5 mL) was added and the resultant yellow mixture was vigorously stirred at rt for 4 h. The yellow gelatinous mass was further diluted with Et_2O (30 mL), celite was added and the mixture was filtered through a pad of celite. The filter cake was washed with Et_2O (ca. 60 mL) until it turned dry and granular. The filtrate was concentrated and epoxy alcohol **I-131** was isolated in 75% yield (0.45 g) after purification by column chromatography (5% EtOAc in hexanes).

Data for epoxy alcohol **I-123**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.65-7.67 (4H, m), 7.35-7.42 (6H, m), 5.40 (2H, m), 3.71-3.76 (4H, m), 2.78-2.90 (4H, m), 2.16-2.18 (4H, m), 1.56-1.65 (4H, m), 1.03 (9H, s).

(((2*R*,3*R*)-3-((*Z*)-6-((2*S*,3*S*)-3-((Benzyloxy)methyl)oxiran-2-yl)hex-3-en-1-yl)oxiran-2-yl)methoxy)(*tert*-butyl)diphenylsilane

To a slurry of NaH (6.1 g, 152.4 mmol) in THF (277 mL), **I-131** (64.56 g, 138.55 mmol) was added at 0 ^oC and stirred for 1 h while warming to rt. Benzyl bromide (17.3 mL, 145.48 mmol) was the added drop wise followed by TBAI (2.56 g, 6.93 mmol). The reaction was heated to 60 ^oC for 15 h. After cooling to room temperature H_2O (100 mL)

was carefully added. The layers were separated, aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers after drying ($MgSO_4$) were concentrated. Benzyl ether **I-132** was obtained as pale yellow oil (69.33 g, 90% yield) after chromatographic purification (5% EtOAc in hexanes).

Data for monobenzyl ether **I-132**: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.64-7.67 (4H, m), 7.29-7.45 (11H, m), 5.39 (2H, m), 4.50 (2H, s), 3.69-3.74 (2H, dd, *J* = 4.5, 3.6), 3.21-3.26 (2H, dd, *J* = 3.3, 3.0 Hz), 2.76-2.91 (4H, m), 2.15 (4H, m), 1.55-1.58 (4H, m), 1.03 (9H, s).

(3*S*,4*R*)-1-((2*R*,3*R*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)oxiran-2-yl)-6-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)hexane-3,4-diol

AD-mix-α (89 mg) was dissolved in 1:1 *t*BuOH:H_2O (1 mL). To this clear, orange solution, methane sulfonamide (6 mg, 0.064 mmol) and potassium osmate (0.2 mg, 0.00064 mmol) was added and stirred until all the solids dissolved. The solution was then cooled to 0 ^{o}C upon which **I-132** (0.36 g, 0.64 mmol) was added in one portion. The reaction was vigorously stirred for 24 h after which solid sodium sulfite (95 mg) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 x 10 mL), combined organic layers were dried over Na_2SO_4, concentrated and the crude product was purified by column chromatography (50% EtOAc in hexanes to pure EtOAc) to yield **I-133** (0.30 g, 87% yield).

Data for diol **I-133**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.68 (4H, m), 7.30-7.43 (11H, m), 4.53 (2H, s), 3.87-3.93 (2H, m), 3.57-3.65 (4H, m), 2.90-2.94 (4H, m), 1.54-1.77 (8H, m), 1.03 (9H, s).

(*S*)-2-(Benzyloxy)-1-((2*R*,2'*S*,5*S*,5'*R*)-5'-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyethyl)octahydro-[2,2'-bifuran]-5-yl)ethanol

CH_2Cl_2 (3.0 mL) and TFA (0.16 g, 1.45 mmol) were added dropwise to a solution of **I-133** (1.50 g, 2.54 mmol) in CH_2Cl_2 (8.0 mL) at 0 ^{o}C, and the mixture was stirred at rt for 5 h. The mixture was diluted with CH_2Cl_2, successively washed with saturated aqueous $NaHCO_3$, water, brine, and then dried over Na_2SO_4. Filtration and evaporation of the solvents afforded the crude mixture, which was chromatographed on a silica gel column (50% EtOAc in hexanes) to give **I-134** (1.20 g, 80% yield) as a yellow solid.

Data for **I-134**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.68 (4H, m), 7.30-7.40 (11 H, m), 4.43-4.57 (2H, m), 3.81-4.04 (6H, m), 3.30-3.59 (4H, m), 1.84-1.95 (6H, m), 1.55-1.62 (2H, m), 0.97 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 82.0, 80.3, 79.7, 73.3, 73.2, 73.1, 72.9, 71.7, 71.6, 71.5, 28.6, 28.4, 26.9, 26.2, 25.9, 18.1, 14.1.

(*S*)-1-((2*R*,2'*S*,5*S*,5'*R*)-5'-((*R*)-1-Acetoxy-2-((*tert*-butyldiphenylsilyl)oxy)ethyl)octahydro-[2,2'-bifuran]-5-yl)-2-(benzyloxy)ethyl acetate

To a solution of **I-134** (1.60g, 2.71 mmol) in CH_2Cl_2 (25 mL) at 0 ^{o}C, pyridine (0.88 mL, 10.84 mmol) and DMAP (0.3 g, 0.27 mmol) was added followed by AcCl (0.39 mL,

5.43 mmol). The reaction was stirred under N_2 for 3 h at rt and then removed solvent. The crude product was purified by column chromatography (30% EtOAc in hexanes) providing **I-135** (1.46 g, 80% yield).

Data for **I-135**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.69 (4H, m), 7.32-7.43 (11 H, m), 4.45-4.56 (2H, m), 3.82-4.05 (6H, m), 3.33-3.60 (4H, m), 2.06 (3H, s), 2.02 (3H, s), 1.86-1.97 (6H, m), 1.52-1.63 (2H, m), 1.02 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.5, 138.3, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 82.0, 80.2, 79.7, 73.4, 73.2, 73.1, 72.7, 71.7, 71.5, 71.5, 28.5, 28.4, 26.9, 26.2, 25.9, 21.1, 21.0, 18.1, 14.1.

(*S*)-1-((2*R*,2'*S*,5*S*,5'*R*)-5'-((*R*)-1-Acetoxy-2-((*tert*-butyldiphenylsilyl)oxy)ethyl)octahydro-[2,2'-bifuran]-5-yl)-2-hydroxyethyl acetate

I-135 (0.27 g, 0.40 mmol) was dissolved in 1 : 1 EtOAc : ^{i}PrOH (5 mL). To this solution, 10% Pd-C (105 mg) was added and the mixture was stirred vigorously under H_2 (1 atm). The hydrogenolysis was complete in 3 h after which the reaction was filtered through a celite pad. The filtrated was concentrated and the crude product was purified by flash column chromatography (30% EtOAc in hexanes) to furnish diol **I-136** in 72% yield (0.16 g).

Data for diol **I-136**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64-7.69 (4H, m), 7.32-7.45 (6 H, m), 3.82-4.05 (6H, m), 3.35-3.63 (4H, m), 2.05 (3H, s), 2.03 (3H, s), 1.86-1.97 (6H, m), 1.52-1.63 (2H, m), 1.02 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 138.4, 138.2, 128.3, 128.2, 128.1, 127.5, 127.4, 82.3, 80.5, 79.5, 73.3, 73.2, 72.9, 71.8, 71.6,

71.5, 28.8, 28.4, 26.9, 26.3, 25.9, 21.1, 21.0, 18.5, 14.3.

(*S*)-2-(Benzyloxy)-1-((2*R*,2'*S*,5*S*,5'*R*)-5'-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyethyl)octahydro-[2,2'-bifuran]-5-yl)ethanol

Bis-adjacent THF acetate **I-135** (0.52 g, 0.78 mmol) was dissolved in MeOH (8 mL). Solid K_2CO_3 was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 15 h. The reaction was then diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (10 mL) and H_2O (10 mL). The aqueous layers were mixed and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the solvents were evaporated and the crude product was purified by flash column chromatography (50% EtOAc in hexanes). Bis-THF diol **I-137** was obtained in 67% yield (0.20 g).

Data for bis-THF diol **I-137**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.68 (4H, m), 7.30-7.40 (11 H, m), 4.46-4.57 (2H, m), 3.81-4.04 (6H, m), 3.30-3.59 (4H, m), 1.84-1.95 (6H, m), 1.55-1.62 (2H, m), 0.97 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 82.0, 80.3, 79.7, 73.3, 73.2, 73.1, 72.9, 71.7, 71.6, 71.5, 28.6, 28.4, 26.9, 26.2, 25.9, 18.1, 14.1.

(*R*)-5-((2*S*,2'*R*,5*R*,5'*S*)-5'-((*S*)-2-(Benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)octahydro-[2,2'-bifuran]-5-yl)-2,2,3,3,9,9-hexamethyl-8,8-diphenyl-4,7-dioxa-3,8-disiladecane

To a 0 ^{o}C solution of bis-THF diol **I-137** (0.33 g, 0.56 mmol) in THF (11 mL), triethylamine (0.21 mL, 1.51 mmol) and TBSCl (0.21 g, 1.40 mmol) were added in that

order. After 30 min at the same temperature, saturated $NaHCO_3$ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL), combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford a crude oil. Upon purification of the oil by column chromatography (10% EtOAc in hexanes), bis-TBS ether **I-138** was obtained in 77% yield (0.35 g).

Data for bis-TBS ether **I-138**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.69 (4H, m), 7.30-7.40 (11 H, m), 4.45-4.57 (2H, m), 3.81-4.04 (6H, m), 3.59-3.30 (4H, m), 1.84-1.95 (6H, m), 1.57-1.62 (2H, m), 0.99 (9H, s), 0.87 (9H, s), 0.85 (9H, s), 0.07 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 82.0, 80.3, 79.7, 73.3, 73.2, 73.1, 72.9, 71.7, 71.6, 71.5, 28.6, 28.4, 28.3, 26.9, 26.2, 25.9, 18.1, 17.9, 14.1,-4.9, -4.8, -4.5, -4.4.

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((2*R*,2'*S*,5*S*,5'*R*)-5'-((*R*)-2,2,3,3,9,9-hexamethyl-8,8-diphenyl-4,7-dioxa-3,8-disiladecan-5-yl)octahydro-[2,2'-bifuran]-5-yl)ethanol

I-138 (0.33 g, 0.40 mmol) was dissolved in 1 : 1 EtOAc : ^{i}PrOH (5 mL). To this solution, 10% Pd-C (105 mg) was added and the mixture was stirred vigorously under H_2 (1 atm). The hydrogenolysis was complete in 3 h after which the reaction was filtered through a celite pad. The filtrated was concentrated and the crude product was purified by flash column chromatography (30% EtOAc in hexanes) to furnish diol **I-139** in 82% yield (0.24 g).

Data for diol **I-139**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.70 (4H, m), 7.32-7.44 (6 H, m), 3.85-4.00 (6H, m), 3.58-3.31 (4H, m), 1.85-1.91 (6H, m), 1.58-1.63 (2H, m), 1.00 (9H, s), 0.89 (9H, s), 0.85 (9H, s), 0.08 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 138.2, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 82.0, 80.3, 79.7, 73.3, 73.2, 73.0, 71.7, 71.6, 71.5, 28.5, 28.4, 28.3, 26.9, 26.2, 25.7, 18.1, 17.9, 14.1,-4.9, -4.8, -4.5, -4.4.

(*R*)-5-((2*S*,2'*R*,5*R*,5'*S*)-5'-((*S*)-2-(Benzyloxy)-1-(methoxymethoxy)ethyl)octahydro-[2, 2'-bifuran]-5-yl)-9,9-dimethyl-8,8-diphenyl-2,4,7-trioxa-8-siladecane

To a solution of diol **I-137** (0.16g, 0.28 mmol) in dichloromethane (3 mL), DMAP (13.7 mg, 0.11 mmol), Hünig's base (0.59 mL, 3.36 mmol), methoxylmethyl chloride (0.13 mL, 1.68 mmol), and TBAI (41.4 mg, 0.11 mmol) were added in that order. The reaction was stirred at room temperature overnight. Sat. ammonium chloride solution (10 mL) was added to quench the reaction and the layers were separated. The aqueous layer was extracted with EtOAc (4×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified via fast column chromatography (30% EtOAc in hexanes) to yield the desired fully protected diol **I-143** in 97% yield (0.18 g).

Data for di-MOM ether **I-143**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.69 (4H, m), 7.32-7.40 (11 H, m), 4.91-4.94 (4H, m), 4.46-4.57 (2H, m), 3.80-4.00 (6H, m), 3.35-3.56 (4H, m), 3.05 (3H, s), 3.00 (3H, s), 1.85-1.96 (6H, m), 1.55-1.60 (2H, m), 0.98 (9H, s);

^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 138.2, 138.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3, 82.0, 81.9, 81.7, 80.3, 79.7, 73.3, 73.2, 73.1, 72.9, 71.7, 71.6, 71.5, 68.3, 68.1, 28.6, 28.4, 26.9, 26.2, 25.9, 18.1, 14.1.

(*S*)-2-((2*R*,2'*S*,5*S*,5'*R*)-5'-((*R*)-9,9-Dimethyl-8,8-diphenyl-2,4,7-trioxa-8-siladecan-5-yl)octahydro-[2,2'-bifuran]-5-yl)-2-(methoxymethoxy)ethanol

I-143 (0.18 g, 0.27 mmol) was dissolved in 1 : 1 EtOAc : ^{i}PrOH (5 mL). To this solution, 10% Pd-C (71 mg) was added and the mixture was stirred vigorously under H_2 (1 atm). The hydrogenolysis was complete in 3 h after which the reaction was filtered through a celite pad. The filtrated was concentrated and the crude product was purified by flash column chromatography (80% EtOAc in hexanes to pure EtOAc) to furnish diol **I-144** in 86% yield (0.13 g).

Data for **I-144:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.69 (4H, m), 7.35-7.43 (5 H, m), 4.92-4.95 (4H, m), 3.80-4.02 (6H, m), 3.35-3.53 (4H, m), 3.06 (3H, s), 3.02 (3H, s), 1.86-1.97 (6H, m), 1.55-1.61 (2H, m), 0.97 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.0, 128.3, 128.2, 128.0, 127.8, 127.5, 127.4, 127.3, 82.0, 81.9, 81.7, 80.3, 79.7, 73.2, 73.1, 72.9, 71.7, 71.6, 71.5, 68.3, 68.1, 28.6, 28.4, 26.9, 26.2, 25.9, 18.1, 14.1.

4-((*tert*-Butyldiphenylsilyl)oxy)butan-1-ol[134]

To a solution of l,4-butanediol (15.00 g, 166.00 mmol) in CH_2Cl_2 (30 ml) containing imidazole (11.29 g, 166.00 mmol) was added dropwise *tert*- butylchlorodiphenylsilane (15.0 ml, 57.30 mmol) under argon at room temperature. The solution was stirred at room temperature for 18 h, concentrated in vacuo, and the residue was purified by flash

chromatography (Hex-EtOAc, 30%) to give alcohol **I-152** (10.58 g, 57% yield) as a clear oil.

Data for **I-152:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.69 (10H, m), 3.70 (2H, t, *J* = 5.68 Hz), 3.63 (2H, t, *J* = 5.84 Hz), 2.04 (1H, s), 1.63–1.71 (4H, m), 1.05 (9H, s); ^{13}C NMR (75 MHz, $CDC1_3$) δ 136.0, 134.0, 130.1, 128.1, 64.4, 63.3, 30.3, 29.7, 27.2, 19.6.

4-((*tert*-Butyldiphenylsilyl)oxy)butanal[135]

A solution of oxalyl chloride (4.7 ml, 54.1 mmol) in CH_2Cl_2 (85 mL) was treated with a solution of DMSO (6.5 mL, 91.5 mmol) in CH_2Cl_2 (5 mL) at –78 °C under argon in 10 min. After 15 min at −78 °C, alcohol **I-152** (13.66 g, 41.6 mmol) in CH_2Cl_2 (34 mL) was added in 5 min. After 15 min at –78 °C, triethylamine (29 mL, 208 mmol) was added in 15 min, and the mixture was allowed to warm up to room temperature. The reaction mixture was treated with water (150 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The organic extracts were washed with saturated aqueous NaCl (100 mL), and dried over $MgSO_4$. The filtrate was concentrated in *vacuo*, and the residue was purified by flash chromatography (Hex-EtOAc, 10%) to give aldehyde **I-153** (11.52 g, 85% yield) as an oil.

Data for **I-153:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (1H, d, *J* = 1.68 Hz), 7.66–7.35 (10H, m), 3.69 (2H, t, *J* = 5.97 Hz), 2.55 (2H, dt, *J* = 7.17, 1.65 Hz), 1.89 (2H, tt, *J* = 7.08, 6.02 Hz), 1.04 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.0, 135.9, 134.0, 130.1, 128.1, 63.3, 41.2, 27.2, 25.6, 19.6.

(*E*)-Ethyl 6-((*tert*-butyldiphenylsilyl)oxy)hex-3-enoate

A mixture of **I-153** (13.51 g, 41.4 mmol), monoethyl malonate (6.60 g, 50.0 mmol) and Et_3N (7.0 mL, 50.2 mmol) was heated at 90 ^oC overnight. After addition of ice (100 mL), 2 N HCl (50 mL), and EtOAc (100 mL), the mixture was extracted with EtOAc (2x 100 mL). The organic extracts were washed with saturated aqueous NaCl (100 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, purification of the residue by flash chromatography (Hex-EtOAc, 10%) gave ester **I-154** (13.77 g, 84% yield). Data for **I-154:** ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.64 (4H, m), 7.42–7.25 (6H, m), 5.59–5.55 (2H, m), 3.69 (2H, t, *J* = 6.5 Hz), 3.67 (3H, s), 3.03 (2H, d, *J* = 4.9 Hz), 2.25 (2H, m), 1.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 136.0, 134.3, 131.6, 130.0, 128.0, 124.0, 63.9, 52.1, 38.4, 36.3, 27.2, 19.6.

(4*R*,5*R*)-5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-4-hydroxydihydrofuran-2(3*H*)-one

Ester **I-155** (6.70 g, 17.5 mmol) was added to a mixture of AD-mix-β (25 g, 1.4 g/mmol of **I-155**) and methanesulfonamide (1.67g, 17.5 mmol) in *t*-BuOH (88 mL) and water (88 mL) at 0 ^oC. The solution was stirred at 0 ^oC for 20 h. After addition of saturated aqueous $Na_2S_2O_3$ (100 mL), the mixture was extracted with EtOAc. The extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hex-EtOAc, 2:1) to yield lactone **I-155** (5.37 g, 80% yield, 98% *ee*) as a clear oil.

Data for **I-155:** $[\alpha]_D^{20}$ +27 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.41 (10H, m), 4.59 (1H, qui, *J* = 2.90 Hz), 4.50 (1H, qui, *J* = 4.61 Hz), 3.86 (1H, dt, *J* =10.79, 3.95 Hz), 3.69 (1H, dt, *J* = 10.73, 2.25 Hz), 3.55 (1H, t, *J* = 1.86 Hz), 2.83 (1H, ddd, *J* =

17.83, 5.73, 1.38 Hz), 2.63 (1H, d, J = 17.79 Hz), 2.30 (1H, m), 2.10 (1H, ddt, J = 14.60, 4.81, 2.09 Hz), 1.07 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 135.9, 135.9, 132.5, 132.3, 130.6, 128.4, 84.1, 69.1, 60.8, 38.5, 31.1, 27.2, 19.4.

(3*R*,4*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)hexane-1,3,4-triol

A solution of lactone **I-155** (6.3 g, 16.5 mmol) in THF (35 mL) was slowly added to a suspension of $LiAlH_4$ (626 mg, 16.5 mmol) in THF (35 mL) at –78 ^{o}C. The reaction mixture was warmed to room temperature, and after 30 min, treated with diluted H_2SO_4 (3 wt. %, 58mL) at 0 ^{o}C. The mixture was extracted with EtOAc (4 x 100 mL). The combined organic extracts were dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (Hex-EtOAc, 50%) to yield triol **I-156** (5.0 g, 78% yield) as a clear oil.

Data for **I-156:** $[\alpha]_D^{20}$ -1.9 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, 300 $CDCl_3$) δ 7.68–7.37 (10H, m), 3.91–3.72 (6H, m), 3.73 (1H, br. s), 3.13 (1H, d, J = 4.32), 2.70 (1H, br. s), 1.88–1.65 (4H, m), 1.06 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.94, 135.91, 133.23, 133.14, 130.34, 130.36, 130.33, 128.25, 74.48, 74.44, 63.18, 61.37, 35.54, 35.28, 27.21, 19.43.

(3*R*,4*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-6-iodohexane-3,4-diol

To a stirred solution of **I-156** (0.72 g, 1.85 mmol), triphenylphosphine (0.97 g, 3.70 mmol) and imidazole (0.25 g, 3.70 mmol) in dry CH_3CN/Et_2O 1:2 (5:8 mL) at 0 ^{o}C was added I_2 (0.47 g, 1.85 mmol) in portions. The reaction mixture was left to stir at room temperature for 12 h. The mixture was diluted with pentane/ether (4:1) and filtered

through a silica plug. The colorless filtrate was dried and concentrated in *vacuo* and the residue was chromatographed on silica eluting with hexanes, then 30% EtOAc–hexanes to give **I-157** (0.62 g, 68% yield).

Data for **I-157**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.66 (4H, d, J = 6.6 Hz), 7.36-7.46 (6H, m), 3.69-3.89 (4H, m), 3.18-3.30 (2H, m), 1.95-2.10 (2H, m), 1.65-1.84 (2H, m), 1.03 (9H, s).

(7*R*,8*R*)-10,10-Diethyl-8-(2-iodoethyl)-2,2-dimethyl-3,3-diphenyl-7-((triethylsilyl)oxy)-4,9-dioxa-3,10-disiladodecane

To a solution of the diol **I-157** (0.5 g, 1.0 mmol) in THF (9.5 mL) triethyl amine (3.5 mL) was added followed by triethylsilyl chloride (0.67 mL, 4.0 mmol) and DMAP (49 mg, 0.4 mmol) at ambient temperature. The reaction was stirred under N_2 for 5 h after which time it was quenched by adding saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with 1: 5 EtOAC : hexanes (3 x 10 mL) to afford crude oil which was purified by column chromatography (1% EtOAc in hexanes) providing the fully protected diol **I-158** (0.6 g, 87% yield) as a colorless oil.

Data for diol **I-158:** ^{1}H NMR (300 MHz, $CDCl_3$) δ7.63-7.66 (4H, d, J = 6.6 Hz), 7.35-7.45 (6H, m), 3.68-3.88 (4H, m), 3.18-3.28 (2H, m), 1.97-2.11 (2H, m), 1.68-1.80 (2H, m), 1.03 (9H, s), 0.96-0.99 (18H, m), 0.59-0.62 (12H, m).

2-((4*R*,5*R*)-5-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol

p-Toluenesulfonic acid (*p*-TsOH, 0.19 g, 0.89 mmol) was added as one portion to the

solution of diol **I-156** (2.83 g, 8.9 mmol) and acetone (100 mL). Hot oven dried 4 Å molecular sieves (1.2 g) was also added and the mixed slurry was stirred at room temperature overnight. The slurry was then filtered through a celite pad and washed with EtOAc (4 x 60 mL). The combined organic layers were drided over Na_2SO_4 and concentrated under reduced pressure. Purification via column chromatography (30% EtOAc-hexanes) yielded the protected diol **I-160** in 69% yield (2.62 g).

Data for **I-160**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.66 (4H, d, *J* = 6.6 Hz), 7.33-7.43 (6H, m), 3.68-3.89 (6H, m), 1.58-1.83 (4H, m), 1.37 (3H, s), 1.34 (3H, s), 1.03 (9H, s).

***tert*-Butyl(2-((4*R*,5*R*)-5-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)diphenyl silane**

To a stirred solution of **I-160** (0.79 g, 1.85 mmol), triphenylphosphine (0.97 g, 3.70 mmol) and imidazole (0.25 g, 3.70 mmol) in dry CH_3CN/Et_2O 1:2 (5:8 mL) at 0 ºC was added I_2 (0.47 g, 1.85 mmol) in portions. The reaction mixture was left to stir at room temperature for 12 h. The mixture was diluted with pentane/ether (4:1) and filtered through a silica plug. The colorless filtrate was dried and concentrated in *vacuo* and the residue was chromatographed on silica eluting with hexanes, then 10% EtOAc–hexanes to give **I-161** (0.69 g, 70% yield).

Data for **I-161**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.67 (4H, d, *J* = 6.6 Hz), 7.34-7.42 (6H, m), 3.66-3.87 (4H, m), 3.18-3.30 (2H, m), 1.99-2.15 (2H, m), 1.73-1.79 (2H, m), 1.34 (6H, s), 1.04 (9H, s).

***tert*-Butyl(2-((4*R*,5*R*)-5-(6-((4-methoxybenzyl)oxy)hex-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethoxy)diphenylsilane**

To a solution of **I-159** (2.12 g, 11.15 mmol) in THF (98 mL), *n*-BuLi (1.6 M solution in THF, 7.00 mL, 11.15 mmol) was added at -78 ^{o}C. After stirring for 10 min, **I-161** (5.00 g, 9.29 mmol) in HMPA (6.5 mL) was added and the mixture was stirred for 12 h at 0 ^{o}C. Saturated NH_4Cl (aq.) solution (100 mL) was added to quench the reaction. EtOAc (50 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and the solvent was evaporated to afford a crude product. Purification by column chromatography (5% EtOAc in hexanes) gave **I-162** in 78% yield (4.34 g).

Data for **I-162**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65-7.66 (4H, d, J = 6.0 Hz), 7.34-7.41 (8H, m), 6.84-6.86 (2H, d, J = 8.4 Hz), 4.45 (2H, s), 3.79-3.83 (2H, m), 3.77 (3H, s), 3.69-3.70 (2H, m), 3.49-3.51 (2H, t, J = 7.2 Hz), 2.24-2.44 (4H, m), 1.67-1.79 (4H, m), 1.33 (3H, s), 1.32 (3H, s), 0.95 (9H, s).

2-((4*R*,5*R*)-5-(6-((4-Methoxybenzyl)oxy)hex-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol

To a solution of di-TBDPS ether **I-162** (0.021 g, 0.035 mmol) in THF (2 mL), TBAF (1.0 M solution in THF, 35 μL, 0.035 mmol) was added at room temperature. After stirring for 16 h at room temperature, saturated NH_4Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) were added and the layers were separated. The aqueous layers were extracted with EtOAc (3 x 8 mL). The organic layers were combined,

dried over anhydrous Na_2SO_4, and the solvent was evaporated to afford a crude product. Purification by column chromatography (80% EtOAc in hexanes to pure EtOAc) gave **I-163** (10 mg) in 76% yield.

Data for **I-163**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.26 (2H, m), 6.84-6.87 (2H, m), 4.45 (2H, s), 3.75-3.81 (7H, m), 3.48-3.52 (2H, t, *J* = 6.9 Hz), 2.28-2.45 (4H, m), 1.67-1.82 (4H, m), 1.37 (3H, s), 1.36 (3H, s).

(4*R*,5*R*)-4-(2-Iodoethyl)-5-(6-((4-methoxybenzyl)oxy)hex-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane

To a stirred solution of **I-163** (4.4 g, 9.4 mmol), triphenylphosphine (5.0 g, 19.0 mmol) and imidazole (1.3 g, 19.0 mmol) in dry CH_3CN/Et_2O 1:2 (16.7:33.3 mL) at 0 ºC was added I_2 (4.8 g, 19.0 mmol) in portions. The reaction mixture was left to stir at room temperature for 1 h. The mixture was diluted with pentane/ether (4:1) and filtered through a silica plug. The colorless filtrate was dried and concentrated in vacuo and the residue was chromatographed on silica eluting with hexanes, then 10% EtOAc–hexanes to give **I-164** (3.2 g, 72% yield).

Data for **I-164**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.26 (2H, m), 6.84-6.87 (2H, m), 4.46 (2H, s), 3.79 (3H, s), 3.53-3.75 (2H, m), 3.48-3.53 (2H, t, *J* = 7.2 Hz), 3.19-3.30 (2H, m), 2.40-2.46 (4H, m), 2.02-2.06 (2H, m), 1.67-1.74 (2H, m), 1.35 (6H, s).

(4*R*,5*R*)-4-(6-((4-Methoxybenzyl)oxy)hex-3-yn-1-yl)-5-(6-((2-methoxyethoxy)methoxy)hex-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane

To a solution of **I-165** (0.18 g, 1.11 mmol) in THF (10 mL), *n*-BuLi (1.6 M solution

in THF, 0.70 mL, 1.11 mmol) was added at -78 ^{o}C. After stirring for 10 min, **I-164** (0.44 g, 0.93 mmol) in HMPA (0.6 mL) was added and the mixture was stirred for 12 h at 0 ^{o}C. Saturated NH_4Cl (aq.) solution (10 mL) was added to quench the reaction. EtOAc (5 mL) were added and the layers were separated. The aqueous layers were extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and the solvent was evaporated to afford a crude product. Purification by column chromatography (5% EtOAc in hexanes) gave **I-166** in 77% yield (0.36 g).

Data for **I-166**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.26 (2H, m), 6.84-6.87 (2H, m), 4.72 (2H, s), 4.46 (2H, s), 3.78 (3H, s), 3.50-3.72 (10H, m), 3.38 (3H, s), 2.27-2.45 (8H, m), 1.69-1.71 (4H, m), 1.34 (6H, s).

(4*R*,5*R*)-4-((*Z*)-6-((4-Methoxybenzyl)oxy)hex-3-en-1-yl)-5-((*Z*)-6-((2-methoxyethoxy) methoxy)hex-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane

The titled compound **I-167** was prepared by hydrogenation of **I-166** (0.3 g, 0.6 mmol) in dry ethanol (0.3 mL) in the presence of Lindlar catalyst (0.01 g) under 1 atm of H_2 at room temperature. The reaction mixture was filtered with suction through a pad of celite. The filter cake was washed several times with diethyl ether. This mixture was concentrated and **I-167** was obtained as pale yellow oil (0.3 g, 98% yield) after chromatographic purification (10% EtOAc in hexanes).

Data for **I-167**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.24 (2H, d, J = 6.6 Hz), 6.84-6.86 (2H, d, J = 6.6 Hz), 5.38-5.46 (4H, m), 4.69 (2H, s), 4.42 (2H, s), 3.77 (3H, s), 3.66-3.67 (2H, m), 3.52-3.59 (6H, m), 3.41-3.43 (2H, t, J = 7.2 Hz), 3.37 (3H, s), 2.31-2.36 (4H,

m), 2.11-2.22 (4H, m), 1.53-1.59 (4H, m), 1.34 (6H, s).

(3*S*,4*R*)-1-((4*R*,5*R*)-5-((3*R*,4*S*)-3,4-Dihydroxy-6-((2-methoxyethoxy)methoxy)hexyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-((4-methoxybenzyl)oxy)hexane-3,4-diol

Compound **I-167** (0.67 g, 1.75 mmol) was added to a mixture of AD-mix-α (2.5 g, 1.4 g/mmol of **I-167**) and methanesulfonamide (0.17g, 1.75 mmol) in *t*-BuOH (9 mL) and water (9 mL) at 0 ^{o}C. The solution was stirred at 0 ^{o}C for 20 h. After addition of saturated aqueous $Na_2S_2O_3$ (10 mL), the mixture was extracted with EtOAc. The extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (Hex-EtOAc, 2:1) to yield **I-168** (0.72 g, 72% yield) as a white solid.

Data for **I-168:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20-7.22 (2H, d, *J* = 8.4 Hz), 6.84-6.85 (2H, d, *J* = 8.4 Hz), 4.68 (2H, s), 4.43 (2H, s), 3.77 (3H, s), 3.54-3.71 (14H, m), 3.37 (3H, s), 1.49-1.82 (12H, m), 1.34 (6H, s).

(*S*)-1-((2*R*,2'*R*,5*S*,5'*R*)-5'-((*R*)-1-Acetoxy-3-((4-methoxybenzyl)oxy)propyl)octahydro-[2,2'-bifuran]-5-yl)-3-((2-methoxyethoxy)methoxy)propyl acetate

Trimethylortho acetate (31 μL, 0.24 mmol) was added to a solution of tetraol **I-168** (57.4 mg, 0.1 mmol) and in CH_2Cl_2 (3 mL) at rt. After complete consumption of the tetraol (ca. 20 min, as judged by TLC), BF_3•OEt_2 (8 μL, 0.06 mmol) was rapidly added to the reaction. After 30 min, the reaction was slowly poured into saturated $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL).

Combined organic layers were dried (anhydrous Na_2SO_4), concentrated under reduced pressure and the crude product was purified by flash column chromatography (40% EtOAc in hexanes to 60% EtOAc in hexanes) to furnish bis-THF acetate mixture **I-169** (the mixture of diastereomers) (20 mg, 35% yield) as a clear oil.

Data for **I-169**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22-7.27 (2H, m), 6.82-6.87 (2H, m), 4.66 (2H, s), 4.45 (2H, s), 3.81-4.04 (6H, m), 3.79 (3H, s), 3.46 (3H, s), 3.62-3.30 (8H, m), 2.28 (3H, s), 2.25 (3H, s), 1.84-2.10 (12H, m).

(10*Z*,14*R*,15*R*,18*Z*)-23-(4-Methoxyphenyl)-2,5,7,22-tetraoxatricosa-10,18-diene-14,15-diol

To a stirred, ice-cold solution of **I-167** (0.05 g, 0.10 mmol) in anhydrous CH_2Cl_2 (1 mL) under an inert atmosphere was added TMSOTf (0.04 g, 0.20 mmol). The resulting solution was stirred at the same temperature for the specified time (TLC monitoring), followed by quenching the reaction by addition of a saturated aqueous $NaHCO_3$ solution. After stirring the mixture for 5 min, the organic layer was separated and the aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2 (three times). The combined organic layers were dried over anhydrous Na_2SO_4. Concentration of the solvent under reduced pressure and column chromatographic purification of the residue (40% EtOAc in hexanes to 60% EtOAc in hexanes) provided the pure **I-170** (35 mg, 76% yield).

Data for **I-170**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.25 (2H, d, J = 6.6 Hz), 6.85-6.87 (2H, d, J = 6.6 Hz), 5.39-5.46 (4H, m), 4.69 (2H, s), 4.41 (2H, s), 3.78 (3H, s), 3.66-3.68 (2H, m), 3.52-3.60 (6H, m), 3.42-3.45 (2H, t, J = 7.2 Hz), 3.38 (3H, s), 2.31-2.36 (4H,

m), 2.11-2.23 (4H, m), 1.54-1.58 (4H, m);.

(14*R*,15*R*,*Z*)-17,17-Diethyl-15-((*Z*)-6-((4-methoxybenzyl)oxy)hex-3-en-1-yl)-14-((triethylsilyl)oxy)-2,5,7,16-tetraoxa-17-silanonadec-10-ene

To a solution of the diol **I-170** (0.05 g, 0.10 mmol) in THF (1 mL) triethyl amine (0.35 mL) was added followed by triethylsilyl chloride (0.07 mL, 0.4 mmol) and DMAP (4.9 mg, 0.04 mmol) at ambient temperature. The reaction was stirred under N_2 for 5 h after which time it was quenched by adding saturated $NaHCO_3$ solution (1 mL). The aqueous layer was extracted with 1:5 EtOAC:hexanes (3 x 1 mL) to afford a crude oil which was purified by column chromatography (5% EtOAc in hexanes) providing the fully protected diol **I-171** (52 mg, 78%) as a colorless oil.

Data for **I-171**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.25 (2H, d, J = 6.6 Hz), 6.85-6.87 (2H, d, J = 6.6 Hz), 5.40-5.45 (4H, m), 4.68 (2H, s), 4.42 (2H, s), 3.75 (3H, s), 3.65-3.68 (2H, m), 3.50-3.59 (6H, m), 3.42-3.45 (2H, t, J = 7.2 Hz), 3.39 (3H, s), 2.31-2.34 (4H, m), 2.11-2.22 (4H, m), 1.54-1.59 (4H, m), 0.91-0.98 (18H, m), 0.56-0.63 (12H, m).

(10*S*,11*R*,14*R*,15*R*,18*S*,19*R*)-23-(4-Methoxyphenyl)-14,15-bis((triethylsilyl)oxy)-2,5,7,22-tetraoxatricosane-10,11,18,19-tetrao

Compound **I-171** (0.08 g, 0.18 mmol) was added to a mixture of AD-mix-α (0.25 g, 1.4 g/mmol of **I-171**) and methanesulfonamide (0.02g, 0.17 mmol) in *t*-BuOH (1 mL) and water (1 mL) at 0 ^{o}C. The solution was stirred at 0 ^{o}C for 20 h. After addition of saturated aqueous $Na_2S_2O_3$ (1 mL), the mixture was extracted with EtOAc. The extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The

residue was purified by flash chromatography (Hex-EtOAc, 2:1) to yield **I-172** (0.11 g, 80% yield) as a white solid.

Data for **I-172:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20-7.24 (2H, d, *J* = 8.4 Hz), 6.86-6.87 (2H, d, *J* = 8.4 Hz), 4.67 (2H, s), 4.42 (2H, s), 3.77 (3H, s), 3.54-3.73 (14H, m), 3.38 (3H, s), 1.51-1.83 (12H, m), 0.92-0.97 (18H, m), 0.56-0.62 (12H, m).

I.10 References

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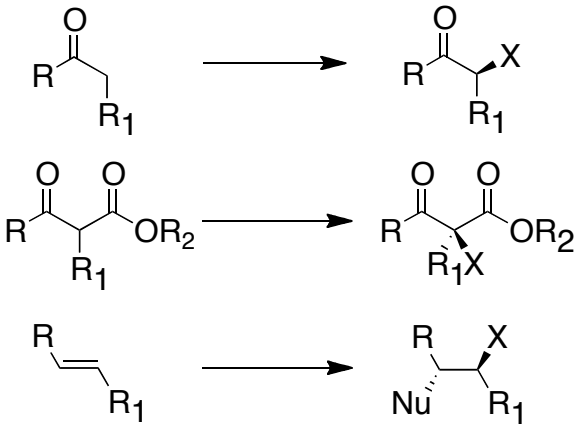
CHAPTER II

Asymmetric Organocatalytic Halocyclization Reactions

II.1. Introduction

Although the field of asymmetric catalysis has flourished over the last four decades,[1] there are some areas that remain virtually untouched. One of these areas, is electrophilic addition to olefins. Here we discuss methods that accomplish asymmetric halogen addition reactions of olefins. The products of these reactions, chiral nonracemic



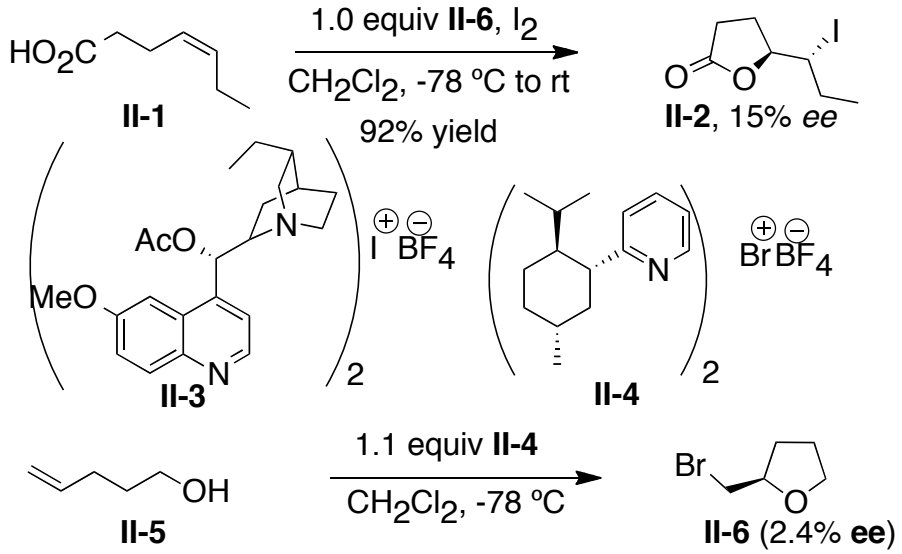
Scheme II-1: Catalytic asymmetric halogenation of carbonyl, dicarbonyl and olefins

halogenated compounds are the most versatile building blocks in synthesis. Halogen incorporation also alters the physical properties of molecules, including steric and electronic effects that are related to biological activity.[2, 3] Over 4000 halogenated natural products have been discovered; the carbon–halogen bonds are generated in these natural

products enzymatically.[2] The catalytic asymmetric α-halogenation of carbonyl and 1,3-dicarbonyl compounds (Scheme II-1) has seen recent interest.[4, 5, 6] These reactions can now be accomplished by a different methods. Electrophile-promoted nucleophilic addition reactions to olefins (Scheme II-1) are among the most powerful transformations in organic chemistry.

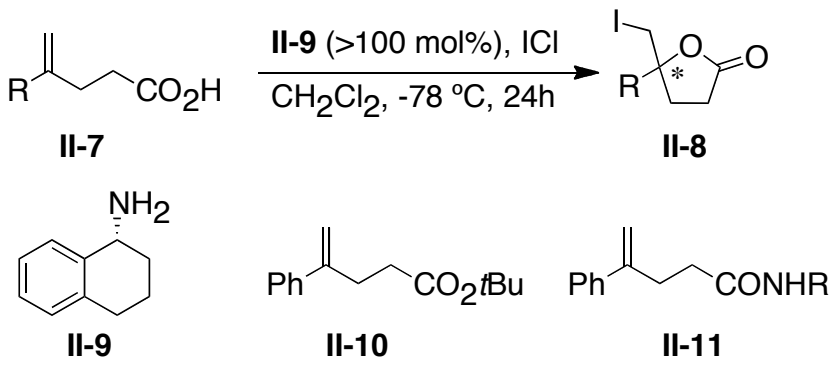
II.1.1 Asymmetric Halogenation of Olefins: Stoichiometric Methods

A few examples of asymmetric olefin halogenation have been studied. The most successful approaches to this problem was the use of stoichiometric chiral selenium or mercury reagents prepared by using multistep routes.[7, 8, 9] A few stoichiometric enantioselective halocyclization reactions have been reported, but most results in selectivity are moderate. The few highly effective methods are limited in scope. This is despite the fact that developing an asymmetric halocyclization reaction is a long-standing goal in asymmetric synthesis.[10] There are different examples in the literature that show a **"**chiral halogen**"** analogue should be able to transfer to products stereochemically when reacting with prochiral olefins. This reagent-controlled reactions has met with only limited success in halogenation reactions. Grossman and Trupp[11] reported the first reagent-controlled stereoselective halolactonization using a chiral iodonium species, in which the source of asymmetry was the dihydroquinidine–iodine complex **II-3**. The selectivities of 5-exo iodolactonization of **II-1** to **II-2** were up to 14% *ee* (Scheme II-2).



Scheme II-2: Early work on asymmetric halocyclization reactions

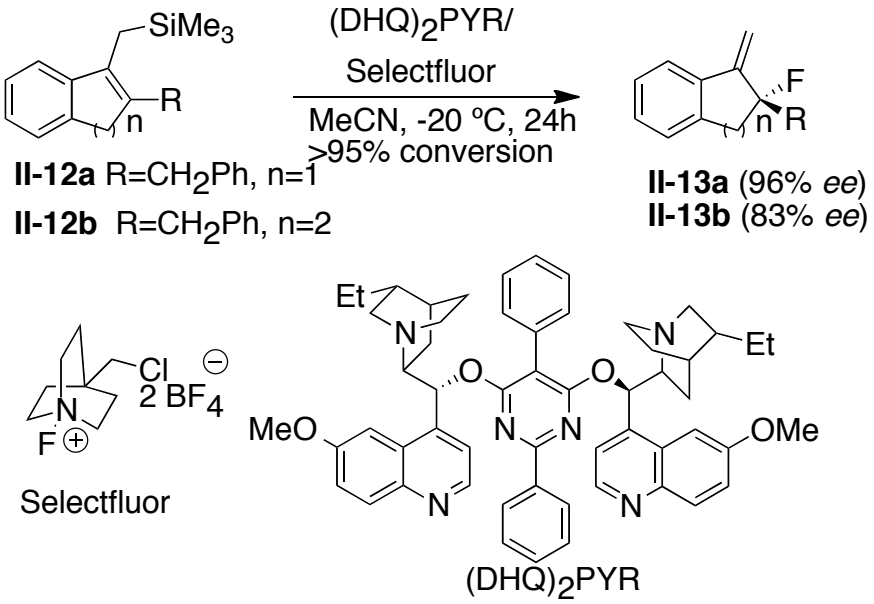
Cui and Brown[12] also showed that the pyridine complex **II-4** could induce the enantioselectivity in the bromocyclization of 4-penten-1-ol **II-5** (2.4% *ee*). Wirth and co-workers showed that the addition of non-racemic chiral primary amines gave higher levels of enantioselectively in iodolactonization reactions (<40 % ee, Scheme II-3).[13] The mixture of ICl as halogen source and **II-9** gave the best results with prochiral carboxylic acids **II-7**. The increase in selectivity of substrates of aryl ring with electron-withdrawing groups is due to the altered geometry of the intermediate iodonium ion, which is less stabilized and more reactive.[13] Reaction of the solid amine–ICl complex with carboxylic acids under solid-state reaction conditions, supports the idea that it is a chiral halogen complex that induces asymmetry during face-selective attack of the double bond.[14] Ester **II-10**, and amides **II-11** can be cyclized under similar reaction without a major drop in enantioselectivity.



Scheme II-3: Amines catalyze iodolactonization in low *ee*

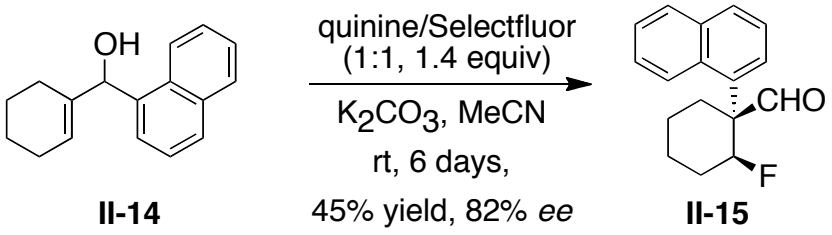
In 2003, Gouverneur and co-workers reported that the electrophilic fluorodesilylation with the enantiopure *N*-fluorocinchona alkaloids provided a highly efficient method for preparation of allylic fluorides with high *ee*. The $(DHQ)_2PYR$/Selectfluor combination fluorinated cyclic allylsilanes in MeCN to give five and six membered chiral allyl fluorides (Scheme II-4).

An asymmetric semipinacol rearrangement of racemic allylic alcohols, also mediated



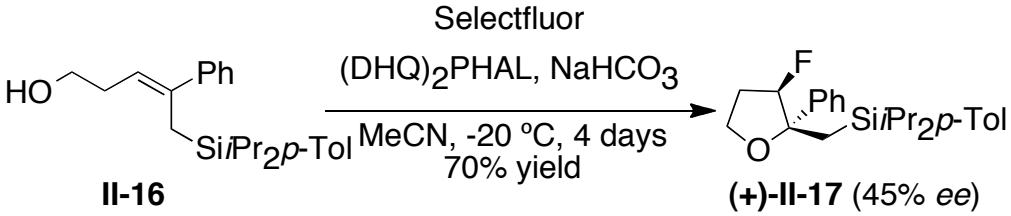
Scheme II-4: Enantioselective fluorodesilylation of allyl silne

by a combination of chinchona alkaloids and Selectfluor.[16] Best results were obtained with excess quinine/Selectfluor in MeCN in the presence of an inorganic base. The yields are low, but analysis of recovered starting materialshowed that it was racemic, so kinetic resolution was ruled out as the enantiodetermining step. Electron-donating groups in the *ortho* or *para* positions on the migrating aromatic ring were necessary to get better enantioselectivity. The highest reported *ee* is a naphthyl group (Scheme II-5).



Scheme II-5: Quinine/Selectfluor mediated asymmetric semipinacol rearrangement

Examples of enantioselective fluorocyclization of alkenes are scarce. Gouverneur and co-workers[17] recently reported the first asymmetric example of enantioselective fluorocyclization. The $(DHQ)_2PHAL$/Selectfluor combination could provide asymmetry

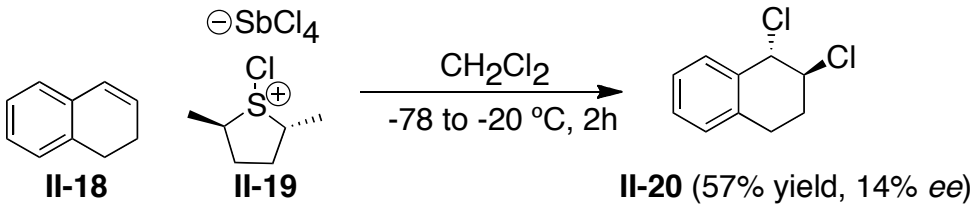


Scheme II-6: Enantioselective fluorocyclization

in the cyclization of prochiral allyl silane **II-16** to produce **II-17** (70% yield, 45 % *ee*) (Scheme II-6).

Snyder group developed a number of new racemic reagents for polyene

cyclizations.[18] Initial explorations illustrated that C2-symmetrical sulfide derivatives can induce enantioselectivity in the chlorination of olefin **II-18** (Scheme II-7).



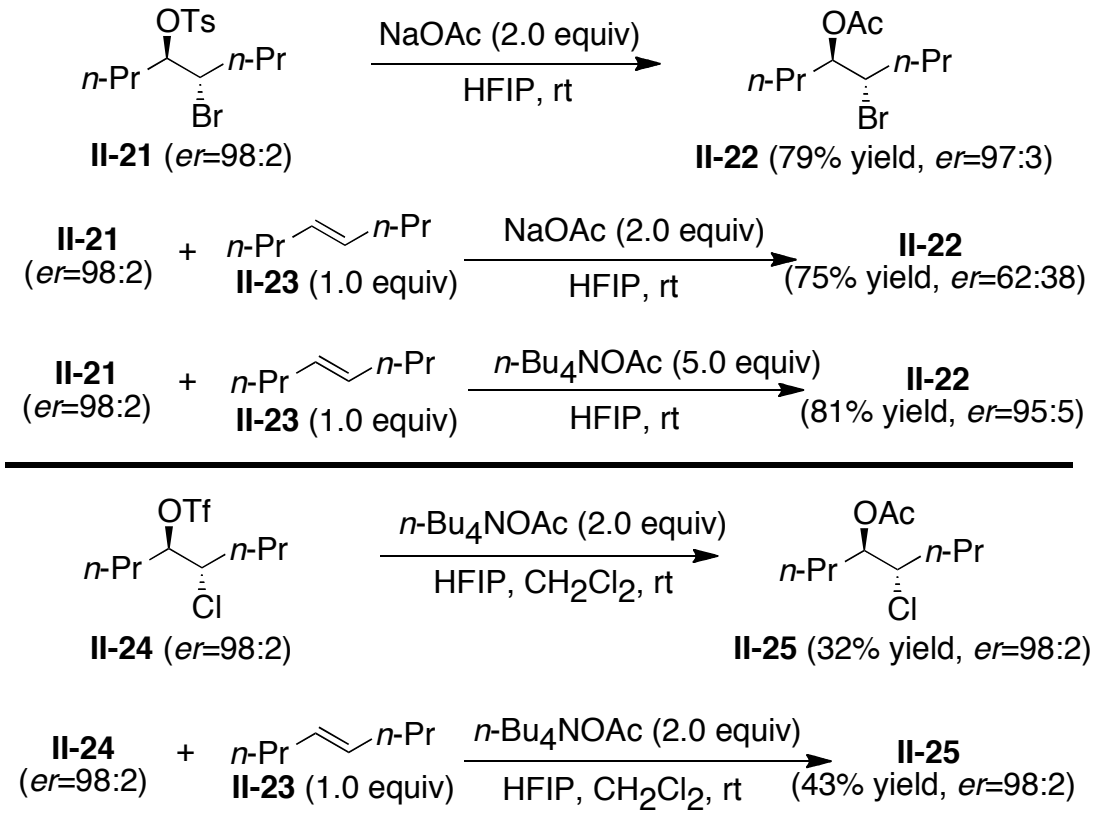
II-18 **II-19** **II-20** (57% yield, 14% *ee*)

Scheme II-7: C2-symmetric sulfide can induced asymmetry in chlorination reaction

II.1.2 Asymmetric Halogenation of Olefins: Catalytic Methods

There are a few catalytic asymmetric examples for olefin halogenation. Many of these results have been reported in the last few years. Denmark and co-workers,[19] demonstrating the careful mechanistic work of Brown and co-workers,[20, 21] have shown that enantiopure bromonium ions[22] may undergo degenerate halogen-exchange reactions with olefins.[20] The unreacted alkene is present until the end of the reaction, so the relative rates of racemization and nucleophilic capture must be overcome to achieve a successful catalytic enantioselective bromination. When tosylate **II-21** was treated in hexafluoroisopropanol (HFIP) with NaOAc, complete retention of configuration was observed (Scheme II-8). Addition of (*E*)-4-octene **II-23** to the reaction mixture caused a dramatic loss of enantiospecificity, which could not be improved by using a large excess of NaOAc.

Substituting *n*-Bu_4NOAc led to enhancement of the enantiospecificity. Chloronium ions, were found to have lower stability than bromonium ions but enantiomeric erosion



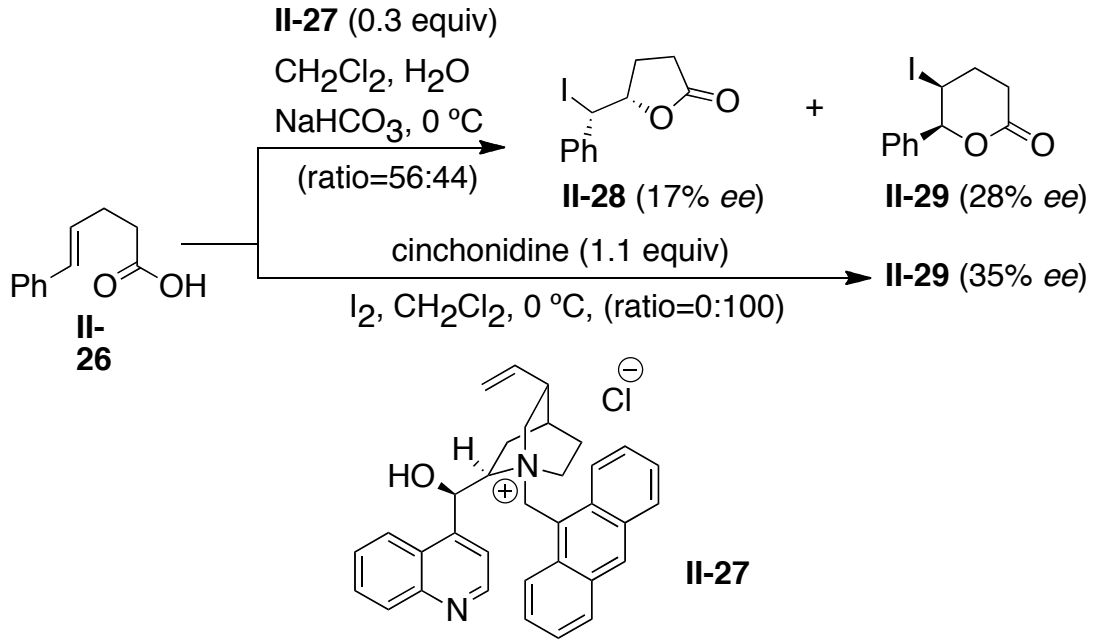
Scheme II-8: Mechanistic work on racemization of bromonium ions

was not observed in conversion of **II-24** to **II-25** even in the presence of **II-23**. The inverse relationship between chemical and stereochemical stability is attributed to the relative electronegativity of the halonium ions. The more electronegative chlorine places more positive charge on the carbon atom, and the less electronegative bromine carries more of the positive charge. The bromonium ion is more stable toward elimination and rearrangement, but allows olefin to olefin transfer of bromine by nucleophilic attack by the olefin at bromine,[19] following formation of the olefin π complex.[20]

Another mechanistic study by Denmark and co-worker showed that sulfur, selenium, and phosphorus donors can accelerate halocyclization reactions with NBS and

N-iodosuccinimide (NIS).[23]

In 1979 Julia and co-worker reported addition of chlorine to a variety of alkenes under asymmetric phase-transfer conditions.[24] More recently, chiral quaternary ammonium salts **II-27** derived from cinchona alkaloids were found to induce low levels



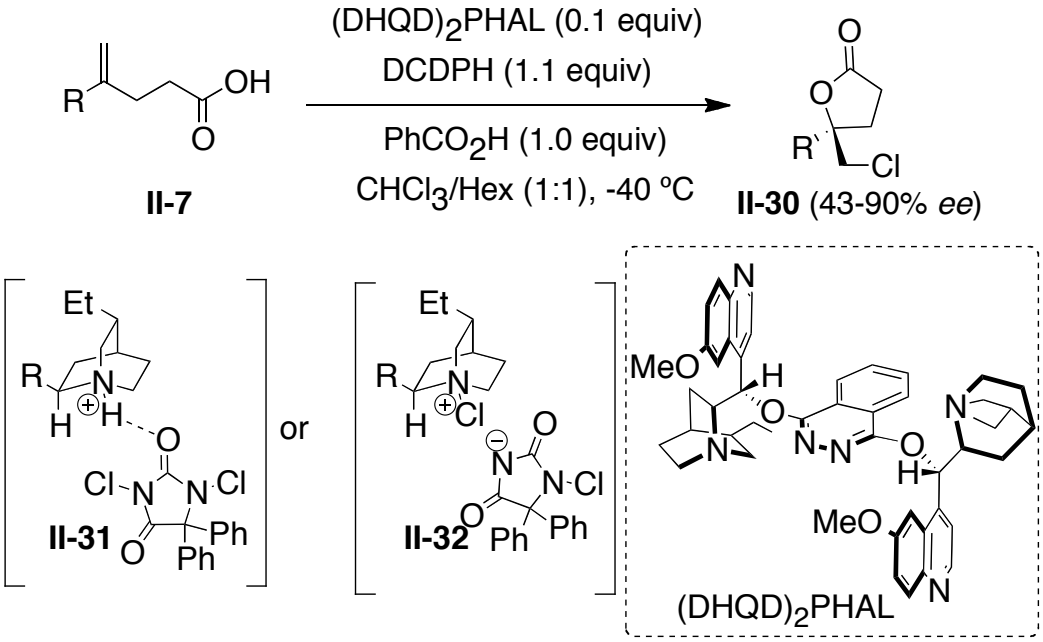
Scheme II-9: Iodolactonization catalyzed by chiral quaternary ammonium salt

of asymmetry (<35% *ee*) during iodolactonizations of *trans*-5-aryl-4-pentenoic acids **II-26** (Scheme II-9) under catalytic conditions.[25] When using stoichiometric alkaloids, cinchonidine provided exclusively **II-29**.[26]

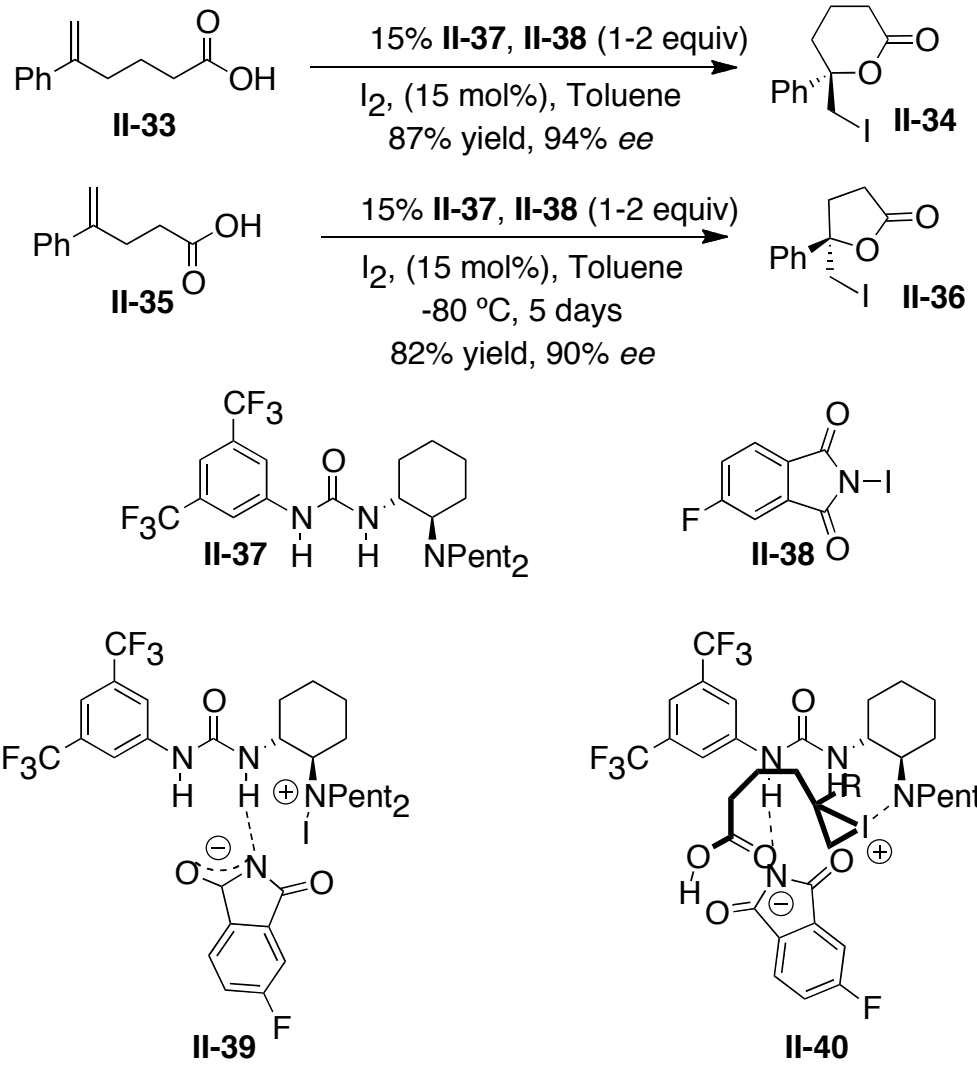
Several organocatalytic methods for enantioselective halolactonization of carboxylic acids were reported in 2010. All of these studies use bifunctional catalysts. Our group[27] reported the first catalytic enantioselective chlorolactonization of exocyclic 4-substituted pentenoic acids **II-7** mediated by $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ and DCDPH (1,3-dichloro-5,5-diphenylhydantoin). When substrates **II-7** were allowed to react in

$CHCl_3$–Hexane, in the presence of benzoic acid, the corresponding chlorolactones **II-30** were obtained with high enantioselectivities (Scheme II-10).

Aliphatic substituents led to lower enantioselectivity. ^1H NMR spectroscopy experiments suggest a hydantoin/catalyst complex (**II-31** or **II-32**) imparts enantioselectivity and rate acceleration. Subsequent mechanistic studies indicate the N1 chlorine of the dichlorodiphenyl hydantoin serves as an inductive activator, and the N3 chlorine is delivered to the substrate.[28]



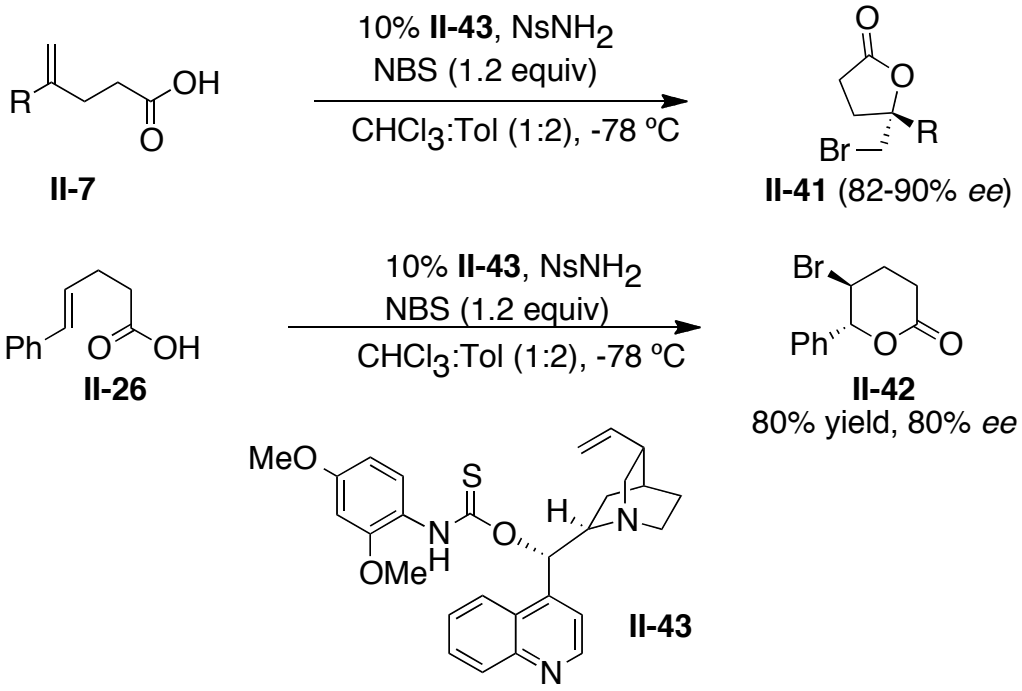
Scheme II-10: Catalytic enantioselective chlorolactonization



Scheme II-11: Jacobsen's catalytic asymmetric iodolactonization reaction

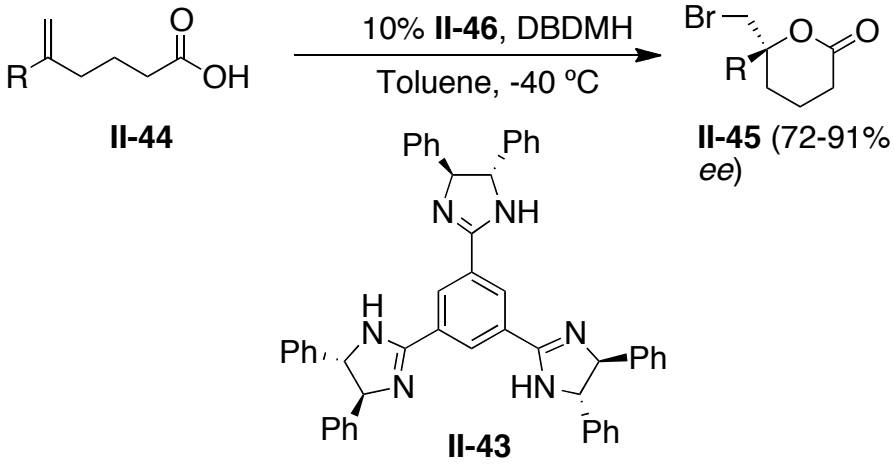
Jacobsen and co-worker used a aminourea catalyst to achieve enantioselectivity iodolactonization.[29] Tertiary aminourea complex **II-37** combined with an I^+ source gave five and six-membered iodolactones with high enantioselectivity. They used the catalytic I_2 in combination with an *N*-iodoimide, with *N*-iodo-4-fluorophthalimide **II-38**. In the case of 5-substituted hexenoic acid derivatives (such as **II-33**, Scheme II-11), a correlation between the electronic properties of the olefin substituent and

enantioselectivity was observed, with electron deficient derivatives undergoing more enantioselective cyclization. Mechanistically, the iodonium ion of hexenoic acid **II-33** formed intermediate iodonium ion complex **II-40**, which keeps a tertiary amino iodoium ion interaction during cyclization. In the case of pentenoic acid **II-35**, a lower I_2 loading was needed.



Scheme II-12: Catalytic enantioselective bromolactonization

Catalytic enantioselective bromolactonization of the exocyclic pentenoic acids **II-7** can be mediated by cinchonine derived thiocarbamate catalysts **II-43** (Scheme II-12).[30] The high levels of enantioselectivity are proposed to be due to the rigid skeleton and bifunctional nature of the catalyst **II-43**. Structural variation of the catalyst shows that the NH and S of the thiocarbamate are necessary for the high selectivity. The optimized procedure was also found to be applicable to the formation of an enantioenriched



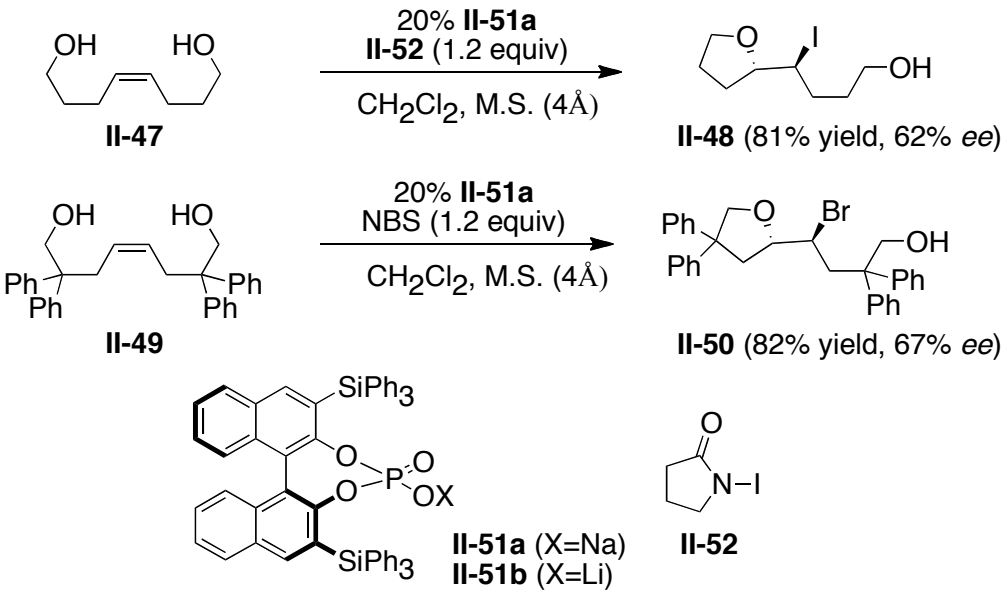
Scheme II-13: Catalytic enantioselective bromocyclizations

δ-lactone **II-42**.

Asymmetric bromolactonization catalyzed by a C3-symmetric chiral trisimidazoline **II-46**[31] with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) was also recently reported (Scheme II-13). Fujioka and co-workers suggest that a chiral-ion pair between the catalysts and substrate causes enantioselectivity, but they did not rule out the possibility of the catalyst activating the brominating agent.

Hennecke and co-workers recently reported a promising organocatalytic approach to haloetherfications by desymmetrization of *in situ* generated *meso* halonium ions.[32] The approach is based on selectively opening halonium ions in the presence of a chiral counteranion and aims to circumvent the potentially insufficient stereochemical integrity of halonium ions by alkene-to-alkene transfer.[19, 21] Treatment of symmetrical diol **II-47** with chiral phosphoric acid salt **II-51a** in the presence of electrophilic iodine sources

gave enantioenriched **II-48** under practical reaction conditions. Enantioselectivities for bromocyclizations can reach up to 67% *ee* (Scheme II-14). The authors suggest that

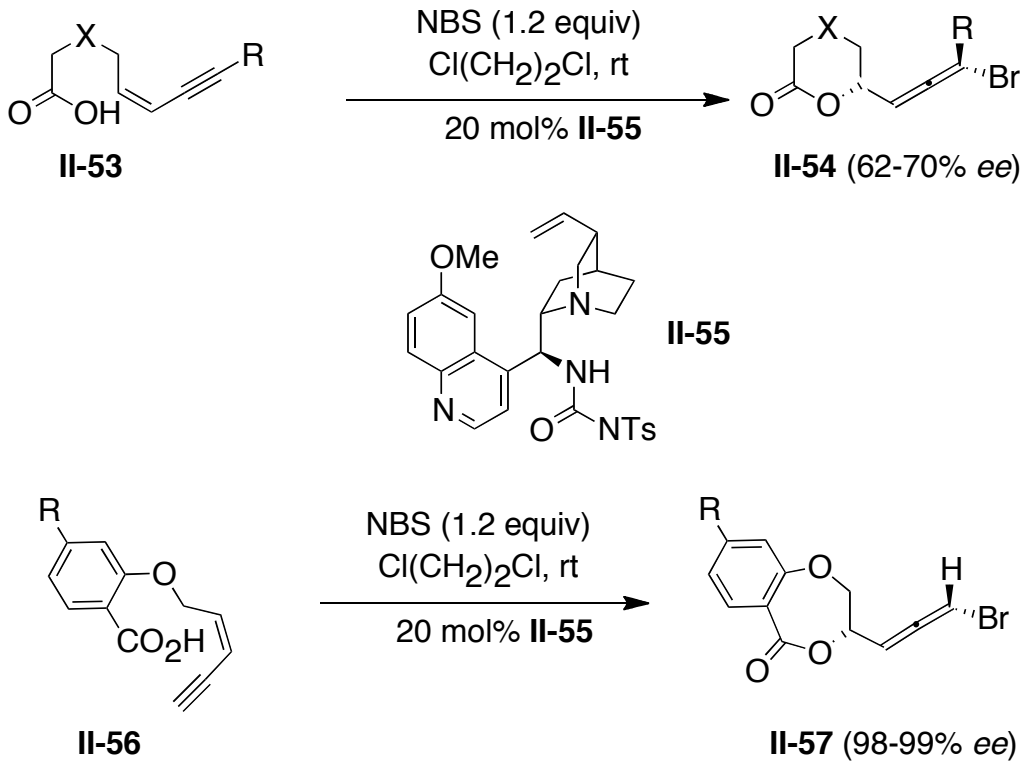


Scheme II-14: Counterion controlled asymmetric opening of *meso*-halonium ions

similar levels of enantioselectivity were observed by using sodium salt **II-51a** or lithium salt **II-51b**, and also show that the catalyst cannot be acting as a Lewis acid, but can activates the halogenating agent prior to halonium ion generation.

The Tang group recently discovered a DABCO-catalyzed *syn*-selective 1,4-bromolactonization of enynes. This reaction gave axially chiral allenes as the major products[33] and the same group also demonstrated that the catalyst **II-55** promotes highly enantioselective bromolactonization of (*Z*)-enynes **II-53** and **II-56** to give bromoallenes **II-54** and **II-57** (Scheme II-15).[34] Reactions with catalysts related to **II-55** revealed the importance of the hydrogen bond donating urea, as well as the configuration at the center bearing this group. The quinuclidine nitrogen of the catalyst is also critical for activity

and it is proposed that **II-55** may both activate the system by deprotonation of the acid and activation of the NBS by hydrogen bonding.



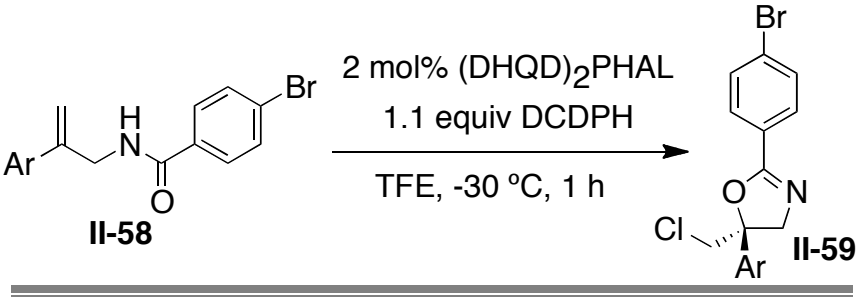
Scheme II-15: Enantioselective bromolactonization of conjugated (*Z*)-enyne

II.2. A Catalytic Asymmetric Chlorocyclization of Unsaturated Amides[35]

We have recently reported the catalytic asymmetric chlorolactonization of alkenoic acids.[27] We were interested by the possibility of a one-step access to chiral heterocycles such as oxazolines and dihydrooxazines by a catalytic asymmetric halocyclization of unsaturated amides. The conversion of benzamide **II-58** to oxazoline **II-59** was studied in the presence of $(DHQD)_2PHAL$ as the best catalyst candidate affording the desired oxazoline **II-59** in 68-98% *ee* (Table II-1) with DCDPH as the terminal chlorine source.[35] Reactions with other chlorenium sources were marred with poor

enantioselectivities and/or poor conversions. Solvent screening process revealed trifluoroethanol (TFE) to be the optimal solvent for the chlorocyclization. The effect of catalyst loading, concentration and temperature was also studied. It was observed that the stereoselectivity of this reaction was not diminished even at a catalyst loading of 2 mol%.

Table II-1: Chlorocyclization of 1,1-disubstituted olefin substrates



II-58 **II-59**

Entry	R	Yield (%)[a]	*ee* (%)[b]
1	Ph	93	98
2	3-NO_2-Ph	75	68
3	3-OMe-Ph	72	93
4	4-F-Ph	65	87
5	4-Br-Ph	89	84
6	4-Cl-Ph	94	87

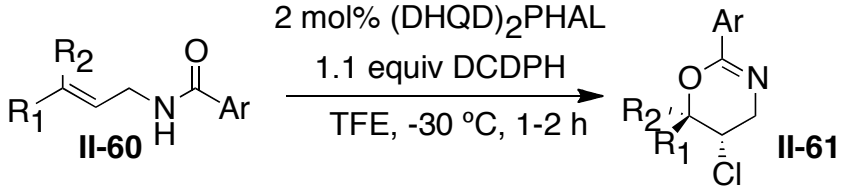
[a]Isolated yields after column chromatography. [b]*ee*s were determined by HPLC analysis.

It also emerged that a concentration of 0.04 M and a temperature of -30 ^{o}C was optimal.[35]

We discovered that the same reaction conditions could be extended to *trans*-disubstituted and trisubstituted olefin substrates which yielded the corresponding dihydro-4-H-1,3-oxazines (Table II-2). These reactions were more stereoselective and

almost all of the substituted phenyl rings evaluated gave 20->99% enantioselectivity. The

Table II-2: Chlorocyclizaion of *trans*-disubstituted olefin substrates

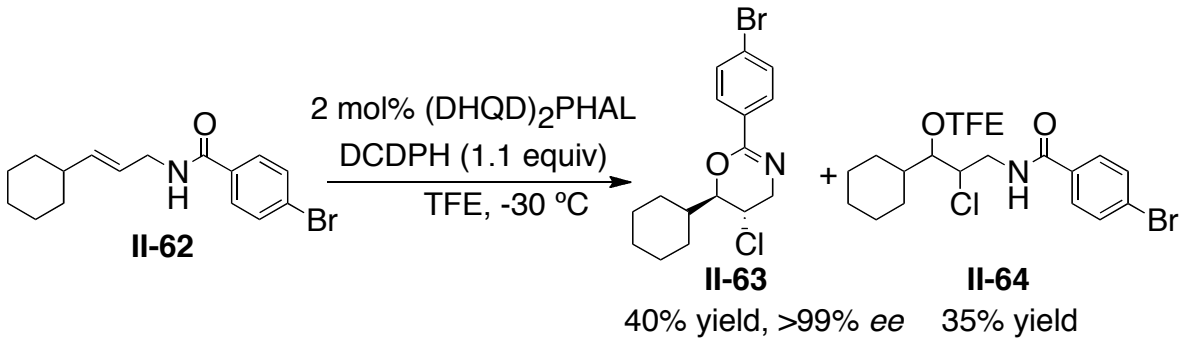


Entry	R^1	R^2	Ar	Yield (%)[a]	*ee* (%)[b]
1	Ph	H	4-Br-Ph	91	99
2	Ph	H	4-OMe-Ph	93	>99
3	4-F-Ph	H	4-Br-Ph	99	95
4	4-BrPh	H	4-Br-Ph	85	93
5	4-CF_3-Ph	H	4-Br-Ph	94	95
6	4-OMe-Ph	H	4-Br-Ph	84	20
7	4-Me-Ph	H	4-Br-Ph	93	60
8	2-Me-Ph	H	4-Br-Ph	99	87
9	2-Me-Ph	H	4-OMe-Ph	64	91
10	Ph	Ph	4-Br-Ph	92	86

[a]Isolated yields after column chromatography. [b]*ee*s were determined by HPLC analysis.

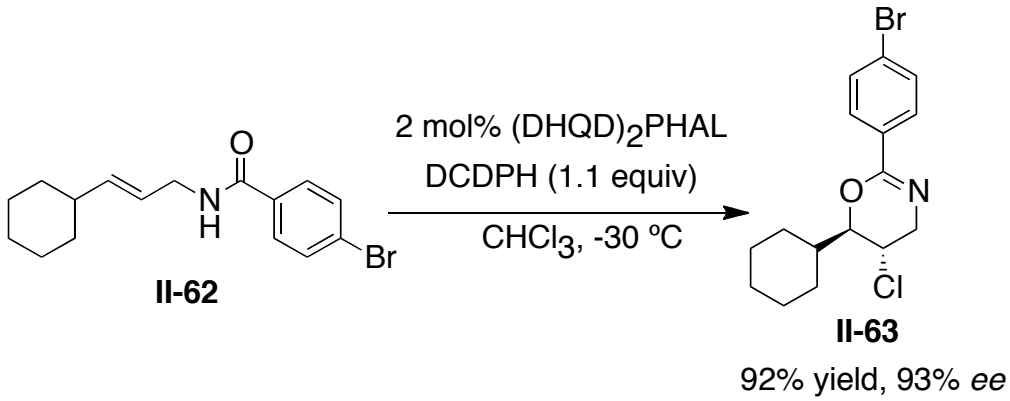
4-Br-Ph was determined as the optimal amide end functionality for the 1,1 and *trans* disubstituted olefin substrates. Electron deficient aryl rings presented no problems yielding excellent stereoselectivities (Table II-2, entries 2, 3, 5). Electron rich

substituents led to significant erosion of stereoselectivity. For example the 4-OMe-Ph substituted amide gave the corresponding product in only 20% *ee* and 84% isolated yield



Scheme II-16: Chlorocyclization of aliphatic olefin in TFE

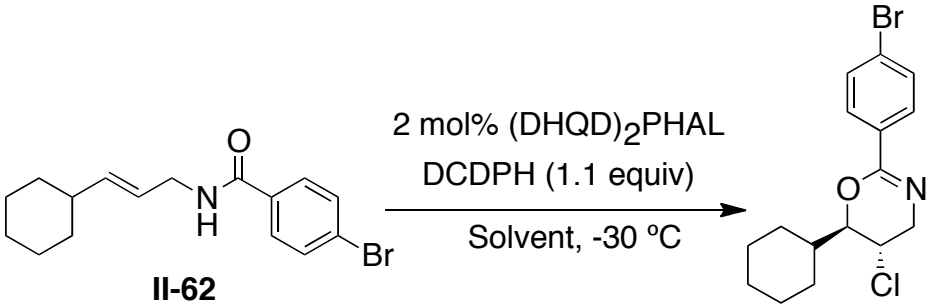
(Table II-2, entry 6). The 4-Me-Ph substituent also gave only moderate levels of stereoinduction affording product in 60% *ee* (Table II-2, entry 6). The 2-Me-Ph group was better tolerated returning the corresponding product in excellent yield (99%) and good enantioselectivity (87% *ee*, Table II-2, entry 8). This result indicates that the amide



Scheme II-17: Chlorocyclization of aliphatic olefin in $CHCl_3$

end functionality is an invaluable handle for electronic and steric fine-tuning, allowing for the systematic optimization of the enantioselectivity for a given substrate. Trisubstituted olefin substrate was also compatible with this chemistry (Table II-2, entries

Table II-3: Solvent screen of chlorocyclization of aliphatic olefin



II-62 **II-63**

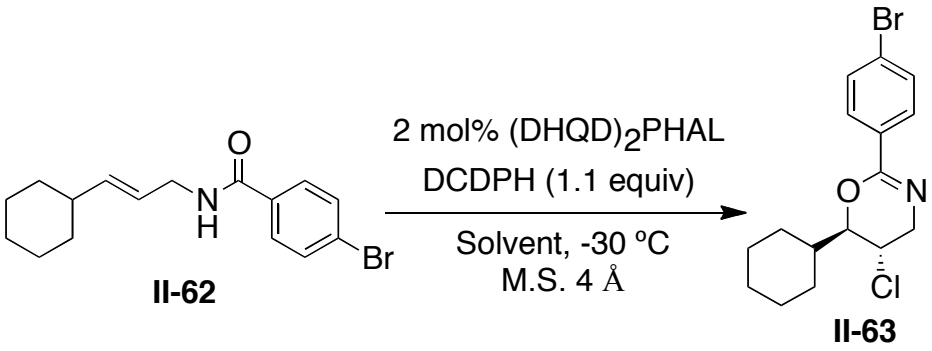
Entry	Solvent	Yield (%)[a]	*ee* (%)[b]
1	TFE	40	>99
2	$CHCl_3$	92	93
3	$CHCl_3$-TFE (9:1)	92	87
4	$CHCl_3$-TFE (8:2)	94	79
5	$CHCl_3$-TFE (1:1)	90	53

[a]Isolated yields after column chromatography. [b]*ee*s were determined by HPLC analysis.

10). The absolute stereochemistry of 2-(4-bromophenyl)-5-chloro-6-phenyl-5,6-dihydro-4*H*-1,3-oxazine (Table II-2, entry 1) was verified by X-ray diffraction and was inferred by analogy for other substrates.[35]

Substrates with aliphatic olefin substituents were next studied. Substrate **II-62** was prepared and evaluated using the standard conditions shown in Table II-2. The main problem for this reaction was the incorporation of TFE as a nucleophile to generate **II-64** in 35% yield along with the desired product **II-63** in 40% yield and >99% *ee* (Scheme II-16). To solve this problem, we examined other solvents that cannot participate as

Table II-4: Solvent screen of chlorocyclization of aliphatic olefin



II-62 **II-63**

Entry	Solvent	Yield (%)[a]	*ee* (%)[b]
1	$CHCl_3$-Hex (1:1)	94	64
2	CH_3CN-CCl_4 (1:1)	87	80
3	1-nitropropane	77	>99

[a]Isolated yields after column chromatography. [b]*ee*s were determined by HPLC analysis.

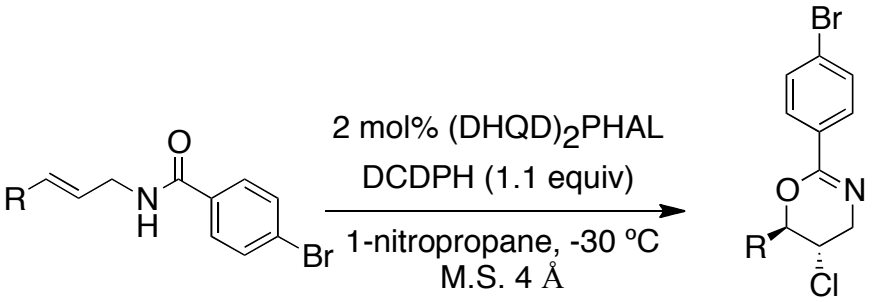
nucleophile (Scheme II-17). This reaction proceeded well in $CHCl_3$ and provided the desired product in high yield (92%) and good selectivity (93% *ee*) albeit with lower selectivity in comparison to TFE. Next, we studied different mixture of $CHCl_3$ and TFE. In all cases the enantioselectivity drop although the yield of the reactions remained good (Table II-3).

The enantioselectivity of the reaction in $CHCl_3$-Hex was less selective than $CHCl_3$ (64% *ee*, Table II-4, entry 1). The selectivity could be further enhanced to 80% *ee* when CH_3CN-CCl_4 was utilized as the solvent, however it was still lower than $CHCl_3$ (Table II-4, entry 2). Fortunately, the use of 1-nitropropane in the presence of 4 Å molecular sieves alleviated our problem and the product **II-63** was obtained in high yield and high

selectivity (>99% *ee*, Table II-4, entry 3).

Likewise, the conformationally more flexible *n*-pentyl substituent was also well tolerated and returned the corresponding product in excellent yield (90%) and *ee* (>99%

Table II-5: Chlorocyclization of aliphatic olefin substrates



Entry	R	Yield (%)[a]	*ee* (%)[b]
1	Cy	77	>99
2	*n*-C_5H_{11}	90	>99
3	CH_2Cy	80	88

[a]Isolated yields after column chromatography. [b]*ee*s were determined by HPLC analysis.

ee, Table II-5, entry 2). Cy-CH_2 substitute also produced the corresponding product in good enantioselectivity (88% *ee*, Table II-5, entry 3).[35] It is important to note that no regioisomeric 5 membered ring products were detected under the optimized reaction conditions for aliphatic substrates. Also, the absolute stereochemistry of products with aliphatic substituents was the same as that for products with aryl substituents (as verified by X-ray diffraction of **II-63**).[35] Substrates with *Z*-olefins did not undergo halocyclization to the desired products presumably due to stereoelectronic constraints

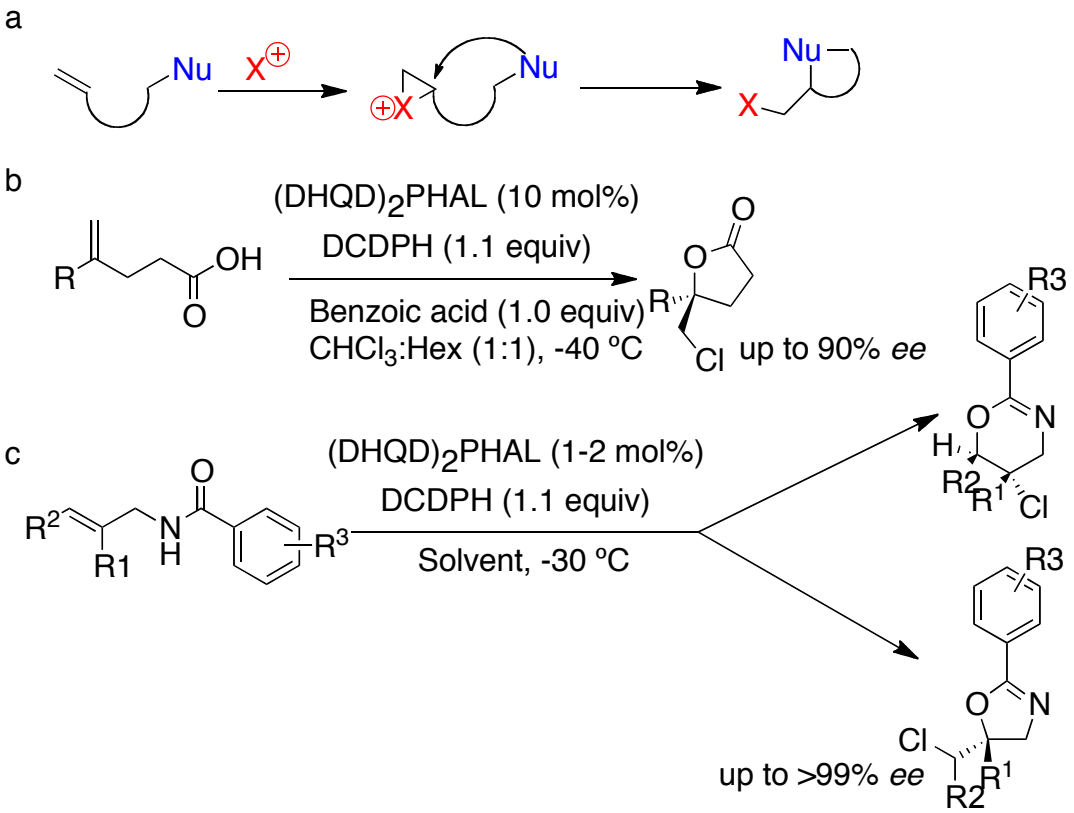
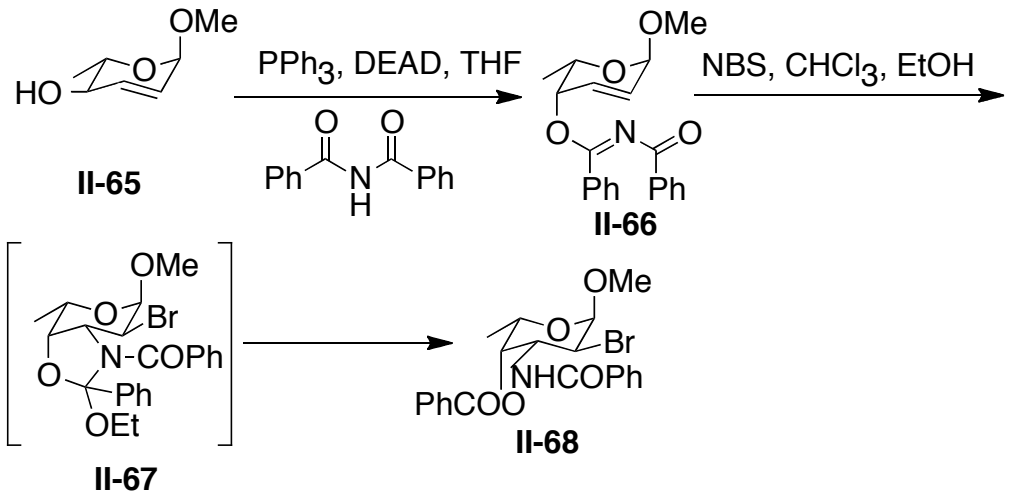


Figure II-1: a) Generalized halocyclization reaction, b) Recently developed catalytic enantioselective chlorolactonization reaction and c) chlorocyclization of unsaturated amides

which are well precedented in halolactonization reactions of similar substrates.[36]

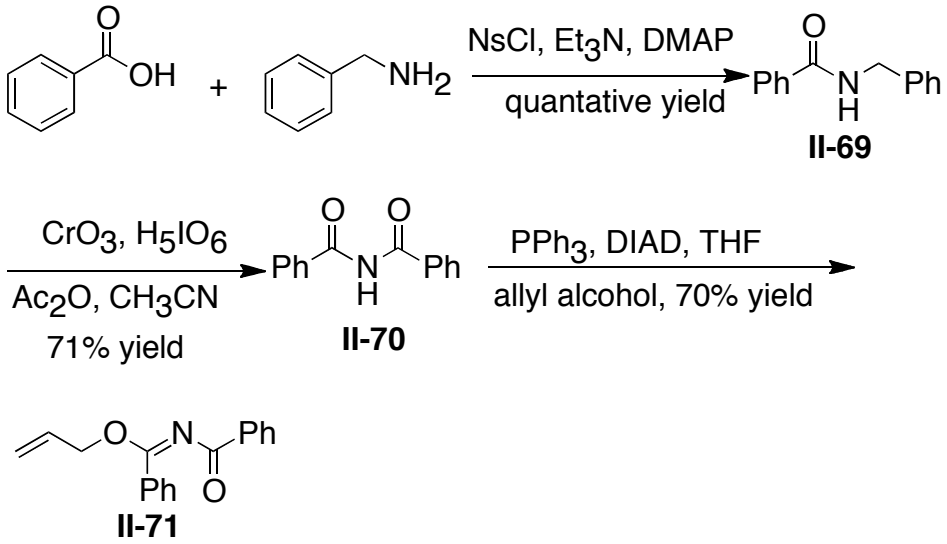
II.3. Evaluation of Other Reactions With $(DHQD)_2PHAL$ Catalyst System

Electrophilic halocyclizations of olefins, depicted in general terms in Figure II-1, are common and important reactions in organic chemistry; however controlling the enantioselectivity of these reactions is not trivial.[37, 38] Two challenges in this class of asymmetric transformations are: (1) developing an efficient catalyst system which delivers the halenium to the olefin in an enantioselective fashion and (2) preventing racemization of the resulting chiral halonium, which can be eroded by a process known as olefin to olefin transfer.[19]



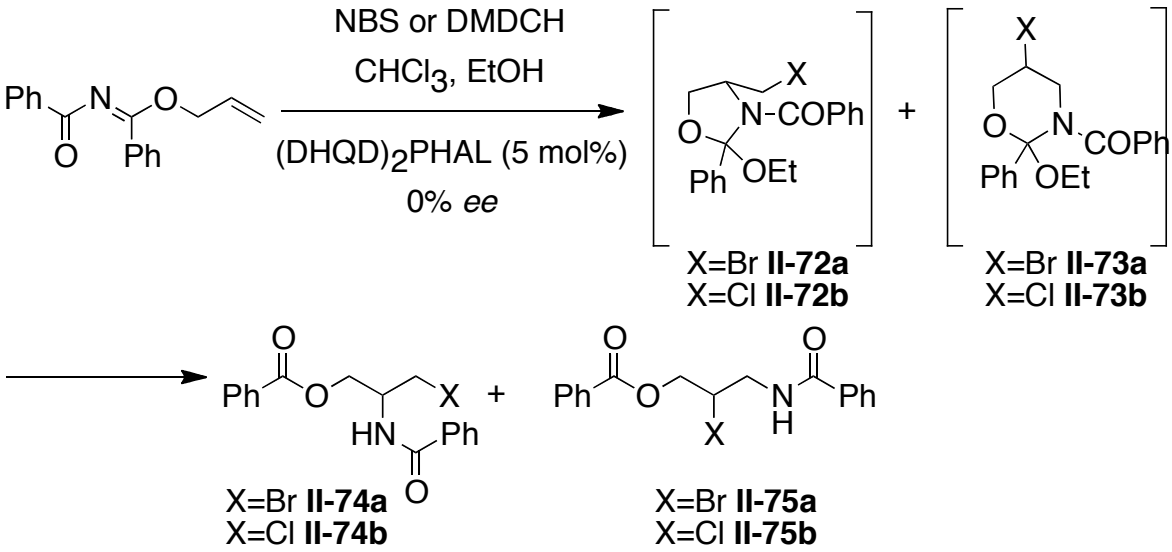
Scheme II-18: Synthesis of the benzoate-amide **II-68**

The general, mechanism of all halocyclizations involves the formation of a halonium intermediate, which then undergoes attack by an intramolecular nucleophile to create a ring. Based on this mechanism, two different strategies can be used to acquire high enantioselectivity in various halocyclizations. One relies on the chiral delivery of the



Scheme II-19: Synthesis of the imidate **II-71**

halenium to the olefin, while the other relies on the asymmetric attack of the nucleophile to the halonium. A recent breakthrough in our lab has led to the development of a



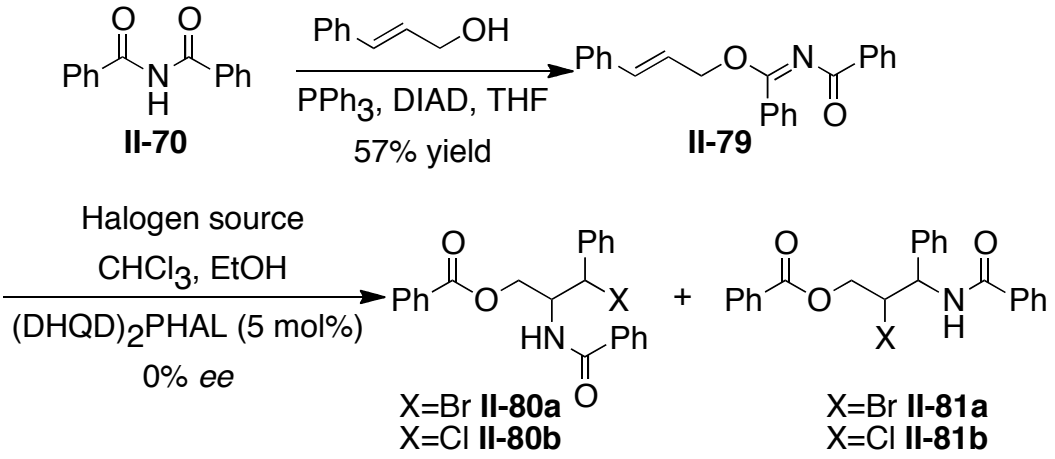
Scheme II-20: Reaction of imidate **II-71** with NBS and DCDMH

catalytic, enantioselective chlorolactonization of alkenoic acids[27, 28] and chlorocyclization of unsaturated amides (Figure II-2).[35] Disscused in this chapter are the application of the $(DHQD)_2PHAL$ catalyst system for the development the other asymmetric halocyclization.

In 1985, Sammes and Thetford showed that the imidate **II-66** with *N*-bromosuccinimide in chloroform containing ethanol produced the *ortho*-amide **II-67**, which was readily hydrolyzed *in situ,* under acidic conditions, to give the benzoate-amide **II-68** (Scheme II-18).[39]

We attempted to develop an asymmetric version of this reaction under our catalytic system. For this purpose, imidate **II-71** was synthesized in a few steps as is shown in

Table II-6: Reaction of imidate **II-79** with different halogen sources and temperature

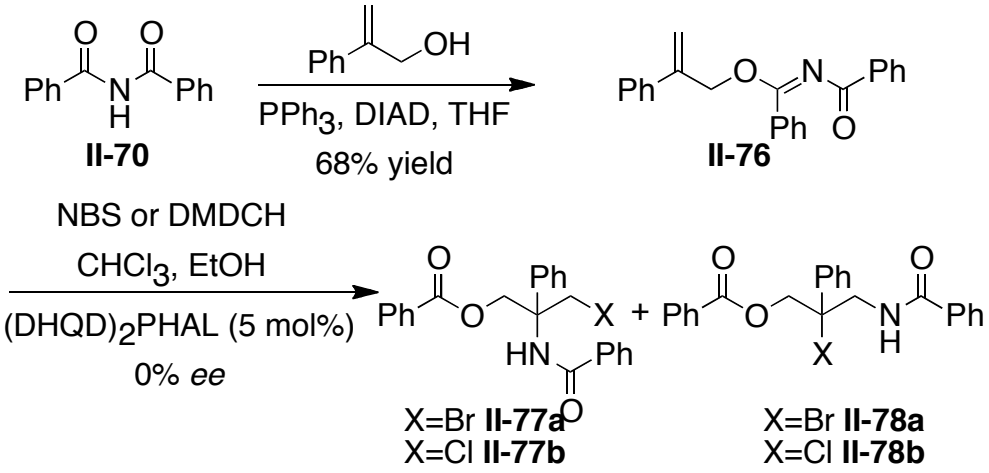


Entry	Halogen source	Temperature	Conversion (%)	**II-80**:**II-81**
1	NBS	rt	77	1:1
2	NBS	-40 ^{o}C	80	1:1
3	DCDMH	rt	90	1:1
4	DCDMH	-40 ^{o}C	50	1:1.5
5	TCCA	rt	90	1:1
6	TCCA	-40 ^{o}C	80	1:1

Scheme II-19. Amidation of benzoic acid with benzyl amine, followed by oxidation of the methylene provided **II-70**. Mitsunobu reaction afforded our desired imidate **II-71** in 70% yield. Imidate **II-71,** under our catalytic system reacted with NBS to provide regioisomers **II-74a** and **II-75a** (1:1 ratio) with no apparent enantioselectivity. The lack of regio and enantioselectivity was also observed when DCDMH was used as the chlorionium source (Scheme II-20).

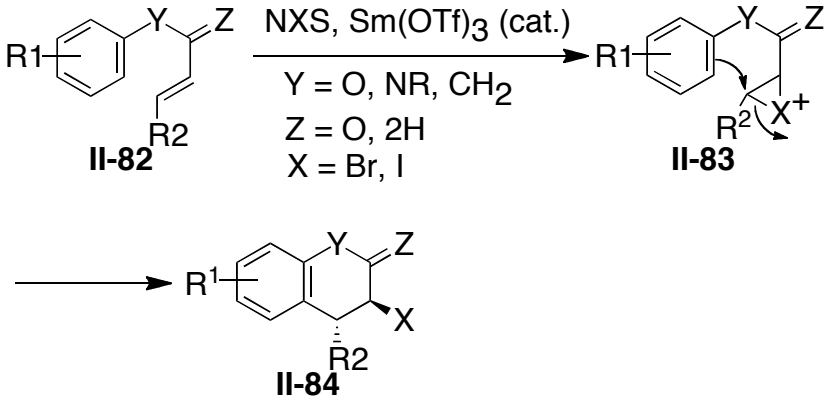
The 1,1-disubstituted olefin **II-76** was synthesized in hopes of gaining

regioselectivity. Suprisingly, the reaction of imidate **II-76** with NBS or DCDMH in the presence of $(DHQD)_2PHAL$ provided once again a 1:1 regioisomeric mixture of products without enantioselectivity (Scheme II-21).



Scheme II-21: Reaction of imidate **II-76** with NBS and DCDMH

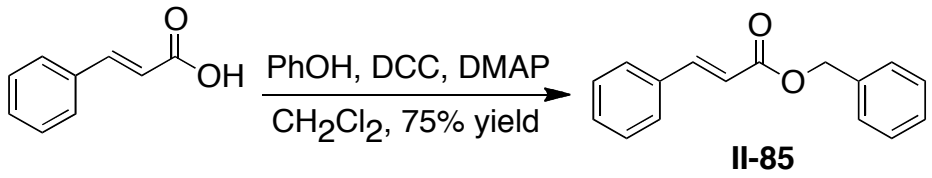
Since addition of phenyl group in C2 was not helpful for improving the regio and enantioselectivity, the *trans*-substituted imidate was examined. Table II-6 shows the use of a variety of halogen sources and temperature utilized for this reaction. The best result



Scheme II-22: Lewis acid catalyzed intramolecular haloarylation of alkenes using *N*-halosuccinimide (NXS) as the halogen source

was obtained when DCDMH at -40 ^{o}C was used to give **II-81a**:**II-81b** (1:1.5), in 50% conversion after 24 h (Table II-6, entry 4). No enantioselectivity was observed in any of the examples. The lack of success was probably due to low interaction of substrate and catalyst. In order to develop new asymmetric reaction with $(DHQD)_2PHAL$ catalyst, the other halocyclization reactions was examined.

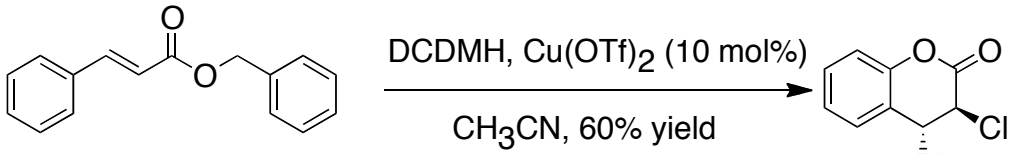
Hajra and co-workers in 2005 developed a Lewis acid catalyzed intramolecular haloarylation of alkenes using inexpensive and easily available *N*-halosuccinimide (NXS) as



II-85

Scheme II-23: Synthesis of alkene **II-85**

the halogen source. This catalytic process is a regio and stereoselective method and is utilized to synthesize a diverse range of structural motifs, such as chromanones, chromans, quinolones, tetrahydroquinolines and tetralins with halofunctionality (Scheme II-22).[40]



II-85 **II-86**

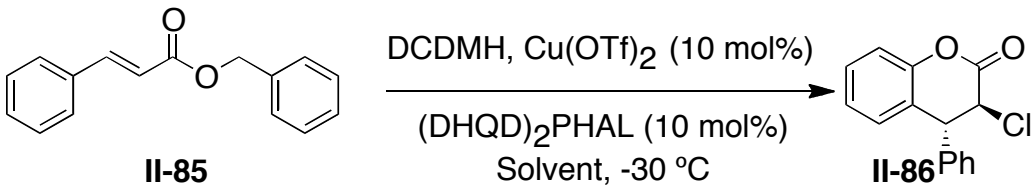
Scheme II-24: Racemic intramolecular haloarylation of alkene **II-85**

We tested the intramolecular haloarylation reactionwith our catalytic system. The desired olefin was synthesized in one step as shown in Scheme II-23.

Initially, the racemic haloarylation of alkene **II-85** was examined, in the presence of

DCDMH as the halogen source in acetonitrile with copper triflate instead of samarium triflate (the best second catalyst for this reaction),[40] providing the desired product in 60%

Table II-7: Solvent screen for chloroarylation of **II-85**



II-85 **II-86**

Entry	Solvent	*ee* (%)[a]	Entry	Solvent	*ee* (%)[a]
1	CH_3CN	0	6	acetone	0
2	$CHCl_3$	2	7	THF	0
3	CH_2Cl_2	0	8	TFE	4
4	DMSO	0	9	$CHCl_3$-Hex (1:1)	2
5	DMF	0	10	1-nitropropane	1

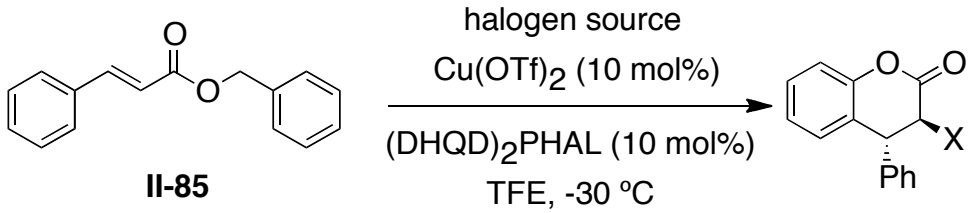
[a] *ee*s were determined by HPLC analysis.

yield (Scheme II-24).

This reaction in the presence of $(DHQD)_2PHAL$ showed no enantioselectivity, so a comprehensive solvent screen was performed in an attempt to drive the enantioselectivity of the reaction higher. Ten different solvents were screened in the test reaction (**II-85** to **II-86**). The range of solvents screened included protic, aprotic, non-polar and polar examples (Table II-7). None of the solvents led to high enantioselectivity of the desired product **II-86**. TFE retuned the product in 4% *ee* accounting for the highest selectivity

obtained for this reaction (Table II-7, entry 8). We decided to investigate the enantioselectivity of the chlorocyclization reaction in the presence of different hydantoins and other chlorine sources. We investigated three hydantoins with different substituentsat C5 (Table II-8). In the TFE solvent system, going from dichloro-dimethyl hydantoin (4% *ee*, Table II-8, entry 1) to dichloro-diphenyl hydantoin (Table II-8, entry 2) the selectivity

Table II-8: Halogen source screening



II-85

Entry	Halogen source	*ee* (%)[a]	Entry	Halogen source	*ee* (%)[a]
1	DCDMH	4	4	NCS	0
2	DCDPH	4	5	TCCA	0
3	DCDHH	2	6	NBS	0

remain almost the same. The removal of the C5 substitute on the chlorohydantoin returned **II-86** in lowered 2% *ee* (Table II-8, entry 3). *N*-Chlorosuccinimide and trichloroisocyanuric acid (TCCA) produced an inferior result (0% *ee*, entries 4, 5). It is also noteworthy that the transformation in the presence of *N*-bromosuccimide (NBS) provides the desired product **II-86** in racemic mixture (Table II-8, entry 6).

II.3.1. Synthesis of Asymmetric Cyclic Sulfates by Halocyclization

Cyclic sulfates are versatile electrophiles.[41, 42] They react with a variety of nucleophiles to facilitate the construction of natural products[43] and specific functionality, such as

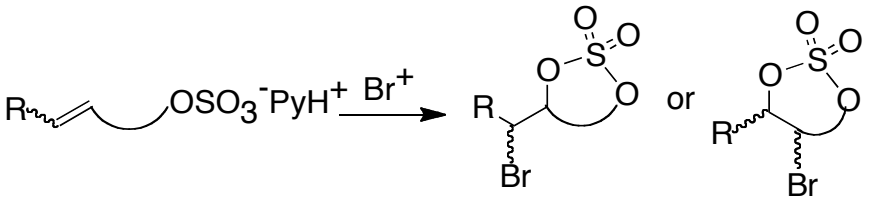
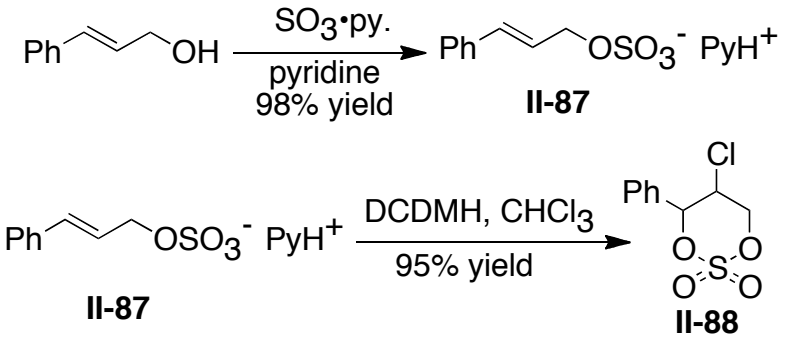


Figure II-2: Synthesis of cyclic sulfates by

aziridines,[44] modified sugars,[45] and cyclopropane derivatives.[46, 47] The use of cyclic sulfates was limited by the lack of an efficient method for their synthesis[48] until the advent of methods for the oxidation of cyclic sulfite intermediates.[49] Access to cyclic sulfates incorporating a wider range of functional groups would expand applications. Kiessling and co-workers report a new method for cyclic sulfate synthesis (Figure II-2).[50] Via halocyclization reactions, six-membered and larger cyclic sulfate ring systems can be generated; these compounds are difficult to access through cyclic sulfite intermediates. Moreover, a diversity of functional groups can be incorporated into the halocyclization substrates, including those that are incompatible with oxidants needed to convert cyclic sulfites to sulfates. The halocyclization process occurs with predictable regioselectivity, and the resulting products can be selectively modified. Significantly, this approach to cyclic sulfate formation introduces two new stereocenters, which could be used advantageously in organic syntheses (Figure II-2).[50]

Initial efforts were geared towards establishing a test reaction to screen solvents for the asymmetric induction of cyclic sulfates. Our test substrate **II-87** was synthesized in one step from *trans*-cinnamyl alcohol. A racemic chlorocyclization of corresponding sulfate returned the desired product **II-88** in 95% yield (Scheme II-25). An initial screen

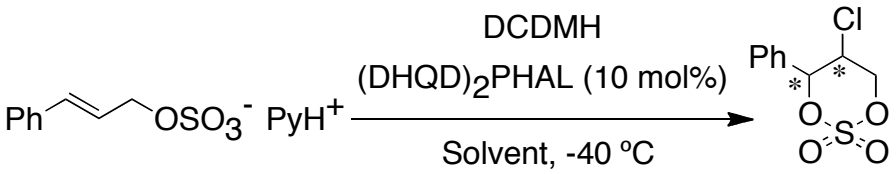


Scheme II-25: Racemic chlorocyclization of sulfate **II-87**

was conducted whereby a number of different solvents were assayed in the test reaction (**II-87** to **II-88**). A control experiment with our catalytic reaction conditions employing 10 mol% of $(DHQD)_2PHAL$ at -40 ^oC in chloroform (Table II-9, entry 1) returned halosulfate **II-88** in 10% *ee*. Changing the solvent to acetonitrile resulted in a more selective transformation (14% *ee*, Table II-9, entry 2). Mixture of chloroform-hexanes (1:1) provided **II-88** in 20% *ee* (Table II-9, entry 4). Excitingly, going to more polar and protic solvents such as *n*-PrOH increased the selectivity up to 93% (Table II-9, entry 5).

The major problem for this transformation is the low stability of product **II-88**, which decomposed after a few hours even stored cold.

Table II-9: Solvent screening for chlorocylization of **II-87**



II-87 **II-89**

Entry	Solvent	yield (%)[a]	*ee* (%)[b]
1	$CHCl_3$	82	10
2	CH_3CN	87	14
3	CH_2Cl_2	75	12
4	$CHCl_3$-Hex	79	20
5	*n*-PrOH	88	93

[a]Isolated yields after column chromatography. [b]*ee*s were determined by HPLC analysis.

Having discovered optimal conditions for the asymmetric chlorosulfonation of **II-87,** a number of analogous sulfate were prepared and evaluated using the standard conditions described above. In total, three additional 4-substituted sulfates were prepared (Figure

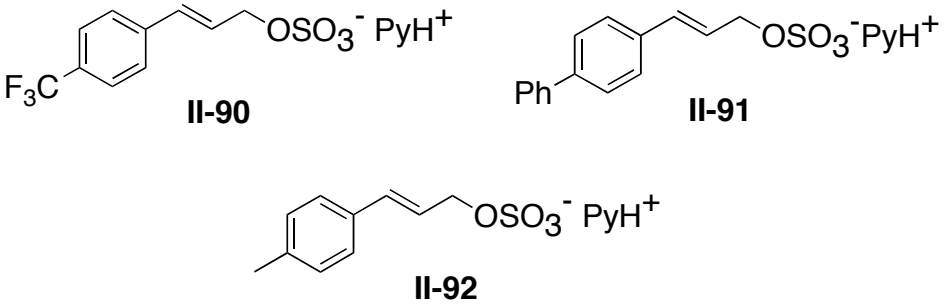
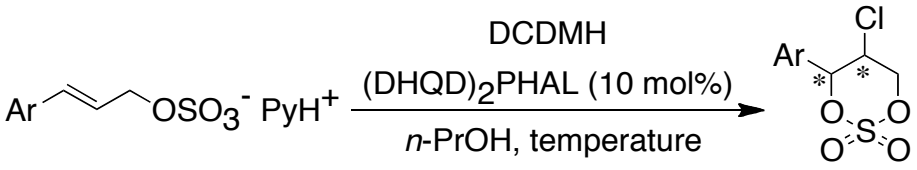


Figure II-3: 4-Substituted sulfate substrate

II-3). These substrates were readily prepared from their corresponding *trans*-cinnamyl alcohol with sulfur trioxide pyridine complex.[50]

Substrate **II-90** was subjected to the chlorocyclization protocol at -40 ºC however no product was obtained after 24 h, presumably as a result of the electron poor nature of the olefin. Increasing the temperature to -20 ^{o}C, 40% conversion was observed in 45% *ee*. The reaction reached to 100% conversion at 0 ºC but the enantioselectivity decreased to

Table II-10: Substrate scope of for chlorocylization reaction



Entry	Substrate	Temperature (^{o}C)	Conversion (%)	*ee* (%)[a]
1	**II-90**	-40	0	-
2	**II-90**	-20	40	45
3	**II-90**	0	100	10
4	**II-91**	-40	100	-
5	**II-92**	-40	100	-

[a] *ee*s were determined by HPLC analysis.

10% (Table II-10). The cyclized product of substrate **II-91** was not stable and after work-up decomposed. From ^{1}HNMR the main product is the elimination of the cyclic sulfate. The *para*-methyl substituted substrate **II-92** returned chloro cyclized sulfate, base on crude NMR analysis, however it also decomposed after a few minutes. The aryl ring

with electron deficient group was the main problem for having low reactivity in low temperature and the enantioselectivity dropped by increasing the temperature. The product of aryl ring with electron deficient groups were not stable.

II.4 Experimental Section

Commercially available starting materials were obtained from Aldrich or Fluka and were used without further purification. Unless otherwise mentioned, solvents were purified as follows: tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone; methylene chloride (CH_2Cl_2) and toluene ($PhCH_3$) was dried over calcium hydride (CaH_2) and freshly distilled prior to use; DMF, DMSO, Et_3N, and HMPA were distilled from CaH_2 and stored over 4 Å molecular sieves. 4 Å molecular sieves were dried at 160 ^{o}C under vacuum prior to use. All of the spectral data for known compounds either match those reported by Aldrich or by comparison to the literature report.

^{1}H NMR spectra were measured at 300, 500 or 600 MHz on a Varian Gemini-300, a Varian VXR-500 or Varian Inova-600 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for $CDCl_3$). ^{13}C NMR spectra were measured at 75 MHz on a Varian Gemini-300, at 125 MHz on a Varian VXR-500 or 150 MHz on a Varian Inova-600 instrument. Chemical shifts are reported relative to the central line of $CDCl_3$ (δ 77.0 ppm). High resolution mass spectra were measured at the Michigan State University, Mass Spectrometry Laboratory. Optical rotations were measured on a Perkin-Elmer polarimeter (model 341) using a 1 mL capacity quartz cell with a 10 cm path length in chloroform.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F_{254}

plates. Compounds were visualized with UV light, potassium permanganate stain, *p*-anisaldehyde stain or phosphomolybdic acid in EtOH. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 μm silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments. GC analysis was performed using HP (6890 series) GC system equipped with an Altech SE-54, 30 m × 320 μm × 0.25 μm column. Enantiomeric excess for all products was judged by HPLC analysis using DAICEL CHIRALPAK OJ-H, OD-H or AS-H columns.

α–Phthalimido aryl ketones were synthesized from commercially available α–bromo acetophenones by previously reported methods.[51]

1-Phthalimido-2-(4-bromophenyl)-2-ethanone

MP: 229 – 233 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 5.06 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 168.2, 134.6, 133.5, 132.7, 132.6, 130.0, 129.8, 124.0, 44.5.

1-Phthalimido-2-(4-chlorophenyl)-2-ethanone

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 167.8, 140.6, 134.3, 134.2, 132.7, 132.2, 129.5, 129.3, 123.6, 44.1.

1-Phthalimido-2-(4-fluorophenyl)-2-ethanone

MP: 151 – 152 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-7.99 (m, 2H), 7.87-7.85 (m, 2H), 7.73-7.71 (m, 2H), 7.15 (t, *J* = 8.5 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 168.2, 134.6, 132.6, 131.2, 123.9, 116.7, 116.5, 116.4, 44.4; HRMS: Calcd. for $C_{16}H_{10}FNO_3$: 283.0645; Found: 283.0639.

1-Phthalimido-2-(3-nitrophenyl)-2-ethanone

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (t, *J* = 2.0 Hz, 1H), 8.49 (ddd, *J* = 8.5, 2.0, 1.0 Hz, 1H), 8.32 (ddd, *J* = 8.5, 1.0, 0.5 Hz, 1H), 7.90 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 – 7.78 (m, 3H), 5.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 167.6, 135.6, 134.3, 133.6, 132.1, 130.3, 128.3, 123.7, 123.1, 44.3.

1-Phthalimido-2-(3-methoxyphenyl)-2-ethanone

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.58 (td, *J* = 7.5, 1.5 Hz, 1H), 7.49 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.15 (ddd, *J* = 7.5, 2.5, 1.5 Hz, 1H), 5.09 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 167.9, 160.0, 135.7, 134.1, 132.3, 129.9, 123.6, 120.6, 120.5, 112.4, 55.5, 44.3.

$MePPh_3Br$ (1.07g, 3 mmol, 1.5 equiv) was suspended in anhydrous toluene (10 mL) and cooled in an ice bath. NaHMDS (3 mL of 1.0 M solution in THF, 3 mmol, 1.5 equiv) was added drop wise under N_2 and the resulting yellow slurry was stirred for 0.5 h at 0 °C. The reaction vessel was then cooled to -78 °C (dry ice- acetone) and the ketone (2 mmol, 1.0 equiv) was added in a single portion under N_2. After a further 10 min. the cooling bath was removed and the reaction was allowed to warm to ambient temperature.

A reflux condenser was attached and the reaction was refluxed (bath temp. ~120 °C) for 12-24 h (till reaction was complete by TLC). The reaction was poured into water (100 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were washed sequentially with water (1 x 20 mL) and brine (1 x 20 mL) and then dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude products. Pure products were obtained after column chromatography on silica gel using EtOAc-Hexane gradient elution.

2-(3-Nitrophenyl)-3-phthalimido-1-propene

50% yield (white solid); R_f: 0.43 (30% EtOAc-Hex) (UV, PMA)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (t, *J* = 2.0 Hz, 2H), 8.12 (ddd, *J* = 8.4, 2.0, 1.0 Hz, 1H), 7.81 – 7.84 (m, 3H), 7.70 (dd, *J* = 5.4, 2.5 Hz, 2H), 5.56 (s, 1H), 5.34 (t, *J* = 1.5 Hz, 1H), 4.17 (t, *J* = 1.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 148.4, 140.7, 140.2, 134.2, 132.3, 131.8, 129.4, 123.5, 122.9, 121.5, 117.1, 41.1; HRMS: Calcd. for $C_{17}H_{12}N_2O_4$: 308.0797; Found: 308.0797.

2-(3-Methoxyphenyl)-3-phthalimido-1-propene

75% (84% brsm) yield (Yellowish solid); R_f: 0.19 (15% EtOAc- Hex)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 4.5, 3.0 Hz, 2H), 7.69 (dd, *J* = 4.5, 3.0 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.06 – 7.08 (m, 1H), 7.02 (t, *J* = 2.5 Hz, 1H), 6.80 – 6.83 (m, 1H), 5.43 (s, 1H), 5.15 (d, *J* = 1.5 Hz, 1H), 4.67 (t, *J* = 1.5 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 159.5, 142.3, 139.9, 134.0, 132.0, 129.4, 123.4, 118.9,

114.7, 114.2, 113.8, 111.9, 55.3, 41.5; HRMS: Calcd. for $C_{18}H_{15}NO_3$: 293.1052; Found: 293.1046.

2-(4-Fluorophenyl)-3-phthalimido-1-propene

71% (82% brsm) yield (white solid); R_f: 0.52 (30% EtOAc-Hex) (UV, PMA); MP: 85 – 87 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.4, 3.0 Hz, 2H), 7.69 (dd, J = 5.4, 3.0 Hz, 2H), 7.44 (dd, $^2J_{H\text{-}H}$ = 9.0 Hz, $^3J_{H\text{-}F}$ = 5.4 Hz, 2H), 6.99 (dd, $^2J_{H\text{-}H}$ = $^2J_{H\text{-}F}$ = 9.0 Hz, 2H), 5.37 (s, 1H), 5.16 (t, J = 1.5 Hz, 1H), 4.65 (t, J = 1.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 162.6 (d, $^1J_{C\text{-}F}$ = 245.6 Hz), 141.6, 134.5 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 134.0, 131.9, 128.1 (d, $^3J_{C\text{-}F}$ = 6.6 Hz), 123.4, 115.2 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 114.3 (d, $^5J_{C\text{-}F}$ = 1.1 Hz), 41.5; HRMS: Calcd. for $C_{17}H_{12}NO_2F$: 281.0852, Found: 281.0842.

2-[2-(4-bromophenyl)allyl]isoindoline-1,3-dione

95% Yield (White solid); R_f: 0.32 (20% EtOAc-Hexanes) (UV, PMA) ; MP: 125-128 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 5.7, 3.0 Hz, 2H), 7.68 (dd, J = 5.7, 3.0 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 5.42 (s, 1H), 5.21 (d, J = 0.9 Hz, 1H), 4.65 (t, J = 0.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.1, 167.8, 134.2, 133.1, 132.3, 132.2, 129.6, 129.4, 123.6, 44.0; HRMS: Calcd. for $C_{17}H_{12}BrNO_2$: 341.0051; Found: 341.0047.

2-(4-Chlorophenyl)-3-phthalimido-1-propene

77% Yield (White solid); R_f: 0.52 (30% EtOAc-Hexanes) (UV, PMA); MP: 114-119 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.67 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.40 (s, 1H), 5.19 (s, 1H), 4.64 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 141.5, 136.8, 134.0, 131.9, 128.5, 127.7, 123.3, 114.8, 41.3; HRMS: Calcd. for $C_{17}H_{12}NO_2Cl$: 297.0557, Found: 297.0558.

3-Phthalimido-2-aryl-1-propene (1 mmol, 1.0 equiv) was dissolved in MeOH (5 mL). $NH_2NH_2•H_2O$ (98 μL, 1.5 mmol, 1.5 equiv) was introduced into the reaction vessel and the resulting suspension was stirred overnight. The reaction was then diluted with water (5 mL) and most of the MeOH was removed by rotary evaporation. Concentrated HCl (1 mL) was added and the resulting suspension was stirred for a further 30 min at ambient temperature. The precipitated solids were filtered and the filter cake was washed with water (2 x 2 mL). The combined filtrates were basified with solid NaOH and extracted with ether (3 x 5 mL) and concentrated to give the crude 2-arylprop-2-en-1-amines which were used in the next reaction without any purification.

A solution of amine (9.0 mmol, 1.0 equiv), triethyl amine (1.04 mL, 18.0 mmol, 2.0 equiv) and a catalytic amount of DMAP in DCM (50 mL) was cooled in an ice bath. To it was added *p*-BrBzCl (2.93 g, 13.5 mmol, 1.5 equiv) drop wise. After the addition was complete, the reaction was allowed to warm to rt. After 2 h, the reaction was diluted with an equal amount of water and extracted with DCM (3 x 25 mL). The combined organics were washed with brine (1 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product as a yellow solid. It was recrystallized from MeOH to obtain the pure product **II-58** that was purified by column chromatography.

4-Bromo-N-(2-phenylallyl)benzamide

White solid; MP: 157 – 159 °C; R_f: 0.54 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.30 (m, 1H), 6.13 (br s, 1H), 5.50 (s, 1H), 5.29 (s, 1H), 4.51 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 144.1, 138.2, 133.2, 131.8, 131.6, 128.6, 128.5, 128.2, 128.0, 126.2, 126.1, 114.3, 43.8; HRMS: Calcd. for $C_{16}H_{14}NOBr$: 315.0259, Found: 315.0273.

4-Bromo-N-[2-(3-nitrophenyl)allyl]benzamide

Brown solid; MP: 124 -125 °C; R_f: 0.33 (30% EtOAc-Hexanes) (UV, I_2, anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (t, *J* = 2.4 Hz, 1H), 8.12 – 8.14 (m, 1H), 7.77 – 7.79 (m, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 6.23 (br s, 1H), 5.62 (s, 1H), 5.45 (t, *J* = 1.4 Hz, 1H), 4.54 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 142.5, 140.0, 132.8, 132.0, 131.9, 129.6, 128.5, 126.5, 122.9, 121.1, 116.6, 43.4; HRMS: Calcd. for $C_{16}H_{13}N_2O_3Br$: 360.0110, Found: 360.0127.

4-Bromo-N-[2-(3-methoxyphenyl)allyl]benzamide

MP: 128 – 130 °C

R_f: 0.21 (30% EtOAc- Hex) (UV, I_2, anisaldehyde)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.02 (qd, *J* = 7.5, 1.0 Hz, 1H), 6.98 (t, *J* = 2.0 Hz, 1H), 6.84 (ddd, *J* = 7.5, 2.5, 1.0 Hz, 1H), 6.16 (br s, 1H), 5.49 (d, *J* = 0.5 Hz, 1H), 5.28 (d, *J* = 1.0 Hz, 1H),

4.48 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 159.8, 144.0, 139.7, 133.2, 131.8, 129.6, 128.5, 126.2, 118.5, 114.5, 113.7, 111.9, 55.3, 43.9; HRMS: Calcd. for $C_{17}H_{16}NO_2Br$: 345.0365, Found: 345.0352.

4-Bromo-N-[2-(4-fluorophenyl)allyl]benzamide

White solid; MP: 155 – 157 °C; R_f: 0.50 (30% EtOAc-Hexanes) (UV, I_2, anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2), 7.42 (dd, J_{H-H} = 8.4 Hz, $^4J_{H-F}$ = 5.4 Hz, 2H), 7.02 (t, J_{H-H} = $^4J_{H-F}$ = 8.4 Hz, 2H), 6.10 (br s, 1H), 5.44 (s, 1H), 5.27 (s, 1H), 4.48 (d, J = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C-F}$ = 246.6 Hz), 163.5, 143.2, 134.2 (d, $^4J_{C-F}$ = 3.5 Hz), 133.1, 128.5, 127.8 (d, $^3J_{C-F}$ = 8.0 Hz), 126.3, 115.5 (d, $^2J_{C-F}$ = 21.3 Hz), 114.2, 43.8; HRMS: Calcd. for $C_{16}H_{13}NOBrF$: 333.0165, Found: 333.0154.

4-Bromo-N-[2-(4-bromophenyl)allyl]benzamide

Yellowish solid; MP: 152 – 154 °C; R_f: 0.50 (30% EtOAc-Hexanes) (UV, I_2, anisaldehyde)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.15 (br s, 1H), 5.49 (s, 1H), 5.31 (s, 1H), 4.48 (d, J = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 143.2, 137.0, 133.0, 132.1, 131.9, 131.5, 128.5, 127.7, 114.9, 43.6; HRMS: Calcd. for $C_{16}H_{13}NOBr_2$: 392.9364, Found: 392.9376.

4-Bromo-N-[2-(4-chlorophenyl)allyl]benzamide

White solid; MP: 152 – 154 °C; R_f: 0.50 (30% EtOAc-Hexanes) (UV, I_2, anisaldehyde) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.14 (br s, 1H), 5.49 (d, *J* = 1.2 Hz, 1H), 5.30 (d, *J* = 0.6 Hz, 1H), 4.48 (dd, *J* = 6.0, 0.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 143.1, 136.5, 133.0, 131.9, 128.8, 128.5, 127.4, 114.8, 43.6; HRMS: Calcd. for $C_{16}H_{13}NOBrCl$: 348.9869, Found: 348.9865.

General procedure for the catalytic asymmetric chlorocyclization of unsaturated amides: DCDPH (35 mg, 0.11 mmol, 1.1 equiv) was suspended in trifluoroethanol (TFE, 2.2 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to -30 °C in an immersion cooler. $(DHQD)_2PHAL$ (1.56 mg, 312 μL of a 5 mg/mL solution in TFE, 2 mol%) was then introduced. After stirring vigorously for 10 min, the substrate (0.10 mmol, 1.0 equiv) was added in a single portion. The vial was capped and the stirring was continued at -30 °C till the reaction was complete (TLC). The reaction was quenched by the addition of 10% aq. Na_2SO_3 (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexanes as the eluent.

(*R*)-2-(4-Bromophenyl)-5-(chloromethyl)-5-(3-nitrophenyl)-4,5-dihydrooxazole

Colorless film; R_f: 0.28 (30% EtOAc-Hexanes) (UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (t, *J* = 1.8 Hz, 1H), 8.21 (ddd, *J* = 8.4, 2.4, 1.2 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.74 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.59 – 7.61 (m, 2H), 4.52 (d, *J* = 15.6 Hz, 1H), 4.21 (d, *J* = 15.6 Hz, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 3.87 (d, = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.1, 148.5, 143.4, 131.9, 131.2, 130.0, 129.8, 126.7, 125.8, 123.5, 120.4, 87.3, 65.3, 50.3; HRMS: Calcd. for $C_{16}H_{12}N_2O_3ClBr$: 393.9720, Found: 393.9704.

Resolution of enantiomers: CHIRALCEL OJ-H, 10% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 47.1 min, RT2 = 54.5 min; $[\alpha]_D^{20}$ = -95.0 (c = 1.0, $CHCl_3$)

(*R*)-2-(4-Bromophenyl)-5-(chloromethyl)-5-(3-methoxyphenyl)-4,5-dihydrooxazole

Colorless film; R_f: 0.21 (15% EtOAc- Hex) (UV)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.57(d, *J* = 8.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.93 – 6.95 (m, 2H), 6.84 – 6.87 (m, 1H), 4.46 (d, *J* = 14.5 Hz, 1H), 4.19 (d, *J* = 14.5 Hz, 1H), 3.90 (d, *J* = 11.5 Hz, 1H), 3.82 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 159.9, 143.0, 131.7, 130.0, 129.8, 128.5, 126.3, 117.1, 113.1, 111.4, 87.8, 65.0, 55.3, 51.0; HRMS: Calcd. for $C_{17}H_{15}NO_2ClBr$: 378.9975, Found: 378.9994.

Resolution of enantiomers : CHIRALCEL AS-H, 5% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 10.7 min, RT2 = 16.6 min; $[\alpha]_D^{20}$ = -134.0 (c = 1.0, $CHCl_3$)

(*R*)-2-(4-Bromophenyl)-5-(chloromethyl)-5-(4-fluorophenyl)-4,5-dihydrooxazole

Colorless oil; R_f: 0.50 (30% EtOAc-Hexanes) (UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.37 (dd, $^3J_{H\text{-}H}$ = 9.0 Hz, $^4J_{H\text{-}F}$ = 5.4 Hz, 2H), 7.08 (t, $^3J_{H\text{-}H} = {}^3J_{H\text{-}F}$ = 9.0 Hz, 2H), 4.46 (d, *J* = 14.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{C\text{-}F}$ = 246.0 Hz), 162.2, 137.1 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 132.0, 131.8, 129.8, 128.5, 126.8 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 126.4, 126.2, 115.8 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 87.6, 65.1, 50.8; HRMS: Calcd. for $C_{16}H_{12}NOClBrF$: 366.9775, Found: 366.9759.

Resolution of enantiomers : CHIRALCEL OJ-H, 5% IPA-Hex, 1.0 mL/min, RT1 = 12.5 min, RT2 = 23.1 min.; $[\alpha]_D^{20}$ = -87.8 (c = 1.0, $CHCl_3$)

(*R*)-2,5-Bis(4-bromophenyl)-5-(chloromethyl)-4,5-dihydrooxazole

Colorless gum; R_f: 0.53 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 4.45 (d, *J* = 15.0 Hz, 1H), 4.15 (d, *J* = 15.0 Hz, 1H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.79 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2, 140.3, 132.0, 131.8, 129.8, 126.7, 126.5, 126.1, 122.5, 87.6, 65.0, 50.6; HRMS: Calcd. for $C_{16}H_{12}NOClBr_2$: 426.8782, Found: 426.8786.

Resolution of enantiomers: CHIRALCEL OJ-H, 5% IPA-Hex, 1.0 mL/min, RT1 = 14.8 min, RT2 = 20.5 min; $[\alpha]_D^{20}$ = -96.7 (c = 1.0, $CHCl_3$)

(*R*)-2-(4-Bromophenyl)-5-(chloromethyl)-5-(4-chlorophenyl)-4,5-dihydrooxazole

Yellow gum; R_f: 0.48 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.46 (d, *J* = 15.0 Hz, 1H), 4.16 (d, *J* = 15.0 Hz, 1H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.80 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2, 139.8, 134.4, 131.8, 129.8, 129.0, 128.9, 128.5, 126.4, 126.1, 87.5, 65.0, 50.7; HRMS: Calcd. for $C_{16}H_{12}NOCl_2Br$: 382.9479, Found: 382.9484.

Resolution of enantiomers: CHIRALCEL OJ-H, 5% IPA-Hex, 1.0 mL/min, RT1 = 12.9 min, RT2 = 18.9 min; $[\alpha]_D^{20}$ = -58.8 (c = 1.0, $CHCl_3$)

Allylic alcohols were synthesized from the corresponding aldehydes or ketones by a HWE reaction followed by DIBAL reduction of the resulting ester (typical yields were ~ 95% for the two steps). The bromination of the allylic alcohols gave the corresponding allyl bromides which were used without purification in the subsequent one pot azide displacement–Staudinger reduction sequence.

Allyl bromide (1.0 equiv) dissolved in THF-H_2O (4:1) (5 mL/mmol) was treated with 1.1 equivalents of NaN_3 at rt. After TLC analysis revealed the complete consumption of starting material (~ 20 min.), 2.0 equivalents of PPh_3 was added to the reaction vessel. After 2 h at ambient temperature, the reaction was concentrated to remove most of the THF. The resulting suspension was diluted with aq. HCl and extracted with ether (3x). The aqueous layer was then basified by adding solid KOH and extracted with ether (3x).

The combined organics were dried (anhydrous Na_2SO_4) and concentrated to give the crude amine which was usually pure enough to use in the next step. Typical yield over three steps was 55–60%.

The crude amines from the previous step were reacted with the *p*-benzyl acid chloride using the same protocol as described for the synthesis of **II-58** to give the products **II-60** which were purified by column chromatography.

N-Cinnamyl-4-bromobenzamide

White solid; MP: 148 – 150 °C; R_f: 0.50 (30% EtOAc-Hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 9.0 Hz, 2H), 7.21 – 7.38 (m, 5H), 6.59 (d, J = 15.9 Hz, 1H), 6.27 (td, J = 15.9, 3.3 Hz, 1H), 6.18 (br s, 1H), 4.22 (dt, J = 4.8, 1.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 136.3, 133.2, 132.8, 131.8, 128.6, 128.5, 127.9, 126.4, 126.2, 125.1, 42.2; HRMS: Calcd. for $C_{16}H_{14}NOBr$: 315.0259, Found: 315.0241.

(*E*)-4-Bromo-N-[3-(4-fluorophenyl)allyl]benzamide

Yellowish solid; MP: 164 – 165 °C; R_f: 0.42 (30% EtOAc-Hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.32 (dd, $J_{H\text{-}H}$ = 8.7 Hz, $^4J_{H\text{-}F}$ = 5.4 Hz, 2H), 6.99 (t, $^2J_{H\text{-}H} = {}^3J_{H\text{-}F}$ = 8.7 Hz), 6.54 (d, J = 15.3 Hz, 1), 6.13 – 6.23 (m, 2H), 4.21 (dt, J = 6.0, 1.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 162.2 (d, $^1J_{C\text{-}F}$ = 245.6 Hz), 133.0, 132.3 (d, $^4J_{C\text{-}F}$ = 3.5 Hz), 131.7, 131.4, 128.3, 127.7 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 126.1, 124.6 (d, $^5J_{C\text{-}F}$ = 2.2 Hz), 115.4 (d, ^2J

$_{C\text{-}F}$ = 21.8 Hz), 41.9; HRMS: Calcd. for $C_{16}H_{13}NOBrF$: 333.0165, Found: 333.0169.

(*E*)-4-Bromo-N-[3-(4-bromophenyl)allyl]benzamide

MP: 170 – 173 °C; R_f: 0.42 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.50 (d, *J* = 16.2 Hz, 1H), 6.25 (td, *J* = 16.2, 6.6 Hz, 1H), 6.20 (br s, 1H), 4.21 (dt, *J* = 6.6, 1.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 135.3, 133.1, 131.9, 131.8, 131.5, 128.5, 127.9, 126.3, 126.0, 121.7, 42.1; HRMS: Calcd. for $C_{16}H_{13}NOBr_2$: 392.9364, Found: 392.9369.

(*E*)-4-Bromo-N-{3-[4-(trifluoromethyl)phenyl]allyl}benzamide

MP: 156 – 158 °C; R_f: 0.38 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 6.59 (d, *J* = 15.6 Hz, 1H), 6.36 (td, *J* = 15.6, 6.6 Hz, 1H), 6.32 (br s, 1H), 4.25 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 139.8, 133.0, 131.9, 131.6, 131.1, 129.6 (q, $^2J_{C\text{-}F}$ = 32.7 Hz), 128.6, 128.5, 128.0, 126.4, 123.7 (q, $^1J_{C\text{-}F}$ = 270.9 Hz), 125.5 (q, $^3J_{C\text{-}F}$ = 4.1 Hz), 42.0; HRMS: Calcd. for $C_{17}H_{13}NOF_3Br$: 383.0133, Found: 383.0139.

(*E*)-4-Bromo-N-[3-(4-methoxyphenyl)allyl]benzamide

MP: 156 – 158 °C; R_f: 0.38 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.51 (d, *J* = 16.2 Hz, 1H), 6.30 (br s, 1H), 6.10

(td, J = 16.2, 6.6 Hz, 1H), 4.17 (d, J = 6.4 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 159.4, 133.3, 132.4, 131.8, 129.1, 128.6, 127.6, 126.1, 122.7, 114.0, 55.3, 42.3; HRMS: Calcd. for $C_{17}H_{16}NO_2Br$: 345.0364, Found: 345.0382.

(*E*)-4-Bromo-N-(3-p-tolylallyl)benzamide

MP: 136 – 138 °C; R_f: 0.47 (30% EtOAc-Hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 7.10 (d, J = 7.5 Hz, 2H), 6.53 (d, J = 16.0 Hz, 1H), 6.27 (br s, 1H), 6.19 (td, J = 16.0, 6.0 Hz, 1H), 4.19 (dt, J = 6.0, 1.5 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 137.7, 133.6, 133.3, 132.7, 131.8, 129.3, 128.6, 126.3, 126.2, 124.0, 42.3, 21.2; HRMS: Calcd. for $C_{17}H_{16}NOBr$: 329.0415, Found: 329.0414.

(*E*)-4-Bromo-N-(3-o-tolylallyl)benzamide

MP: 130 – 132 °C; R_f: 0.50 (30% EtOAc-Hexanes)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 9.0 Hz, 2H), 7.40 – 7.42 (m, 1H), 7.11 – 7.15 (m, 3H), 6.81 (d, J = 15.6 Hz, 1H), 6.19 (br s, 1H), 6.14 (td, J = 15.6, 6.0 Hz, 1H), 4.24 (t, J = 6.0 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 135.4, 135.3, 133.3, 131.8, 130.8, 130.3, 128.5, 127.8, 126.3, 126.2, 126.1, 125.7, 42.5, 19.8; HRMS: Calcd. for $C_{17}H_{16}NOBr$: 329.0415, Found: 329.0399.

4-Bromo-N-(3,3-diphenylallyl)benzamide

MP: 191 – 192 °C; R_f: 0.63 (30% EtOAc-Hexanes)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 9.0 Hz, 2H), 7.53 (d, J = 9.0 Hz, 2H), 7.31 – 7.41 (m, 3H), 7.18 – 7.30 (m, 7H), 6.16 (t, J = 6.9 Hz, 1H), 6.09 (br s, 1H), 4.13 (dd, J =

6.9, 5.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 145.1, 141.5, 138.9, 133.3, 131.8, 129.6, 128.5, 128.5, 128.2, 127.7, 127.4, 126.1, 124.0, 39.5; HRMS: Calcd. for $C_{22}H_{18}NOBr$: 391.0572, Found: 391.0576.

(*E*)-4-Bromo-N-(3-cyclohexylallyl)benzamide

MP: 108 – 112 °C; R_f: 0.54 (30% EtOAc-Hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 6.03 (br s, 1H), 5.62 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.43 – 5.49 (m, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 1.94 (m, 1H), 1.61 – 1.71 (m, 5H), 1.10 – 1.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 140.3, 133.5, 131.8, 128.5, 126.0, 122.8, 42.2, 40.4, 32.8, 26.1, 26.0; HRMS: Calcd. for $C_{16}H_{20}NOBr$: 321.0728, Found: 321.0726.

(*E*)-4-Bromo-N-(oct-2-enyl)benzamide

MP: 75 – 76 °C; R_f: 0.54 (30% EtOAc-Hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 6.34 (br s, 1H), 5.62 – 5.67 (m, 1H), 5.45 – 5.51 (m, 1H), 3.95 (dt, *J* = 6.0, 1.0 Hz, 2H), 1.96 – 2.00 (m, 2H), 1.21 – 1.36 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 134.4, 133.4, 131.7, 128.5, 125.9, 125.1, 42.1, 32.2, 31.3, 28.7, 22.4, 13.9; HRMS: Calcd. for $C_{15}H_{20}NOBr$: 309.0728, Found: 309.0735.

(*E*)-4-Bromo-N-(4-cyclohexylbut-2-enyl)benzamide

Waxy solid; R_f: 0.45 (20% EtOAc- Hex)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 6.02 (br s, 1H), 5.63 – 5.69 (m, 1H), 5.46 – 5.52 (m, 1H), 3.99 (dt, *J* = 6.0, 1.0 Hz, 2H), 1.92 (t,

J = 6.5 Hz, 2H), 1.61 – 1.68 (m, 5H), 1.07 – 1.32 (m, 4H), 0.83 – 0.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 133.5, 133.2, 131.8, 128.5, 126.2, 126.0, 42.1, 40.2, 37.7, 33.1, 26.5, 26.3; HRMS: Calcd. for $C_{17}H_{22}NOBr$: 335.0885, Found: 335.0866.

General procedure for the catalytic asymmetric chlorocyclization of unsaturated amides: DCDPH (35 mg, 0.11 mmol, 1.1 equiv) was suspended in trifluoroethanol (TFE, 2.2 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to -30 °C in an immersion cooler. $(DHQD)_2PHAL$ (1.56 mg, 312 μL of a 5 mg/mL solution in TFE or 1-nitropropane (in the presence of molecular sieves), 2 mol%) was then introduced. After stirring vigorously for 10 min, the substrate (0.10 mmol, 1.0 equiv) was added in a single portion. The vial was capped and the stirring was continued at -30 °C till the reaction was complete (TLC). The reaction was quenched by the addition of 10% aq. Na_2SO_3 (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexanes as the eluent.

(5*S*, 6*R*)-2-(4-Bromophenyl)-5-chloro-6-phenyl-5,6-dihydro-4H-1,3-oxazine

Colorless needles; MP: 93 – 95 °C; R_f: 0.50 (15% EtOAc-Hexanes)

^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.34 – 7.42 (m, 5H), 5.21 (d, J = 7.2 Hz, 1H), 4.19 (dt, J = 7.5, 4.8 Hz, 1H), 3.95 (dd, J = 17.1,

4.8 Hz, 1H), 3.75 (ddd, J = 17.1, 7.5, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 137.0, 131.5, 131.4, 129.1, 128.9, 128.7, 126.7, 125.6, 80.7, 53.8, 49.8; HRMS: Calcd. for $C_{16}H_{13}NOBrCl$: 348.9869, Found: 348.9853.

Resolution of enantiomers: CHIRALCEL AS-H, 3% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 6.7 min, RT2 = 10.7 min; $[\alpha]_D^{20}$ = -17.8 (c = 0.50, $CHCl_3$)

(5*S*,6*R*)-2-(4-Methoxyphenyl)-5-chloro-6-phenyl-5,6-dihydro-4H-1,3-oxazine

White solid; MP: 98 – 100 °C; R_f: 0.25 (20% EtOAc-Hex) (UV)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 2H), 7.36 – 7.41 (m, 5H), 6.87 (d, J = 9.0 Hz, 2H), 5.23 (d, J = 8.0 Hz, 1H), 4.21 (dt, J = 8.0, 4.5 Hz, 1H), 3.93 (dd, J = 16.5, 4.5 Hz, 1H), 3.82 (s, 3H), 3.76 (dd, J = 16.5, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 156.2, 137.0, 129.2, 129.1, 128.7, 127.8, 126.7, 113.6, 80.9, 55.4, 55.3, 49.4; HRMS: Calcd. for $C_{16}H_{13}NOBrCl$: 348.9869, Found: 348.9853.

Resolution of enantiomers: CHIRALCEL AS-H, 4% IPA-Hexane, 0.7 mL/min, 254 nm, RT1 = 16.7 min, RT2 = 22.5 min; $[\alpha]_D^{20}$ = -45.9 (c = 1.0, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-(4-fluorophenyl)-5,6-dihydro-4H-1,3-oxazine

White film; R_f: 0.54 (15% EtOAc- Hex) (UV)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.36 (dd, $^2J_{H\text{-}H}$ = 8.5 Hz, $^3J_{F\text{-}H}$ = 5.0 Hz, 2H), 7.11 (t, $^2J_{H\text{-}H}$ = $^2J_{F\text{-}H}$ = 8.5 Hz, 2H), 5.15 (d, J = 8.5 Hz, 1H), 4.13 (dt, J = 8.5, 5.0 Hz, 1H), 3.98 (dd, J = 17.5, 5.0 Hz, 1H), 3.75 (dd,

J = 17.5, 8.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1 (d, $^{1}J_{C\text{-}F}$ = 247.1 Hz), 154.4, 132.7 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 131.4, 131.3, 128.9, 128.7 ($^{3}J_{C\text{-}F}$ = 8.7 Hz), 125.7, 115.7 ($^{2}J_{C\text{-}F}$ = 21.8 Hz), 80.2, 53.8, 50.3; HRMS: Calcd. for $C_{16}H_{12}NOBrClF$: 366.9775, Found: 366.9767.

Resolution of enantiomers: CHIRALCEL AS-H, 5% IPA-Hexane, 1.0 mL/min, 250 nm, RT1 = 7.0 min, RT2 = 9.3 min; $[\alpha]_D^{20}$ = -29.4 (c = 1.0, $CHCl_3$)

(5*S*,6*R*)-2,6-Bis(4-bromophenyl)-5-chloro-5,6-dihydro-4H-1,3-oxazine

Colorless film; R_f: 0.50 (15% EtOAc- Hex) (UV)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 5.13 (d, J = 8.0 Hz, 1H), 4.11 (dt, J = 8.0, 4.5 Hz, 1H), 3.97 (dd, J = 17.5, 5.0 Hz, 1H), 3.75 (dd, J = 17.5, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 135.9, 131.9, 131.4, 131.3, 128.9, 128.6, 125.8, 123.3, 80.2, 53.6, 50.2; HRMS: Calcd. for $C_{16}H_{12}NOBr_2Cl$: 426.8974, Found: 426.8982.

Resolution of enantiomers: CHIRALCEL AS-H, 5% IPA-Hexane, 1.0 mL/min, 250 nm, RT1 = 6.4 min, RT2 = 8.6 min; $[\alpha]_D^{20}$ = -9.6 (c = 1.0, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-[4-(trifluoromethyl)phenyl]-5,6-dihydro-4H-1,3-oxazine

White film; R_f: 0.48 (15% EtOAc – Hex) (UV)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.49 – 7.53 (m, 4H), 5.22 (d, J = 8.5 Hz, 1H), 4.14 (dt, J = 8.5, 5.0 Hz, 1H), 3.99 (dd, J = 17.5

Hz, 5.0 Hz, 1H), 3.77 (dd, *J* = 17.5, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 140.7, 131.5, 131.4 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz), 131.2, 128.9, 127.4, 125.9, 125.8 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 123.7 (q, $^{1}J_{C\text{-}F}$ = 270.9 Hz), 80.1, 53.5, 50.3; HRMS: Calcd. for $C_{17}H_{12}NOF_3BrCl$: 416.9743, Found: 416.9721.

Resolution of enantiomers: CHIRALCEL AS-H, 3% IPA-Hexane, 0.8 mL/min, 254 nm, RT1 = 7.2 min, RT2 = 9.1 min; $[\alpha]_D^{20}$ = -30.7 (c = 1.0, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-(4-methoxyphenyl)-5,6-dihydro-4H-1,3-oxazine

Colorless film; R_f: 0.44 (15% EtOAc – Hex) (UV)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 5.14 (d, *J* = 8.1 Hz, 1H), 4.16 (dt, *J* = 8.1, 4.8 Hz, 1H), 3.97 (dd, *J* = 17.1, 4.8 Hz, 1H), 3.82 (s, 3H), 3.74 (dd, *J* = 17.1, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 154.6, 131.6, 131.3, 129.0, 128.9, 128.2, 125.6, 114.1, 80.5, 55.3, 54.0, 50.2; HRMS: Calcd. for $C_{17}H_{15}NO_2BrCl$: 378.9975, Found: 378.9982.

Resolution of enantiomers: CHIRALCEL AS-H, 3% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 8.5 min, RT2 = 12.3 min; $[\alpha]_D^{20}$ = +4.7 (c = 0.75, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-*p*-tolyl-5,6-dihydro-4H-1,3-oxazine

Colorless film; R_f: 0.56 (15% EtOAc- Hex) (UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ7.80 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.17 (d, *J* = 7.8 Hz, 1H), 4.18 (dt, *J* = 7.8, 4.8

Hz, 1H), 3.96 (dd, *J* = 17.4, 4.8 Hz, 1H), 3.74 (dd, *J* = 17.4, 7.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.5, 139.1, 134.1, 131.6, 131.4, 129.4, 128.9, 126.7, 125.6, 80.7, 53.9, 50.0, 21.2; HRMS: Calcd. for $C_{17}H_{15}NOBrCl$: 363.0026, Found: 363.0037.

Resolution of enantiomers: CHIRALCEL AS-H, 3% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 5.7 min, RT2 = 7.4 min; $[\alpha]_D^{20}$ = -4.3 (c = 1.0, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-o-tolyl-5,6-dihydro-4H-1,3-oxazine

Colorless film; R_f: 0.54 (15% EtOAc- Hex) (UV)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.20 – 7.30 (m, 4H), 5.49 (d, *J* = 8.2 Hz, 1H), 4.25 (dt, *J* = 8.2, 4.8 Hz, 1H), 3.99 (dd, *J* = 17.1, 4.8 Hz, 1H), 3.78 (dd, *J* = 17.1, 8.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 136.1, 135.3, 132.0, 131.6, 131.4, 131.2, 130.8, 129.0, 128.9, 126.6, 126.0, 125.6, 77.6, 53.2, 49.9, 19.4; HRMS: Calcd. for $C_{17}H_{15}NOBrCl$: 363.0026, Found: 363.0032.

Resolution of enantiomers: CHIRALCEL OJ-H, 3% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 9.7 min, RT2 = 11.7 min; $[\alpha]_D^{20}$ = +7.2 (c = 0.9, $CHCl_3$)

(5*S*,6*R*)-5-Chloro-2-(4-methoxyphenyl)-6-o-tolyl-5,6-dihydro-4H-1,3-oxazine

Yellowish solid; MP: 87 – 90 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.0 Hz, 2H), 7.23 – 7.29 (m, 5H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.53 (d, *J* = 7.0 Hz, 1H), 4.27 (dt, *J* = 7.0, 5.0 Hz, 1H), 3.99 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.78 – 3.83 (m, 4H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 155.3, 136.1, 135.6, 130.8, 129.0, 128.8, 125.5, 126.2, 125.1, 113.4, 77.4, 55.3, 53.6, 50.0,

19.4; HRMS: Calcd. for $C_{18}H_{18}ClNO_2$: 315.1026, Found: 315.1030.

Resolution of enantiomers: CHIRALCEL OD-H, 1% IPA-Hexane, 0.8 mL/min, 250 nm, RT1 = 25.8 min, RT2 = 27.7 min; $[\alpha]_D^{20}$ = -1.7 (c = 1.0, $CHCl_3$)

(*S*)-2-(4-Bromophenyl)-5-chloro-6,6-diphenyl-5,6-dihydro-4H-1,3-oxazine

White film; R_f: 0.35 (15% EtOAc- Hex) (UV)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.35 – 7.39 (m, 4H), 7.20 – 7.30 (m, 6H), 5.19 (dd, *J* = 3.8, 2.0 Hz, 1H), 3.89 (dd, *J* = 18.0, 2.0 Hz, 1H), 3.75 (dd, *J* = 18.0, 3.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 131.6, 129.2, 128.9, 128.4, 128.2, 127.8, 125.2, 124.5, 56.1, 49.4; HRMS: Calcd. for $C_{22}H_{17}NOBrCl$: 425.0182, Found: 425.0166.

Resolution of enantiomers: CHIRALCEL AS-H, 5% IPA-Hexane, 1.0 mL/min, 254 nm, RT1 = 8.3 min, RT2 = 14.8 min; $[\alpha]_D^{20}$ = +44.7 (c = 0.50, $CHCl_3$)

(5*S*, 6*R*)-2-(4-Bromophenyl)-5-chloro-6-cyclohexyl-5,6-dihydro-4H-1,3-oxazine

White solid; R_f: 0.33 (15% EtOAc- Hex) (UV, PMA)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 4.12 – 4.17 (m, 1H), 4.02 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.94 (dd, *J* = 16.5, 4.0 Hz, 1H), 3.63 (dd, *J* = 16.5, 8.0 Hz, 1H), 1.85-1.95 (m, 1H), 1.60-1.84 (m, 6H), 1.22 – 1.45 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7, 131.9, 131.4, 128.8, 126.9, 125.4, 82.4, 50.5, 50.2, 38.5, 29.7, 29.5, 26.3, 26.2, 25.8, 25.7; HRMS: Calcd. for $C_{16}H_{19}NOBrCl$: 355.0339, Found: 355.0333.

Resolution of enantiomers: CHIRALCEL AS-H, 1% IPA-Hexane, 1 mL/min, RT1 = 5.5

min; RT2 = 7.8 min; $[\alpha]_D^{20}$ = +50.3 (c = 0.50, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-pentyl-5,6-dihydro-4H-1,3-oxazine

Colorless liquid; R_f: 0.63 (15% EtOAc- Hex) (UV, PMA)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 2H), 4.17 (dt, *J* = 8.5, 3.0 Hz, 1H), 3.91 – 3.97 (m, 2H), 3.62 (dd, *J* = 10.0, 18.5 Hz, 1H), 1.87 – 2.03 (m, 1H), 1.65 – 1.71 (m, 1H), 1.31 – 1.37 (m, 3H), 1.24 – 1.27 (m, 3H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 133.6, 131.3, 128.8, 126.1, 125.6, 125.4, 78.7, 52.8, 50.6, 32.3, 31.5, 24.3, 22.5, 14.0; HRMS: Calcd. for $C_{15}H_{19}NOBrCl$: 343.0339, Found: 343.0319.

Resolution of enantiomers: CHIRALCEL OD-H, 100% Hexane, 1 mL/min, RT1 = 52.1 min; RT2 = 62.2 min; $[\alpha]_D^{20}$ = +33.9 (c = 0.50, $CHCl_3$)

(5*S*,6*R*)-2-(4-Bromophenyl)-5-chloro-6-(cyclohexylmethyl)-5,6-dihydro-4H-1,3-oxazine

Colorless oil ; R_f: 0.66 (20% EtOAc- Hex)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.26–4.30 (m, 1H), 3.89-3.97 (m, 2H), 3.63 (dd, *J* = 16.8, 7.8 Hz, 1H), 1.81-1.86 (m, 2H), 1.61-1.74 (m, 6H), 1.55-1.59 (m, 1H), 1.15-1.33 (m, 3H), 0.93-1.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 131.9, 131.4, 128.8, 125.4, 76.7, 53.4, 50.3, 40.2, 34.1, 33.8, 32.4, 26.4, 26.2, 26.1; HRMS: Calcd. for $C_{17}H_{21}NOBrCl$: 369.0495, Found: 369.0487.

Resolution of enantiomers: CHIRALCEL OD-H, 100% Hexane, 1 mL/min, RT1 = 30.0

min; RT2 = 48.5 min; $[\alpha]_D^{20}$ = +69.9 (c = 1.0, $CHCl_3$)

To a stirred solution of the benzoic acid (1.22 g, 10 mmol) in CH_3CN (100 mL) was added Et_3N (2.81 mL, 20 mmol), DMAP (0.24 g, 2 mmol), and NsCl (2.21 g, 10 mmol). After being stirred for 20 min, benzyl amine (1.18 g, 11 mmol) in CH_3CN (30 mL) was added under ice bath and stirring was continued for 30 min at room temperature. After evaporation of the solvent, the residue was extracted with CH_2Cl_2 (2 x 50 ml). The extract was washed with saturated $NaHCO_3$ (50 mL), water (50 mL), dried ($MgSO_4$) and concentrated. The crude product was chromatographed on a short silica gel column with ethyl acetate as eluent to give **II-69** in quantitative yield (2.11 g).

Colourless solid, MP: 118–120 ^oC

^1H NMR ($CDCl_3$, 600 MHz) δ 7.36–7.32 (m, 2H), 7.32–7.22 (m, 6H), 7.19–7.15 (d, J = 7.1, 2H), 5.79 (br s, 1H), 4.41 (d, J = 5.8, 2H), 3.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 171.1, 138.2, 134.9, 129.6, 129.2, 128.8, 127.61, 127.56, 127.55, 43.9, 43.7.

A mixture of H_5IO_6 (6.90g, 30 mmol) and CrO_3 (25 mg, 5 mol%) in acetonitrile (70 mL) was stirred at room temperature for 30 min, then acetic anhydride (3.1 g, 30 mmol) was added. The resulting mixture was cooled to 0 °C. The amide **II-69** (1.05 g, 5 mmol) was added in one portion. After the reaction was complete (monitored by TLC), the reaction mixture was quenched by addition of ice-water (70 g), extracted with EtOAc (2 x 70 mL), washed respectively with sat. $NaHCO_3$ solution (80 mL), sat. $Na_2S_2O_3$ solution (80 mL) and brine (80 mL). The organic portion was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash

chromatography (SiO_2, hexanes: EtOAc = 6 : 1) to give pure **II-70** in 71% yield (0.80 g). White solid, MP: 146–148 ^oC

^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.50 (m, 4 H), 7.53–7.60 (m, 2 H), 7.83–7.89 (m, 4 H), 9.49 (br. s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.3, 128.9, 133.2, 133.7, 167.1.

Diisopropyl azodicarboxylate (0.6 mL, 4.9 mmol) was added dropwise to a precooled (0 ^oC) solution of dibenzamide (1.0 g, 4.4 mmol), Ph_3P (1.3 g, 4.9 mmol), allyl alcohol (0.25 g, 4.4 mmol), and THF (20 mL). The resulting mixture was maintained for 1 h at 0 ^oC and then allowed to warm to rt. After 2 h, the reaction was concentrated, and the residue was purified by flash chromatography (20:1 hexane-EtOAc) to afford **II-71** (70% yield, 0.8 g) as colorless oil.

^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.2 Hz, 2H), 7.60 (d, J = 7.2 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.6Hz, 2H), 7.40 (t, J = 7.3Hz, 1H), 7.30 (t, J = 7.4 Hz, 2H), 5.58 (m, 1H), 5.25 (1H, dd, J = 10.4, 1.7 Hz), 5.36 (1H, dd, J = 17.4, 1.7 Hz), 4.91 (d, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 176.0, 158.4, 134.8, 134.2, 132.7, 131.5, 130.6, 129.4, 128.5, 128.4, 128.2, 117.1, 64.9.

General procedure: Halogen source (0.11 mmol) was suspended in $CHCl_3$-EtOH (2:1, 2.2 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to appropriate temperature. $(DHQD)_2PHAL$ (3.90 mg, 312 μL of a 5 mg/mL solution in $CHCl_3$ (in the presence of molecular sieves), 5 mol%) was then introduced. After stirring vigorously for 10 min, the substrate (0.10 mmol) was added in a single portion. The vial was capped and the stirring was continued at appropriate temperature

till the reaction was complete (TLC). The reaction was quenched by the addition of 10% aq. Na_2SO_3 (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexanes as the eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-8.10 (m, 4H), 7.21-7.60 (m, 6H), 4.69 (dd, *J* = 4.7 and 11.3 Hz, 1 H), 4.41 (dd, *J* = 5.9 and 11.3 Hz, 1 H), 4.08 (m, 1H), 3.60-3.74 (m, 2H); ^{13}CNMR (125 MHz, $CHCl_3$) δ 167.8, 167.5, 133.8, 133.5, 131.8, 129.8, 129.3, 128.6, 128.5, 127.0, 63.1, 51.2, 33.2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-8.05 (m, 4H), 7.46-7.58 (m, 6H), 4.68 (dd, *J* = 4.7 and 11.3 Hz, 1 H), 4.38 (dd, *J* = 6.0 and 11.3 Hz, 1 H), 4.10 (m, 1H), 3.65-3.70 (m, 2H); ^{13}CNMR (125 MHz, $CHCl_3$) δ 171.1, 168.4, 133.9, 133.3, 131.6, 130.0, 129.2, 128.9, 128.4, 127.1, 63.2, 51.5, 45.8.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.08 (m, 4H), 7.22-7.55 (m, 6H), 4.60 (dd, *J* = 4.8 and 11.0 Hz, 1 H), 4.41 (dd, *J* = 6.1 and 11.0 Hz, 1 H), 4.07-4.19 (m, 1H), 3.62-3.70 (m, 2H); ^{13}CNMR (125 MHz, $CHCl_3$) δ 167.5, 167.3, 133.9, 133.5, 131.9, 129.7, 129.0, 128.3, 128.1, 127.0, 63.3, 55.5, 48.6.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-8.05 (m, 4H), 7.48-7.60 (m, 6H), 4.65 (dd, *J* = 4.8 and 11.1 Hz, 1 H), 4.35 (dd, *J* = 6.2 and 11.1 Hz, 1 H), 4.11-4.15 (m, 1H), 3.66-3.74 (m, 2H); ^{13}CNMR (125 MHz, $CHCl_3$) δ 171.2, 168.6, 134.0, 133.5, 131.8, 130.5, 129.4,

129.2, 128.4, 127.1, 63.4, 57.0, 51.9.

A 500-mL, one-necked flask was charged with cinnamic acid (2.96 g, 20.00 mmol), 20 mL of dry dichloromethane, benzyl alcohol (6.48 g, 60.00 mmol), and 4-dimethylaminopyridine (0.2 g, 16.00 mmol). The solution was stirred and cooled in an ice bath to 0 ^{o}C, and dicyclohexylcarbodiimide (4.56 g, 22 mmol) was added over a 5 min period. After 5 min at 0 ^{o}C the ice bath was removed and the dark-brown reaction mixture was stirred for 3 h at room temperature. The dicyclohexylurea that had precipitated was removed by filtration through a fritted Büchner funnel, and the filtrate was washed with two portions of 0.5 N hydrochloric acid (5 mL) and two portions of saturated sodium bicarbonate solution (5mL). The organic solution is dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexanes (10%) as the eluent in 75% yield (3.57 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 16.0 Hz, 1H), 7.54-7.36 (m, 10H), 6.49 (d, J = 16.0 Hz, 1H), 5.27 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 145.1, 136.1, 134.4, 130.2, 128.8, 128.5, 128.2, 128.1, 128.0, 117.9, 66.3.

General procedure: Halogen source (0.11 mmol) was suspended in TFE (2.2 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to -30 ^{o}C. $(DHQD)_2PHAL$ (7.80 mg, 10 mol%) was then introduced along with $Cu(OTf)_2$ (3.61 mg, 10 mol%). After stirring vigorously for 10 min, the substrate (0.10 mmol) was added

in a single portion. The vial was capped and the stirring was continued at -30 ^{o}C till the reaction was complete (TLC). The reaction was quenched by the addition of 10% aq. Na_2SO_3 (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexanes as the eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.68 (m, 9H), 4.59 (d, *J* = 2.2 Hz, 1H), 4.40 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 122.3, 121.8, 128.8, 128.7, 123.6, 123.4, 116.8, 52.5, 40.1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.66 (m, 9H), 4.88 (d, *J* = 2.2 Hz, 1H), 4.73 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 122.5, 121.5, 128.9, 128.7, 123.5, 123.3, 117.4, 45.8, 40.5.

General procedure for the formation pyridinium sulfates: The alcohol (1.0 equiv) was dissolved in freshly distilled pyridine to generate a 0.1 M solution. Sulfur-trioxide pyridine (SO_3•Py) complex (1.25 equiv) was then added, and the resulting mixture was stirred at rt for 1 h. The excess SO_3•Py then was quenched with a small amount of freshly distilled methanol. The resulting solution was concentrated under reduced pressure. (Note: avoid heating above 30 ^{o}C, as decomposition of the product pyridinium sulfate can occur). The resulting crude oil was then purified by flash chromatography to afford the sulfate salt (CH_2Cl_2-MeOH 4:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (m, 2H), 8.31 (brs, 1H), 7.21-7.46 (m, 8H), 6.65 (d, *J* = 16.2 Hz, 1H), 6.34-6.37 (m, 1H), 4.78 (d, *J* = 5.4 Hz, 2H).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (m, 2H), 7.98-8.03 (m, 2H), 7.40-7.62 (m, 6H), 6.64-6.69 (d, *J* = 15.3 Hz, 1H), 6.39-6.48 (m, 1H), 4.77 (d, *J* = 5.7 Hz, 2H).

General procedure: DCDMH (10 mg, 0.041 mmol, 1.1 equiv) was suspended in *n*-PrOH (1.4 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to the appropriate temperature. $(DHQD)_2PHAL$ (3.0 mg, 10 mol%) was then introduced. After stirring vigorously for 10 min, the substrate (0.037 mmol, 1.0 equiv) was added in a single portion. The vial was capped and the stirring was continued at the appropriate temperature until the reaction was complete (TLC). The reaction was quenched by the addition of H_2O (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexane (20-50%) as the eluent.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.41 (m, 5H), 5.97 (d, *J* = 10.8 Hz, 1H), 4.79-4.83 (t, *J* = 12.0 Hz, 1H), 4.69-4.71 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.47-4.52 (ddd, *J* = 12.0, 4.8, 4.8 Hz, 1H).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.68 (m, 9H), 5.65-5.68 (d, *J* = 10.5 Hz, 1H), 4.68-4.85 (ddd, *J* = 11.4, 4.8, 4.8 Hz, 2H), 4.33-4.42 (ddd, *J* = 10.5, 4.8, 4.8 Hz, 1H).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.74 (m, 2H), 7.56-7.59 (m, 2H), 5.65-5.69 (d, *J* =

10.2 Hz, 1H), 4.68-4.81 (ddd, *J* = 11.4, 4.8, 4.8 Hz, 2H), 4.23-4.32 (ddd, *J* = 10.2, 4.8, 4.8 Hz, 1H).

II.5 References

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CHAPTER III

Solvent-Dependent Enantiodivergent Chlorocyclization of Unsaturated Carbamates

III.1 Introduction

The field of asymmetric organocatalysis has witnessed tremendous advancements over the past decades.[1] The field has matured to the point that a widely diverse array of transformations leading to molecular scaffolds of varying complexities has been developed. A major contributor to these developments has been the equally impressive arsenal of experimental and theoretical tools that have become accessible to synthetic chemists. As a consequence, detailed mechanistic investigations of stereoselective reactions are routinely undertaken to better understand the underlying principles for the origins and erosion of stereoselectivity.[2-4] For example, the determination of the enthalpic and entropic activation parameters has led to a systematic and predictable optimization of both catalyst structure and reaction conditions for many stereoselective transformations.[5-7] Nonetheless, certain aspects of asymmetric catalysis such as enantiodivergent syntheses have not succumbed to a detailed mechanistic investigation. This is attributable, primarily, to the exceptionally rare occurrence of this phenomenon whereby either enantiomer of a desired product can be obtained using the same chiral catalyst.[8-12] Furthermore, numerous reaction variables such as temperature, additives and solvent can contribute to this phenomenon. Of all these parameters, the effect of solvent

is perhaps the least predictable given that catalyst conformations and solute solvent interactions may vary significantly in different solvents and these factors will likely play a pivotal role in determining the stereoselectivity.[13-17] Sohtome and coworkers have developed an enantiodivergent catalytic Mannich-type reaction by utilizing conformationally flexible organocatalysts. The simple methodology has a broad aromatic N-Boc imine substrate scope and it enables selective access to both enantiomers of the Mannich adducts using a single chiral organocatalyst in different solvents (Figure III-1).[13]

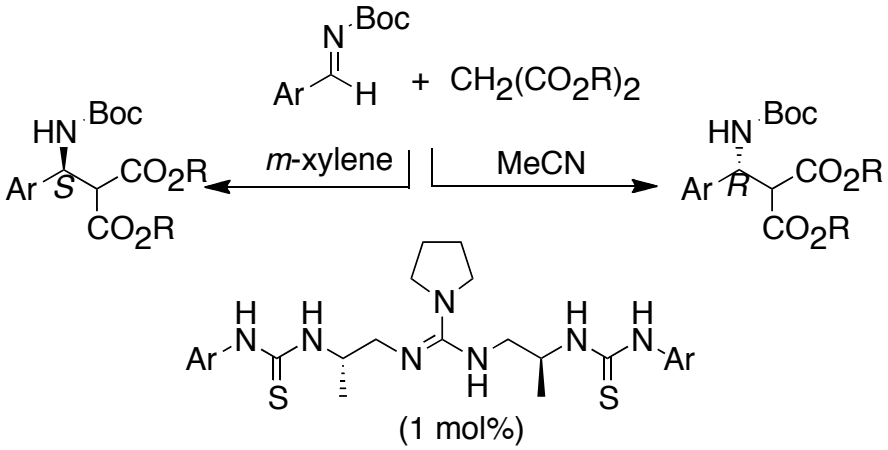


Figure III-1: Catalyzed enantiodivergent Mannich-type reactions with various aromatic *N*-Boc imines

In rare cases where synthetically meaningful enantiodivergent reactions have been developed, they have not been accompanied with an in depth study of the possible sources that contribute to the enantiodivergence. During the course of our studies aimed at developing enantioselective olefin halogenation reactions,[18, 19] we stumbled upon a solvent dependent enantiodivergent reaction. A detailed kinetic analysis of this reaction

using Eyring plot analyses [20] has helped us to determine the enthalpic and entropic drivers for the observed solvent dependent enantiodivergence of this reaction.

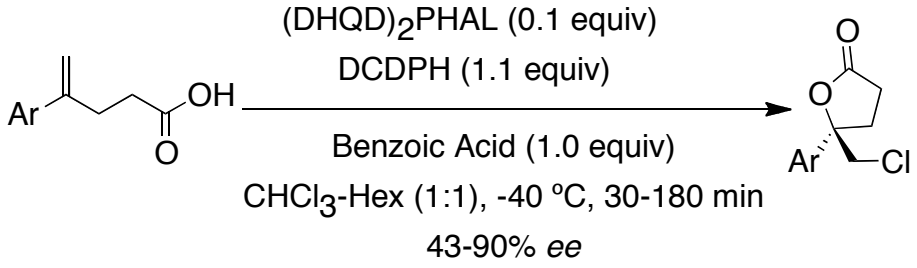


Figure III-2: The $(DHQD)_2PHAL$ mediated halolactonization

The hitherto overlooked research area of catalytic asymmetric halogenation of olefins has witnessed a renewed interest in recent years. Our group has previously reported a novel organocatalytic asymmetric chlorolactonization that returns chiral chlorolactones

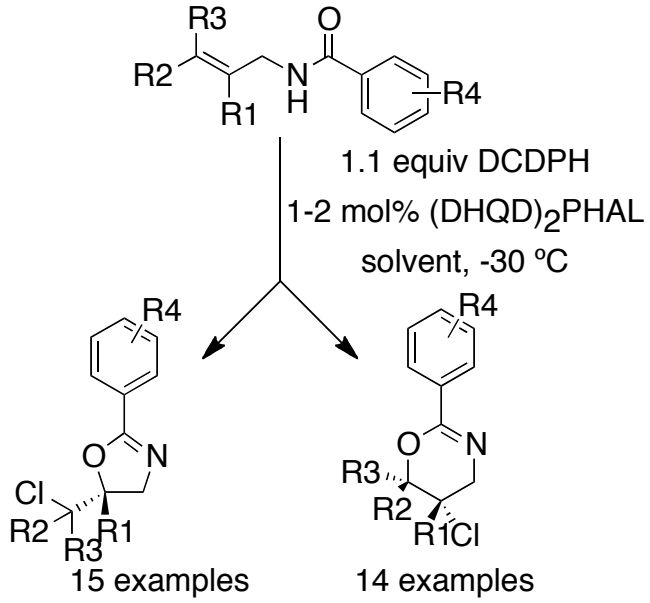
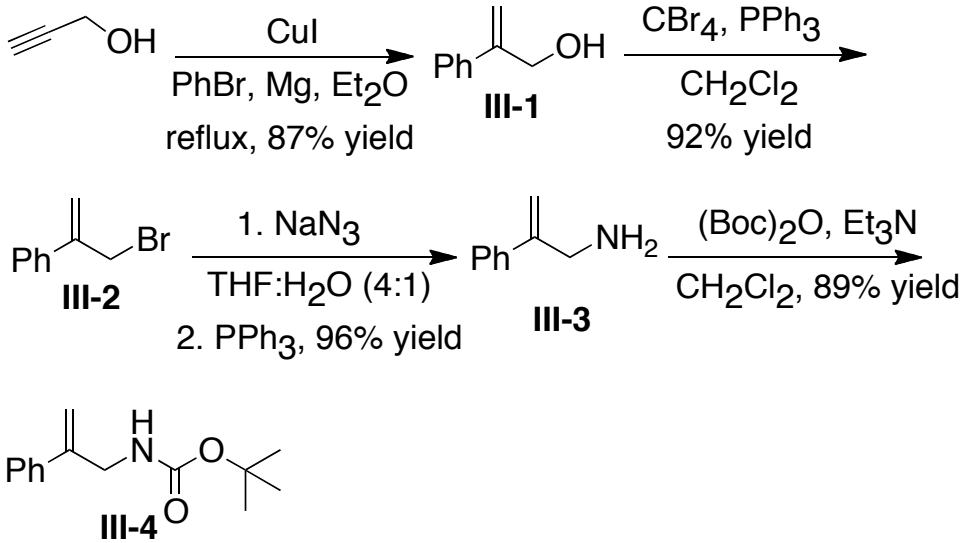


Figure III-3: The $(DHQD)_2PHAL$ mediated halocyclization of unsaturated amides

by action of $(DHQD)_2PHAL$ and dichloro diphenylhydantoin (DCDPH). This methodology represents the first example of a catalytic, enantioselective halolactonization that proceeds with synthetically useful enantioselectivities (figure III-2).[18]

We also have developed a highly stereoselective chlorocyclization of unsaturated amides to chiral heterocycles mediated by catalytic amounts (1–2 mol %) of the commercially available $(DHQD)_2PHAL$. The reaction is operationally simple with no need to resort to strictly anhydrous or inert reaction conditions. The reaction scope is fairly general with regards to the substitution pattern of the olefin. Both aliphatic and aromatic residues on the olefin are well tolerated. (Figure III-3).[19]

III.2 Solvent Screen for the Chlorocyclization Reaction of Unsaturated Carbamates



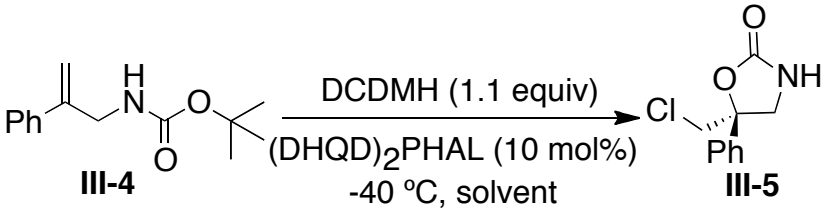
Scheme III-1: Synthesis of carbamate **III-4**

With the discovery that Cinchona alkaloid based ligands were effective in providing

halocyclized product with high enantioselectivities,[18, 19] the conversion of carbamates to oxazolidinones was studied with this catalytic system in different solvents. The synthesis of our test substrate **III-4** is shown in Scheme 1II-1. The coupling of bromobenzene and propargyl alcohol was achieved by copper iodide to provide **III-1**. Bromination of alcohol **III-1** followed by azide displacement and hydrolyzation gave the desired amine **III-3**. Formation of carbamate **III-4** was achieved by Boc protection of amine in 89% yield.

A comprehensive solvent screen was undertaken in an attempt to drive the enantioselectivity of the reaction higher. Fourteen different non alcoholic solvents were screened in the test reaction (**III-4** to **III-5**). Carbamate **III-4** (0.037 mmol) was cyclized in the presence of dichloro-dimethyl hydantoin (DCDMH) as a chlorine source in appropriate solvent (1.4 mL, 0.025 M in substrate) at -40 ^{o}C. A range of solvents were screened including polar and non-polar examples (Table III-1). CH_3CN and $CHCl_3$ returned carbamate **III-4** in 14 and 22% *ee*, respectively (Table III-1, entries 2,3). Interestingly, a 1:1 mixture of these solvents with hexane improved enantioselectivities to 27 and 47% *ee* respectively (Table III-1, entries 4,5). The mixture of $CHCl_3$:hexane (1:1) gave the best selectivity. Other mixture solvents with chloroform including toluene (43% ee, entry 6), cyclohexane (41% ee, entry 8), pentane (40% ee, entry 9), benzene (32% ee, entry 10) and heptane (40% ee, entry 11) were all found to be slightly less selective than mixture of chloroform with hexane. The reaction in pure hexane gives no cyclized product due to low solubility of the substrate and cartalyst in hexane (Table III-1, entry

Table III-1: Aprotic solvent screen for chlorocyclization reaction



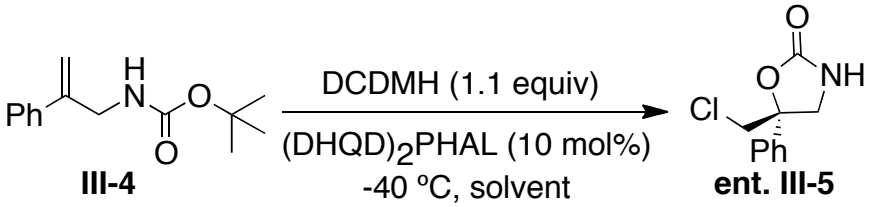
Entry	Solvent	*ee*[a] (%)	Entry	Solvent	*ee*[a] (%)
1	CH_2Cl_2	+2	8	$CHCl_3$:Cyclohexane[b]	+41
2	CH_3CN	+14	9	$CHCl_3$:Pentane[b]	+40
3	$CHCl_3$	+22	10	$CHCl_3$:benzene[b]	+32
4	CH_3CN:Hexane[b]	+27	11	$CHCl_3$:Heptane[b]	+40
5	$CHCl_3$:Hexane[b]	+47	12	Hexane	-
6	$CHCl_3$:Toluene[b]	+43	13	CH_2Cl_2:Hexane[b]	+26
7	CH_3CN:CCl_4[b]	+25	14	acetone	-20[c]

[a]ees were determined by GC analysis. [b]1:1 mixture. [c]ent.**III-5** was obtained.

12). Interestingly, the use of polar solvents such as yielded the opposite enantiomer in 20% *ee* (Table III-1, entry 14), a net change of 67 percentage points! The reason for this dramatic reversal in selectivity was not clear, but led to trials of protic solvents for this reaction.

The switch in enantioselectivity was observed in all protic solvents (Table III-2). The best results are obtained when *n*-PrOH (-74% *ee*, entry 4), *n*-BuOH (-61% *ee*, entry 6), and *i*-BuOH (-65% *ee*, entry 7) were used. Trifluoroethanol (TFE) proved to be less

Table III-2: Protic solvent screen for chlorocyclization reaction



III-4 **ent. III-5**

Entry	Solvent	*ee*[a] (%)	Entry	Solvent	*ee*[a] (%)
1	Trifluoroethanol	-37	7	*i*-BuOH	-65
2	EtOH	-52	8	pentanol	-52
3	MeOH	-36	9	TFE:EtOH[b]	-56
4	*n*-PrOH	-74	10	TFE:MeOH[b]	-49
5	IPA	-50	11	TFE:*n*-PrOH[b]	-72
6	*n*-BuOH	-61	12	TFE:IPA[b]	-56

[a]*ee*s were determined by GC analysis. [b]1:1 mixture.

selective than other alcoholic solvents (-37% *ee*, Table III-2, entry 1) but when mixed with EtOH (-56% *ee*, entry 9), MeOH (-49% *ee*, entry 10), and IPA (-56% *ee*, entry 12) the selectivity increased except for *n*-PrOH (-72% *ee*, entry 11). The reaction achieved highest enantioselectivity for **III-5** in CH_3Cl:Hexane (+47% *ee*) and in *n*-PrOH **ent.III-5** (-74% *ee*).

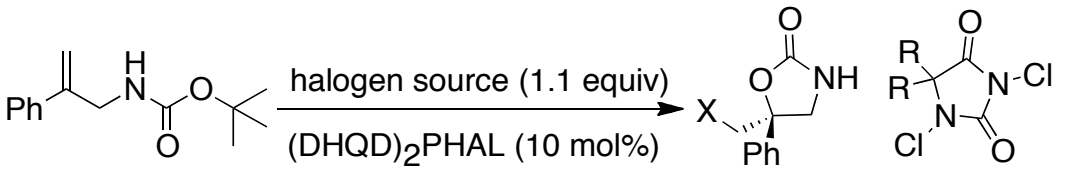
III.3 Halogen Source Screen for the Chlorocyclization Reaction of Unsaturated Carbamates

In addition to screening the chlorocyclization reaction in different protic and aprotic solvents, it was also interesting to investigate the enantioselectivity of the chlorocyclization reaction in the presence of different hydantoin and other chloronium sources. We investigated three hydantoins with different substituents in C5 (Table III-3). In CH_3Cl:Hexane solvent system, going from dimethyl-dichloro hydantoin (+47% *ee*, entry 1) to diphenyl-dichloro hydantoin (+46% *ee*, entry 2), the selectivity remained the same. The removal of the C5 substitution returned **III-5** in a substantially lowered +28 *ee* (Table III-3, entry 3). Similarly, trichloroisocyanuric acid (TCCA) produced an inferior result (+21% *ee*, entry 4). It is also noteworthy that the transformation in the presence of *N*-chlorosuccimide (NCS) provides the desired product **III-5** in racemic mixture (Table III-3, entry 5).

In *n*-PrOH, the maximum selectivity was observed when dimethyl-dichloro hydantoin (-74% *ee*, entry 6) was used in the presence of dichloro-dihydro hydantoin selectivity dropes to -70 *ee* (Table III-3, entry 8). The transformation in the presence of dichloro-diphenyl hydantoin did not proceed to completion after 24 h due to low solubility of DPDCH in *n*-PrOH (Table III-3, entry 7). TCCA and NCS did not improve the selectivity. Various bromonium sources were also screened for this transformation, but only low levels of stereoinduction were observed in the presence of dibromo-dimethyl hydantoin (-31% *ee*, entry 11). *N*-Bromosuccimide (NBS) provides the

bromocyclized product in good yield (86%) but no enantioselectivity (Table III-3, entry

Table III-3: Halogen source screening



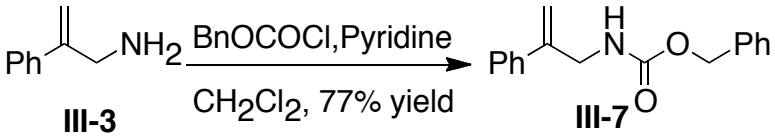
III-4 **III-6**

Entry	Solvent	Halogen source	Yield[a](%)	*ee*[b] (%)
1	$CHCl_3$: Hexane[c]	DCDMH	95	+47
2	$CHCl_3$: Hexane[c]	DCDPH	98	+46
3	$CHCl_3$: Hexane[c]	DCDHH	78	+28
4	$CHCl_3$: Hexane[c]	TCCA	90	+21
5	$CHCl_3$: Hexane[c]	NCS	57	0
6	*n*-PrOH	DCDMH	88	-74[d]
7	*n*-PrOH	DCDPH	NR	-
8	*n*-PrOH	DCDHH	86	-70[d]
9	*n*-PrOH	TCCA	90	-57[d]
10	*n*-PrOH	NCS	51	-67[d]
11	*n*-PrOH	DBDMH	90	-31[d]
12	*n*-PrOH	NBS	86	0

[a]Isolated yields after column chromatography. [b]*ee*s were determined by GC analysis. [c]1:1 mixture. [d]ent.**III-6** was obtained.

12). The investigation of alternative chlorine sources failed to provide a more selective transformation than the initially optimized (DCDMH) chlorine source.

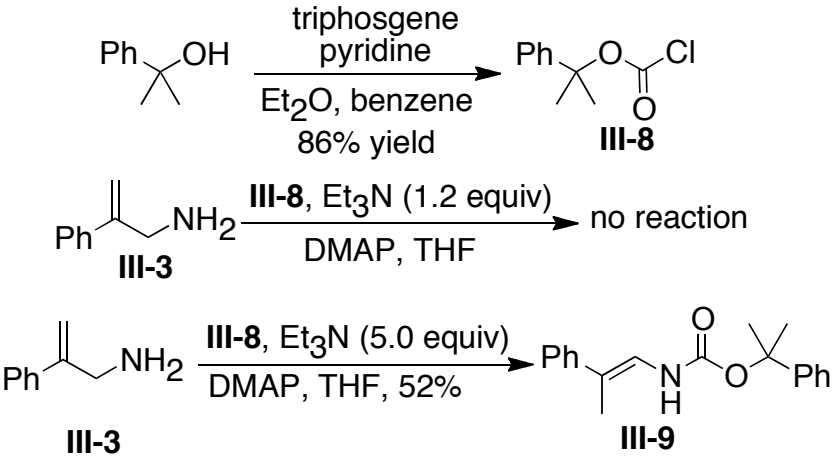
III.4 The Effect of Carbamate Structure on Enantioselectivity of Chlorocyclization Reaction of Unsaturated Carbamates



III-3 **III-7**

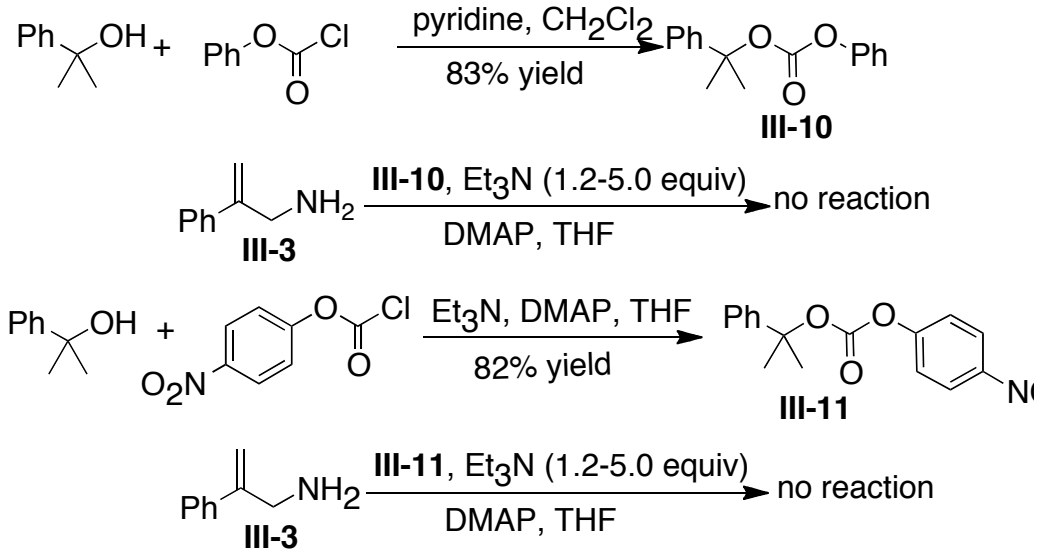
Scheme III-2: Synthesis of carbamate **III-7**

In an effort to further improve the stereoselectivity of this transformation, different carbamates were studied in the two optimized solvent systems. We tried to synthesize carbamates with more bulky group than *t*-butyl like dimethylphenyl and less bulky group such as benzyl. The synthesis of **III-7** by protection of amine **III-3** is outlined in Scheme III-2.



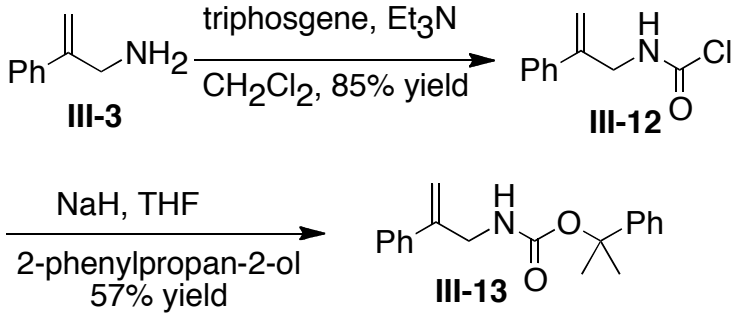
Scheme III-3: Attempts to make desired dimethylphenyl carbamate

The first attempt to synthesize dimethylphenyl carbamate started with formation of corresponding chloroformate **III-8** in 86% yield. The reaction of amine **III-3** with in the presence of Et_3N (1.2 equiv) was failed and starting material was isolated. The reaction proceeded to provide enamine **III-9** as a major product in 52% yield by increasing the amount of the Et_3N to 5.0 equivalents (Scheme III-3).



Scheme III-4: Attempts to make desired dimethylphenyl carbamate

Next, the reaction of amine **III-3** with carbonate **III-10** instead of chloroformate was studied. The desired carbonate **III-10** was synthesized as shown in Scheme III-4.

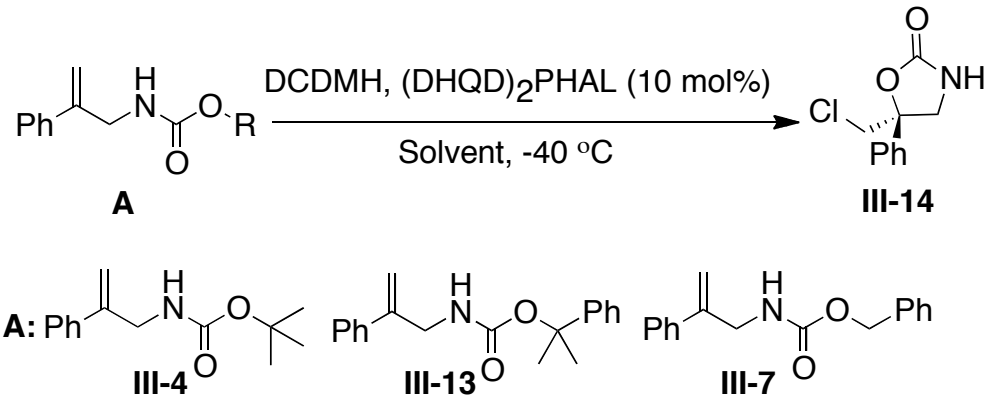


Scheme III-5: Synthesis of carbamate **III-13**

However, the reaction of amine **III-3** in the presence of different equiv (1.2-5.0) of triethyl amine did not provide any product and, instead starting material was isolated (Scheme III-4). One problem could be the low activity of carbonate **III-10**, so carbonate **III-11** with a nitro group in *para* position was prepared. Unfortunately, the reaction failed once again yielding the isolated starting material for the reaction of amine **III-3** with carbonate **III-11** (Scheme III-4). Finally, the desired carbamte **III-13** was synthesized from carbamic chloride **III-12** and 2-phenylpropan-2-ol in the presence of sodium hydride (Scheme III-5).

The chlorocyclization of carbamtes (**III-4**, **III-13**, **III-7**) under optimized condition was studied. Modulation of the *t*-butyl group to benzyl or dimethyl phenyl did not affect the stereoselectivity of the reaction in *n*-PrOH (Table 4, entries 4-6). Conversely, the stereoselectivity diminished in the $CHCl_3$-Hexane solvent system (Table 4, entries 1-3). Contrasting trends in the enantioselectivity were observed as a function of carbamate structure in the two different solvent systems. This observation is likely an indication of different modes of catalyst-substrate interaction in different solvents.

Table III-4: The effect of carbamate structure on enantioselectivity



Entry	Carbamate	Solvent	Yield[a](%)	*ee*[b] (%)
1	**III-4**	$CHCl_3$: Hexane[c]	95	+47
2	**III-13**	$CHCl_3$: Hexane[c]	78	+25
3	**III-7**	$CHCl_3$: Hexane[c]	80	+13
4	**III-4**	*n*-PrOH	88	-74[d]
5	**III-13**	*n*-PrOH	85	-73[d]
6	**III-7**	*n*-PrOH	82	-71[d]

[a]Isolated yields after column chromatography. [b]*ee*s were determined by GC analysis. [c]1:1 mixture. [d]ent.**III-14** was obtained.

III.5 Eyring Plot analyses[20]

In recent years, the observation of temperature effects in connection with the Eyring theory[20] has been used to gain a better understanding of the factors influencing the stereochemical outcome of various reactions. In particular, studies of enantio- and diastereoselective reactions by varying the reaction temperature have shed light on

solvent effects and stereoselectivity.[21] Analysis of the logarithmic values of stereoselectivity as a function of reciprocal temperature results in a linear relationship for the equation reported in Figure III-4, known as the modified Eyring equation,[22] where

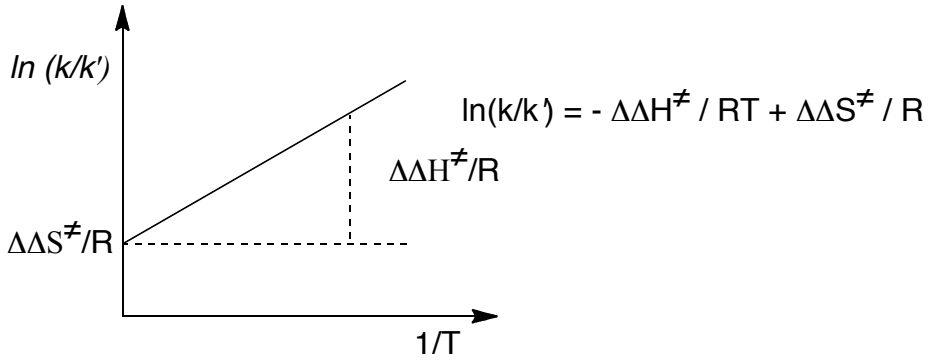
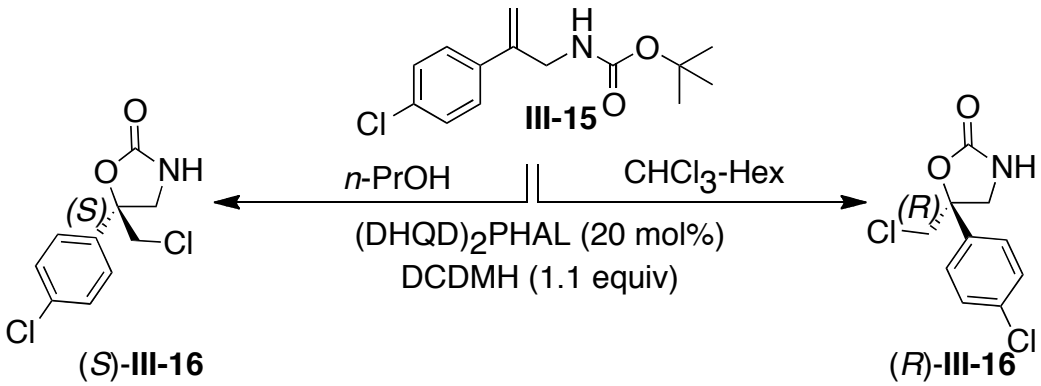


Figure III-4: Stereoselectivity and thermodynamic parameters: a graphic representation of the Eyring equation

ln(k/k') is the natural logarithm of stereoselectivity, and k and k' are the overall rate constants of the reactions leading to the two stereoisomers. According to Eyring theory, when this relationship is plotted, the slope corresponds to the difference in the overall activation enthalpies ($\Delta\Delta H^{\neq}$) and the intercept represents the difference in the overall



Scheme III-6: Test reaction for Eyring plot analyses

activation entropies ($\Delta\Delta S^{\neq}$) (Figure III-4). The influence of solvent on stereoselectivity can be considered as a macroscopic effect related to solute–solvent interactions at the molecular level. These interactions differently affect the reaction paths leading to the two stereoisomers by changing the activation parameters and therefore the stereoselectivity.

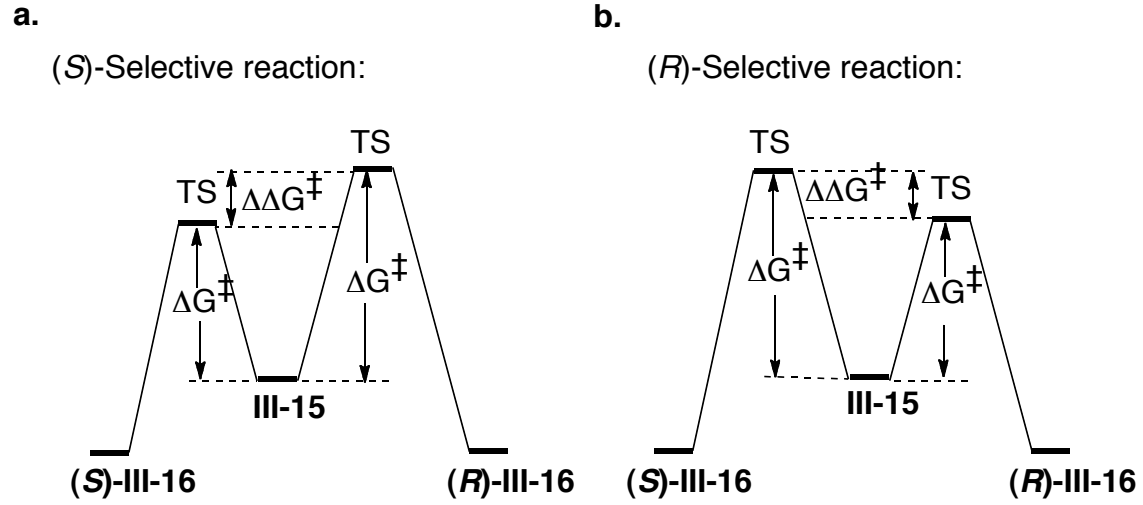


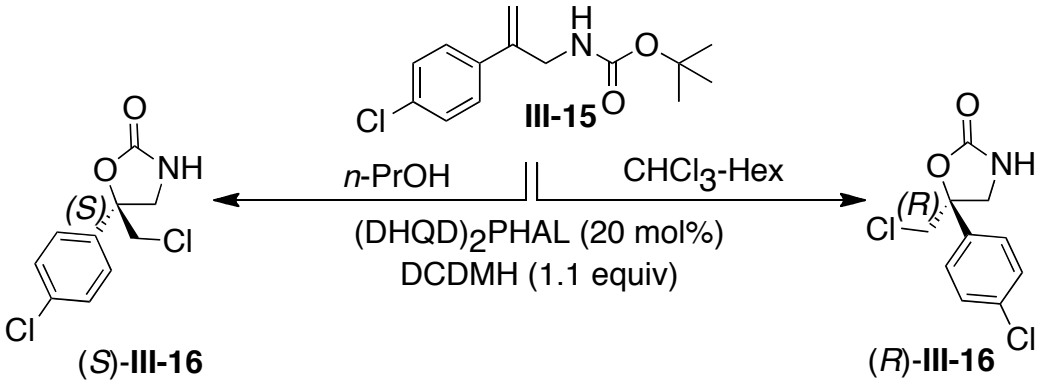
Figure III-5: Energy diagrams in the chlorocyclization reaction; (a) (*S*)-Selective reactions. (b) (*R*)-Selective reactions.

The solvent effect can be so significant that it can switch the stereoselectivity from enthalpy control (where $\Delta\Delta S^{\neq} \approx 0$) to entropy control (where $\Delta\Delta H^{\neq} \approx 0$).[23]

In our system, with suitable solvents in hand for accessing either enantiomer, our efforts focused on comparing the divergent mechanisms that generate the *R* or the *S* enantiomers selectively. To investigate this, the chlorocyclization of carbamate **III-15** (synthesized in the same manner shown in Scheme III-1) was selected as a test reaction for further studies. The absolute stereochemistry of (*S*)-**III-16** was verified by X-ray diffraction and was inferred by analogy for other substrates (Scheme III-6). Eyring plot analyses were run for the cyclization of **III-15** in the presence of 20 mol% of catalyst.

Increased catalyst loading was employed to eliminate the background reaction at 0 °C. The energy diagram for the chlorocyclization of carbamate **III-15** based on the transition state theory is illustrated in Figure III-5. The enantioselectivity in the reaction should increase, as the absolute value of $\Delta\Delta G^{\neq}$ becomes larger.

Table III-5: The effect of temperature on the chlorocyclization reaction of carbamate **III-15**



Solvent	Temp (°C)	*ee* (%)[a]	Config.	Solvent	Temp (°C)	*ee* (%)[a]	Config.
n-PrOH	0	54	*S*	$CHCl_3$-Hex	0	65	*R*
n-PrOH	-10	60	*S*	$CHCl_3$-Hex	-10	63	*R*
n-PrOH	-20	68	*S*	$CHCl_3$-Hex	-20	60	*R*
n-PrOH	-25	70	*S*	$CHCl_3$-Hex	-25	41	*R*
n-PrOH	-30	74	*S*	$CHCl_3$-Hex	-30	28	*R*
n-PrOH	-40	74	*S*	$CHCl_3$-Hex	-40	20	*R*
n-PrOH	-55	74	*S*	$CHCl_3$-Hex	-55	6	*R*

[a] *ee*s were determined by GC analysis.

In the course of this effort, significant temperature effects on the enantiodivergent chlorocyclization reactions were observed (Table III-5). As the reaction temperature

increased the *R* selectivity in $CHCl_3$-Hexane also increased for the cyclization reaction of carbamate **III-15** (+82% *ee* at 0 ^{o}C as compared to +47% *ee* at -40 ^{o}C). Conversely, a decrease in reaction temperature resulted in an increase in the *S* selectivity during the formation of oxazolidinone **III-16** in *n*-PrOH (-74% *ee* at -40 ^{o}C as compared to -54% *ee* at 0 ^{o}C). The difference in temperature profiles between the *R*-selective and *S*-selective reactions suggest that enthalpy-entropy compensation may contribute to this solvent dependent enantiodivergent system.

We hoped to address three important aspects using Eyring plot analyses–first, to explain the different trends in the temperature dependence of enantioselectivity in protic versus aprotic solvents; second, to explain the dependence (or the lack of it) of carbamate structure on the enantioselectivity in the two solvent systems and third, to determine the nature of substrate catalyst interactions on the basis of the differential activation parameters obtained from the Eyring plots. The relative rates for the formation of the *S* and *R* products are represented by Equations (1) and (2), respectively, where $\Delta\Delta S^{\neq}$ represents the differential activation entropy and $\Delta\Delta H^{\neq}$ represents the differential activation enthalpy.

$$\ln(k_S/k_R) = - \Delta\Delta H^{\neq}_{S\text{-}R} / RT + \Delta\Delta S^{\neq}_{S\text{-}R} / R \qquad (1)$$

$$\ln(k_R/k_S) = - \Delta\Delta H^{\neq}_{R\text{-}S} / RT + \Delta\Delta S^{\neq}_{R\text{-}S} / R \qquad (2)$$

The difference in the Gibbs free energy of activation for the formation of the two diastereomeric transition states can then be correlated to the differential enthalpy ($\Delta\Delta H^{\neq}$)

and entropy ($\Delta\Delta S^{\neq}$) of activation parameters using Equation 3. A more negative value for $\Delta\Delta G^{\neq}$ will indicate a more spontaneous formation of one diastereomeric transition state over the other. Attention must be drawn to the fact that the contribution of $\Delta\Delta S^{\neq}$ to the value of $\Delta\Delta G^{\neq}$ is temperature dependent unlike the contribution of $\Delta\Delta H^{\neq}$ (See SI).

$$\Delta\Delta G^{\neq} = \Delta\Delta H^{\neq} - T\Delta\Delta S^{\neq} \quad (3)$$

In accord with the above Equations, plots of the natural logarithms of the relative rates of formation of (*S*)-**III-16** product, in *n*-PrOH versus reciprocal temperatures were fitted to straight lines with good correlation coefficients (Figure III-6). These observations confirm that a single mechanism is operative in the catalytic process occurring in *n*-PrOH over the temperature range of 0 ^{o}C to -30 ^{o}C where maximum stereoselectivity was observed at -30 ^{o}C.

(*S*)-Selective reaction:

y = -4.2752 + 1.4957 x

$-\Delta\Delta H^{\neq}_{S\text{-}R} / R = +1.4957$ $\Delta\Delta H^{\neq}_{S\text{-}R} = -12.4$ kJ mol^{-1}

$\Delta\Delta S^{\neq}_{S\text{-}R} / R = -4.2752$ $\Delta\Delta S^{\neq}_{S\text{-}R} = -35.5$ J mol^{-1} K^{-1}

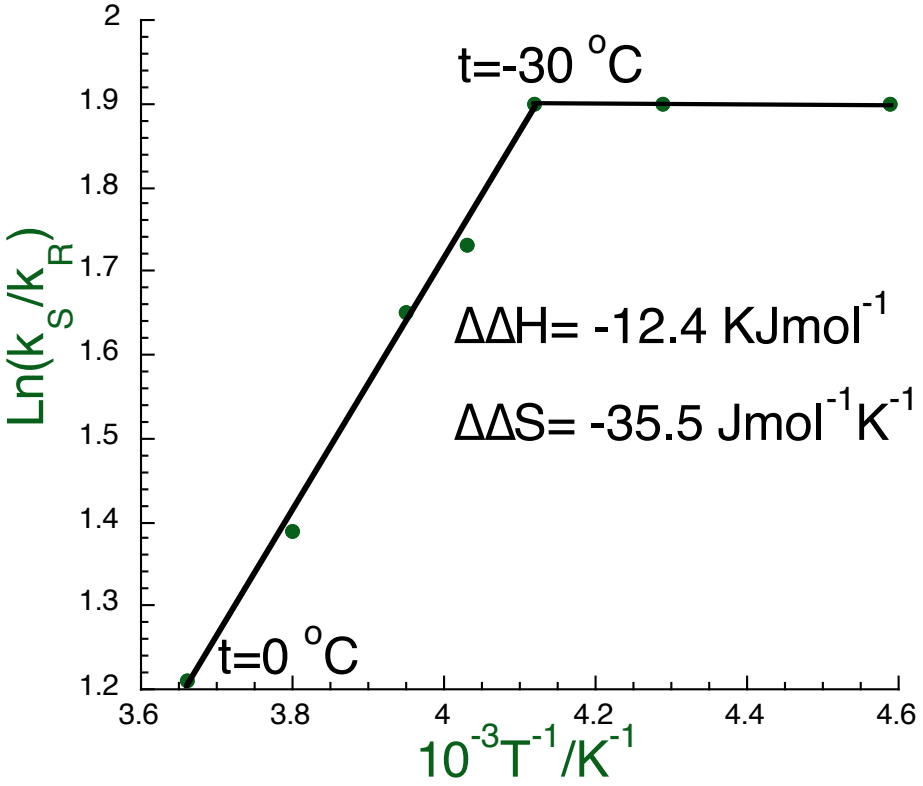


Figure III-6: Eyring plots of ln[(100 + %ee)/(100 - %ee)] vs. 1/T for chlorocyclization reactions in *n*-PrOH

On the other hand, Eyring plots of this reaction in $CHCl_3$-Hexane (1:1) showed two T_{inv} at -20 °C and -30 °C. This interruption marks two linear trends, one at a higher T (higher streoselectivity) and one at a lower T with different slopes and intercepts that confirm two different operative mechanisms at different temperatures (Figure III-7).

(*R*)-Selective reaction:

y = 3.8324 – 0.62203 x

$-\Delta\Delta H^{\neq}_{S\text{-}R} / R = -0.62203$ $\qquad$ $\Delta\Delta H^{\neq}_{S\text{-}R} = +5.2$ kJ mol^{-1}

$\Delta\Delta S^{\neq}_{S\text{-}R} / R = +3.8324$ $\qquad$ $\Delta\Delta S^{\neq}_{S\text{-}R} = +31.8$ J mol^{-1} K^{-1}

(*R*)-Selective reaction:

$y = 4.5202 – 0.9585\ x$

$-\Delta\Delta H^{\neq}_{S\text{-}R} / R = -0.9585$ $\qquad\qquad$ $\Delta\Delta H^{\neq}_{S\text{-}R} = +8.0\ kJ\ mol^{-1}$

$\Delta\Delta S^{\neq}_{S\text{-}R} / R = +4.5202$ $\qquad\qquad$ $\Delta\Delta S^{\neq}_{S\text{-}R} = +37.6\ J\ mol^{-1}\ K^{-1}$

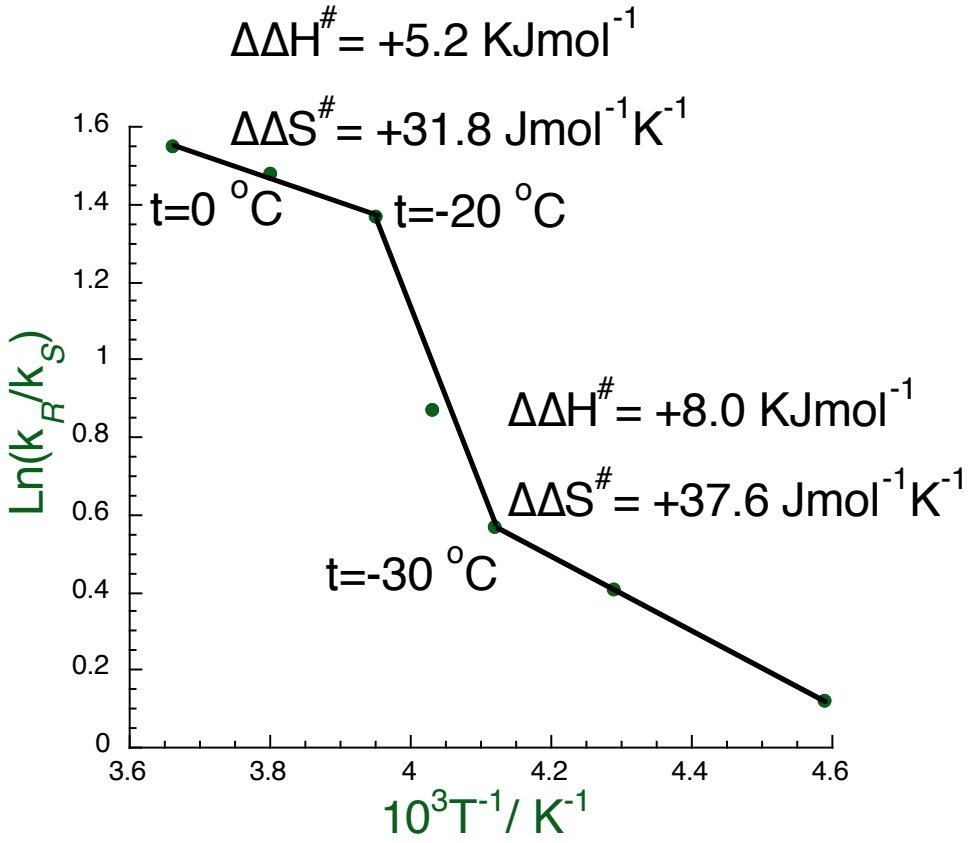


Figure III-7: Eyring plots of ln[(100 + %ee)/(100 - %ee)] vs. 1/T for chlorocyclization reactions in $CHCl_3$-Hexane

As summarized in Table III-6, the enthalpy-entropy compensation in $CHCl_3$-Hexane is different at -30 °C (243 K) as opposed to 0 °C (273 K). At 273 K, the contribution of the decreased entropy of activation ($-T\Delta\Delta S^{\neq}_{R\text{-}S}$ = -8.7 kJ mol^{-1}) far outweighs the unfavorable decrease in the differential enthalpy of activation (+5.2 kJ mol^{-1}) to result in one diastereomeric TS being favored over the other by 3.5 kJ mol^{-1}. Therefore the stereoselectivity of the *R*-selective chlorocyclization reaction in $CHCl_3$-Hexane is governed by the differences in the entropies of activation ($\Delta\Delta S^{\neq}_{R\text{-}S}$) leading to the two possible enantiomeric products. This result is likely manifested by the dependence of

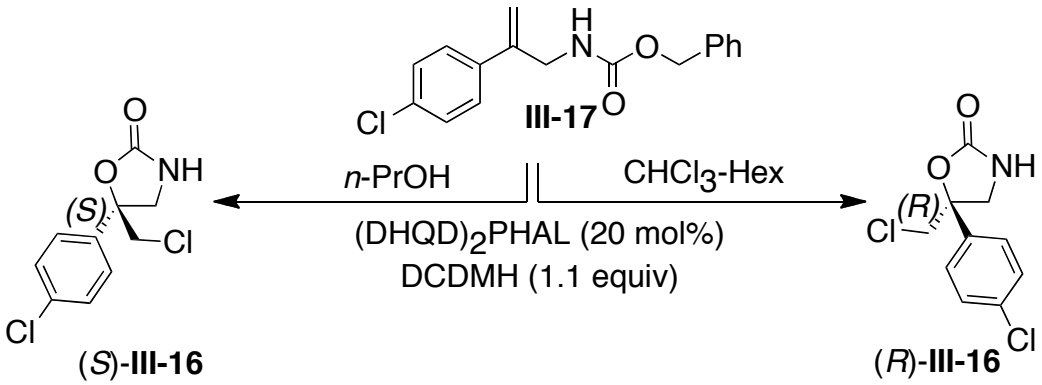
Table III-6: Differential enthalpy, entropy and Gibbs free energy for the chlorocyclization reaction

Solvent	Temp (K)	$\Delta\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta\Delta S^{\neq}$ (J mol^{-1} K^{-1})	$\Delta\Delta G^{\neq}$ (kJ mol^{-1})
$CHCl_3$-Hex	243	+8.0	+37.6	-1.1
$CHCl_3$-Hex	273	+5.2	+31.8	-3.5
n-PrOH	243	-12.4	-35.5	-3.8
n-PrOH	273	-12.4	-35.5	-2.7

enantioselectivity on the steric bulk of the carbamate in $CHCl_3$-Hexane with bulkier carbamates predictably giving lower enantioselectivities. In contrast, in the *S*-selective reaction in *n*-PrOH, negative values of $\Delta\Delta H^{\neq}_{S\text{-}R}$ and $\Delta\Delta S^{\neq}_{S\text{-}R}$ control the stereoselectivity.

The increase in differential enthalpy activation (-12.4 kJ mol^{-1}) is offset by the increased differential entropy of activation (-35.5 J $mol^{-1}K^{-1}$). The latter has a net lower

Table III-7: The effect of temperature on the chlorocyclization reaction of carbamate **III-6**



Solvent	Temp (^oC)	*ee* (%)[a]	Config.	Solvent	Temp (^oC)	*ee* (%)[a]	Config.
n-PrOH	0	60	*S*	$CHCl_3$-Hex	0	20	*R*
n-PrOH	-20	68	*S*	$CHCl_3$-Hex	-20	15	*R*
n-PrOH	-30	74	*S*	$CHCl_3$-Hex	-30	10	*R*
n-PrOH	-40	74	*S*	$CHCl_3$-Hex	-40	8	*R*

[a] *ee*s were determined by GC analysis.

contribution at lower temperatures ($-T\Delta\Delta S^{\neq}$ = +8.6 kJ mol^{-1} at 243 K as opposed to +9.7 kJ mol^{-1} at 273 K) leading to one TS being favored over the other by 3.8 kJ mol^{-1} at 243 K (-30 ^oC). Hence $\Delta\Delta H^{\neq}_{S\text{-}R}$ term is the major influence on lowering the $\Delta\Delta G^{\neq}_{S\text{-}R}$ of the favored pathway, indicating that the *S*-selective reaction is governed by differences in the enthalpies of activation ($\Delta\Delta H^{\neq}_{S\text{-}R}$). These results seem to suggest that the stabilizing interactions between the substrate and catalyst (presumably by means of π stacking

interactions of the olefin substituent and the catalyst) contribute significantly more than the steric repulsion between the substrate and catalyst in *n*-PrOH. Experimental observations of the negligible effect of the carbamate bulk on the enantioselectivity of this reaction in *n*-PrOH (See Table III-4) seem to confirm this hypothesis.

As shown in Table III-4, modulation of the *t*-butyl group to benzyl or dimethyl phenyl did not affect the stereoselectivity of the reaction in *n*-PrOH but the stereoselectivity is diminished in the $CHCl_3$-Hexane solvent system. The benzyl carbamate **III-17** was synthesized to compare its Eyring plots of benzyl activation parameters with that of the carbamate **III-15**. The effect of temperature in the formation of (*S*)-**III-16**, in *n*-PrOH and $CHCl_3$-Hexane was studied (Table III-7).

(*S*)-Selective reaction:

$y = -2.2574 + 1.0105\ x$

$-\Delta\Delta H^{\neq}_{S\text{-}R} / R = +1.0105$ $\qquad\qquad$ $\Delta\Delta H^{\neq}_{S\text{-}R} = -8.4\ kJ\ mol^{-1}$

$\Delta\Delta S^{\neq}_{S\text{-}R} / R = -2.2574$ $\qquad\qquad$ $\Delta\Delta S^{\neq}_{S\text{-}R} = -18.8\ J\ mol^{-1}\ K^{-1}$

The plots of the natural logarithms of the relative rates for the formation of (*S*)-**III-16**, in *n*-PrOH versus reciprocal temperatures were fitted to straight lines with good correlation coefficients (Figure III-8). The results closely mirror those observed for carbamate **III-15,** albeit with lower $\Delta\Delta H^{\neq}_{S\text{-}R}$ and $\Delta\Delta S^{\neq}_{S\text{-}R}$. This reaction is also enthalpy driven.

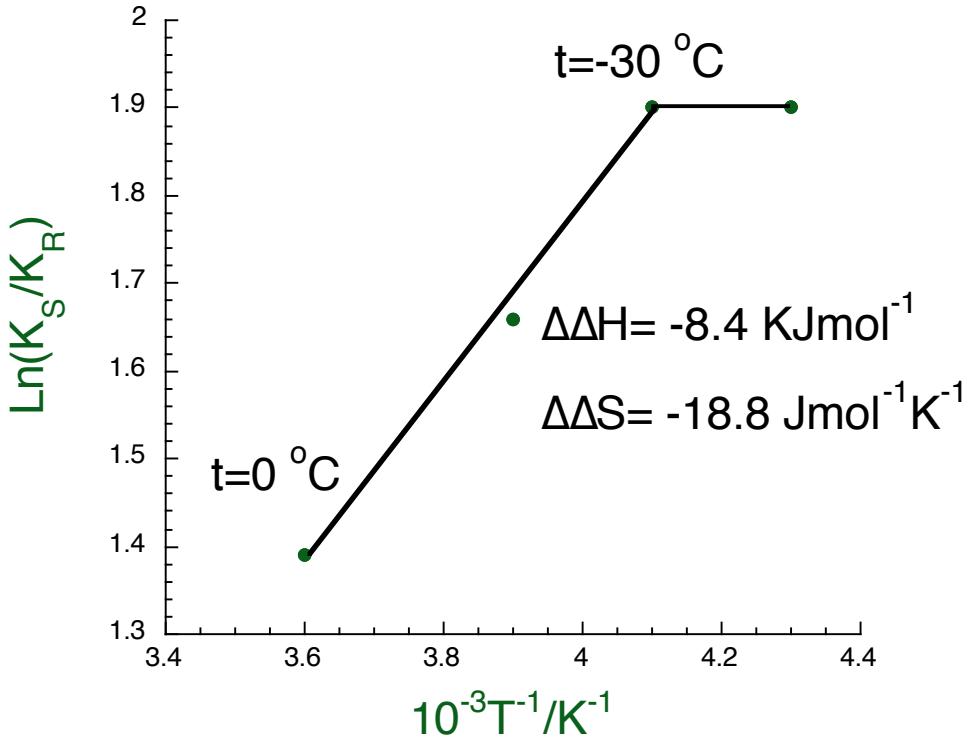


Figure III-8: Eyring plots of ln[(100 + %ee)/(100 - %ee)] vs. 1/T for chlorocyclization reactions of carbamate **III-17** in *n*-PrOH

On the other hand, Eyring plots of the reaction of carbamate **III-17** in $CHCl_3$-Hexane (1:1) showed a different pattern ascompared to carbamate **III-15**. Two T_{inv} at -20 °C and -30 °C were observed. In comparison to **III-15** $\Delta\Delta H^{\neq}_{R\text{-}S}$ and $\Delta\Delta S^{\neq}_{R\text{-}S}$ for **III-17** were lower (Figure III-9). The stereoselectivity for the *R*-selective chlorocyclization reaction of carbamte **III-17** in $CHCl_3$-Hexane is also governed by the differences in the entropy of activation ($\Delta\Delta S^{\neq}_{R\text{-}S}$).

(*R*)-Selective reaction:

y = 1.6841 – 0.55701 x

$-\Delta\Delta H^{\neq}_{S\text{-}R} / R = -0.55701$ $\Delta\Delta H^{\neq}_{S\text{-}R} = +4.6$ kJ mol^{-1}

$\Delta\Delta S^{\neq}_{S\text{-}R} / R = +1.6841$ $\Delta\Delta S^{\neq}_{S\text{-}R} = +14.0$ J mol^{-1} K^{-1}

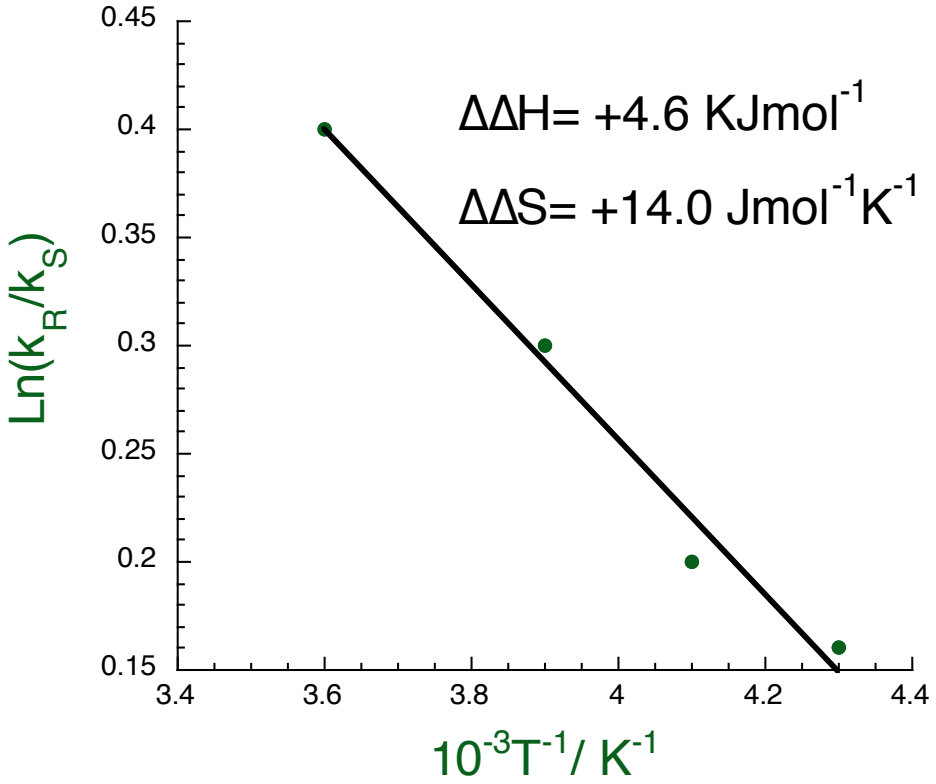


Figure III-9: Eyring plots of ln[(100 + %ee)/(100 - %ee)] vs. 1/T for chlorocyclization reactions of carbamate **III-17** in $CHCl_3$-Hexane

One can also imagine that the switch in enantioselectivity by changing the solvent from $CHCl_3$-Hexane to *n*-PrOH can be due to conformational changes of the catalyst in different solvents. To test this hypothesis the conformation of the catalyst was examined by NMR ROESY studies in deuterated methanol as replacement *n*-PrOH. The observed ROESY between the ethyl group of the quinuclidine moiety and also H_c with H_d indicates that the catalyst, $(DHQD)_2PHAL$, adapts an open conformation (Figure III-10),

which is also supported by the small H_a-H_b coupling constant (suggesting the dihedral angle close to 90 degree). These ROESY studies suggests that $(DHQD)_2PHAL$ adopts the same conformation to what Sharpless has reported for the $(DHQD)_2PHAL$ in chloroform.[24] These results together suggest that the origin of the solvent-dependent stereodiscrimination is controlled by the enthalpy-entropy compensation and not conformational changes in the catalyst.

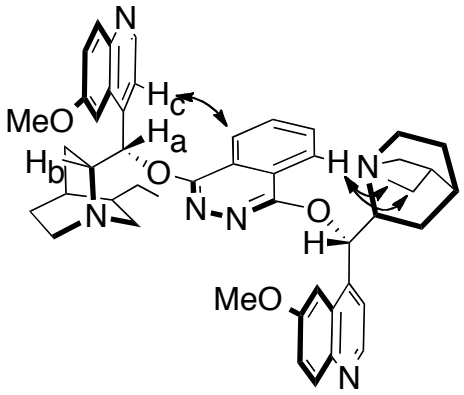


Figure III-10: Structure of $(DHQD)_2PHAL$ in chloroform and methanol based on the NMR ROESY studies

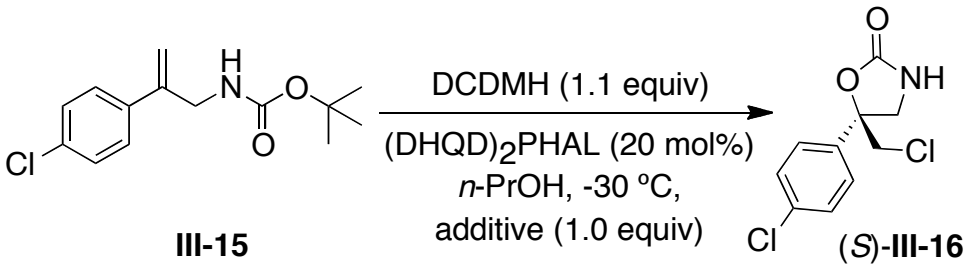
III.6 Additive Optimization Experiments

With the discovery that -30 °C was an optimal temperature in providing chloro-oxazolidinone (*S*)-**III-16** in *n*-PrOH and 0 °C was the effective temperature for (*R*)-**III-16** in $CHCl_3$-Hexane, a series of experiments were conducted to optimize the selectivity. Initial efforts focused on evaluating the selectivity of the reaction by addition of different acids. Several acidic additives were screened for reaction in *n*-PrOH. Addition of 1.0 equivalent of *p*-TsOH or acetic acid resulted in decreased selectivities

(Table III-8, entries 2,3), citric acid had little effect (Table III-8, entry 4). Unlike other acid additives, benzoic acid (1.0 equiv) generated a reproducible increase in selectivity to 91% *ee* (Table III-8, entry 5). Further increase of benzoic acid to 2.0 and 5.0 equivalents did not offer any additional increases in selectivity.

Since benzoic acid and acetic acid have almost the same acidity, the increase in selectivity with benzoic acid cannot be solely due to acidity, and points to interaction between benzoic acid and substrate or catalyst. Other substituted benzoic acids with

Table III-8: Acid additives loading screening in *n*-PrOH



III-15 (*S*)-**III-16**

Additive	Yield (%)[a]	*ee* (%)[b]
-	89	-74
p-TsOH	90	-20
AcOH	87	-20
Citric acid	92	-73
Benzoic acid	94	-91

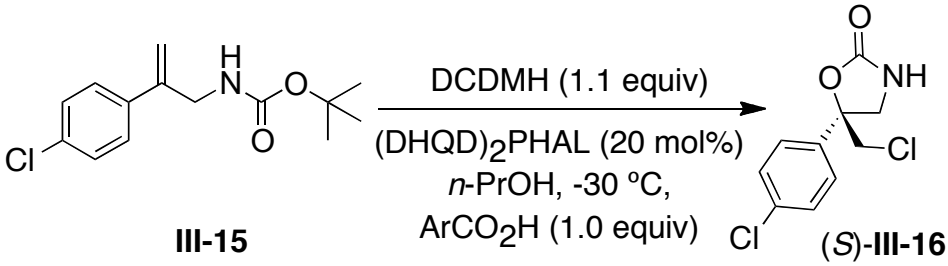
[a]Isolated yields after column chromatography. [b]*ee*s were determined by GC analysis.

electron donating and electron withdrawing groups were screened. As outlined in Table III-9, electron donating groups (entries 2, 5, 7, 12) and electron withdrawing groups

(entries 3, 4, 6) did not improved the selectivity. Having more bulky benzoic acid (entry 8) or with two electron donating groups (entries 10, 11) did not change the selectivity. 3,5-Dinitro benzoic acid provides the desired product with the lowest selectivity (80% *ee*, Table III-9, entry 9).

Overall, addition of 1.0 equivalent of benzoic acid resulted in increasing the selectivity of the chlorocyclization reaction in *n*-PrOH. The effect of this additive on the reaction in $CHCl_3$-Hexane was then studied (Table III-10). A drop in selectivity was realized when 1.0 or 5.0 equivalents of benzoic acid was added to reaction in

Table III-9: Screening of different benzoic acid



III-15 (*S*)-**III-16**

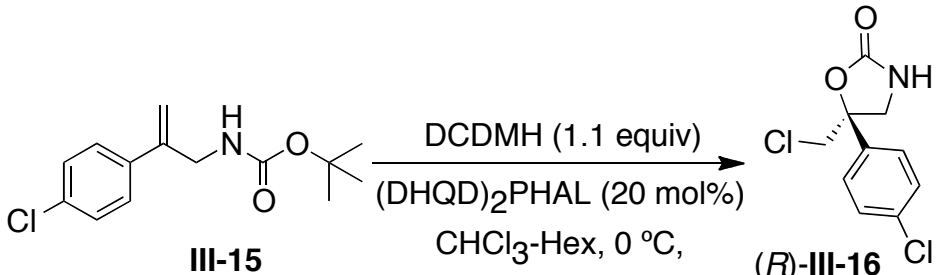
Entry	Ar	*ee* (%)[a]	Entry	Ar	*ee* (%)[a]
1	Ph	-91	7	3-hydroxy-Ph	-86
2	4-amino-Ph	-87	8	2,4,6-trimethyl-Ph	-88
3	3-chloro-Ph	-88	9	3,5-dinitro-Ph	-80
4	4-cyano-Ph	-83	10	3,5-dimethoxy-Ph	-89
5	4-methoxy-Ph	-86	11	3,5-dimethyl-Ph	-89
6	4-nitro-Ph	-83	12	4-hydroxy-Ph	-85

[a] *ee*s were determined by GC analysis.

$CHCl_3$-Hexane (Table III-10, entries 2, 3). Triethyl amine was tolerated at 0.1 equivalent loading (60% *ee*), but a significant drop in selectivity was observed when larger amounts

were added. Addition of 1.0 equvalent not only led to low selectivity (26% *ee*) but also resulted in low coversion of reaction (entries 4-7). Imidazole (0.1 equivalent) were decreased the selectivity to 28% *ee* (entry 8) and a larger amount (1.0 equivalent) cause a complete loss of selectivity and low conversion (entry 9). Diisopropyl ethylamine resulted in low selectivity (entry 10) and both diisopropyl amine and pyridine cause no conversion of the reaction (entries 11 and 12). Inorganic bases such as sodium carbonate had little effect on the selectivity (entry 13). Addition of Lewis acids such as copper triflate (entry 14) and silver triflate (entry 15) produced a decline from 65% *ee* to 56% and 44% *ee*, respectively. Drying agents had little effect on the stereochemical course of the reaction. The addition of anhydrous magnesium sulfate (entry 16) led to the production of (*R*)-**III-16** with lower selectivity. The addition of 20% w/w loading of activated 4 Å molecular sieves returned the chlorooxazolidinone in 61% *ee* (entry 17). In summary, the best results were obtained with no additive for $CHCl_3$-Hexane solvent system.

Table III-10: Screen of additives loading in $CHCl_3$-Hexane



III-15 (*R*)-**III-16**

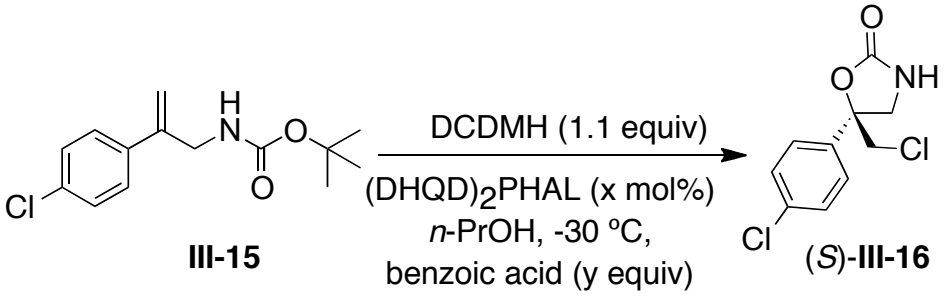
Entry	Additive	Additive (equiv)	Yield (%)[a]	*ee* (%)[b]
1	-	-	85	+65
2	Benzoic acid	1.0	80	+58
3	Benzoic acid	5.0	87	+52
4	Et_3N	0.1	92	+60
5	Et_3N	0.2	78	+46
6	Et_3N	0.5	70	+38
7	Et_3N	1.0	20	+26
8	Imidazole	0.1	79	+28
9	Imidazole	1.0	18	0
10	*i*-Pr_2NEt	0.1	78	+36
11	*i*-Pr_2NH	1.0	0	-
12	Pyridine	1.0	0	-
13	Na_2CO_3	0.1	83	+60
14	$Cu(OTf)_2$	0.1	81	+56
15	AgOTf	0.1	83	+44
16	$MgSO_4$	1.0	79	+56
17	Molecular sieves	20% w/w	83	+61

[a]Isolated yields. [b]*ee*s were determined by GC analysis.

III.7 Catalyst and Additive Loading Screening in *n*-PrOH

As a final screen, the chlorocyclization reaction in *n*-PrOH was evaluated using different loading of catalyst and benzoic acid as the optimal additive for this reaction. By going down to 1 mol percent of catalyst the same selectivity was observed, but 0.5 mol

Table III-11: Catalyst and additive loading screening in *n*-PrOH



III-15 (*S*)-**III-16**

X	Y	Yield (%)[a]	*ee* (%)[b]
20.0	1.0	94	-91
10.0	1.0	90	-91
1.0	1.0	88	-92
0.5	1.0	94	-86
0.1	1.0	90	-74
1.0	0.5	98	-92
1.0	0.1	91	-90

[a]Isolated yields after column chromatography. [b]*ee*s were determined by GC analysis.

percent of catalyst returned (*S*)-**III-16** in slightly lower enantiopurity (Table III-11, entry 4). The loading of the catalyst could be reduced to 0.1 mol percent while still maintaining relatively moderate selectivity (74% *ee*, Table III-11, entry 5). In short, the catalyst loading study with the improved reaction conditions confirmed the catalyst loading of 1 mol percent to be optimal for maintaining enantioselectivity near 90% *ee*.

We next turned to a study of the benzoic acid loading. So far the best results (Table III-11, entry 6) were obtained by adding 0.5 equivalent of benzoic acid. By addition of 0.1 equivalent of benzoic acid a slight drop in selectivity (90% *ee*) of the reaction was realized to (Table III-11, entry 7).

III.8 Substrate Scope for Enantiodivergent Chlorocyclization Reaction

Having discovered optimal conditions for the enantiodivergent chlorocyclization of carbamates, a number of analogues carbamates were prepared and evaluated using the standard conditions. In total, ten carbamates were prepared (Figure III-11). All the

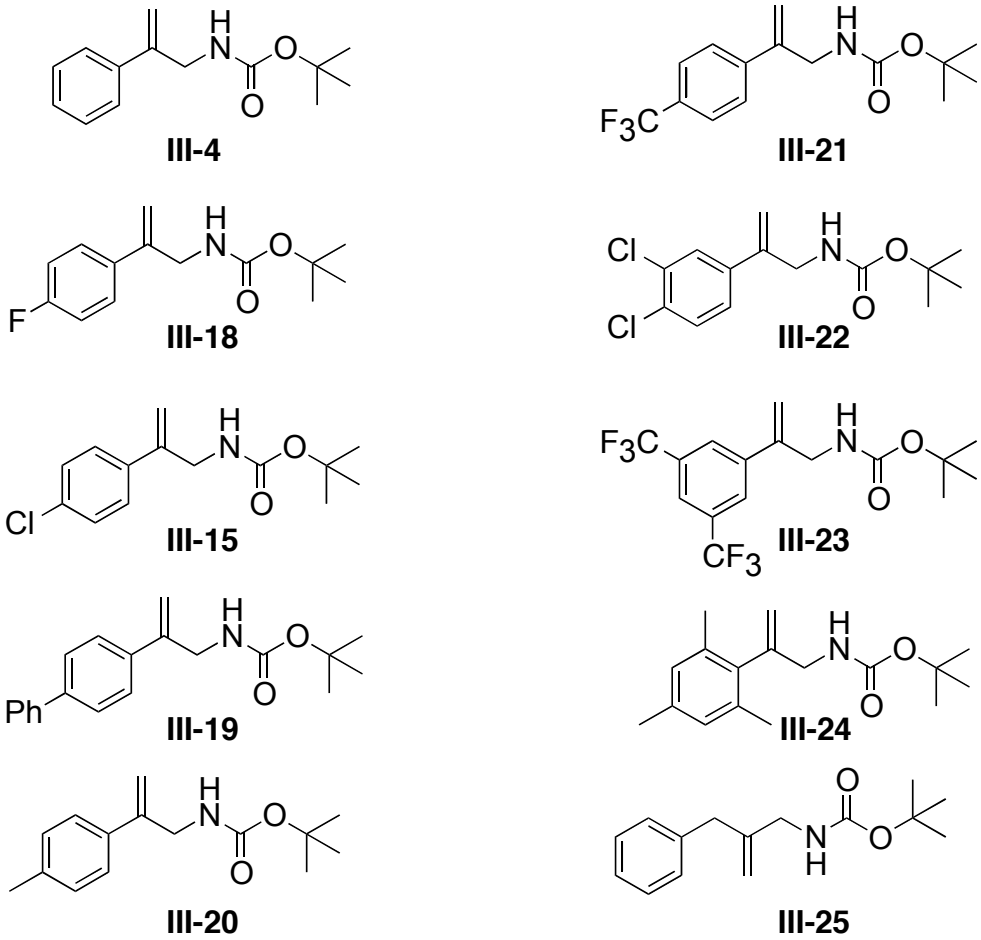
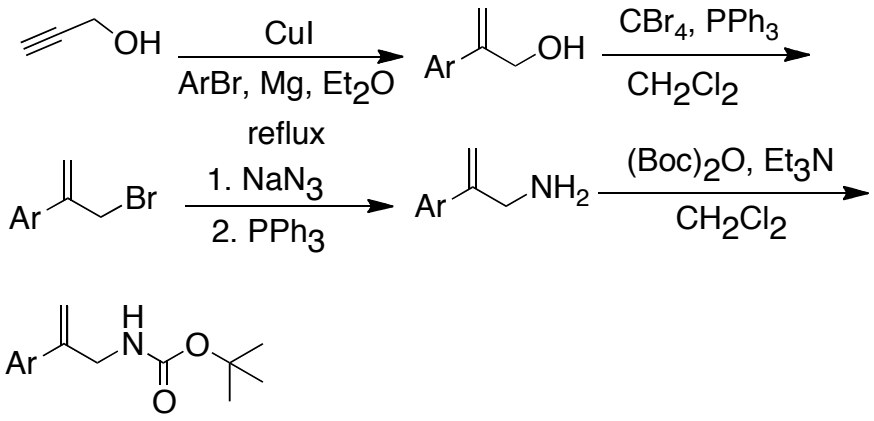


Figure III-11: Carbamate substrates

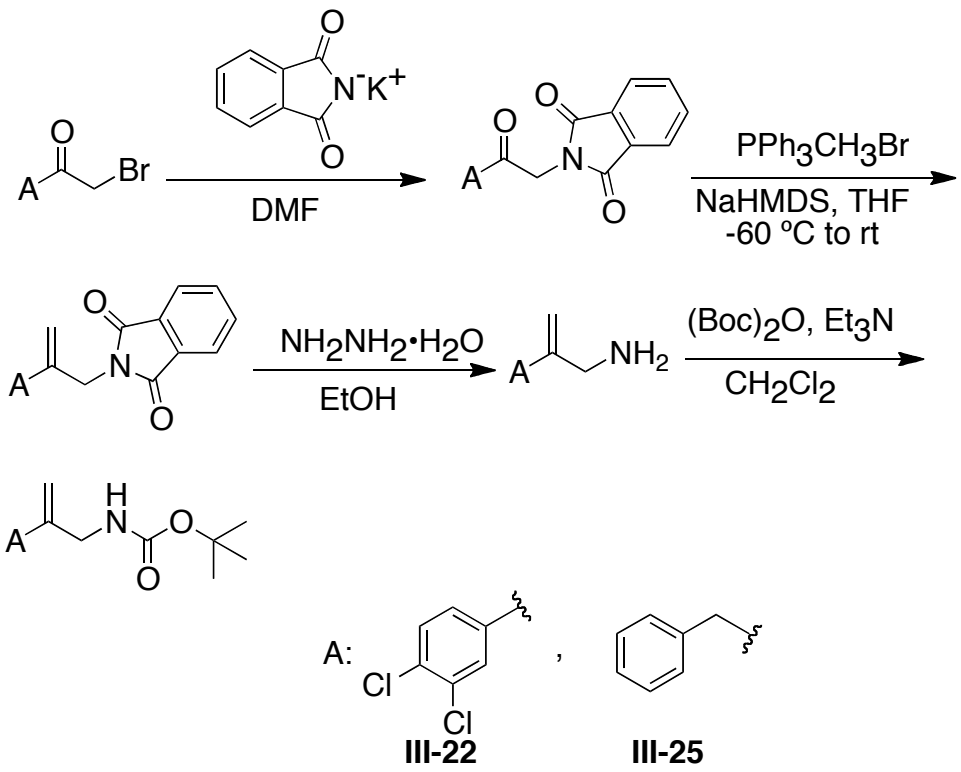
substrate were readily prepared in a similar fashion as shown in Scheme III-7, with the exception of substrate **III-22** and **III-25**, which faced low conversion in the first step of coupling with propargyl alcohol. For those two substrates, an alternative way outlined in Scheme III-8 was used.



Scheme III-7: Synthesis of carbamate substrates

Aside from exploring the substrate scope for this new reaction this exercise was undertaken to confirm some of the hypotheses gleaned from the Eyring plot analyses. For example, it was expected that any significant changes in steric parameters of the substrate will likely affect enantioselectivities in $CHCl_3$-Hexane more significantly than in *n*-PrOH.

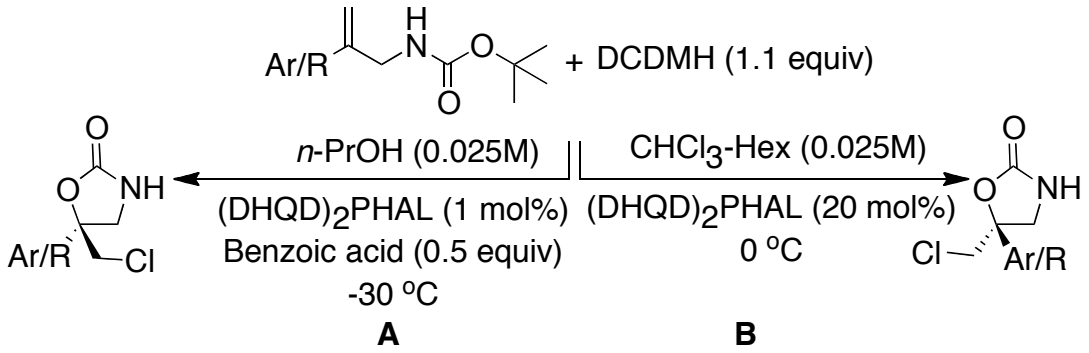
As summarized in Table III-12, a series of substrates with aryl substituents on the olefin gave consistently high enantioselectivity (-80 to -92% *ee*) in *n*-PrOH. The enantioselectivity in *n*-PrOH was independent of the electron rich/poor nature of the aryl substituent and also independent of the steric bulk of the substituent. In sharp contrast, in the $CHCl_3$-Hexane solvent system, even small variations in the aryl substituent had



Scheme III-8: Synthesis of carbamate **III-22** and **III-25**

profound effect on the enantioselectivity (+82 to -6% *ee*) of the transformation. A few trends and results merit special mention. Comparison of entries 1-3 indicate that the enantioselectivity progressively decreases as the size of the substituent at the *para* position of the ring increases indicating that steric (and hence entropic destabilization) factors play a vital role in the $CHCl_3$-Hexane system. Comparison of entries 5 and 6 indicate that the two isosteric but electronically different substituents 4-$CF_3C_6H_4$ and 4-$CH_3C_6H_4$ give practically no stereoinduction in $CHCl_3$-Hexane (+2% *ee* and 0% *ee* respectively) confirming that electronic (and hence enthalpic stabilization) factors play a negligible role in $CHCl_3$-Hexane. Having two electron withdrawing group in *meta* positions resulted in no conversion after 24 h (Table III-12, entry 9).

Table III-12: Substrate scope for enantiodivergent chlorocyclization reaction



Entry	Ar/R	Yield (%) (**A**)[a]	*ee* (%) (**A**)[b]	Yield (%) (**B**)[a]	*ee* (%) (**B**)[b]
1	C_6H_5	87	-80	83	+82
2	4-F-C_6H_4	92	-87	90	+75
3	4-Cl-C_6H_4	98	-92	97	+65
4	4-Ph-C_6H_4	86	-86	83	+50
5	4-Me-C_6H_4	90	-82	86	0
6	4-CF_3-C_6H_4	78	-80	80	+2
7	3,4-Cl-C_6H_3	80	-88	81	+22
8	2,4,6-Me-C_6H_2[c]	58 (70)[d]	-83	40 (50)[d]	-6
9	3,5-ditrifluoromethyl-Ph	-	-	-	-
10	$PhCH_2$	87	-51	80	+65

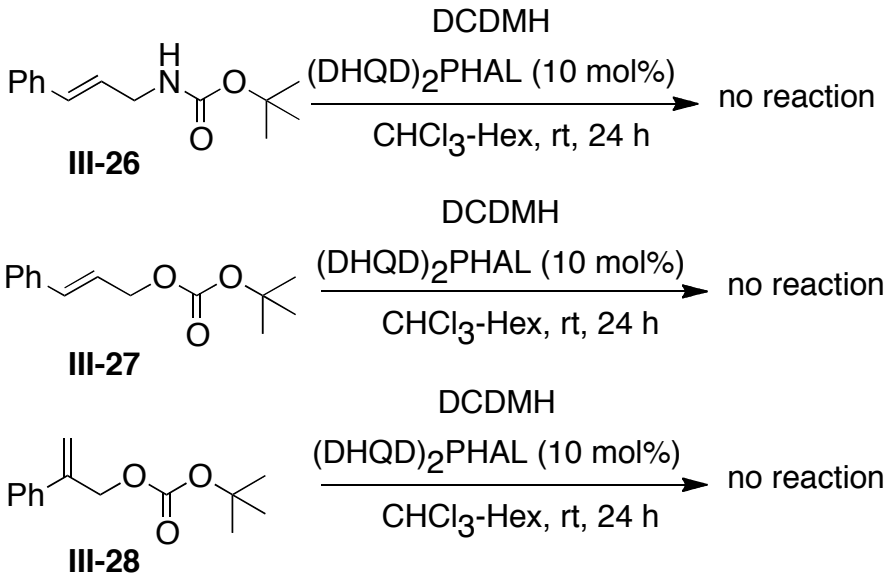
[a]Isolated yields after column chromatography. [b]*ee*s were determined by GC and HPLC analyses. [c]In the presence of 2.0 equiv DCDMH. [d]Conversion of the

Finally, a benzyl substituent gave better enantioselectivity in the $CHCl_3$-Hexane solvent system (+65% ee) as opposed to the *n*-PrOH solvent system (-51% ee; Table III-12, entry

10) indicating that interactions between catalyst and substrate may be crucial in *n*-PrOH while reducing steric interactions between substrate and catalyst is of greater importance in the $CHCl_3$-Hexane system.

In *n*-PrOH, the fact that the enantioselectivity observed in this cyclization is independent of the carbamate structure, taken together with the necessity of the aromatic ring, raises the possibility that stabilizing interactions between substrate and catalyst may play a key role in asymmetric induction. An Eyring analysis of the enantioselectivity for the cyclization of carbamate **III-15** was linear over a 30 ^{o}C range (Figure III-6). Evaluation of the differential activation parameters derived from these plots revealed that the enantioselectivity was enthalpically controlled. This enthalpy driven behavior suggests the potential for a strong interaction between the carbamate and the catalyst in the dominant transition state for the transformation. On the other hand, the entropically controlled behavior of this reaction in $CHCl_3$-Hexane suggests a much weaker intermolecular interaction between the carbamate and catalyst. Further, the results from the substrate scope study in $CHCl_3$-Hexane indicate a strong steric interaction between the substrate and catalyst, leading to the erosion of selectivity as the steric demand of the substrate aryl ring increased. These observations further added credence to the entropy driven nature of this reaction in $CHCl_3$-Hexane. Nonetheless, we are still pursuing a more refined understanding of the factors that lead to this relatively rare solvent dependant divergence in enantio-selectivity with the *same chiral catalyst*.

We were delighted to see if the same reaction conditions could be extended to *trans*-disubstituted and 1,1-disubstituted carbonate olefin substrates. *trans*-Disubstituted carbamate **III-26** shows no conversion in the presence and absence of catalyst. The



Scheme III-9: The test reaction of carbamate **III-26** and carbonate **III-27** and **III-28**

reason can be the geometry of *trans* carbamate, which cannot adopt the necessary trajectory for cyclization. There is also no reaction for *trans* and 1,1-disubstituted carbonate. This results show that the presence of nitrogen in substrate is important for cyclization (Scheme III-9).

In conclusion, we have developed the first solvent dependent enantiodivergent chlorocyclization of carbamates catalyzed by $(DHQD)_2PHAL$. This methodology enables selective access to both enantiomers of oxazolidinones using a single chiral organocatalyst. Kinetic analyses uncovered that the origin of solvent-dependent

stereodiscrimination is controlled by the enthalpy-entropy compensation. The stereoselectivities of *S*-selective cyclization in alcoholic solvents are governed by the differences in the enthalpies of activation ($\Delta\Delta H^{\neq}_{S\text{-}R}$), whereas the stereodiscrimination process for the *R*-selective reaction is governed by differences in the entropies of activation ($\Delta\Delta S^{\neq}_{R\text{-}S}$). Additional efforts to understand the mechanism of this rare enantioswitching process are underway.

III.9 Experimental Section

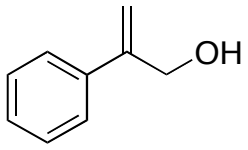
Commercially available starting materials were obtained from Aldrich or Fluka and were used without further purification. Unless otherwise mentioned, solvents were purified as follows: tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone; methylene chloride (CH_2Cl_2) and toluene ($PhCH_3$) was dried over calcium hydride (CaH_2) and freshly distilled prior to use; DMF, DMSO, Et_3N, and HMPA were distilled from CaH_2 and stored over 4 Å molecular sieves. 4 Å molecular sieves were dried at 160 ^oC under vacuum prior to use. All of the spectral data for known compounds either match those reported by Aldrich or by comparison to the literature report.

^1H NMR spectra were measured at 300, 500 or 600 MHz on a Varian Gemini-300, a Varian VXR-500 or Varian Inova-600 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for $CDCl_3$). ^{13}C NMR spectra were measured at 75 MHz on a Varian Gemini-300, at 125 MHz on a Varian VXR-500 or 150 MHz on a Varian Inova-600 instrument. Chemical shifts are reported relative to the central line of $CDCl_3$ (δ 77.0 ppm). High resolution mass spectra were measured at the Michigan State University, Mass Spectrometry Laboratory. Optical rotations were measured on a Perkin-Elmer polarimeter (model 341) using a 1 mL capacity quartz cell with a 10 cm path length in chloroform.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica

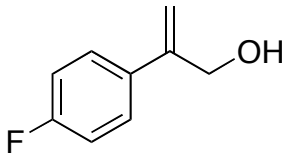
gel 60 F_{254} plates. Compounds were visualized with UV light, potassium permanganate stain, *p*-anisaldehyde stain or phosphomolybdic acid in EtOH. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 μm silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments. GC analysis was performed using HP (6890 series) GC system equipped with an Altech SE-54, 30 m × 320 μm × 0.25 μm column. Enantiomeric excess for all products was judged by GC and HPLC analysis using DAICEL CHIRALPAK OD-H column.

General procedure for the synthesis of allylic alcohol: To a solution of magnesium (0.24 g, 10 mmol) in Et_2O (10 mL) aryl bromide (10 mmol) was added at 0 ^oC. The reaction mixture was heated to reflux for 2 h. CuI (0.11 g, 0.6 mmol) was then added at room temperature. The reaction mixture was allowed to stir at rt for 0.5 h. Propargyl alcohol (0.23 g, 4 mmol) in Et_2O (4 mL) was added dropwise at rt. The reaction was then heated to reflux for 24 h. After cooling to rt, NH_4Cl (aq.) was added dropwise carefully. The organic phase was separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed in *vacuo*. Crude products were purified by silica gel column chromatography using EtOAc-Hexane (30%) as the eluent.



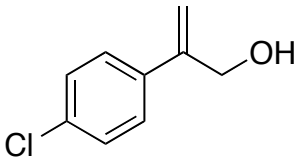
87% yield, colorless liquid

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.35 (m, 5H), 5.45 (d, *J* = 1.2 Hz, 1H), 5.33 (d, *J* = 1.2 Hz, 1H), 4.53 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.1, 138.4, 128.4, 127.8, 125.9, 112.3, 64.6.



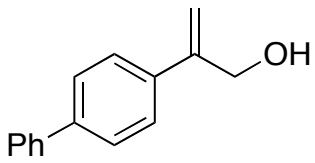
88% yield, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.42 (m, 2H), 6.98-7.04 (m, 2H), 5.39 (d, *J* = 1.2 Hz, 1H), 5.31 (d, *J* = 1.2 Hz, 1H), 4.48 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 146.2, 134.5, 127.8, 127.7, 112.7, 65.1.



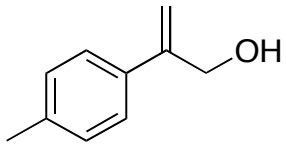
80% yield, colorless liquid

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5, 2H), 7.30 (d, *J* = 8.5, 2H), 5.44 (d, *J* = 1.2, 1H), 5.34 (d, *J* = 1.2, 1H), 4.48 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 136.9, 133.7, 128.6, 127.4, 113.3, 64.9.



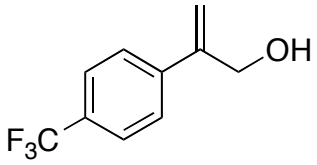
83% yield, white solid, MP: 116 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.60 (m, 9H), 5.52 (d, *J* = 1.2 Hz, 1H), 5.37 (d, *J* = 1.2 Hz, 1H), 4.57 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.2, 141.2, 141.1, 137.8, 129.3, 127.7, 127.5, 127.4, 126.9, 113.2, 65.5.



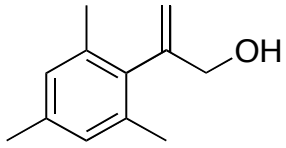
88% yield, white solid, MP: 50 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.41 (d, *J* = 1.2 Hz, 1H), 5.28 (d, *J* = 1.2 Hz, 1H), 4.51 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.8, 137.6, 134.4, 129.2, 126.0, 114.8, 65.2, 21.2.



78% yield, white solid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.68 (m, 4H), 5.51 (d, *J* = 1.2 Hz, 1H), 5.43 (d, *J* = 1.2 Hz, 1H), 4.54 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 142.1, 129.9, 126.4, 125.4, 123.8, 114.8, 64.8.

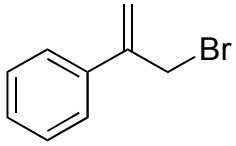


78% yield, colorless liquid

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86 (s, 2H), 5.54 (d, *J* = 1.2 Hz, 1H), 4.96 (d, *J* = 1.2 Hz, 1H), 4.18 (d, *J* = 6.0 Hz, 2H), 2.26 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$)

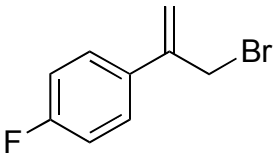
δ 144.9, 136.6, 135.7, 128.7, 128.1, 113.7, 61.9, 20.8, 19.7.

General procedure for the synthesis of allylic bromide: To a solution of allyl alcohol (0.81 mmol) in DCM (1.5 mL), PPh_3 (0.25 g, 0.97 mmol) was added at 0 ^oC, and the mixture was stirred for 10 min. CBr_4 (0.046 g, 0.89 mmol) was added portionwise, and the mixture was stirred for 3 h at 0 ^oC. The solvent was concentrated in *vacuo*, and the crude product was purified by silica gel column chromatography using pentane to yield allyl bromide.



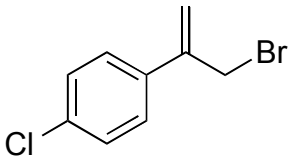
92% yield, colorless liquid

^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5H), 5.54 (d, J = 1.2 Hz, 1H), 5.47 (d, J = 1.2 Hz, 1H), 4.37 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 137.6, 128.5, 128.3, 126.1, 117.2, 34.2.



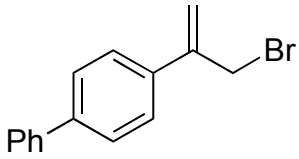
95% yield, colorless liquid

^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.42 (m, 2H), 7.01-7.07 (m, 2H), 5.47 (d, J = 1.2 Hz, 1H), 5.45 (d, J = 1.2 Hz, 1H), 4.33 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 146.6, 132.7, 129.5, 116.3, 113.6, 34.1.

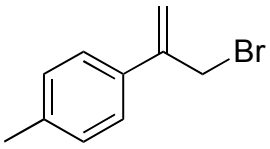


90% yield, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.36 (m, 4H), 5.45 (d, *J* = 1.2 Hz, 1H), 5.55 (d, *J* = 1.2 Hz, 1H), 4.33 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.1, 138.2, 136.0, 131.4, 130.2, 119.0, 34.2.

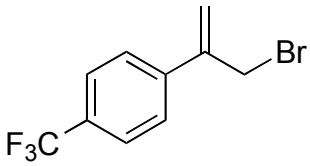


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.61 (m, 9H), 5.60 (d, *J* = 1.2 Hz, 1H), 5.50 (d, *J* = 1.2 Hz, 1H), 4.40 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 141.3, 141.1, 138.4, 129.3, 127.9, 127.7, 127.5, 126.8, 113.2, 35.0.



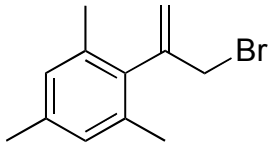
98% yield, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.50 (d, *J* = 1.2 Hz, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.35 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.0, 137.7, 134.6, 129.0, 126.5, 116.1, 35.2, 21.3.



94% yield, colorless liquid

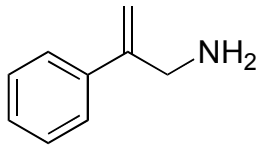
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.71 (m, 4H), 5.58 (d, *J* = 1.2 Hz, 1H), 5.56 (d, *J* = 1.2 Hz, 1H), 4.35 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 142.9, 130.0, 126.9, 125.6, 124.0, 115.4, 32.4.



90% yield, colorless liquid

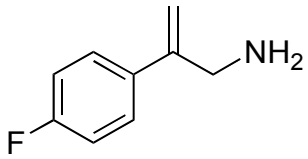
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.80 (s, 1H), 5.72 (d, *J* = 1.2 Hz, 1H), 5.09 (d, *J* = 1.2 Hz, 1H), 4.12 (s, 2H), 2.26 (s, 3H), 2.37 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.7, 136.5, 135.0, 128.8, 128.1, 113.9, 32.9, 20.9, 19.8.

General procedure for the synthesis of allylic amine: Allyl bromide (4.20 mmol) dissolved in THF-H_2O (4:1) (20 mL) was treated with NaN_3 (0.33 g, 5.04 mmol) at rt. After TLC analysis revealed the complete consumption of starting material, PPh_3 (1.65 g, 6.30 mmol) was added to the reaction vessel. After 8 h at ambient temperature, the reaction was concentrated to remove most of the THF. The resulting suspension was diluted with HCl (aq.) and extracted with ether (3 x 50). The aqueous layer was then basified by adding solid KOH and extracted with ether (3 x 50). The combined organics were dried (Na_2SO_4) and concentrated to give the crude amine, which was usually pure enough to use in the next step.



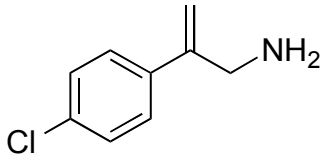
96% yield, yellow liquid

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.40 (m, 5H), 5.33 (d, *J* = 1.2 Hz, 1H), 5.20 (d, *J* = 1.2 Hz, 1H), 3.70 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 139.5, 132.3, 131.5, 128.3, 111.0, 45.8.



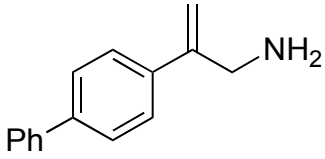
75%, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.42 (m, 2H), 6.97-7.03 (m, 2H), 5.27 (d, *J* = 1.2 Hz, 1H), 5.19 (d, *J* = 1.2 Hz, 1H), 3.65 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.9, 147.5, 132.6, 132.2, 131.6, 128.2, 127.4, 114.9, 45.3.



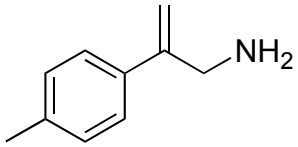
71% yield, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.35 (m, 4H), 5.32 (d, *J* = 1.2 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 3.66 (d, *J* = 5.5 Hz, 2H), 1.40 (br s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.1, 138.3, 136.7, 131.6, 130.4, 120.5, 45.2.



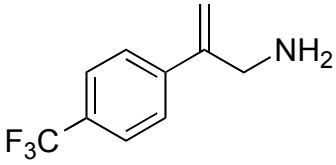
95% yield, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.69 (m, 9H), 5.70 (br s, 2H), 5.39 (d, *J* = 1.2 Hz, 1H), 5.24 (d, *J* = 1.2 Hz, 1H), 3.74 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 141.0, 139.7, 138.4, 129.1, 128.3, 127.9, 127.1, 126.8, 113.5, 45.0.



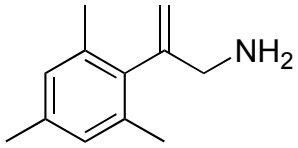
77% yield, colorless liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.29 (d, *J* = 1.2 Hz, 1H), 5.16 (d, *J* = 1.2 Hz, 1H), 3.68 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.2, 136.8, 132.4, 131.7, 128.8, 111.2, 43.3, 20.8.



90% yield, yellow liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.69 (m, 4H), 5.39 (d, *J* = 1.2 Hz, 1H), 5.32 (d, *J* = 1.2 Hz, 1H), 3.71 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.3, 140.2, 131.6, 128.5, 128.0, 123.8, 112.7, 45.0.



87% yield, yellow liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 5.43 (d, *J* = 1.2 Hz, 1H), 4.89 (d, *J* = 1.2 Hz, 1H), 3.36 (s, 2H), 2.23 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.1, 137.2,

135.3, 128.9, 128.1, 114.2, 44.9, 20.8, 19.8.

A mixture of 2-bromo-1-(3,4-dichlorophenyl) ethanone (4.0 g, 15.4 mmol), potassium phthalimide (3.0 g, 16.2 mmol) and dry DMF (17 mL) was heated overnight at 55 °C under nitrogen, after which the solvent was removed under reduced pressure. The solid residue was triturated with $CHCl_3$ (20 mL), filtered, and washed with $CHCl_3$ (3 x 20 mL). The combined organic extracts were successively washed with aqueous NaOH (0.2 M, 20 mL) and H_2O (40 mL), and then dried ($MgSO_4$). The solvent was removed at reduced pressure to afford a crude solid, which was purified by flash chromatography on silica gel using EtOAc-hexane (10%) to give the product (67% yield, 3.4 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.81 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.75 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 5.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 167.7, 138.8, 134.2, 133.9, 133.8, 132.1, 131.1, 130.1, 127.1, 123.6, 44.0.

To a stirred suspension of (bromomethyl) triphenylphosphonium bromide (4.5 g, 10.2 mmol) in THF (60 mL) under nitrogen at -60 ^{o}C was added sodium bis(hexamethylsilyl)amide (6 mL, 2.0 M in THF). The resulting red solution was stirred at -60 ^{o}C for 40 min, and then a solution of starting material (3.1 g, 9.2 mmol) in THF (10 mL) was added. The reaction was allowed to warm slowly to rt and stirred overnight before being quenched with H_2O and extracted with Et_2O. The extract was dried over $MgSO_4$, filtered and concentrated to dryness. Flash chromatography using hexane afforded the product (77% yield, 2.3 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.44 (t, *J* = 0.9 Hz, 1H), 5.26 (t, *J* = 1.5 Hz, 1H), 4.63 (t, *J* = 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 140.6, 138.5, 134.2, 132.6, 132.1, 131.9, 130.3, 128.5, 125.7, 123.5, 16.1, 41.0.

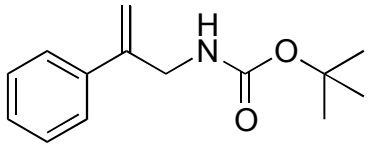
The starting material (0.24 g, 0.74 mmol) was suspended in EtOH (2 mL) and hydrazine hydrate (0.07 mL, 64% solution, 1.48 mmol) was added. The mixture was heated to reflux for 1.5 h. The reaction was then cooled to rt and H_2O (5 mL) was added. The solution was concentrated in *vacuo*. To the residue was added aqueous solution of HCl (10%, 5 mL) and the mixture was stirred at 90 ^{o}C for 15 h. After cooling to 0 ^{o}C the white precipitate was filtered off. The filtrate was basified with NaOH pellets and extracted with CH_2Cl_2 (three times). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure to afford the desired amine (80% yield, 0.12 g).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.35 (d, *J* = 1.2 Hz, 1H), 5.28 (d, *J* = 1.2 Hz, 1H), 3.66 (s, 2H), 1.25 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 139.9, 132.6, 131.6, 130.3, 128.1, 125.4, 113.0, 45.9.

The starting material (0.20 g, 0.74 mmol) was then suspended in EtOH (2 mL) and hydrazine hydrate (0.07 mL, 64% solution, 1.48 mmol) was added. The mixture was

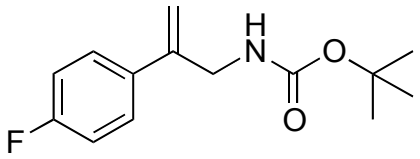
heated to reflux for 1.5 h, was cooled to rt and H_2O (5 mL) was added. The solution was concentrated in *vacuo*. To the residue was added aqueous solution of HCl (10%, 5 mL) and the mixture was stirred at 90 ^oC for 15 h. After cooling to 0 ^oC the white precipitate was filtered off. The filtrate was basified with NaOH pellets and extracted with CH_2Cl_2 (three times). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure to afford the free amine (84% yield, 0.9 g). ^1H NMR (300 MHz, $CDCl_3$) δ 7.13-7.25 (m, 5H), 4.94 (d, J = 1.2 Hz, 1H), 4.88 (d, J = 1.2 Hz, 1H), 3.70 (s, 2H), 3.36 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.3, 138.2, 132.3, 131.9, 128.3, 114.8, 45.3, 41.0.

A solution of di-*tert*-butyl dicarbonate (0.71 g, 3.14 mmol) in dry DCM (1 mL) was added under nitrogen at 0 ^oC to a solution of allylamine (0.5 g, 2.85 mmol) and triethylamine (0.87 mL, 6.27 mmol) in dry DCM (2 mL). The reaction mixture was stirred at rt for 24 h. The solvent was removed in *vacuo*, and the residue was dissolved with DCM (6 mL) and water (4 mL). The aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with water (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting mixture was purified by flash chromatography on silica gel using EtOAc-hexane (10%) to give the carbamate.



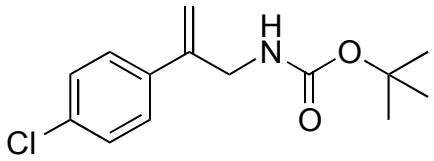
89% yield, yellow liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.41 (m, 5H), 5.40 (d, *J* = 1.2 Hz, 1H), 5.21 (d, *J* = 1.2 Hz, 1H), 4.62 (br s, 1H), 4.17 (d, *J* = 5.5 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 144.7, 138.5, 128.1, 127.5, 125.8, 112.6, 78.9, 43.9, 28.1.



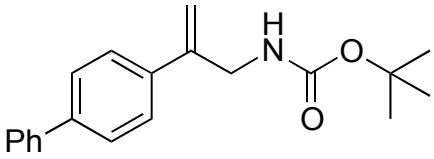
87% yield, yellow liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.38 (m, 2H), 6.95-7.02 (m, 2H), 5.32 (d, *J* = 1.2 Hz, 1H), 5.18 (d, *J* = 1.2 Hz, 1H), 4.11 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 155.6, 145.8, 128.0, 127.7, 115.7, 112.6, 78.7, 43.9, 28.0.



92% yield, white liquid

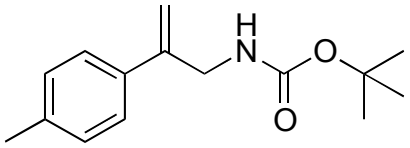
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.32 (m, 4H), 5.39 (d, *J* = 1.2 Hz, 1H), 5.22 (d, *J* = 1.2 Hz, 1H), 4.59 (br s, 1H), 4.15 (d, *J* = 5.5 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 145.9, 137.2, 133.8, 128.8, 127.4, 112.8, 79.2, 44.0, 28.2.



90% yield, white liquid

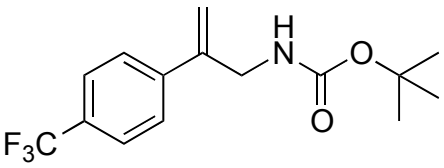
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.59 (m, 9H), 5.47 (d, *J* = 1.2 Hz, 1H), 5.24 (d, *J* = 1.2 Hz, 1H), 4.62 (br s, 1H), 4.20 (d, *J* = 5.5 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 154.8, 147.3, 141.5, 141.1, 138.0, 129.4, 127.8, 127.7, 127.3, 126.9, 113.0, 78.8, 44.1, 28.1.



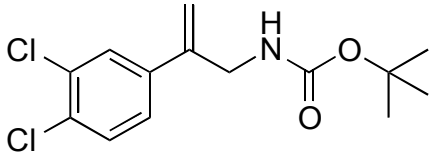
80% yield, white liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.36 (d, *J* = 1.2 Hz, 1H), 5.16 (d, *J* = 1.2 Hz, 1H), 4.13 (d, *J* = 5.5 Hz, 2H), 2.33 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.4, 147.9, 137.6, 134.2, 129.0, 126.2, 114.5, 78.9, 44.1, 28.2, 21.2.



86% yield, yellow liquid

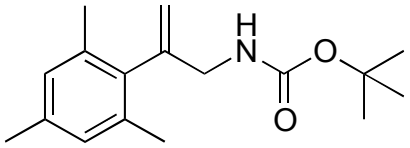
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.65 (m, 4H), 5.45 (d, *J* = 1.2 Hz, 1H), 5.30 (d, *J* = 1.2 Hz, 1H), 4.17 (d, *J* = 5.5 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 146.1, 142.3, 129.8, 126.6, 125.5, 123.7, 114.6, 79.0, 43.8, 28.1.



87% yield, white solid; MP: 77 ^{o}C

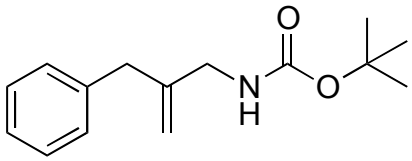
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 5.40 (d, *J* = 1.2 Hz, 1H), 5.25 (d, *J* = 1.2 Hz, 1H), 4.60 (br s, 1H), 4.09 (d, *J* = 5.5

Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 142.9, 138.5, 132.3, 131.5, 130.1, 127.9, 125.3, 114.4, 79.4, 43.8, 28.1.



91% yield, yellow liquid

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 5.38 (d, J = 1.2 Hz, 1H), 4.89 (d, J = 1.2 Hz, 1H), 3.79 (s, 2H), 2.25 (s, 3H), 2.19 (s, 6H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 144.8, 136.4, 135.7, 128.8, 128.3, 113.8, 79.2, 43.9, 28.1, 20.7, 19.7.



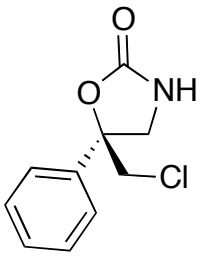
87% yield, white liquid

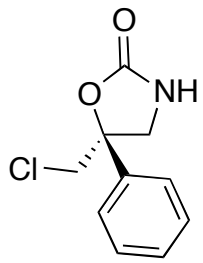
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.29 (m, 5H), 4.97 (d, J = 1.2 Hz, 1H), 4.83 (d, J = 1.2 Hz, 1H), 3.64 (d, J = 5.5 Hz, 2H), 3.34 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 142.4, 138.5, 132.4, 131.8, 128.3, 114.5, 79.4, 44.8, 41.0, 28.1.

General procedure for the catalytic asymmetric chlorocyclization of carbamates in *n*-PrOH (A): DCDMH (10 mg, 0.041 mmol, 1.1 equiv) was suspended in *n*-PrOH (1.4 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to -30 ^{o}C in an immersion cooler. $(DHQD)_2PHAL$ (0.3 mg, 1 mol%) was then introduced along with benzoic acid (3 mg, 0.018 mmol, 0.5 equiv). After stirring vigorously for 10 min, the substrate (0.037 mmol, 1.0 equiv) was added in a single

portion. The vial was capped and the stirring was continued at -30 ^{o}C until the reaction was complete (TLC). The reaction was quenched by the addition of 2% aq. NaOH (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexane (20-50%) as the eluent.

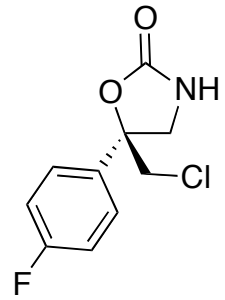
General procedure for the catalytic asymmetric chlorocyclization of carbamates in $CHCl_3$-Hex (B): DCDMH (10 mg, 0.041 mmol, 1.1 equiv) was suspended in $CHCl_3$-Hex (1:1 mixture, 1.4 mL) in a screw capped vial equipped with a stir bar. The resulting suspension was cooled to 0 ºC in an immersion cooler. $(DHQD)_2PHAL$ (6 mg, 20 mol%) was then introduced. After stirring vigorously for 10 min, the substrate (0.037 mmol, 1.0 equiv) was added in a single portion. The vial was capped and the stirring was continued at 0 ^{o}C until the reaction was complete (TLC). The reaction was quenched by the addition of 2% aq. NaOH (3 mL) and diluted with DCM (3 mL). The organics were separated and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organics were dried over Na_2SO_4 and concentrated in the presence of a small quantity of silica gel. Pure products were isolated by column chromatography on silica gel using EtOAc-Hexane (20-50%) as the eluent.

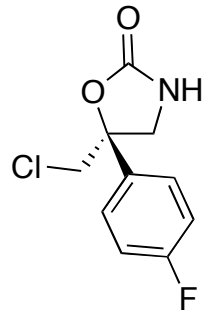




^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.41 (m, 5H), 5.29 (br s, 1H), 4.11 (d, J = 9.0 Hz, 1H), 3.74-3.86 (ddd, J = 12.0, 9.0, 12.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 144.7, 128.1, 127.6, 125.8, 112.6, 44.0, 28.1; HRMS: Calcd. for $C_{10}H_{10}ClNO_2$ 211.0400, Found: 211.0402.

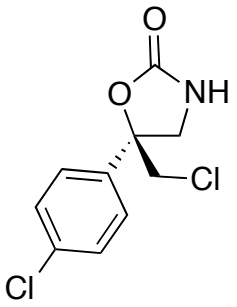
Resolution of enantiomers: GAMMA DEX 225; 60 °C for 2 min, 60 °C to 140 °C ramp (2 °C/min), 140 °C for 10 min, 140 °C to 220 °C (1 °C/min), 220 ºC for 40 min; RT_1 = 124.4 min (*S*-enantiomer), RT_2 = 125.1 min (*R*-enantiomer); $[\alpha]_D^{20}$ = +12.5, -12.8 (c = 0.66, $CHCl_3$)

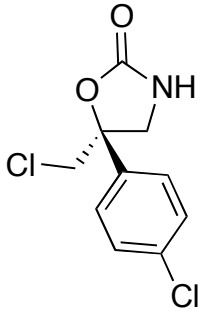




^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.39 (m, 2H), 7.06-7.12 (m, 2H), 5.08 (br s, 1H), 4.09 (d, J = 9 Hz, 1H), 3.70-3.85 (ddd, J = 12.0, 9.0, 12.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5 (d, $^{1}J_{C,F}$ = 247 Hz), 155.6, 145.6, 128.0 (d, $^{3}J_{C,F}$ = 8.6 Hz), 115.9 (d, $^{2}J_{C,F}$ = 21.2 Hz), 112.6, 43.9, 28.2; HRMS: Calcd. for $C_{10}H_9ClFNO_2$ 229.0306, Found: 229.0310.

Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220 °C ramp (5 °C/min), 220 °C for 40 min; RT_1 = 37.6 min (*S*-enantiomer), RT_2 = 38.6 min (*R*-enantiomer); $[\alpha]_D^{20}$ = +4.8, -4.1 (c = 0.58, $CHCl_3$)

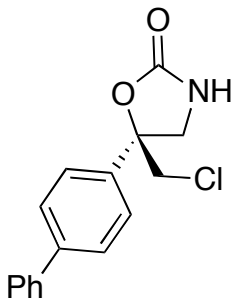


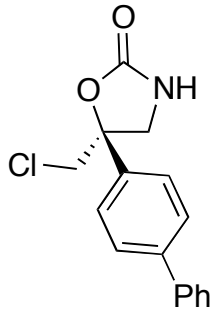


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.41 (m, 4H), 5.30 (br s, 1H), 4.08 (d, *J* = 9 Hz, 1H), 3.70-3.84 (ddd, *J* = 12.0, 9.0, 12.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 145.7, 134.0, 128.9, 127.5, 112.8, 43.8, 28.2; HRMS: Calcd. for $C_{10}H_9Cl_2NO_2$ 245.0010, Found: 245.0019.

Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220 °C ramp (5 °C/min), 220 °C for 60 min; RT_1 = 53.9 min (*S*-enantiomer), RT_2 = 56.3 min (*R*-enantiomer); $[\alpha]_D^{20}$ = -6.0, +4.5 (c = 0.33, $CHCl_3$)

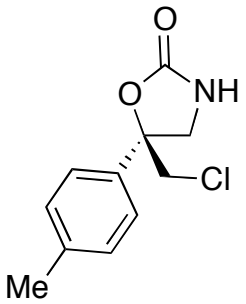
ORTEP drawing of the (*S*)-product (at 50% thermal ellipsoids):

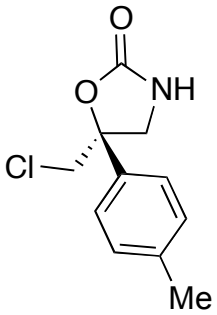




^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.64 (m, 9H), 5.11 (br s, 1H), 4.10 (d, *J* = 9 Hz, 1H), 3.77-3.91 (ddd, *J* = 12.0, 9.0, 12.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 147.5, 141.3, 141.1, 138.1, 130.1, 127.8, 127.2, 126.7, 112.8, 44.0, 28.1; HRMS: Calcd. for $C_{16}H_{14}ClNO_2$ 287.0713, Found: 287.0708.

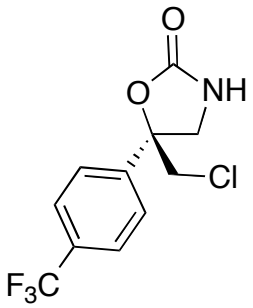
Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220 °C ramp (5 °C/min), 220 °C for 200 min; RT_1 = 192.2 min (*S*-enantiomer), RT_2 = 199.1 min (*R*-enantiomer); $[\alpha]_D^{20}$ = -8.0, +4.5 (c = 0.5, $CHCl_3$)

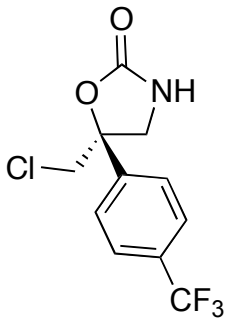




^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.28 (d, *J* = 8.0, 2H), 7.18-7.21 (d, *J* = 8.0, 2H), 5.34 (br s, 1H), 4.08 (d, *J* = 9 Hz, 1H), 3.71-3.84 (ddd, *J* = 12.0, 9.0, 12.0 Hz, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 147.8, 137.9, 129.3, 126.3, 113.8, 44.1, 28.2, 21.2; HRMS : Calcd. for $C_{11}H_{12}ClNO_2$ 225.0557, Found: 225.0550.

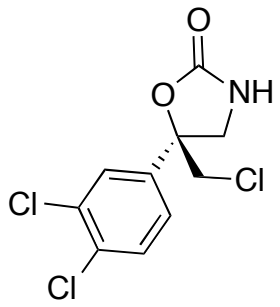
Resolution of enantiomers: CHIRALCEL OD-H, 5% IPA-Hexane, 0.5 mL/min, 208 nm, RT_1 = 81.5 min (*S*-enantiomer), RT_2 = 93.9 min (*R*-enantiomer); $[\alpha]_D^{20}$ = -25.0 (c = 0.33, $CHCl_3$)

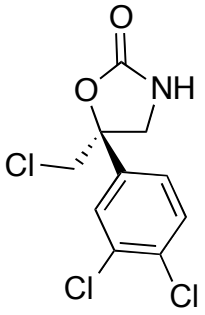




^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.65 (m, 4H), 5.38 (s, 1H), 4.14 (d, *J* = 9 Hz, 1H), 3.74-3.88 (ddd, *J* = 12.0, 9.0, 12.0 Hz, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 146.3, 142.5, 129.8, 126.7, 123.7, 114.4, 43.9, 28.1; HRMS: Calcd. for $C_{11}H_9ClF_3NO_2$ 279.0274, Found: 279.0286.

Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220 °C ramp (5 °C/min), 220 °C for 40 min; RT_1 = 35.9 min (*S*-enantiomer), RT_2 = 37.3 min (*R*-enantiomer); $[\alpha]_D^{20}$ = +16.0, -0.5 (c = 0.083, $CHCl_3$)

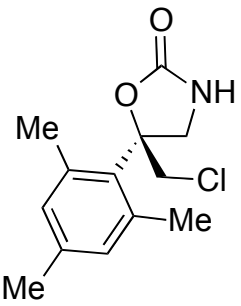


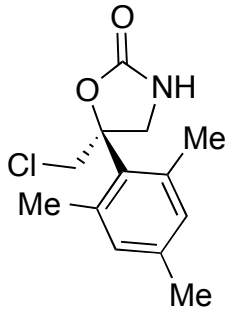


^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.47-7.51 (m, 2H), 5.75 (br s, 1H), 4.07 (d, *J* = 9 Hz, 1H), 3.70-3.84 (ddd, *J* = 12.0, 9.0, 12.0 Hz, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.6, 144.7, 128.5, 128.1, 127.6, 125.8, 124.5, 112.6, 44.0, 28.1; HRMS: Calcd. for $C_{10}H_8Cl_3NO_2$ 278.9621, Found: 278.9620.

Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220 °C ramp

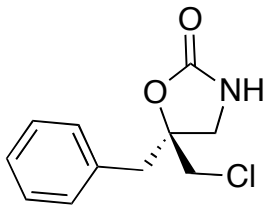
(5 °C/min), 220 °C for 100 min; RT_1 = 87.2 min (*S*-enantiomer), RT_2 = 96.8 min (*R*-enantiomer); $[\alpha]_D^{20}$ = -8.3, +2.1 (c = 0.58, $CHCl_3$)

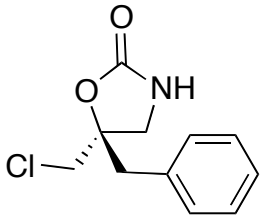




^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 5.12 (br s, 1H), 4.19 (d, *J* = 9 Hz, 1H), 3.82-3.90 (ddd, *J* = 12.0, 9.0, 12.0 Hz, 3H), 2.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 145.0, 136.3, 135.9, 128.7, 113.8, 43.9, 28.1, 20.8, 19.7; HRMS: Calcd. for $C_{13}H_{16}ClNO_2$ 253.0869, Found: 253.0874.

Resolution of enantiomers: GAMMA DEX 225; 90 °C for 2 min, 90 °C to 220 °C ramp (5 °C/min), 220 °C for 60 min; RT_1 = 53.3 min (*S*-enantiomer), RT_2 = 55.5 min (*R*-enantiomer); $[\alpha]_D^{20}$ = -52.0, -4.0 (c = 0.083, $CHCl_3$)





^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.31 (m, 5H), 4.93 (br s, 1H), 3.62 (d, *J* = 8.5 Hz, 1H), 3.58 (d, *J* = 11.5 Hz, 1H), 3.49 (d, *J* = 11.5 Hz, 1H), 3.40 (d, *J* = 8.5 Hz, 1H), 3.10 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.5, 142.6, 138.5, 132.5, 128.3, 114.3, 44.3, 41.1, 28.1; HRMS: Calcd. for $C_{11}H_{12}ClNO_2$ 225.0557, Found: 225.0551.

Resolution of enantiomers: GAMMA DEX 225; 60 ^{o}C for 2 min, 60 ^{o}C to 140 ^{o}C ramp (2 ^{o}C/min), 140 ^{o}C for 10 min, 140 ^{o}C to 220 ºC (1 ºC/min), 220 ºC for 40 min; RT_1 = 127.8 min (*S*-enantiomer), RT_2 = 128.0 min (*R*-enantiomer); $[\alpha]_D^{20}$ = -14.8, +19.0 (c = 0.66, $CHCl_3$)

III.10 References

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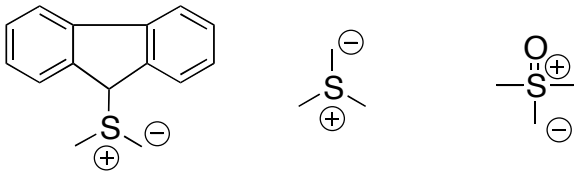
CHAPTER IV

Sulfur Ylide-Mediated Chemistry

IV.1. Introduction

The first literature example of a sulfur ylide-mediated epoxidation reaction was reported by Johnson in 1958.[1] Reaction of the stable and isolable 9-dimethylsulfonium fluorenylide **IV-1** (Figure IV-1) with 4-nitrobenzaldehyde did not afford an alkene, which had been expected on the basis of related reactions of phosphorus ylides. Instead, an epoxide was isolated. Several years later, Corey and Chaykovsky developed alternative ylides (dimethylsulfonium ylide **IV-2** and dimethylsulfoxonium ylide **IV-3**, Figure

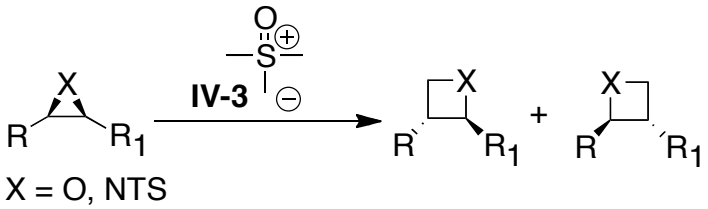


IV-1 **IV-2** **IV-3**

Figure IV-1: First literature example of sulfur ylides

IV-1),[2] which have since found widespread use in synthesis.[3] The reaction of a sulfonium ylide with an aldehyde initially forms betaine intermediates that undergoes subsequent ring closure to furnish an epoxide with regeneration of the sulfide. To render the process catalytic, the sulfide must be converted back into the ylide under suitably mild conditions. This is particularly important when chiral sulfides are employed. Two

general methods exist for converting a sulfide into a sulfur ylide: alkylation with a suitable electrophile followed by deprotonation of the resulting sulfonium salt or reaction with a diazo compound in the presence of a metal catalyst. The addition of dimethylsulfonium methylide **IV-2** to carbonyl compounds is irreversible and generates epoxides from aldehydes and ketones, even if the substrates are α,β–unsaturated carbonyls.[4, 5] In contrast, the stabilized dimethylsulfoxonium methylide **IV-3** can be generated and used at rt or even higher temperatures. As a consequence of the increased stability, the ylide is much less reactive than dimethylsulfonium methylide **IV-2**. It will also react with carbonyls to form epoxides, but reacts with α,β–unsaturated carbonyls systems to form cyclopropanes as a result of the reversibility of its addition to carbonyls.[4, 5] In addition to their nucleophilic properties, both ylides can also function as reasonably strong bases, the less stabilized ylide **IV-2** functioning as a stronger base than the stabilized **IV-3**.



Scheme IV-1: The ylide-mediated ring expansion of epoxides and aziridines

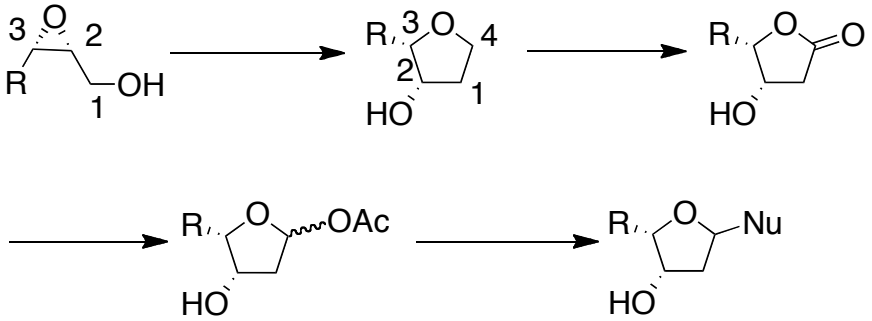
There are various other uses for sulfur ylides, for example, 2,3-sigmatropic rearrangement reactions and other rearrangements such as the Stevens reaction. Other reported ylide chemistry is the ring expansion of epoxides and aziridines to the

corresponding oxetanes and azetidines, respectively (Scheme IV-1).[6, 7] It is necessary to use the more stable dimethylsulfoxonium methylide **IV-3** as the carbon transfer reagent, as elevated temperatures are usually necessary to effect these transformations. The use of dimethylsulfonium methylide **IV-2** yields the corresponding allylic alcohols and amines from epoxides and aziridines, respectively.[8, 9]

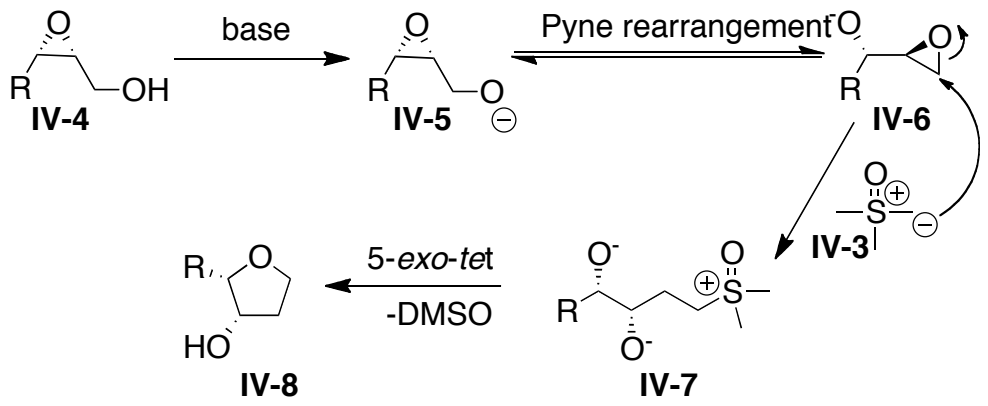
The scope of the ring expansion reactions using **IV-3** is limited to *cis* substituted and terminal epoxides/aziridines. Due to the steric hindrance encountered in opening *trans* or highly substituted heterocycles with dimethylsulfoxonium methylide **IV-3**. Exceptions are epoxides/aziridines that contain highly electron-withdrawing groups, such as electron-deficient aromatic rings. In these selected cases, **IV-3** can be induced to open more hindered epoxides and aziridines.

IV.1.1. The Ylide-Mediated Homologative Ring Expansion of 2,3-Epoxy-1-ols

Three factors are of great importance in accomplishing the transformation of the 2,3-epoxy-1-ol to the 2,3-disubstituted THF ring (Scheme IV-2). The first issue is to



Scheme IV-2: Transformation of 2,3-epoxy-1-ols to 2,3,5-trisubstituted tetrahydrofurans



Scheme IV-3: An ylide-mediated homologative ring expansion relay of epoxy alcohol **IV-4** to **IV-8**

determine the best reagent to transfer a carbon atom to the 2,3-epoxy-1-ol. A second issue is concerned with where the new carbon-carbon bond must be formed (between the C1 of the 2,3-epoxy-1-ol and C4 of the appropriate nucleophile). Finally, a method for cyclization to the final THF must be found, as a new bond between the oxygen of the THF and C4 must be formed. A potential solution to all three of these issues is illustrated in Scheme IV-3.

The control of regiochemistry of nucleophilic attack on the 2,3-epoxy-1-ol was the first issue to be addressed (Scheme IV-3). There are two electrophilic positions at C2 and C3 of the 2,3-epoxy-1-ol, but nucleophilic attack at either of those carbons would not lead to the desired tetrahydrofuran. Rather, attack of the nucleophile at C1 of the epoxy alcohol is necessary. The Payne rearrangement reaction has been shown to be a very useful method for revealing the latent electrophilicity of the C1 carbon.[10] The importance of a Payne rearrangement into the reaction shown in Scheme IV-3 should allow for selective ylide attack at C1 of the epoxy alcohol **IV-6**, which would lead to the

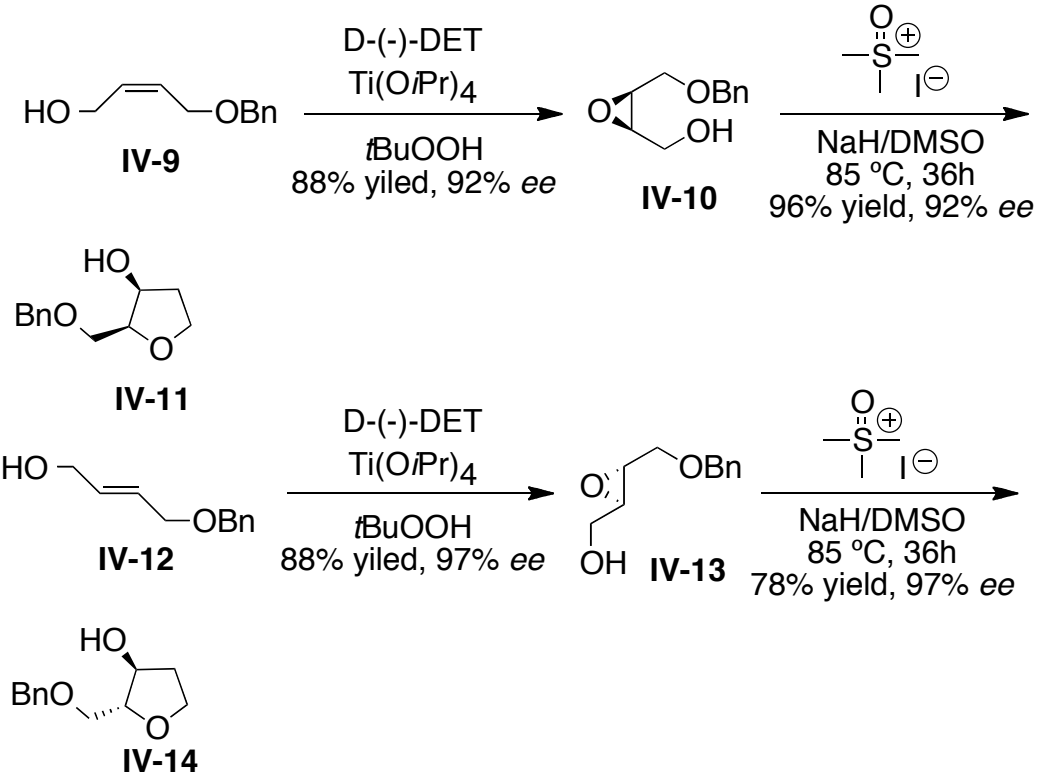
intermediate **IV-7** (Scheme IV-3).

The next question was to determine what nucleophile could be used to attack the less hindered 1,2-epoxy-3-ol generated via the Payne rearrangement reaction. It was envisioned that the best way to accomplish both the ring opening of the epoxy alcohol and subsequent closure to the heterocycle might be to use a compound that contains within itself both a good nucleophile and a good leaving group, or in other words S_N2, an ylide. The nucleophilic carbon portion of the ylide could attack the 2,3-epoxy-1-ol, at the same time installing a good leaving group in the molecule. An intramolecular displacement of the leaving group by an alkoxide present in **IV-7** could yield either an oxetane or the desired THF via a 5-*exo*-*tet* ring closure. Ylides are present in a number of synthetically important transformations, most notably the Wittig reaction to form alkenes from carbonyl compounds and phosphonium ylides.[11] However, phosphonium ylides have not been shown to be particularly reactive toward epoxides. Sulfur ylides, on the other hand, especially dimethylsolfonium and dimethylsulfoxinium methylide, have been shown to react readily with epoxides to formed allylic alcohols or oxetanes, respectively.[8] Thus, it might be feasible to use the anionic carbon portion of a sulfur ylide to transfer a carbon to the epoxy alcohol substrates, utilizing dimethylsulfide or DMSO as a good leaving group for cyclization to the 2,3-substituted tetrahydrofuran (Scheme IV-3).

Nucleophilic substitution reactions of 2,3-epoxy alcohols, easily accessed via Sharpless asymmetric epoxidation, are a useful method for the preparation of many types

of enantiomerically enriched compounds.[12-14] We were interested in transferring the chirality of an epoxy alcohol to a tetrahydrofuran (THF) via a ring expansion reaction. It was envisioned that this could be accomplished by attacking the epoxide with a carbon-based nucleophile containing within itself a good leaving group.

A common reaction illustrating the use of such a nucleophile is the Wittig olefination.[10, 15] Preliminary screening of phosphonium, ammonium, arsenium, and sulfur-based ylides prompted the use of dimethylsulfoxonium methylide, an ylide useful

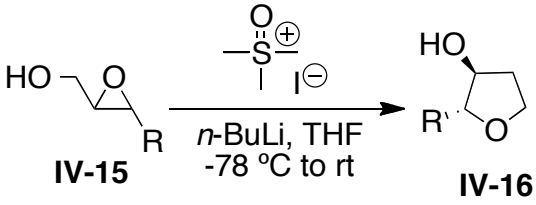


Scheme IV-4: Synthesis of 2,3-disubstituted THF rings

for the preparation of oxetanes from epoxides.[8, 11, 16a] The heat stability, reactivity, and easy preparation of this ylide [16b] allows convenient access to 2,3-disubstituted THF rings

in a highly distereoselective and enantioselective fashion. The overall strategy is depicted in Scheme IV-4. Asymmetric epoxidation of allylic alcohols such as **IV-9** and **IV-12** yields epoxides **IV-10** and **IV-13**, respectively. The reaction of **IV-10** and **IV-13** with the ylide generated from trimethylsulfoxonium iodide affords the 2,3-disubstituted THF rings **IV-11** and **IV-14** in good yields with complete control of stereochemistry.[4, 5] Thus, a *cis* epoxide yields the corresponding *cis*-disubstituted THF ring while the *trans* epoxide gives the *trans*-disubstituted THF ring.

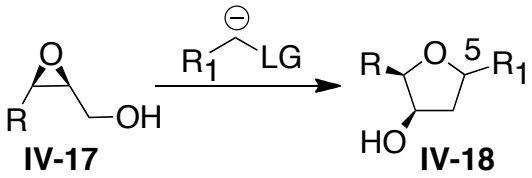
This new method for the synthesis of 2,3-disubstituted THF rings was develop in our group.[17] The stereochemistry that is set by the asymmetric epoxidation is translated fully to the final product. Since it is relatively simple to obtain 2,3-epoxy-alcohols in high enantiomeric excess via the Sharpless asymmetric epoxidation, this can be a powerful methodology in gaining entry into the synthesis of THF rings with stereodefined substituents (Scheme IV-5).



Scheme IV-5: Synthesis of 2,3-disubstituted THF rings **IV-16**

IV.2 The Use of Alternate Ylides for Extension of THF Rings Formation

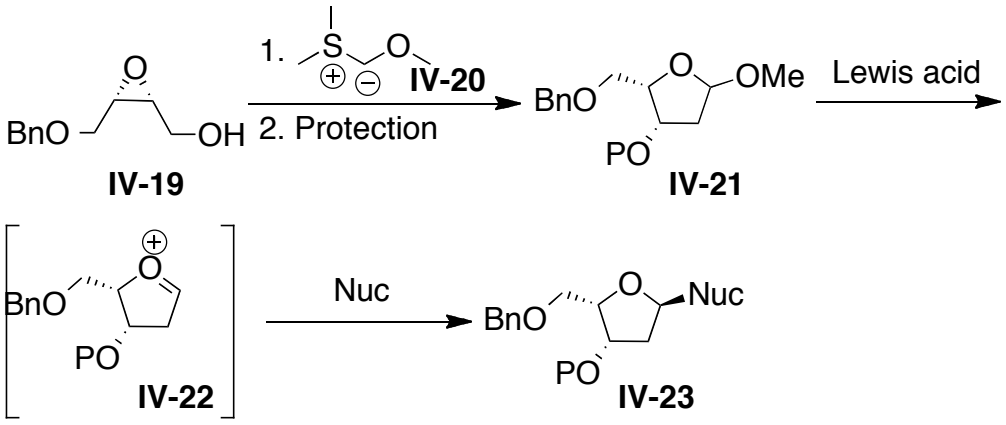
Alternate ylides can be used to initiate the epoxide opening reaction. Ylides that transfer alkyl groups other than methylenes can provide an additional source for the



Scheme IV-6: Synthesis of 2,3,5-trisubstituted THF rings **IV-18**

synthesis of THF rings.[18-27] These ylides will enable access to C5-substituted ring systems (Scheme IV-6).

To address the shortcoming associated with using substituted ylides (lack of stereochemical control at C5), bis-functionalized ylides was studies. For example, reaction of the ylide generated from **IV-20** with **IV-19** should yield **IV-22**. The product **IV-22** is an acetal, which upon treatment with a Lewis acid will lead to the formation of an oxonium species. Intermolecular trapping of the oxonium, along the lines demonstrated elegantly by Woerpel and coworkers should lead to the synthesis of 2,3,5-trisubstituted THF rings such as **IV-23** with absolute control of stereochemistry (Scheme IV-7).[28, 29] A number of these ylides undergo epoxide formation with ketones/aldehydes provides strong evidence that under the appropriate reaction conditions we should be able to direct the reactions as desired towards the synthesis of multiply substituted THF rings.[30-34]



Scheme IV-7: Proposed synthesis of 2,3,5-trisubstituted THF rings

IV.2.1 Method Development for Ylide-Mediated Ring Expansion

Nucleophilic substitution reactions of 2,3-epoxy alcohols, easily accessed via Sharpless asymmetric epoxidation, are a useful method for the preparation of many types of enantiomerically enriched compounds.[15, 35-39] As previously mentioned in the introduction, we were interested in transferring the chirality of an epoxy alcohol to a tetrahydrofuran (THF) via a ring expansion reaction with the substitution of different nucleophiles at C5 (shown in Scheme IV-7). It was envisioned that this could be accomplished by attacking the epoxide at C1 (via a Payne rearrangement reaction) with a carbon-based nucleophile containing within itself a good leaving group. Preliminary screening of phosphonium, ammonium, arsenium, and sulfur-based ylides prompted the use of dimethylsulfoxonium methylide, an ylide useful for the preparation of oxetanes from epoxides.[11, 40, 41] It was hope that the utilization of the ylides should provide

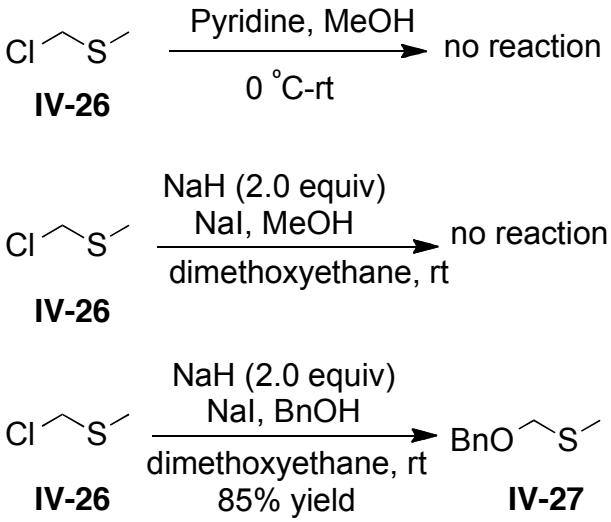
access to 2,3,5-trisubstituted THF rings with stereochemical control.

To begin the study, the racemic epoxide was generated by treatment of the *cis*-allylic alcohol with mCPBA. The synthesis of desired bis-functionalized sulfonium and sulfoxonium ylides (Figure IV-2) was considered. First, the synthesis of sulfonium ylide

IV-24 **IV-25**

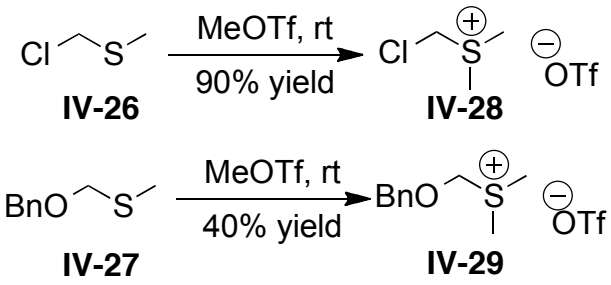
Figure IV-2: Desired bis-functionalized ylides

IV-25 with methoxy group as a leaving group was attempted. Sulfide **IV-26** was treated with methanol in the presence of pyridine, however, no desired product was obtained after 24 h (Scheme IV-8). Use of sodium hydride (2.0 equiv) as base and addition of



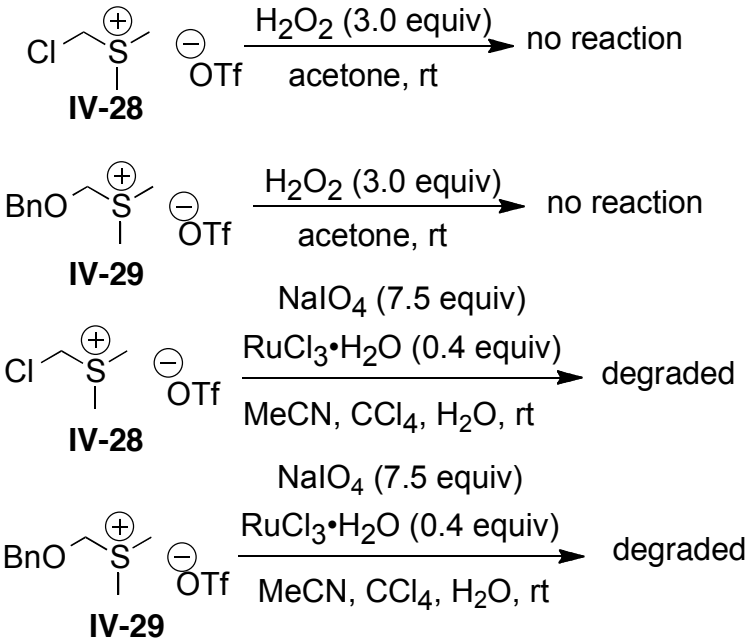
Scheme IV-8: Attempt for synthesis of bis-functionalized ylides

sodium iodide still did not lead to product. Replacement of methanol with benzyl alcohol under the same reaction condition provided the desired sulfide **IV-27** was prepared in 85% yield (Scheme IV-8).



Scheme IV-9: Synthesis of bis-functionalized ylides **IV-39** and **IV-40**

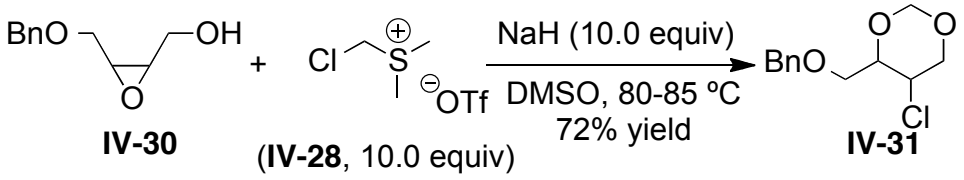
Treatment of sulfide **IV-27** with methyl iodide to generate the desired bis-functionalized sulfonium ylide, was not successful and led to degradation. Reversing



Scheme IV-10: Attempts for oxidation of sulfonium **IV-39** and **IV-40**

the order of alkylation was considered. Methylation of **IV-26** in the presence of methyl iodide failed, however, the use of methyl triflate yielded sulfonium **IV-28** in 90% yield (Scheme IV-9). Methylation of sulfide **IV-27** under the same reaction condition also provided the desired sulfonium **IV-29** in 40% yield (Scheme IV-9).

The synthesis of the sulfoxonium by the oxidation of sulfonium **IV-28** and **IV-29** was pursued using two different approaches. Oxidation with hydrogen peroxide failed gives the desired product. Use of sodium periodate and catalytic amount of the ruthenium chloride also failed, leading to the degradation of the starting material (Scheme IV-10).

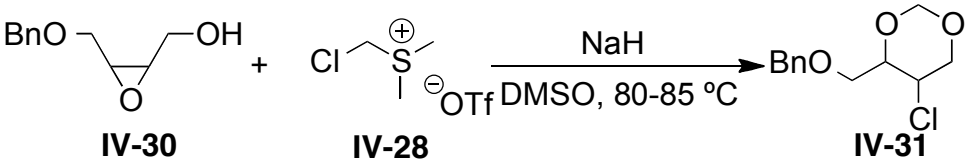


Scheme IV-11: Reaction of epoxy alcohol **IV-41** with sulfonium **IV-39**

With the failure of the sulfonium oxidation, the reaction of the epoxy alcohol **IV-30** with the sulfonium **IV-28** and **IV-29** was examined. The reaction of epoxy alcohol with sulfonium **IV-29** in the presence of sodium hydride and DMSO failed, returning starting material. The same reaction condition was also applied with sulfonium **IV-28** (Scheme IV-11). Interestingly, the reaction of epoxy alcohol **IV-30** with 10.0 equiv of sulfonium **IV-28** proceeded well to generate the unexpected chloro-1,3-dioxane **IV-31** in 72% yield as the sole diastereomer, with no formation of the desired 2,3,5-trisubstituted THF rings.

Loadings, ranging from 2.0 to 5.0 equivalents of sulfonium **IV-28** were investigated for this reaction. Five equivalent of sulfonium **IV-28** were tolerated relatively well and

Table IV-1: Sulfonium and base loadings study



IV-30 **IV-28** **IV-31**

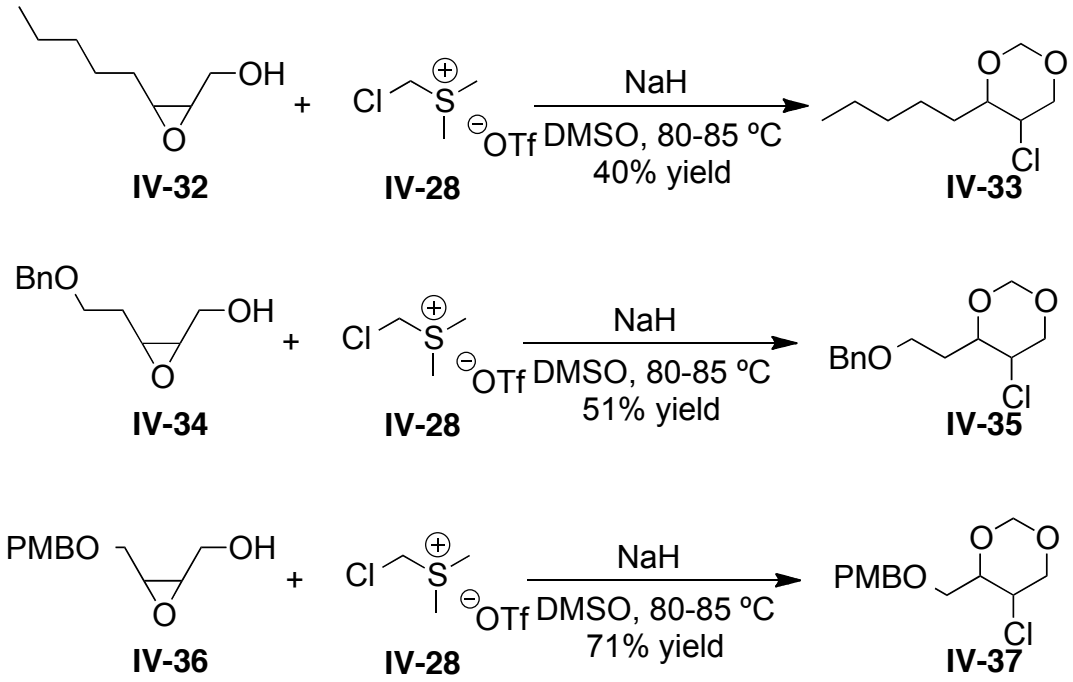
Entry	Equiv of **IV-39**	Equiv of NaH	Yield (%)[a, b]
1	10.0	10.0	72
2	5.0	10.0	70
3	2.0	10.0	50[c]
4	10.0	5.0	65
5	10.0	4.0	40[d]

[a]Isolated yields after column chromatography. [b]100% conversion. [c]60% conversion. [d]50% conversion.

produced the product in 70% yield. Lower amounts (2.0 equiv) caused an incomplete conversion of the reaction (Table IV-1, entries 2, 3). Decreasing the amounts of sodium hydride produced a shallow decline from 72% yield with 10.0 equivalents to 65% yield with 5.0 equivalents (Table IV-1, entry 4). A significant drop in conversion (50%) was realized when 4.0 equiv of base were added (Table IV-1, entry 5).

Various *cis*-epoxy alcohols were prepared from the corresponding allylic alcohol using mCPBA. Replacement of the OBn group from with pentyl (**IV-32)**, the reaction proceeded to generate the desired chloro-1,3-dioxane as the only product in moderate yield (40%), with 35% of starting material was isolated as well (Scheme IV-12).

Substrate **IV-34,** with the oxygen one carbon further away from the epoxide generated the desired product **IV-35** in 51% yield. In this reaction 28% of starting material was also



Scheme IV-12: Substrate scope

isolated (Scheme IV-12). These results show that the presence of oxygen in C4 is necessary for full conversion. Other substrate examined was **IV-36** with PMB as a

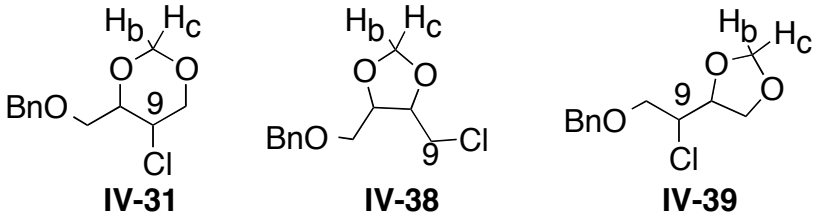


Figure IV-3: Other possible products

protecting group, this substrate led to full conversion and produced **IV-37** in 71% yield (Scheme IV-12).

The 1D and 2D-NMR of the product is consistent with the three structures illustrated in Figure IV-3. C9 (55.1 ppm), bearing the chloride is the most up-field carbon in the 13C-NMR spectrum (all other sp3 carbon resonances are expected down-field since they are oxygen substitute). The DEPT spectrum clearly shows C9 as a methine, therefore, eliminating **IV-38** as a possibility. To distinguish between **IV-31** and **IV-39**, the coupling

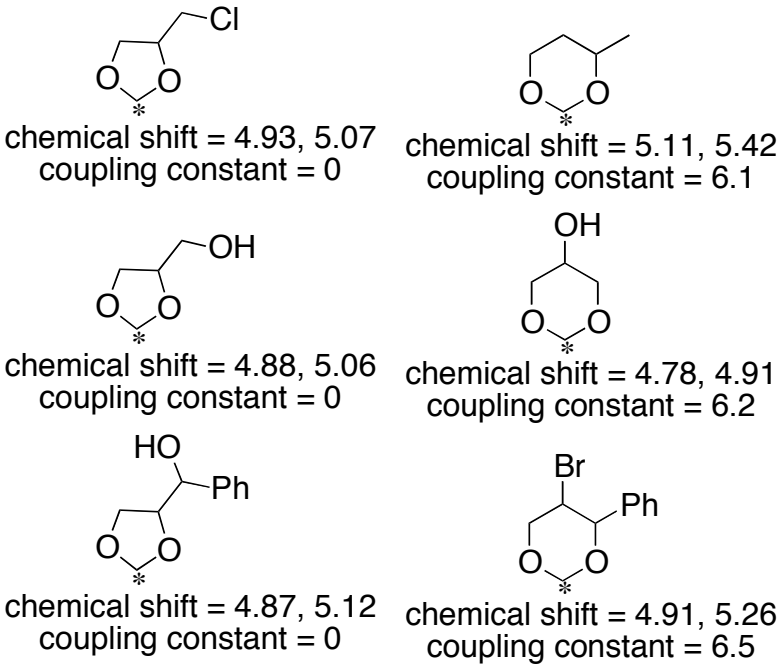
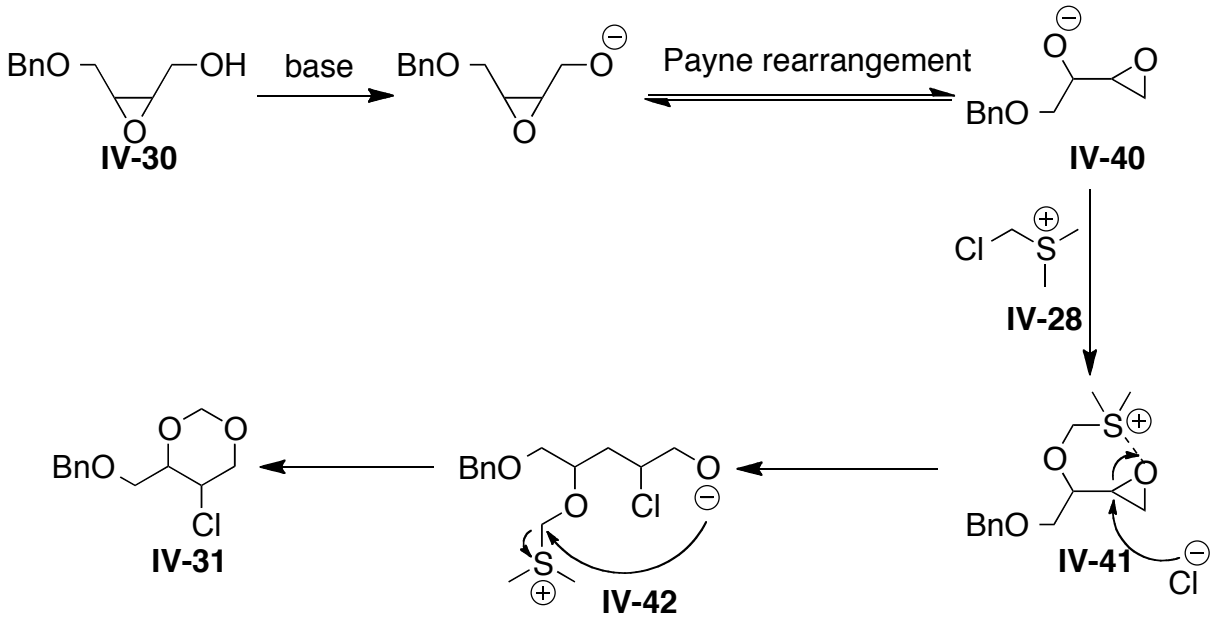


Figure IV-4: Some literature examples for 1,3- dioxolane and 1,3-dioxane

of H_b and H_c was investigated. The coupling constant for H_b and H_c is 6.0 Hz (chemical shifts are 4.75 and 5.13 Hz). According to examples found in the literature, the coupling constant of similar 1,3-dioxolane hydrogens in 5 membered ring systems is 0-2 Hz and for 6 membered ring systems is 6.0 Hz (Figure IV-4 illustrates a number of these examples).[42] The observed coupling constant of 6.0 Hz for H_b and H_c suggests structure

IV-31 as the product.

A possible explanation for this unexpected transformation is shown in Scheme IV-13. The epoxy alcohol **IV-30** would generate **IV-40** via a Payne rearrangement reaction.



Scheme IV-13: Proposed mechanism

Reaction of sulfonium salt **IV-28** with ethoxide **IV-40** will generate **IV-41**. Attack of Cl^- at C2 of the epoxy alcohol is necessary to generate **IV-42** (sulfonium inter or intra molecular can coordinate to the epoxide and activate it like a Lewis acid).[43] Finally, ring closing of **IV-42** would lead to the formation of the product **IV-31**.

IV.3 Experimental Section

Commercially available starting materials were obtained from Aldrich or Fluka and were used without further purification. Unless otherwise mentioned, solvents were purified as follows: tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone; methylene chloride (CH_2Cl_2) and toluene ($PhCH_3$) was dried over calcium hydride (CaH_2) and freshly distilled prior to use; DMF, DMSO, Et_3N, and HMPA were distilled from CaH_2 and stored over 4 Å molecular sieves. 4 Å molecular sieves were dried at 160 ^oC under vacuum prior to use. All of the spectral data for known compounds either match those reported by Aldrich or by comparison to the literature report.

^1H NMR spectra were measured at 300, 500 or 600 MHz on a Varian Gemini-300, a Varian VXR-500 or Varian Inova-600 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for $CDCl_3$). ^{13}C NMR spectra were measured at 75 MHz on a Varian Gemini-300, at 125 MHz on a Varian VXR-500 or 150 MHz on a Varian Inova-600 instrument. Chemical shifts are reported relative to the central line of $CDCl_3$ (δ 77.0 ppm). High resolution mass spectra were measured at the Michigan State University, Mass Spectrometry Laboratory. Optical rotations were measured on a Perkin-Elmer polarimeter (model 341) using a 1 mL capacity quartz cell with a 10 cm path length in chloroform.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica

gel 60 F_{254} plates. Compounds were visualized with UV light, potassium permanganate stain, *p*-anisaldehyde stain or phosphomolybdic acid in EtOH. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 μm silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments.

A solution of sulfide (104 mmol) in dry CH_2Cl_2 (100 mL) was cooled to -78 °C, methyl triflate (12.0 mL, 106 mmol) was added, and the mixture was kept at rt for 3 h. The volatile compounds were evaporated and the solid residue was crystallized (EtOAc) to give the product.

(Chloromethyl)dimethylsulfonium trifluoromethanesulfonate[44]

MP: 50 – 51 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 2H), 2.89 (s, 6H).

((Benzyloxy)methyl)dimethylsulfonium trifluoromethanesulfonate

MP: 48 – 49 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.31 (m, 5H), 5.50 (s, 2H), 4.62 (s, 2H), 2.90 (s, 6H).

(*Z*)-4-(Benzyloxy)but-2-en-1-ol[17]

A solution of *cis*-2-buten-1,4-diol (8.8 g, 100 mmol, 1.0 equiv) in THF (250 mL) was added dropwise to a suspension of NaH (4.4 g of a 60% dispersion in mineral oil, 110 mmol, 1.1 equiv, washed 2 x with dry pentane) in a 4:1 mixture of dry THF/DMSO (500 mL). The mixture was stirred at rt for 30 min, then a solution of benzyl bromide (18.9 g,

110 mmol, 1.1 equiv) in THF (250 mL) was added dropwise, followed immediately by tetrabutylammonium iodide (18.5 g, 50 mmol, 0.5 equiv) in one portion. The mixture was heated to 60 ^{o}C overnight. After cooling, an equal volume of water was added and the mixture extracted with portions of diethyl ether (3 x 200 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was column chromatographed using 3:1 hexanes/ethyl acetate to give the title compound as a clear to pale yellow oil (15.4 g, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.8 (m, 2H), 4.5 (s, 2H), 4.15 (m, 2H), 4.1 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 132.3, 128.2, 127.6, 127.56, 127.5, 72.1, 65.4, 58.1.

(*Z*)-4-((4-Methoxybenzyl)oxy)but-2-en-1-ol[45]

A solution of cis-2-buten-1,4-diol (8.8 g, 100 mmol) in THF (250 mL) was added dropwise to a suspension of NaH (4.4 g of a 60% dispersion in mineral oil, 110 mmol, washed 2 x with dry pentane) in a 4:1 mixture of dry THF/DMSO (500 mL). The mixture was stirred at rt for 30 min, then a solution of *p*-methoxybenzyl bromide (22.0 g, 110 mmol) in THF (250 mL) was added dropwise, followed immediately by tetrabutylammonium iodide (18.5 g, 50 mmol) in one portion. The mixture was heated to 60 ^{o}C overnight. After cooling, an equal volume of water was added and the mixture extracted with portions of diethyl ether (3 x 200 mL).. The combined organics were washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed

under reduced pressure. The residue was column chromatographed using 3:1 hexanes/ethyl acetate to give the title compound as a clear to pale yellow oil (18.5 g, 89% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.27 (m, 2H), 6.84-6.88 (m, 2H), 5.70-5.85 (m, 2H), 4.44 (s, 2H), 4.16 (m, 2H), 4.06 (d, *J* = 5.4 Hz, 2H), 3.79 (s, 3H), 1.82 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.3,129.7, 129.2, 127.6, 113.6, 71.8, 65.0, 58.0, 54.9.

Oct-2-yn-1-ol[17]

A solution of 2-octynaldehyde (2.0 g, 16.1 mmol) was placed in dry THF (100 mL) and cooled to -20 ^{o}C. DIBAL (11.8 mL of 1.5 M solution in toluene, 17.7 mmol) was added dropwise and the reaction was stirred for 3 h. A saturated solution of Rochelle's salt was carefully added, followed by 0.2 mL glycerol/mmol of DIBAL-H and the biphasic system was stirred at rt for 6 h. The reaction was extracted 3 x with portions of ethyl acetate, the combined organics were washed with brine, and dried over anhydrous sodium sulfate. The crude product was purified via column chromatography (hexanes/ethyl acetate) to give the alcohol in 78% yield (1.6 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (d, 2H, *J* = 6.8 Hz), 2.2 (t, 2H, *J* = 7.1 Hz), 1.9 (br s, 1H), 1.5 (t, 2H, *J* = 7.1 Hz), 1.2-1.4 (m, 4H), 0.9 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.1, 78.3, 51.0, 30.9, 28.2, 22.0, 18.5, 13.8.

General procedure for alkyne reduction: The alcohol (7.9 mmol) was placed in ethyl acetate (20 mL) and 5 drops of chloroform. Lindlar's catalyst (500 mg) was added and the flask was evacuated and filled with a hydrogen atmosphere using a balloon. The

suspension was stirred at rt for 5 h, the catalyst was removed via filtration through a pad of celite and the filtrate evaporated under reduced pressure. The crude product was obtained and was not further purified, but subjected to next step.

(*Z*)-Oct-2-en-1-ol[46]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50–5.73 (m, 2H), 4.20 (d, J = 5.6 Hz, 2H), 2.07 (td, J = 6.9, 6.8Hz, 2H), 1.51 (br s, 1H), 1.21–1.41 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3, 128.2, 58.5, 31.4, 29.2, 27.4, 22.5, 14.0.

(*Z*)-5-(Benzyloxy)pent-2-en-1-ol[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5H), 5.8 (m, 1H), 5.6 (m, 1H), 4.5 (s, 2H), 4.1 (m, 2H), 3.5 (t, 2H), 3.1 (br s, 1H), 2.4 (dd, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 130.7, 128.6, 128.2, 127.5, 127.46, 72.8, 68.9, 57.4, 27.7.

((2-Iodoethoxy)methyl)benzene[47]

The monobenzylated ethylene glycol (5.0 g, 32.9 mmol) was placed in benzene and iodine (16.5 g, 66.0 mmol), triphenylphosphine (17.5 g, 72.5 mmol) and imidazole (5.5 g, 82.5 mmol) were added and the mixture was stirred vigorously for 4 h. The benzene was evaporated at rt and diethyl ether was added to the residue. The resulting slurry was filtered, the filtrate evaporated and the residue chromatographed (9:1 hexanes/ethyl acetate) to give the iodide in 81% yield (7.0 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.36 (m, 5H), 4.58 (s, 2H), 3.73 (t, J = 6.7 Hz, 2H), 3.28 (t, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.7, 128.1, 128.0, 73.1, 71.0.

3.2 **((5-(Benzyloxy)pent-2-yn-1-yl)oxy)(*tert*-butyl)diphenylsilane**[17]

Dry tetrahydrofuran was combined with BPS-protected propargyl alcohol (11.2 g, 38.2 mmol) and cooled to -78 ^{o}C. A solution of *n*-BuLi (21.5 mL, 1.6 M solution in hexanes, 34.4 mmol) was added dropwise over 20 min. The reaction was allowed to stir for 1 h, then HMPA that had been distilled over calcium hydride was added and the reaction was stirred an additional 30 min. The iodide (5.0 g, 19.1 mmol) dissolved in THF (20 mL) was added dropwise over 15 min and the reaction was stirred at -78 ^{o}C for 1 h, warmed to 0 ^{o}C for 1 h, then warmed to rt overnight. An equal volume of water was added and the mixture was extracted 3x with ethyl acetate. The combined organics were washed with brine, dried over sodium sulfate, and the solvent was removed under reduced pressure to give the product in 68% yield (5.5 g) after column chromatography (9:1 hexanes/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (m, 4H), 7.4 (m, 11H), 4.6 (s, 2H), 4.4 (m, 2H), 3.5 (m, 2H), 2.5 (m, 2H), 1.1 (s, 9H); ^{13}C NMR δ (75 MHz, $CDCl_3$) 135.6, 133.2, 129.8, 129.7, 129.4, 128.4, 127.6, 82.2, 79.5, 73.0, 72.9, 68.3, 52.9, 26.7, 20.2.

5-(Benzyloxy)pent-2-yn-1-ol[17]

The protected propargyl alcohol (5.0 g, 11.7 mmol) was placed in tetrahydrofuran and a solution of tetrabutylammonium fluoride (35.1 mL, 1.0 M solution in tetrahydrofuran, 35.1 mmol) was added. The solution was stirred overnight and an equal volume of water added. The mixture was extracted 3 x with ethyl acetate, the combined organics were washed with brine, dried over sodium sulfate and the solvent was removed under reduced

pressure. The residue was purified by column chromatography (3:1 hexanes/ethyl acetate) to give the alcohol in 90% yield (2.0 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5H), 4.6 (s, 2H), 4.2 (m, 2H), 3.6 (t, 2H), 2.55 (m, 2H), 2.0 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 83.0, 79.5, 72.9, 68.2, 51.2, 20.1.

General procedure for epoxidation: The allylic alcohol (7.9 mmol, 1.0 eq) was placed in dichloromethane (70 mL) and mCPBA (1.9 g, 8.3 mmol, 1.05 eq, as a 77 weight % reagent) was added. The reaction was stirred at rt for 3 h and quenched with water and sodium carbonate. The organic layer was separated and the aqueous layer was extracted 3 x with portions of dichloromethane. The combined organics were washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified via column chromatography (hexanes/ethyl acetate) to give the product.

3-((Benzyloxy)methyl)oxiran-2-yl)methanol[17]

^{1}H NMR (300 MHz, $CDCl_3$) 7.36-7.40 (m, 5H), 4.59 (dd, *J* = 11.7, 11.7 Hz, 2H), 3.70-3.80 (m, 4H), 3.27-3.33 (m, 2H), 2.06 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 137.3, 128.4, 127.9, 127.8, 73.3, 67.9, 60.5, 55.7, 54.7.

(3-Pentyloxiran-2-yl)methanol[48]

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88-3.96 (m, 1H), 3.59-3.68 (m, 1H), 2.90-2.99 (m, 2H), 1.79 (br s, 1H), 1.24-1.71 (m, 8H), 0.84-0.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.7, 58.5, 56.1, 31.7, 31.6, 25.7, 22.7, 14.1.

(3-(2-(Benzyloxy)ethyl)oxiran-2-yl)methanol[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.50 (s, 2H), 3.80 (m, 1H), 3.50-3.70 (m, 3H), 3.20 (m, 2H), 3.05 (m, 1H), 2.05 (m, 1H), 1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 128.5, 128.1, 127.9, 73.5, 66.6, 59.9, 55.3, 54.8, 28.0.

(3-(((4-Methoxybenzyl)oxy)methyl)oxiran-2-yl)methanol[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.90 (m, 2H), 4.45-4.55 (m, 2H), 3.80 (s, 3H), 3.60-3.80 (m, 5H), 3.25 (m, 1H), 3.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 129.5, 129.4, 113.9, 73.11, 67.7, 60.7, 55.6, 55.3, 54.7.

Sodium hydride (4.0 g as a 60% dispersion in mineral oil, 100 mmol, 10.0 equiv, washed twice with pentane dried over sodium metal) was placed in a flame-dried flask and dry dimethylsulfoxide (100 mL) was added via syringe. Sulfonium (27.5 g, 100 mmol, 10.0 equiv) was added in small portions over 20-30 min. After addition of the Sulfonium **IV-28** was complete, the reaction was stirred for an additional 30 min until the bubbling of the milk-white suspension ceased. The epoxy alcohol (10 mmol, 1.0 equiv) dissolved in a small amount of DMSO was added dropwise and the reaction was covered with aluminum foil and heated to 80-85 ^{o}C for 36 h. The dark brown mixture was cooled and diluted with 2 x volume of water and saturated ammonium chloride (1 mL). The reaction was extracted several times with ethyl acetate, the combined organics were washed with brine and dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure, the residue was column chromatographed using a hexane/ethyl acetate gradient to give product.

4-((Benzyloxy)methyl)-5-chloro-1,3-dioxane

^{1}H NMR (500 MHz, $CDCl_3$) 7.25-7.36 (m, 5H), 5.12-5.13 (d, *J* = 6.0 Hz, 1H), 4.74-4.75 (d, *J* = 6.0 Hz, 1H), 4.51-4.59 (q, *J* = 11.5, 7.5 Hz, 2H), 4.17-4.21 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.00-4.06 (m, 3H), 3.564-3.67 (m, 1H), 3.58-3.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 137.7, 128.5, 128.9, 127.9, 94.0, 76.8, 73.8, 71.9, 70.2, 55.1; HRMS: Calcd. for $C_{12}H_{15}ClO_3$: 242.0709, Found: 242.0710.

5-Chloro-4-pentyl-1,3-dioxane

^{1}H NMR (500 MHz, $CDCl_3$) 5.15 (d, *J* = 6.0 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.22-4.25 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.00-4.07 (m, 3H), 1.25-1.69 (m, 8H), 0.85-0.93 (m, 3H).

5-Chloro-4-(((4-methoxybenzyl)oxy)methyl)-1,3-dioxane

^{1}H NMR (500 MHz, $CDCl_3$) 7.27 (m, 2H), 6.92 (m, 2H), 5.13 (d, *J* = 6.0 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.56-4.64 (dd, *J* = 11.5, 11.5 Hz, 2H), 4.20-4.26 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.05-4.09 (m, 3H), 3.82 (s, 3H), 3.65-3.72 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.63-3.66 (dd, *J* = 6.0, 6.0 Hz, 1H).

IV.4 References

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