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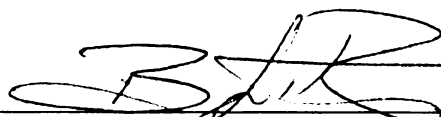
METHODOLOGY AND KINETIC STUDIES OF OXONE
PROMOTED OXIDATION REACTIONS AND STRUCTURE
REASSIGNMENT, TOTAL SYNTHESIS AND STRUCTURE-
ACTIVITY RELATIONSHIP STUDIES OF *ANNONACEOUS*
ACETOGENINS

presented by

JUN YAN

has been accepted towards fulfillment
of the requirements for the

Ph.D. degree in Chemistry



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METHODOLOGY AND KINETIC STUDIES OF OXONE PROMOTED
OXIDATION REACTIONS AND STRUCTURE REASSIGNMENT, TOTAL
SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF
ANNONACEOUS ACETOGENINS

Volume I

By

Jun Yan

A DISSERTATION

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ABSTRACT

METHODOLOGY AND KINETIC STUDIES OF OXONE PROMOTED OXIDATION REACTIONS AND STRUCTURE REASSIGNMENT, TOTAL SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF *ANNONACEOUS* ACETOGENINS

By

Jun Yan

This dissertation first describes the Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) promoted oxidation reaction. It is believed that Oxone or its pure active component potassium peroxymonosulfate (KHSO_5) is the efficient oxidant which can be used in the oxidative cleavage of α -hydroxyketones, α -diones, and β -diones, as well as in the oxidation of aldehydes. The corresponding kinetic and mechanistic studies led to postulate the reasonable mechanism of these reactions.

Moreover, this dissertation discussed the total synthesis and the related structure-activity relationship (SAR) studies of natural product *Annonaceous* acetogenins. We have synthesized the proposed structure of mucoxin, the first hydroxylated nonclassical acetogenin and found the mismatch in the NMR spectra. The latter library synthesis of a series of diastereomers of truncated mucoxin and the NMR analyses led to the summary of four trends, which can be used to predict the relative configurations in the natural product. Finally, the real structure of mucoxin was synthesized and the related SAR studies of mucoxin and its analogs were examined. Because of the inefficiency in the synthesis of analogs of mucoxin, our further SAR investigations focus on the ether linked analogs of 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.

An efficient method for a regio- and stereoselective double cyclization of polyhydroxylated systems to form bis-adjacent THF rings with ether linkages was developed.

To My Parents

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KEY TO SYMBOLS AND ABBREVIATIONS

Å	angstrom
A	pre-exponential factor
Ac	acetyl
AcOH	acetic acid
acac	acetoacetate
α_D	optical rotation
Ar	aryl
aq.	aqueous
Bn	benzyl
C	concentration
CDCl ₃	deuterated chloroform
CH ₂ Cl ₂	dichloromethane
CSA	camphorsulfonic acid
Cy	cyclohexyl
δ	chemical shift (parts per million)
D	dextro (denotes configurational relationship with (<i>R</i>)-(+)-glyceraldehyde)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
<i>de</i>	diastereomeric 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
DMSO	dimethyl sulfoxide
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
<i>dr</i>	diastereomeric ratio
E _a	Arrhenius activation energy
ECCD	exciton coupled circular dichroism
ED ₅₀	Effective Dose to 50 percent
<i>ee</i>	enantiomeric excess
EI	electric ionization
equiv	equivalent(s)
Et ₃ N	trimethylamine
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol

FAB	fast atom bombardment		
$\Delta G^\ddagger$	free-energy of activation		
g	gram(s)		
GC	gas chromatography		
$\Delta H^\ddagger$	enthalpy of activation		
h	hour(s)		
HMPA	hexamethyl phosphoramide		
HRMS	high resolution mass spectrometry		
Hunig's base	<i>N,N</i> -diisopropylethylamine		
HWE	Horners-Wadsworth-Emmons reaction		
Hz	Hertz		
IC ₅₀	half maximal inhibitory concentration		
ⁱ PrOH	isopropyl alcohol		
IR	infrared spectrum		
<i>J</i>	coupling constant		
<i>K</i>	transmission coefficient		
<i>k</i>	rate constant		
<i>k_{obs}</i>	observed rate constant		
KHMDS	potassium bis(trimethylsilyl)amide		
KHSO ₅	potassium peroxymonosulfate		
L	levo (denotes configurational relationship with (<i>S</i>)-(-)-glyceraldehyde)		
LAH	lithium aluminum hydride		
LDA	lithium diisopropylamine		
LiHMDS	lithium bis(trimethylsilyl)amide		
M	molar (concentration)		
<i>m</i> CPBA	4-chloroperbenzoic acid		
MDR	multidrug resistant		
MeCN	acetonitrile		
MeOH	methanol		
mL	milliliter		
mmol	millimole		
MOM	methoxymethyl		
Ms	methane sulfonate		
MS	mass spectrometry		
NADH	nicotinamide adenine dinucleotide		
NaHMDS	sodium bis(trimethylsilyl)amide		
NBS	<i>N</i> -bromosuccinimide		
NMM	<i>N</i> -methylmorpholine		
NMR	nuclear magnetic resonance		
nOe	nuclear Overhauser effect		
OAc	acetate		
OTf	trifluoromethanesulfonate		

OsO ₄	osmium tetroxide
σ	substituent constant
ρ	reaction constant
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
<i>p</i> TSA	<i>p</i> -toluenesulfonic acid
<i>R</i>	rectus (Cahn-Ingold-Prelog system)
RCM	ring-closing metathesis
RT	room temperature
Δ <i>S</i> [‡]	entropy of activation
<i>S</i>	sinister (Cahn-Ingold-Prelog system)
SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
SAR	structure-activity relationship
<i>t</i>	reaction time
T	temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBA-OX	tetra- <i>n</i> -butylammonium peroxymonosulfate
TBDPS	<i>t</i> -butyldiphenylsilyl
TBHP	<i>t</i> -butyl hydroperoxide
TBS	<i>t</i> -butyldimethylsilyl
TBSOTf	<i>t</i> -butyldimethylsilyl trifluoromethanesulfonate
^t BuOH	<i>t</i> -butyl alcohol
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TMEDA	tetramethylethylenediamine
Ts	toluene sulfonate
T.S. [‡]	transition state
TsOH	<i>p</i> -toluenesulfonic acid
<i>v</i>	reaction rate

Chapter I

DIRECT OXIDATIVE CLEAVAGE OF 1,2- AND 1,3-DICARBONYLS TO ESTERS WITH POTASSIUM PEROXYMONOSULFATE (KHSO₅)

I.1. Introduction

Oxidation reactions comprise an important group of organic reactions. They are widely used to synthesize a large variety of compounds and are also important in biological systems, since many of the energy generating related reactions are oxidations. There are a large number of oxidation methods in use which utilize a variety of reagents. For example, transition metal derivatives in high oxidation states such as the chromium (VI), permanganate ion, and osmium (VIII) are effective reagents for the oxidative transformation of a variety of functional groups.^{1,2} They can easily oxidize alcohols, aldehydes, ketones, olefins, or even unfunctionalized carbon atoms.³⁻¹² In addition, catalytic processes using transition metal catalysts along with other oxidants such as molecular oxygen and peroxides have also been developed.¹³ Even though the oxidation of transition metals is very efficient, the limitation of these reagents is their toxic character and the high cost.

Green chemistry is defined such that the chemical design, manufacture, use, and disposal do not use and generate the hazardous chemicals in the sequence.¹⁴ The goal of green chemistry is to reduce or eliminate the hazards associated with processes and products. In recent years, green chemistry has drawn more and more

attention because it is the base for environmentally benign chemical synthesis. The synthetic processes are designed in such a way that the waste products are kept at a minimum; such they have a minimum effect on the environment and their disposal is convenient.¹⁵ In oxidation reactions, Oxone ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) has become an increasingly popular oxidant because it is a nontoxic, stable, and low cost “green reagent”; the byproducts of which are also nontoxic inorganic salts.

I.1.1. History of Oxone

In 1898, Caro^{16, 17} was the first to find that nitrosobenzene could be formed during the oxidation of aniline with ammonium persulfate $[(\text{NH}_4)_2\text{S}_2\text{O}_8]$ (persulfate stands for the symmetrical peroxodisulfate $\text{S}_2\text{O}_8^{2-}$). During further studies he noticed that the addition of ammonium or potassium persulfate to concentrated sulfuric acid could produce a new oxidant which was later called by Baeyer and Villiger as Caro’s acid (the formula was accepted as H_2SO_5).

Baeyer and Villiger then reported the first preparation of this new oxidant and explored its composition right after Caro.¹⁸ The stable solid oxidant had a composition of $\text{KHSO}_5 \cdot 7\text{KHSO}_4 \cdot 2\text{K}_2\text{SO}_4$. It was prepared by adding 11 g (0.11 mol) of concentrated sulfuric acid to 10 g (0.037 mol) of a potassium persulfate powder in a mortar. After 10 min, 30 g (0.17 mol) of potassium sulfate was added and the mixture was grated until a very dry powder was obtained.¹⁶ The triple salt is now commercially available^{16, 19, 20} with a higher content of active oxygen containing two parts KHSO_5 , one part KHSO_4 , and one part K_2SO_4 , and is sold under the name of Oxone. This white powder (5.2% active-oxygen content) is a convenient and very

powerful oxidizing reagent, and moreover its inexpensive price (\$ 10/kg) has further lend itself to its growing popularity.

The active component of Oxone is potassium peroxymonosulfate (KHSO_5). It has been studied in various fields such as physical chemistry and computational chemistry. The X-ray structure of KHSO_5 confirms the existence of a short oxygen-oxygen bond²⁰ (1.460 Å instead of 1.497 Å in H_2O_2) with a hydrogen atom on one side and SO_3^- group on the other side, which is capable of providing a sulfate as good leaving group in the case of an O-O bond heterolytic cleavage (Figure I-1).

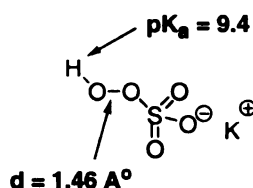


Figure I-1: Schematic representation of the X-ray structure of KHSO_5

Potassium peroxymonosulfate is known to be among the strongest oxidants¹⁹⁻²² ($E^\circ = 1.82$ V for the redox couple $\text{HSO}_5^-/\text{HSO}_4^-$). It is stable under acidic conditions (pH = 2-7) and is decomposed under basic conditions (pH > 9).²³ The water solution of KHSO_5 is relatively stable with a loss of active oxygen of only 5% in three days with an unmodified pH and 25 °C. Other physical characteristics of HSO_5^- have also been discussed.²³⁻²⁸ For example, molecular vibrational spectra²⁹ including IR and Raman spectra of both the solid and the aqueous solution were measured and it was found that the intramolecular force fields of HSO_5^- are very similar to those of the isoelectronic ion SO_4F^- , in which an F atom replaces the OH group.

I.1.2. Purification of Oxone

Considering there is only 5.2% active-oxygen content in Oxone, several methods have been developed to prepare the pure salt, KHSO_5 .²⁹⁻³² One example was reported by Appelman and coworkers in 1985.²⁹ They convert a concentrated solution of reagent grade sodium peroxydisulfate ($\text{Na}_2\text{S}_2\text{O}_8$) to the acid by passage through a cation exchange resin followed by hydrolysis at 50 °C until no peroxydisulfate remained. The solution was then raised to pH 3.5 by addition of solid KHCO_3 in an ice bath to yield solid $\text{KHSO}_5 \cdot \text{H}_2\text{O}$. A modification of this method has been reported by Connick's group in 1993,³² during their kinetic and mechanistic study of the oxidation of HSO_3^- by HSO_5^- . Their method was based on a straightforward filtration protocol starting from Oxone solution, followed by evaporation and recrystallization to yield a pure product of $\text{KHSO}_5 \cdot \text{H}_2\text{O}$ (99.8% by iodometric oxidation). However, this pure oxidant has not been widely used in organic synthesis, most probably due to the less convenient procedures of purification and scale-up.

Our group has developed a modified, straightforward and stepwise procedure for the preparation of pure $\text{KHSO}_5 \cdot \text{H}_2\text{O}$ (>99% activity) from Oxone in 2002.³³ Since KHSO_5 is more soluble in water than the corresponding sulfate salt and is dissolved preferentially, commercially available Oxone is dissolved in deionized water and swirled for 5 min. After filtration, the initial pH 1.0 is adjusted to 3.5 by adding solid KHCO_3 . The pink slurry is filtered, washed with methanol and combined with the original water filtrate. The slightly cloudy solution containing water and

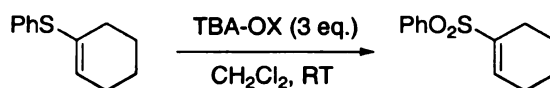
methanol (1:3 v/v) was put in a freezer overnight to crystallize the purified $\text{KHSO}_5 \cdot \text{H}_2\text{O}$. Moreover, $\text{KHSO}_5 \cdot \text{H}_2\text{O}$ can be dried under vacuum at room temperature to yield anhydrous KHSO_5 . This method is a facile procedure and can be applied to a large scale production (0.5 mol scale, 300 g was tried). The oxidation experiments using various substrates such as aldehyde and olefin show that the purified $\text{KHSO}_5 \cdot \text{H}_2\text{O}$ is as effective as Oxone, but requires only half the mass of oxidant, thus making the reactions easier to workup, and requires less mass in large scale reactions.³³

I.1.3. Other peroxymonosulfate oxidizing reagents

Generally, oxidation reactions using Oxone are performed in solution of water, alcohol, acetone or DMF, due to its high solubility. This solvent profile and/or the pH-controlled conditions associated with the use of Oxone have limited its application as an oxidant. Thus, several other peroxymonosulfate oxidizing reagents have been reported.

Tetraalkylammonium salts of Oxone, which include ammonium peroxymonosulfate, tetra-*n*-butylammonium peroxymonosulfate (TBA-OX), tetra-*n*-pentylammonium peroxymonosulfate and tetra-*n*-hexylammonium peroxymonosulfate have been used extensively.^{34,35} The first report was in 1985 by Dehmlow³⁴ and coworkers. They developed a method to prepare these ammonium salts by cationic exchange from Oxone. Three years later, in 1988, Trost's group³⁵ prepared TBA-OX and used it for oxidations under completely anhydrous conditions. TBA-OX was formed via stirring a solution of Oxone and tetrabutylammonium

bisulfate ($n\text{Bu}_4\text{NHSO}_4$) followed by methylene chloride extraction. The active oxidizing reagent $n\text{Bu}_4\text{NHSO}_5$ is obtained at 37.5% active by weight. However, it can be dissolved in methylene chloride, chloroform, acetone, acetonitrile and water. Only partial solubility can be achieved in benzene, anhydrous THF, or anhydrous dioxane. It provides the possibility of anhydrous oxidation conditions. In their paper, they reported the successful oxidation reactions of sulfides to sulfones with TBA-OX in CH_2Cl_2 (Scheme I-1). Our group has also reported the preparation of



Scheme I-1: Oxidation of sulfides to sulfones with TBA-OX

analytically pure TBA-OX from $\text{KHSO}_5 \cdot \text{H}_2\text{O}$.³³ Because the solubility of $n\text{Bu}_4\text{NHSO}_5$ (352 mg/mL) in CH_2Cl_2 is higher than that of $n\text{Bu}_4\text{NHSO}_4$ (168 mg/mL), it is easy to imagine that extracting more $n\text{Bu}_4\text{NHSO}_5$ over $n\text{Bu}_4\text{NHSO}_4$ should be possible. Based on this fact, varying amounts of $n\text{Bu}_4\text{NHSO}_4$ were used to extract TBA-OX in CH_2Cl_2 . Figure I-2 shows that the preparation of analytically pure TBA-OX (>98%) is simply accomplished by extracting pure $\text{KHSO}_5 \cdot \text{H}_2\text{O}$ (1 equiv.) with $n\text{Bu}_4\text{NHSO}_4$ (1.2 equiv.).

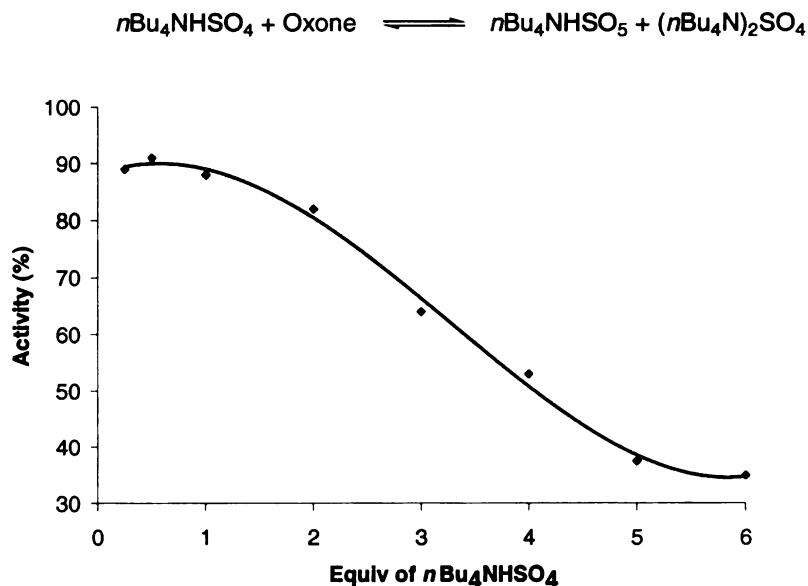
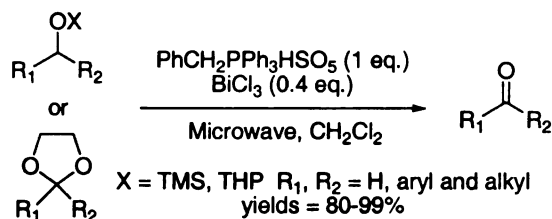


Figure I-2: Extraction of TBA-OX from Oxone into CH_2Cl_2 with various equiv. of $n\text{Bu}_4\text{NHSO}_4$

The other soluble peroxymonosulfate oxidizing reagent was developed by Hajipour's group in 2001.³⁵ They reported using benzyltriphenylphosphonium peroxymonosulfate ($\text{PhCH}_2\text{PPh}_3\text{HSO}_5$) as a reagent for oxidative deprotection reactions. This reagent has been prepared by the dropwise addition of an aqueous solution of benzyltriphenylphosphonium chloride ($\text{PhCH}_2\text{PPh}_3\text{Cl}$) to an aqueous solution of Oxone at room temperature. After filtration and drying the precipitate, iodometric titration shows that there is almost 99% active oxidizing agent by weight. This reagent can be used to deprotect trimethylsilyl (TMS) ethers, tetrahydropyranyl (THP) ethers and ethylene acetals to afford carbonyl compounds in the presence of a catalytic amount of bismuth chloride (Scheme I-2). The reactions give good to high yields under microwave irradiation.³⁵

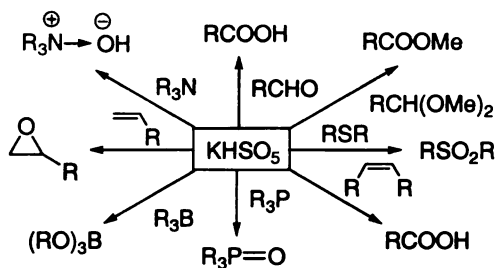


Scheme I-2: Oxidative deprotection of TMS and THP ethers with $\text{PhCH}_2\text{PPh}_3\text{HSO}_5$

I.1.4. Oxidative transformations

Oxone is a powerful green oxidizing reagent that has been proven to be valuable for various organic transformations, including the oxidation of aldehydes to acids or esters, alkenes to epoxides, amines to N-oxides, sulfides to sulfones and so on.

Scheme I-3 illustrates a summary of these transformations.^{21, 36-46}



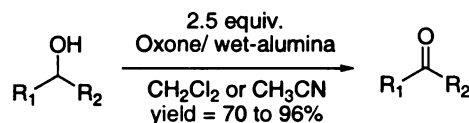
Scheme I-3: Oxidative transformations mediated by Oxone

I.1.4.1. Oxidation of alcohols, aldehydes and ketones

Oxone is an efficient oxidant for alcohols, aldehydes and ketones. It was first discovered by Baeyer and Villiger, who pointed out that persulfuric reagent could convert cyclic ketones to lactones.⁴⁷ In the early 1960's, Kennedy and Stock⁴⁸ reported that the mixture of $\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ (1:1:1) can be used to oxidize a variety of organic substances including hydroxyl and carbonyl compounds. In their paper, secondary alcohols could be oxidized to ketones in quantitative yields. Later on, in 1991, Morimoto and coworkers discovered that the oxidation of secondary aliphatic, alicyclic, and benzylic alcohols with Oxone-wet alumina reagent afforded

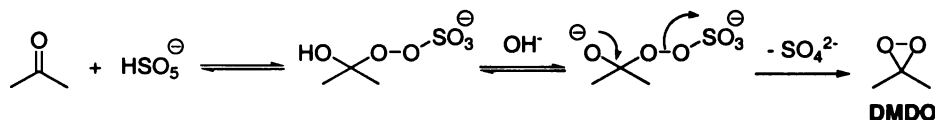
the corresponding ketones in good yields under mild conditions (Scheme I-4).⁴⁹

Oxone is a great oxidant for the conversion of aldehydes to carboxylic acids and



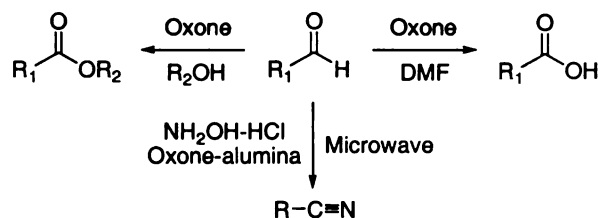
Scheme I-4: Oxidation of *s*-alcohols with Oxone

esters.^{19, 50-52} Both Baumstark's⁵⁰ and Webb's⁵¹ work showed that the oxidation of aldehydes to carboxylic acids was promoted by dimethyl dioxirane (DMDO), which was generated directly or *in situ* from Oxone (Scheme I-5). Our group pursued the



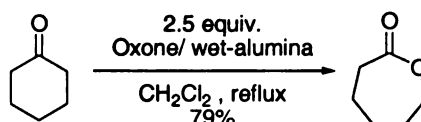
Scheme I-5: DMDO generation from acetone and Oxone

optimization of this aldehyde oxidation. With DMF as solvent, an efficient one-pot procedure provided aldehyde oxidation to carboxylic acids. Moreover, direct conversion of aldehydes in alcoholic solvents to the corresponding esters was also demonstrated, which was a valuable alternative to the traditional metal-mediated oxidations.⁵² Aldehydes also can be oxidized to nitriles in a one-pot reaction under microwave irradiation on alumina in solid state (Scheme I-6).⁵³



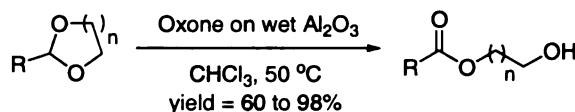
Scheme I-6: Facile oxidation of aldehydes to acids, esters and nitriles with Oxone

Ketone functional groups can be converted to esters via the known Baeyer-Villiger oxidation reaction.⁵⁴⁻⁵⁶ For example, the reaction of Oxone in the presence of wet alumina with solutions of cyclic ketones in methylene chloride provides Baeyer-Villiger oxidation products affording the corresponding lactones (Scheme I-7).⁵⁵



Scheme I-7: Synthesis of lactones by the oxidation of ketones with Oxone

Moreover, symmetrical cyclic and acyclic acetals could be directly oxidized to their corresponding esters with Oxone in good yields.⁴⁶ This method helps to remove acetal protecting groups and generates esters in a simple and rapid way (Scheme I-8). This transformation was also been demonstrated in 2001 by Wang



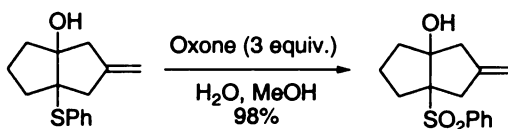
Scheme I-8: Oxidation of acetals to esters with Oxone

and Zhu, who used Caro's acid to oxidize fluorohaloalkyl diethyl acetals to the corresponding esters.⁵⁷

I.1.4.2. Heteroatom oxidation

Oxone has also been used for the oxidation of heteroatoms, including nitrogen, sulfur, phosphorous, and boron containing substrates. Generally, amines are oxidized to either nitro compounds, nitroxides, or hydroxylamines depending on the reaction conditions and the substrates.⁵⁸⁻⁶¹ Sulfides can be selectively oxidized to sulfones in aqueous solution with Oxone even in highly functionalized molecules

(Scheme I-9).^{41, 42, 62} Phosphorous containing compounds, including various

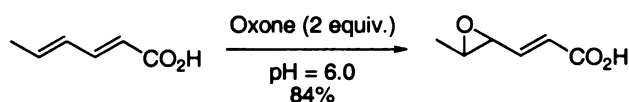


Scheme I-9: Oxidation of sulfide in a functionalized molecule

phosphorous, phosphothio- and phosphoseleno derivatives, are oxidized to the corresponding oxides.³⁹ Finally, boronic acids and boronic esters can be converted to the alcohols in good to excellent yields.^{40, 63}

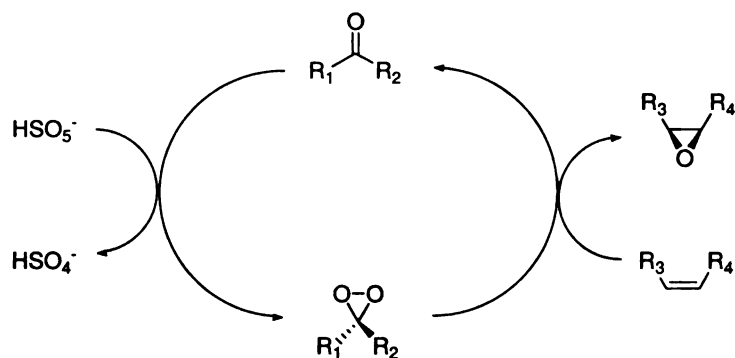
I.1.4.3. Epoxidation of olefins

Generally, Oxone can epoxidize alkenes via the *in situ* generation of a dioxirane intermediates from Oxone and ketones. This provides a complementary approach to the traditional methods for synthesizing epoxides.^{38, 64-66} Curci and coworkers reported this epoxidation in 1980 and developed the stereoselective and regioselective version in 1982.⁶⁴ Under the normal reaction conditions, electron-rich double bonds react faster than electron-deficient double bonds (Scheme I-10).⁶⁶ The general



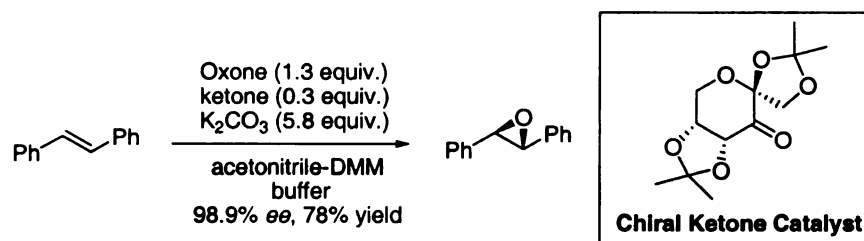
Scheme I-10: Regioselectivity of alkene epoxidation with Oxone

catalytic cycle as shown in Scheme I-11, involves the formation of a dioxirane by nucleophilic attack of Oxone at the carbonyl carbon with loss of potassium hydrogen sulfate followed by the transfer of oxygen to the alkene substrate to form the epoxide and regenerate the initial ketone. From this cycle, one can presume that if chiral ketones are used in the epoxidation instead of the simple acetone to form chiral dioxiranes, stereoselective epoxidations could occur.⁶⁷⁻⁸⁰ The famous example is Shi



Scheme I-11: General catalytic cycle of alkene epoxidation

epoxidation,⁶⁷ which uses fructose-derived ketones as catalyst (Scheme I-12). This asymmetric epoxidation has proven to be a powerful method in organic synthesis and has been widely used in both total synthesis and methodological studies.^{67, 81}

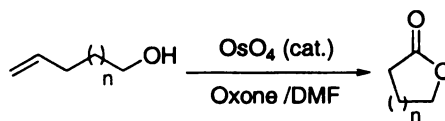


Scheme I-12: Example of a Shi epoxidation

I.1.4.4. Oxidative cleavage

Oxidative cleavage reaction can be applied to a variety of substrates including alkenes, alkynes and dicarbonyl compounds. The two major methodologies of oxidative cleavage for alkenes are ozonolysis and cleavage of 1,2-diols obtained from olefin dihydroxylation. In 2002, our group developed a mild alternative pathway to ozonolysis using Oxone as the co-oxidant for oxidative cleavage of olefins using osmium tetroxide (OsO_4).⁸² This method can be used to convert olefins to the corresponding carboxylic acids or ketones by using a catalytic amount of OsO_4 (0.01 equiv.) and Oxone (4 equiv.) in DMF. A variety of monosubstituted,

1,1-disubstituted, 1,2-disubstituted, trisubstituted, and tetra-substituted olefins containing various functional groups react successfully to form the desired products in good to high yields. Similarly, if the cleavage is coupled with intramolecular trapping by an alcohol moiety, lactones can be formed efficiently (Scheme I-13).⁸³

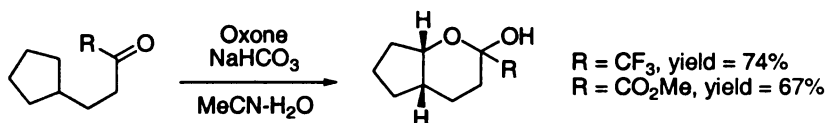


Scheme I-13: Direct lactonization of alkenols via oxidative cleavage

Also alkynes could be transformed to carboxylic acids with Oxone oxidative cleavage catalyzed by ruthenium (RuO_2).⁸⁴ Using a RuO_2 (3 mol %)/Oxone (3.3 equiv.)/ NaHCO_3 (9.9 equiv.) system in a mixed acetonitrile, water and ethyl acetate solvents, both internal and terminal alkynes can be oxidized to carboxylic acids in excellent yield. Moreover, oxidation of α - or β -dicarbonyl compounds with Oxone tends to go through the oxidative cleavage pathway, which provides the corresponding carboxylic acids.

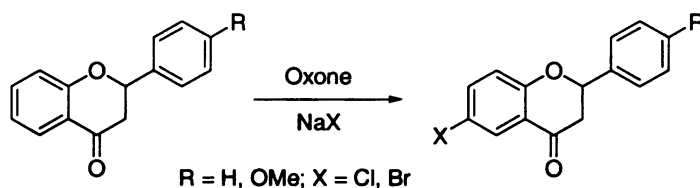
I.1.4.5. Other oxidative transformations

Besides the reactions discussed in the previous section, Oxone can also be used for the oxidation of unactivated C-H bonds and selective halogenation reactions. Yang's group⁸⁵ has demonstrated that dioxiranes generated *in situ* from ketones and Oxone can undergo intramolecular oxidation of unactivated C-H bonds at δ sites of ketones to yield tetrahydropyrans (Scheme I-14). In 2002, Bovicelli and coworkers



Scheme I-14: Selective oxidation of δ C-H bond

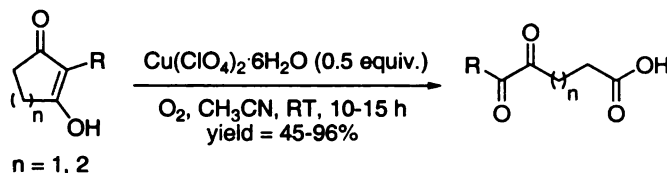
found that when using NaX combined with Oxone, selective halogenation could occur in flavonoids, which is important for the synthesis of both biologically active substances and intermediates (Scheme I-15).⁸⁶



Scheme I-15: Selective halogenation of flavanones

I.2. Previous Work for Oxidative Cleavage of 1,2- and 1,3-Dicarbonyl Compounds

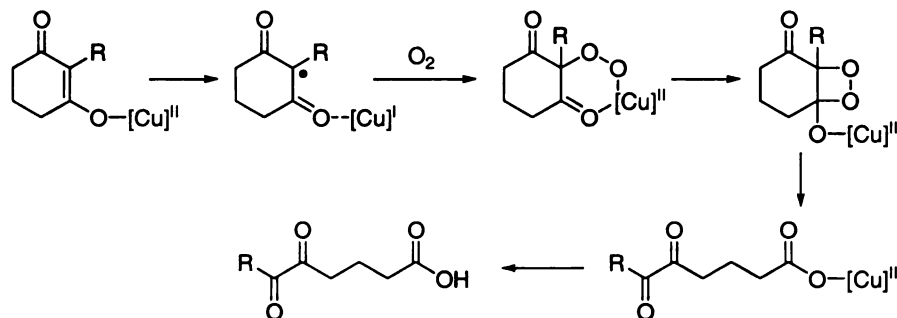
Oxidative cleavage of α -hydroxyketones, α -diones, and β -diones to their corresponding dicarboxylic acids is well preceded with reagents such as oxygen with bismuth (0) as a catalyst, sodium percarbonate, calcium hypochlorite, alkaline peroxide, copper perchlorate, and methylrhenum trioxide.^{38, 54, 87-93} For example, in 1994, Brocca and coworkers reported the oxidative cleavage of 2-substituted cycloalkane-1,3-diones by copper perchlorate in acetonitrile in an oxygen atmosphere (Scheme I-16).⁹³ A plausible mechanism of this transformation includes the coordination of the enol with Cu(II), followed by the reaction with oxygen generating



Scheme I-16: Oxidative cleavage of 2-substituted cycloalkane-1,3-diones

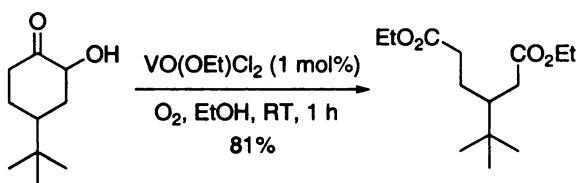
a peroxide which undergoes cyclization to a dioxetane. This intermediate favors a 4-membered ring-opening sequence leading to the formation of the corresponding

dioxocarboxylic acid (Scheme I-17).



Scheme I-17: A plausible mechanism for the oxidative cleavage of 1,3-diketones

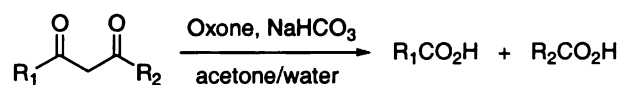
In addition, vanadium-based systems have been reported to convert α -hydroxyketones or α -diones into the corresponding methyl or ethyl esters in the presence of the appropriate alcohols.^{94, 95} One nice example is the chemoselective cleavage of α -hydroxyketones with a catalytic amount of dichloroethoxyvanadium under an oxygen atmosphere reported by Momose and coworkers.⁹⁵ During this sequence, diethyl esters are formed directly with ethanol as solvent (Scheme I-18).



Scheme I-18: Example of an oxyvanadium-catalyzed cleavage of α -hydroxyketones

All of these examples use either stoichiometric or catalytic amounts of metals combined with oxygen or peroxide as co-oxidant. It was discovered that using Oxone as a reagent, the oxidative cleavage could occur directly without metal mediation. In 1988, Panda discussed a kinetic and mechanistic study for the oxidation of α -diketones with Oxone.⁸⁷ The kinetic data provide the plausible Baeyer-Villiger type mechanism. In addition, as reported by Ashford and Grega, the

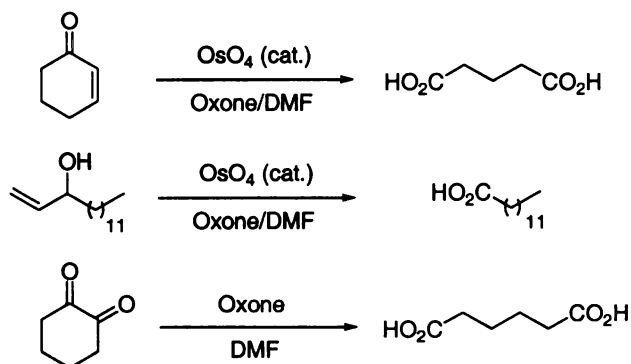
oxidative cleavage of 1,3-dicarbonyls with Oxone gives one carbon shortened carboxylic acids when using Oxone-NaHCO₃ in acetone and water mixture (Scheme I-19).⁹⁶ They successfully applied their methodology to develop a commercial process to prepare androst-4-ene-17-β-carboxylic acid from progesterone.



Scheme I-19: Oxidative cleavage of 1,3-dicarbonyls with Oxone by Ashford and Grega

I.3. Direct Oxidative Cleavage of α-Hydroxyketones, α-Diones, and β-Diones to Dimethyl Esters with KHSO₅

Work in our laboratory has previously focused on the use of Oxone as a co-oxidant for the oxidative cleavage of olefins and the oxidation of aldehydes to acids and ester.^{33, 52, 82, 83, 97} The continuing studies with the Oxone-mediated oxidative cleavage of olefins with a variety of reactants showed that neither α, β-unsaturated carbonyls nor α-hydroxyolefins provided the expected α-ketoacids or α-hydroxyacids, but instead the one carbon shortened carboxylic acid products were isolated. This also led to the investigation of α-diones, which are cleaved under similar conditions to provide the desired diacid (Scheme I-20). These observations



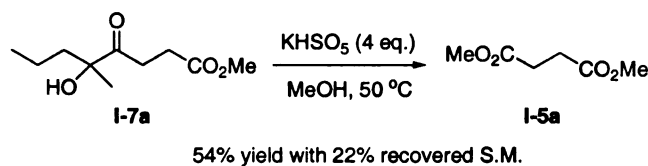
Scheme I-20: Previous results for Oxone-mediated oxidative cleavage

are similar to those by Ashford and Grega⁹⁶ regarding the oxidative cleavage of β -diones shown in Scheme I-19.

All these results encouraged us to further study the oxidative cleavage of α - and β -diones and α -hydroxyketones using Oxone as oxidant. The previous work has provided the well-developed methods to prepare carboxylic acids based on oxidative cleavage of α -hydroxyketones and α - or β -diones. However, only a few pathways have been reported for the oxidative cleavage of ketones to esters. During our studies on the oxidation of aldehydes, the direct conversion of aldehydes in alcoholic solvents to their corresponding esters was discovered.⁵² This result led us to postulate that during the oxidative cleavage of α -hydroxyketones and α - or β -diones, it was possible to form the diesters using alcoholic solvents instead of DMF. We have successfully developed a mild and efficient method that utilizes potassium peroxymonosulfate (KHSO_5) as the sole oxidant for the direct transformation of the aforementioned functional groups to yield esters in good to high yield.⁹⁸

In order to prove the hypothesis, various α -hydroxyketones, α - or β -diones were subjected to the oxidation sequence with methanol as the solvent. The desired dimethyl ester products could be formed with the purified (>95%) dry Oxone, KHSO_5 (4 equiv.), after stirring the reaction at room temperature for 18 hours. It should be noted that even though KHSO_5 was used in all the oxidative cleavage reactions, the same products and comparable yields could be obtained when using commercially available Oxone.

As can be seen from Table I-1, oxidation of α -hydroxyketones and α - or β -diones in methanol provided good to excellent yields of the desired dimethyl esters. For instance, α -hydroxyketones **I-1** and **I-2** (entries 1 and 2) provided products **I-1a** and **I-2a** in 98% and 69% yield, respectively. Cyclic α -diones **I-3** and **I-4** (entries 3 and 4) were converted efficiently to their corresponding dimethyl esters **I-1a** and **I-2a**, with no effect on the ring size of the substrates. Cyclic β -diones **I-5** and **I-9** (entries 5 and 9) afforded diesters **I-5a** and **I-8a** in 85% and 99% yield. The same situation could be observed for the acyclic β -diones **I-8** and **I-11** (entries 8 and 11), which also provided dimethyl esters in good yield. Mono substitution of β -diones at C2 did not affect the reaction (entries 6 and 10). However, the bis-2-substitution of β -dione **I-7** did effect the reaction significantly providing the tertiary hydroxyketone **I-7a** in 65% yield. Interestingly, **I-7a** did not undergo further oxidation reaction without heating, presumably due to the steric constraints that hinder the nucleophilic attack of the oxidant at the carbonyl carbon. Heating the reaction to 50 °C helped to initiate the oxidative cleavage but with poor conversion leading to only 54% of the desired diester and 22% of the starting material being recovered (Scheme I-21). The structurally



Scheme I-21: Oxidative cleavage of **I-7a** at 50 °C

related cyclic tertiary hydroxyketone **I-16** reacted at room temperature affording a 4:1 mixture of the dimethyl ester **I-1a** and the keto ester **I-16a** in a modest 50% yield.

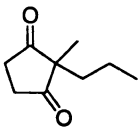
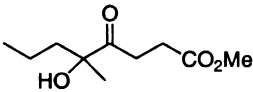
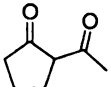
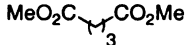
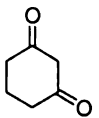
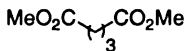
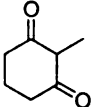
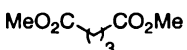
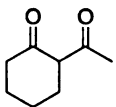
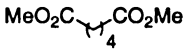
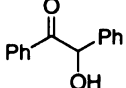
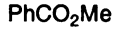
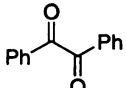
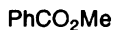
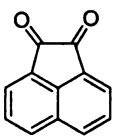
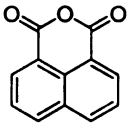
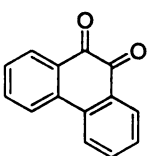
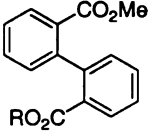
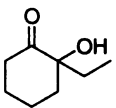
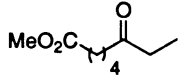
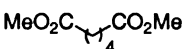
These two products could not be separated via chromatography; the ratio was determined from the NMR integration.

Benzil **I-12** and benzoin **I-13** were also subjected to the same reaction conditions. Since at room temperature there were no reactions, increasing the temperature was required. Heating the reactions to 50 °C gave a facile conversion to methyl benzoate (entries 12 and 13) in good yield. Additionally, the α -dione **I-14** did not yield the expected diester but provided anhydride **I-14a** in 98% yield. This transformation may be due to the high stability of the 6-membered cyclic anhydride. The α -dione **I-15**

Table I-1: Oxidative cleavage of α -hydroxyketones, α - or β -diones in MeOH^a

Entry	Substrate		Product		Yield (%) ^b
1	 (dimer)	I-1		I-1a	98
2		I-2		I-2a	69
3		I-3		I-1a	90
4		I-4		I-2a	79
5		I-5		I-5a	85
6		I-6		I-5a	80

Table I-1: Oxidative cleavage of α -hydroxyketones, α - or β -diones in MeOH (continued)

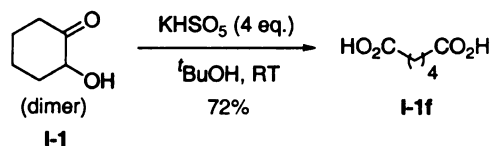
Entry	Substrate	Product	Yield (%) ^b
7			65
8			86
9			99
10			86
11			78
12 ^c			73
13 ^c			77
14			98
15			19 64
16		 	10 40

^a Substrate (1 equiv), KHSO₅ (4 equiv), RT, 18 h. ^b Isolated yields.^c Reactions performed at 50 °C.

also did not give the diester exclusively, affording both the dimethyl and monomethyl esters in 19% and 64% yield, respectively.

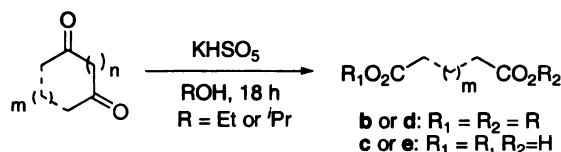
I.4. Oxidative Cleavage of α -Hydroxyketones, α -Diones, and β -Diones with KHSO_5 Using Ethanol and Isopropyl Alcohol as Solvent

Using methanol as solvent, dimethyl esters could be formed efficiently in one simple step with high yield. These reactions provide a valuable alternate to form esters starting from α -hydroxyketones, α - or β -diones as compared to other related metal-mediated processes. Encouraged by the previous results, other alcohols were used in the same sequence in order to make different esters. Reactions in ethanol and isopropanol proved to be quite reluctant to yield diesters exclusively, and instead, a reproducible mixture of mono- and diesters were obtained. The overall yield of these products remained high as can be seen from Table I-2. Oxidative cleavage of α -hydroxyketones **I-1**, α -diones **I-3**, cyclic and acyclic β -diones **I-5**, **I-6**, **I-10**, and **I-11** in both EtOH and *i*PrOH gave a mixture of mono- and diesters with the overall yield of 51-86%. Benzil **I-12** and benzoin **I-13** again proved to be more difficult substrates requiring heating of the reactions to 50 °C. Generally, yields of diethyl esters were higher than the corresponding diisopropyl esters; however, significant amounts of monoesters were isolated in all reactions. Oxidation of α -dione **I-14** still afforded anhydride product **I-14a** in both alcoholic solvents in excellent yield (98% and 90%). This reaction was not affected by solvents. Moreover, reaction of α -hydroxyketones **I-1** with *t*BuOH provided the diacid exclusively (Scheme I-22).



Scheme I-22: Oxidative cleavage of I-1 in *t*BuOH to form dicarboxylic acid I-1f

Table I-2: Oxidative cleavage of α -hydroxyketones, α - or β -diones in EtOH and *i*PrOH^a



Entry	Substrate ^d	Solvent	Product	Yield (%) ^b
1	I-1	EtOH	I-1b / I-1c	49:25
2	I-3	EtOH	I-1b / I-1c	44:28
3	I-5	EtOH	I-5b / I-5c	61:25
4	I-6	EtOH	I-5b / I-5c	42:38
5	I-10	EtOH	I-10b / I-10c	62:14
6	I-11	EtOH	I-1b / I-1c	35:48
7 ^c	I-12	EtOH	I-12b / I-12c	25:37
8 ^c	I-13	EtOH	I-12b / I-12c	44:37
9	I-14	EtOH	I-14a	98
10	I-1	<i>i</i> PrOH	I-1d / I-1e	34:45
11	I-3	<i>i</i> PrOH	I-1d / I-1e	33:18
12	I-5	<i>i</i> PrOH	I-5d / I-5e	31:31
13	I-6	<i>i</i> PrOH	I-5d / I-5e	30:38
14	I-10	<i>i</i> PrOH	I-10d / I-10e	24:45
15	I-11	<i>i</i> PrOH	I-1d / I-1e	40:43
16 ^c	I-12	<i>i</i> PrOH	I-12d / I-12e	15:51
17 ^c	I-13	<i>i</i> PrOH	I-12d / I-12e	38:43
18	I-14	<i>i</i> PrOH	I-14a	90

^a Substrate (1 equiv), KHSO₅ (4 equiv), RT, 18 h. ^b Isolated yields.

^c Reactions performed at 50 °C. ^d See Table I-1 for structures.

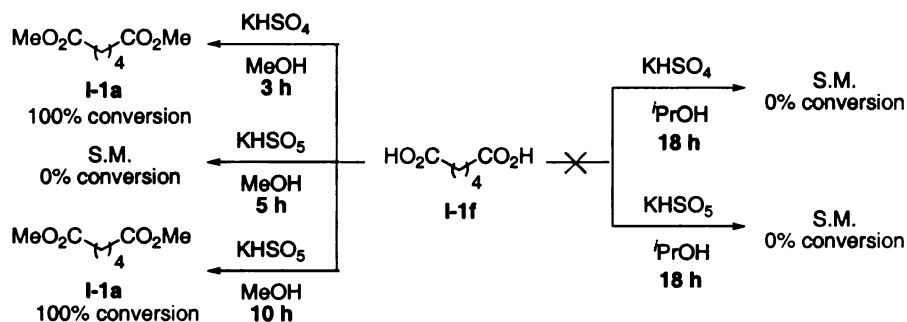
All of these experiments demonstrated that the diesters were more difficult to form when larger alcohols were used. Sterically hindered *tert*-butyl alcohol did not provide any esters as products. This is in agreement with our previous observations, which

showed that oxidation of aldehydes in ⁱBuOH with Oxone provided carboxylic acids without any trace of the desired ester.⁵²

I.5. The Corresponding Mechanistic Study

The mixed products observed during the oxidation in ethanol and isopropyl alcohol prompted a corresponding mechanistic study for their origins. Initially it was of interest to discern whether all the reactions proceeded through monoesters, and then the remaining carboxylic acids reacted with alcohol to form diesters via Fischer esterification, i.e., monoesters or dicarboxylic acids are the products of the oxidation, or whether there are different and competing pathways that could account for the isolation of both mono- and diesters.

To address these two different mechanistic interpretations, adipic acid was treated with KHSO₅ or KHSO₄ in both MeOH and ⁱPrOH (Scheme I-23). KHSO₄, the



Scheme I-23: Fischer esterification experiments for adipic acid analyzed by GC

presumed byproduct of the oxidation reaction, has been implicated in Fischer esterifications. Because of its acidity, it has been used in general acidic Fischer esterifications under heat or microwave-assisted conditions.⁹⁹⁻¹⁰¹ When adipic acid was mixed with either KHSO₅ or KHSO₄ in ⁱPrOH for 18 h, the only product detected by GC was the starting material; no esterified products was formed. Alternatively,

adipic acid in MeOH and KHSO_4 led to the generation of dimethyl adipate only in 1 h, and after 3 h, all the starting material had been converted to the diester. However, the same reaction with KHSO_5 did not yield any esterified product after 5 h. Conversion to the diester was observed after 9 h, presumably due to the auto-decomposition of KHSO_5 to KHSO_4 in the wet alcoholic solvent. Three additional experiments were performed to better understand the process. Firstly, the mixture of KHSO_5 and MeOH was stirred for 9 h. Iodometric titration³³ of the latter solution indicated about 1% loss in oxidative activity. This result demonstrated that the auto-decomposition of KHSO_5 to KHSO_4 in wet MeOH could occur slowly. Secondly, the mixture of KHSO_5 , adipic acid (0.25 equiv) and MeOH was stirred for 9 h. Iodometric titration of this solution indicated about 4% loss in oxidative activity. This proved that addition of adipic acid led to increased decomposition of KHSO_5 during the 9 h span. Finally, the mixture of 4% KHSO_4 , adipic acid and MeOH was stirred. Only after 1 h, the dimethyl ester product was detected by GC (> 80% conversion), which indicated that even trace amount of KHSO_4 could catalyze the formation of diester via Fischer esterification. Although the diester could have formed directly, the latter results suggest that a Fischer esterification process is also a viable mechanistic path.

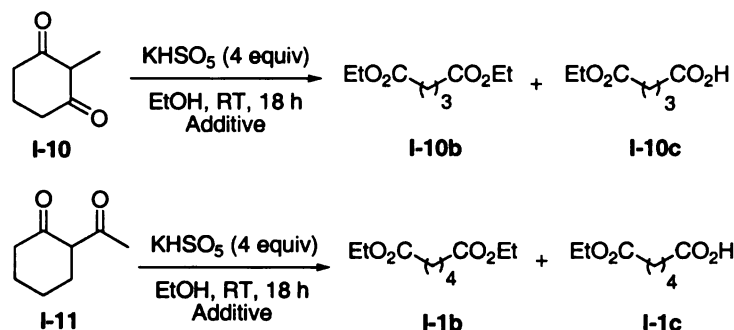
All of these results are in direct contrast to the oxidative cleavage of 1,2-cyclohexanedione **I-3**, which shows a nearly complete conversion to dimethyl adipate after 3 h. Since there is no Fischer esterification product of adipic acid with KHSO_5 in methanol even after 5 h, which indicates that the rate of Fischer

esterification is much slower than oxidative cleavage, it seems unlikely that **I-3** is converted to adipic acid, which in turn is esterified under the reaction conditions. More evidence of the latter is realized with experiments that demonstrate that neither KHSO_5 nor KHSO_4 can convert simple carboxylic acids to isopropyl esters, but yet mono- and diisopropyl esters are isolated upon oxidation of α -hydroxyketones, α - or β -diones. Although it is not possible to present a detailed mechanistic picture from these experiments, it seems likely that the oxidative cleavage of the functional groups presented here is faster than Fischer esterification of their corresponding carboxylic acids, and that the formation of the isolated mono- and diesters most probably occurs via different mechanisms. In other words, one can imagine that diesters can originate without the intermediacy of monoesters, although it can not be ruled out (at least for generation of dimethyl esters) that some supplementary Fischer esterification of monoesters to diesters is occurring.

Since acidic KHSO_4 could catalyze Fischer esterification as shown above, we needed to clarify whether the acid could help to promote Fischer esterification during oxidative cleavage and convert all the monoesters to diesters as the final products or not. For this purpose sulfuric acid and toluenesulfonic acid (TsOH) were used in the reactions with EtOH as the solvent (Table I-3). The results show that the ratio of diethyl esters and monoesters does not change significantly with addition of acid. Although for some reactions, the yield of diethyl esters is slightly higher in the presence of acid than under standard conditions, the acid additive did not convert all the monoesters to diesters. It is believed that the acid additive has no significant

enhancement of the Fischer esterification when larger alcohols are used.

Table I-3: Acid additive in oxidative cleavage

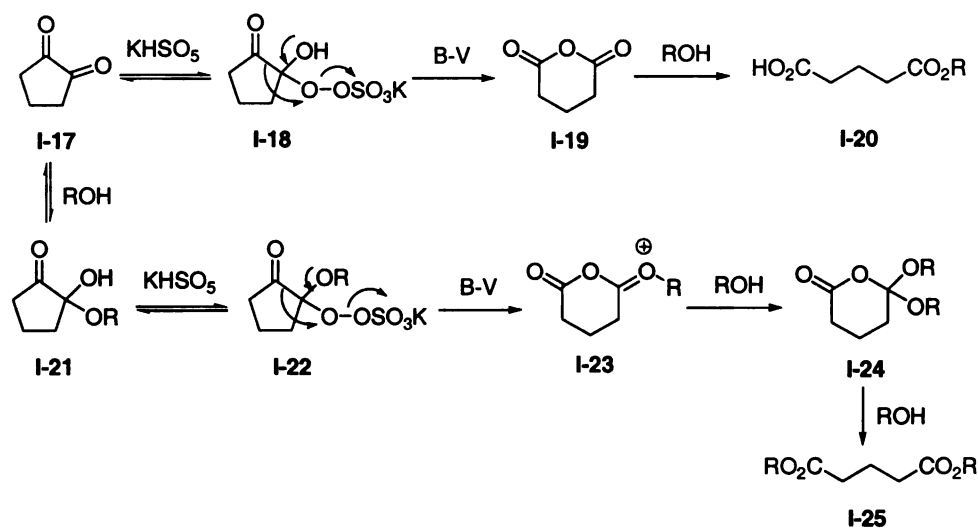


Acid Additive	Product	Isolated Yield (%)
None		54 : 14
H_2SO_4 (1 equiv)	I-10b / I-10c	62 : 21
TsOH (1 equiv)		54 : 21
None		35 : 48
H_2SO_4 (1 equiv)	I-1b / I-1c	44 : 36
TsOH (1 equiv)		60 : 22

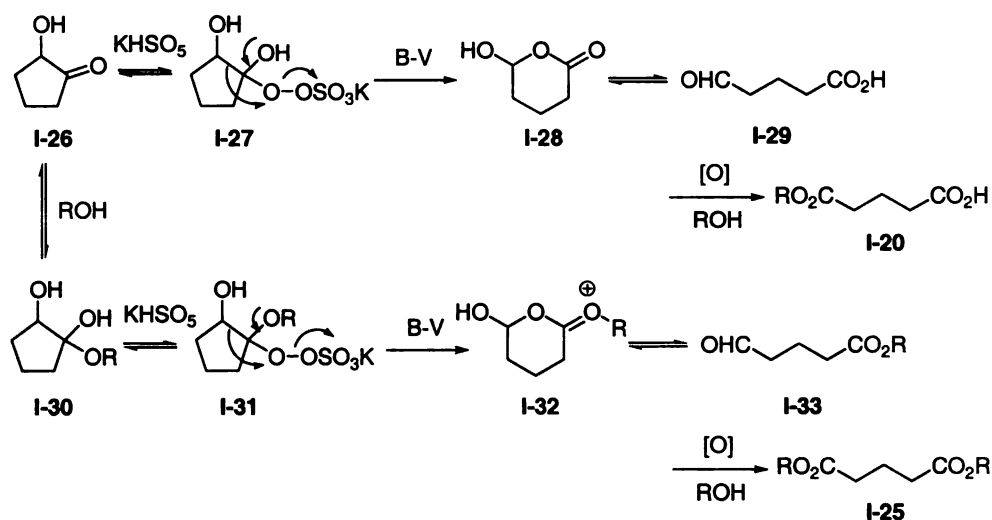
One possibility that can lead to both mono- and diesters formation in alcoholic solvents is that the conjugated enol tautomer plays an important role in the oxidative cleavage. This hypothesis has been supported by oxidation of compound **I-7**, which has two substituted groups between two carbonyl functionalities and no conjugated enol tautomer could be formed during the sequence. As seen from Table I-1, oxidation of this substrate only afforded ring-opening product **I-7a** without any further cleavage occurring.

Notably, oxidative cleavage of α -hydroxyketones and α - or β -diones need not necessarily and probably do not proceed via the same mechanistic pathway. Schemes I-24, I-25, and I-26 depict possible routes to both monoesters and diesters from α -diones, α -hydroxyketones, and β -diones. The route to monoesters would

most probably involve the intermediacy of a peroxyhemiacetal, which upon Baeyer-Villiger type rearrangement would lead to the carboxylic acid functionality of the monoesters. This is shown for α -diones and α -hydroxyketones (intermediates **I-18** and **I-27**), which upon oxidative rearrangement lead to the monoester **I-20** or the aldehyde **I-29**, respectively. Further oxidation of the aldehyde with KHSO_5 in the alcoholic solvent would lead to the monoester **I-20**. Conversely, the intermediate of

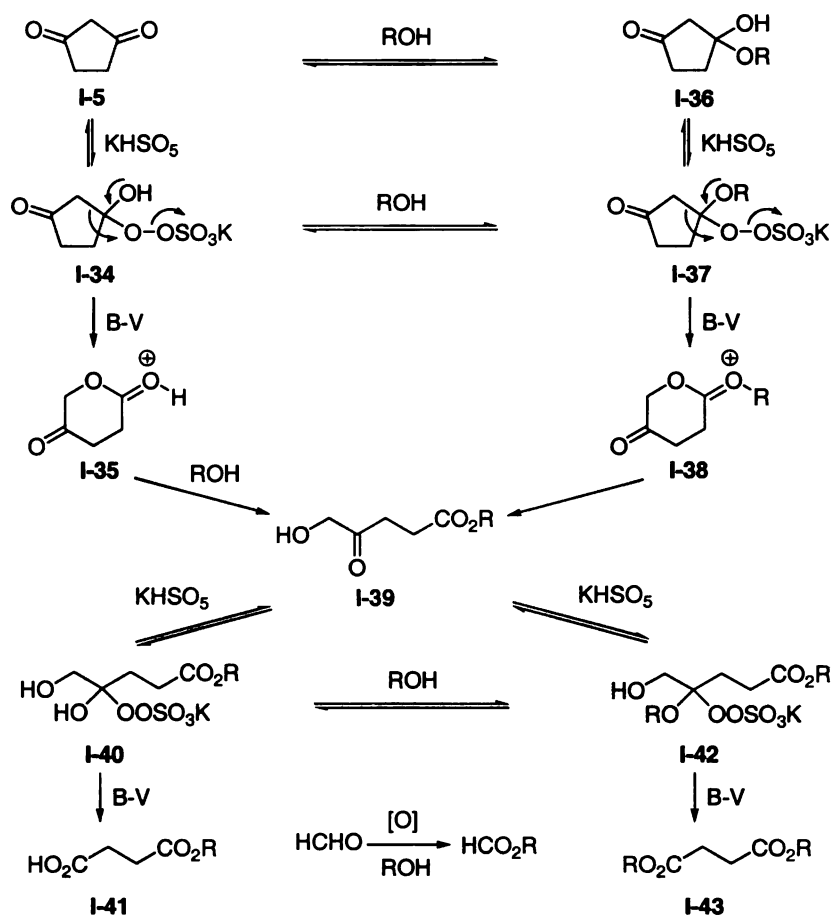


Scheme I-24: Probable mechanistic routes for the oxidative cleavage of α -diones



Scheme I-25: Probable mechanistic routes for the oxidative cleavage of α -hydroxyketones

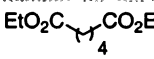
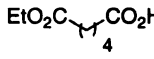
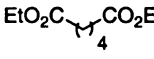
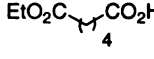
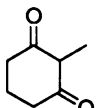
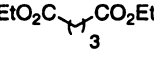
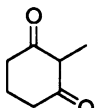
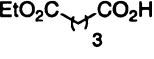
a peroxyacetal, such as **I-22** or **I-31**, could lead to the isolation of the diester **I-25** without the need for esterification of monoesters to the diesters. In a similar manner, β -diones could also lead to either mono- or diesters. Presumably, for this kind of substrates, the first Baeyer-Villiger rearrangement gives the oxidative ring-opening product α -hydroxyketone **I-39**. Although we have not observed this via NMR spectroscopy, the more hindered substrate **I-7** was reacted to give the same kind of product without further cleavage. Then the intermediate peroxyhemiacetal **I-40** or peroxyacetal **I-42** is formed, which leads to the second Baeyer-Villiger rearrangement to afford either mono- or diesters as the oxidative cleavage products.



Scheme I-26: Probable mechanistic routes for the oxidative cleavage of β -diones

Based on the previous probable mechanistic routes, it is easy to predict that the oxidative cleavage of different substrates requires different amount of oxidant. The number of equivalents of oxidant required for different substrates has been examined in all three cases. Table I-4 shows the results of these experiments. It is clear that a

Table I-4: Equivalents of oxidant necessary for complete conversion of different substrates^a

Entry	Substrate	Equiv of Oxidant	Product	Yield (%) ^b
1	 I-3	0.5	crude NMR showed there was S.M. left	---
2		1.0	 I-1b	42
			 I-1c	33
3	 I-1	2.0	 I-1b	44
			 I-1c	28
4	 I-10	0.5	crude NMR showed there was S.M. left	---
5		1.0	crude NMR showed there was S.M.	---
6		2.0	 I-10b	61
7	 I-10	3.0	 I-10c	10

^a Substrate (1 equiv), oxidant = KHSO₅, EtOH, RT, 18 h. ^b Isolated yield.

minimum of 1 equiv of KHSO₅ for α -dione **I-3** and 2 equiv of KHSO₅ for α -hydroxyketone **I-1** in EtOH are necessary for their oxidation to yield the ratio of

products listed in Table I-2 (entries 1 and 2). Increasing the amount of oxidant did not change the ratio of the mono- and diester products isolated. In addition, β -dione **I-10** required a minimum of 3 equiv of KHSO_5 to yield consistent product ratio listed in Table I-2 (entry 5) due to the oxidative cleavage of the intermediate α -hydroxyketone. All these observations are in line with the postulated mechanism depicted in Schemes I-24, I-25 and I-26.

I.6. Summary

In conclusion, the oxidative cleavage of α -hydroxyketones and α - or β -diones to esters with KHSO_5 is a valuable addition to the oxidation reactions of Oxone chemistry. These results demonstrate a new methodology to oxidatively cleave the aforementioned functional groups. It can be applied to the direct synthesis of esters using the environmentally benign reagent KHSO_5 without the need for the use of transition metal oxides. The sequence may prove to be a useful alternative to other metal-mediated processes.

In addition, a related mechanistic study of the oxidative cleavage provides a plausible mechanistic interpretation of the reactions. It suggests that the oxidative cleavage of α -hydroxyketones and α - or β -diones proceeds through different routes to provide the desired mono- and diester products.

I.7. Experimental Section

General Information:

All commercially available starting materials and solvents were used without further purification. Commercially available starting materials were obtained from Aldrich. Some compounds were prepared as previously reported. 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 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 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 or at 125 MHz on a Varian VXR-500 instrument. Chemical shifts are reported relative to the central line of CDCl_3 (δ 77.0 ppm). Infrared spectra were recorded using a Nicolet IR/42 spectrometer FT-IR (thin film, NaCl cells). High resolution mass spectra were measured at the Michigan State University, Mass Spectrometry Laboratory.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F₂₅₄ plates. Compounds were visualized with UV light, potassium permanganate stain or *p*-anisaldehyde stain. 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 containing Altech SE-54, 30 m $\times$ 320 μm $\times$ 0.25 μm column.

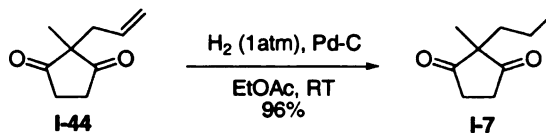
General Procedure for Oxidation of α -Hydroxyketons, α - or β -Diones with

Oxone: The substrate (1 equiv) was dissolved in the appropriate solvent (methanol, ethanol, isopropanol or *tert*-butanol (0.2 M)). Dry KHSO_5 (4 equiv, 95% pure, preparation was based on the procedure published by our group³³) was added to the solution in one portion and stirred at room temperature for 18 h. The reactions were monitored by TLC, GC, or NMR analysis. After the substrate had been consumed the reaction was diluted with Et_2O and filtered through a pad of Celite. The filtrate was collected and concentrated under reduced pressure to yield the crude product. Products were purified by silica gel column chromatography.

Compounds that were Compared with the Aldrich Database: Dimethyl esters **I-1a**, **I-2a**, **I-5a**, **I-8a**; methyl benzoate **I-12a**; 1,8-naphthalic anhydride **I-14a**, diethyl esters **I-1b**, **I-5b**, **I-10b**; ethyl benzoate **I-12b**; diisopropyl ester **I-1c** and benzoic acid **I-12c**; adipic acid **I-1f**.

Compounds that were Compared to the Literature Reports: Dimethyl ester **I-15a**,¹⁰² monomethyl ester **I-15b**,¹⁰³ monoethyl esters **I-5c**,¹⁰⁴ **I-10c**,¹⁰⁵ diisopropyl esters **I-1d**,¹⁰⁶ **I-5d**,¹⁰⁷ diisopropyl benzoate **I-12d**,⁵² monoisopropyl esters **I-5e**,¹⁰⁸ **I-10e**.¹⁰⁹

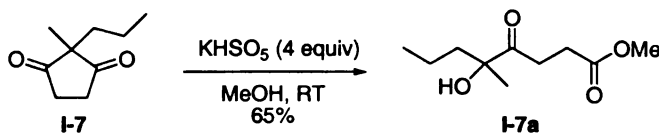
Data for Newly Synthesized Compounds:



2-Methyl-2-propylcyclopentane-1,3-dione (I-7)¹¹⁰: To a room temperature solution of 2-allyl-2-methyl-1,3-cyclopentadione **I-44** (148 μL , 1.0 mmol) in EtOAc (10 mL)

10% Pd-C (92 mg, 5% by wt) was added in. A hydrogen filled balloon was attached and the system was purged under vacuum and replaced with hydrogen gas. The reaction was stirred at RT for 15 h. The Pd-C was then filtered through a Celite pad and washed with EtOAc (3×5 mL). The solvent was removed under reduced pressure providing **I-7** as a colorless oil (148 mg, 96% yield) and did not require additional purification.

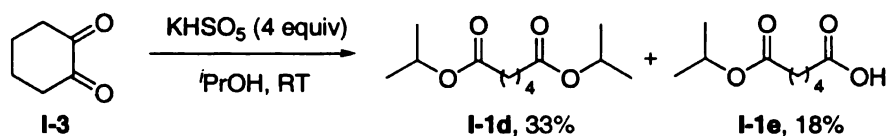
Partial data for **I-7**: ^1H NMR (300 MHz, CDCl_3): δ 2.68 (4H, s), 1.54-1.49 (2H, m), 1.12-1.04 (2H, m), 1.02 (3H, s), 0.76 (3H, t, $J = 7.1$ Hz).



Methyl 5-hydroxy-5-methyl-4-oxooctanoate (I-7a): KHSO_5 (547 mg, 3.6 mmol) was added in one portion to a solution of diketone **I-7** (145 mg, 0.9 mmol) in methanol (8 mL) at RT (the salt is not completely soluble). The reaction was stirred at RT for 18 h, after which it was diluted with Et_2O (8 mL) and the precipitate (presumably unreacted KHSO_5 and byproduct KHSO_4 generated during the reaction) was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (20% EtOAc/hexanes) to furnish ester **I-7a** as a colorless oil (58 mg, 65% yield).

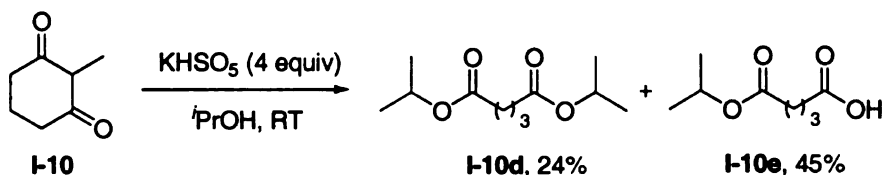
Data for **I-7a**: ^1H NMR (300 MHz, CDCl_3): δ 3.63 (3H, s), 2.87-2.72 (2H, m), 2.61-2.56 (2H, m), 1.66-1.60 (2H, m), 1.32 (3H, s), 1.09-0.97 (2H, m), 0.85 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 212.8, 172.9, 78.7, 51.8, 41.8, 30.8, 27.6, 25.5, 16.5, 14.2; IR (thin film) 3400, 2961, 1741, 1713, 1441, 1373, 1242, 1173, 1047

cm⁻¹; LRMS (70 ev, EI) *m/z* 202 [M]⁺, 184 [M-H₂O]⁺, 171 [M-CH₃O]⁺; HRMS (CI) calcd for C₁₀H₁₉O₄, 203.1283 *m/z* [M+H]⁺, observed, 203.1283 *m/z*.



6-Isopropoxy-6-oxohexanoic acid (I-1e): KHSO₅ (608 mg, 4 mmol) was added in one portion to a solution of 1,2-dione **I-3** (112 mg, 1 mmol) in isopropanol (10 mL) at room temperature. The reaction was stirred at RT for 18 h, after which it was diluted with Et₂O (8 mL) and the precipitate (presumably unreacted KHSO₅ and byproduct KHSO₄ generated during the reaction) was filtered through a pad of Celite. All the filtrate was concentrated, and the crude product was purified by silica gel column chromatography (20% EtOAc/hexanes) to furnish diester **I-1d** (70 mg, 33%) and monoester **I-1e** (32 mg, 18%) as colorless oils.

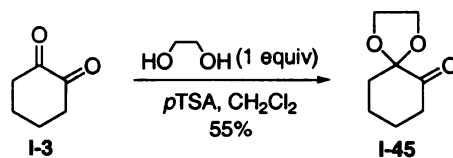
Data for **I-1e**: ¹H NMR (300 MHz, CDCl₃): δ 11.05 (1H, br), 4.95 (1H, sept, *J* = 6.32 Hz), 2.32 (2H, t, *J* = 6.87 Hz), 2.25 (2H, t, *J* = 7.14 Hz), 1.67-1.57 (4H, m), 1.17 (6H, d, *J* = 6.04 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 179.6, 172.9, 67.6, 34.2, 33.6, 24.3, 23.9, 21.7; IR (thin film) 3210, 2982, 2939, 1730, 1729, 1375, 1242, 1182, 1109, 1047, 939, 822 cm⁻¹; LRMS (70 ev, EI) *m/z* 170 [M-H₂O]⁺, 129 [M-OCH(CH₃)₂]⁺; HRMS (CI) calcd for C₉H₁₇O₄, 189.1127 *m/z* [M+H]⁺, observed, 189.1128 *m/z*.



Diisopropyl glutarate (I-10d): KHSO₅ (608 mg, 4 mmol) was added in one portion to a solution of 1,3-dione **I-10** (126 mg, 1 mmol) in isopropanol (10 mL) at room

temperature. The reaction was stirred at RT for 18 h after which it was diluted with Et₂O (8 mL) and the precipitate (presumably unreacted KHSO₅ and byproduct KHSO₄ generated during the reaction) was filtered through a pad of Celite. The crude products were purified by silica gel column chromatography (20% EtOAc/hexanes) to furnish diesters **I-10d** (51 mg, 24%) and **I-10e** (77 mg, 45%) as colorless oils.

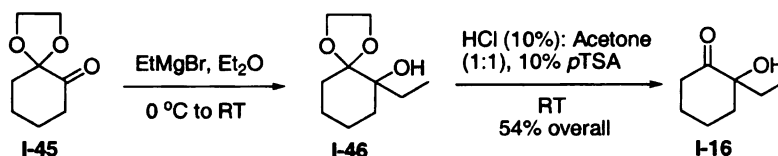
Data for **I-10e**: ¹H NMR (300 MHz, CDCl₃): δ 4.96 (2H, sept, *J* = 6.32 Hz), 2.27 (4H, t, *J* = 7.14 Hz), 1.88 (2H, p, *J* = 7.14 Hz), 1.18 (12H, d, *J* = 6.32 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 172.5, 67.6, 33.6, 21.8, 20.2; IR (thin film) 2982, 2934, 1732, 1375, 1256, 1202, 1181, 1109, 1057, 1011, 970, 933 cm⁻¹; LRMS (70 ev, EI) *m/z* 216 [M]⁺, 157 [M-OCH(CH₃)₂]⁺; HRMS (CI) calcd for C₁₁H₂₁O₄, 217.1440 *m/z* [M+H]⁺, observed, 217.1440 *m/z*.



2-Oxocyclohexane-1-spiro-2'-(1',3'-dioxolane) (**I-45**)^{111, 112}: 1,2-Cyclohexanedione **I-3** (134 mg, 1.2 mmol) was dissolved in methylene chloride (8 mL). *p*-Toluenesulfuric acid monohydrate (190 mg, 0.1 mmol) and ethylene glycol (56 μL, 1.0 mmol) were added to the solution and the reaction was stirred at RT for 15 h. The solution was poured into water (10 mL) to workup the reaction and extracted with CH₂Cl₂ (3×10 mL). The combined organic layer was dried over anhydrous Na₂SO₄. Filtration followed by concentrated under reduced pressure gave the crude product, which was purified by silica gel column chromatography (20% EtOAc/hexanes) to

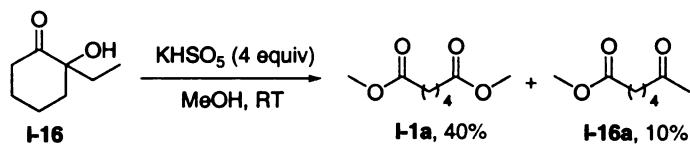
furnish mono-protected dione **I-45** (85 mg, 55%) as a colorless oil.

Partial data for **I-45**: ^1H NMR (300 MHz, CDCl_3): δ 3.98-3.62 (4H, m), 2.38-2.48 (2H, m), 1.57-1.98 (6H, m).



2-Ethyl-2-hydroxycyclohexanone (I-16)¹¹³: A solution of protected ketone **I-45** (200 mg, 1.2 mmol) in diethyl ether (10 mL) was cooled to $0\text{ }^\circ\text{C}$. Ethyl magnesium bromide solution (3.0 M in diethyl ether, 0.5 mL, 1.5 mmol) was dropwise added to the cold solution. The reaction mixture was increased to room temperature and stirred for 2 h. After the reaction was finished (monitored by TLC), 10% (v/v) HCl solution (5 mL), Acetone (5 mL) and *p*-toluenesulfuric acid (19 mg, 10%) were added to it and the mixture was stirred at RT for 12 h. The reaction mixture was quenched by successive addition of aqueous NaHCO_3 (sat.) until the solution stopped bubbling. The mixture was separated and extracted by EtOAc ($5\times 10\text{ mL}$). The combined organic level was dried over MgSO_4 . Filtration followed by concentrated under reduced pressure gave the crude product, which was purified by silica gel column chromatography (10% EtOAc/hexanes) to furnish desired product **I-16** (76 mg, 54% in two steps) as a colorless oil.

Partial data for **I-45**: ^1H NMR (300 MHz, CDCl_3): δ 3.92 (1H, br), 2.46-2.37 (2H, m), 2.19-2.00 (2H, m), 1.94-1.81 (2H, m), 1.78-1.49 (4H, m), 0.73 (3H, t, $J = 8.9\text{ Hz}$); ^{13}C NMR (75 MHz, CDCl_3): δ 214.8, 79.5, 40.2, 38.0, 30.0, 28.9, 22.4, 7.3.



*The mixture of oxidative cleavage of 2-ethyl-2-hydroxycyclohexanone (**I-1a** + **I-16a**):*

KHSO_5 (304 mg, 2 mmol) was added in one portion to a solution of 2-ethyl-2-hydroxycyclohexanone **I-16** (75 mg, 0.5 mmol) in methanol (5 mL) at room temperature. The reaction was stirred at RT for 18 h after which it was diluted with Et_2O (5 mL) and the precipitate (presumably unreacted KHSO_5 and byproduct KHSO_4 generated during the reaction) was filtered through a pad of Celite. The crude products were purified by silica gel column chromatography (15% EtOAc /hexanes) to furnish the mixture of diester **I-1a** and ketoester **I-16a** (48 mg, 50%) as a colorless oil.

Partial data for the mixture of **I-1a** and **I-16a**: ^1H NMR (300 MHz, CDCl_3): δ 3.61 (6H, s), 2.40-2.22 (4H+1.4H, m), 1.68-1.52 (4H+1.1H, m), 1.00 (0.86H, t, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 204.0, 171.9, 51.8, 41.9, 35.9, 34.0, 22.1, 21.7, 20.8, 14.3, 8.2.

I.8. References

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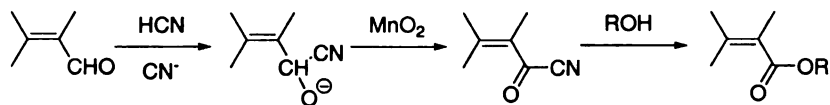
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CHAPTER II

MECHANISTIC STUDIES OF ALDEHYDES OXIDATION TO CARBOXYLIC ACIDS WITH OXONE

II.1. Introduction

Carboxylic acids and esters comprise an important group of synthetic targets in organic chemistry. The oxidation of aldehydes to carboxylic acids and esters is a very important transformation and, therefore, numerous methods have been well-developed. For example, transition metals such as Mn(VII), Cr(VI) and Ag(I) are good reagents to oxidize aldehydes to the corresponding carboxylic acids.¹⁻³ Buffered sodium chlorite is also a convenient oxidant.^{4,5} The reaction of conjugated aldehydes with MnO₂ in the presence of cyanide ion in an alcoholic solvent is a convenient method of converting aldehydes directly to esters.⁶ Several aldehydes were converted to the corresponding methyl esters in high yield (>85%) and it was demonstrated that the reaction sequence included the conversion of the conjugated aldehyde to the acyl cyanide, which is solvolysed under the reaction conditions (Scheme II-1).

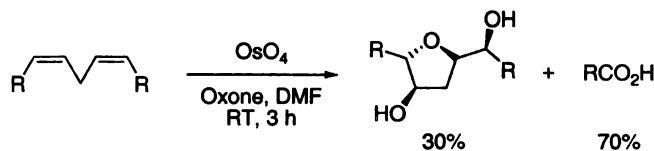


Scheme II-1: Oxidation of conjugated aldehydes to esters with MnO₂

As described in Chapter I, with interest in green chemistry, Oxone is an effective and rapidly growing “green reagent”. This is because of Oxone’s stability, ease of use, non-toxic nature, non-polluting byproducts, and cost effectiveness. Oxone is widely

II.1.1. Previous work of Oxone mediated oxidation of aldehydes

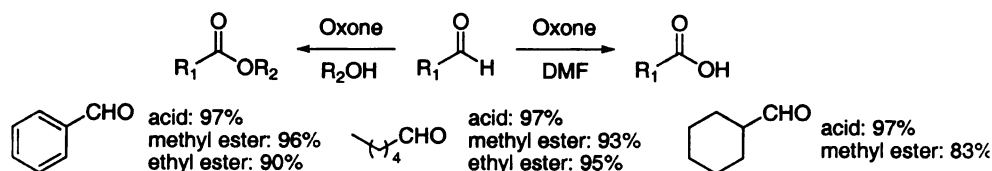
Our initial interest in this area involved the investigation of the oxidative cyclization of 1,4-dienes.¹¹ During this study it was observed that over-oxidation gave significant amounts of carboxylic acids as the major byproduct (Scheme II-2). This



provided the possibilities for further studies on oxidative cleavage of olefins, which could afford carboxylic acids directly from various kinds of olefins in high yield.¹² During this sequence, aldehydes were observed as the immediate oxidation products,

which were converted to the final isolable carboxylic acids. This led to an exploration of the direct oxidation of aldehydes to carboxylic acids under the same conditions.

In 2003, our group published an optimized protocol for the oxidation of aldehydes to the corresponding carboxylic acids. During the process a new route for the direct conversion of aldehydes to esters was also explored (Scheme II-3).¹³ This method is



Scheme II-3: Facile oxidation of aldehydes to acids and esters with Oxone

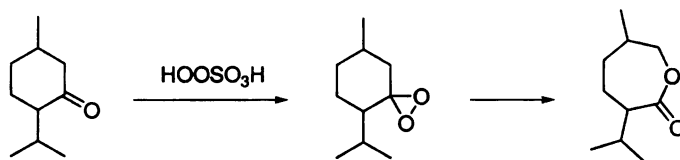
not only effective at converting aromatic aldehydes to carboxylic acids, but also useful for aliphatic substrates (see examples in Scheme II-3). The reactions are facile, high yielding, and easy to workup, providing a mild oxidative alternative for organic synthesis.

II.1.2. Previous mechanistic studies of Oxone mediated oxidation of aldehydes

In order to understand the details of the reaction, related mechanistic studies of Oxone mediated oxidation of aldehydes were initiated. Most of the results obtained were centered on the use of dimethyl dioxirane (DMDO) mediated oxidation.

II.1.2.1. History of dioxiranes

The first literature reference to a dioxirane was published by Baeyer and Villiger in a publication describing the Baeyer-Villiger rearrangement of a ketone.¹⁴ In this paper they suggested that in the conversion of the cyclic ketone to its corresponding lactone by monoperoxysulfuric acid, an intermediate dioxirane was generated (Scheme II-4).



Scheme II-4: The first report of a dioxirane by Baeyer and Villiger

During later study the competing mechanisms were also considered,¹⁵ but the original dioxirane pathway still could not be ruled out.

The first report of the preparation of dioxiranes was published in 1972.¹⁶ In this patent, perfluorodiethyldioxirane **II-1** and

chloro(difluoromethyl)(trifluoromethyl)dio

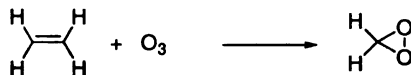
xirane **II-2** (Figure II-1) were prepared by



fluorine oxidation. Later on, ozonolysis at

Figure II-1: The first reported dioxiranes

low temperature provided a new example of dioxirane preparation.¹⁷⁻²⁰ In 1977 Lovas and coworkers reported that dioxirane was prepared via ozonolysis of ethylene at -130 to -75 °C (Scheme II-5).^{21, 22} Moreover, photo-oxidation using oxygen could also produce some dioxiranes.²³⁻²⁷



Scheme II-5: Ozonolysis of ethylene to prepare dioxirane

Nowadays, the most commonly used method for preparing dioxiranes is the oxidation of ketones by peracids, including Oxone.²⁸⁻³⁰ This methodology originated from a mechanistic study by Montgomery in 1974.³¹ In his paper, he introduced the idea that certain ketones enhanced the rate of decomposition of monoperoxysulfuric acid. Furthermore he found that some oxidation reactions are catalyzed by the

presence of ketones. It was obvious that the monoperoxysulfate anion was added to the ketone to generate an adduct, which acted as the oxidant in the reactions. Later on, Edwards, Curci and coworkers reported that the *in situ* generation of dioxiranes was responsible for the reactivity.³²⁻³⁵ Murray's group developed the procedure for isolation of the dioxiranes in 1985.²⁸ They have modified the *in situ* procedure so as to permit distillation of methyldioxiranes from the generation vessel containing Oxone and acetone. The dioxirane was obtained as a solution in the precursor ketone. The solution of dioxirane obtained in this way could be stored for several days in the freezer with little or no decomposition. The highest yield was obtained in the concentration ranging from 0.04 to 0.18 M. More sterically hindered ketones lead to decreasing yield of dioxirane.

II.1.2.2. Physical characteristics of dioxiranes

During previous studies, people used both physical and chemical methods to characterize the newly-developed oxidant dioxiranes. Lovas and Suenram prepared dioxirane by the ozone-ethylene system and characterized it by both mass spectrometry and microwave methods.²² They analyzed the data and found that the dioxirane has C-O and O-O bond lengths of 1.3878 and 1.5155 Å, respectively. Kuczkowski had earlier shown that ethylene ozonide has C-O and O-O bond lengths of 1.416 and 1.461 Å, respectively.^{36, 37} Thus the dioxirane has a shorter C-O bond and a longer O-O bond than the ozonide. These differences were attributed to the ring strain of the three-membered ring of dioxirane. The peroxide bond is the longest so far known,^{38, 39} which implies a rather unstable entity, easily undergoing homolysis of the O-O bond to

afford bisoxymethylene diradical ($\bullet\text{O-CR}_2\text{-O}\bullet$).

A weak $n\text{-}\pi^*$ absorption of different dioxiranes is exhibited in the UV region of 300-350 nm. This absorption extends into the visible region; hence generally the dioxiranes are pale yellow in color.^{29, 30, 40}

About the thermochemistry of dioxiranes, a number of theoretical analyses of the H_2CO_2 entity have been performed.⁴¹⁻⁵² The possible fates of the dioxirane after bond breaking include carbonyl oxide (**II-4**), peroxyethylene diradical (**II-5**), and bisoxymethylene diradical (**II-6**) (Figure II-2). Comparing the stability of these

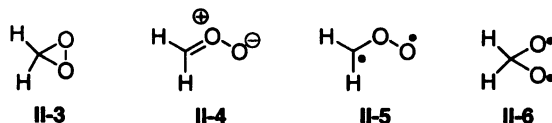


Figure II-2: Three possible fates of dioxirane thermo-bond breaking

formations, the energy diagram shown in Figure II-3 can be derived.²⁹ The most stable intermediate is the bisoxymethylene diradical (**II-6**), which indicates that the O-O bond is the weakest bond in the molecule.

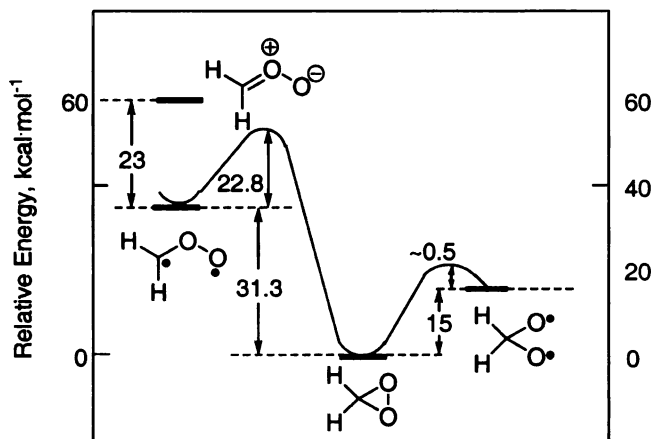


Figure II-3: Energy diagram of three possible fates of dioxirane

II.1.2.3. Chemical reactivity of dioxiranes

Both the *in situ* generated and the isolated dioxiranes are used in organic transformations. Epoxidations, heteroatom oxidations, and C-H insertion reactions are the best investigated oxidations using dioxiranes.^{28-36, 38-62} Dimethyl dioxirane (DMDO), obtained from acetone, displays impressive reactivity. It has been well-established as an extraordinary oxidizing reagent during the last decade. Figure II-4 summarizes the chemical reactivity of DMDO.²⁹ It is obvious to see that DMDO

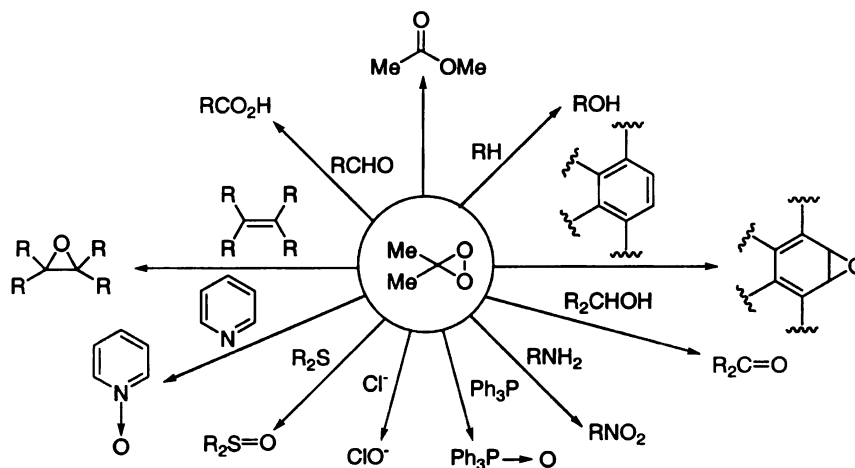
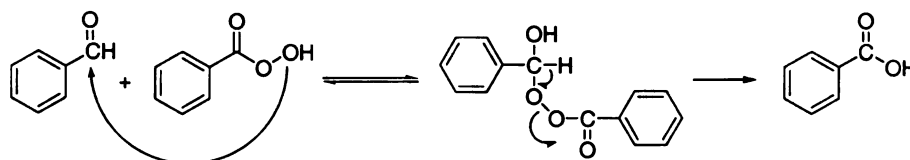


Figure II-4: Summary of dimethyl dioxirane (DMDO) mediated reactions

could rearrange to methyl acetate.²⁸ It is efficiently used to perform epoxidations of alkenes via oxygen atom transfer.^{28, 33-35, 54, 55, 61} DMDO is also known for its oxidation of alcohols,⁵⁹ nitrogen (amines, azo compounds, and pyridine),^{28, 30, 34, 40, 56, 58, 62} sulfur (sulfides),^{28, 30, 38, 60} chloride,^{31-33, 35} and phosphine.²⁸ In addition, effective insertions into C-H bonds of alkanes^{53, 54, 57, 59} and aldehydes²⁸ have been reported to give the corresponding alcohols and carboxylic acids as the products.

II.1.2.4. Previous mechanistic studies of Oxone mediated oxidation of aldehydes

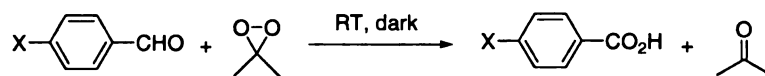
Early in 1969, Ogata and Sawaki reported kinetic studies on the oxidation of benzaldehyde with perbenzoic acid in H₂O-alcohol or H₂O-dioxane mixed solvents.⁶³ Later in 1972, they published a full paper and summarized all their results, suggesting a Baeyer-Villiger type mechanism for this reaction (Scheme II-6).⁶⁴ This study



Scheme II-6: Baeyer-Villiger type mechanism of benzaldehyde oxidation with perbenzoic acid reported by Ogata and Sawaki

suggested that the rate-determining step of the reaction can change depending upon the nature of the aldehyde substituents. In some cases, the carbonyl addition step was rate-determining, while in others, the hydride migration proved to be the slowest step.

Work by Baumstark and coworkers demonstrated that aromatic aldehyde oxidations promoted by DMDO (Scheme II-7) proceed through a radical mechanism.¹⁰ Here

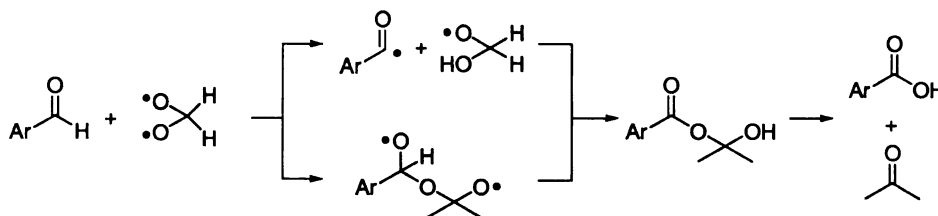


Scheme II-7: DMDO oxidation of aromatic aldehydes reported by Baumstark and coworkers

DMDO could either be distilled away from acetone and Oxone or made *in situ*. During their studies, the effect of molecular oxygen on the reaction was examined. They found that the reactions run under pure O₂ were faster than those open to the atmosphere. In the presence of O₂, aldehydes with electron-donating groups appeared to be more reactive than those with electron-withdrawing groups. However, under

argon, where DMDO was the sole oxygen-atom source, the yield of carboxylic acid seemed to depend on the stability of DMDO rather than the electronic nature of the aldehyde. Furthermore, the relative reactivity series suggests that the reaction would have a small, negative ρ value. This result is opposite from that obtained for the oxidation of substituted benzaldehydes by perbenzoic acid ($\rho = +1.2$).^{63, 64} Thus, mechanistically, the reaction appears to be unrelated to the Baeyer-Villiger reaction. Moreover, for the Baeyer-Villiger oxidation of *p*-anisaldehyde by perbenzoic acid, the aryl migration product *p*-methoxyphenol (obtained from hydrolysis of *p*-anisyl formate) is the major product under neutral or acidic conditions. However, no aryl migration is observed for the oxidation of the same substrate under inert atmosphere in the absence of light. The results clearly indicate that the DMDO-mediated oxidations do not occur via a routine Baeyer-Villiger mechanism.

A free-radical process has been suggested by Baumstark, as shown in Scheme II-8.¹⁰ Under inert atmosphere, the aldehydic hydrogen atom is abstracted by DMDO,

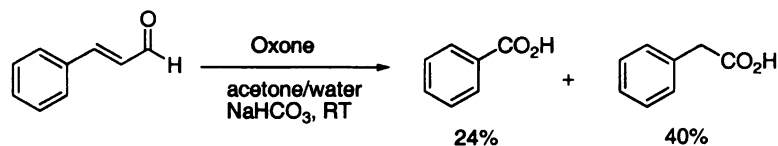


Scheme II-8: Free-radical mechanism of DMDO mediated oxidation of aromatic aldehydes

yielding a caged radical pair. The unstable “hemi-ketal” could then produce the carboxylic acid and acetone as the final products. Likewise, addition of DMDO to the carbonyl group followed by intramolecular hydrogen atom abstraction could give the same “hemi-ketal” intermediate of the observed products. The intermolecular

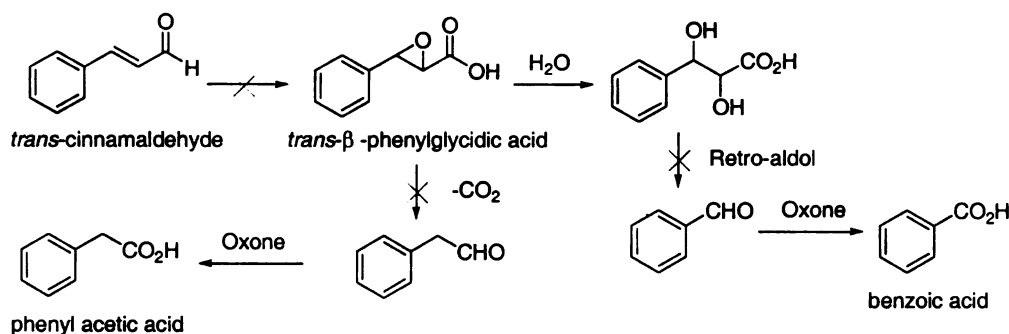
hydrogen abstraction route was consistent with the observation by Murray that ozonide was not produced during the oxidation of acetaldehyde.²⁸ Direct insertion of the oxygen-atom from DMDO or opening of the dioxirane to the carbonyl oxide²⁹ could not be ruled out, but seemed less likely.

Webb's oxidative protocol of aldehydes with Oxone in aqueous acetone or acetonitrile was said not be able to generate DMDO *in situ*.⁸ During their studies, they observed no significant difference in the oxidation rates in the presence or absence of acetone, which proved that DMDO was not generated during the sequence. More surprisingly, the oxidation of *trans*-cinnamaldehyde did not produce either *trans*-cinnamic acid or *trans*- β -phenylglycidic acid. The only products isolated with or without acetone were benzoic acid and phenyl acetic acid (Scheme II-9). In order



Scheme II-9: Webb's oxidative protocol

to elucidate the possible mechanism, they prepared an authentic sample of *trans*- β -phenylglycidic acid and subjected this material to their reaction conditions. They did not observe the formation of any benzoic acid or phenyl acetic acid (Scheme II-10).⁸ It was known that the epoxidation of the alkene to *trans*-cinnamaldehyde did not occur, which also proved no DMDO generation. But the details of the mechanism are still not clear and no further mechanistic interpretation has been provided in their paper. Additionally, Curini demonstrated that acetals could undergo oxidation to esters with Oxone.⁶⁵ However, further mechanistic studies were not pursued.



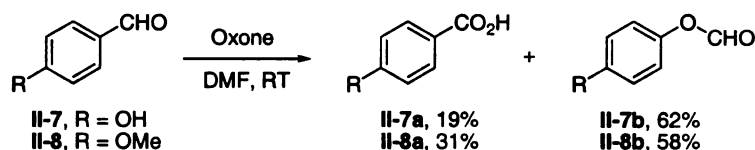
Scheme II-10: Mechanistic study of oxidation of *trans*-cinnamaldehyde

II.2. Initial Empirical Observations for the Mechanistic Investigation of Oxone

Mediated Aldehyde Oxidation

As discussed before, our methodology using Oxone in DMF or alcoholic solvents could prepare carboxylic acids or esters by directly oxidizing aldehydes.¹³ However, so far we have gained little mechanistic insight into the role of Oxone as the oxidant. Therefore, we have undertaken a mechanistic investigation for the conversion of aldehydes to carboxylic acids and esters using various analytical techniques and kinetic experiments.

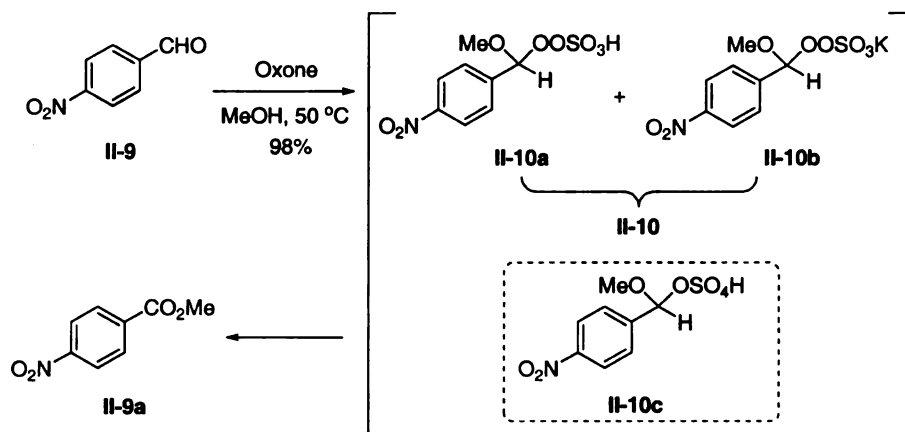
Several empirical observations stimulated us to pursue a mechanistic study of the Oxone mediated aldehyde oxidation process. Firstly, in the oxidation of electron rich aromatic aldehydes, i.e. 4-hydroxybenzaldehyde **II-7** and *p*-anisaldehyde **II-8**, the formate esters **II-7b** and **II-8b** were isolated as the major products in 62% and 58% yield, respectively (Scheme II-11).¹³ Baumstark demonstrated that if the oxidation proceeds through a free-radical mechanism, the phenolic products (obtained from



Scheme II-11: Oxone oxidation of electron rich aromatic aldehyde

hydrolysis of formate esters) could not be formed under inert atmosphere in the absence of light.¹⁰ In our oxidations of *p*-anisaldehyde with Oxone in DMF, the product ratio did not change in the absence of light and oxygen, which suggests that radicals are not generated in these reactions. In addition, this result is consistent with previous observations for the oxidation of electron rich aromatic aldehydes that are presumed to undergo a Baeyer-Villiger reaction where the phenolic products were obtained.⁸

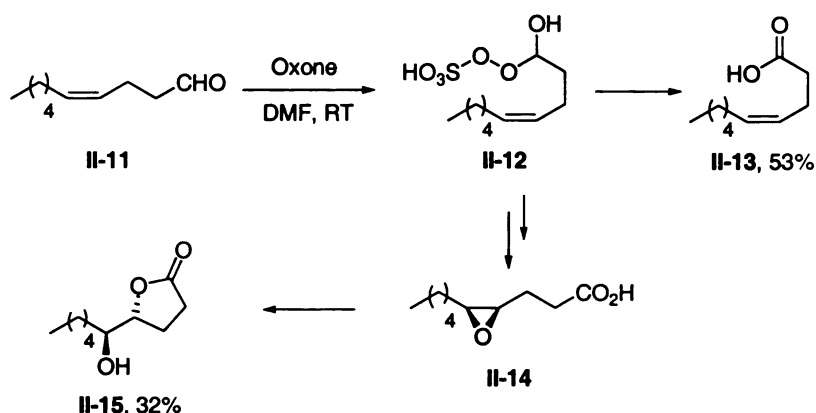
Secondly, oxidation of electron deficient aromatic aldehydes such as 4-nitrobenzaldehyde **II-9**, in the presence of methanol at room temperature provided a mixture of two products, presumably the acetals **II-10** (Scheme II-12).⁶⁶ These acetals



Scheme II-12: Intermediate acetal mixtures **II-10** in the oxidation of 4-nitrobenzaldehyde were not the monomethyl or dimethylacetal as confirmed by NMR experiments and were suspected to be peroxysulfate acetals. Increasing the reaction temperature from RT to 50 °C cleanly provided the desired methyl ester **II-9a**. In addition, subjecting the mixture of **II-10** to methanol at 50 °C did produce the desired ester **II-9a** along with some starting material **II-9**. The ¹H NMR of **II-10** suggested the presence of two different acetals (attempts to separate them by crystallization were not successful).⁶⁶

We found that careful column chromatography could provide two distinct acetals **II-10a** and **II-10b** in small quantities along with aldehyde **II-9** due to hydrolysis of **II-10** on the silica gel column. Treatment of those two compounds at 50 °C in MeOH showed that **II-10a** was converted to ester **II-9a** completely, while **II-10b** gave a 1:1 mixture of ester **II-9a** and aldehyde **II-9**. IR and ¹H NMR analysis also revealed that **II-10a** contained an OH group while **II-10b** did not. The IR spectra of these compounds also showed characteristic signals for nitro and sulfate. Raman spectroscopy did not give any useful information and all attempts to obtain single crystals were unsuccessful. The ¹H NMR shift of the benzylic methine proton in the proposed peroxysulfate acetal is in agreement with that of known peroxy acetals.^{67, 68} Therefore we propose that **II-10a** is the free acid while **II-10b** is the potassium salt. An alternative structure to **II-10a** could be the inverted peroxysulfate acetal **II-10c**, however, we believe that compound **II-10c** should not undergo clean conversion to **II-9a**. We suspect that the electron-withdrawing nitro group prevents the peroxysulfate acetal from undergoing a facile Baeyer-Villiger conversion.

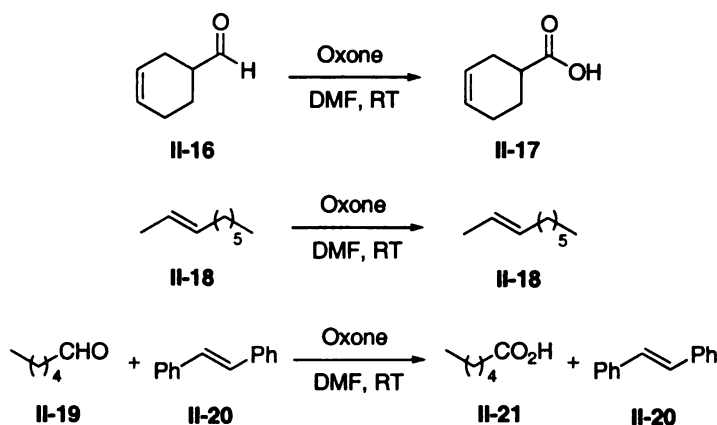
The third observation was that the conversion of *cis*-4-decenal **II-11** yielded significant amounts of the γ -lactone by-product **II-15** (Scheme II-13).⁶⁶ It was surprising to find this by-product and we subsequently investigated its origins. It was well known that Oxone is not an epoxidizing reagent under the utilized reaction conditions. Scheme II-14 shows several examples confirming that olefins are inert to Oxone-mediated oxidation conditions. For example, oxidation of 1,2,3,6-tetrahydrobenzaldehyde **II-16** afforded 1,2,3,6-tetrahydrobenzoic acid **II-17** as



Scheme II-13: Intramolecular epoxidation of *cis*-4-decenal to provide γ -lactone

the pure product. Subjecting 2-nonene **II-18** to Oxone under identical reaction conditions did not yield any epoxide, and the starting material was recovered quantitatively. Furthermore, epoxides were not observed in the oxidation of hexanal **II-19** with the presence of *trans*-stilbene **II-20**.⁶⁶

Based on the aforementioned results, the lactone **II-15** is certainly not derived from



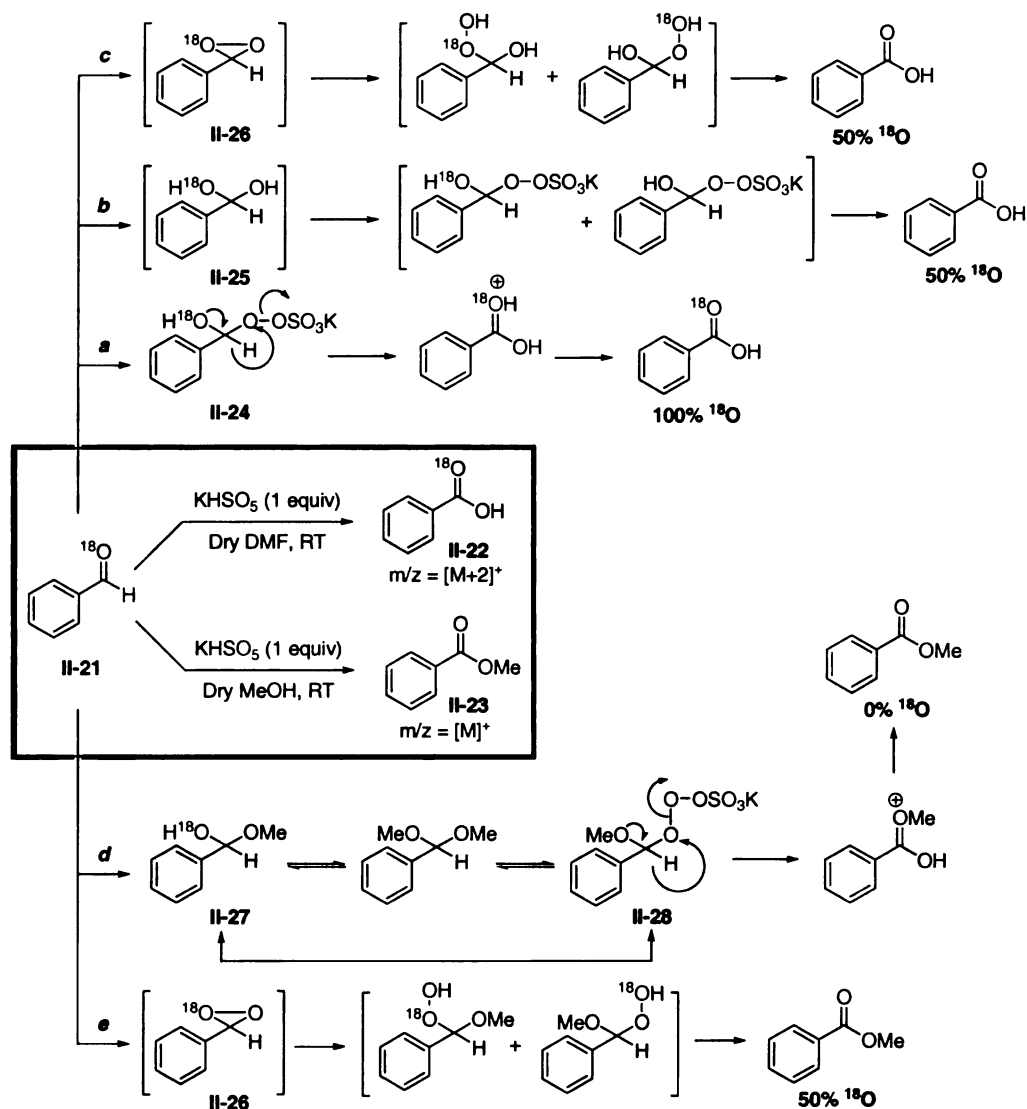
Scheme II-14: Oxone does not epoxidize olefins under the reaction conditions

an intermolecular epoxidation event (Scheme II-13). However, based on the stereochemistry of the product, the lactone is most probably produced from the intramolecular ring opening of an intermediate epoxide. It is hypothesized that an intermediate peroxy species **II-12** could intramolecularly epoxidize the olefin, which

proceeds through a cyclization to form the lactone **II-15** (Scheme II-13). Similar intramolecular epoxidations have been observed by Corey and coworkers in unsaturated fatty peroxyacids.⁶⁹

II.3. Isotope Labeling and NMR Analysis for Mechanistic Studies

In order to understand the mechanism of the oxidation of aldehydes to carboxylic acids and esters, the oxidation of ¹⁸O-labeled benzaldehyde to benzoic acid and methyl benzoate was studied and the products were analyzed by mass spectrometry. ¹⁸O-labeled aldehyde **II-21** was prepared directly from ¹⁸O-labeled water and benzaldehyde,⁷⁰ and was used in oxidation with 1 equiv of anhydrous KHSO₅.⁷¹ Scheme II-15 shows the possible routes for the oxidation of an aldehyde to carboxylic acid (route *a*, *b*, and *c*) and ester (route *d* and *e*). If the oxidation of benzaldehyde to benzoic acid involves either the formation of the hydrate **II-25** of the aldehyde (route *b*) or the dioxirane **II-26** (route *c*), the isolated product benzoic acid would contain 50% of the original ¹⁸O-label. However, the nucleophilic attack of benzaldehyde with Oxone in route *a* and subsequent Baeyer-Villiger rearrangement of intermediate **II-24** would lead to benzoic acid with full retention of the ¹⁸O-label. The isolated benzoic acid **II-22**, obtained from the oxidation of the ¹⁸O-labeled benzaldehyde in DMF with KHSO₅, was analyzed by GC/MS and was shown to have fully retained the ¹⁸O-label. This result suggests that route *a* shown in Scheme II-15 as the most possible path for the aldehyde oxidation.



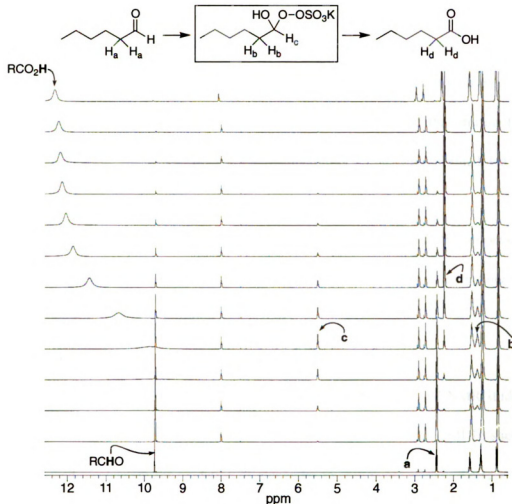
Scheme II-15: Oxidations of ^{18}O labeled benzaldehyde

Similarly, the oxidation of benzaldehyde to methyl benzoate was investigated with the ^{18}O -labeled aldehyde II-21.⁶⁶ In the previous studies, it was demonstrated that the route to esters could not simply go through a Fischer esterification of the acid in the bulk alcoholic solvent by subjecting a carboxylic acid to the reaction conditions (Oxone and ROH) and quantitatively isolating the starting material. The formation of the esters should proceed through a direct pathway. In the oxidations with MeOH, as in

previous examples, the intermediate dioxirane **II-26** (route *e*) would lead to the methyl ester with 50% of the original ^{18}O -label (Scheme II-15). However, formation of the hemiacetal, and either the direct conversion to peroxide **II-28**, or its formation through the dimethyl acetal, followed by a Baeyer-Villiger rearrangement would yield the product with no ^{18}O -label left (route *d*). The oxidation of ^{18}O -labeled benzaldehyde was performed with 1 equiv KHSO_5 in dry methanol, and the isolated methyl benzoate **II-23** was analyzed by GC/MS. The product did not exhibit any $[\text{M}+2]^+$ peak, which suggested that route *d* was operational for this oxidative esterification.

Further proof for the suggested mechanisms are provided through low temperature NMR studies. Oxidations of hexanal in d_7 -DMF at 10 °C were carried out using purified anhydrous KHSO_5 .⁷¹ Figure II-5 shows a series of NMR traces collected during the oxidation of hexanal in d_7 -DMF. As expected, the evolution of product signals is counterbalanced with the disappearance of signals from hexanal. However, there are also a set of transient signals H_b and H_c that build up in concentration as the reaction progresses. The transient signal H_c at $\delta = 5.51$ ppm is assigned to the hemiacetal proton of the intermediate peroxy species. This chemical shift of the methine in peroxy intermediate correlates well with the expected shift for hemiacetals.^{67, 72} The transient signal H_b also falls within the expected region for a methylene adjacent to a hemiacetal.^{67, 72} The upfield shift of H_a to H_b indicates that after the formation of the peroxy intermediate, the carbonyl functionality has disappeared. On the contrary, the downfield shift of H_b to H_d indicates the regeneration of the carbonyl group, as a carboxylic acid. In addition the integration

ratio of $H_b : H_c$ is 2:1 as expected.



^a Oxidation of hexanal in d_7 -DMF with Oxone at 10 °C (10 min elapsed between each spectrum) exhibits transient signals **b** and **c** that are assigned to the α -methylene and the hemiacetal proton of the boxed intermediate, respectively.

Figure II-5: NMR study of hexanal oxidation^a

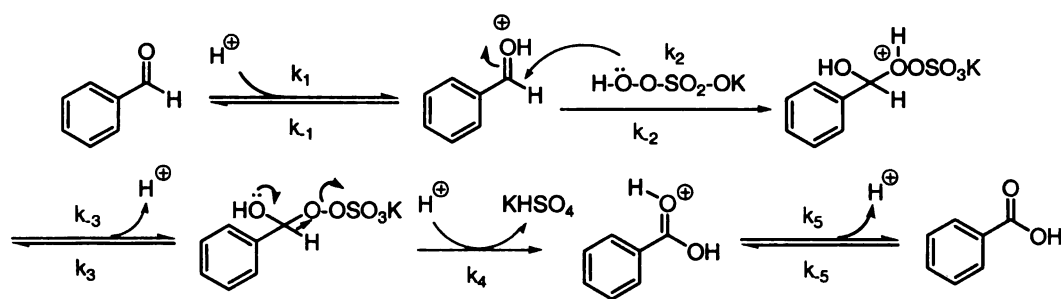
A similar transient signal was observed in the oxidation of benzaldehyde in d_7 -DMF at $\delta = 6.63$ ppm, which was assigned to the benzylic proton of the corresponding peroxy hemiacetal **II-24** (as shown in Scheme II-15).⁶⁶ Since the oxidation of benzaldehyde is facile, there was little accumulation of the intermediate species as can be seen in the oxidation of hexanal. From the previous results, it was known that

aromatic aldehydes with electron-withdrawing groups such as 4-nitrobenzaldehyde showed much slower conversion to the product. Therefore we carried out the oxidation of this substrate in d_7 -DMF and anhydrous pure KHSO_5 at 10°C . A transient signal at $\delta = 6.77$ ppm was observed which was significantly stronger as compared to that in benzaldehyde. All of these results showed that during this oxidation reaction, the active peroxy intermediate was successfully formed via an addition of KHSO_5 to aldehyde.

All work related to the isotope labeling and NMR analysis of the KHSO_5 promoted aldehyde oxidation was performed by Benjamin R. Travis, a PhD graduate from the Borhan laboratory, in collaboration with myself.

II.4. Kinetic Studies

All the previous empirical observations and subsequent isotope and NMR studies have led us to suggest a mechanism for this oxidation reaction. Scheme II-16 shows the proposed mechanism for oxidation of aldehydes to carboxylic acids. There is an



Scheme II-16: Proposed mechanism for oxidation of aldehydes to carboxylic acids

initial nucleophilic attack with KHSO_5 on the protonated carbonyl group of the aldehyde, which further promotes a Baeyer-Villiger rearrangement to the corresponding protonated carboxylic acid. The following deprotonation then provides the desired

final product. Furthermore, by using KHSO_5 in its pure form we can reasonably suggest that neither radicals nor dioxiranes are involved in this mechanistic process.

We have proposed a Baeyer-Villiger type mechanism. In order to verify this conclusion we undertook a kinetic study of this oxidation, initially using our most straightforward example with benzaldehyde and pure KHSO_5 . Chemical kinetics deal with the rate at which chemical reactions proceed, which can help us to understand the details of the chemical process.

II.4.1. Rate law

Generally, the first goal of a kinetic study is to determine the rate law of the reaction. A rate law is a mathematical statement of how the reaction rate depends on concentration.⁷³⁻⁷⁸

$$v = f(\text{concentration})$$

In a large number of reactions the rate law is found to depend on a simple power of the concentrations of the reactants. For example:

$$v = k [\text{A}]^x [\text{B}]^y [\text{C}]^z$$

The proportionality constant (k) is called the rate constant; the manner by which the reaction velocity was defined ensures that k will always be a positive number. The exponents (x , y , and z) define the order of reaction; for example, if $x = 1$, the reaction is said to be first order in reactant A. The sum of the exponents, $x + y + z$, is the overall order of the reaction. For the determination of the rate law, the experimental methods do not measure the real rates but, instead, concentrations as a function of time, $C(t)$. Therefore, we first have to make a connection between the derivative, dC / dt , that

enters into the rate law and $C(t)$. There are various methods to determine the rate law of the reaction. Two widely used methods are the initial-rate method and the isolation method.

The initial-rate method is useful when the concentration of more than one reactants enter into the rate law. For example, consider the reaction:



Then the rate law of the reaction is:

$$v = k[A]^x[B]^y$$

If the initial concentration of A is $[A_0]$, and of B is $[B_0]$, the initial rate is:

$$v_0 = k[A_0]^x[B_0]^y$$

$$\ln v_0 = \ln k + x \ln [A_0] + y \ln [B_0]$$

Since $[A_0]$ and $[B_0]$ can be varied independently, x and y can be both determined.

The isolation method is the most widely used strategy. In this method we choose the initial conditions so that the reactant A is present in a concentration much lower than all other reactants, that is, we “isolate” A from the system with the other reactants. The result is that only the concentration of A changes significantly during the reaction and the changes of the concentration of other reactants can be ignored. Thus the rate law takes the simplified form as:

$$v = k[A]^x[B_0]^y = k_{obs}[A]^x$$

x is determined as described previously, and the effective rate constant k_{obs} is $k[B_0]^y$.

By varying the initial concentration $[B]_0$ in two runs (numbered 1 and 2) we can obtain

$$k_{1obs} / k_{2obs} = ([B_{01}] / [B_{02}])^y$$

The only unknown in this expression is y which therefore can be determined.

For the general reactions, we can get the integrated rate law as following:

1) First-order reactions:

$$v = -(d[A] / dt) = k[A]^1$$

The variables $[A]$ and t are separated and integrated from $t = 0$, $[A] = [A_0]$:

$$\int_{[A_0]}^{[A]} (d[A] / [A]) = -k \int_0^t dt$$

The result can be expressed in various ways:

$$\ln ([A_0] / [A]) = kt$$

$$\ln [A] = \ln [A_0] - kt$$

It is obvious that the first-order rate constant has units of $[\text{time}]^{-1}$ and is independent of the units used for $[A]$. If one plots $\ln[A]$ vs. t , the result should be a straight line with the slope as the rate constant k .

2) Second-order reaction:

$$v = -(d[A] / dt) = k[A]^2$$

The equation is integrated from $t = 0$, $[A] = [A]_0$:

$$\int_{[A_0]}^{[A]} (d[A] / [A])^2 = -k \int_0^t dt$$

The results give:

$$1/[A] = 1/[A_0] + kt$$

The second-order rate constant must have units of $[\text{concentration}]^{-1}[\text{time}]^{-1}$; a typical choice is $\text{L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$. When $1/[A]$ is plotted vs. t , the result should also be the straight line with the slope as the rate constant k .

Based on these methods, it is required to determine the concentration of reactants at

different times. To accomplish this, GC analysis was used to determine concentrations. The standard curves of benzaldehyde and benzoic acid were obtained by plotting different known concentrations vs. corresponding integral area of the peaks. Using these standard curves, any concentration could be acquired after GC experiments at different reaction time.

At the very beginning, the ratio of the reactants was changed and the concentration of benzaldehyde at different time was detected by using GC analysis. Both $1/[\text{PhCHO}]$ vs. reaction time and $-\ln[\text{PhCHO}]$ vs. reaction time were plotted. But neither of them gave a straight line ($R < 0.8$). Therefore it was decided to follow the isolation method. Since GC analysis was used to detect the concentration of benzaldehyde, the concentration of KHSO_5 needed to be in greater excess as compared to the concentration of benzaldehyde. However, the solubility of KHSO_5 in DMF, which is the solvent for this oxidation, is only 100 mg/mL. Considering this low solubility, in order to maintain great excess of KHSO_5 (at least 30 times) than the benzaldehyde concentration, the required concentration of benzaldehyde was too small to obtain the precise integration of peaks from the GC. Therefore, it was apparent that GC analysis was not a good method for this study.

A more appropriate analytical method for the determination of the reactant concentration appeared to be UV spectrophotometry.⁷⁸ The absorption of benzaldehyde is $\lambda = 226 \text{ nm}$, $\epsilon = 9,800 \text{ M}^{-1}\cdot\text{cm}^{-1}$. Using the isolation method, the concentration of benzaldehyde at different times could be calculated from its UV absorbance. The obtained concentration were plotted as both $1/[\text{PhCHO}]$ and

$-\ln[\text{PhCHO}]$ vs. reaction time. However, it was still hard to obtain a reasonable rate law. The problem was due to the DMF solvent, which has a broad absorbance between 200 nm and 280 nm. Therefore, it was still inaccurate to obtain the precise concentration of benzaldehyde from its absorbance.

II.4.1.1. Iodometric method to determine the pseudo-order of KHSO_5

Notably, another general method used in the kinetic study of oxidation reactions is the iodometric method.⁷⁹⁻⁸³ Chandramohan and coworkers reported the kinetic and mechanistic study of the oxidation of indole-3-acetic acid with Oxone.⁸⁰ They succeeded in using the iodometric method to obtain the kinetic measurements. In addition, this method has been used in determining the purity of KHSO_5 .⁷¹ The new kinetic studies were carried out under pseudo-first-order conditions with a large excess of benzaldehyde with respect to dry KHSO_5 at 298 K. Reactions were followed by determining the unreacted KHSO_5 as a function of time with the iodometric method. The unreacted KHSO_5 was quenched by KI and the liberated iodine was titrated against a standard sodium thiosulphate solution with starch as the indicator.^{80, 83}

In addition, during the kinetic studies, it was found that acid had an effect on the reaction. Table II-1 shows that the rate constant (calculated as pseudo-first-order in

Table II-1: Effect of added acid on the rate constant

Concentration of TsOH (mol/L)	Rate Constant (s^{-1})
0	0.0359
0.001	0.0297
0.005	0.0545
0.010	0.0586
0.015	0.0704

KHSO₅) increases significantly when more amounts of *p*-toluenesulfuric acid was added into the reaction. This result indicates that in order to keep pseudo-first-order conditions for KHSO₅, great excess of acid needs to be added to the solution. In this kinetic study, sulfuric acid was chosen as the acid additive because it has the same anion as the byproduct KHSO₄ and it has no ionic effect on the reaction.

Using the initial-rate method to calculate the kinetic data obtained from iodometric titration, it is believed that this reaction is pseudo-first-order in KHSO₅. Table II-2 and Figure II-6 shows the initial-rate method for the determination of the reaction order

Table II-2: Initial-rate method for determining the order of KHSO₅^a

10 ² Initial [KHSO ₅] ₀ (mol/L)	10 ⁴ Initial Rate <i>v</i> ₀ (mol/L•s ⁻¹)	ln [KHSO ₅] ₀	ln <i>v</i> ₀
0.8269	0.4929	-4.79524	-9.91779
1.273	0.7361	-4.36379	-9.51673
1.628	0.9333	-4.11782	-9.27937
2.186	1.194	-3.82310	-9.03303
2.789	1.617	-3.57949	-8.72977

^a[PhCHO] = 2.50 mol/L, [H₂SO₄] = 1.00 mol/L, solvent is pure DMF, T = 298 K

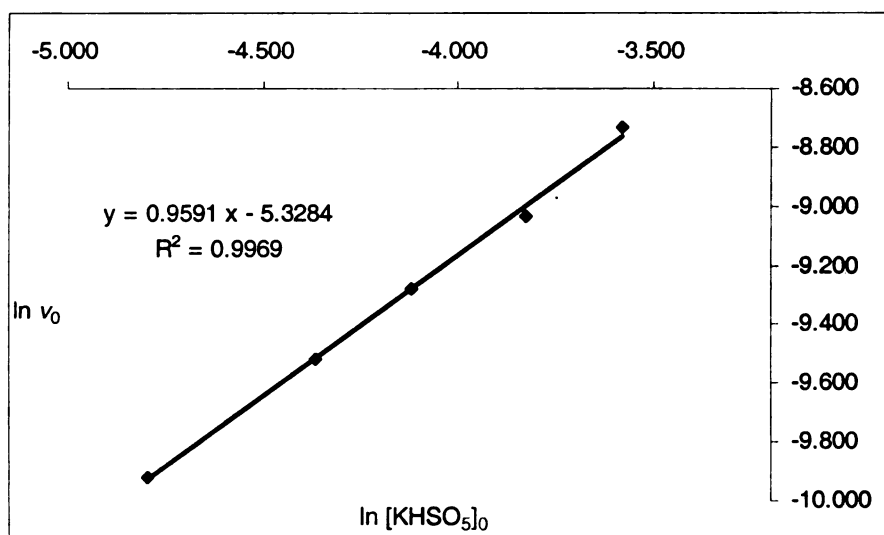


Figure II-6: Initial-rate method for determining the order of KHSO₅

for KHSO_5 . Here the initial rate v_0 can be found by plotting $[\text{A}]$ vs. t and drawing the tangent line at $t = 0$. The plot gives a straight line with R equal to 0.9984, and the slope of 0.9591. Based on the previous equation:

$$\ln v_0 = x \ln [\text{A}_0] + \ln k$$

the slope of the plot is the value of x , which shows a perfect match for a pseudo-first-order reaction in KHSO_5 . In addition, based on the equation

$$\ln [\text{A}] = -k_{\text{obs}}t + \ln [\text{A}_0]$$

the plot of $\ln [\text{KHSO}_5]$ vs. reaction time t should give a straight line with a negative slope, where the absolute value of the slope is the observed rate constant. Table II-3 shows that different initial concentration of KHSO_5 does not affect the observed rate constant k_{obs} . This also proves that the reaction is pseudo-first order in KHSO_5 .

Table II-3: Observed rate constant with different initial concentrations of KHSO_5

$10^2 [\text{KHSO}_5]_0$ (mol/L)	10^3 Rate Constant k_{obs} (s^{-1})
0.8269	5.51
1.273	5.34
1.628	5.88
2.186	5.69
2.789	5.88

II.4.1.2. Iodometric method to determine the order of benzaldehyde

Based on the success of obtaining the order of KHSO_5 using iodometric titration, the same method was used for determining the reaction order in benzaldehyde. In order to find the order of benzaldehyde, we kept the concentration of KHSO_5 at the same value, which was much lower than that of benzaldehyde and sulfuric acid, and vary the concentration of benzaldehyde. With only $[\text{PhCHO}]$ changed, we can

evaluate the apparent rate constant that corresponds to a new value of [PhCHO].

Since the isolation method gives the equation

$$v = k[A]^x[B_0]^y = k_{obs}[A]^x$$

then

$$k_{obs} = k[B_0]^y$$

$$k_{obs}' = k[B_0']^y$$

The ratio of k_{obs} and k_{obs}' can help to obtain the order of reactant B:

$$k_{obs}/k_{obs}' = ([B_0]/[B_0'])^y$$

$$\ln(k_{obs}/k_{obs}') = y \ln([B_0]/[B_0'])$$

By plotting $\ln k_{obs}$ vs. $\ln [PhCHO]_0$, a straight line is obtained (Table II-4 and

Table II-4: Determination of the order of benzaldehyde^a

Initial [PhCHO] ₀ (mol/L)	10 ³ Rate Constant k_{obs} (s ⁻¹)	$\ln [PhCHO]_0$	$\ln k_{obs}$
0.500	0.744	-4.79524	-9.91779
1.000	2.03	-4.36379	-9.51673
1.500	2.82	-4.11782	-9.27937
2.000	3.22	-3.82310	-9.03303
2.500	5.88	-3.57949	-8.72977

^a[KHSO₅] = 0.015 mol/L, [H₂SO₄] = 1.00 mol/L, solvent is pure DMF, T = 298 K

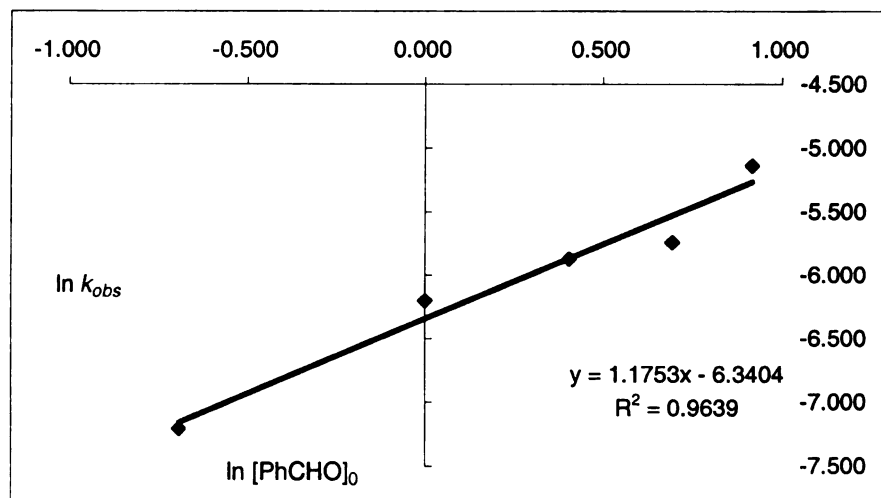


Figure II-7: Determination of the order of benzaldehyde

Figure II-7). The plot gives R equal to 0.9818, with a slope of 1.1753, suggesting a pseudo-first order rate for benzaldehyde.

II.4.1.3. Iodometric method to determine the order of acid.

Using exactly the same method used for determining the order of benzaldehyde, the effect in changing the concentration of acid was investigated. Based on the same equation

$$\ln (k_{obs}/k_{obs}') = y \ln ([C_0]/[C_0'])$$

Table II-5: Determination of the order of sulfuric acid^a

Initial [H ₂ SO ₄] ₀ (mol/L)	10 ³ Rate Constant <i>k_{obs}</i> (s ⁻¹)	ln [H ₂ SO ₄] ₀	ln <i>k_{obs}</i>
0.3068	4.280	-1.18156	-5.4538
0.3049	4.326	-1.18777	-5.44311
0.5009	4.711	-0.69135	-5.35786
0.6034	4.251	-0.50517	-5.46060
0.7513	4.472	-0.28595	-5.40992
1.0007	5.124	0.00070	-5.27382
1.2506	4.998	0.22362	-5.29872
1.5031	5.516	0.40753	-5.20010

^a[KHSO₅] = 0.010 mol/L, [PhCHO] = 2.50 mol/L, solvent is pure DMF, T = 298 K

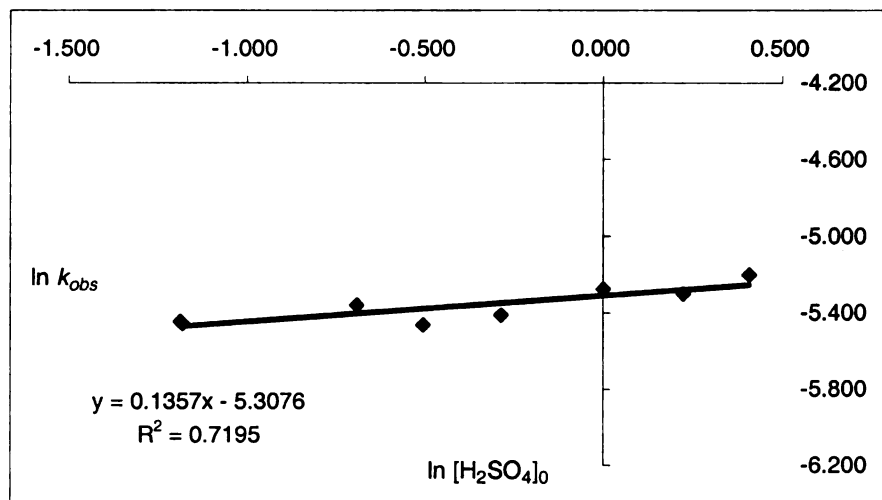


Figure II-8: Determination of the order of sulfuric acid

plotting $\ln k_{obs}$ vs. $\ln [\text{H}_2\text{SO}_4]_0$, affords a straight line (Table II-5 and Figure II-8). The plot gives a flat line with the slope equal to 0.1357. Since the order of sulfuric acid is the slope of this graph, which is close to 0, this reaction was found to be pseudo-zero-order with respect to acid.

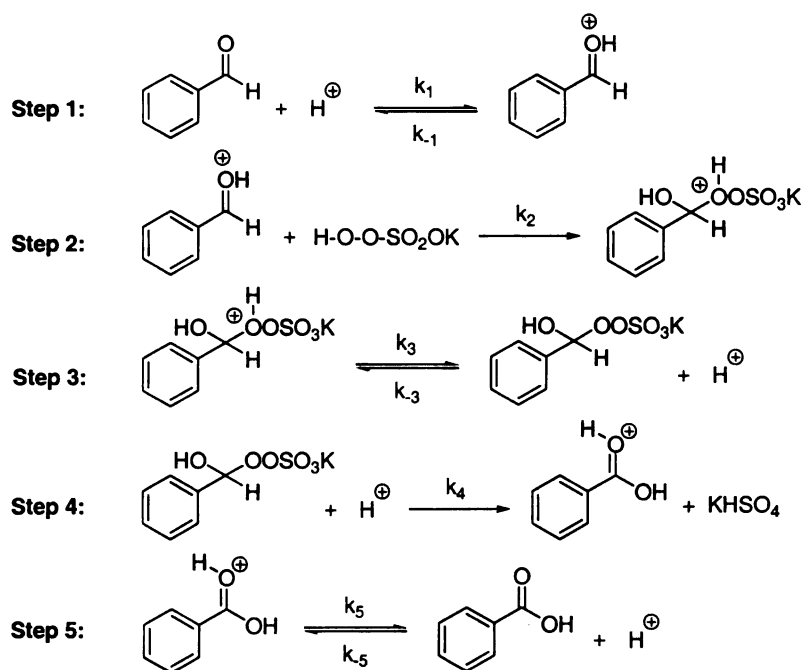
II.4.1.4. Discussion: rate law determines the rate-determining step in the sequence

Analysis of the kinetic data revealed that the oxidation of benzaldehyde by KHSO_5 is first-order in both substrates, PhCHO and KHSO_5 , and zero-order in acid additive. It is therefore in accordance with the observation, that the rate law for the disappearance of KHSO_5 is given as follows:

$$-d [\text{KHSO}_5] / dt = k [\text{KHSO}_5] \cdot [\text{PhCHO}]$$

where k is a second-order rate constant.

The rate law provides the information that both KHSO_5 and aldehyde are involved in the rate-determining step. In our proposed mechanism (Scheme II-17), the step containing both KHSO_5 and aldehyde is step 2, with step 1 being a preequilibrium. This demonstrates that the nucleophilic attack with KHSO_5 on the aldehyde carbonyl group is the rate-determining step in the reaction. This conclusion compares favorably with the original kinetic work of Friess and Soloway, who postulated that the formation of the peroxy hemiacetal intermediate was slow and constituted the rate-determining step.⁸⁴



Scheme II-17: Proposed mechanism of aldehyde oxidation with KHSO_5

In addition, the previous work shows that the statements on the kinetics of the Baeyer-Villiger reaction should take into account the acidity of the reaction solution.⁸⁴⁻⁸⁸ Table II-1 also shows that our reaction rate increases with an increase in the concentration of acid additive, which is the evidence of acid catalysis of the reaction. Since the acid is not involved in the rate-determining step, the reaction is categorized as the specific acid catalysis (specific acid catalysis occurs when proton transfer is not rate determining, while general acid catalysis occurs when proton transfer is rate determining^{89, 90}). Therefore, it is believed that there is a rapid protonation equilibrium with respect to other reactants under the present experimental conditions, which is in accordance with our proposed mechanism. With excess acid in the reaction, the protonation of benzaldehyde is in the rapid equilibrium, which has no effect on the reaction rate. However, if the concentration of acid is low, the

protonation equilibrium can be in competition with the nucleophilic attack.

II.4.2. Temperature effects

Rate constants strongly depend on temperature, typically increasing rapidly with increasing temperature. A rough rule for many reactions in solution is that near room temperature k doubles for each 10 °C increase in temperature.⁷⁵ In 1878, Hood was first attempted to develop an empirical equation to describe the dependence of the rate constant k upon the reaction temperature T .⁷⁴ In 1889, Arrhenius gave a theoretical justification for Hood's equation, which was generally accepted and known as the Arrhenius equation:^{74, 75}

$$k = A e^{-E_a / RT}$$

or

$$\ln k = \ln A - E_a / RT$$

where A and E_a are constants characteristic of the reaction. E_a is the Arrhenius activation energy and A is the pre-exponential factor, which can be determined using graphical or analytical methods. The rapid increase in k as T increases is mainly due to the increase in the number of collisions whose energy exceeds the activation energy.

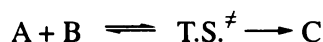
The nature of the rate constant k can be discussed in terms of transition-state theory.⁹¹ This is the general theory for analyzing the energetic and entropic components of a reaction process. In transition-state theory, a reaction is assumed to involve the formation of an activated complex that goes on to product at an extremely rapid rate. The rate of decomposition of the activated complex has been calculated from the assumptions of the theory to be $6 \times 10^{12} \text{ s}^{-1}$ at room temperature and is given by the expression:⁹²⁻⁹⁵

$$\text{rate of activated complex decomposition} = \frac{\kappa kT}{h}$$

in which κ is the transmission coefficient, which is usually taken to be 1; k is Boltzmann's constant; h is Planck's constant, and T is absolute temperature. The rate of reaction is thus given by the following expression:

$$\text{rate of reaction } \nu = \frac{\kappa kT}{h} [\text{activated complex}]$$

If the activated complex is considered to be in equilibrium with its component molecules, the formation of transition state (T.S.[‡]) can be shown as a bimolecular reaction:



which has the equilibrium constant equal to

$$K^{\ddagger} = \frac{[\text{T.S.}^{\ddagger}]}{[A][B]}$$

This equilibrium is related to the free energy required for attainment of the transition state. Here the double-dagger superscript ([‡]) is used to specify that the process under consideration involves a transition state or activated complex. Thus the thermodynamic formulation of transition-state theory begins by defining the standard free-energy change for the formation of the activated complex:

$$\Delta G^{\ddagger} = -RT \ln K^{\ddagger}$$

This free-energy is referred to as the free-energy of activation. Combining all the equations, the rate of the reaction is given by

$$\text{rate of reaction } \nu = \frac{\kappa kT}{h} [\text{T.S.}^{\ddagger}] = \frac{\kappa kT}{h} K^{\ddagger} [A][B]$$

Since the equilibrium constant:

$$K^{\ddagger} = e^{-\Delta G^{\ddagger} / RT}$$

$$v = \frac{\kappa kT}{h} e^{-\Delta G^\ddagger / RT} [A][B]$$

Comparison with the expression for the rate of any one-step reaction

$$v = k_r[A][B]$$

reveals that the magnitude of $\Delta G^\ddagger$ will be the factor that determines the magnitude of k_r at any given temperature:

$$k_r = \frac{\kappa kT}{h} e^{-\Delta G^\ddagger / RT}$$

The standard free energy for the formation of the activated complex can be separated into enthalpic and entropic contributions with:

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

Thus the temperature dependence of reaction rate has the relationship with the enthalpy and entropy components of the free energy of activation:

$$k_r = \frac{\kappa kT}{h} (e^{-\Delta H^\ddagger / RT})(e^{-\Delta S^\ddagger / R})$$

The term $\frac{\kappa kT}{h} (e^{-\Delta S^\ddagger / R})$ varies only slightly with changing T compared to the term $e^{-\Delta H^\ddagger / RT}$ because of the exponential nature of the latter. To a good approximation, we can assume the term $\frac{\kappa kT}{h} (e^{-\Delta S^\ddagger / R})$ does not change with varying the temperature.

Therefore:

$$\frac{k_r}{T} = \text{Constant} \cdot e^{-\Delta H^\ddagger / RT}$$

$$\ln \frac{k_r}{T} = \frac{-\Delta H^\ddagger}{RT} + \text{Constant}$$

If we plot $-\ln(k_r/T)$ vs. $1/T$, there would be a straight line with the slope equal to $\Delta H^\ddagger/R$.

Once $\Delta H^\ddagger$ is determined in this manner, $\Delta S^\ddagger$ is available from the relationship

$$\Delta S^\ddagger = \frac{\Delta H^\ddagger}{T} + R \ln \frac{h k_r}{\kappa kT}$$

$$\frac{\Delta S^\ddagger}{R} = \frac{\Delta H^\ddagger}{RT} + \ln \frac{k_r}{T} + \ln \frac{h}{\kappa k}$$

$$\ln \frac{k_r}{T} = -\frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R} - \ln \frac{h}{\kappa k}$$

Hence the intercept of the same plot of $-\ln (k_r/T)$ vs. $1/T$ is $\frac{\Delta S^\ddagger}{R} - \ln \frac{h}{\kappa k}$.

II.4.2.1. Effects of temperature

From these deductions, analysis of the rate constant at different temperatures could help us to determine both the enthalpy of activation and entropy of activation. The temperature study between 261 K and 327 K revealed a significant increase in rate as the temperature increased. Higher temperature was not evaluated due to the instability of the oxidant, KHSO_5 , at elevated temperatures. Table II-6 depicts the rate constant at various temperatures and Figure II-9 is the plot of $-\ln (k_r/T)$ vs. $1/T$, which gives a good straight line with R equal to 0.9841.

The enthalpy of activation ($\Delta H^\ddagger$) is calculated from the slope of the plot shown in Figure II-8. Since the slope (m) of the plot is equal to $\Delta H^\ddagger/R$, the enthalpy of activation is:

$$\Delta H^\ddagger = R \times m = 8.314 \times 3.773 \times 10^3 = 31.37 \times 10^3 \text{ J}\cdot\text{mol}^{-1}$$

which means

$$\Delta H^\ddagger = 31.37 \text{ KJ}\cdot\text{mol}^{-1}$$

The entropy of activation ($\Delta S^\ddagger$) is calculated from the intercept of the same plot.

Since the intercept (y) of the plot is equal to $\frac{\Delta S^\ddagger}{R} - \ln \frac{h}{\kappa k}$, the entropy of activation is:

$$\Delta S^\ddagger = R \times [\ln(h/\kappa k) + y]$$

$$= 8.314 \times [\ln (6.626 \times 10^{-34} / 1.38 \times 10^{-23}) - 1.583]$$

$$= - 210.46 \text{ J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$$

Table II-6: Rate constants of different temperatures^a

Temperature (K)	10^3 Rate Constant $k_{obs} \text{ (s}^{-1}\text{)}$	$-\ln (k_{obs}/T)$	$10^3 1/T$
261	0.7225	12.80	3.831
273	1.027	12.49	3.663
297	5.319	10.93	3.367
306	7.967	10.56	3.268
327	12.73	10.15	3.058

^a[KHSO₅] = 0.010 mol/L, [PhCHO] = 2.50 mol/L, [H₂SO₄] = 1.00 mol/L, solvent is pure DMF.

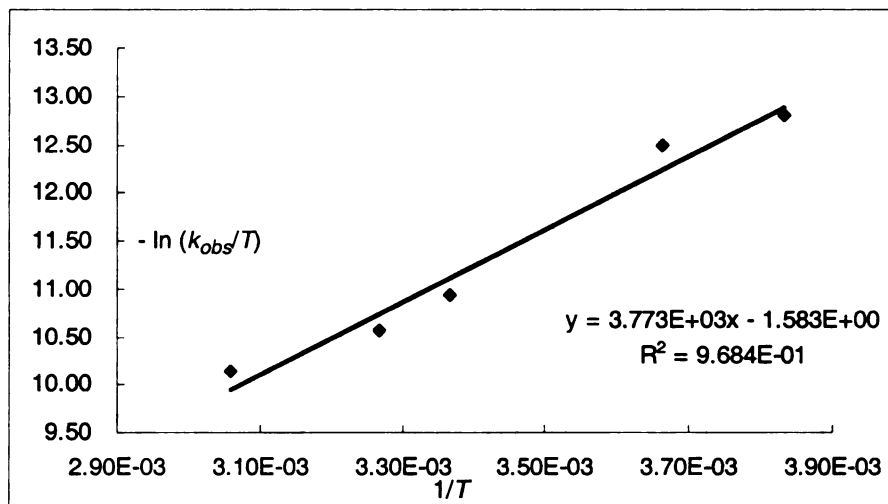


Figure II-9: Temperature effect on the oxidation reaction

II.4.2.2. Discussion: temperature effects reveal information regarding enthalpy and entropy of activation

The magnitudes of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ reflect the transition-state structure, whose reacting bonds are partially formed and partially broken.^{91, 96} The enthalpy of activation ($\Delta H^\ddagger$) reveals the difference in structure between starting material and the activated complex at the transition state. In other words, $\Delta H^\ddagger$ reflects the energy required for bond

reorganization during the formation of the activated complex. Generally, the determination of $\Delta H^\ddagger$ for a reaction is useful in evaluation of mechanistic hypothesis only when models are available to predict the activation enthalpies expected.⁸⁹ Our proposed mechanism is the Baeyer-Villiger mechanism of aldehydes oxidation; prior data for the activation enthalpy of reactions proceeding via the Baeyer-Villiger mechanism are between 25 KJ•mol⁻¹ and 67 KJ•mol⁻¹.^{63, 97} Comparing with our kinetic experiments and calculation, which gives the enthalpy of activation equal to 31.4 KJ•mol⁻¹, our aldehydes oxidation reaction is in accordance with the Baeyer-Villiger mechanism.

The entropy of activation is an indication of the change in the extent of organization of the atoms in the formation of the activated complex.^{91, 96} If translational, vibrational, or rotational degrees of freedom are lost in going to the transition state, there will be a decrease in the entropy of activation. On the contrary, an increase of translational, vibrational, or rotational degrees of freedom will result in a positive entropy of activation. Our aldehydes oxidation shows a negative value of $\Delta S^\ddagger$ equal to -210 J•mol⁻¹•K⁻¹. It is obvious that in the rate-determining step, the formation of peroxy hemiacetal complex from both aldehyde and KHSO₅ leads to a loss of degrees of freedom in going to the transition state. The reported Baeyer-Villiger oxidation of aldehydes also has negative entropies of activation ranging from -46 J•mol⁻¹•K⁻¹ to -171 J•mol⁻¹•K⁻¹.^{63, 97} Our reaction has activation entropy data with the same trend as the reported Baeyer-Villiger mechanism, the larger negative value might be due to solvent effects (the reported reaction used H₂O/alcohol mixed solvent,⁶³ while our reactions are

performed in DMF).

II.4.3. Substituent effect

In many kinds of reactions, the relationship between substituent groups and chemical properties can be expressed quantitatively and is useful both for interpreting reaction mechanisms and for predicting reaction rates and equilibrium.⁹¹ The most widely used principle for this relationship is the Hammett equation, which relates rates and equilibrium of many reactions of compounds containing substituted phenyl groups.⁹⁸⁻¹⁰⁰ In the 1930s, Hammett reported that there was a relationship between the acid strength of substituted benzoic acids and the rates of many other chemical reactions, for example, the rates of the alkaline hydrolysis of a series of *meta* and *para*-substituted benzoic esters.⁹⁹ The plot of $\log k / k_0$ versus $\log K / K_0$ gave a straight line, which illustrated a linear correlation of acid dissociation constants of benzoic acids with rates of alkaline hydrolysis of ethyl benzoate. Here k_0 and k are the rate constant for the ethyl benzoate and other substituted esters; K_0 and K are the corresponding acid dissociation constants. This line defines an equation in which m is the slope:

$$\log \frac{k}{k_0} = m \cdot \log \frac{K}{K_0}$$

Substituting K and k with the appropriate free energy of activation gives:

$$\begin{aligned}\log k - \log k_0 &= m (\log K - \log K_0) \\ -\frac{\Delta G^\ddagger}{2.3RT} + \frac{\Delta G_0^\ddagger}{2.3RT} &= m \left(-\frac{\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} \right) \\ -\Delta G^\ddagger + \Delta G_0^\ddagger &= m (-\Delta G + \Delta G_0) \\ \Delta \Delta G^\ddagger &= m \Delta \Delta G\end{aligned}$$

The linear correlation indicates that the change in free energy of activation ($\Delta\Delta G^\ddagger$) upon introduction of a series of substituent groups is directly proportional to the change in the free energy of ionization ($\Delta\Delta G$) that is caused by the same series of substituents of benzoic acid.

However, not all the reactions can provide such correlations. Generally, it is believed that the linear correlation is derived from the relationship between the correlation equation and the free-energy changes involved in the processes. Hammett has formalized this type of relationship, called the linear free-energy relationship, which explains the various correlations arising from the directly proportional changes in free energies.^{98, 100, 101} The relationship can be expressed as

$$\log \frac{K}{K_0} = \sigma \rho$$

$$\log \frac{k}{k_0} = \sigma \rho$$

The term σ can be defined as the substituent constant, which is determined for a series of substituent groups by measurement of the acid dissociation constant of the substituted benzoic acid. It can also be used in the correlation of other reaction series. The term ρ is defined as the reaction constant, and $\rho = 1$ is assigned for the standard reaction, which is the ionization of benzoic acid.

The Hammett equation can also be expressed in terms of free energy:

$$\log \frac{K}{K_0} = \log K - \log K_0 = -\frac{\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma \rho = \sigma$$

since $\rho = 1$ for the standard reaction. Combining with the equation $\Delta\Delta G^\ddagger = m \Delta\Delta G$, then:

$$m \sigma = \Delta \Delta G^\ddagger = -\frac{\Delta G^\ddagger}{2.3RT} + \frac{\Delta G_0^\ddagger}{2.3RT} = \log k - \log k_0 = \log \frac{k}{k_0}$$

$$m = \rho$$

which means that the slope of the plot of $\log \frac{k}{k_0}$ vs. $\log \frac{K}{K_0}$ is the reaction constant ρ .

The substituent effect only discusses the *meta* or *para*-substitution because these sites can be assumed only to have electronic effects; *ortho*-substitution will have a combination of both electronic and steric effects. The value of substituent constant σ reflects the interaction of the substituent with the reaction site. Generally, if $\sigma > 0$, the substituent groups are electron-withdrawing groups because, they favor the ionization of the benzoic acid; if $\sigma < 0$, the substituents are electron-donating groups because they have the opposite effect. The value of reaction constant ρ reflects the charge development at the reaction center. Generally, if $\rho > 0$, the aromatic ring has higher electron density in the transition state than in the starting material, which means the reaction is favored by electron-withdrawing substituents; if $\rho < 0$, the aromatic ring has lower electron density in the transition state than the starting material, which means the reaction is favored by electron-donating substituents.^{89, 91, 101} Thus the linear free-energy relationships can provide useful information about the nature of reaction and its transition state.

II.4.3.1. The Hammett plot

Our experiments about the substituent effect were carried out with benzaldehyde and different substituted benzaldehydes under comparable conditions. Since some of the substituted benzaldehydes did not have very good solubility in DMF, they did not

have the same initial concentration. Even though the starting concentrations were different, in order to use the isolated method, the concentrations of aldehydes were still maintained in great excess relative to KHSO_5 . Thus the observed pseudo-first order rate constants (k_{obs}) of various substituted benzaldehydes were determined by using the same method mentioned before, which could be converted to a comparable rate constant (k_r) with eliminating the effect of the different starting concentrations of aldehydes:

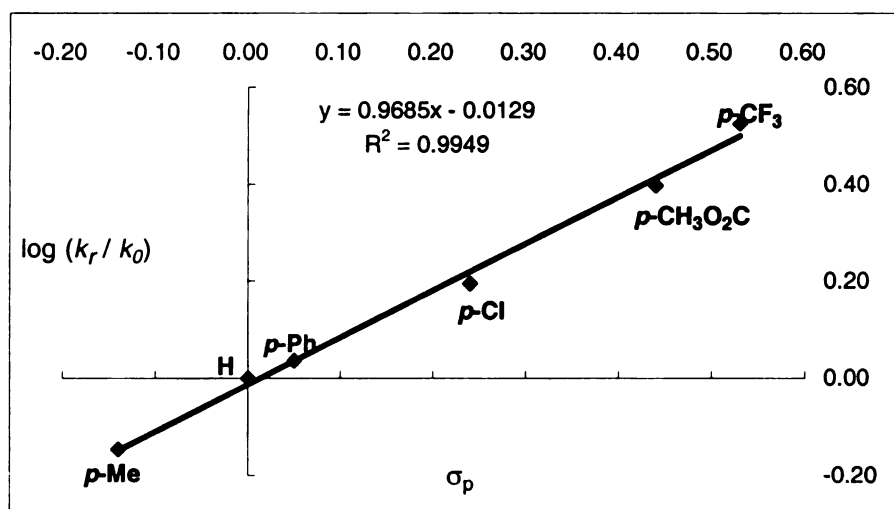
$$k_r = \frac{k_{obs}}{[\text{aldehyde}][\text{H}_2\text{SO}_4]}$$

Table II-7 depicts the rate constants of different aldehydes and Figure II-10 is the plot of $\log (k_r/k_0)$ vs. σ_p ,^{91, 102} which gives a good straight line with R equal to 0.9974. This represents a perfect match with the Hammett linear free-energy relationship. As described before, the slope of the Hammett plot is the value of reaction constant ρ , which is equal to 0.9685.

Table II-7: Rate constants of different substrates^a

Substituent Groups	σ_p^b	$10^3 k_{obs} (s^{-1})$	[aldehyde]	$10^3 k_r (s^{-1})$	$\log (k_r/k_0)$
H	0.00	5.319	2.459	2.163	0.00
<i>p</i> -Me	-0.14	3.276	2.054	1.545	-0.1461
<i>p</i> -Ph	0.05	4.678	1.991	2.349	0.03582
<i>p</i> -Cl	0.24	6.800	2.003	3.387	0.1948
<i>p</i> -CH ₃ O ₂ C	0.44	4.327	0.801	5.402	0.3975
<i>p</i> -CF ₃	0.53	1.492	2.058	7.250	0.5253

^a[KHSO₅] = 0.010 mol/L, [H₂SO₄] = 1.00 mol/L, solvent is pure DMF, T = 298 K. ^bValues of σ_p are from reference 102.

**Figure II-10: The Hammett plot**

II.4.3.2. Discussion: the Hammett plot shows the substituent effect

It should be noted that besides the σ_p values we used to obtain the Hammett plot, σ_+ and σ_- values are also used.^{75, 89, 91, 96, 102} These are substituent constants which reflect the resonance effects for different reactions. The σ_+ values are used for reactions in which there is direct resonance interaction between an electron-donor substituent and a cationic reaction center, whereas the σ_- values show there is a direct resonance interaction between an electron-rich substituent and an anionic reaction center. Since

the effect of different resonating substituents on the aromatic ring (electron donating, electron withdrawing, or neutral) is not apparent for the mechanism in question, common practice dictates plotting $\log (k_r/k_0)$ against all three substituent constants (σ_+ , σ_- and σ) to find the best fit. Table II-8 shows the data of σ_+ and σ_- values for the substituted benzaldehydes. Then plot $\log (k_r/k_0)$ versus σ_+ or σ_- , as shown in Figure II-11 and Figure II-12. It is obvious that the Hammett relationship is poorly correlated

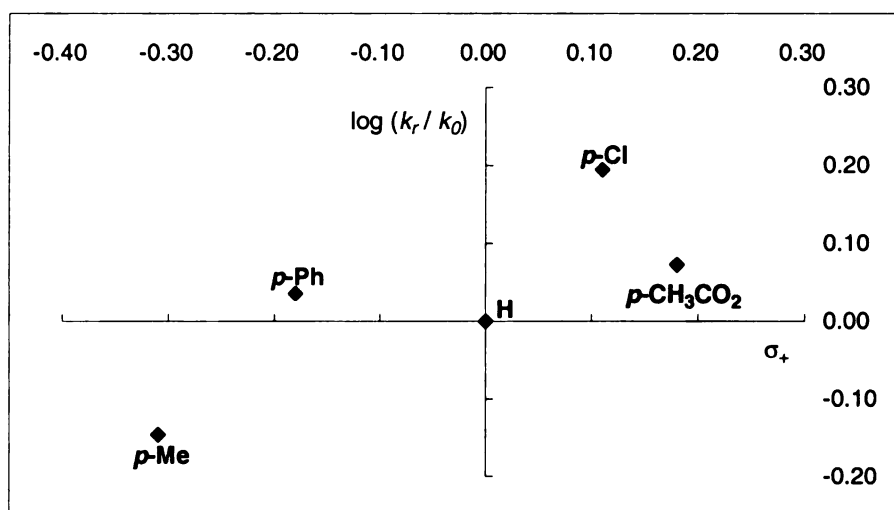


Figure II-11: The Hammett plot of σ_+ values

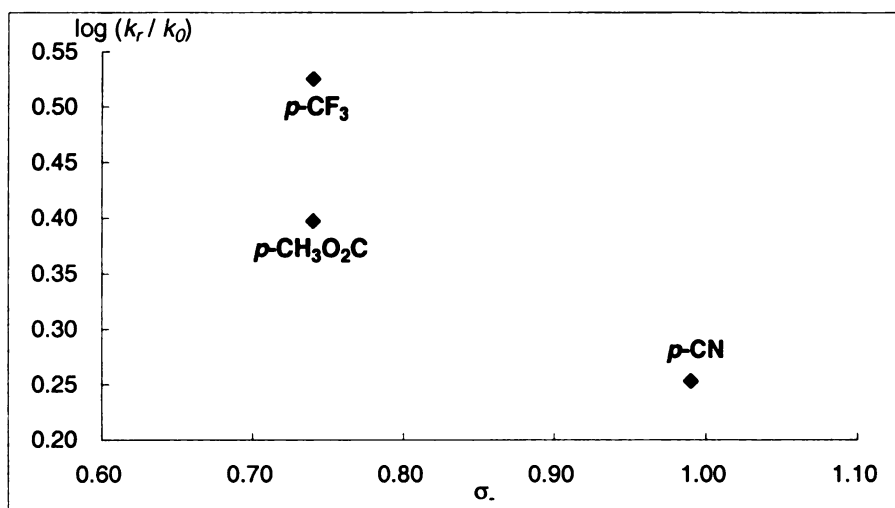


Figure II-12: The Hammett plot of σ_- values

with either σ_+ or σ_- , which suggests a negligible resonance effect in the transition state. In our proposed mechanism, the intermediate peroxy hemiacetal should be formed from the transition state with a similar structure, which is not affected by resonance effects.

The relatively small ρ value implies that the activated complex is not highly charged.¹⁰¹ It is clear to see that in the rate-determining step, there is a relatively small redistribution of charges in the transition state during the formation of the peroxy hemiacetal, which is in accordance with the kinetic data.

Moreover, in the Baeyer-Villiger rearrangement of benzaldehyde, migrating groups can be either hydrogen or aryl group. The reported Baeyer-Villiger oxidation of benzaldehyde with perbenzoic acid in the mixed H₂O/alcohol solvents gave a positive ρ value of 1.1-1.8 when hydrogen migration occurs.^{63, 87, 103} Alternatively, it provided negative ρ values when aryl groups migrate.^{63, 103} Our KHSO₅ oxidation has a ρ value equal to 0.97, which is close to the value for the perbenzoic acid oxidation of benzaldehyde with a hydrogen migration. Therefore, it suggests a similarity in mechanism, which supports our proposed Baeyer-Villiger mechanism.

II.5. Summary

In summary, based on all the mechanistic studies, we can suggest a Baeyer-Villiger type mechanism for the oxidation of aldehydes to provide carboxylic acids promoted by KHSO₅ in DMF. KHSO₅, a good nucleophile, attacks the carbonyl carbon of the protonated aldehyde. The formed peroxy hemiacetal intermediate undergoes a Baeyer-Villiger rearrangement to give the final product. This method is a mild alternative to metal mediated oxidations of aldehydes.

II.6. Experimental Section

General Information:

All commercially available starting materials and solvents were used without further purification. Commercially available starting materials were obtained from Aldrich. All of the spectral data for known compounds either match those reported by Aldrich or by comparison to the literature report.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F₂₅₄ plates. Compounds were visualized with UV light, potassium permanganate stain or *p*-anisaldehyde stain. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 µm silica gel. GC analysis was performed using HP (6890 series) GC system containing Altech SE-54, 30 m × 320 µm × 0.25 µm column. UV analysis was performed using a Perkin-Elmer Lambda 40 UV/Vis spectrometer.

¹H NMR spectra were measured at 300 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for CDCl₃). ¹³C NMR spectra were measured at 75 MHz on a Varian Gemini-300 or at 125 MHz on a Varian VXR-500 instrument. Chemical shifts are reported relative to the central line of CDCl₃ (δ 77.0 ppm). 2D-COSY and DEPT spectra were recorded on 300 MHz NMR spectrometer in CDCl₃.

General Procedure for Oxidation of Aldehyde to Carboxylic Acid: The aldehyde (1 equiv) was dissolved in DMF (0.1 M). Oxone (1 equiv) or KHSO_5 (1 equiv, 95% pure, preparation was based on the procedure published by our group⁷¹) was added in one portion and stirred at RT for 3 h. The reactions were monitored by TLC and GC analysis. 1N HCl was used to dissolve the salts of byproduct and EtOAc was added to extract the products. The organic extract was washed with 1N HCl (3×) and brine, dried over Na_2SO_4 , and the solvent was removed under reduced pressure to obtain the crude product. Products were purified by silica gel column chromatography.

General Iodometric Method: All the reactions were carried out in the small vials. Prepared 5% (w/w) KI (1 mL) and 1% (v/v) H_2SO_4 (2 mL) in the 25 mL Erlenmeyer flask. After the required reaction time, poured the reaction solution into the Erlenmeyer flask and shook it. Use MeOH to wash the vial (3×1 mL). Added MeOH to the solution until it converted all the aldehyde to acetal and then dissolved completely into water. The dark yellow solution was immediately titrated with about 2.000×10^{-3} mol/L $\text{Na}_2\text{S}_2\text{O}_3$ solution to a yellow color. Then added some drops of starch indicator (starch was solved into boiling water) to convert the solution to a dark blue color. Used the same $\text{Na}_2\text{S}_2\text{O}_3$ solution to continue titrating until a colorless endpoint.

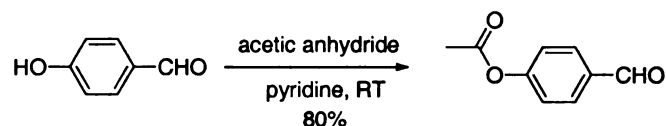
General Kinetic Measurements: All kinetic studies were carried out in pure DMF under pseudo-first-order conditions with a large excess of benzaldehyde or substituted benzaldehyde and sulfuric acid over KHSO_5 . The reaction was run at a

constant temperature, which was followed by estimating the unreacted KHSO_5 as a function of time by using the iodometric method. From the titrated values, plot of $-\ln [\text{KHSO}_5]$ vs. time was made to give a straight line and from the slope of such a plot, the pseudo-first-order rate constant, k_{obs} (s^{-1}) was obtained. It was checked that the results were reproducible within $\pm 5\%$ error.

Compounds that were Reported: All the compounds in isotope labeling and NMR analysis of the KHSO_5 promoted aldehyde oxidation were reported in the PhD dissertation of Benjamin R. Travis.

In substrate effect study, different aromatic aldehyde were used in the measurement. Before the kinetic study, all the oxidation reactions were carried out under normal conditions and the substituted benzoic acids were isolated from silica gel chromatography in order to make sure the reactions were successful. The products were compared with the Aldrich data base shown as following: *p*-toluic acid, biphenyl-4-carboxylic acid, 4-chlorobenzoic acid, 4-(trifluoromethyl)benzoic acid, 4-cyanobenzoic acid, 4-acetoxybenzoic acid and mono-methyl terephthalate.

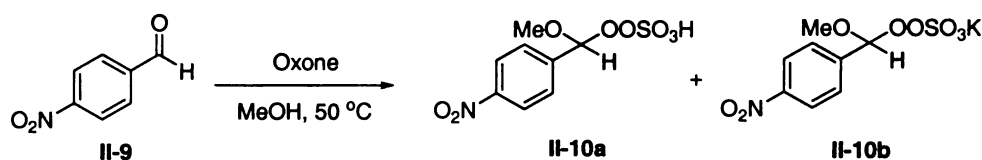
Data for Newly Synthesized Compounds:



4-Acetoxybenzaldehyde: To a room temperature solution of 4-hydroxybenzaldehyde (8.2 g, 0.067 mol) in pyridine (15 mL) acetic anhydride (12.7 mL, 0.14 mol) was added in slowly. The reaction was stirred at RT for 15 h. 15 mL HCl (10%, v/v) aqueous solution was added to quench the reaction and stirred for 15 min. The

solution was extracted with EtOAc (3×20 mL). The combined organic layer was dried over anhydrous Na₂SO₄. Filtration followed by concentrating provided crude product, which was purified by distillation under reduced pressure to give pure product 4-acetoxybenzaldehyde (11.8 g, 80%) as a colorless oil.

Data for *4-Acetoxybenzaldehyde*: ¹H NMR (300 MHz, CDCl₃): δ 9.96 (1H, s), 7.87 (2H, *J* = 0.9 Hz), 7.23 (2H, *J* = 0.9 Hz), 2.30 (3H, s). (The data was compared with the Aldrich database.)



Data for *4-Nitrobenzaldehyde-methyl-peroxysulfate acetal (II-10a)*:⁶⁶ ¹H NMR (300 MHz, CDCl₃): δ 8.22 (d, 2H, *J* = 8.4 Hz), 7.66 (d, 2H, *J* = 7.14 Hz), 5.80 (s, 1H), 3.70 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 142.5, 131.0, 128.1, 123.5, 106.2, 56.5; IR (thin film) 3420, 3115, 3082, 2940, 2842, 1523, 1349, 1205, 1097, 1013, 854.

Data for *4-Nitrobenzaldehyde-methyl-potassiumperoxysulfate acetal (II-10b)*:⁶⁶ ¹H NMR (300 MHz, CDCl₃): δ 8.22 (d, 2H, *J* = 9.1 Hz), 7.66 (d, 2H, *J* = 9.0 Hz), 5.76 (s, 1H), 3.65 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 148.2, 142.7, 127.9, 123.3, 105.6, 56.7; IR (thin film) 3117, 2939, 1510, 1353, 1315, 1200, 1097, 980, 854.

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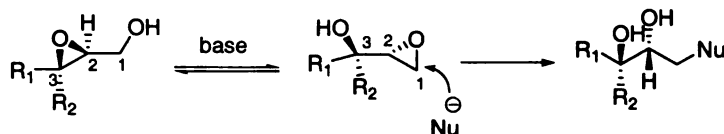
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CHAPTER III

TRI- AND TETRA-SUBSTITUTED AZIRIDINES IN AZA-PAYNE REARRANGEMENTS

III.1. Introduction

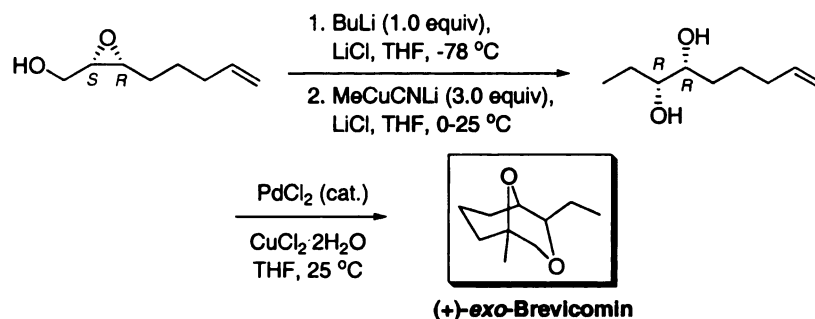
The Payne rearrangement is an epoxide migration that generally occurs under basic conditions via an intramolecular S_N2 mechanism.¹ One important aspect of the Payne rearrangement is that the reaction is usually stereospecific, proceeding through an inversion of configuration at the C-2 position of the epoxide ring (Scheme III-1).¹⁻⁴



Scheme III-1: Payne rearrangement followed by nucleophilic ring-opening

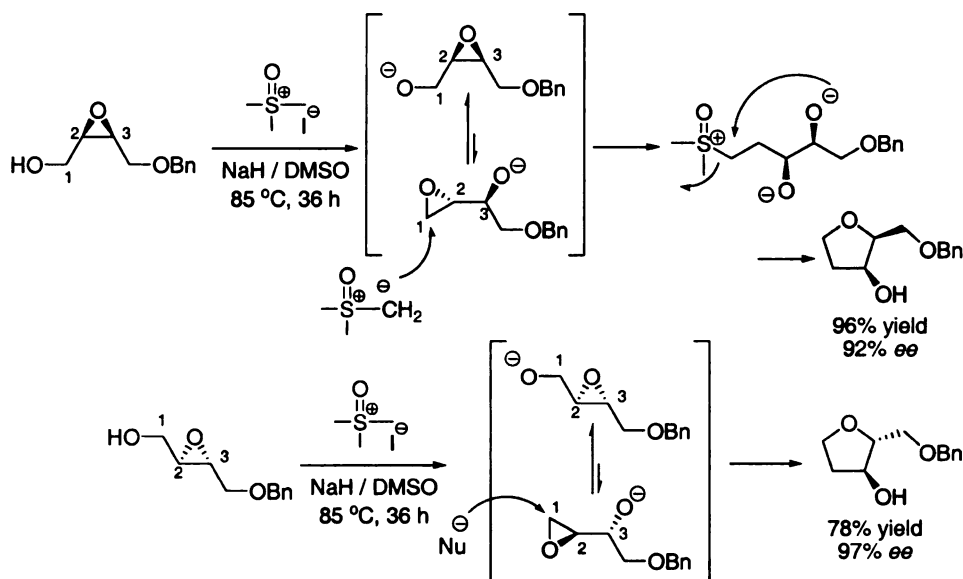
Since the Sharpless asymmetric epoxidation⁵ to prepare chiral 2,3-epoxy alcohols has been well developed, the regioselective nucleophilic ring-opening at the C-1 position of more reactive terminal epoxides resulting from the Payne rearrangement of 2,3-epoxy alcohols under basic conditions has become an important protocol for the synthesis of polyfunctional synthetic targets (Scheme III-1).² For example, in 1990, Sutherland and coworkers reported a five-step enantioselective total synthesis of (+)-*exo*-Brevicomin, an aggregation pheromone of the Western Pine beetle *Dendroctonus brevicomis*.⁶ The key step of this synthesis is a base-mediated Payne-rearrangement-nucleophilic trapping procedure, which can form the desired

diol intermediate, followed by the intramolecular Heck reaction to give the final product (Scheme III-2).⁶



Scheme III-2; Synthetic application of the Payne-rearrangement-nucleophilic trapping

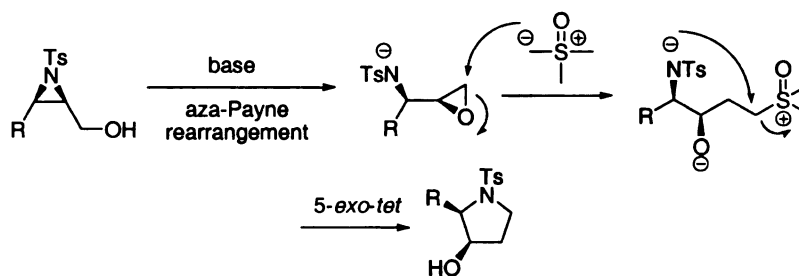
In previous work in our group, we have used the Payne rearrangement to control attack at the C-1 position with dimethylsulfoxonium methylide, which leads to the synthesis of a series of 2,3-substituted tetrahydrofurans (THF).⁷ Scheme III-3 shows two examples of this methodology containing both *cis*- and *trans*-epoxides as the substrates. Payne rearrangement followed by nucleophilic epoxide opening with the ylide at C-1 leads to the generation of a bis-alkoxide, which can undergo 5-*exo-tet*



Scheme III-3: Synthesis of 2,3-disubstituted THF rings using Payne rearrangement

ring closure to yield the desired product. These reactions can give high yields and form the THF rings in high regio- and stereoselective fashion from epoxy alcohols. As described before, the Payne rearrangement is useful to control the regioselectivity because terminal epoxides are more sterically accessible than 2,3-disubstituted epoxides for the nucleophilic attack of dimethylsulfoxonium ylide. Scheme III-3 also shows that the Payne rearrangement of *trans*-epoxide is not as facile as that of *cis*-epoxides because *cis*-epoxides can release much more steric strain during the sequence. This is presumably the reason that the yield for obtaining 2,3-*trans*-THF rings is lower than that of 2,3-*cis*-THF rings, which originate from *trans*- and *cis*-epoxy alcohols, respectively. In addition, most alkyl-substituted and trisubstituted 2,3-epoxy-1-ols do not undergo sufficient Payne rearrangement to allow for successful nucleophilic attack on the less hindered 1,2-epoxy-3-ols, which give mixtures of products resulting from competing nucleophilic attack at C-2 and C-3, as well as base mediated elimination reactions.

It is known that pyrrolidines are important nitrogen-containing heterocycles and they are present in a large number of biologically active natural products and pharmaceuticals.⁸⁻¹⁸ Enantiomerically pure pyrrolidines are also used as chiral auxiliaries for various organic transformations.¹⁹⁻²⁵ Therefore it is important to develop efficient pathways to synthesize pyrrolidines in enantiomerically and diastereomerically pure forms. With the development of the dimethylsulfoxonium methylide mediated Payne rearrangement to prepare 2,3-disubstituted THF rings, it was interesting to investigate an ylide-based aza-Payne rearrangement of aziridinols,

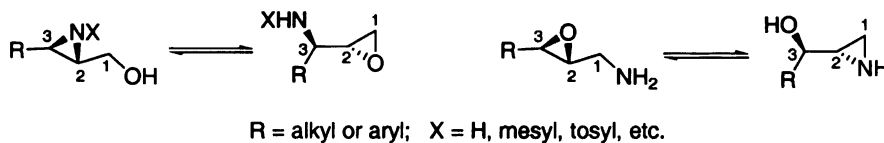


Scheme III-4: A one-carbon relay ring expansion to form pyrrolidines via aza-Payne rearrangements

which could lead to the preparation of pyrrolidines (Scheme III-4). If the aza-Payne rearrangement is favored to form epoxide over aziridine, the subsequent nucleophilic attack of the terminal epoxide could form the bis anion, which could undergo a 5-*exo-tet* ring-closure with loss of DMSO to yield the desired pyrrolidine. In order to investigate this ring expansion method to form pyrrolidines, a study of the aza-Payne rearrangement of a variety of substituted aziridines was necessary.

Aziridines are very important structural units of biologically active molecules and natural products.²⁶⁻⁴⁰ Currently, there is significant interest in the synthesis and reactions of aziridines and their *N*-activated analogs.⁴¹⁻⁴⁹ The term of “*N*-activated aziridines” has been introduced by Ham for aziridines which contain substituents capable of stabilizing a negative charge which is formed on the aziridine nitrogen in the transition state when the aziridines react with a nucleophile.⁵⁰ The methanesulfonyl, acyl, alkoxycarbonyl and arenesulfonyl groups serve as good activating groups. Due to their high reactivity and ability to undergo regioselective ring-opening reactions with a wide range of nucleophilic reagents, aziridines are useful substrates in a number of important synthetic transformations.

Recently, the aza-Payne rearrangement of both activated aziridinemethanols and 2,3-epoxy amines has been reported (Scheme III-5).⁵¹⁻⁵⁹ This reaction holds great



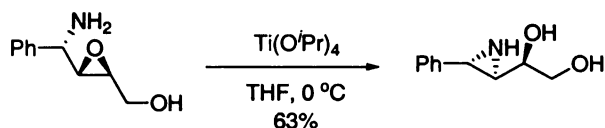
Scheme III-5: The aza-Payne rearrangement

promise for the synthesis of nitrogen-containing bioactive compounds. Different conditions could shift the equilibrium of the reaction. Moreover, compared to the Payne rearrangement, besides the reaction conditions, since the nitrogen in aziridines could have an extra group attached to it, the equilibrium of the aza-Payne rearrangement also can be controlled by the protecting groups on the nitrogen.

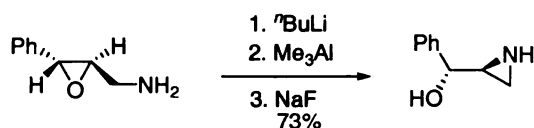
In order to successfully use the aza-Payne rearrangement in organic synthesis, it is important to control the equilibrium under various conditions. Even though there is no systematic investigation of the aza-Payne rearrangement, some groups have already developed both Lewis acid and base mediated aza-Payne rearrangements.⁵¹⁻⁵⁹

III.1.1. Aza-Payne rearrangements of epoxy amines

In general, with no groups or with non-activating groups on the nitrogen of epoxy amines, the equilibrium of the aza-Payne rearrangement prefers to form aziridinols from epoxy amines. Several groups reported the Lewis acid mediated aza-Payne rearrangement of epoxy amines.^{51, 57, 58, 60-64} Sato and coworkers found that the ring-opening of the epoxide moiety of 4-amino-2,3-epoxy-1-alkanol with $\text{Ti}(\text{O}^i\text{Pr})_4$ to afford the aziridine as a single product (Scheme III-6).⁵⁸ Vaultier and coworkers reported that trimethylaluminum could mediate the transformation of primary



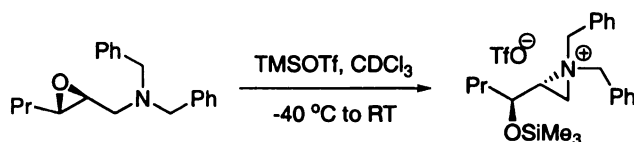
Scheme III-6: $\text{Ti}(\text{O}^i\text{Pr})_4$ mediated the aza-Payne rearrangement to give aziridinols



Scheme III-7: $n\text{-BuLi}$ - Me_3Al mediated the aza-Payne rearrangement to give aziridinols

2,3-epoxy amines into aziridinols via the aza-Payne rearrangement (Scheme III-7).⁵⁷

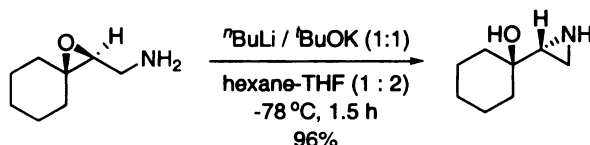
Rayner's group found that *N*, *N*-dibenzyl or diallyl substituted 2,3-epoxy amines could rearrange to the aziridinium salts using Lewis acids such as trimethylsilyl trifluoromethanesulfonate (TMSOTf).^{62, 63} Scheme III-8 shows one example of 2,3-epoxy-*N*, *N*-dibenzyl derivatives, which is treated with TMSOTf in CDCl_3 at -40 °C and the reaction is allowed to warm to room temperature. The ^1H NMR spectra



Scheme III-8: TMSOTf mediated the aza-Payne rearrangement to give aziridinium salt

of the resulting solution clearly shows clean formation of the aziridinium salt, which is stable for a number of days at room temperature. Here the benzyl or allyl groups on the nitrogens are non-activating groups. Other Lewis acids such as $\text{BF}_3 \cdot \text{OEt}_2$,⁶¹ or silica gel⁶⁰ could also mediated similar aza-Payne rearrangement of epoxy amines. In addition, Ibuka and coworkers found that treatment of the 2,3-epoxy amines with a mixture of 1.5 equiv of $n\text{-BuLi}$ and 1.5 equiv of $t\text{-BuOK}$ ('super base')⁶⁴ at -78 °C also

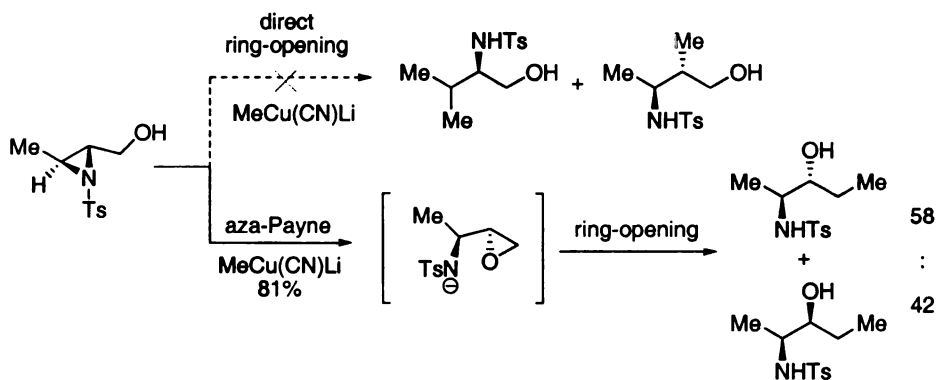
provided pure aziridine alcohols in high yield (Scheme III-9).⁵¹ The only exception is found when the C-2 carbon is substituted; steric hindrance may be responsible for the low yield in such cases (methyl substituted substrate gave 40% yield).



Scheme III-9: Super base mediated the aza-Payne rearrangement to give aziridine alcohols

II.1.2. Aza-Payne rearrangements of *N*-activated aziridinols

The opposite equilibrium of the aza-Payne rearrangement can be obtained when there are activating groups on the nitrogens of aziridinols.^{52, 55, 56, 65-70} The original observation was based on the study of organocuprate reactions of aziridine alcohols by Ibuka and coworkers.^{53, 68, 70, 71} They found that the reaction of 2-aziridinemethanol with methylcyanocuprate afforded two products. Scheme III-10 shows that the two products are secondary alcohols, not primary alcohols, which suggests that the aza-Payne rearrangement was followed by a ring-opening pathway instead of the directly attacking the aziridines. Ibuka and coworkers further studied



Scheme III-10: Organocuprate mediated ring-opening of aziridine alcohol

the equilibrium by both chemical and theoretical studies in simple systems.^{51, 69} Their study showed that activation by the introduction of a strong electron-withdrawing group on the nitrogen atom of the aziridine was required to push the equilibrium towards the epoxy amine. From *ab initio* calculations, the energy minimum of a mesyl-protected aza-anion was predicted to be 18.6 kcal/mol lower than that of the corresponding oxa-anion (Figure III-1). The aza-anion is more

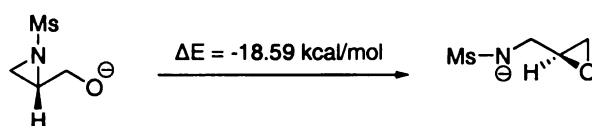
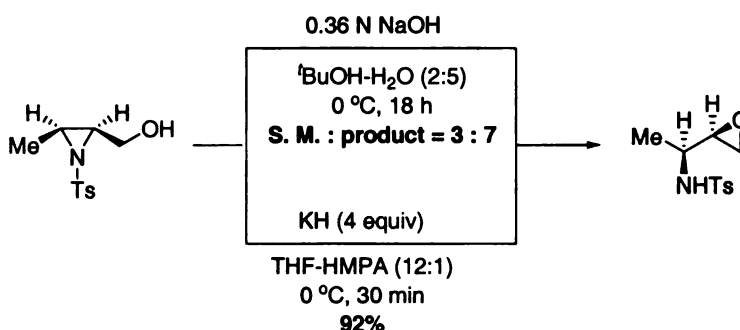


Figure III-1: Theoretical calculation of energy difference of aza and oxa anions

thermodynamically stable than the oxa-anion. Experiments were carried out to show that the aqueous alkaline conditions (such as aqueous sodium hydroxide solution) lead to incomplete conversion, while bases such as NaH, KH or *t*BuOK give clean and efficient rearrangements (Scheme III-11).⁶⁹ Moreover, they found that THF or a

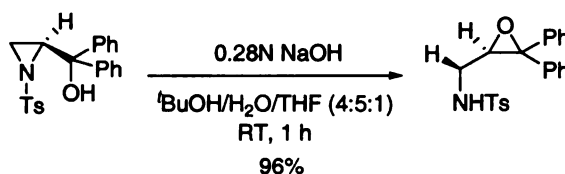


Scheme III-11: Base mediated aza-Payne rearrangement to give epoxy amines

mixed solvent of THF and HMPA is the solvent of choice and the rearrangement yields strongly depend on temperature, which should be carefully controlled. Under these conditions, both the 2,3-disubstituted aziridinols and the terminal aziridine with

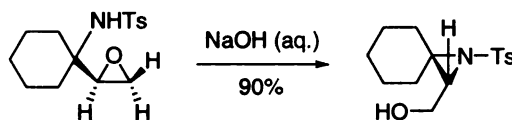
a secondary or tertiary hydroxymethyl group at the C-2 position could undergo the aza-Payne rearrangement to give the pure epoxy amines in high yield.^{51, 69} All the experimental results are comparable with their theoretical calculation, which shows that the formation of the epoxy amines is expected to predominate by treatment of activated aziridine alcohols with a base.⁶⁹

Volatron and Bouyacoub also performed a theoretical DFT study, which suggested that the aza-Payne rearrangement proceeded by a S_N2 mechanism.⁶⁵ The same rearrangement of α,α -disubstituted aziridinemethanols was discussed by Hu and coworkers.^{66, 67} Their reaction system utilized NaOH in a mixed solvent of t BuOH/H₂O/THF (4:5:1) or NaH in a mixed solvent of THF/HMPA (10:1). The aza-Payne rearrangement provides the corresponding epoxy amines in up to 99% yield (Scheme III-12). The reaction is sensitive both to the nature of solvent and to the presence of the counter-ion (such as Na⁺ and K⁺).



Scheme III-12: Hu's method of aza-Payne rearrangement to form epoxy amines

The only exception of the aza-Payne rearrangement of epoxy amines with activated groups on the nitrogen to form aziridinols was reported by Moulines and coworkers in 1992 (Scheme III-13).⁵⁹ Under basic conditions,

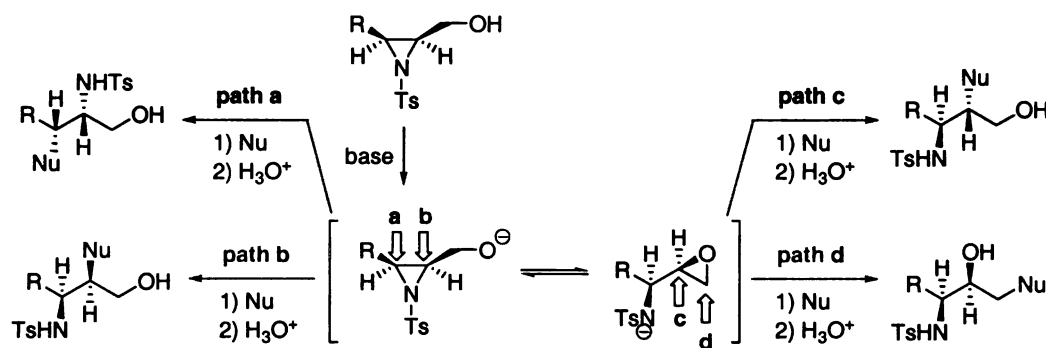


Scheme III-13: Moulines' aza-Payne rearrangement of activated epoxy amines

N-tosyl-oxiranemethylamines were converted to the corresponding aziridinols in good to excellent yields with aqueous sodium hydroxide. In their paper, they did not explain why these substrates favored the opposite equilibrium compared to other activated aziridinols. One possible reason might be the steric hindrance of the α -cyclohexyl group of the epoxy amines, which might shift the equilibrium to the less hindered aziridinols.

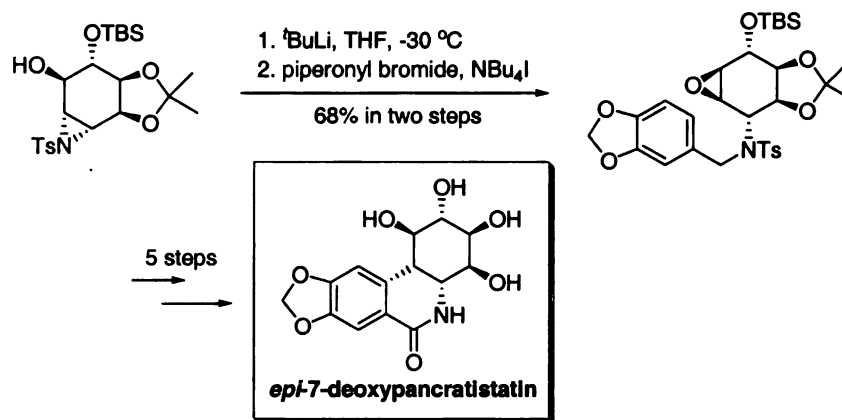
III.1.3. Applications of aza-Payne rearrangements

By varying the protecting groups on the nitrogen and the reaction conditions, the equilibrium of the aza-Payne rearrangement can be controlled efficiently. One widely used reaction is the aza-Payne rearrangement-nucleophilic attack reaction, which can prepare acyclic chiral amino alcohols.^{51, 68-70} Scheme III-14 shows four possible routes. It is clear that by controlling the equilibrium of the aza-Payne rearrangement and the position of the nucleophilic attack, different *N*-protected 1,2- or 1,3-amino alcohols can be prepared via regio- and stereoselective fashion.



Scheme III-14: Aza-Payne rearrangement-nucleophilic attack reaction to prepare chiral amino alcohols

In addition, the aza-Payne rearrangement is also used in the total synthesis of natural products or biological compounds.^{72, 73} For example, in 2002, Hudlicky and coworkers reported the total synthesis of *epi*-7-deoxypancratistatin, one of the amaryllidaceae alkaloids, via aza-Payne rearrangement and intramolecular cyclization reactions.⁷³ The product of aza-Payne rearrangement of the alkoxide is the *N*-alkylated amino oxirane as shown in Scheme III-15 and the nitrogen anion is quenched with piperonyl bromide to give the desired product, which can be converted to the final product in five steps.



Scheme III-15: Total synthesis example with using aza-Payne rearrangement

III.2. Synthesis of Tri- and Tetra-Substituted Aziridinols

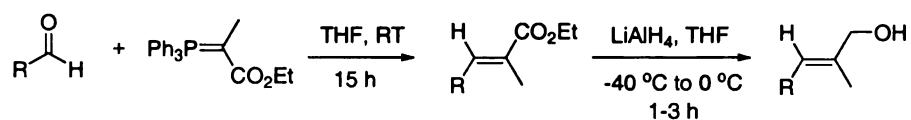
Even though different methods have been developed to control the equilibrium of the aza-Payne rearrangement, to our knowledge, the use of this reaction on more highly substituted compounds, such as 2,3,3- or 2,2,3-trisubstituted and tetra-substituted aziridinols, has not been studied. This was crucial for us to study since we desired to extend the one-carbon homologative ring expansion methodology to the synthesis of highly substituted pyrrolidines.

III.2.1. Synthesis of 2,2,3-trisubstituted aziridinols

Various *N*-substituted 2,2,3-trisubstituted aziridinols could be synthesized via Sudalai's aziridination method reported in 2003.⁷⁴ The methodology entails the treatment of the corresponding allylic alcohols with chloroamine-T and catalytic NBS.

Trisubstituted alkenols were synthesized via the Wittig reaction followed by lithium aluminum hydride (LiAlH₄) reduction of the resulting α,β -unsaturated esters (Table III-1). Benzaldehyde **III-1**, and 4-substituted benzaldehydes with both electron-donating and electron-withdrawing groups (**III-2** and **III-4**, respectively) were used to prepare the corresponding allylic alcohols **III-1b**, **III-2b** and **III-4b** in good yields (entry 1, 2 and 4). 4-Nitrobenzaldehyde **III-3** was converted to the conjugate ester **III-3a** in 84% yield. However, the reduction of the ester group did not give the desired allylic alcohol, since the nitro-group was also reduced by LiAlH₄ (entry 3). Entry 5 shows the preparation of allylic alcohol **III-5b** starting from the aliphatic aldehyde **III-5**.

Table III-1: Synthesis of trisubstituted alkenols^a



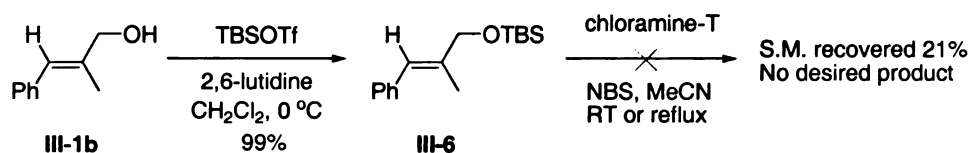
Entry	Substrate	Alkene	Yield (%) ^b	Alkenol	Yield (%) ^b
1	 III-1	 III-1a	87	 III-1b	76
2	 III-2	 III-2a	88	 III-2b	77
3	 III-3	 III-3a	84	no desired product	---
4	 III-4	 III-4a	92	 III-4b	76
5	 III-5	 III-5a	60	 III-5b	53

^a Substrate (1 equiv), Ylide (1.2 equiv), RT, 15 h; LiAlH₄ (2 equiv), -40 °C to 0 °C.

^b Isolated yields, *E:Z* ratio > 97%.

The following step was to attempt the NBS catalyzed aziridination of allylic alcohols with chloramine-T.⁷⁴ It was not clear whether the free hydroxyl group would have any effect on the aziridination reaction. Therefore, a TBS group was used to protect the allylic alcohol **III-1b** to provide **III-6** in 99% yield. The ensuing

aziridination did not give any desired product, even after refluxing and the only pure-isolated compound was the starting material **III-6** (Scheme III-16). However,



Scheme III-16: Aziridination of protected allylic alcohol **III-6**

under the same conditions the free alcohol **III-1b** (Table III-2, entry 1), provided the desired aziridinol **III-1c** efficiently in 85% yield. Other allylic alcohols **III-2b**,

Table III-2: Synthesis of 2,3,3-trisubstituted aziridinols^a

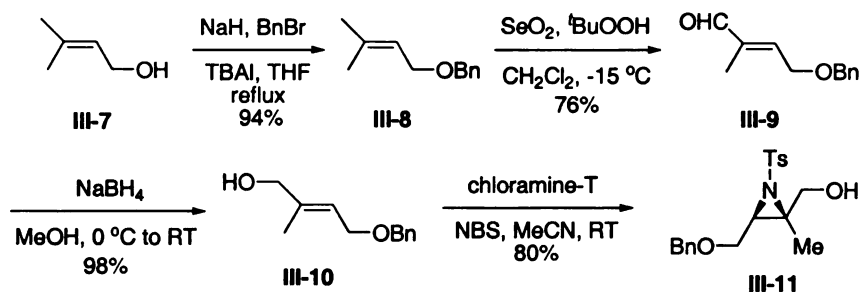
Entry	Allylic Alcohol	Aziridinol	Yield (%) ^b	
1	 III-1b	 III-1c	85	
2	 III-2b	 III-2c	71	
3	 III-4b	 III-4c	56	
4	 III-5b	 III-5c	60	

^a Substrate (1 equiv), anhydrous chloramines-T (1 equiv), NBS (20%), MeCN, RT, 15 h

^b Isolated yields.

III-4b, and **III-5b** were subjected to identical conditions and all the 2,2,3-trisubstituted aziridinols **III-2c**, **III-4c** and **III-5c** could be synthesized as desired (entries 2, 3, and 4).

The synthesis of 2,2,3-trisubstituted aziridinol **III-11** is shown in Scheme III-17. Benzylation of 3-methyl-2-butenol followed by allylic oxidation with selenium dioxide gave the conjugate aldehyde **III-9**, which underwent reduction to provide allylic alcohol **III-10**. The same procedure of aziridination gave the racemic aziridinol **III-11** in 80% yield.

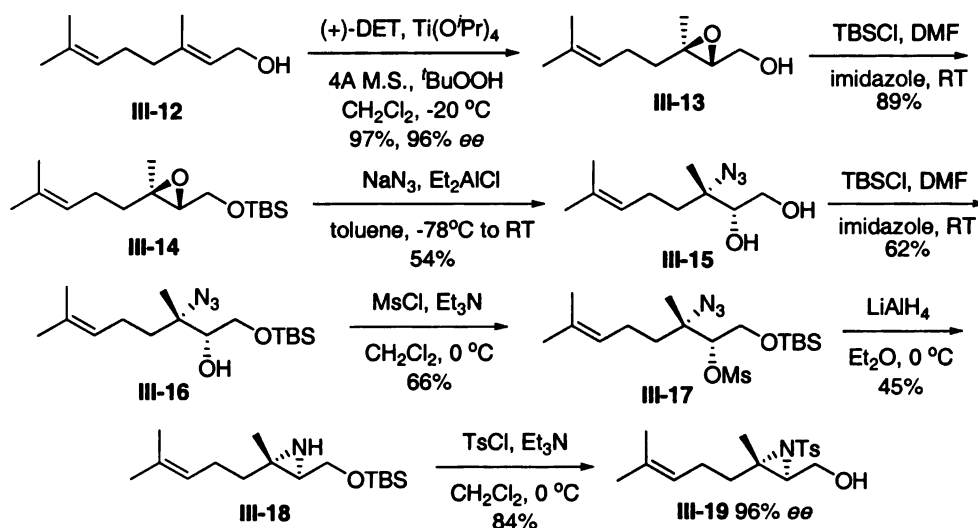


Scheme III-17: Synthesis of 2,2,3-trisubstituted aziridinol **III-11**

III.2.2. Synthesis of 2,3,3-trisubstituted aziridinols⁷⁵

Acyclic enantiomerically pure 2,3,3-trisubstituted aziridinol **III-19** was obtained. **III-4b**, and **III-5b** were subjected to identical conditions and all the 2,2,3-trisubstituted aziridinols **III-2c**, **III-4c**, and **III-5c** could be synthesized as desired (entries 2, 3, and 4).

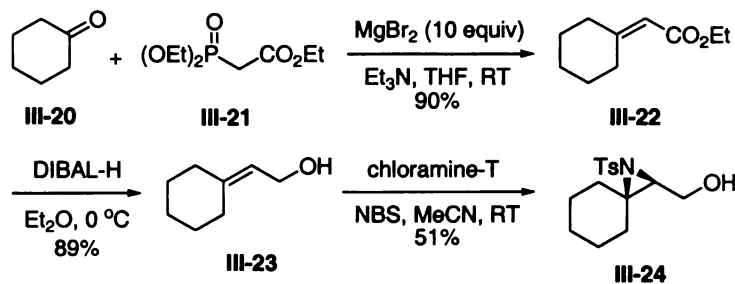
The synthesis of 2,2,3-trisubstituted aziridinol **III-11** is shown in Scheme III-17. via the asymmetric epoxide following a procedure developed by Coates and coworkers (Scheme III-18).⁷⁶ Ring-opening of the protected asymmetric epoxide **III-14** with sodium azide was followed by a two-step protection to give intermediate



Scheme III-18: Synthesis of 2,3,3-trisubstituted aziridinol **III-19**

III-17. The one-pot Staudinger reduction / cyclization and tosyl protection provided the desired aziridinol **III-19** as a single enantiomer.

Cyclic 2,3,3-trisubstituted aziridinol **III-24** was synthesized using the same procedure as described for preparing 2,2,3-trisubstituted aziridinols (Scheme III-19).



Scheme III-19: Synthesis of cyclic 2,3,3-trisubstituted aziridinol **III-24**

The conjugate ester **III-22** was prepared according to the modified Horner-Wadsworth-Emmons method of Rathke and coworkers.⁷⁷ Subsequent DIBAL-H reduction and racemic aziridination gave the desired product **III-24**.

III.2.3. Synthesis of tetra-substituted aziridinols

There are not many efficient methods to prepare tetra-substituted aziridinols due

to the steric of the olefin. The only reported pathway is the stereoselective nucleophilic attack of an azirine, as described by Davis and coworkers.⁷⁸⁻⁸¹ However, since the synthesis of azirines is not routine, we opted to apply the previously discussed aziridination conditions to tetra-substituted olefins.

The standard Wittig reaction to prepare tetra-substituted olefins failed under various conditions (Table III-3). Three different substrates, ethyl methyl ketone

Table III-3: Various conditions for the Wittig reaction^a

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}_1 - \text{C} - \text{R}_2 \end{array} + \text{Ph}_3\text{P} = \text{C}(\text{Me})\text{CO}_2\text{Et} \xrightarrow[\text{X}]{\text{conditions}} \begin{array}{c} \text{R}_1 \\ \diagdown \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{R}_2 \quad \text{CO}_2\text{Et} \end{array}$$

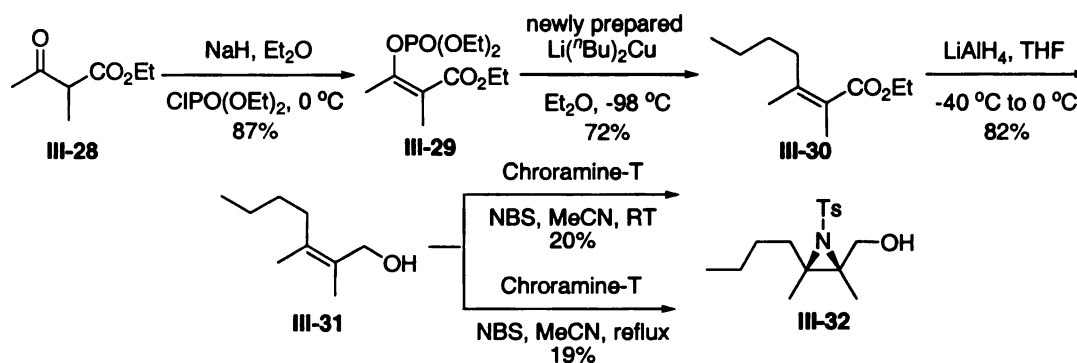
Entry	R ₁	R ₂	Substrate	Solvent	Temperature	Result
1	Et	Me	III-25	benzene	reflux	no product
2	ⁿ Bu	Me	III-26	benzene	reflux	no product
3				CH ₂ Cl ₂	RT	no product
4	ⁿ Hexyl	Me	III-27	THF	RT	S.M.
5				THF	0 °C to RT	recovered
6				THF	RT to reflux	no product

^a Substrate (1 equiv), Ylide reagent (1.2 equiv), 15 h.

III-25, *n*-butyl methyl ketone III-26, and *n*-hexyl methyl ketone III-27 were used in the Wittig reaction and none of which under various conditions (various solvents and temperatures) provided the desired tetra-substituted olefins. In 1987, Isaacs and El-Din reported that the application of high pressure could promote some difficult Wittig reactions, which included the formation of tetra-substituted olefins.⁸² The reaction between a number of ketones and [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane was performed at 9 Kbar, and as expected the desired products could be obtained. However, only acetone gave good yields of the corresponding tetra-substituted olefin, while other ketones only gave low

yields.

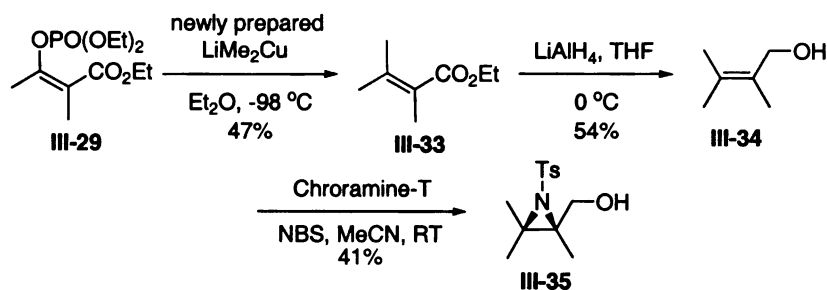
Other alternative methods to prepare tetra-substituted olefins were also considered. In 1979, Weiler and coworkers published the stereoselective synthesis of β -substituted α,β -unsaturated esters.⁸³ In their paper, they discussed the preparation of β -substituted α,β -unsaturated esters from β -keto esters in good yields and stereoselectivities. Their methodology was attempted to prepare the tetra-substituted olefin and aziridinol shown in Scheme III-20. The anion from methyl acetoacetate



Scheme III-20: Synthesis of tetra-substituted aziridinol **III-32**

III-28 was reacted with diethyl phosphorochloridate to yield the corresponding enol phosphate **III-29** as a single *cis*-isomer. This enol phosphate was then coupled with newly prepared lithium dibutylcuprate to produce the β -substituted α,β -unsaturated ester **III-30** in good yield, providing an efficient way to generate tetra-substituted olefin stereoselectively. LiAlH_4 reduction of **III-30** and aziridination of the corresponding alcohol gave the tetra-substituted aziridinol **III-32**. Presumably the sterics of the reacting olefin led to low yield of aziridination. Increasing the reaction temperature did not help to increase the yield of the reaction, and on the contrary, the higher temperature led to more side-reactions. Using lithium dimethylcuprate

instead of lithium dibutylcuprate, a similar tetra-substituted olefin **III-33** was synthesized via the same method (Scheme III-21). Since this substrate was sterically less demanding than substrate **III-30**, the aziridination gave higher yield to provide tetra-substituted aziridinol **III-35**.



Scheme III-21: Synthesis of tetra-substituted aziridinol **III-35**

III.3. Aza-Payne Rearrangement of Tri- and Tetra-Substitued Aziridinols

The aza-Payne rearrangement of tri- and tetra-substituted tosylated aziridinols was accomplished in good to excellent yields using 4.0 equiv of NaH in THF (Table III-4).

Table III-4: Aza-Payne rearrangement of tri- and tetra-substituted aziridinols to epoxy amines^a

Entry	Aziridinol	Method	Epoxy Amine	Yield (%) ^b
1	 III-1c	A	 III-1d	81
2	 III-2c	A	 III-2d	93

Table III-4: Aza-Payne rearrangement of tri- and tetra-substituted aziridinols to epoxy amines (continued)

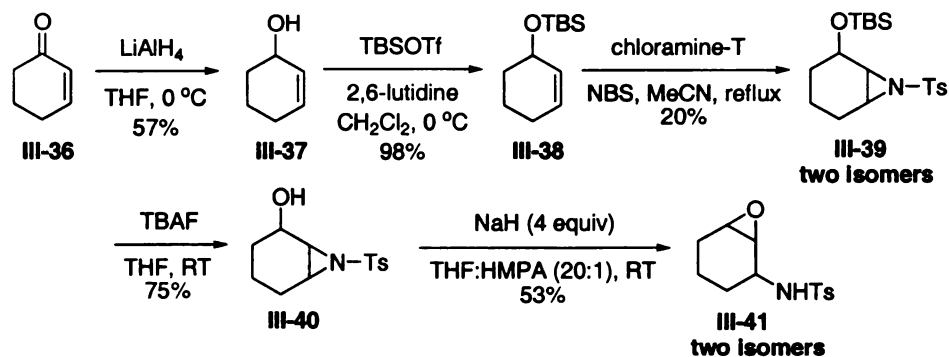
Entry	Aziridinol	Method	Epoxy Amine	Yield (%) ^b	Entry	Aziridinol
3		III-4c	A		III-4d	66
4		III-5c	A		III-5d	70
5		III-11	A		III-11d	94
6		III-19	A		III-19d	89
7		III-24	A		III-24d	93
8		III-32	A		III-32d	43
9		III-32	B		III-32d	80
10		III-32	C		III-32d	67
11		III-35	C		III-35d	74

^a Method A: aziridinol (1.0 equiv), NaH (4.0 equiv), THF(0.1M), RT. Method B: aziridinol (1.0 equiv), NaH (4.0 equiv), THF/HMPA (1:1, 0.1M), RT. Method C: aziridinol (1.0 equiv), NaH (4.0 equiv), THF/HMPA (20:1, 0.1M), RT. ^b Isolated yields.

Firstly, a series of 2,2,3-trisubstituted aziridinols bearing an aryl group at C-3 were examined (entries 1, 2, and 3). An electronic component to the facility of the aza-Payne rearrangement was noted, as the *p*-methoxyphenyl-containing substrate **III-2c** gave a 93% yield of the epoxy amine, while the *p*-trifluoromethylphenyl-containing substrate **III-4c** gave only 66% yield of **III-4d**. The electron-rich aziridinol was more active than its electron-deficient counterpart. The 2,2,3-trialkylsubstituted aziridinol **III-5c** and **III-11** provided the corresponding epoxy amine **III-5d** and **III-11d** in good to excellent yields (entries 4 and 5). The aza-Payne rearrangement was facile under these conditions even though the electrophilic center was tertiary. It was also noted that the 2,3,3-trisubstituted aziridinol **III-19** derived from geraniol was converted successfully to the epoxy amine **III-19d** as a single stereoisomer in excellent yield (entry 6), despite the fact that the analogous geraniol epoxide was resistant to the Payne rearrangement and gave only 14% of the tetrahydrofuran product.⁷ A cyclic 2,3,3-trisubstituted substrate **III-24** was also successful in the aza-Payne rearrangement (entry 7), the analogous epoxy alcohol substrate giving only 21% yield of the desired THF-containing product in the previous work.⁷ Finally, the tetra-substituted aziridinols **III-32** and **III-35** also underwent successful aza-Payne rearrangement to yield epoxy amine **III-32d** and **III-35d**, respectively. However, probably due to sterics, these substrates reacted less efficiently than tri-substituted substrates. Under the same conditions, **III-32** only gave 43% yield of the desired product (entry 8). High temperature did not help to improve the yield and gave a messy reaction. HMPA was found to be necessary to

improve the yield of the transformation (entry 9). It was remarkable that after reducing the amount of HMPA to 1/20, the reaction still afforded the desired product in good yields (entries 10 and 11).

The aza-Payne rearrangement of hindered substrates was also examined by subjecting **III-39** the same reaction conditions (Scheme III-22). 2-Cyclohexenone **III-36** was reduced with LiAlH_4 to yield intermediate **III-37**. Aziridination of alkenol **III-37** failed to provide any desired aziridinol; TBS protection of the free hydroxyl group followed by aziridination of **III-38** gave 20% yield of desired product as the mixture of two stereoisomers **III-39**. After removing the TBS group with TBAF, the aza-Payne rearrangement of **III-40** with NaH (4.0 equiv) in THF:HMPA (20:1) solution gave the desired epoxy amine **III-41** as the mixture of two isomers.



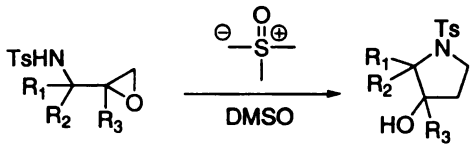
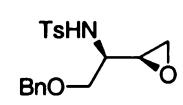
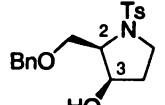
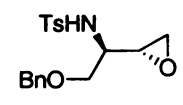
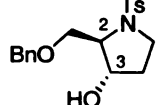
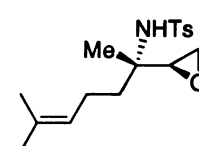
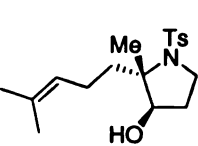
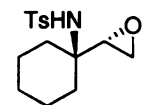
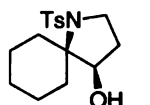
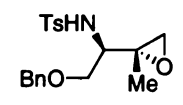
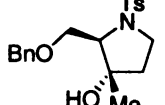
Scheme III-22: Aza-Payne rearrangement of aziridinol **III-40** to afford epoxy amine **III-41**

III.4. A One-Carbon Homologative Relay Ring Expansion to Form Diastereomerically and Enantiomerically pure 2,3-Disubstituted Pyrrolidines

Based on previous results, the aza-Payne rearrangement can successfully provide epoxy amines using NaH in THF. Therefore, the dimethylsulfoxonium methylide

mediated one-carbon homologative relay ring expansion to form pyrrolidines was investigated. A number of the epoxy amine products were treated with dimethylsulfoxonium methylide in DMSO at 85 °C to afford the corresponding 2,3-substituted pyrrolidine rings in good to excellent yields and with complete control

Table III-5: Conversion of epoxy amines to 2,3-substituted pyrrolidines^a

					
Entry	Epoxy Amine		Pyrrolidine		Yield (%) ^b
1		III-42		III-42e	99
2		III-43		III-43e	97
3		III-19d		III-19e	86
4		III-24d		III-24e	52
5		III-11d		III-11e	88

^a Epoxy amine (1 equiv), dimethylsulfoxonium methylide (4-8 equiv), DMSO (0.1M), 80-85 °C, 24 h. ^b Isolated yield.

of diastereoselectivity (Table III-5).⁷⁵ Epoxy amines **III-42** and **III-43**, generated from the disubstituted *cis*- and *trans*-aziridinols using the same conditions for the aza-Payne rearrangement, gave the *cis*- and *trans*-disubstituted pyrrolidine **III-42e** and **III-43e** in excellent yield (entries 1 and 2). The relative stereochemistries were

verified by nOe experiments that showed a greater enhancement of the H-2 proton when H-3 of the *cis* product was irradiated as compared to the *trans* product. To further establish the relative stereochemistry of the substituents at C-2 and C-3, an X-ray crystal structure of compound **III-43e** was obtained that clearly indicated the

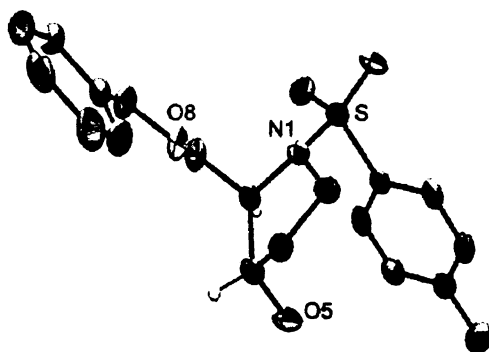
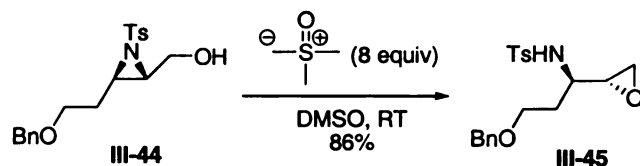


Figure III-2: X-ray crystal structure of compound **III-43e**. Most of the hydrogen atoms are not shown for better clarity.

trans orientation of the C-2 and C-3 substituents (Figure III-2). Epoxy amines derived from 2,3,3-trisubstituted aziridinols (Table III-4) also gave good yields of the pyrrolidines bearing a quaternary nitrogen center (Table III-5, entries 3 and 4). The hindered nature of the nucleophilic nitrogen in **III-24d** (entry 4), along with the strain of the spiro ring system, presumably led to a lower yield of pyrrolidine **III-24e**. Entry 5 illustrates the conversion of epoxy amine **III-11d**, to pyrrolidine **III-11e** containing a chiral 3° hydroxyl group at C-3. The relative stereochemistry of this trisubstituted pyrrolidine was established via nOe enhancement observed between the benzyl-protected hydroxymethyl side chain at C-2 and the C-3 methyl group. This again verified the anticipated stereochemical transformation of the reaction based on the mechanism depicted in Scheme III-4.

Having established high efficiency in the preparation of pyrrolidines from

aziridinols in two steps, aza-Payne rearrangement followed by treatment of isolated products with dimethylsulfoxonium methylide, a one-pot preparation of pyrrolidine was examined. Previous experiments showed that the ylide itself could serve as the base to promote aza-Payne rearrangement in DMSO (Scheme III-23), which gave the



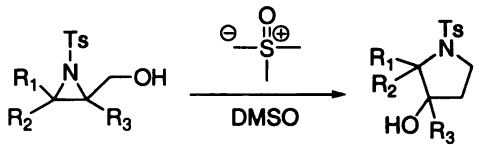
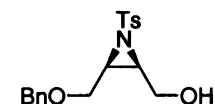
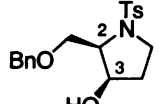
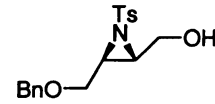
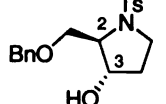
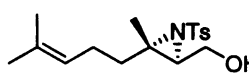
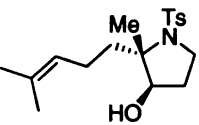
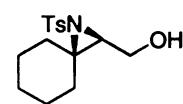
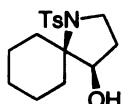
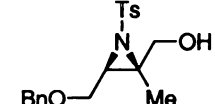
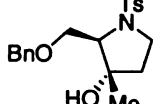
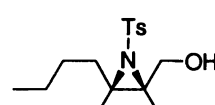
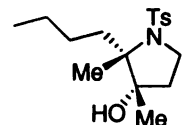
Scheme III-23: Ylide mediated aza-Payne rearrangement of aziridinol **III-44**

identical yield as using NaH in THF. This provided possibilities for further nucleophilic attack from the ylide followed by ring-closure to form pyrrolidine in one-step. Because the aza-Payne rearrangement is an intramolecular process, which may compete favorably with the intermolecular process of aziridine ring-opening with the ylide, and since the epoxide is less hindered than the aziridine in the nucleophilic attack by the ylide, we believed that the one-pot pyrrolidine formation could occur even though the aziridine has higher reactivity as compared with the epoxide. Moreover, it was found that heating the reaction to 85 °C was necessary to cause ylide ring-opening of the aziridine. Therefore, the aza-Payne rearrangement could be accomplished at a lower temperature and then the temperature could be raised to 85 °C to promote epoxide ring-opening and subsequent ring-closure to the pyrrolidine. In this manner, the undesired ring-opening of the aziridine should not compete with the desired epoxide ring-opening by the ylide.

The attempted one-pot reaction to form pyrrolidines was successful. Aziridinol **III-46** was treated with dimethylsulfoxonium methylide (generated by refluxing

trimethylfulfoxonium iodide with NaH in THF for 4 h), stirred at room temperature for 4 h, and heated to 80 °C overnight in a sealed tube. In this manner the pyrrolidine **III-42e** could be obtained in 82% yield (Table III-6, entry 1). The *cis*-substituted aziridinol gave 2,3-*cis*-pyrrolidine while the *trans*-substitued aziridinol gave 2,3-*trans*-pyrrolidine in high stereocontrol. Trisubstituted aziridiols (entries

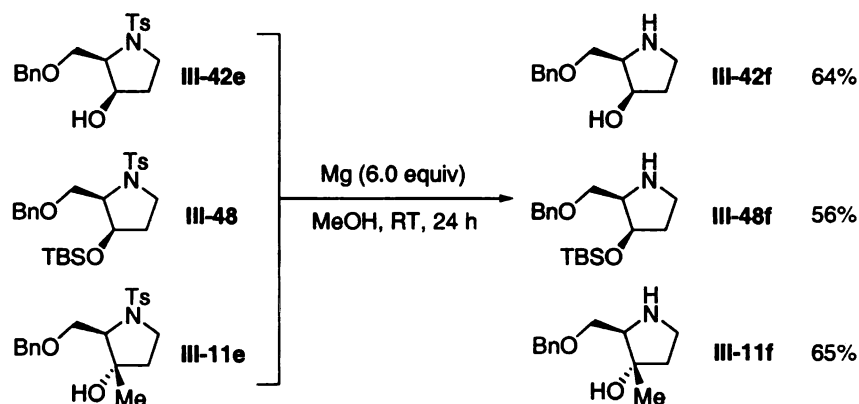
Table III-6: One-pot conversion of aziridinols to 2,3-substituted pyrrolidines^a

					
Entry	Aziridinol		Pyrrolidine		Yield (%) ^b
1		III-46		III-42e	82
2		III-47		III-43e	78
3		III-19		III-19e	70%
4		III-24		III-24e	69
5		III-11		III-11e	79
6		III-32		III-32e	67

^a Aziridinol (1 equiv), dimethylsulfoxonium methylide (8 equiv), DMSO (0.1 M), RT for 4 h followed by heating at 80 °C for 24 h. ^b Isolated yield.

3-5) proceeded under the reaction conditions to give pyrrolidines in good yields, as well as the tetra-substituted aziridiol (entry 6). Thus, a successful one-pot strategy for the synthesis of pyrrolidines from aziridinols was developed by decoupling the roles of the ylide as a base and a nucleophile by adjusting the reaction temperature.

Finally, the pyrrolidine products were subjected to deprotection conditions in order to ascertain the efficiency in removal of the nitrogen activating group. The tosyl-protected pyrrolidines could be deprotected with sodium naphthalide in glyme in moderate to good yields, but a substantial amount of debenzylated product was also formed for benzyl-protected substrates.⁸⁴ In contrast, the tosyl group was easily removed under mild conditions using Mg metal in MeOH to provide the free aziridines.⁸⁵ Using this condition on the pyrrolidines obtained from the one-pot reaction, the tosyl group could be removed in moderate yield (Scheme III-24) without affecting other protecting groups.



Scheme III-24: Deprotection of pyrrolidine products

All work related to the pyrrolidines synthesis was performed by Jennifer M. Schomaker, a PhD graduate from the Borhan laboratory, in collaboration with myself.

III.5. Summary

In summary, the aza-Payne rearrangement under basic conditions with NaH in THF favors the formation of epoxy amines. Since the aza-Payne rearrangement of highly substituted substrates has not been well-studied, we examined the aza-Payne rearrangement of 2,2,3- or 2,3,3-trisubstituted and tetra-substituted aziridinols. The ability to use tri- and tetra-substituted aziridinols in the aza-Payne rearrangement allows transfer of the terminal oxygen to a sterically hindered tertiary center, yielding a quaternary hydroxyl center upon opening of the unhindered epoxide with various nucleophiles. This can yield synthetically useful 1,2-amino alcohols of various substitution patterns that might not otherwise be easily accessible.

Moreover, based on the aza-Payne rearrangement, an one-pot efficient method has been developed for the synthesis of 2,3-substituted pyrrolidine rings via completing the relay of the three-membered to the five-membered nitrogen-containing ring system. The whole process takes place with complete transfer of stereochemistry and can be applied to sterically hindered aziridinols. Since it is simple to access these substrates in high enantiomeric excess, this can be a powerful methodology for synthesizing 2,3-substituted pyrrolidines with different substitution patterns enantiomerically and stereomerically.

III.6. Experimental Section

General Information:

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 (Et₂O) were freshly distilled from sodium/benzophenone; methylene chloride (CH₂Cl₂) and toluene was dried over calcium hydride (CaH₂) and freshly distilled prior to use; HMPA, Et₃N, DMSO, and DMF were distilled from CaH₂ and stored over 4Å molecular sieves. All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen.

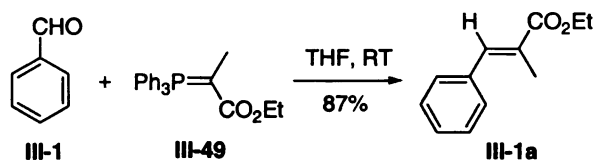
¹H NMR spectra were measured at 300 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for CDCl₃). ¹³C NMR spectra were measured at 75 MHz on a Varian Gemini-300 or at 125 MHz on a Varian VXR-500 instrument. Chemical shifts are reported relative to the central line of CDCl₃ (δ 77.0 ppm). Infrared spectra were recorded using a Nicolet IR/42 spectrometer FT-IR (thin film, NaCl cells). High resolution mass spectra were measured at the Michigan State University, Mass Spectrometry Laboratory.

Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F₂₅₄ plates. Compounds were visualized with UV light, potassium permanganate stain or *p*-anisaldehyde stain. Column chromatographic purifications were performed using Silicycle 40-60 Å, 30-75 μ m silica gel. All compounds

purified by chromatography were sufficiently pure for use in further experiments.

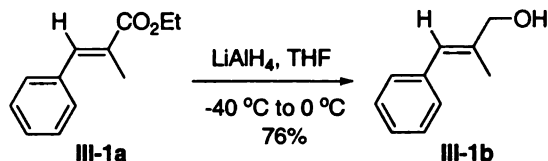
GC analysis was performed using HP (6890 series) GC system containing Altech SE-54, 30 m $\times$ 320 μ m $\times$ 0.25 μ m column.

Data for Newly Synthesized Compounds:



(*E*)-ethyl 2-methyl-3-phenylacrylate (**III-1a**)⁸⁶: To a room temperature solution of benzaldehyde **III-1** (0.1 mL, 1.0 mmol) in THF (5 mL) (carbethoxyethylidene)triphenylphosphorane (430 mg, 1.2 mmol) was added in. The reaction was stirred at RT for 15 h. Add some silica gel to the reaction and the solvent was removed under reduced pressure providing yellow powder, which was purified by silica gel column chromatography (3% EtOAc/hexanes) to furnish conjugate ester **III-1a** as a colorless oil (165 mg, 87% yield).

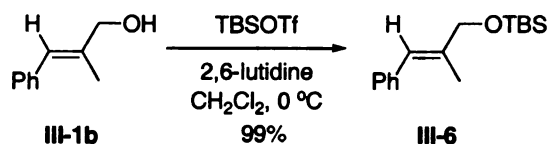
Data for **III-1a**: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (1H, s), 7.42-7.26 (5H, m), 4.26 (2H, q, J = 7.2 Hz), 2.10 (3H, s), 1.34 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 138.6, 135.9, 129.6, 128.6, 128.3, 128.2, 60.8, 14.3, 14.0.



(*E*)-2-methyl-3-phenylprop-2-en-1-ol (**III-1b**)⁸⁷: Lithium aluminum hydride (35 mg, 0.93 mmol) was suspended in 2 mL THF. The mixture was cooled to -40 °C. A solution of the ester (88 mg, 0.46 mmol) in 1 mL THF was added slowly dropwise.

The mixture was warmed to 0 °C for 1 hr. 10% HCl solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH₄ has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5×). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (20% EtOAc/hexanes) to give the desired primary alcohol in 76% yield.

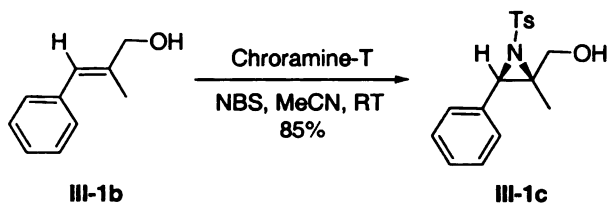
Data for **III-1b**: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.19 (5H, m), 6.51 (1H, s), 4.17 (2H, s), 1.89 (3H, s), 1.76 (1H, br); ¹³C NMR (75 MHz, CDCl₃) δ 168.3, 142.5, 127.6, 60.4, 31.5, 28.6, 28.2, 22.5, 14.3, 14.0, 12.3.



(E)-*tert*-butyldimethyl(2-methyl-3-phenylallyloxy)silane (**III-6**): The solution of allylic alcohol **III-1b** (43 mg, 0.29 mmol) in CH₂Cl₂ (2 mL) was cooled to 0 °C. 2,6-lutidine (41 μL, 0.35 mmol) and TBSOTf (86 μL, 0.35 mmol) were added dropwise to the solution. The reaction was stirred at 0 °C for 1 h. Saturated NH₄Cl (aq., 4 mL) was added to quench the reaction. Separation followed by extraction with CH₂Cl₂ (3×3 mL) gave the colorless organic level, which dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (3% EtOAc/hexanes) to give the protected alcohol **III-6** in 99% yield (75 mg).

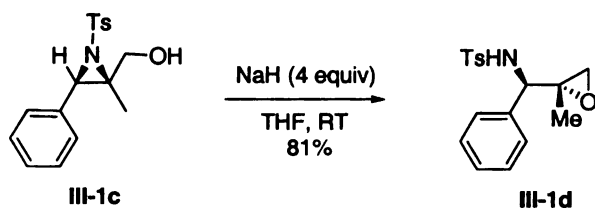
Data for **III-6**: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.16 (5H, m), 6.56 (1H, s), 4.18

(2H, s), 1.84 (3H, s), 0.97-0.91 (9H, m), 0.15-0.11 (6H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.0, 137.4, 128.9, 128.0, 126.1, 123.7, 68.5, 25.9, 18.4, 15.0, -5.2.



(2-Methyl-3-phenyl-1-tosylaziridin-2-yl)methanol (III-1c): The corresponding alkene (55 mg, 0.37 mmol) was placed in 6 mL of dry acetonitrile and treated with anhydrous Chloramine-T (85 mg, 0.37 mmol) and a catalytic amount of NBS (13 mg, 0.074 mmol) at RT. The reaction rapidly turned to bright yellow slurry. The reaction was stirred at RT overnight, the diluted with an equal amount of water. The reaction was extracted with portions of ethyl acetate (3 $\times$), the combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvents were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give the aziridinol **III-1c** in 85% yield.

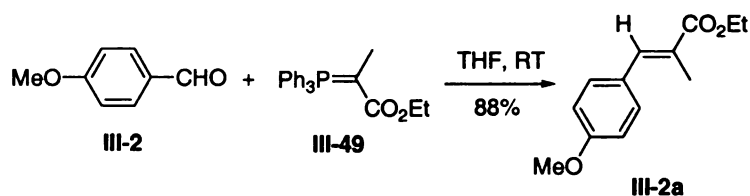
Data for **III-1c**: ^1H NMR (300 MHz, CDCl_3) δ 7.84 (2H, d, J = 8.2 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.24-7.21 (3H, m), 7.18-6.98 (2H, m), 4.21 (1H, s), 4.21-4.16 (2H, m), 3.21-3.17 (1H, br), 2.42 (3H, s), 1.15 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 144.2, 137.4, 133.0, 129.6, 128.3, 127.8, 127.1, 127.0, 65.5, 60.3, 59.2, 51.3, 21.6, 16.0, 14.1; IR (thin film) 3526 (br), 2934, 1599, 1497, 1453, 1404, 1321, 1290, 1156, 1092, 1042, 932, 874 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3\text{S}$, 318.1164 m/z ($\text{M}+\text{H}$) $^+$; observed, 318.1171 m/z .



4-Methyl-N-(2-methyloxiran-2-yl)(phenyl)methylbenzenesulfonamide (**III-1d**):

Sodium hydride (25 mg, 1.06 mmol, 4.0 equiv) was suspended in 3 mL of dry THF and the latter aziridinol **III-1c** (84 mg, 0.26 mmol, 1.0 equiv) was added. The suspension was stirred at RT for 4 h and carefully quenched with saturated ammonium chloride solution. The aqueous layer was extracted (3×) with portions of ethyl acetate and the volatiles were removed via rotary evaporation. The residue was purified using column chromatography (10% EtOAc/hexanes) to give the epoxy amine **III-1d** in 81% yield.

Data for **III-1d**: ^1H NMR (300 MHz, CDCl_3) δ 7.46 (2H, d, $J = 8.2$ Hz), 7.20-7.03 (7H, m), 5.26 (1H, d, $J = 5.5$ Hz), 4.33 (1H, m), 2.60 (1H, d, $J = 4.3$ Hz), 2.50 (1H, d, $J = 4.4$ Hz), 2.32 (3H, s), 1.25 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 143.1, 137.0, 136.5, 129.2, 128.3, 127.9, 127.6, 127.1, 60.8, 58.7, 51.7, 21.4, 18.9; IR (thin film) 3277 (br), 2926, 1653, 1599, 1495, 1456, 1329, 1101, 1090, 1063, 814 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_3\text{S}$, 318.1164 m/z ($\text{M}+\text{H}$) $^+$; observed, 318.1161 m/z .

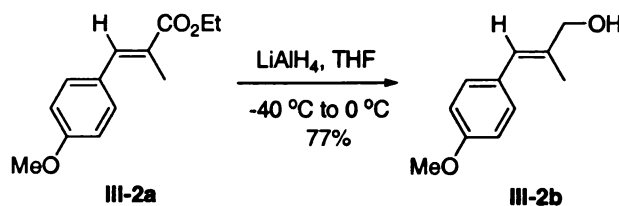


(*E*)-ethyl 3-(4-methoxyphenyl)-2-methylacrylate (**III-2a**)⁸⁶:

(Carbethoxyethylidene)triphenylphosphorane (0.87 g, 2.4 mmol) was suspended in 10 mL THF. Anisaldehyde (0.24 mL, 2.0 mmol) was added dropwise to the yellow

slurry. The reaction was allowed to stir overnight. Some silica gel was added to the reaction mixture. The solvent was removed under reduced pressure and the yellow solid was purified via column chromatography (3% EtOAc) to give the alkene **III-2a** in 88% yield.

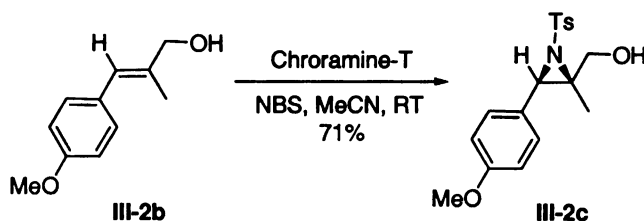
Data for **III-2a**: ^1H NMR (300 MHz, CDCl_3) δ 7.61 (1H, s), 7.34 (2H, d, $J = 8.8$ Hz), 6.88 (2H, d, $J = 8.8$ Hz), 4.22 (2H, q, $J = 7.1$ Hz), 3.78 (3H, s), 2.09 (3H, s), 1.31 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 168.8, 159.5, 138.2, 131.3, 128.4, 126.3, 113.7, 60.6, 55.1, 14.2, 13.9.



(*E*)-3-(4-methoxyphenyl)-2-methylprop-2-en-1-ol (**III-2b**)⁸⁸: Lithium aluminum hydride (78 mg, 2.04 mmol) was suspended in 6 mL THF. The mixture was cooled to -40 °C. A solution of the ester (225 mg, 1.02 mmol) in 3 mL THF was added slowly dropwise. The mixture was warmed to 0 °C for 1 hr. 10% HCl solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH_4 has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5 $\times$). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (20% EtOAc/hexanes) to give the desired primary alcohol **III-2b** in 77% yield.

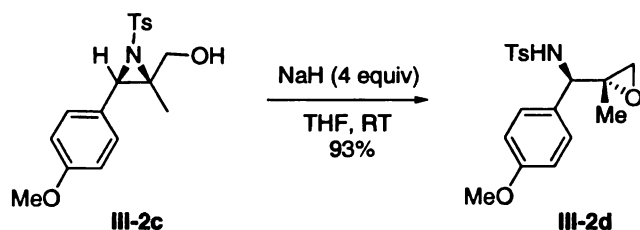
Data for **III-2b**: ^1H NMR (300 MHz, CDCl_3) δ 7.19 (2H, d, $J = 8.8$ Hz), 6.84 (2H, d,

$J = 8.8$ Hz), 6.43 (1H, s), 4.13 (2H, s), 3.78 (3H, s), 2.23 (1H, br), 1.87 (3H,s); ^{13}C NMR (75 MHz, CDCl_3) δ 158.0, 136.0, 130.1, 129.9, 124.5, 113.5, 69.0, 55.1, 15.2.



[3-(4-Methoxyphenyl)-2-methyl-1-tosylaziridin-2-yl]methanol (**III-2c**): The corresponding alkene **III-2b** (135 mg, 0.76 mmol) was placed in 10 mL of dry acetonitrile and treated with anhydrous Chloramine-T (173 mg, 0.76 mmol) and a catalytic amount of NBS (27mg, 0.15 mmol) at RT. The reaction rapidly turned to bright yellow slurry. The reaction was stirred at RT overnight, the diluted with an equal amount of water. The reaction was extracted with portions of ethyl acetate (3 $\times$), the combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvents were removed via rotary evaporation. The residue was purified using column chromatography (30% EtOAc/hexanes) to give the aziridinol **III-2c** in 71% yield.

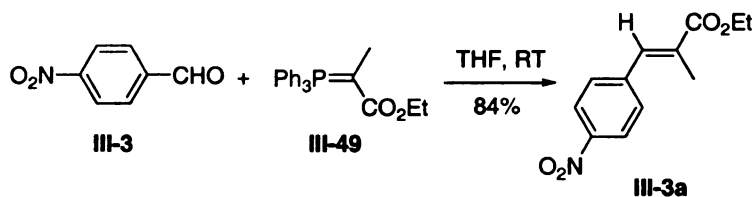
Data for **III-2c**: ^1H NMR (300 MHz, CDCl_3) δ 7.82 (2H, d, $J = 8.2$ Hz), 7.28 (2H, d, $J = 8.0$ Hz), 6.92 (2H, d, $J = 8.8$ Hz), 6.75 (2H, d, $J = 8.5$ Hz), 4.15-4.12 (2H, m), 3.71 (3H, s), 2.40 (3H, s), 1.15 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 159.2, 144.1, 137.4, 129.6, 128.1, 127.0, 124.8, 113.7, 65.4, 59.1, 55.1, 51.0, 21.5, 15.9; IR (thin film) 3522 (br), 2957, 2934, 2838, 1736, 1613, 1516, 1458, 1400, 1349, 1250, 1157, 1092, 1036, 880, 816 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_4\text{S}$, 348.1270 m/z ($\text{M}+\text{H}$) $^+$; observed, 348.1274 m/z .



N-[(4-methoxyphenyl)(2-methyloxiran-2-yl)methyl]-4-methylbenzenesulfonamide

(III-2d): Sodium hydride (36 mg, 1.50 mmol, 4.0 equiv) was suspended in 10 mL of dry THF and the aziridinol **III-2c** (130 mg, 0.37 mmol, 1.0 equiv) was added. The suspension was stirred at RT for 4 hr and carefully quenched with saturated ammonium chloride solution. The aqueous layer was extracted (3×) with portions of ethyl acetate and the volatiles were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give the epoxy amine **III-2d** in 93% yield.

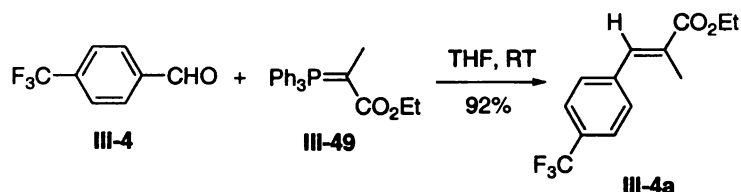
Data for **III-2d**: ^1H NMR (300 MHz, CDCl_3) δ 7.47 (2H, d, $J = 8.0$ Hz), 7.06 (2H, d, $J = 8.0$ Hz), 6.96 (2H, d, $J = 8.5$ Hz), 6.63 (2H, d, $J = 8.8$ Hz), 5.57 (1H, d, $J = 6.1$ Hz), 4.27 (1H, d, $J = 6.1$ Hz), 3.70 (3H, s), 2.57 (1H, d, $J = 4.4$ Hz), 2.47 (1H, d, $J = 4.4$ Hz), 2.31 (3H, s), 1.22 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 159.1, 142.9, 137.1, 129.1, 128.6, 128.5, 127.0, 113.5, 60.4, 58.7, 55.1, 51.7, 21.3, 18.6; IR (thin film) 3279 (br), 2934, 1613, 1514, 1443, 1327, 1250, 1101, 1094, 1067, 1034, 814 cm^{-1} .



(E)-ethyl-2-methyl-3-(4-nitrophenyl)acrylate (**III-3a**)⁸⁹: In 10 mL THF, (carbethoxyethylidene)triphenylphosphorane (0.87 g, 2.4 mmol) was suspended. *P*-

nitrobenzaldehyde (0.302 mg, 2.0 mmol) was added dropwise to the yellow slurry. The reaction was allowed to stir overnight. Some silica gel was added to the reaction mixture. The solvent was removed under reduced pressure and the yellow solid was purified via column chromatography (3% EtOAc/hexanes) to give the alkene **III-3a** in 84% yield.

Data for **III-3a**: ^1H NMR (300 MHz, CDCl_3) δ 8.18 (2H, d, $J = 8.8$ Hz), 7.63 (1H, s), 7.47 (2H, d, $J = 8.8$ Hz), 4.23 (2H, q, $J = 7.1$ Hz), 2.06 (3H, s), 1.30 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 167.6, 147.0, 142.4, 135.8, 132.1, 130.1, 123.5, 61.2, 14.1, 14.0.

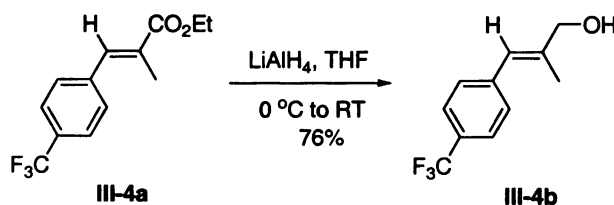


(*E*)-ethyl-2-methyl-3-(4-(trifluoromethyl)phenyl)acrylate (**III-4a**):

(Carbethoxyethylidene)triphenylphosphorane (0.87 g, 2.4 mmol) was suspended in 10 mL THF. α,α,α -trifluoro-*p*-tolualdehyde (0.27 mL, 2.0 mmol) was added dropwise to the yellow slurry. The reaction was allowed to stir overnight. Some silica gel was added to the reaction mixture. The solvent was removed under reduced pressure and the yellow solid was purified via column chromatography (3% EtOAc/hexanes) to give the alkene **III-4a** in 92% yield.

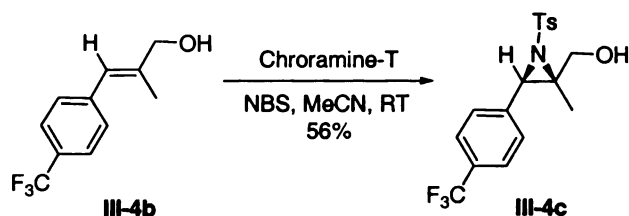
Data for **III-4a**: ^1H NMR (300 MHz, CDCl_3) δ 7.66-7.58 (3H, m), 7.47-7.40 (2H, m), 4.26 (2H, q, $J = 7.1$ Hz), 2.07 (3H, s), 1.34 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 168.2, 139.5, 136.9, 130.8, 129.7, 128.1, 125.3, 125.2, 61.1, 14.3, 14.0; IR (thin film) 2917, 2849, 1738, 1462, 1325, 1252, 1127 cm^{-1} ; LRMS (70 ev, EI) m/z

258 [M]⁺, 213 [M-CH₃CH₂O]⁺; HRMS (ES) calcd for C₁₃H₁₃F₃O₂, 258.0868 *m/z* [M+H]⁺; observed, 258.0869 *m/z*.



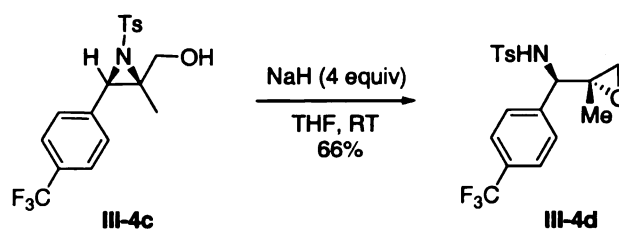
(*E*)-2-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (**III-4b**): Lithium aluminum hydride (0.14 g, 3.68 mmol) was suspended in 10 mL THF. The mixture was cooled to 0 °C. A solution of the ester (0.475 g, 1.84 mmol) in 2 mL THF was added dropwise over 10 min. The mixture was warmed to room temperature for 1 hr. 10% HCl solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH₄ has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5×). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (15% EtOAc/hexanes) to give the desired primary alcohol **III-4b** in 76% yield.

Data for **III-4b**: ¹H NMR (300 MHz, CDCl₃) δ 7.54 (2H, d, *J* = 7.9 Hz), 7.32 (2H, d, *J* = 8.2 Hz), 6.53 (1H, s), 4.17 (2H, s), 2.42 (1H, br), 1.85 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 141.2, 139.9, 128.9, 129.4, 126.7, 125.0, 123.2, 68.2, 15.1; IR (thin film) 3387 (br), 2926, 1653, 1616, 1456, 1325, 1420, 1327, 1165, 1124, 1069, 1017 cm⁻¹; LRMS (70 ev, EI) *m/z* 216 [M]⁺, 201 [M-CH₃]⁺; HRMS (ES) calcd for C₁₁H₁₁F₃O, 216.0762 *m/z* [M+H]⁺; observed, 216.0762 *m/z*.



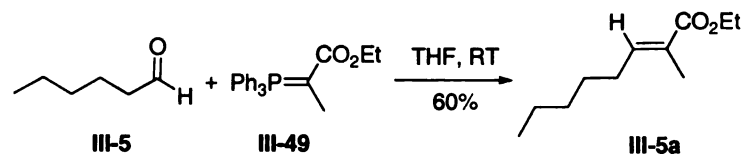
[2-methyl-1-tosyl-3-(4-(trifluoromethyl)phenyl)aziridin-2-yl]methanol (**III-4c**): The corresponding alkene **III-4b** (300 mg, 1.39 mmol) was placed in 15 mL of dry acetonitrile and treated with anhydrous Chloramine-T (316 mg, 1.39 mmol) and a catalytic amount of NBS (49 mg, 0.28 mmol) at RT. The reaction rapidly turned to bright yellow slurry. The reaction was stirred at RT overnight, the diluted with an equal amount of water. The reaction was extracted with portions of ethyl acetate (3×), the combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvents were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give the aziridinol **III-4c** in 56% yield.

Data for **III-4c**: ^1H NMR (300 MHz, CDCl_3) δ 7.82 (2H, d, $J = 8.2$ Hz), 7.52-7.42 (3H, m), 7.30 (2H, d, $J = 6.9$ Hz), 7.11 (2H, d, $J = 7.8$ Hz), 4.23-4.18 (2H, m), 2.41 (3H, s), 1.12 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 144.5, 137.1, 129.7, 129.4, 129.0, 127.4, 127.0, 126.8, 126.7, 125.3, 125.2, 65.1, 60.4, 59.1, 50.5, 21.5, 20.9, 16.0, 14.0; IR (thin film) 3447 (br), 2919, 2849, 1653, 1618, 1456, 1325, 1159, 1127, 1068 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{18}\text{H}_{19}\text{F}_3\text{NO}_3\text{S}$, 386.1038 m/z $[\text{M}+\text{H}]^+$; observed, 386.1054 m/z .



4-Methyl-N-(2-methyloxiran-2-yl)(4-(trifluoromethyl)phenyl)methylbenzenesulfonamide (**III-4d**): Sodium hydride (45 mg, 1.87 mmol) was suspended in 10 mL of dry THF and the aziridinol **III-4c** (84 mg, 0.26 mmol) was added. The suspension was stirred at RT for 4 h and carefully quenched with saturated ammonium chloride solution. The aqueous layer was extracted (3×) with portions of ethyl acetate and the volatiles were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give the epoxy amine **III-4d** in 66% yield.

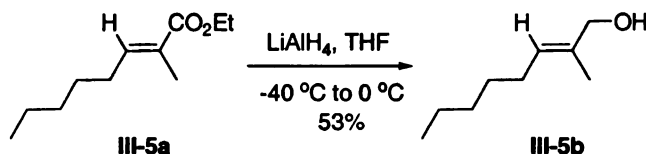
Data for **III-4d**: ^1H NMR (300 MHz, CDCl_3) δ 7.43 (2H, d, $J = 8.0$ Hz), 7.33 (2H, d, $J = 8.2$ Hz), 7.16 (2H, d, $J = 7.9$ Hz), 7.03 (2H, d, $J = 8.2$ Hz), 5.70 (1H, d, $J = 6.3$ Hz), 4.44 (1H, d, $J = 6.3$ Hz), 2.56-2.49 (2H, m), 2.29 (3H, s), 1.29 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 143.5, 140.4, 136.7, 129.4, 129.3, 128.1, 127.0, 125.1, 125.0, 60.6, 58.4, 51.7, 21.2, 18.8; IR (thin film) 3276 (br), 2932, 2874, 1620, 1599, 1437, 1327, 1183, 1125, 1069, 858, 814 cm^{-1} .



(E)-ethyl-2-methyloct-2-enoate (**III-5a**)⁸⁹: In 10 mL THF, (carbethoxyethylidene)triphenylphosphorane (0.87 g, 2.4 mmol) was suspended. Hexanal (0.24 mL, 2.0 mmol) was added dropwise to the yellow slurry. The

reaction was allowed to stir overnight. Some silica gel was added to the reaction mixture. The solvent was removed under reduced pressure and the yellow solid was purified via column chromatography (3% EtOAc/hexanes) to give the alkene **III-5a** in 60% yield.

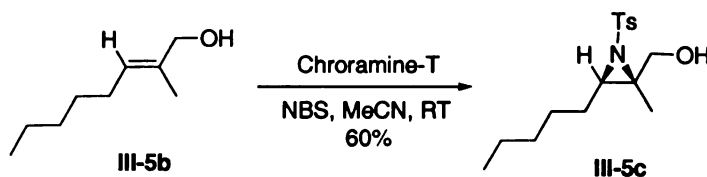
Data for **III-5a**: ^1H NMR (300 MHz, CDCl_3) δ 6.79-6.69 (1H, m), 4.16 (2H, q, J = 7.2 Hz), 2.19-2.08 (2H, m), 1.80 (3H, s), 1.50-1.32 (2H, m), 1.32-1.21 (7H, m), 0.87 (3H, t, J = 6.9 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 168.3, 142.5, 127.6, 60.4, 31.5, 28.6, 28.2, 22.5, 14.3, 14.0, 12.3.



(*E*)-2-methyloct-2-en-1-ol (**III-5b**)⁹⁰: Lithium aluminum hydride (87 mg, 2.28 mmol) was suspended in 10 mL THF. The mixture was cooled to $0\text{ }^\circ\text{C}$. A solution of the ester **III-5a** (0.21 g, 1.14 mmol) in 2 mL THF was added dropwise over 10 min. The mixture was warmed to room temperature for 1 hr. 10% HCl solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH_4 has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5 $\times$). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (10% EtOAc/hexanes) to give the desired primary alcohol **III-5b** in 53% yield.

Data for **III-5b**: ^1H NMR (300 MHz, CDCl_3) δ 5.41-5.33 (1H, m), 3.95 (2H, s), 2.05-1.91 (2H, m), 1.69 (1H, br), 1.61 (3H, s), 1.98-1.21 (6H, m), 0.97-0.82 (3H, m);

^{13}C NMR (75 MHz, CDCl_3) δ 134.5, 126.5, 68.9, 31.5, 29.1, 27.5, 22.5, 14.0, 13.5.

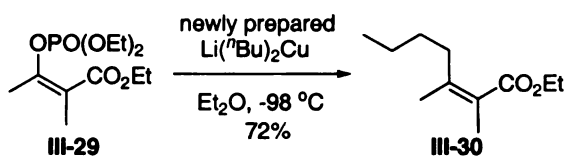


[2-methyl-3-pentyl-1-tosylaziridin-2-yl]methanol (**III-5c**): The corresponding alkene **III-5b** (84 mg, 0.59 mmol) was placed in 10 mL of dry acetonitrile and treated with anhydrous Chloramine-T (135 mg, 0.59 mmol) and a catalytic amount of NBS (21 mg, 0.12 mmol) at RT. The reaction rapidly turned to bright yellow slurry. The reaction was stirred at RT overnight, the diluted with an equal amount of water. The reaction was extracted with portions of ethyl acetate (3 $\times$), the combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvents were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give aziridinol **III-5c** in 60% yield.

Data for **III-5c**: ^1H NMR (300 MHz, CDCl_3) δ 7.78 (2H, d, J = 8.2 Hz), 7.27 (2H, d, J = 7.9 Hz), 4.01-3.92 (2H, m), 3.18-3.08 (1H, m), 3.01-2.96 (1H, m), 2.40 (3H, s), 1.47-1.25 (1H, m), 1.38 (3H, s), 1.21-1.07 (6H, m), 1.16 (3H, t, J = 3.3 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 143.9, 137.5, 129.4, 127.1, 65.6, 57.6, 50.5, 31.1, 27.0, 26.9, 22.3, 21.5, 16.1, 13.7; IR (thin film) 3522 (br), 2957, 2930, 2861, 1462, 1317, 1156, 1092, 1038, 922, 816 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{S}$, 312.1633 m/z [$\text{M}+\text{H}$] $^+$; observed, 312.1649 m/z .

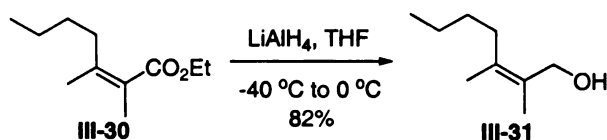
mL, 1.1 mmol) was introduced and stirring was continued for 2 h at RT. The reaction mixture was stirred with excess solid ammonium chloride for 20 min, filtered through Celite pad, and the solvent evaporated under reduced pressure. The enol phosphate **III-29** was then purified by silica gel chromatography (20% to 50% EtOAc/hexanes) in 87% yield as a colorless oil.

Data for **III-29**: ^1H NMR (300 MHz, CDCl_3) δ 4.19-3.95 (6H, m), 2.03-1.98 (3H, m), 1.82-1.71 (3H, m), 1.37-1.18 (9H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 166.7, 148.9, 114.1, 64.2, 60.2, 17.8, 15.8, 14.4, 13.9.



(*Z*)-ethyl-2,3-dimethylhept-2-enoate (**III-30**)⁸³: 2.5 M *n*-butyllithium (4.90 mL, 12.24 mmol) in hexanes was added to a white suspension of newly purified cuprous iodide (1.17g, 6.12 mmol) in dry ether (10 mL) under nitrogen and at -50 °C. The resulting dark brown solution was stirred at -50 °C for 15 min before use. The enol phosphate **III-29** (0.69g, 2.45 mmol) in dry ether (5 mL) was added to a cooled, -50 °C to -98 °C, solution of the lithium dibutylcuprate solution prepared as described above. The resulting dark purple solution was stirred at -98 °C for 2 h and worked up by pouring it into saturated ammonium chloride solution. The aqueous layer was extracted with ether (4×). The extracts were combined, washed with brine (2×), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography (3% to 10% EtOAc/hexanes) to provide tetra-substituted alkene **III-30** in 72% yield.

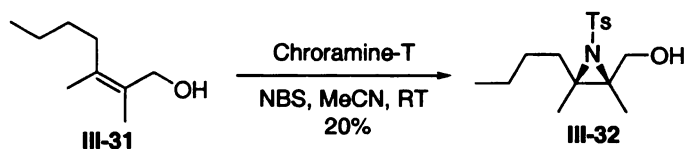
Data for **III-30**: ^1H NMR (300 MHz, CDCl_3) δ 4.14 (2H, q, $J = 6.6$ Hz), 2.29 (2H, t, $J = 7.4$ Hz), 1.81 (3H, s), 1.74 (3H, s), 1.42-1.22 (7H, m), 0.87 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 169.9, 146.1, 122.6, 100.5, 59.9, 36.1, 30.6, 22.8, 20.0, 15.8, 14.2, 13.9.



(*Z*)-2,3-dimethylhept-2-en-1-ol (**III-31**): Lithium aluminum hydride (0.25 g, 6.53 mmol) was suspended in 10 mL THF. The mixture was cooled to -40 $^\circ\text{C}$. A solution of the ester **III-30** (0.60 g, 3.27 mmol) in 3 mL THF was added dropwise over 10 min. The mixture was warmed to 0 $^\circ\text{C}$ for 1 hr. Saturated ammonium chloride solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH_4 has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5 $\times$). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (10% EtOAc/hexanes) to give the desired primary alcohol **III-31** in 82% yield.

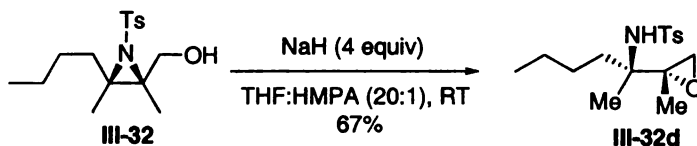
Data for **III-31**: ^1H NMR (300 MHz, CDCl_3) δ 4.09 (2H, s), 2.07 (2H, t, $J = 7.4$ Hz), 1.72 (3H, s), 1.65 (3H, s), 1.38-1.17 (6H, m), 1.09 (1H, br), 0.88 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 133.8, 127.6, 63.6, 33.8, 31.3, 22.7, 18.8, 16.6, 14.0; IR (thin film) 3316 (br), 2968, 2926, 2848, 1437, 1223, 1008 cm^{-1} ; LRMS (70 ev, EI) m/z 142 $[\text{M}]^+$, 124 $[\text{M}-\text{H}_2\text{O}]^+$; HRMS (ES) calcd for $\text{C}_9\text{H}_{18}\text{O}$, 142.1358 m/z $[\text{M}+\text{H}]^+$;

observed, 142.1365 m/z .



(3-Butyl-2,3-dimethyl-1-tosylaziridin-2-yl)methanol (**III-32**): The alkene **III-31** (110 mg, 0.77 mmol) was placed in 10 mL of dry acetonitrile and treated with anhydrous Chloramine-T (176 mg, 0.77 mmol) and a catalytic amount of NBS (28 mg, 0.15 mmol) at RT. The reaction rapidly turned to bright yellow slurry. The reaction was stirred at RT overnight, the diluted with an equal amount of water. The reaction was extracted with portions of ethyl acetate (3 $\times$), the combined organic layer was washed with brine, dried over anhydrous sodium sulfate and the solvents were removed via rotary evaporation. The residue was purified using column chromatography (10% to 20% EtOAc/hexanes) to give the tetra-substituted aziridinol **III-32** in 20% yield.

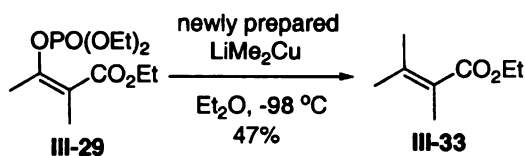
Data for **III-32**: ^1H NMR (300 MHz, CDCl_3) δ 7.77 (2H, d, J = 8.2 Hz), 7.27 (2H, d, J = 7.9 Hz), 3.82-3.78 (1H, m), 3.64-3.58 (1H, m), 2.40 (3H, s), 1.76-1.62 (2H, m), 1.62 (3H, s), 1.53 (3H, s), 1.29-1.08 (6H, m), 0.82 (3H, t, J = 4.4 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 143.6, 139.0, 129.4, 126.9, 100.5, 64.9, 57.1, 34.1, 28.3, 22.7, 21.5, 16.7, 14.6, 13.9; IR (thin film) 3513 (br), 2959, 2932, 2872, 1458, 1381, 1316, 1289, 1156, 1092, 1046, 918, 814 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{S}$, 312.1633 m/z [$\text{M}+\text{H}$] $^+$; observed, 312.1642 m/z .



4-Methyl-N-[2-(2-methyloxiran-2-yl)hexan-2-yl]benzenesulfonamide (**III-32d**):

Sodium hydride (11 mg, 0.45 mmol) was suspended in 2 mL of dry THF and 0.1 mL dry HMPA. The aziridinol **III-32** (35 mg, 0.11 mmol) was added. The suspension was stirred at RT overnight and carefully quenched with saturated ammonium chloride solution. The aqueous layer was extracted (3×) with portions of ethyl acetate and the volatiles were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give the desired product epoxy amine **III-32d** in 67% yield.

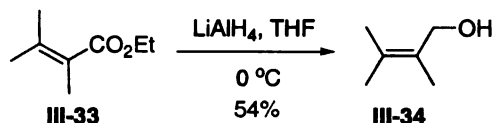
Data for **III-32d**: ^1H NMR (300 MHz, CDCl_3) δ 7.71 (2H, d, $J = 8.2$ Hz), 7.24 (2H, d, $J = 8.0$ Hz), 4.88 (1H, s), 2.61 (1H, d, $J = 9.3$ Hz), 2.38- 2.35 (4H, m), 1.61-1.41 (2H, m), 1.24-1.04 (10H, m), 0.80 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 142.9, 140.1, 129.4, 126.9, 60.6, 59.2, 49.4, 37.4, 25.3, 22.7, 22.0, 21.4, 17.4, 13.8; IR (thin film) 3285 (br), 2955, 2872, 1456, 1387, 1327, 1155, 1094, 978, 816 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_3\text{S}$, 312.1633 m/z [$\text{M}+\text{H}$] $^+$; observed, 312.1619 m/z .



Ethyl 2,3-dimethylbut-2-enoate (**III-33**)⁸³: 1.6 M methyllithium (16.4 mL, 26.2 mmol) was added to a white suspension of newly purified cuprous iodide (2.5 g, 13.1 mmol) in dry ether (20 mL) under nitrogen and at 0 $^\circ\text{C}$. The colorless solution was used directly. The enol phosphate **III-29** (2.45 g, 8.75 mmol) in ether (5 mL) was added to a cooled, 0 $^\circ\text{C}$ to $-98\text{ }^\circ\text{C}$, solution of the lithium dimethylcuprate prepared as above. The resulting red cloudy solution was stirred at $-98\text{ }^\circ\text{C}$ for 1 h and worked up by

pouring it into saturated ammonium chloride solution. The aqueous layer was extracted with ether (4×). The extracts were combined, washed with brine (2×), dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The product was purified by silica gel chromatograph (3% EtOAc/hexanes) to give desired product **III-33** in 47% yield.

Data for **III-33**: ^1H NMR (300 MHz, CDCl_3) δ 4.16 (2H, q, $J = 7.1$ Hz), 1.98 (3H, s), 1.83 (3H, s), 1.78 (3H, s), 1.27 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 169.5, 142.6, 122.4, 59.7, 22.6, 22.1, 15.4, 14.1.

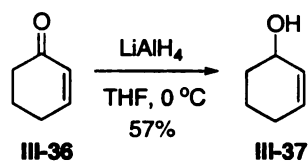


2,3-Dimethylbut-2-en-1-ol (**III-34**)⁹¹: Lithium aluminum hydride (0.266 g, 7.0 mmol) was suspended in 10 mL THF. The mixture was cooled to 0 °C. A solution of the ester **III-33** (0.50 g, 3.5 mmol) in 5 mL THF was added dropwise over 10 min. The mixture was stirred at 0 °C for 2 hr. Saturated ammonium chloride solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH_4 has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5×). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (10% EtOAc/hexanes) to give the desired primary alcohol **III-34** in 54% yield.

Data for **III-34**: ^1H NMR (300 MHz, CDCl_3) δ 4.05 (2H, s), 1.88 (1H, br), 1.68 (6H, s), 1.62 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 128.8, 127.3, 63.6, 20.7, 19.8, 16.4.

dry HMPA. The aziridinol **III-35** (69 mg, 0.26 mmol) was added. The suspension was stirred at rt overnight and carefully quenched with saturated ammonium chloride solution. The aqueous layer was extracted (3×) with portions of ethyl acetate and the volatiles were removed via rotary evaporation. The residue was purified using column chromatography (20% EtOAc/hexanes) to give the desired product epoxy amine **III-35d** in 74% yield.

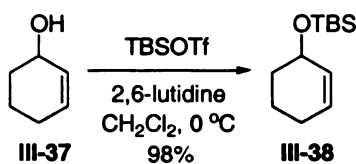
Data for **III-35d**: ^1H NMR (300 MHz, CDCl_3) δ 7.72 (2H, d, $J = 8.2$ Hz), 7.25 (2H, d, $J = 8.2$ Hz), 4.89 (1H, s), 2.90 (1H, d, $J = 4.4$ Hz), 2.48 (1H, d, $J = 4.4$ Hz), 2.38 (3H, s), 1.27 (3H, s), 1.21 (3H, s), 1.19 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 143.0, 140.1, 129.5, 126.9, 61.2, 57.3, 51.8, 24.3, 23.0, 21.4, 17.3; IR (thin film) 3277 (br), 2986, 2930, 1456, 1381, 1323, 1159, 1093, 999, 815 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_3\text{S}$, 270.1164 m/z $[\text{M}+\text{H}]^+$; observed, 270.1169 m/z .



2-Cyclohexenol (**III-37**)⁹²: Lithium aluminum hydride (0.15 g, 4.0 mmol) was suspended in 6 mL THF. The mixture was cooled to 0 °C. A solution of the ketone **III-36** (0.19 mL, 2.0 mmol) in 2 mL THF was added dropwise over 10 min. The mixture was stirred at 0 °C for 2 hr. Saturated ammonium chloride solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH_4 has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5×). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed under

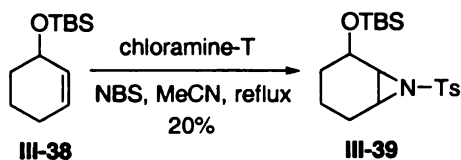
reduced pressure and the residue was purified using column chromatography (10% EtOAc/hexanes) to give the allylic alcohol **III-37** in 57% yield.

Data for **III-37**: ^1H NMR (300 MHz, CDCl_3) δ 5.89-5.63 (2H, m), 4.12 (1H, s), 2.16 (1H, br), 2.03-1.46 (6H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 130.2, 129.9, 65.3, 31.8, 24.9, 18.9.

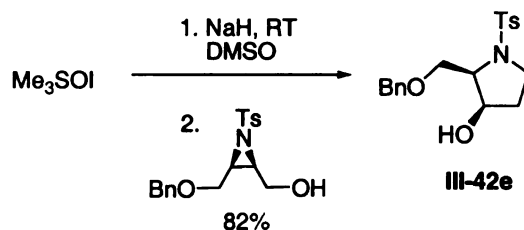


Tert-butyl(cyclohex-2-enyloxy)dimethylsilane (**III-38**)⁹³: The solution of allylic alcohol **III-38** (92 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. 2,6-lutidine (0.16 mL, 1.41 mmol) and TBSOTf (0.34 mL, 1.41 mmol) were added dropwise to the solution. The reaction was stirred at 0 °C for 1 h. Saturated NH_4Cl (aq., 10 mL) was added to quench the reaction. Separation followed by extraction with CH_2Cl_2 (3×10 mL) gave the colorless organic level, which dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was purified using column chromatography (3% EtOAc/hexanes) to give the protected alcohol **III-38** in 98% yield (195 mg).

Data for **III-38**: ^1H NMR (300 MHz, CDCl_3) δ 5.75-5.68 (1H, m), 5.63-5.57 (1H, m), 3.62-3.51 (1H, m), 2.02-1.14 (6H, m), 0.98-0.80 (9H, m), 0.12- -0.98 (6H, m).



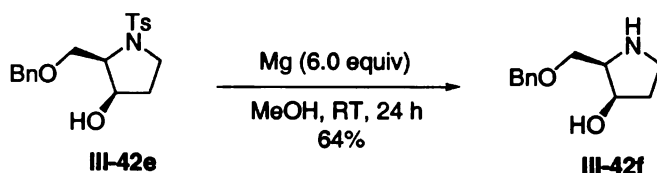
2-(Tert-butyltrimethylsilyloxy)-7-tosyl-7-aza-bicyclo[4.1.0]heptane (**III-39**): The



2-(Benzyloxymethyl)-1-tosylpyrrolidin-3-ol (III-42e): Dimethylsulfoxonium methyllide was prepared fresh for each reaction. Sodium hydride (0.175 g as a 60% dispersion in mineral oil, 4.38 mmol, 8.0 equiv, washed twice with hexane dried over sodium metal) was placed in a flame-dried flask and dry dimethylsulfoxide (5 mL) was added via syringe. Trimethylsulfoxonium iodide (0.96 g, 4.38 mmol, 8.0 equiv) was added in small portions over 20-30 min. After addition of the trimethylsulfoxonium iodide was complete, the reaction was stirred for an additional 30 min until the bubbling of the milk-white suspension ceased. The aziridinol (0.19 g, 0.55 mmol, 1.0 equiv) dissolved in a small amount of DMSO (1 mL) was added dropwise and the reaction was stirred at RT for 4 h to complete the aza-Payne rearrangement. The reaction was then covered with aluminum foil and heated to 80-85 °C for 36 h. The dark brown mixture was cooled and diluted with 2× volume of water and 1 mL of saturated ammonium chloride. The reaction was extracted several times with ethyl acetate, the combined organics washed with brine and dried over sodium sulfate. After evaporation, the residue was column chromatograph (30% to 40% EtOAc/hexanes) to give compound **III-42e** in 82% yield as a thick oil that eventually crystallized to a mushy solid.

Data for **III-42e**: ^1H NMR (300 MHz, CDCl_3) δ 7.7 (d, 2H, $J = 8.2$ Hz), 7.2-7.4 (overlapping m, 7H), 4.5 (s, 2H), 4.2 (m, 1H), 4.0 (dd, 1H, $J = 9.6, 4.1$ Hz), 3.85 (dd,

1H, $J = 9.6, 7.4$ Hz), 3.65 (m, 1H), 3.5 (m, 1H), 3.25 (m, 1H), 2.95 (br d, 1H, $J = 4.9$ Hz), 2.4 (s, 3H), 1.8 (m, 1H), 1.6 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.7, 137.4, 134.1, 129.7, 128.5, 128.0, 127.9, 127.4, 73.8, 72.6, 70.1, 61.1, 46.7, 32.8, 21.5. HRMS calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_4\text{S}$, 361.1348 m/z [M] $^+$; observed, 361.1348 m/z .



2-(Benzyloxymethyl)pyrrolidin-3-ol (**III-42f**): Magnesium turnings (20.4 mg, 6.0 equiv, 0.84 mmol) were crushed using a mortar and pestle and suspended in dry MeOH (1.4 mL). The pyrrolidine **III-42e** (50.0 mg, 1.0 equiv, 0.14 mmol) was dissolved in 1.4 mL of MeOH and was added the reaction, which was sonicated for 30 min. The cloudy suspension was allowed to stir vigorously at RT overnight. A small amount of silica gel was added and the MeOH was removed via rotary evaporation. The silica was loaded directly onto a column and eluted first with 1:1 hexanes/ethyl acetate, then 1:1:0.1 hexanes/ethyl acetate/methanol. Finally, a mixture of methanol/triethylamine was used to elute the product in 64% yield.

Data for **III-42f**: ^1H NMR (300 MHz, CDCl_3) δ 7.3 (m, 5H), 4.5 (d, 1H, $J = 11.8$ Hz), 4.45 (d, 1H, $J = 11.8$ Hz), 4.3 (m, 1H), 3.75 (d, 2H, $J = 5.5$ Hz), 3.4 (br s, 2H), 3.2 (m, 1H), 3.0 (dd, 1H, $J = 9.9, 5.5$ Hz), 2.8 (m, 1H), 1.95 (m, 1H), 1.75 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.6, 128.5, 127.9, 127.8, 73.6, 72.9, 69.0, 62.6, 44.0, 35.2. HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{NO}_2$, 208.1338 m/z [$\text{M} + \text{H}$] $^+$; observed, 208.1341 m/z .

III.7. References

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CHAPTER IV

ANNONACEOUS ACETOGENINS: A BRIEF REVIEW

IV.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 roots 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 *Annonaceae* family) (Figure IV-1).¹¹ It contains a set of bis-adjacent

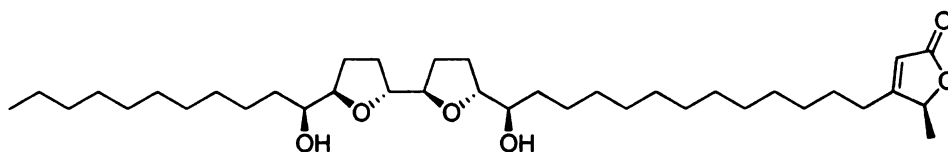


Figure IV-1: The first isolated acetogenin, uvaricin

tetrahydrofuran (THF) rings flanked by two hydroxyl groups and a terminal unsaturated lactone ring, which was connected to the THF moiety through an

unbranched alkyl chain. Uvaricin was demonstrated to have antitumor properties in the *in vivo* PS system (P-338 lymphocytic leukemia in mice).^{11, 12} It showed 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 $T/C \geq 125\%$.¹²

After 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 the structure-activity relationship studies has been growing rapidly.^{5, 7, 9}

IV.2. 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 IV-2).^{2, 7, 9} Several oxygenated functional groups, such as tetrahydrofuran (THF),

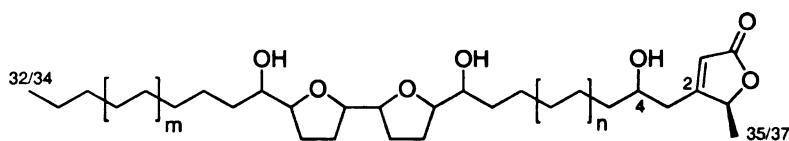


Figure IV-2: General structure of acetogenins

tetrahydropyran (THP), 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 and 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 IV-3.^{2, 5, 7} McLaughlin classified all these congeners based on the number

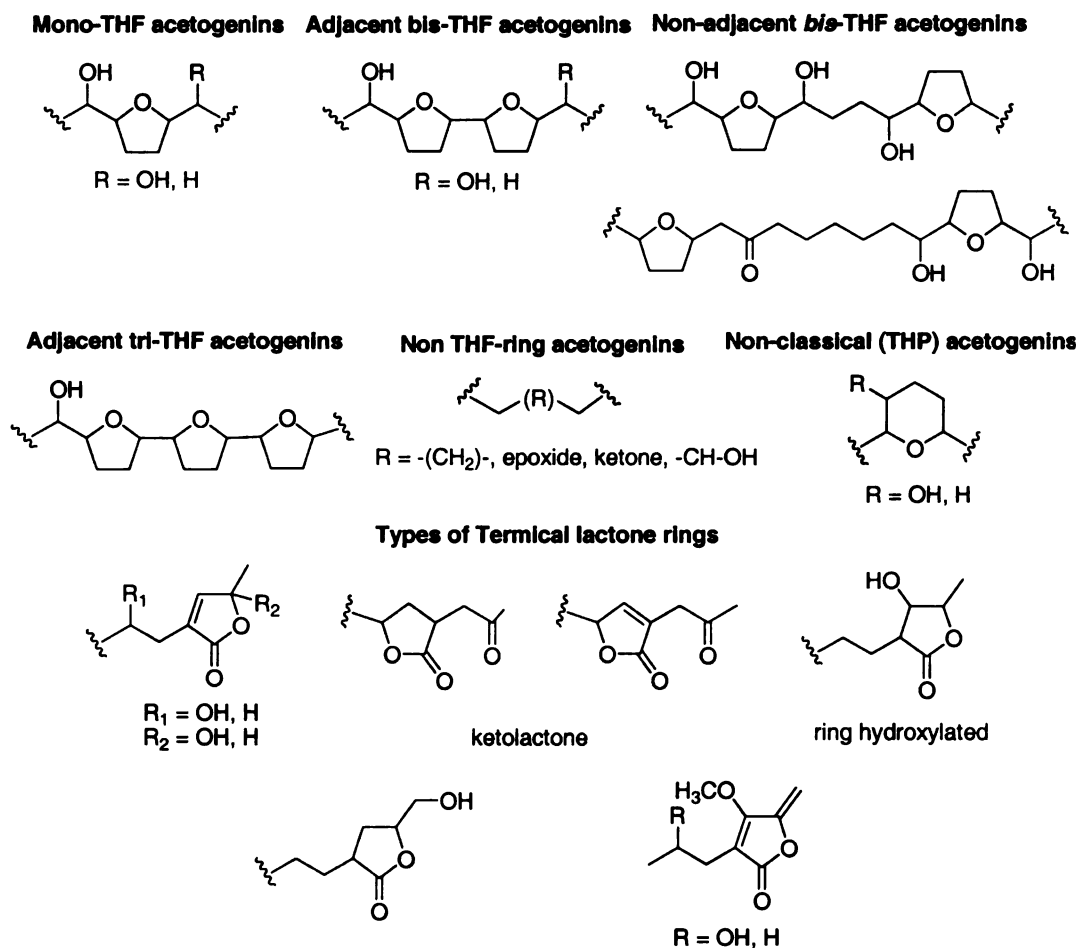


Figure IV-3: Core units for classification of *Annonaceous* acetogenins

and the arrangement of the THF rings including mono-THF, adjacent bis-THF, non-adjacent 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 IV-4 shows some examples of both classical and nonclassical acetogenins.

Compounds **IV-1** to **IV-5** are classical acetogenins with none to three THF units.^{1, 13-16}

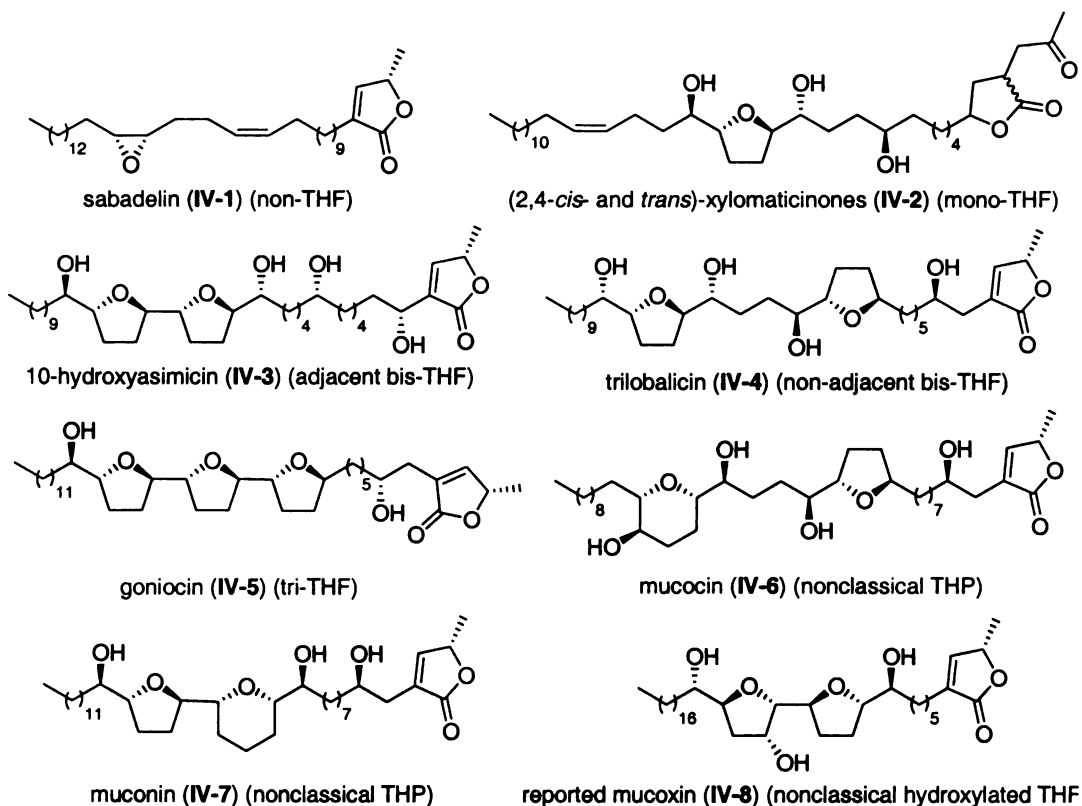


Figure IV-4: Examples of both classical and nonclassical acetogenins

If there are no THF units in the structure, epoxide or double bonds are the most common sub-units such as sababelin **IV-1**, which is a mono-epoxy olefinic acetogenin.¹³ Mucocin **IV-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 **IV-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. Mucocin **IV-8** is the first nonclassical acetogenin containing a hydroxylated THF ring.¹⁸ Two other examples are goniotriocin¹⁴ and donnaienin.²¹

IV.3. Biogenesis

Annonaceous acetogenins seem to be derived through the polyketide pathway. The unique THF, THP, and epoxide rings are presumably formed by poly-epoxidation of an unconjugated polyene followed by tandem inter- or intramolecular cyclization (Figure IV-5).^{3, 22-24} It is clear to see that the *trans* / *cis* relationship in the THF rings

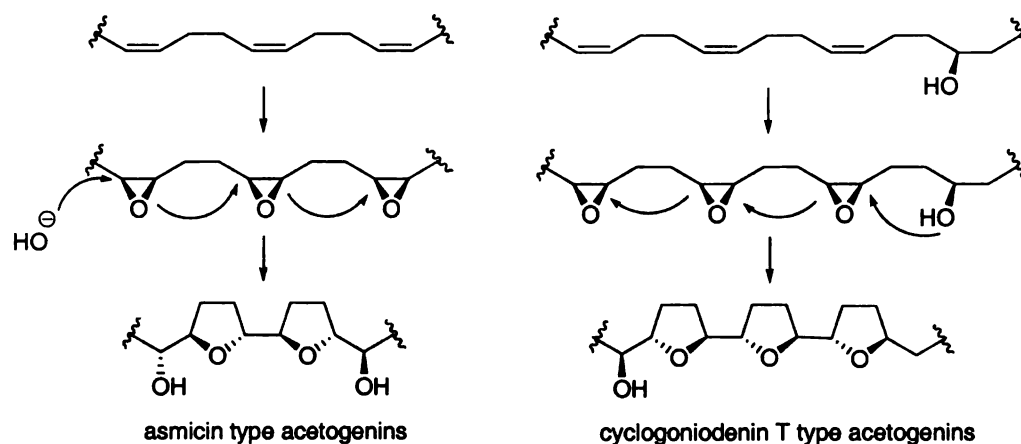


Figure IV-5: Proposed biogenetic schemes for asmicin type and cyclogoniodenin T type acetogenins

can be derived from the selectivity of the epoxidations, and the *erythro* / *threo* relationship between two THF rings and the side hydroxyl groups and the THF rings can be derived from the geometries of the olefins.

The discovery of earlier biosynthetic precursors (non-ring containing compounds, epoxides, ketones, diols, and double bonds), the location of double bonds at the appropriate positions, and the semisynthesis of additional THF rings from double bond-containing acetogenins strongly support this hypothesis.⁵ In addition, the discovery of muridienins, the first bis-unsaturated precursors of mono-THF acetogenins, and chatenaytrienins, the tris-unsaturated natural precursors of the adjacent bis-THF acetogenins, add new evidence that acetogenins are most likely

derived from lacceroic (C32) and ghedoic (C34) fatty acids after enzymatic combination with a three-carbon unit.^{5, 25} However, detailed sequence of these transformations is still unknown.

IV.4. Biological Activity

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

IV.4.1. *In vitro* and *in vivo* cytotoxicity results

Annonaceous acetogenins have been always judged as promising candidates for a future generation of drugs against the current chemotherapy-resistant tumors since the first isolated acetogenin, uvaricin, was announced as a new antitumor compound.¹¹ Many studies to establish the cytotoxic potency of acetogenins for several human tumor cell lines have been undertaken. For example, asimocin and bullanin have shown ED₅₀ values of $\sim 10^{-12}$ $\mu\text{g/mL}$ against A-549 (lung), MCF-7 (breast), and HT-29 (colon) human cancer cell lines, much lower than adriamycin ($\sim 10^{-4}$ to $\sim 10^{-2}$ $\mu\text{g/mL}$), an anticancer drug currently in clinical use.²⁶ Moreover, a series of acetogenins show greater cytotoxic effects against cancerous over noncancerous cells.²⁷

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)²⁸ 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.

IV.4.2. Resistance in multidrug resistant (MDR) tumor cells

Multidrug resistant tumors, whether intrinsic or acquired, continue to limit the life span of cancer patients in remission. They are usually associated with an increased expression of P-glycoprotein, a 170 kDa transmembrane energy-dependent drug efflux pump.⁵ Since acetogenins have potent properties to block ATP production, they are found to selectively inhibit the growth of MDR tumors cells *in vitro* as reported by Schwaller²² and later by McLaughlin and coworkers.^{29, 30} It was observed that the bis-THF acetogenin rolliniastatin-2 was effective against the growth of adriamycin-resistant human mammary adenocarcinoma cells (MCF-7).^{2, 29, 30} It was also demonstrated that another bis-THF acetogenin, bullatacin, inhibited almost all of the growth of the MDR MCF-7/adriamycin-resistant cells but only 50% of the growth of the MCF-7/wide-type cells at the most concentrated dose of 1.0 µg/mL.²⁹ All of these results indicate that acetogenins could inhibit not only normal cancerous cell lines but also multidrug resistant tumor cells.

IV.4.3. Resistant and susceptible insects and pests

A recent insecticide-development study showed that acetogenins are toxic to mosquito larvae, European corn borers, spider mites, melon aphides, Mexican bean beetles, bean leaf beetles, striped cucumber beetles, blowfly larvae, Colorado potato beetles, German cockroach, and free-living nematodes.^{28, 31-33} In order to prove the efficiency of potent pesticidal properties, McLaughlin and coworkers did comparable experiments of different classes of acetogenins vs. technical grades of synthetic compounds such as amidinohydrazone (hydramethylnon), carbamate (propoxur, bendiocarb), organophosphate (chlorpyrifos), and pyrethroid (cypermethrin) to determine their dietary toxicities to insecticide-resistant and insecticide-susceptible strains of the German cockroach.³¹ The results indicated that acetogenins showed higher or comparable rate of killing values (LT_{50}) against both insecticide-susceptible (Jwax) and insecticide-resistant (Muncie) strains (Table IV-1). The adjacent

Table IV-1: LT_{50} values^a for German cockroach fifth instars

Compound Type	Active Ingredient	Jwax	Muncie
adjacent bis-THF	parviflorin	0.8	1.2
acetogenins	asimicin	2.3	3.8
non-adjacent bis-THF	sylvaticin	2.1	8.2
acetogenins	bullatalicin	5.8	10.3
mono-THF acetogenins	annomontacin	24.7	3.8
	gigantetrocin A	20.4	17.8
synthetic compounds	cypermethrin	---	0.2
	chlorpyrifos	0.5	0.2
	hydramethylnon	10.4	6.1
	propoxur	20.4	34.1
	bendiocarb	43.8	39.3

^a Number of days before death of 50% of the population following exposure to toxic baits at a dose of 1000 ppm.

bis-THF acetogenins have the highest values among the three classes of acetogenins. Based on their high potent pesticidal properties, acetogenins are the growing new lead candidates for pesticidal development.

IV.5. 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, 28, 34-36} 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.³⁷⁻³⁹

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.⁴⁰⁻⁴² Further 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 the 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 the cytotoxicity.^{5, 40} They determined the positions of both the THF and lactone ring within liposomal membranes by ¹H NMR and nOe spectroscopy and found that an asimicin-type acetogenin can be in either sickle-shaped or 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 IV-6.⁴³⁻⁴⁵ Here

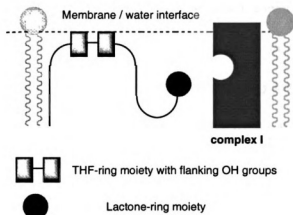


Figure IV-6: Model for the active conformation of acetogenins interacting with complex I in the mitochondrial membrane proposed by McLaughlin, Shimada, and coworkers

the THF rings with flanking hydroxyl groups 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 structural activity study against submitochondrial particles by using 22 representative acetogenins.⁴³ They also studied the three-dimensional structure of the bis-THF rings of the different possible stereoisomers optimized by quantum chemical calculations (MNDO-AM1).⁴³ 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.^{46, 47} 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

IV.6. Structure-Activity Relationship Studies

Although *Annonaceous* acetogenins are thought to inhibit the 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 IV-7).⁴⁸ Thus, there is interest in studying their

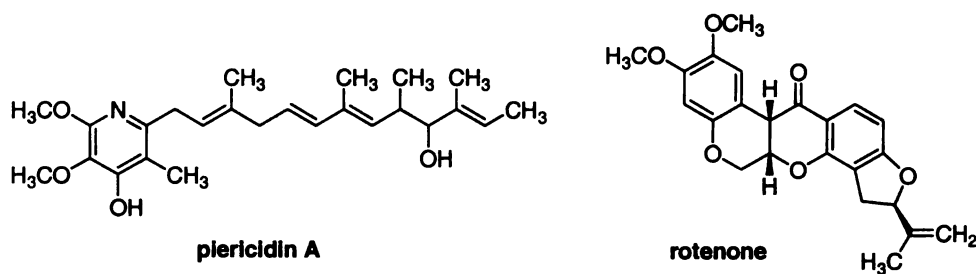


Figure IV-7: Two ordinary complex I inhibitors: piericidin A and rotenone

unusual structural characteristics as well as the strong inhibitory properties of acetogenins. The structure-activity relationship (SAR) studies are very 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 natural 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 the activities. The C-35 acetogenins are more potent than the C-37 compounds when their structure 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 the 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.

Since then, Miyoshi et al.,^{44, 45, 49-55} Yao and Wu et al.,⁵⁶⁻⁶³ Cortes et al.,^{39, 64, 65} Figadère, et al.,^{66, 67} Poupon et al.,⁶⁸⁻⁷⁰ Duval and Lewin et al.,^{71, 72} and Koert et al.⁷³ 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.

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 IV-8 shows one example, bis-THF acetogenin isolated from *Annona bullata*, bullatacin, which is one of the most potent inhibitors of complex I.⁴⁴ All the SAR studies are focused on the relationship of activities and variation of these four domains of the structures.

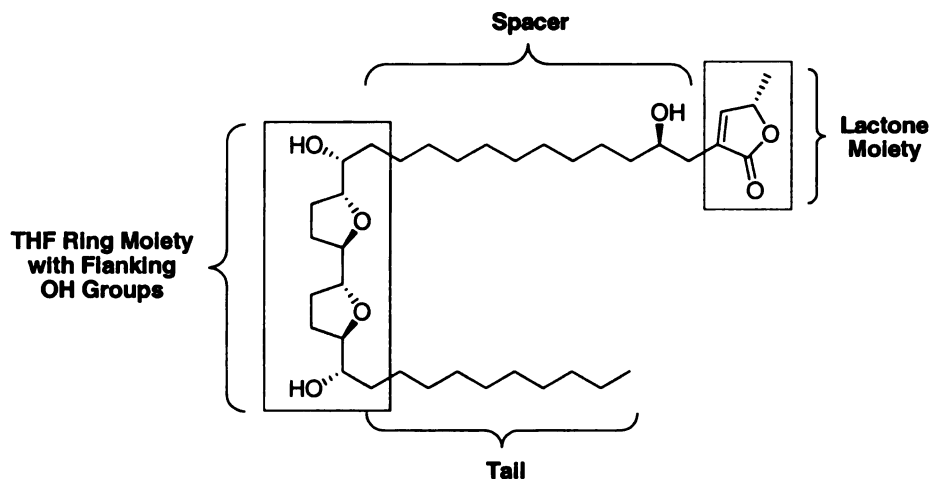
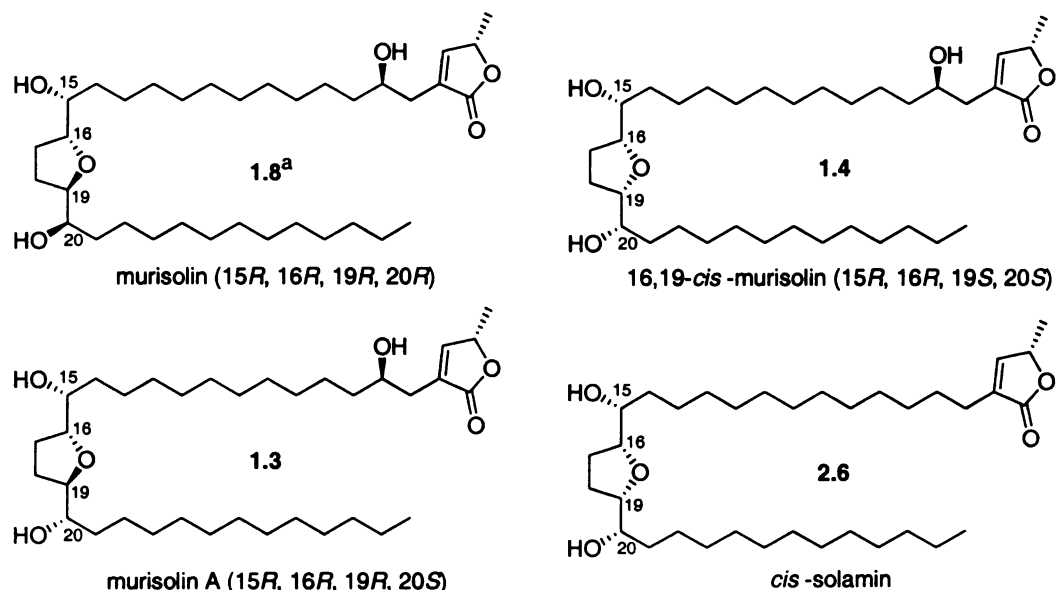


Figure IV-8: Structure of bullatacin

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 the potent activity. Miyoshi, Makabe, and coworkers synthesized a series of diastereomers of natural products and test their

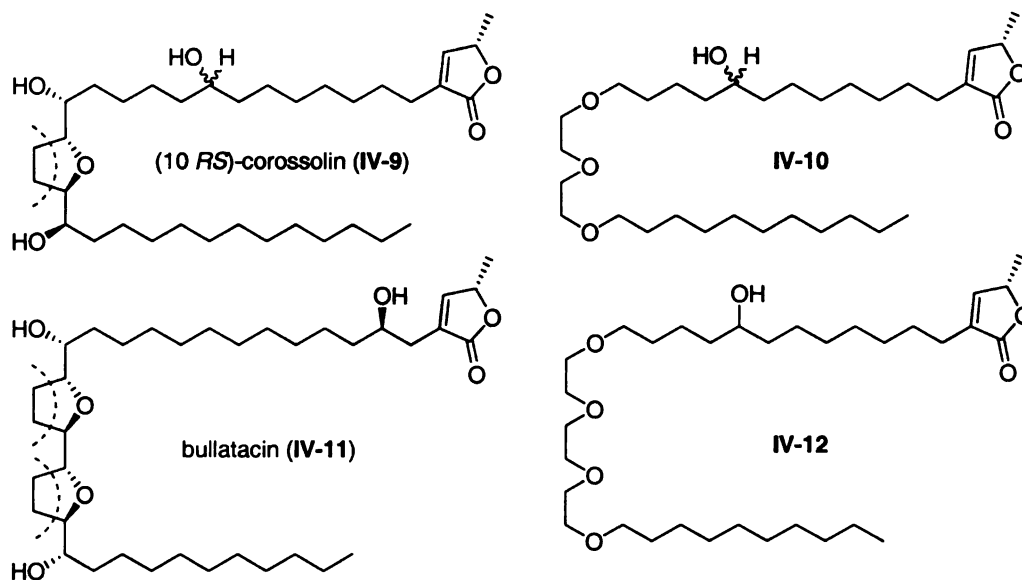


^a IC₅₀ value (nM); bullatacin IC₅₀ = 0.8 nM.

Figure IV-9: Mitochondrial Complex I Inhibitory activity of various acetogenins

bioactivities.⁵³⁻⁵⁵ The inhibitory activity of these acetogenins on complex I shows the comparable IC₅₀ value (examples shows in Figure IV-9⁵⁵). In addition, Yao, Wu, and coworkers found that polyether mimics of acetogenins can lead to remarkable cytotoxicity against human tumor cells (Table IV-2⁵⁶).^{56-61, 63} Both of the synthetic polyether mimics **IV-10** and **IV-12** have comparable cytotoxicity with the similar-size natural acetogenins. These experiments indicate that the THF moiety is not a necessary structural feature for bioactivity.

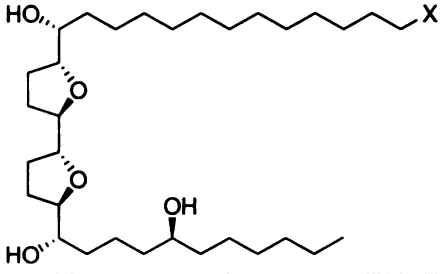
Table IV-2: Cytotoxicity against two human cancer cell lines of acetogenins and their polyether mimics

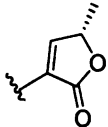
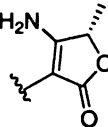
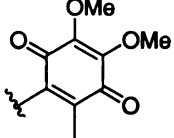
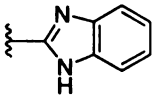
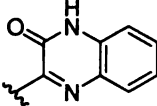
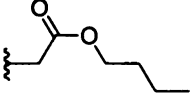


	IG %					
	for HL-60			for K562		
concentration (μM)	100	10	1	100	10	1
(10 <i>RS</i>)-corossolin IV-9	63	56	5	10	2	0
compound IV-10	100	50	0	31	18	0
bullatacin IV-11	73	7	0	53	39	27
compound IV-12	100	65	21	55	25	22

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

Table IV-3: Inhibition of mitochondrial complex I by natural acetogenins and synthetic analogs with various terminal functional groups

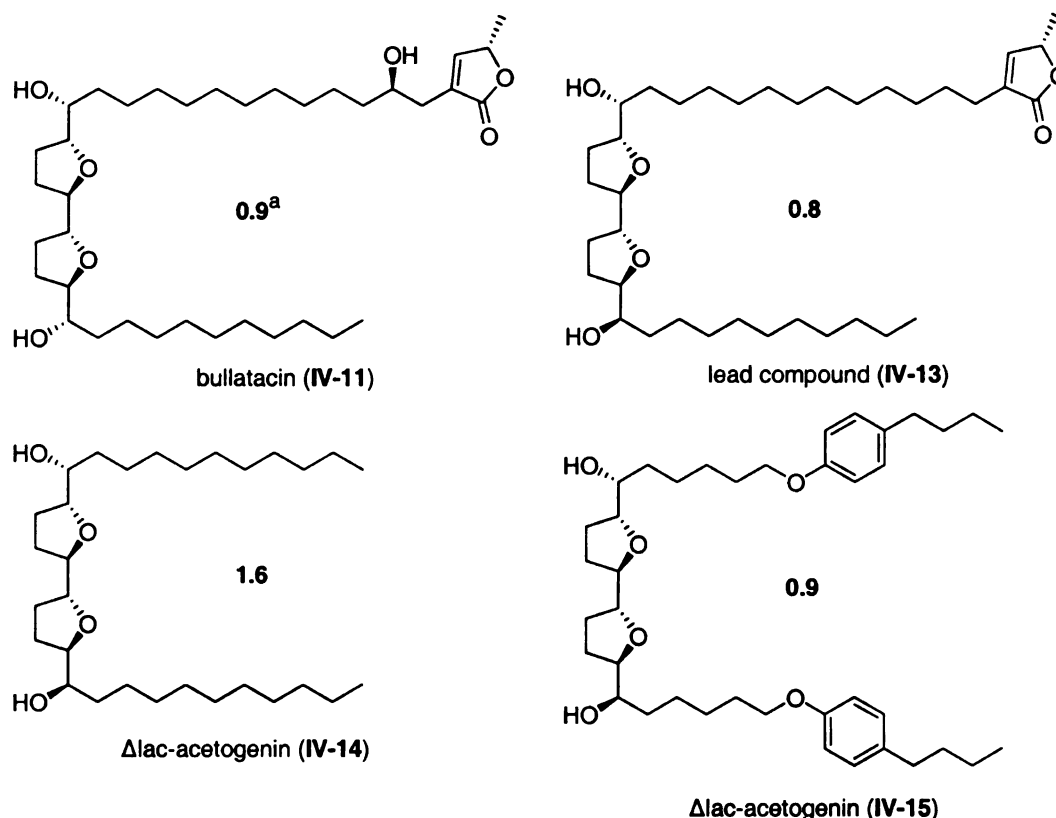


Compound	Group X	Complex I Inhibition IC ₅₀ (nM)	
		NADH oxidase	NADH-DB oxidoreductase
squamocin		0.9	1.3
β-aminosquamocin		---	8.0
quinone analog of squamocin		---	1.7
benzimidazole squamocin		0.9	3.3
quinoxalinone squamocin		2.0	3.3
n-butylester squamocin		2.3	9.2

terminal functional groups such as quinones,⁷³ heterocycles,^{70, 72} substituted benzenes,⁵⁴ or some photoaffinity groups⁶⁸ that are still potent inhibitors of complex I. Table IV-3 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 Δ lac-acetogenins; could still retain

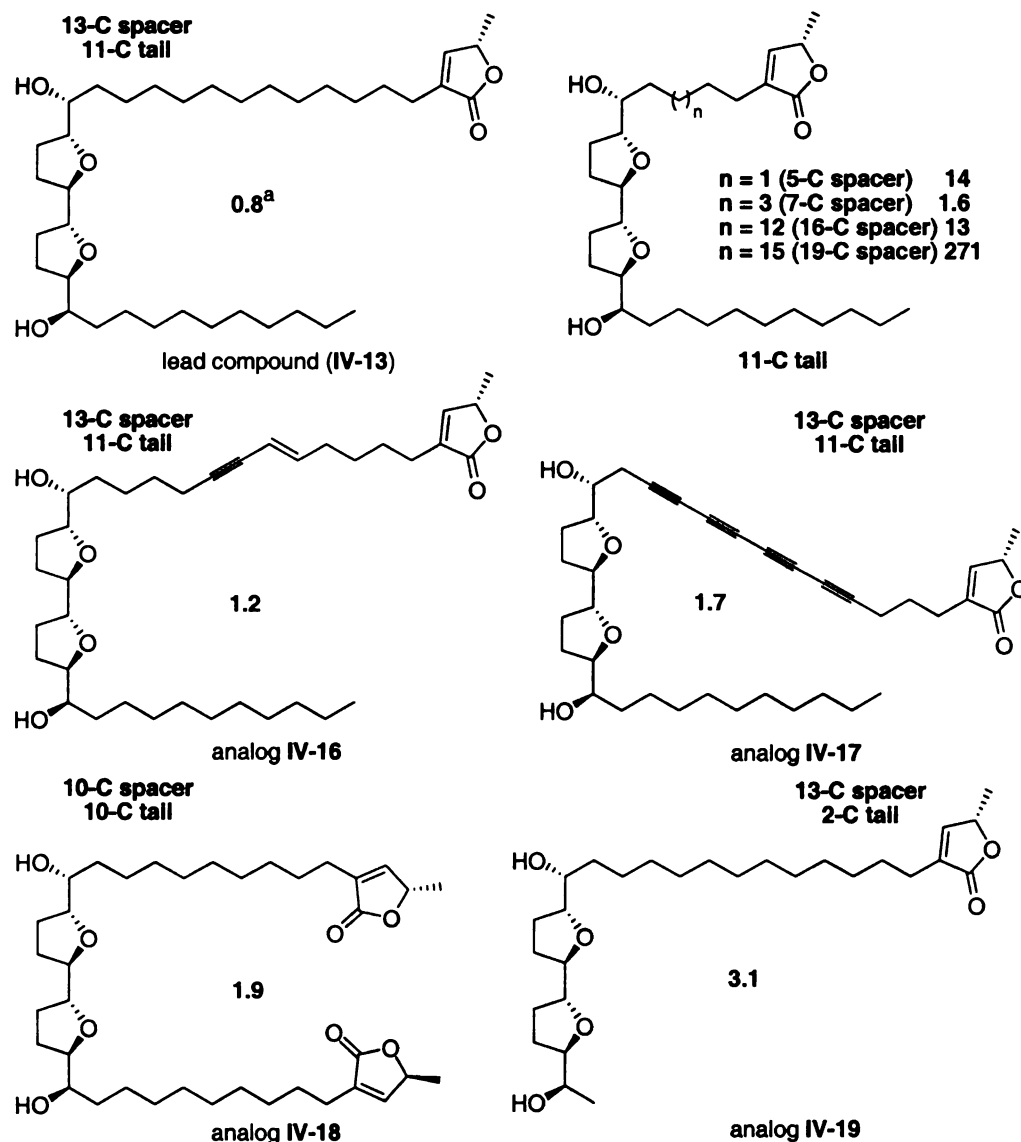


^a The IC₅₀ value (nM) is the molar concentration needed to reduce the control NADH oxidase activity in submitochondrial particles by half.

Figure IV-10: Examples of natural and Δ lac-acetogenins and their IC₅₀ values

similar bioactivity (Figure IV-10).^{50, 52, 54}

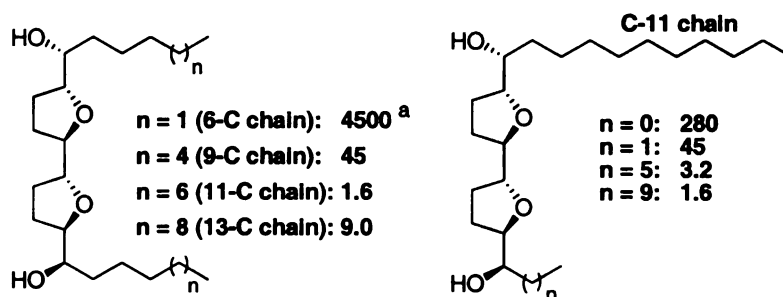
3) The lengths of both spacer and tail are important structural factors for obtaining high activity. Generally, acetogenins act as potent inhibitors only when the THF moiety and the γ -lactone ring are directly linked by an appropriate alkyl spacer (the optimal length of the spacer for inhibition is approximately 13 carbon atoms).^{45, 49-51, 54} However, the spacer portion is not affected by steric congestion when multiple bonds are introduced into different regions of the spacer (Figure IV-11, analog IV-16 and IV-17).⁵¹ The appropriate length of the hydrophobic tail is preferable for the activity, but is not as important as the spacer (Figure IV-11, analog IV-18 and IV-19).



^a The IC₅₀ value (nM) of inhibition for mitochondrial complex I.

Figure IV-11: Variation of the length of spacer and tail of acetogenin analogs

These effects are more significant in Δ lac-acetogenin analogs (Figure IV-12).^{50-52, 54}

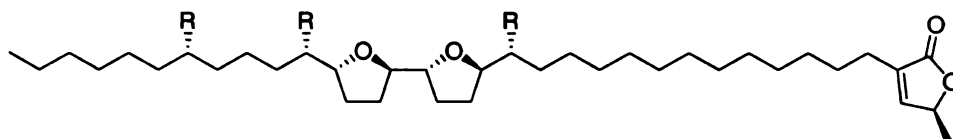


^a The IC₅₀ value (nM) of inhibition for mitochondrial complex I.

Figure IV-12: Variation of the length of alkyl chains in Δ lac-acetogenins

4) The presence of free hydroxyl groups flanking the THF moiety is important to elicit potent activity. Generally, protection of the free hydroxyl groups such as the transformation of the secondary alcohols into acetates or mesylates could lead to significant loss of cytotoxicity (>1000 times, examples in Table IV-4) as well as inhibitory potency (Table IV-5),^{66, 71} while some of these derivatives could retain comparable enzymatic inhibition (such as acetate, examples in Table IV-5).^{64, 71}

Table IV-4: Cytotoxic activity of squamocin and its derivatives



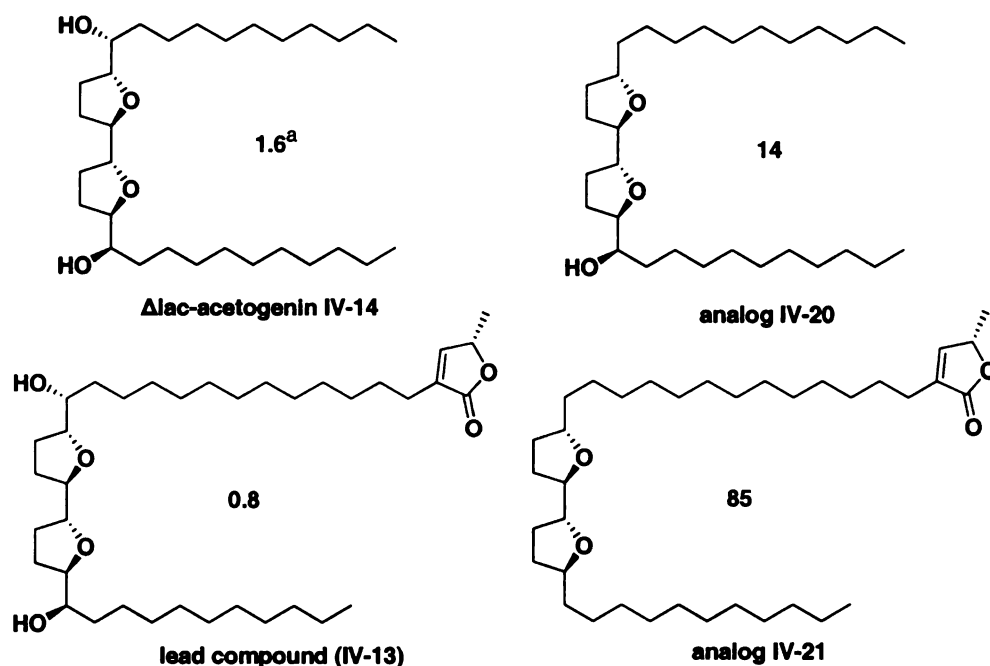
Compound	Group R	KB ^a EC ₅₀ (μM)
squamocin	-OH	1.6×10^{-5}
tritosyl squamocin	-OTs	$< 1.3 \times 10^{-1}$
trimesyl squamocin	-OMs	1.5×10^{-2}
triazido squamocin	-N ₃	$< 1.4 \times 10^{-1}$
triamino squamocin	-NH ₂	2.4×10^{-2}

^a Human epidermoid carcinoma cell lines.

Table IV-5: 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
triazido squamocin	-N ₃	18 ± 2	315 ± 19

Removal of one of the two hydroxyl groups around the THF moiety resulted in a slight, but significant, loss of activity (Figure IV-13, analog **IV-20**). Removal of both hydroxyl groups led to further decreased inhibitory potency of complex I (Figure I-13, analog **IV-21**).⁵⁰



^a The IC₅₀ value (nM) of inhibition for mitochondrial complex I.

Figure IV-13: Comparison of inhibition between acetogenin analogs and their OH-removed derivatives

In summary, some of the previous results of the 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 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 very important. In the SAR studies, Δ lac-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 needed to be considered in the mode of active conformation.

All 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 the efficient 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 out in future.

IV.7. Synthesis

Because their structural diversity and the numerous biological properties, many groups have pursued on the semi-synthesis and total synthesis of *Annonaceous* acetogenins.^{7, 9, 22, 24} Even though acetogenins are found in a large number of plant species, there are only small amounts of each in complex mixtures. On average, about 10-20 mg of material can be obtained from 15 kg of stem bark, after a difficult multistep separation.⁷⁴ Moreover, most acetogenins are waxes or gums, and can not be crystallized for X-ray crystallography in order to determine the complete structure and the absolute configurations of the stereogenic centers. Thus total synthesis is important in order to obtain sufficient amounts of acetogenins, which can be used to confirm the proposed structure, establish the relative or absolute stereochemistry, and perform further biological testing. Furthermore total synthesis is convenient for the SAR study of acetogenins because it can be used to prepare the related analogs.

Since 1991 over forty total syntheses of all types of acetogenins have been reported, as well as semi-synthesis and preparation of structural analogs, illustrating different methodologies to build the skeleton and control the stereochemistry of acetogenins.^{9,}

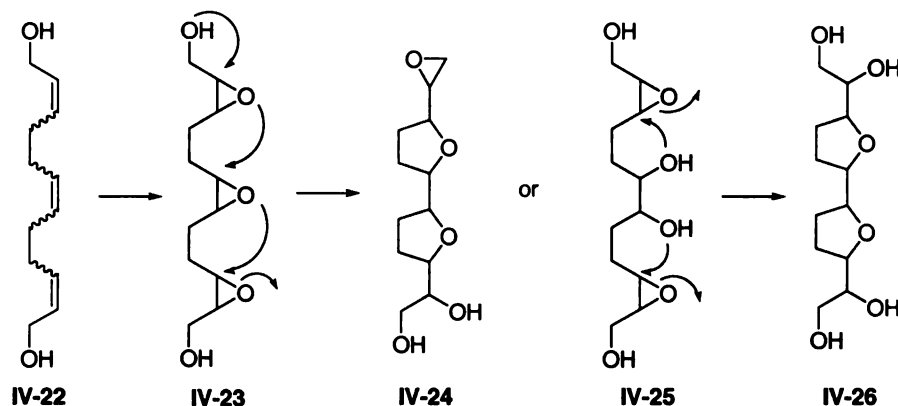
^{55, 75-161} Because the most important acetogenin classes are the THF-containing or THP-containing acetogenins, the following discussion about synthesis of acetogenins will focus on this class of compounds. Generally, most of the approaches to synthesize acetogenins are based on a convergent strategy which consists of preparing both the cyclic ether moiety and the lactone moiety in a stereocontrolled manner and finally by coupling of the two intermediates with the appropriate alkyl chain. The terminal long hydrocarbon chain can be incorporated at an early or later stage in the synthesis.

There are several efficient pathways to synthesize both the cyclic ether and the terminal lactone moiety of acetogenins. The following sections discuss the representative strategies focusing on the construction of the cyclic ether moiety; synthesis of the lactone ring is mentioned in the last section. The completion of the total synthesis of the natural acetogenins is mentioned briefly in some cases. The classification of the synthetic strategies is based on the methodologies used for the construction of the cyclic ether moiety.

IV.7.1. Epoxide ring-opening strategy

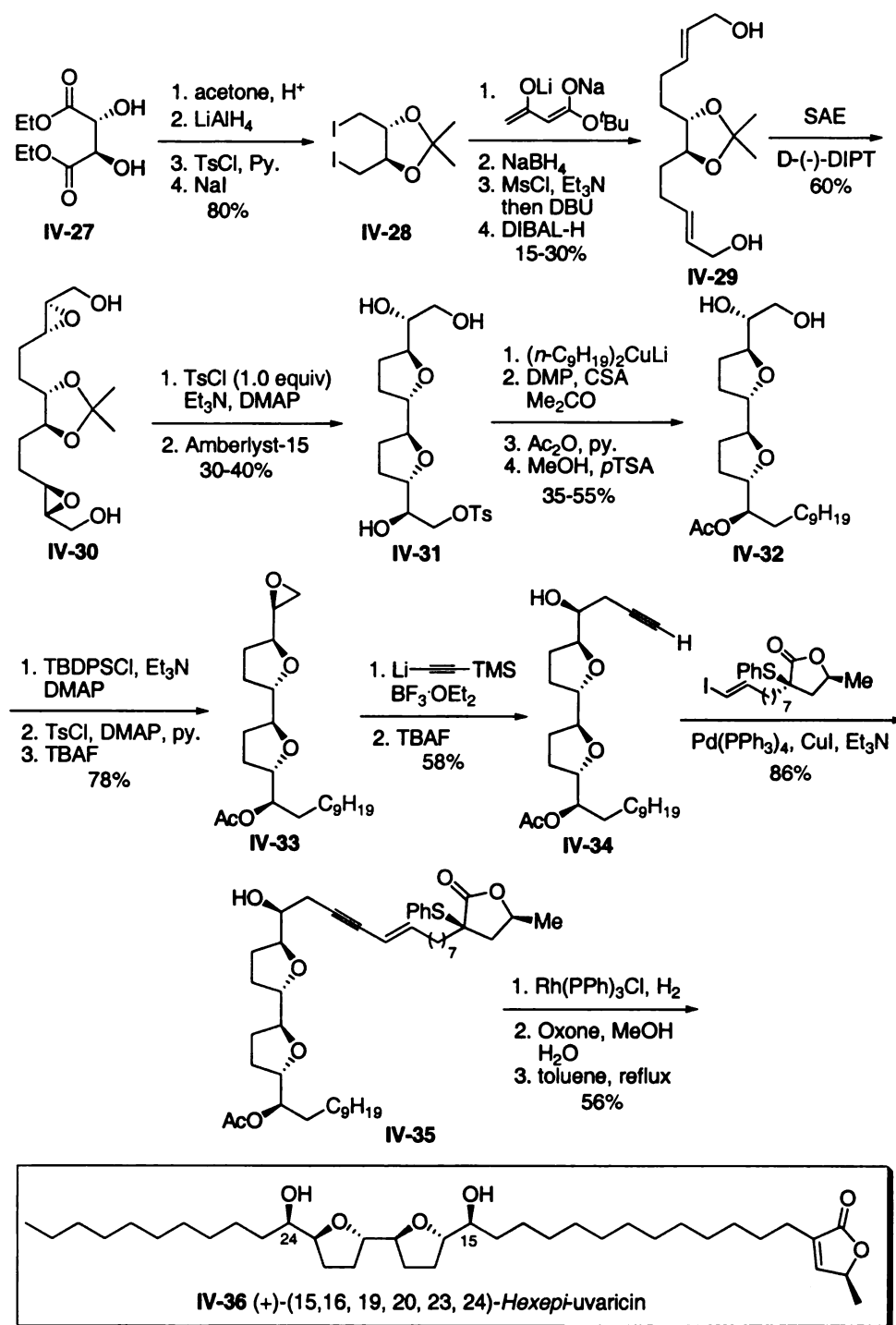
The first synthetic approach to the substructure of acetogenins was reported by Hoye and coworkers in the 1980s (Scheme IV-1).¹⁶²⁻¹⁶⁴ They followed a biomimetic route to design the polyepoxide cascade reaction. Using asymmetric epoxidations to

form triepoxide **IV-23** or diol diepoxide **IV-25** from triene **IV-22**, the triepoxide cascade reaction or inside-out closure of diol diepoxide could provide the adjacent bis-THF moiety **IV-24** or **IV-25**. Here all the stereochemistry could be controlled by asymmetric epoxidations and the stereochemistry of the precursor triene.¹⁶⁴



Scheme IV-1: Hoyer's polyepoxide cascade reactions to construct adjacent bis-THF moieties

In 1991, Hoyer and coworkers applied their methodology in the total synthesis of (+)-(15, 16, 19, 20, 23, 24)-*hexe**pi*-uvaricin,¹⁶⁵ which is the first total synthesis in the field of acetogenins. Since the absolute configuration of uvaricin was not known at that time, they only synthesized the diastereomer of the natural product. However, this total synthesis helped to determine the real structure, including the absolute configuration, of natural uvaricin. In this synthesis (Scheme IV-2), the diiodide derivative **IV-28** of tartaric acid **IV-27** was converted to the (*E*, *E*)-dialkene **IV-29** using Weiler di-anion alkylation.¹⁶⁶ Double Sharpless asymmetric epoxidation¹⁶⁷ of **IV-29** provided the C₂-symmetric diol diepoxide **IV-30**, which was desymmetrized in the next step by the formation of monotosylate **IV-31** in moderate yield. After one-pot acid catalyzed epoxide ring-closing process, the adjacent bis-THF core **IV-31**

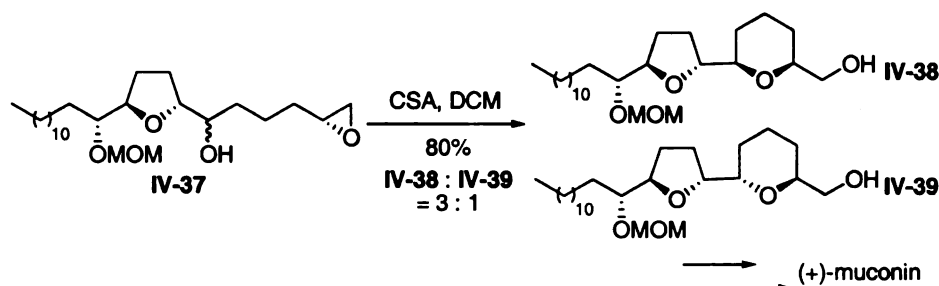


Scheme IV-2: Hoyer's total synthesis of (+)-(15, 16, 19, 20, 23, 24)-hexepl-uvaricin

was formed. Then the long alkyl tail was introduced by cuprate coupling, followed by a three-step sequence to form monoacetate **IV-32**. Next, protection group manipulations provided epoxide **IV-33** in good yield, which was subjected to

nucleophilic ring opening followed by TMS deprotection, to form intermediate **IV-34**. The terminal functional group was then connected to the bis-THF moiety via Pd(0)-catalyzed coupling to yield **IV-35**. Hydrogenation, oxidation of sulfide and thermal elimination of the *in situ* generated sulfoxide completed the total synthesis of compound **IV-36**. Mosher's esterification analysis and NMR spectroscopic comparison with the natural product showed **IV-36** was the diastereomer of natural uvaricin (Figure IV-1) differing at the bis-THF moiety.

A similar strategy was also used successfully in the total synthesis of acetogenins (+)-asimicin, (+)-bullatacin, and (+)-parviflorin by Hoyer and coworkers.^{139, 168} Other groups such as Keinan, et al.,¹⁰⁶ Taber, et al.,¹⁶⁹ Sasaki, et al.,¹⁷⁰ Evans, et al.,¹⁷¹ Morimoto, et al.,¹⁷² Marshall, et al.¹⁷³ have also developed the epoxide-opening strategy based on Hoyer's results and synthesized different substructures or natural acetogenins. In addition, the same idea not only can be used in the construction of bis-THF core, but also can be applied in preparing mono-THF or THP cores. For example, in 2000, Kitahara and coworkers used etherification to construct the THP ring in the total synthesis of (+)-muconin (Scheme IV-3).¹⁷⁴ Epoxide **IV-37** was

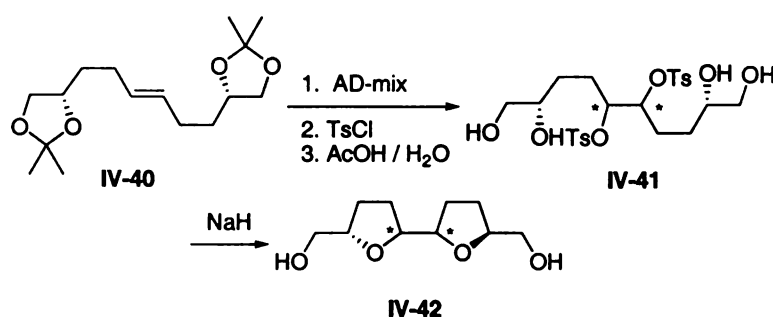


Scheme IV-3: Epoxide-opening reaction for the construction of the THP ring during the total synthesis of (+)-muconin

cyclized smoothly with CSA in CH₂Cl₂ to give a separable mixture of THP ring-containing intermediates **IV-38** and **IV-39** in 3:1 ratio.

IV.7.2. Multiple intramolecular Williamson etherification strategy

Koert and coworkers envisioned the multiple intramolecular Williamson etherification as the ring-closure reaction to construct the THF moiety. Their processes follow a bidirectional and convergent pathway, which stereoselectively leads to oligo-THFs (Scheme IV-4).¹⁷⁵⁻¹⁷⁷ Their starting point for the bidirectional

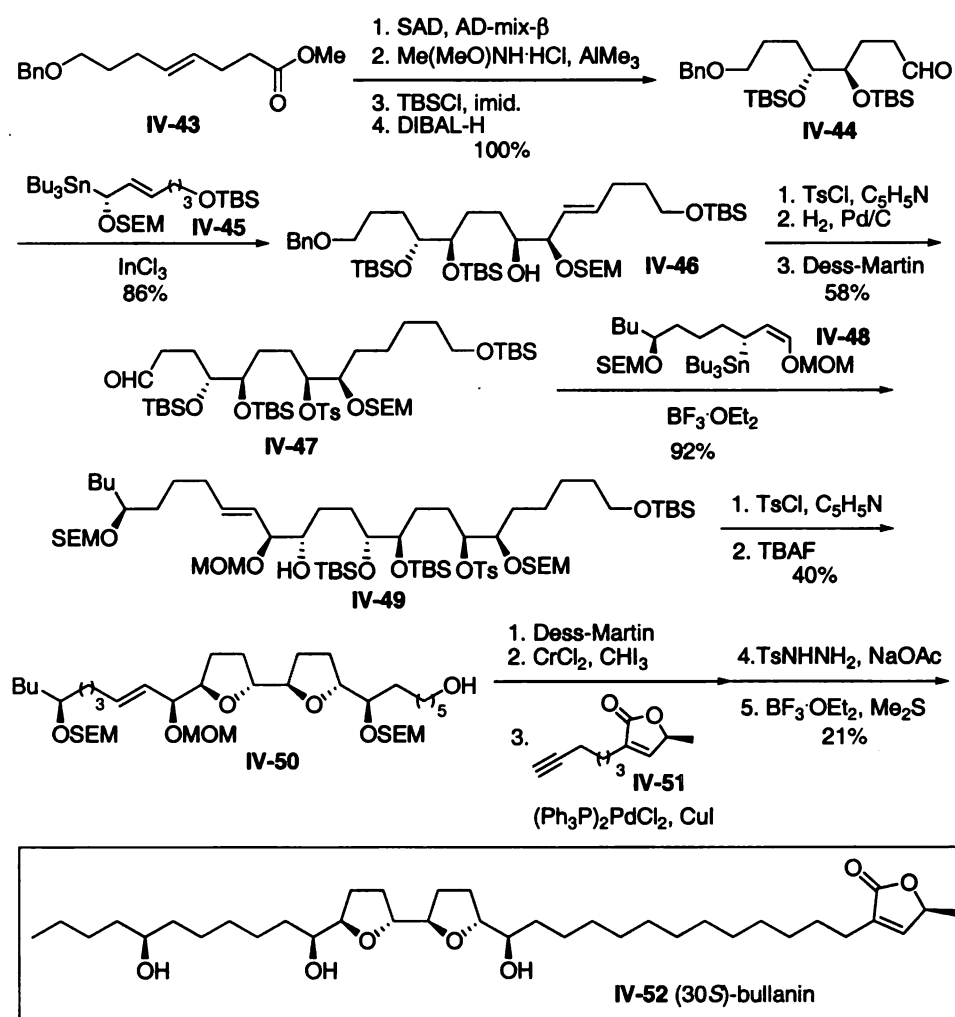


Scheme IV-4: Koert's multiple Williamson etherification pathway to construct oligo-THFs

approach was the C₂-symmetric alkene **IV-40**, which was subjected to the Sharpless asymmetric dihydroxylation¹⁷⁸ to give the diol stereoselectively. Tosylation followed by deprotection provided tetrahydroxylditosylate **IV-41**, which could undergo a multiple Williamson etherification reaction under basic condition to yield the adjacent bis-THF moiety **IV-42**.

Marshall and coworkers were also interested in this efficient bidirectional approach to the bis-THF core of acetogenins.^{117, 118, 120, 121, 179-186} They used chiral α - or γ -oxygenated allylic stannanes to react with a chiral γ , γ' -dialdehyde under appropriate conditions to form *anti* or *syn*-monoprotected 1,2-diol derivatives, which acted as the precursor for the bidirectional Williamson etherification strategy. A nice

example is the total synthesis of (30*S*)-bullananin (Scheme IV-5).¹⁸³ The starting aldehyde **IV-44** was prepared from the Claisen product **IV-43**¹⁸⁷ through Sharpless asymmetric dihydroxylation,¹⁷⁸ Weinreb amide formation,¹⁸⁸ protection of free hydroxyl groups, and the reduction with DIBAL-H. Then using their chiral stannane intermediate **IV-45**, InCl₃ catalyzed addition reaction afforded the expected *anti*-product **IV-46** in good yield. After converting -OBn to the aldehyde in the left side of the molecule, the second chiral stannane nucleophilic addition in the presence of BF₃•OEt₂ proceeded in 92% yield to afford the *syn*-adduct **IV-49** as the only



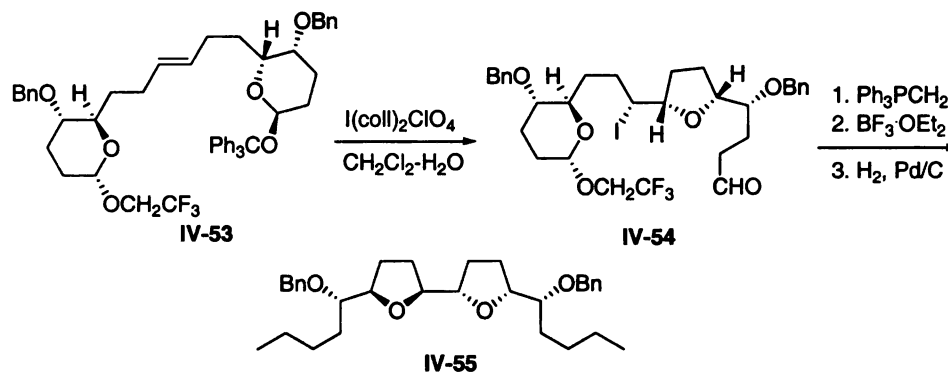
Scheme IV-5: Marshall's total synthesis of (30*S*)-bullananin

diastereomer. Tosylation of the alcohol followed by the one-pot TBS deprotection / Williamson etherification mediated by TBAF gave the desired adjacent bis-THF moiety **IV-50** as the desired product. Introduction of the butenolide moiety and the additional side chain methylenes was effected through Sonogashiro coupling¹⁸⁹ of alkynyl butenolide **IV-51**. The final hydrogenation and global deprotection provided the natural product (30*S*)-bullnin **IV-52**. Their method illustrates the feasibility of preparing useful amounts of bullnin-type acetogenins, as well as their analogs, for further biological studies because it is easy to control the stereochemistry by using different chiral stannane reagents and Sharpless asymmetric dihydroxylation reaction. Their synthesis also confirmed the assigned structure and configuration of natural bullnin.

The multiple Williamson etherification strategy is one of the most widely used processes in the acetogenin synthesis. Other groups such as Tanaka, et al.,¹⁹⁰⁻¹⁹² Keinan, et al.,^{101, 104} Trost, et al.,¹⁹³ Rao, et al.¹⁷⁴ also used this strategy in their synthetic studies of substructures or natural acetogenins.

IV.7.3. Iodoetherification strategy

Mootoo and coworkers reported the iodoetherification strategy to construct the THF core in the synthesis of acetogenins.^{75, 194-199} Their original approach was used for the preparation of *cis*-2,5-disubstituted THFs via the haloetherification reaction of bis-pyranoside alkenes (Scheme IV-6).^{196, 198} In intermediate **IV-53**, one of the monosaccharide fragments is equipped with an activated *cis*-directing aglycone (*t*-butyl or trityl) and the other with a deactivating aglycone (trifluoroethyl).¹⁹⁶ The



Scheme IV-6: Mootoo's iodoetherification method to prepare *cis*-adjacent bis-THF moieties

bis-THF is related to the bis-pyranoside alkene by sequential THF forming reactions: an initial haloetherification involving the ring oxygen of the stereodetermining, activated pyranoside to give a halo-THF-trifluoroethyl pyranoside; then the formation of the adjacent THF via displacement of the halide substituent by the ring oxygen of the deactivated pyranoside. The first step differentiates the two acetal residues, thereby facilitating desymmetrization of the bis-THF core. Figure IV-14 shows the intermediate conformation, which could explain the stereochemistry in this sequence. A chair form reactive conformation involving the four carbon atoms of the eventual THF ring is favored, with a preferred 'up' vs. 'down', orientation of the alkene complex, leading to the *cis*-THF. Bulky groups in the monosaccharide fragments such as trityl residue can introduce high stereoselectivity.

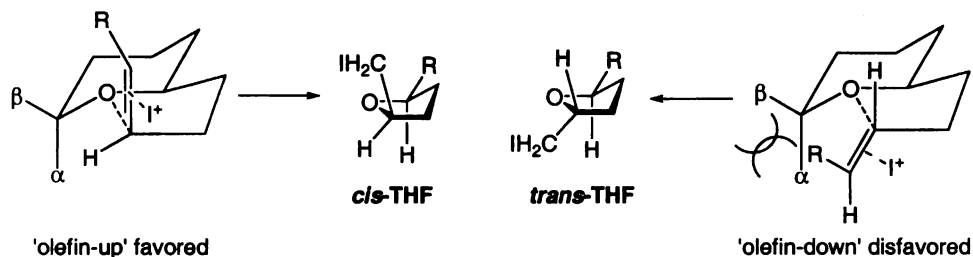
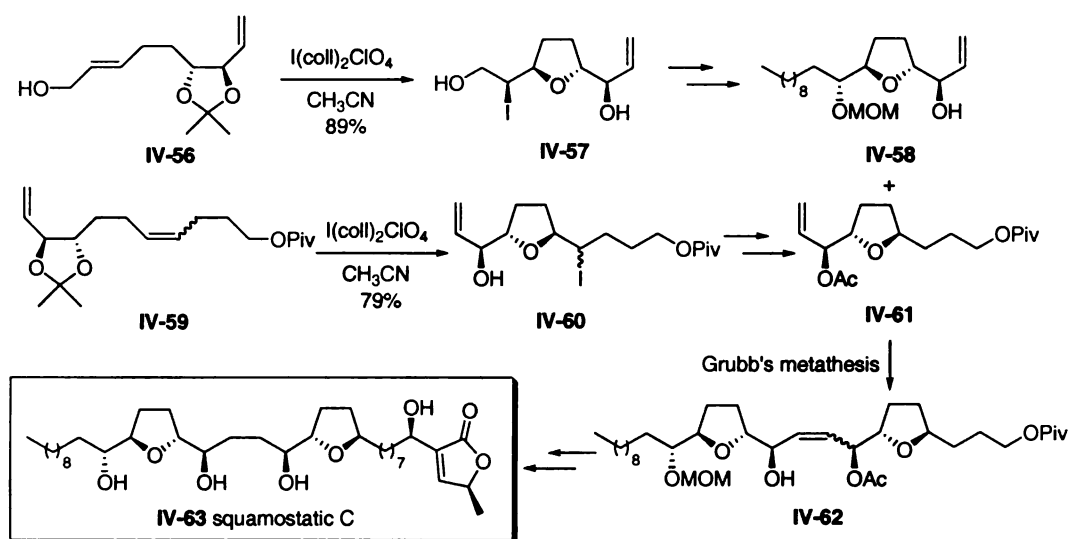


Figure IV-14: Intermediate conformation of iodoetherification reaction

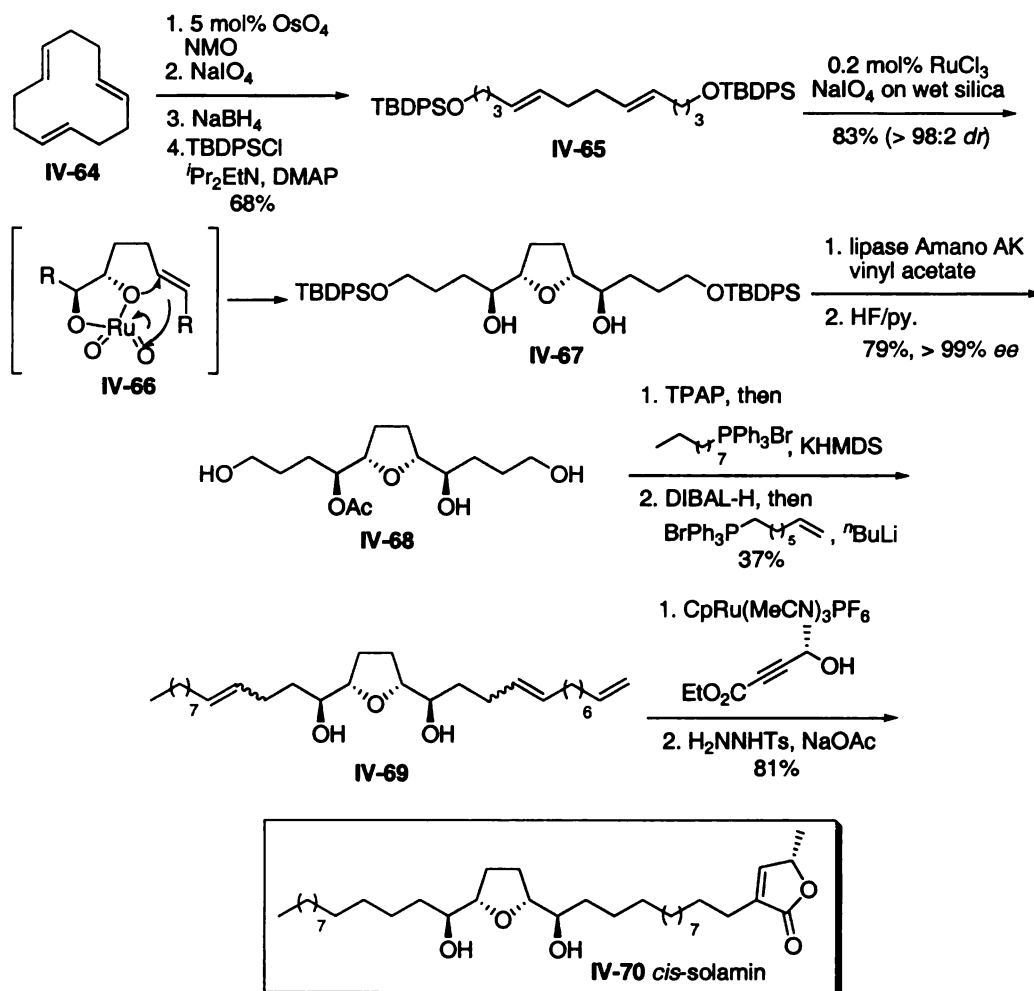
They have applied their iodoetherification methodology to synthesize the natural product squamostatic C, one of the typical non-adjacent bis-THF containing acetogenins (Scheme IV-7).^{75, 197} Two THF precursors **IV-58** and **IV-61** were prepared via the iodoetherification as the key step, and were coupled by Grubb's olefin cross-metathesis to form non-adjacent bis-THF moiety **IV-62**. After installing the butenolide and removing protection groups, squamostatic C was synthesized.



Scheme IV-7: Mootoo's total synthesis of squamostatic C

IV.7.4. Oxidative cyclization strategy

Metal mediated stereospecific oxidative cyclization to form five- or six-membered heterocyclic rings has recently emerged as a powerful methodology for synthesis of THF and THP systems. Some groups reported their studies in the synthetic development for preparing acetogenins and their analogs by using different metals such as osmium,^{92, 200} rhenium,^{201, 202} ruthenium,^{203, 204} cobalt,²⁰⁵ and permanganate.^{143, 206} For example, Stark and coworkers finished the enantioselective total synthesis of *cis*-solamin in 2006 (Scheme IV-8).²⁰³ (*E, E, E*)-1,5,9-Cyclododecatriene **IV-64** was

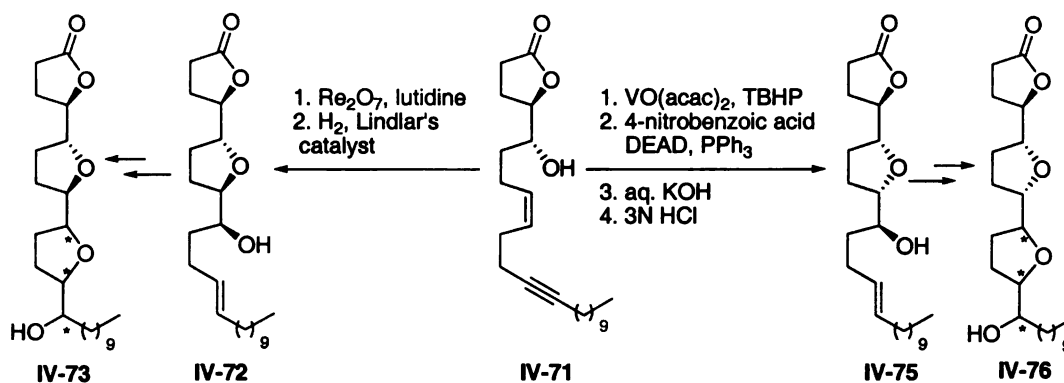


Scheme IV-8: Stark's total synthesis of *cis*-solamin

converted to diene intermediate **IV-65**, which was subjected to the ruthenium tetroxide catalyzed oxidative cyclization²⁰⁷ to afford THF product **IV-67** as a single diastereomer. The excellent diastereoselectivity of this transformation was believed to result from a double *syn* specific [3 + 2] oxidizing addition with a conformationally constrained second intramolecular addition process.²⁰⁷ After an enzymatic desymmetrization of *meso*-diol **IV-67**, deprotection of silyl group gave compound **IV-68**, which underwent the terminal differentiation to install both tail and spacer. The butenolide segment was introduced using a ruthenium(II)-catalyzed Alder-ene

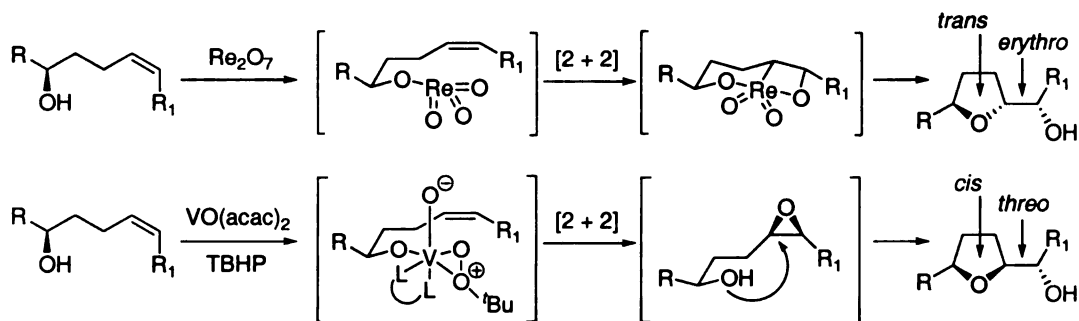
reaction developed by Trost's group.²⁰⁸⁻²¹⁰ Final diimide reduction furnished *cis*-solamin **IV-70**. The total synthesis was achieved in 11 steps with an overall yield of 7.5%.

Sinha and Keinan also used the oxidative cyclization strategy to do the library synthesis of acetogenins (Scheme IV-9).²¹¹ Re_2O_7 mediated cyclization generated



Scheme IV-9: Keinan's library synthesis of bis-THF cores

trans-THF ring (**IV-72**) while $\text{VO}(\text{acac})_2$ generated *cis*-THF ring (**IV-75**). By choosing different metal oxidant, two diastereomeric THF intermediates could be formed from a single hydroxyl olefin **IV-71**. Combined with Mitsunobu inversion, the second oxidative cyclization could afford the second THF ring and flanking hydroxyl group in a stereocontrolled manner (**IV-73** and **IV-76**). Thus eight diastereomers could be formed during the whole sequence from the same starting material. In a similar manner, the remaining 56 isomers were synthesized and some of them were used in total synthesis of asimicin, bullatacin, trilobacin, rolliniastatin, and solamin.²¹¹ The possible mechanism of these two metal mediated oxidative cyclizations is shown in Scheme IV-10. Re_2O_7 mediated cyclization underwent [2 + 2] cyclization to form a [6 + 4]-fused ring system, which gave a *trans*-THF ring with

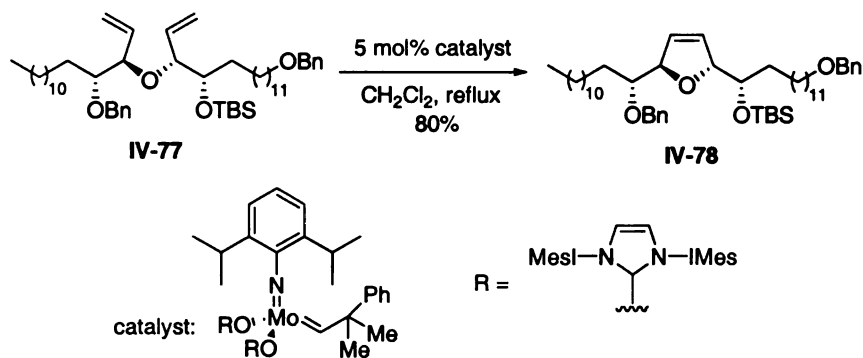


Scheme IV-10: Proposed mechanisms for Re_2O_7 and $\text{VO}(\text{acac})_2$ mediated oxidative cyclization of hydroxyl olefins

an *erythro*-side hydroxyl group. However, $\text{VO}(\text{acac})_2$ mediated cyclization involved the formation of a chiral epoxide, which underwent ring-opening to give the *cis*-THF ring with *threo*-side hydroxyl group.

IV.7.5. Ring-closing metathesis (RCM) strategy

Ring-closing metathesis²¹² is a popular route to construct cyclic structures. Researchers have also used this methodology in the synthesis of acetogenins.^{108, 111, 156} For example, in the total synthesis of solamin reported by Heck and coworkers in 2004 (Scheme IV-11), RCM was used to secure the THF ring.¹¹¹ The diene **IV-77**



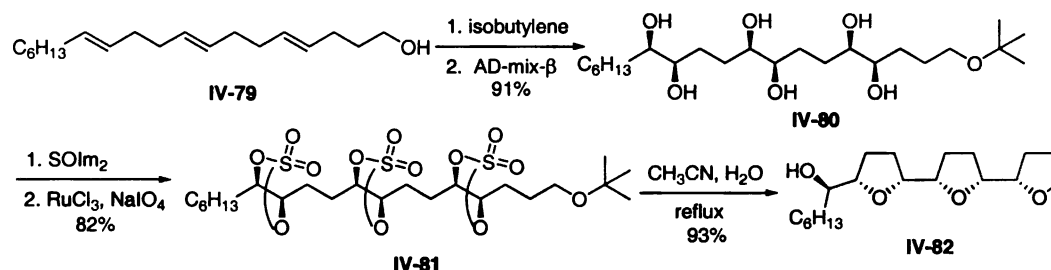
Scheme IV-11: Heck's RCM strategy to generate the central THF core in solamin

was subjected to RCM conditions using several metathesis catalysts. The ruthenium imidazolylidene catalyst^{213, 214} could give produced the desired product **IV-78** in very

good yield and only 5 mol% catalyst. After hydrogenation of the double bond of **IV-78**, the central THF core of solamin was constructed.

IV.7.6. Other strategies

An enantioselective alternative in the synthesis of poly-THF cores from polyepoxide cyclization is the cascade cyclization of cyclic sulfates which was reported by Rychnovsky in 1995 (Scheme IV-12).²¹⁵ The cascade cyclization was

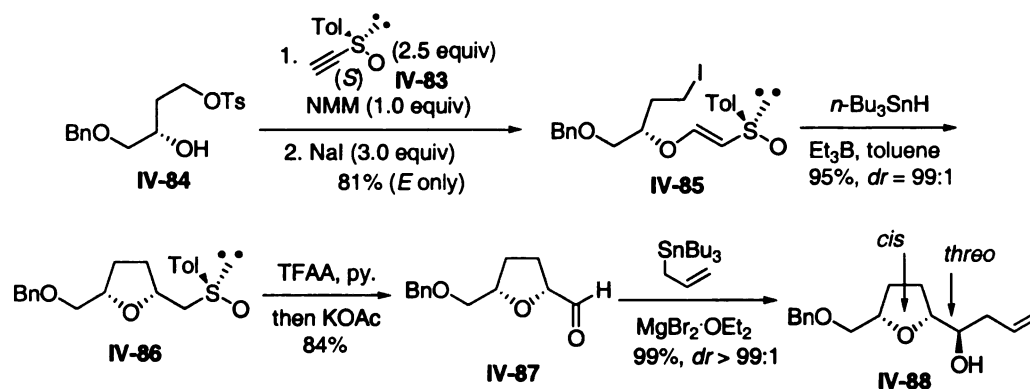


Scheme IV-12: Rychnovsky's cascade cyclization of cyclic sulfates

investigated using alcohol **IV-79**. Protection of the primary alcohol and Sharpless asymmetric dihydroxylation gave hexanol **IV-80** as a single isomer in good yield. After forming the tri-sulfate **IV-81**, cyclization reactions proceeded efficiently after the *in situ* sulfate hydrolysis and were almost completely free of side reactions. They tested this methodology and succeeded in the construction of the C17-C32 fragment of ionomycin which contained the bis-THF fragments.

Lee and coworkers developed the radical cyclization of β -alkoxyvinyl sulfoxides to form THF cores (Scheme IV-13).²¹⁶ The tosylate **IV-84**, obtained from L-malic acid, reacted with chiral sulfoxide reagent **IV-83** in the presence of *N*-methylmorpholine (NMM) followed by iodide substitution and resulted in the formation of enantiomerically pure sulfoxide **IV-85**. When the latter was treated

with tributylstannane and triethylborate, a tetrahydrofuranyl product **IV-86** was



Scheme IV-13: Lee's radical cyclization of β -alkoxyvinyl sulfoxides

obtained via a radical process. Pummerer rearrangement of **IV-86** gave aldehyde **IV-87** in very good yield, which could undergo allylation reaction under chelation-controlled conditions to form *cis*-THF with *threo*-flanking hydroxyl groups in high stereoselectivity. In 2005, they succeeded to apply this methodology to finish the total synthesis of rolliniastatin 1, rollimembrin, and membranacin (Figure IV-15).²¹⁷

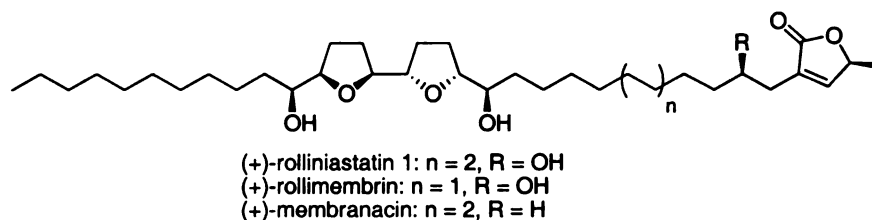
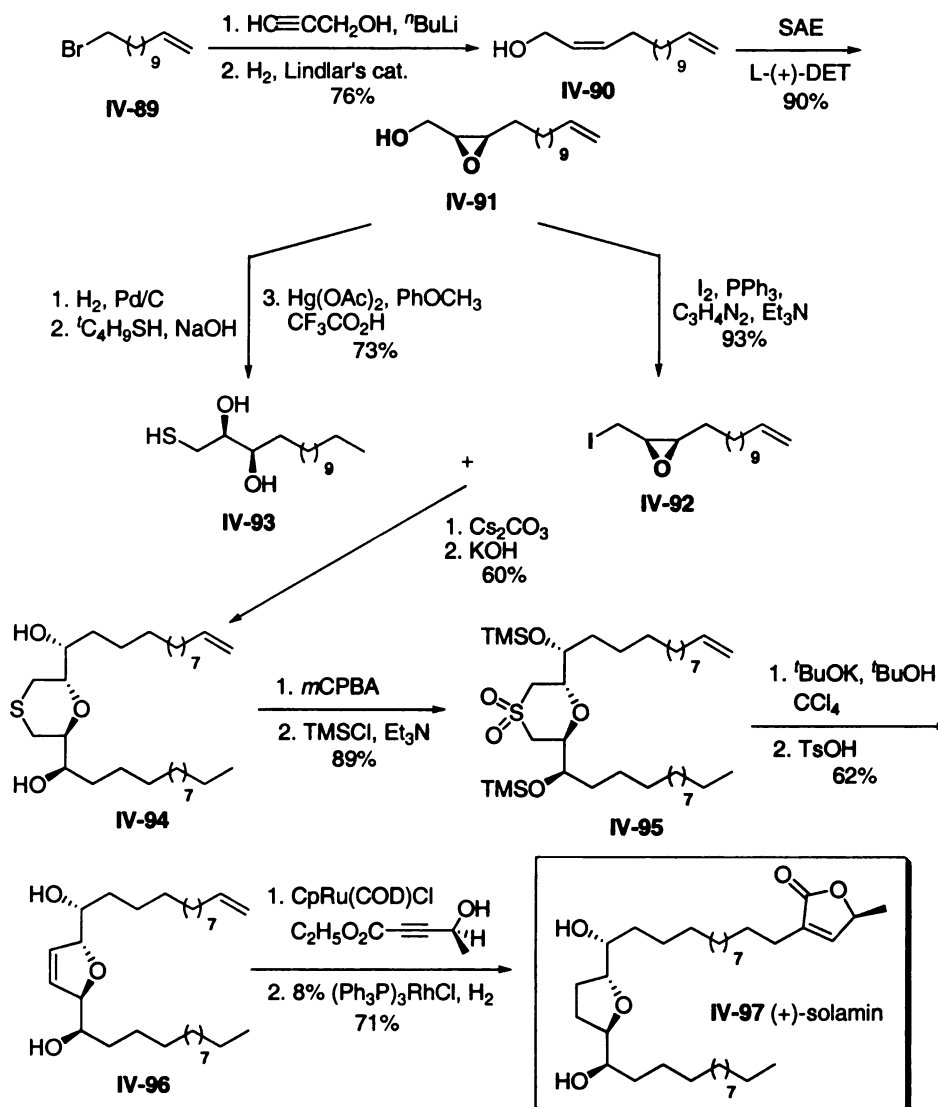


Figure IV-15: Structures of rolliniastatin 1, rollimembrin, and membranacin

Another interesting strategy is a convergent approach via a Ramberg-Backlund olefination^{218, 219} reported by Trost and Shi.²²⁰ Using the Ramberg-Backlund protocol combined with the ruthenium-catalyzed butenolide annulation, they finished the total synthesis of (+)-solamin and analogs in an effective way (Scheme IV-14). Asymmetric epoxidations of **IV-90** produced chiral epoxide **IV-91** in 82% *ee*. After

recrystallization to obtain > 99% *ee*, **IV-91** could be converted to two intermediates



Scheme IV-14: Trost's total synthesis of (+)-solamin

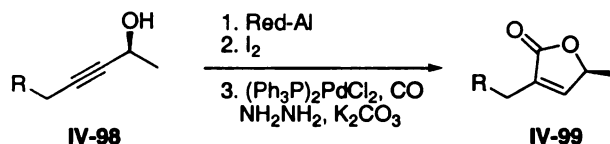
IV-92 and **IV-93**, which were then coupled under basic conditions to provide 1,4-oxathiane **IV-94**. The best protocol of the Ramberg-Bäcklund process involved *in situ* chlorination-rearrangement of the corresponding sulfone **IV-95**, which formed the key intermediate **IV-96**. Ruthenium-catalyzed butenolide annulation of **IV-96** with ynolate followed by chemoselective hydrogenation could give the natural product (+)-solamin. This strategy is highly convergent and easy for preparing

C2-symmetric acetogenins.

IV.7.7. Synthesis of terminal γ -lactone ring (butenolide group)

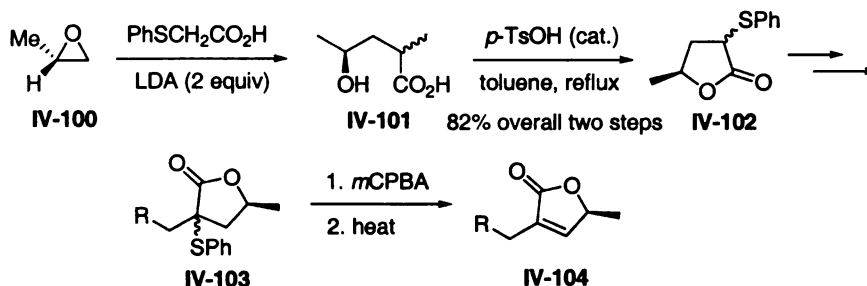
Generally, the terminal butenolide group is synthesized separately from the chiral starting material and combined with the THF moiety in the late stage of the synthesis. There are several general protocols that are widely used in the total synthesis of acetogenins.

Red-Al reduction and iodine treatment of alkynyl alcohol **IV-98** gave a *Z*-vinyl iodide that was carbonylated under Stille conditions²²¹ to produce the butenolide **IV-99** (Scheme IV-15).^{75, 101, 118, 121, 139, 168, 183, 187, 202}



Scheme IV-15: Butenolide synthesis from alkynyl alcohol

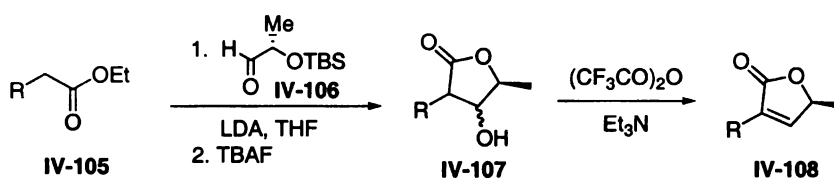
Alkylation of the dianion of (phenylthio)acetic acid with the chiral propylene oxide **IV-100** gave a diastereomeric mixture of 4-hydroxy-2-(phenylthio)pentanoic acids **IV-101** (Scheme IV-16).²²² Without separation, **IV-101** was converted to *cis*- and *trans*- α -substituted γ -valerolactones **IV-102**. After combining this piece with the THF moiety via alkylation, subsequent oxidation of sulfide to sulfone is followed by



Scheme IV-16: Synthesis of butenolide from chiral propylene oxide

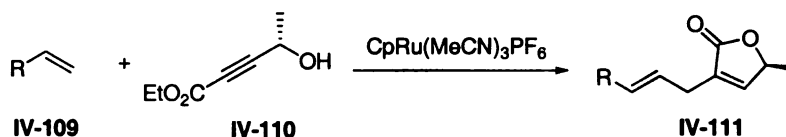
thermal elimination to afford the butenolide **IV-104**.^{106, 108, 111, 167, 185, 223}

The aldol reaction between the lithio enolate of ester **IV-105** and the TBS-protected chiral lactaldehyde **IV-106** afforded the product, which in subsequent treatment with TBAF led to the lactone diastereomers **IV-107** (Scheme IV-17). Dehydration to the butenolide **IV-108** was achieved through treatment with trifluoroacetic anhydride and triethylamine.^{120, 184, 224, 225}



Scheme IV-17: Synthesis of butenolide via aldol reaction

Trost and coworkers developed a ruthenium(II)-catalyzed Alder-ene reaction, which can be used to prepare butenolides (Scheme IV-18).²⁰⁸⁻²¹⁰ Treatment of alkene **IV-109** and known alkyne **IV-110** with a catalytic amount of $\text{CpRu}(\text{MeCN})_3\text{PF}_6$ afforded the coupled product with excellent chemoselectivity and in good yield.^{143, 203, 206, 220}



Scheme IV-18: Synthesis of butenolide via Ru(II)-catalyzed alder-ene reaction

IV.8. Summary

In conclusion, *Annonaceous* acetogenins are a large family of natural products which display a range of noteworthy biological properties. They are believed to be one of the most active class of compounds with high potent activity against

mitochondrial complex I. The structure-activity relationship studies of acetogenins offer some suggestions of their antitumor mechanism. However, the details of the mechanism are still not clear. Organic synthetic chemists have developed several efficient strategies to synthesize acetogenin natural products and their analogs with the ability to vary the stereochemistry and substructures at will.

IV.9. References

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METHODOLOGY AND KINETIC STUDIES OF OXONE PROMOTED
OXIDATION REACTIONS AND STRUCTURE REASSIGNMENT, TOTAL
SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF
ANNONACEOUS ACETOGENINS

Volume II

By

Jun Yan

A DISSERTATION

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CHAPTER V

MUCOXIN: STRUCTURE RE-ASSIGNMENT, TOTAL SYNTHESIS, AND STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

V.1. Introduction

As described in Chapter IV, generally, *Annonaceous* acetogenins belong to two broad groups. Classical acetogenins contain none to three 2,5-disubstituted tetrahydrofuran (THF) units along with a terminal γ -lactone, such as uvaricin¹ and bullatacin.³ 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,⁴ and muconin, which contains a normal THP ring adjacent to another THF ring.² More recently, these THP-containing nonclassical acetogenins have drawn the attention of synthetic chemists due to their novel structural features and biological activities.⁵⁻¹⁰

Until 2006, however, there were no synthetic studies on the hydroxylated THF-containing nonclassical acetogenins. Mucocin (Figure V-1), the first hydroxylated THF-containing nonclassical acetogenin was isolated by McLaughlin and coworkers in 1996 from the bioactive leaf extracts of *Rollinia mucosa*.² [Four acetogenins were previously reported to possess hydroxylated THF rings,¹¹ however

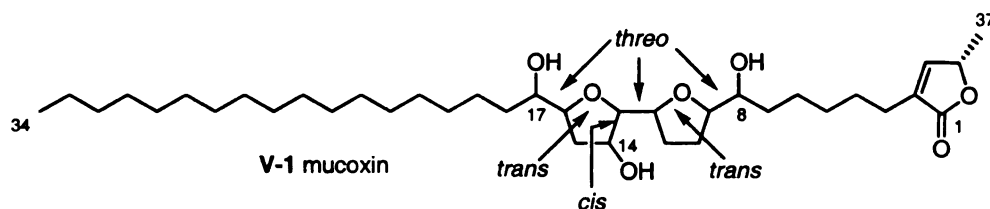


Figure V-1: Proposed structure of mucoxin

their structures were proved erroneous and have been corrected.^{12]} Mucoxin exhibited potent and selective *in vitro* cytotoxicity against MCF-7 cells (breast cancer) in a panel of six human solid tumor cell lines.² It has an ED_{50} value of 3.7×10^{-3} $\mu\text{g/mL}$, which is more potent than adriamycin ($ED_{50} = 1.0 \times 10^{-2}$ $\mu\text{g/mL}$). 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.

V.2. 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 V-1). 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.^{13, 14} Therefore, we chose the enantiomer represented in Figure

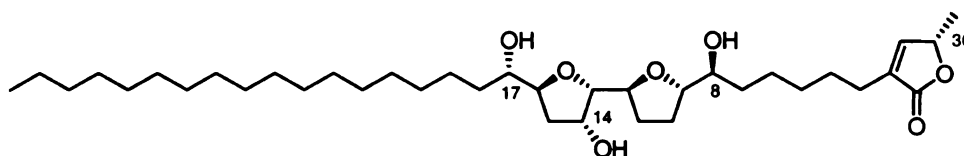


Figure V-2: Synthetic target (mucoxin)

V-2 as the synthetic target and completed the first total synthesis of the proposed structure of mucoxin in 2006.¹⁵

V.2.1. Retrosynthetic analysis

In Chapter IV several syntheses of *Annonaceous* acetogenins were described. 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 V-3.¹⁵ We planned to connect the terminal γ -lactone ring V-4, which could be prepared from the commercially available chiral epoxide V-5 (Chapter IV, 7.7), with the bis-THF moiety

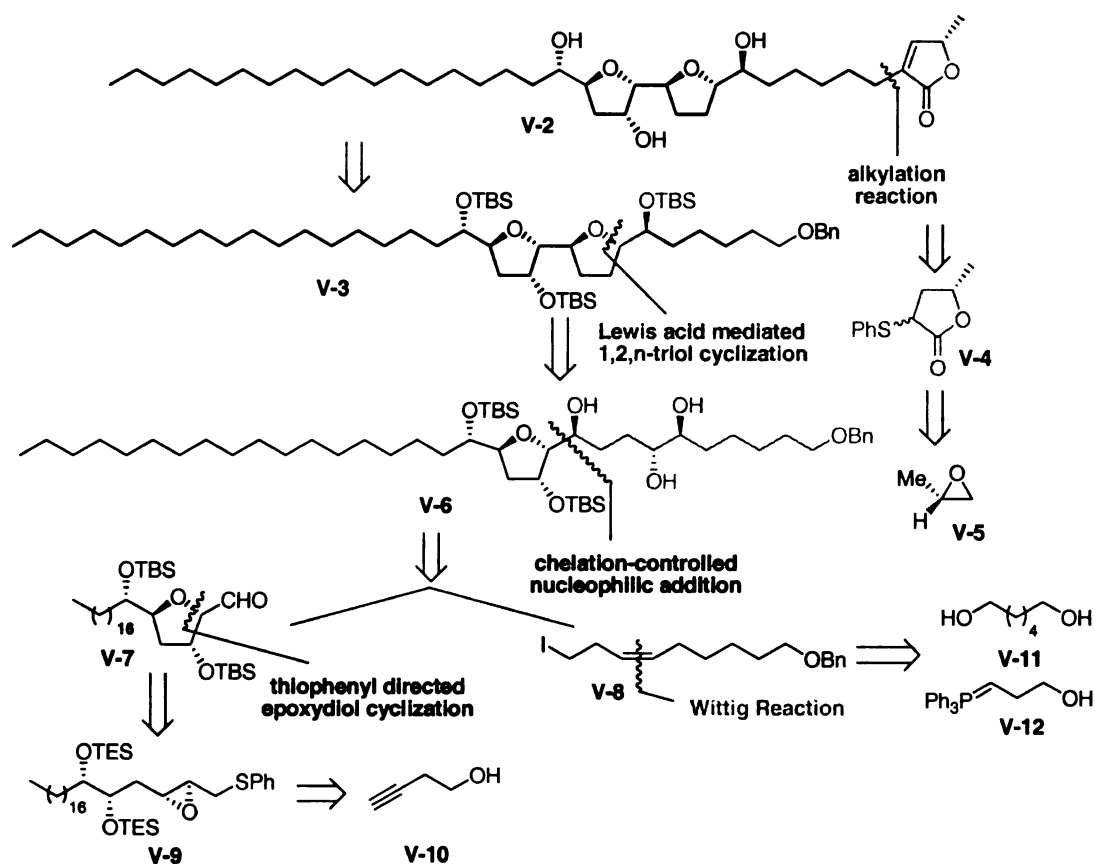
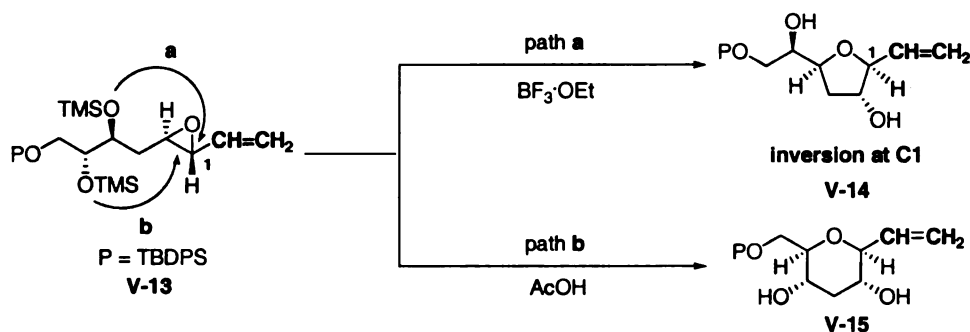


Figure V-3: Retrosynthetic analysis for preparation of mucoxin

V-3 via an alkylation reaction. The 2,5-disubstituted THF ring was formed using our 1,2,*n*-triol cyclization methodology from intermediate V-6.¹⁶ The two adjacent THF cores were coupled via a 1,2-chelation-controlled addition of the Grignard reagent derived from iodide V-8, with THF aldehyde V-7. The 2,3,5-trisubstituted THF V-7 would be accessed using our Lewis acid-catalyzed, thiophenyl group-directed epoxide ring-opening of bis-protected epoxydiol V-9,^{17, 18} which could be derived from the commercially available alkynyl alcohol V-10. Homoallylic iodide V-8 could also be derived from diol V-11 and ylide V-12 via the Wittig reaction.

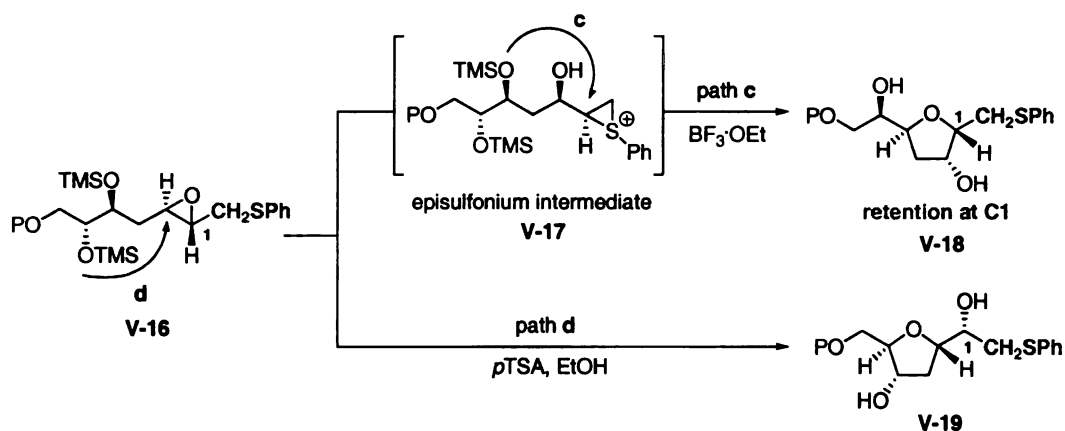
V.2.2. Two methodologies for constructing di- and tri-substituted THF rings

In 2001 and 2003, we reported the neighboring group-assisted intramolecular cyclizations of epoxy diols, which could lead to several different cyclic ethers depending on which of the two hydroxyl groups participates, which carbon in epoxy diols is the site of ring-opening, and how the stereochemistry changes during the cyclizations.^{17, 18} A series of experiments showed that by the appropriate choice of directing group, the type of acid, and the reaction conditions, cyclization of an epoxy diol could be controlled in high stereo- and regioselectivities (Scheme V-1 and



Scheme V-1: Intramolecular cyclizations assisted by the neighboring olefinic groups

Scheme V-2). The bis-protected epoxy diol **V-13** and **V-16** were synthesized from 2-deoxy-D-ribose.¹⁷ For compound **V-13**, the neighboring olefinic group could stabilize the developing positive charge at C1 during the activation and epoxide opening processes (Scheme V-1). Thus, in the presence of a Lewis acid promoter, such as $\text{BF}_3 \cdot \text{OEt}_2$, the cyclized product 2,3,5-trisubstituted THF **V-14** was obtained in 82% yield with the stereochemistry inverted at C1. Interestingly, cyclization of **V-13** using an aqueous Brønsted acid, such as acetic acid, yielded only THP **V-15** as the product. Semiempirical calculations suggested that THP **V-15** is slightly more stable than THF **V-14**.¹⁷ However, THF **V-14** can not be isomerized to THP **V-15** in the presence of Brønsted acid. The regioselectivity in the ring-opening reaction of epoxy diol **V-13** might be due to different energies of transition states under different conditions. For compound **V-16**, the neighboring sulfide group could direct the reaction to a different pathway (Scheme V-2). Activation of the epoxysulfide **V-16**



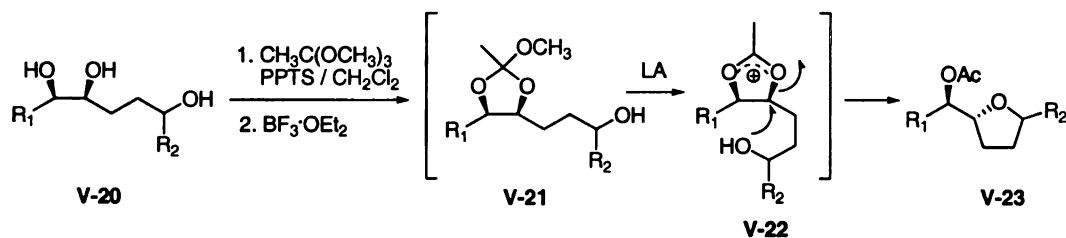
Scheme V-2: Intramolecular cyclizations assisted by the sulfide neighboring groups

with a Lewis acid such as $\text{BF}_3 \cdot \text{OEt}_2$ favored the formation of an intermediate episulfonium ion **V-17**, which upon subsequent intramolecular ring opening yields the 2,3,5-trisubstituted THF **V-18**. The nOe experiments of **V-18** confirmed that the

stereochemistry of C1 was retained, suggesting the formation of an episulfonium ion prior to the cyclization (a double inversion at C1). This episulfonium ion was also observed from rearrangement of the epoxysulfides under acidic additions by other groups.¹⁹⁻²¹ However, when a Brønsted acid such as 1.5 N HCl was used as the promoter, a mixture of THF products **V-19** and **V-18** was formed with **V-19** as the major product (**V-19**:**V-18** = 97:3, the overall yield = 74%).¹⁷ There was also no equilibrium between these two products. One possible reason why THF **V-19** was favored under the strong protic acid conditions might be that the thio group was protonated and thus the corresponding episulfonium ion could not be formed quickly.

This neighboring group-assisted epoxy diol cyclization method provided an efficient pathway to prepare 2,3,5-trisubstituted THF rings, which is an important intermediate in the synthesis of mucoxin. Since all the other synthetic routes are focused on the synthesis of 2,5-disubstituted THF cores, this is the first report to construct a 2,3,5-trisubstituted THF core in acetogenins.¹⁵

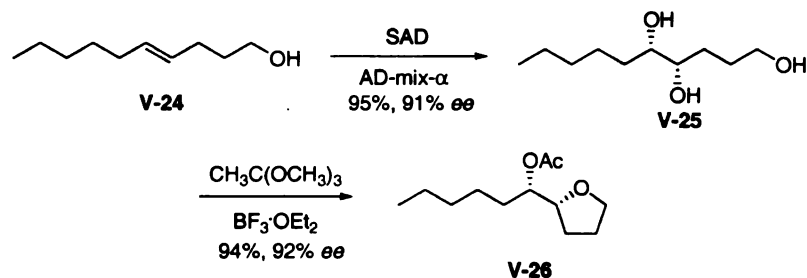
Another useful methodology to construct 2,5-disubstituted THF units was developed by our group in 2005, and involves the one-pot cyclization from 1,2,*n*-triols mediated by Lewis acid (Scheme V-3).¹⁶ The overall strategy depends



Scheme V-3: One-pot cyclization of 1,2,*n*-triols with Lewis acid promoter

on the *in situ* generation of an ortho ester **V-21** from 1,2,*n*-triol **V-20** via the

trans-ortho esterification of trimethyl orthoacetate catalyzed by PPTS. The subsequent ionization of orthoester **V-21** with a Lewis acid affords an active acetoxonium ion **V-22**, which upon the intramolecular cyclization with the pendant hydroxyl group results in the 2,5-disubstituted THF **V-23**. Further experiments simplified this reaction by using $\text{BF}_3 \cdot \text{OEt}_2$ to promote both *trans*-ortho esterification and the subsequent cyclization. This one-step process is simpler and usually gives higher yields. Cyclization of enantiomerically enriched triol **V-25**, derived from the Sharpless asymmetric dihydroxylation²² of alkene **V-24**, gave the THF product **V-26** in 94% yield and complete transfer of chirality (92% *ee*), proving that the whole sequence was a stereospecific process (Scheme V-4). Since it is easy to use asymmetric dihydroxylation reactions to control the stereochemistry of 1,2-diols, this

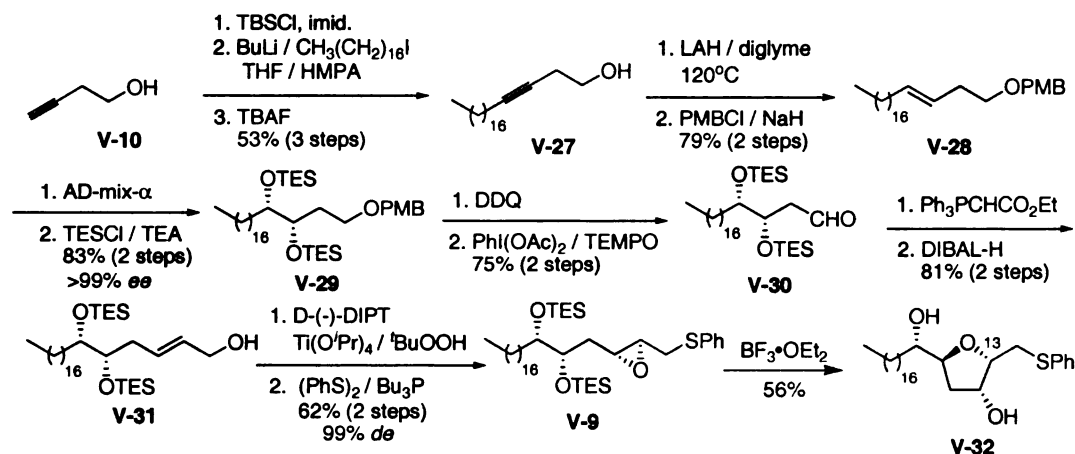


Scheme V-4: Example of a 1,2,*n*-triol cyclization mediated by Lewis acid

method provides an efficient strategy to prepare enantio-pure 2,5-disubstituted THF cores and could be used in the synthesis of acetogenins.

V.2.3. Total synthesis of the proposed structure of mucoxin

The total synthesis of the proposed structure of mucoxin was completed by our group in 2006,¹⁵ utilizing the previously described methodology. The synthesis of the 2,3,5-trisubstituted THF core of mucoxin is shown in Scheme V-5. Alkylation of the lithium acetylide derived from TBS-protected commercially available 3-butyne

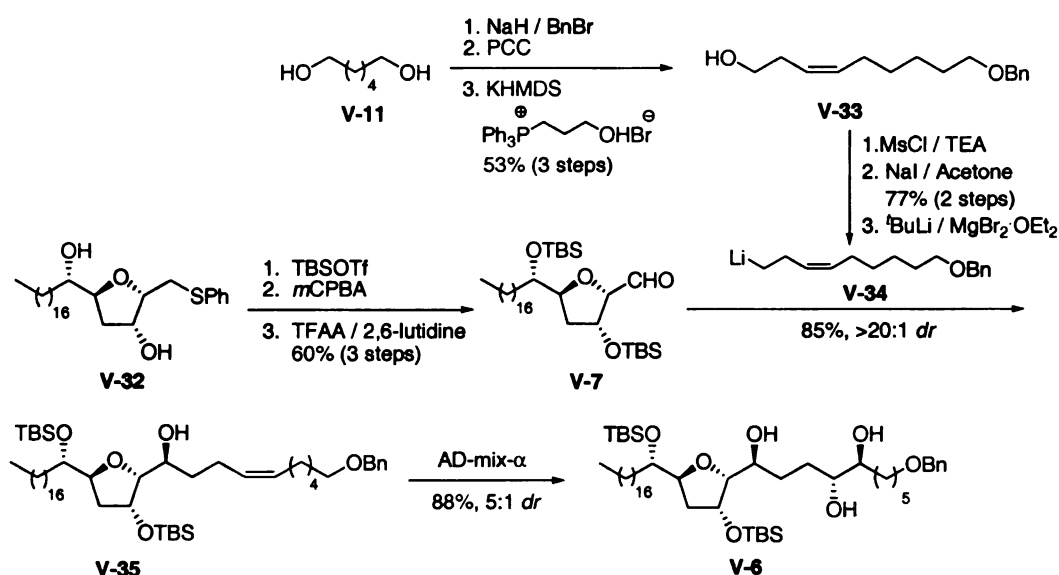


Scheme V-5: Synthesis of 2,3,5-trisubstituted THF **V-34**

V-10 gave the homopropargylic TBS ether, which after TBS deprotection forms homopropargylic alcohol **V-27**. LAH reduction of the triple bond and PMB protection of the alcohol provided the *E*-homoallylic PMB ether **V-28**. Sharpless asymmetric dihydroxylation²² of **V-28** 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 **V-30**, which could undergo Wittig olefination and subsequent DIBAL-H reduction to form allylic alcohol **V-31**. Sharpless asymmetric epoxidation²³ of allylic alcohol **V-31** provided the desired epoxy diol in excellent diastereoselectivity (>99:1, by ¹H NMR) and good yield (73%) under optimized conditions. After converting the epoxy alcohol to the required epoxysulfide precursor **V-9**, the neighboring group-assisted cyclization reaction (shown in blue) under our standard conditions led to the formation of the desired 2,3,5-trisubstituted THF diol **V-32** 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 **V-32** 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 **V-9**. Compared with the required stereochemistry of the THF product **V-32**, the stereochemistry of C13 needed 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 V-6). The free

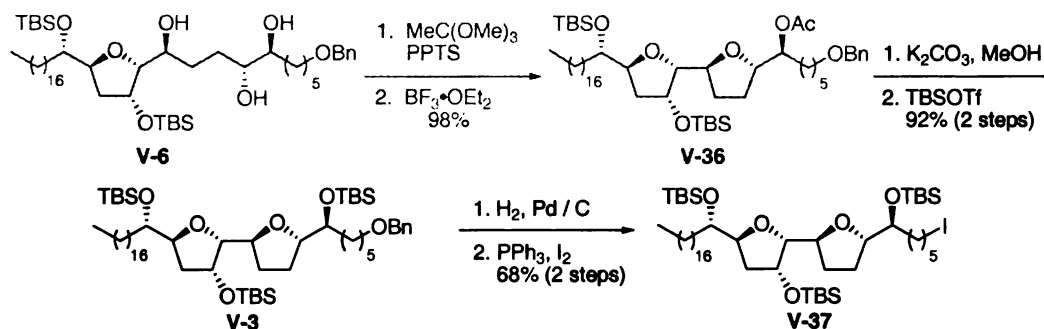


Scheme V-6: Synthesis of triol intermediate V-40

hydroxyl groups of compound **V-32** were protected as TBS ethers, and the product was subjected to Pummerer rearrangement^{24, 25} conditions, providing the desired aldehyde **V-7** in good yield. Synthesis of organolithium reagent **V-34** could be accomplished in a concise process, which involved the monobenylation of commercially available 1,6-hexanediol **V-11**, PCC oxidation, the *Z*-selective Wittig

olefination by *in situ* TMS protection / deprotection of the ylide's hydroxyl group,^{26, 27} iodination via S_N2 displacement, and a lithium-halogen exchange with ^tBuLi. After transmetalation with freshly prepared MgBr₂•OEt₂ at -95 °C,^{28, 29} the Grignard reagent was formed and treated with aldehyde V-7, which was precoordinates with freshly prepared MgBr₂•OEt₂ at -40 °C. This optimized procedure gave the desired chelation-controlled addition product V-35 in good yield and excellent diastereoselectivity. The subsequent Sharpless asymmetric dihydroxylation²² using AD-mix-α proceeded through attacking the olefin from the *si* face to form isomer V-6. Generally, during the SAD reaction, the stereoselectivity for *Z*-olefins is lower than for *E*-olefins, yielding the desired triol in a 5:1 diastereomeric ratio.

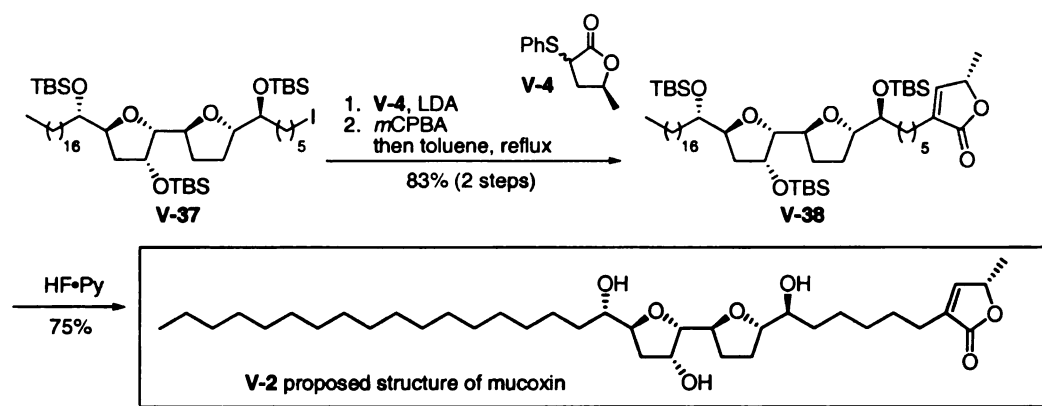
Next, we focused on constructing the disubstituted THF ring (Scheme V-7).



Scheme V-7: Synthesis of bis-THF iodide V-43

Treatment of V-6 with trimethyl orthoacetate and 10 mol% PPTS followed by addition of catalytic amount of BF₃•OEt₂ led to the desired 2,5-disubstituted THF ring in 98% yield as a single diastereomer (shown in red) via our 1,2,*n*-triol cyclization pathway. After converting the acyl group to the silyl group, benzyl-deprotection of V-3 via hydrogenation was followed by iodination to afford the bis-THF iodide V-37.

The final stages of the total synthesis are shown in Scheme V-8. α -Phenylthio- γ -lactone **V-4** was prepared by White's procedure from commercially available thiophenyl acetic acid and chiral epoxide.³⁰ The coupling of iodide **V-37** and α -phenylthio- γ -lactone **V-4** 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 **V-38**, which upon global deprotection using HF $\cdot$ py furnished the target molecule **V-2**, in high purity after HPLC isolation.



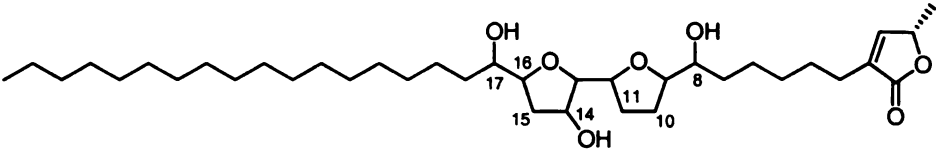
Scheme V-8: Completion of the total synthesis of the proposed structure of mucoxin

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,^{17, 18} and the 2,5-disubstituted THF ring (C8-C12) was constructed using a one-pot 1,2,*n*-triol cyclization strategy.¹⁶ The absolute stereochemistries in **V-2** were established via Sharpless asymmetric epoxidation²³ and dihydroxylation,²² as well as the chelation-controlled addition (**V-7** to **V-35**).

V.3. Comparison of Spectral Data of the Synthetic and Natural Mucoxin

Although the synthesis of the proposed structure of mucoxin was accomplished, both the ^1H 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 (C8-C17) (Table V-1).^{2, 15} In particular, H10, H11, H14, H15, and

Table V-1: Comparison of NMR resonances between natural and synthetic mucoxin



Proton / Carbon	V-2	Natural Mucoxin	$\Delta\delta$ (V-2–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
C17	74.3	73.7	+0.6

H17 exhibited differences of greater than 0.1 ppm as compared to the published spectra of the natural 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 **V-39** (Figure V-4) was synthesized using the epimer of α -phenylthio- γ -lactone **V-4**. ^1H and ^{13}C NMR spectra of epimer **V-39** were found to

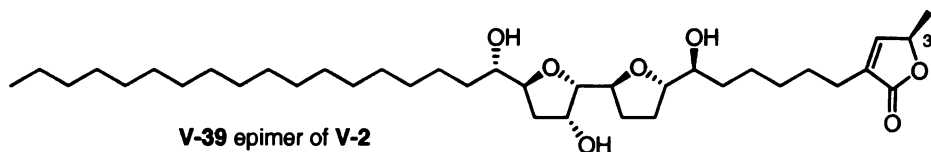


Figure V-4: C36 Epimer of synthesized mucoxin **V-2**

be identical with those of **V-2**, which supported our hypothesis that the 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.

In order to determine whether or not the stereochemistries of the other chiral centers were correctly assigned, the relative and absolute configurations of all the stereogenic centers in the synthetic material were analyzed, as described below.

The C16 and C17 stereocenters were set using Sharpless asymmetric dihydroxylation (SAD) reaction of olefin **V-28** (Scheme V-5). Based on the mnemonic device for the SAD reaction, **V-28** was positioned so that the long alkyl chain occupied the SW quadrant.²² In this orientation, AD-mix- α would react from the *si* face of the olefin to form the *S,S*-diol as the major enantiomer. The absolute configurations were independently determined using both the Mosher's ester analysis,³¹ as well as by Exciton Coupled Circular Dichroism (ECCD) spectroscopy.^{15, 32, 33} The bis-4-dimethylamino benzoate derivative of the *S,S*-diol was prepared for ECCD analysis (Figure V-5).^{15, 32} There are three possible staggered conformers of ester **V-41** (**A**, **B**, and **C** in Figure V-5). Conformer **B** has no ECCD signal due to

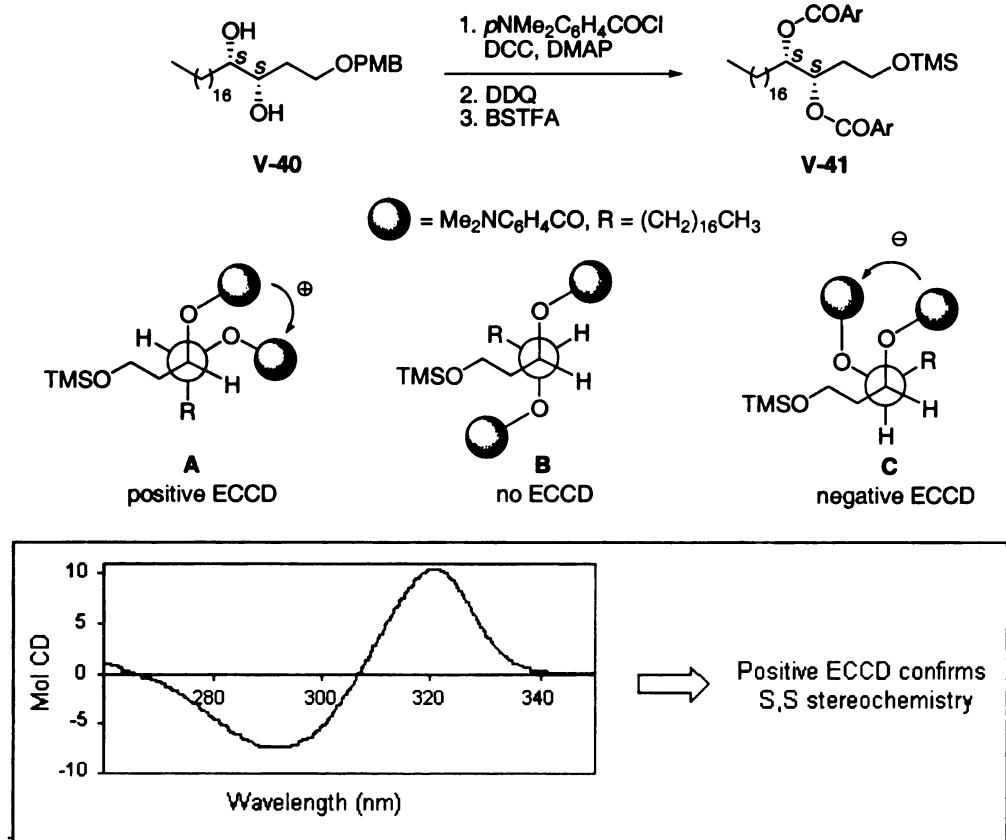
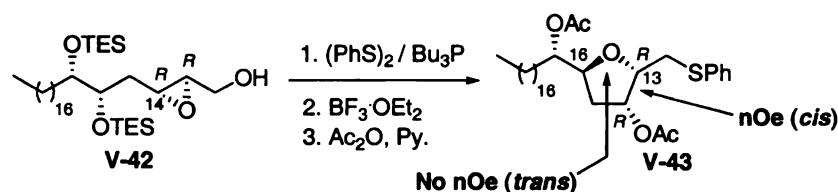


Figure V-5: ECCD of the C16, C17 diol **V-40** confirms the desired *S,S* stereochemistry the 180 °C angle between the two chromophores. Conformer **A** is expected to have the highest population since it suffers from two gauche interactions as opposed to conformer **C** that has three gauche interactions. The clockwise orientation of the transition dipole moments of the coupling chromophores in conformer **A** should give a positive ECCD signal. Therefore, if the absolute configuration of diol **V-40** is *S, S*, the dibenzoate **V-41** should yield a positive ECCD spectrum. Indeed, a positive ECCD spectrum was observed for **V-41** in various solvents ranging from cyclohexane to methanol. A representative spectrum in acetonitrile is shown in Figure V-5, which confirms the assigned configurations of diol **V-40**.

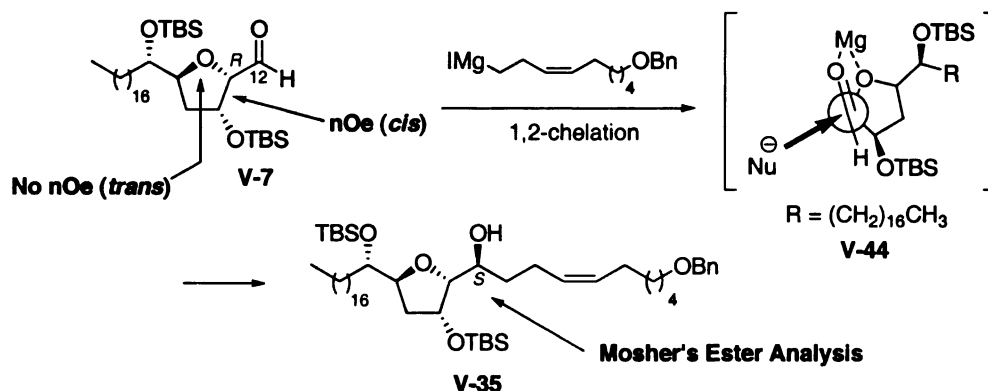
The C13 and C14 stereocenters were set using Sharpless asymmetric epoxidation (SAE) reaction of allylic alcohol **V-31** (Scheme V-5). The configurations at the two epoxide carbons were assigned as *R, R* based on the mnemonic for the SAE reaction.³⁴ The assignment was confirmed after the cyclization of **V-9**. The THF diol **V-32** generated after thiophenyl group-assisted epoxydiol cyclization was acylated to form diacetate **V-43** for ease of characterization (Scheme V-9). A 2,5-*trans* relationship



Scheme V-9: Assignment of absolute configurations of C13 and C14

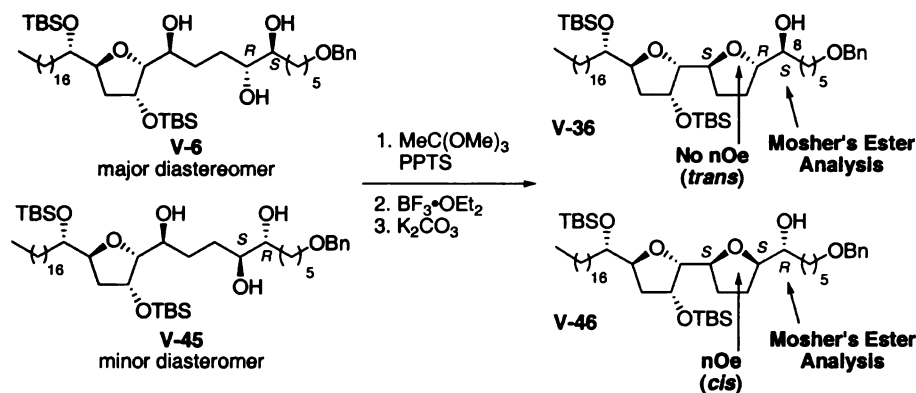
across the THF ring was assigned by the lack of a nOe signal between H13 and H16, where a strong positive nOe signal between H13 and H14 was indicative of the *cis* relationship. Lack of nOe's, especially in five-membered rings, must be examined carefully because of the pseudoaxial-axial disposition of hydrogens in a 1,3-relationship. To confirm the nOe result, the corresponding 2,3,5-trisubstituted THF ring with *cis*-2,5-THF ring was synthesized and positive nOe results were obtained. Because the absolute configuration of C16 was confirmed as *S*, in combination with the nOe experiments discussed above, the stereochemistry of C13 and C14 after cyclization was confirmed as *R* and *R*, respectively. Since the cyclization sequence is double-inversion in C13, the original epoxide **V-42** have also been *R,R* configuration as predicted by the mnemonic.

Next, the stereochemistry of the chelation-controlled addition was examined (Scheme V-10). The 2,3-*cis*, 2,5-*trans*-relationship in THF **V-7** was confirmed by



*n*Oe experiments, which established that no epimerization occurred under the Pummerer rearrangement conditions. Thus, the 1,2-chelation-controlled nucleophilic addition of the Grignard reagent to aldehyde **V-7** set the C12 stereocenter on the basis of model **V-44**. The stereochemistry of the newly formed secondary alcohol was confirmed as *S* with Mosher's ester analysis using both *R* and *S* Mosher's ester derivatives.

The C8 and C9 stereocenters in **V-6** were also set using the SAD reaction of olefin **V-35** (Scheme V-6). The dihydroxylation of a 1,2-disubstituted *cis*-olefin could lead to either a *S,R*- or a *R,S*-diol. After the SAD reaction, triol **V-6** was isolated as a major diastereomer in 74% yield with 14% of the minor diastereomer **V-45**. The absolute configurations of the desired *S,R*-isomer **V-6** was established after cyclization that afforded the hydroxyl THF ring **V-36** (Scheme V-11). The *S* configuration at C8 in **V-36** was established by Mosher's ester analysis. In the same way, the *R* configuration at C9 for triol **V-6** was established. Moreover, 1D-NOESY



Scheme V-11: Stereochemical assignment of C8 and C9

experiments showed no nOe correlation between H9 and H12 in **V-36**, suggesting a *trans*-relationship in the disubstituted THF ring, which could further prove the *R* configuration at C9. Conversely, cyclization of the minor isomer **V-45** of the SAD reaction did yield a *cis*-THF ring **V-46** that exhibited nOe correlation, further confirming the relative and absolute stereochemical assignments.

Based on the latter description, a summary of the stereochemical assignments is shown in Figure V-6. We reason that all the configurations in the C8-C17 region of

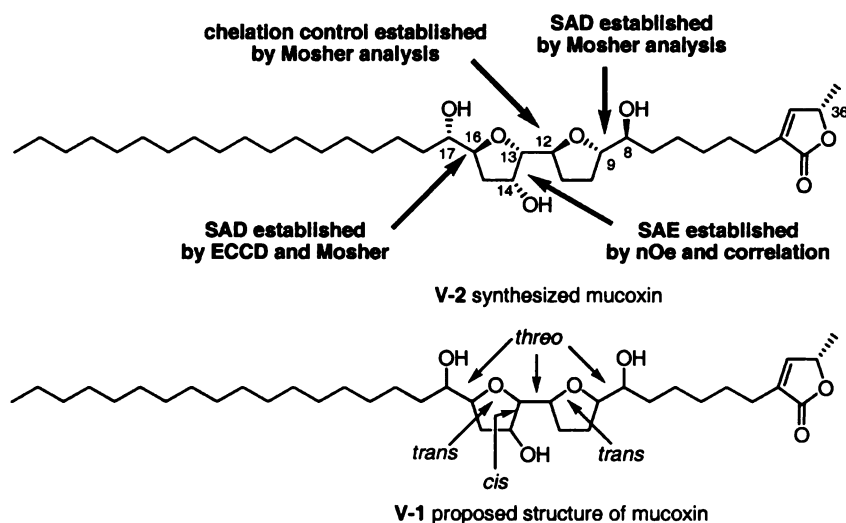


Figure V-6: Structure of synthetic mucxin and proposed structure of mucxin

the synthesized mucoxin V-2 are identical to the proposed relative stereochemistry of natural mucoxin.² Therefore, the disagreement in both ¹H and ¹³C NMR must be due to the misassignments of the natural sample.

All work related to the total synthesis of the proposed structure of Mucoxin was performed by Radha S. Narayan, a PhD graduate from the Borhan laboratory.

V.4. The Strategy towards Structure Elucidation of Mucoxin

We re-examined McLaughlin's structural assignment of mucoxin² 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 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.³⁵ For example, 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.³⁵

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 V-7 indicates all the possible 64 diastereomers of mucoxin, which were encoded in the 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*

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

Figure V-7: 64 possible diastereomers of mucoxin

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 V-8).

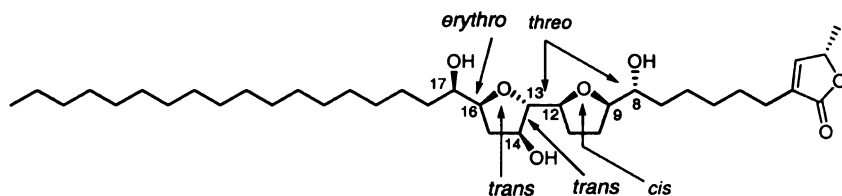


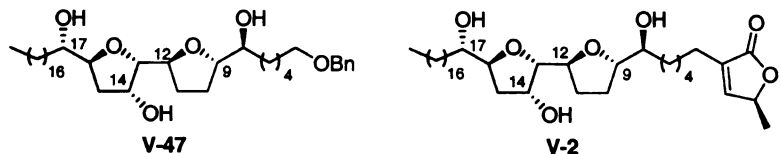
Figure V-8: *ttcETT* Diastereomer of mucoxin

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

that some coherent trends might emerge that, together with the published NMR data of the natural sample, might direct us toward the correct structure of mucoxin.

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 **V-47**, the truncated structure of the synthesized mucoxin **V-2**, and compared their ^1H NMR spectra (Table V-2). The

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



Proton	V-47	V-2	$\Delta\delta$ (V-47 – V-2) (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

^1H NMR chemical shifts in the C8-C17 region of mucoxin analogs **V-47** and **V-2** 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 mucoxin¹⁵ 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

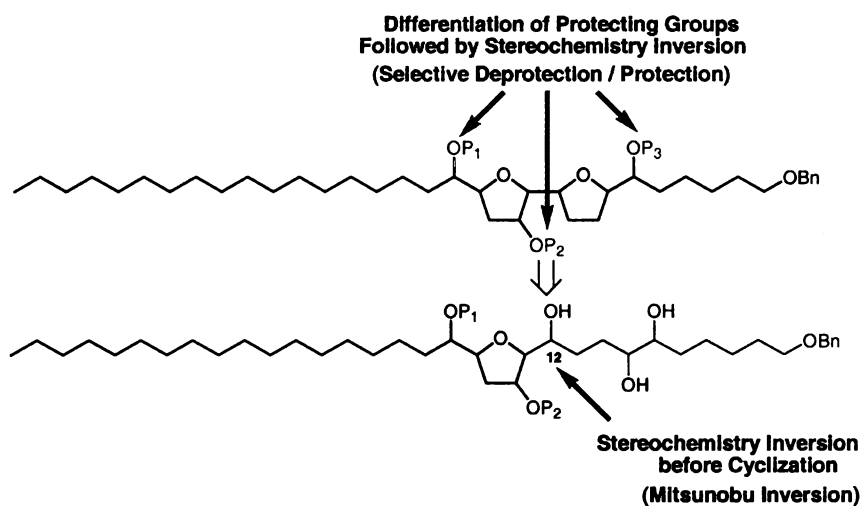


Figure V-9: New synthetic strategy to construct different diastereomers of mucoxin

chiral centers (C8, C14, or C17) could then be inverted by simple techniques such as oxidation/reduction or Mitsunobu inversion (Figure V-9).

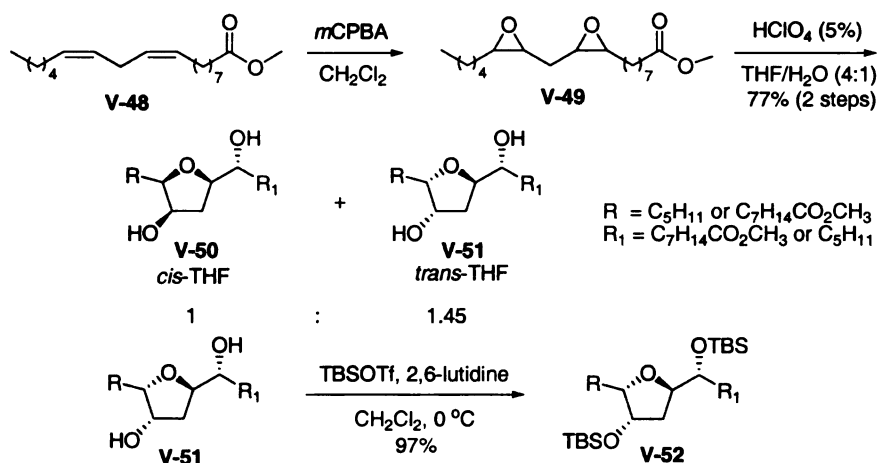
V.5. New Synthetic Pathway and Library Synthesis of Representative Truncated Structures of Mucoxin

The new synthetic pathway was based on selective deprotection / protection of hydroxyl groups and Mitsunobu inversion of free alcohols. Prior to the application of these methods to the real system, several model studies were studied in order to find the optimal conditions.

V.5.1. Studies on the selective deprotection / protection reaction

One of the ways to achieve stereochemical diversity in the bis-THF core is by varying the configuration at the carbon attached to the three hydroxyl groups (C8, C14, and C17). Our first goal was to delineate conditions to differentiate the three hydroxyl groups. Following the reaction sequence used in the preparation of the proposed mucoxin, after the bis-THF core assembly was complete (Scheme V-7), the C8 hydroxyl group was protected as an acyl ester while the C14 and C17 carbinols appeared as TBS ethers. The selective desilylation reaction needed to be examined.³⁶⁻³⁹

A model study of selective desilylation was achieved using a THF ring bearing the same trisubstituted pattern (Scheme V-12). While studying the stereochemical aspects of the hydration of methyl diepoxystearates by cytosolic epoxide hydrolase, Kurth and coworkers reported that^{40, 41} methyl linoleate **V-48** can be oxidized via *m*CPBA epoxidations. The diepoxide product can undergo acidic hydrolysis to

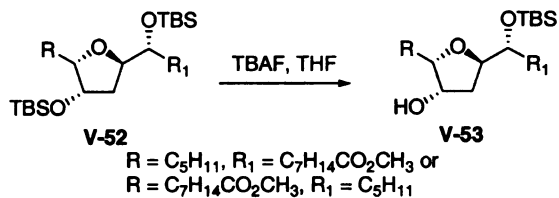


Scheme V-12: Synthesis of trisubstituted THF model compound **V-52**

afford a mixture of *cis*- and *trans*-THFs **V-50** and **V-51** as a 1:1.45 ratio. These two compounds could be separated on a silica gel column to afford pure compounds. The *trans*-THF diol **V-51** was then silylated by TBSOTf to provide di-TBS ether **V-52**, which has the same substitution pattern as the 2,3,5-trisubstituted THF ring in mucoxin and could be used in our model study.

TBAF was the reagent of choice for the selective desilylation reaction.³⁶⁻³⁹ After some experimentation by varying reaction time and temperature, the best conditions

Table V-3: Optimization of the selective deprotection reaction^a



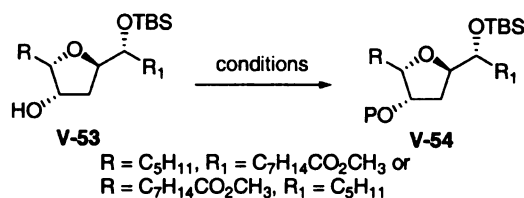
Entry	Temperature (°C)	Time (h)	Yield (%) ^b
1	-20	15	30
2	0	5	44
3	0	15	67
4	RT	3	61
5	RT	5	92

^a TBAF (1.05 equiv), ^b Isolated yield.

that afforded the monoprotected derivatives **V-53** in excellent yield were determined (Table V-3, entry 5). The identity of these monoprotected THF diols were confirmed by 2D-COSY experiments of the corresponding acyl ester derivatives. It was found that the TBS group in the THF ring was easier removed than that in the side alkyl chain.

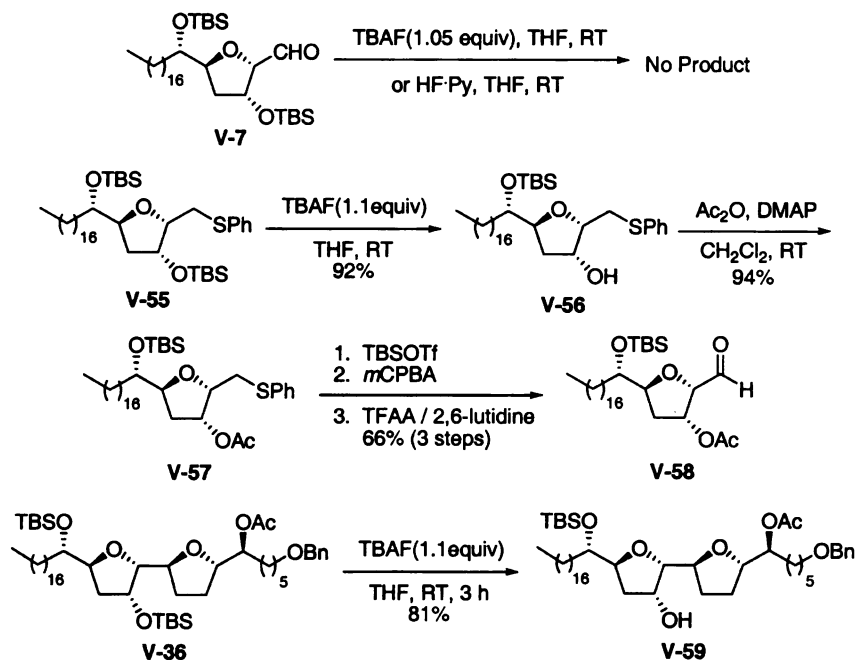
Orthoganol protection of **V-53** was investigated. Different protection groups were used under different conditions.³⁹ However, TBDPS, MOM, and PMB groups did not give the desired product probably due to steric constraints (Table V-4, entries 1-6). Only acylation afforded a high yield of the protected alcohol under mild reaction conditions (entry 7).

Table V-4: Protection reaction in model study



Entry	P	Conditions	Results
1	TBDPS	TBDPSCI, imidazole, DMF, RT	recovered S.M.
2		TBDPSCI, TEA, DMAP, CH_2Cl_2 , RT to reflux	recovered S.M.
3		MOMCl, Pr_2NEt , CH_2Cl_2 , 0 °C to RT	recovered S.M.
4	MOM	$\text{CH}_2(\text{OCH}_3)_2$, P_2O_5 , CHCl_3 , RT	recovered S.M.
5		MOMCl, NaH, THF, RT	S.M. decomposed
6	PMB	PMBCl, NaH, CHCl_3 , RT	S.M. decomposed
7	Ac	Ac_2O , pyridine, RT	90% yield

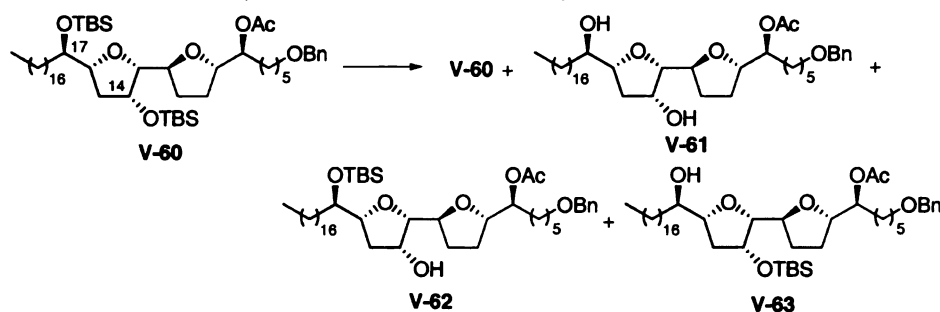
Next the optimized selective deprotection / protection reaction conditions were applied to the real system. Different intermediates in the synthetic process were subjected to these optimized conditions (Scheme V-13). Aldehyde **V-7** decomposed



Scheme V-13: Selective deprotection of different intermediates in total synthesis

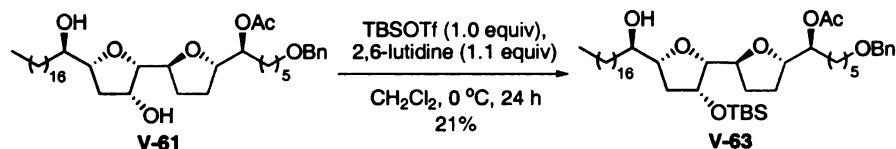
under these conditions and no desired product was isolated. The lack of success was probably due to the instability of the aldehyde under basic conditions. In order to maintain milder conditions, water was added to decrease the basicity of the solution. However, this did not help in obtaining the product. HF•Py was also used to remove the TBS group, however, the reaction was very slow (after 24 h, S.M. was recovered in 61%). Because of the instability of the aldehyde, intermediate **V-55** was used instead of aldehyde **V-7**. Under the same conditions, deprotection of **V-55** gave the mono-TBS ether **V-56** in excellent yield. The ensuing acylation and Pummerer rearrangement gave the desired aldehyde **V-58**. The bis-THF intermediate **V-36** also exhibited similar selectivity in the TBAF mediated silyl deprotection to afford **V-59** in high yield. The yield of this reaction depended on the reaction time. If the reaction was left for more than 15 h, the yield dropped to 71%.

Table V-5: Optimization of the selective deprotection for *cis*-THF V-60



Entry	Conditions	Isolated Yields
1	HF•Py (1.1 equiv), THF, RT, 15 h	V-60 + V-61
2	TBAF : AcOH (1:1), THF, RT, 24 h	98% V-60
3	BF ₃ •OEt ₂ (0.3 equiv), CH ₂ Cl ₂ , 0 °C, 2 h	70% V-60
4	BF ₃ •OEt ₂ (0.3 equiv), CH ₂ Cl ₂ , 0 °C, 6 h	51% V-60 + 17% V-62 + 20% V-61
5	BF ₃ •OEt ₂ (0.5 equiv), CH ₂ Cl ₂ , 0 °C, 5 h	7% V-60 + 14% V-62 + 52% V-61
6	BF ₃ •OEt ₂ (0.5 equiv), CH ₂ Cl ₂ , 0 °C, 3 h	15% V-60 + 38% V-62 + 27% V-61
7	PPTS (0.3 equiv), MeOH, RT, 15 h	54% V-60 + 26% V-63
8	PPTS (0.5 equiv), MeOH, RT, 15 h	46% V-60 + 27% V-63
9	PPTS (1.0 equiv), MeOH, RT, 15 h	22% V-60 + 40% V-63 + 8% V-61

°C, mono-TBS protected product V-63 could be obtained. However, the reaction was very slow and after 24 h, only 21% product was formed and 67% starting diol was recovered. At this point, it was decided that the selective deprotection would be more efficient.



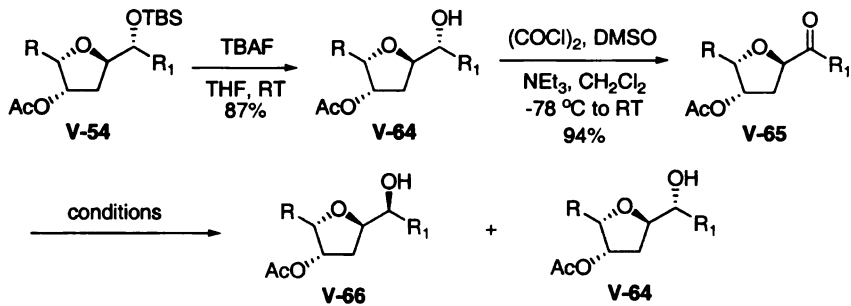
Scheme V-15: Selective protection of diol V-61

V.5.2. Studies on the oxidation / reduction reaction

The molecule V-65 was used for the model study of oxidation / reduction reaction in order to invert the stereochemistry of the carbon connected to the hydroxyl group. It was expected that the 1,2-chelation-controlled reduction could provide a single

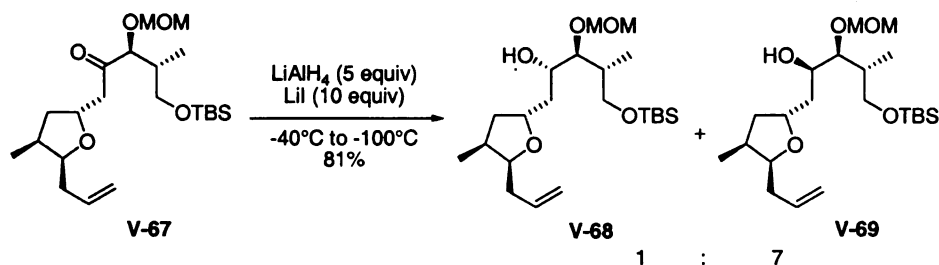
diastereomer. After removing the TBS protection group in **V-54**, Swern oxidation⁴⁴ of the secondary alcohol afforded ketone **V-65** in 94% yield. Subjecting **V-65** to the different chelation-controlled reduction conditions gave the results shown in Table V-6. NaBH₄ did not show any diastereomeric selectivity and gave 1:1 epimeric mixture of alcohols **V-66** and **V-64** (entry 2). Both LiBH₄ and Zn(BH₄)₂⁴⁵ yielded **V-64** as the major isomer, but the diastereomeric ratio was still not high (entries 1 and 3).

Table V-6: Model study of chelation-controlled reduction



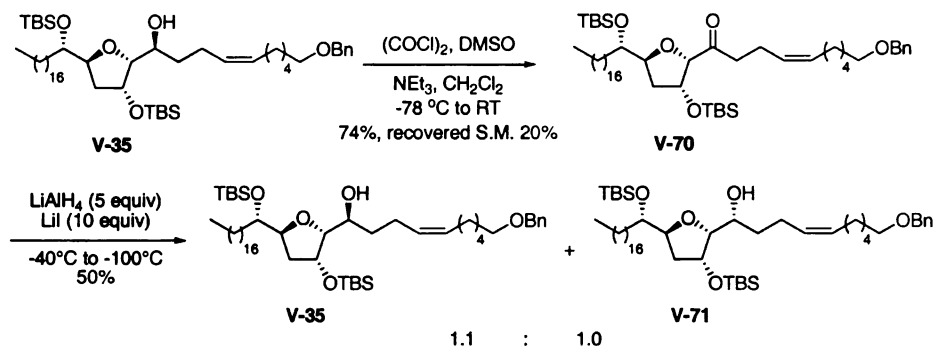
Entry	Conditions	V-66 : V-64	Isolated Yield (%)
1	LiBH ₄ , THF, 0 °C	2:1	92
2	NaBH ₄ , Et ₂ O, -78 °C to 0 °C	1:1	97
3	Zn(BH ₄) ₂ , Et ₂ O, -78 °C to 0 °C	2:1	93

In 2003, Fürstner and coworkers reported the 1,3-chelation-controlled reduction of a THF substrate (Scheme V-16).⁴⁶ Using LiAlH₄ and LiI, the reduction of ketone



Scheme V-16: 1,3-Chelation-controlled reduction of THF substrates

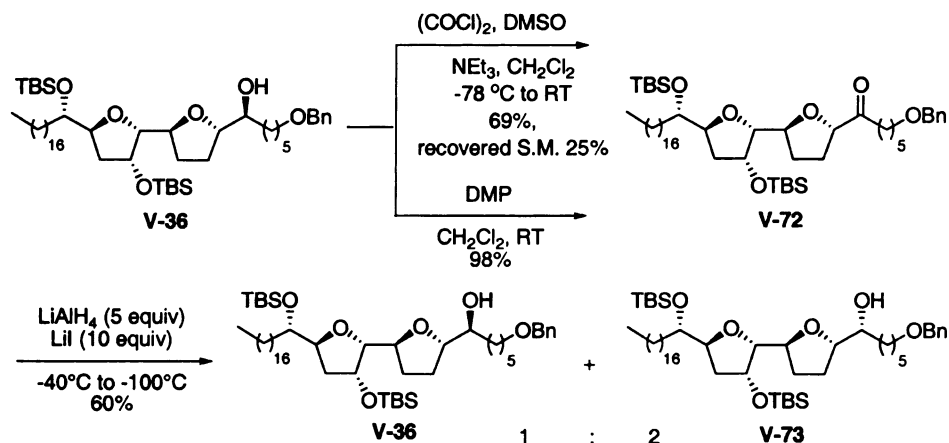
V-67 gave good selectivity and yield of desired secondary alcohol **V-69**. The same



Scheme V-17: 1,2-Chelation-controlled reduction of ketone **V-70**

procedure was applied to the reduction of compound **V-70** (Scheme V-17). Swern oxidation of intermediate **V-35** in Scheme V-6 provided ketone **V-70** in 78% yield along with the recovered starting material **V-35** in 20%. Subjecting **V-70** to Fürstner's conditions gave the chelation-controlled product **V-71** and its epimer **V-35** in only 1.0:1.1 ratio.

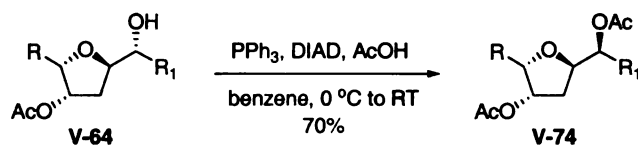
Intermediate **V-36** in Scheme V-7 with bis-THF core was also used in the oxidation / reduction study. Since Swern oxidation of **V-36** could not give higher yield even when the reaction time or the amount of reagents was increased, DMP oxidation was used as the alternative method, which provided the desired ketone **V-72** in 98% yield (Scheme V-18). Using Fürstner's method, ketone **V-72** was reduced to the desired secondary alcohol **V-73** and its epimer **V-36** in a 2:1 ratio. Even though the selectivity of the reduction was not high, the two diastereomers could be separated by silica gel chromatography.



Scheme V-18: Studies of 1,2-chelation-controlled reduction of **V-72**

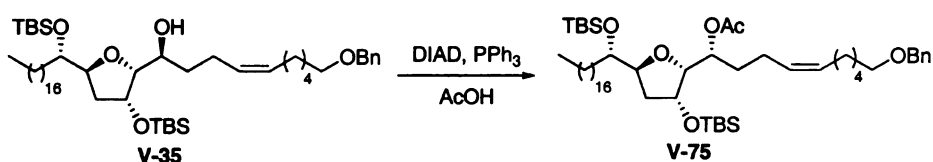
V.5.3. Studies using the Mitsunobu reaction

Because the oxidation / reduction sequence could not give high diastereoselectivity, we considered using the Mitsunobu reaction to convert the stereochemistry of the secondary alcohols.⁴⁷⁻⁴⁹ Model study using compound **V-64** gave the desired product **V-74** in good yield under the general Mitsunobu conditions (Scheme V-19).



Scheme V-19: Mitsunobu reaction in the model study

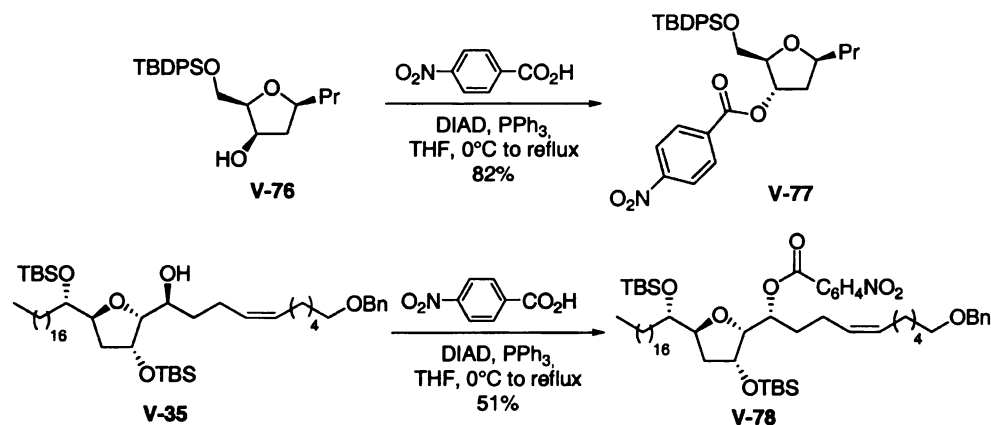
However, when the same conditions were applied to intermediate **V-35**, the reaction did not provide the desired product and all the starting material was recovered. Therefore, optimization of the conditions was in order (Table V-7). This reaction needed to be carried out in an anhydrous aprotic solvent. Five different solvents were tried and benzene was found to be the best, however, only giving the product **V-75** in 10% yield (entry 6). Increasing the reaction temperature

Table V-7: Optimization of the conditions of Mitsunobu reaction for intermediate **V-35**

Entry	Solvent	Temperature	Reagents (equiv)			Yield (%)	S.M. recovered (%)
			PPh ₃	AcOH	DIAD		
1	CH ₂ Cl ₂					0	78
2	Et ₂ O	0 °C to RT	2.0	2.0	3.0	0	90
3	DMF					0	80
4	THF	0 °C to RT	2.0	2.0	3.0	5	67
5		0 °C to reflux	2.0	2.0	3.0	5	65
6		0 °C to RT	2.0	2.0	3.0	10	65
7		0 °C to reflux	2.0	2.0	3.0	9	70
8	Benzene		4.0	4.0	5.0		
9		0 °C to RT	3.0	3.0	3.0	~7%	~80%
10			1.5	1.5	2.0		

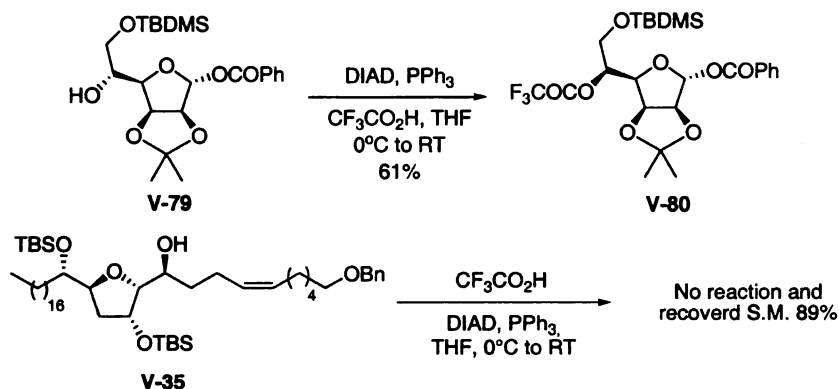
(refluxing the solvents, entries 5 and 7) and varying the amounts of the reagents (entries 8-10) also did not improve the reaction and gave comparable yields. Finally, the order of addition of the reagents was considered. The general procedure is to add dialkylazodicarboxylate (such as DIAD) to a solution of the carboxylic acid, the alcohol, and PPh₃. Since the first step of the reaction is to form the phosphorous adduct,⁴⁹ the protonation of DIAD is important. Thus the order of addition of the reagents could be adjusted to dissolving 5.0 equiv DIAD in benzene followed by addition of 4.0 equiv acetic acid. After stirring the mixture at 0 °C for a while, the solution of alcohol and PPh₃ was added dropwise and the temperature was raised to ambient. However, this reaction still gave 10% yield of product along with 66% of the recovered starting material.

In 1999, Woerpel and coworkers reported a successful Mitsunobu reaction with *p*-nitrobenzoic acid (Scheme V-20), which is more acidic than acetic acid due to the *para*-electron-withdrawing group.⁵⁰ Using the same conditions with intermediate **V-35**, the desired ester **V-78** with the inverted stereochemistry was obtained in moderate yield (Scheme V-20).



Scheme V-20: Mitsunobu reaction using *p*-nitrobenzoic acid

In 2001, Suárez and coworkers reported using trifluoroacetic acid in their Mitsunobu reaction (Scheme V-21), which is also more acidic than acetic acid.⁵¹ However, there was no reaction using our intermediate **V-35** under the latter



Scheme V-21: Mitsunobu reaction using trifluoroacetic acid

conditions (Scheme V-21).

After carefully isolating the products of this Mitsunobu reaction via silica gel chromatography, one elimination byproduct was determined by NMR analysis (Figure V-10). The possible reason for forming this byproduct was the acid-catalyzed

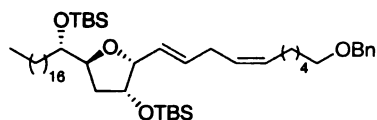
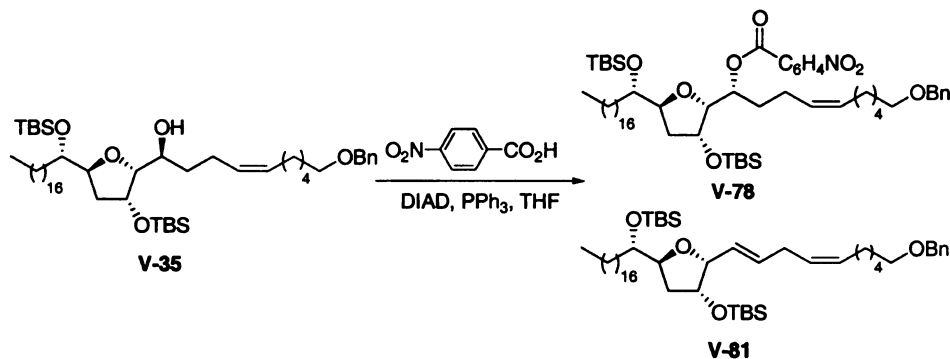


Figure V-10: Elimination byproduct in Mitsunobu reaction

elimination reaction. Optimization of the reaction shown in Scheme V-21 is detailed in Table V-8. Since low temperature does not favor elimination reactions, the reaction temperature was reduced from reflux to room temperature (entry 2).

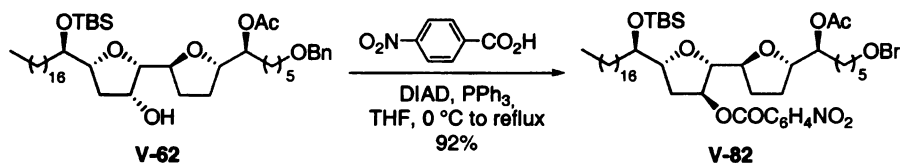
Table V-8: Optimization of Mitsunobu reaction using *p*-nitrobenzoic acid



Entry	Temperature	Alcohol : PPh ₃ : Acid : DIAD	Yield of Ester V-78 (%)	V-78 : V-81	S.M. recovered (%)
1	0 °C to reflux	1 : 4 : 4 : 4	51	2 : 1	0
2	0 °C to RT	1 : 4 : 4 : 4	33	2.5 : 1	52
3	0 °C to RT	1 : 4 : 8 : 4	0	---	89
4	0 °C to RT	1 : 4 : 5 : 4	23	2.5 : 1	54
5	0 °C to RT	1 : 6 : 6 : 6	60	2.5 : 1	1
6	0 °C to RT	1 : 8 : 8 : 8	36	2.5 : 1	20

However, even though this change increased the ratio of the major product; it decreased the reaction rate and after 48 h, there were still 52% starting material recovered. In addition, in order to increase the Mitsunobu reaction rate, greater amounts of the reagents were added (entries 3-6) and it was concluded that when the ratio of starting alcohol and the reagents was equal to 1:6:6:6, the highest yield and ratio of the major product were obtained (entry 5). Therefore, these conditions were chosen as the optimized condition for our Mitsunobu reaction.

The latter Mitsunobu conditions were applied to the bis-THF intermediate **V-62**, which was the selective deprotection product. The desired ester **V-82** with inverted stereochemistry could be formed in excellent yield (Scheme V-22).



Scheme V-22: Mitsunobu reaction to convert stereochemistry of C14 in **V-62**

V.5.4. Library synthesis of representative truncated structures of mucoxin

Our library of synthetic target molecules is shown in Figure V-11. All of them represent different permutations of the relative configuration about two THF rings as well as between the adjacent stereogenic centers. Here we tried to change only one chiral center from one target to another, in hopes that it would provide specific information about the effect on the NMR chemical shifts as it relates to specific stereochemical relationships. Therefore, the library of synthetic targets could offer the chance to build an NMR database in order to obtain some coherent trend(s) in the spectral patterns and the relative configuration between two chiral centers.

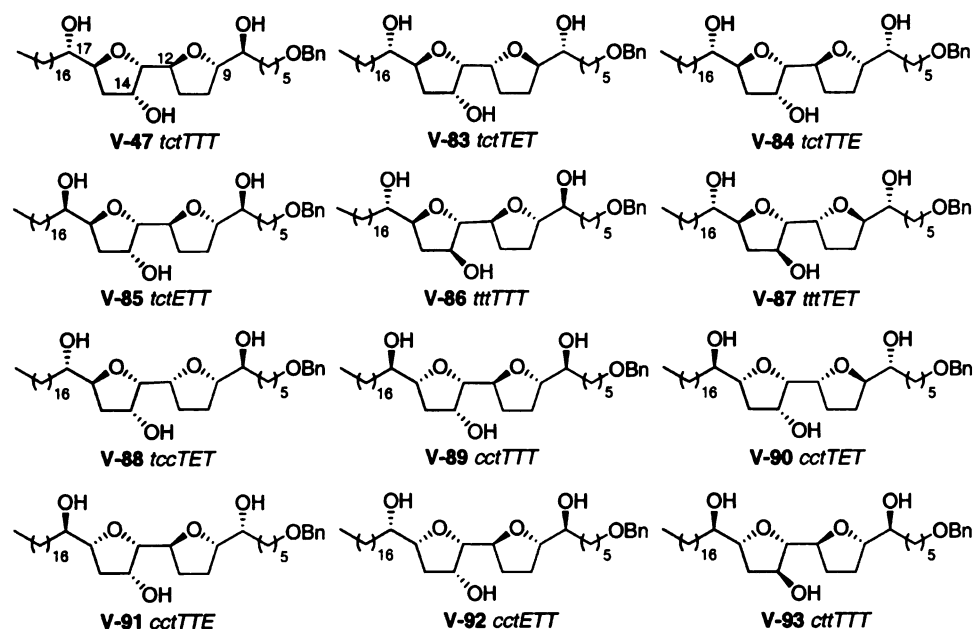
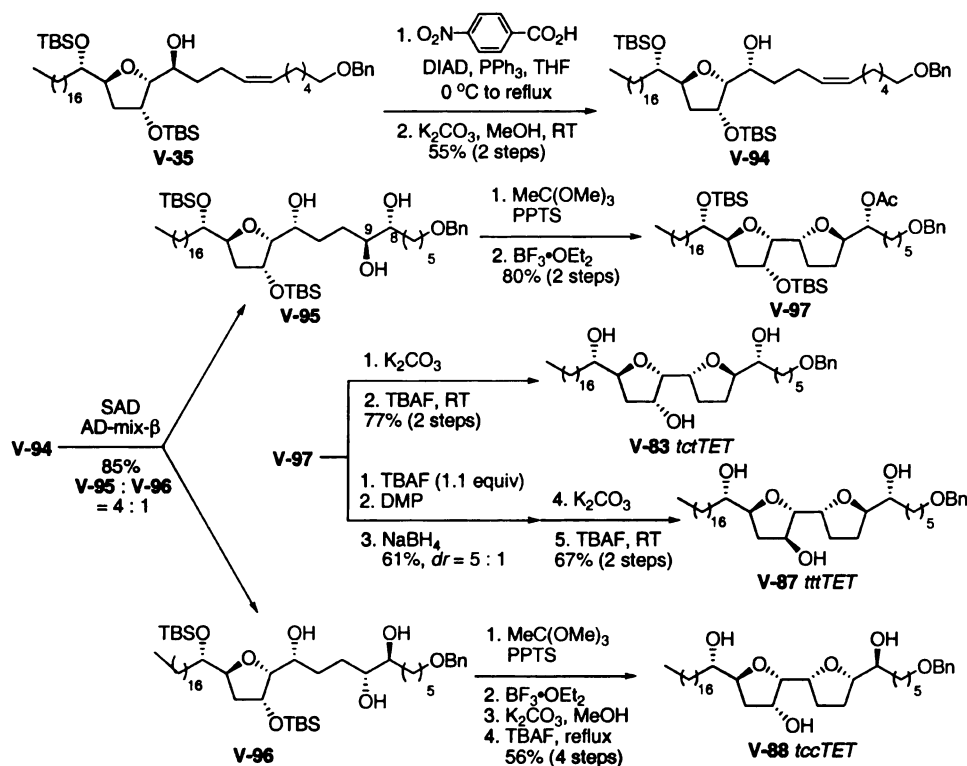


Figure V-11: Library of synthetic targets of mucoxin diastereomers

Our previous work showed that the trisubstituted THF ring (C13-C17) was constructed using neighboring group-assisted epoxydiol cyclization, and the disubstituted THF ring (C8-C12) was constructed using an one-pot 1,2,*n*-triol cyclization strategy (Scheme V-5 and Scheme V-7). Because the epoxydiol and polyol precursors for these two cyclizations were assembled via Sharpless asymmetric epoxidation and dihydroxylation, it was easy to convert the stereochemistry of C8, C9, C13, C14, C16, and C17 by using the different chiral reagents in the asymmetric reactions. The stereochemistry of C12 was controlled by 1,2-chelation-controlled nucleophilic addition, which could be inverted via Mitsunobu reaction. Thus the library of new targets could be synthesized.

The synthesis of stereoisomers **V-83**, **V-87**, and **V-88** is shown in Scheme V-23. Using the previously optimized conditions, Mitsunobu reaction followed by the

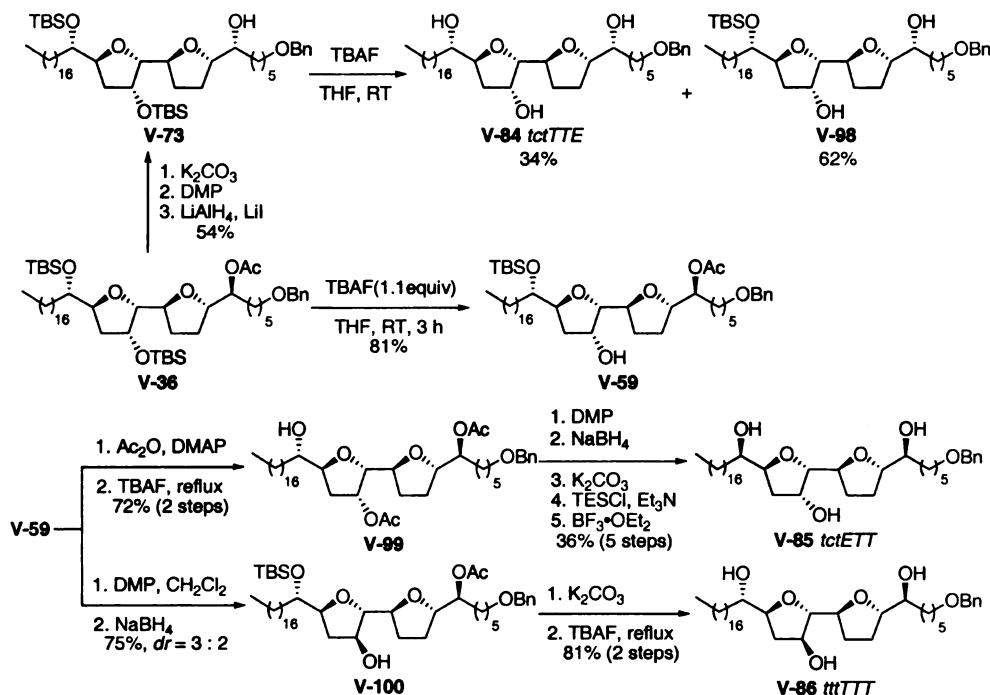


Scheme V-23: Synthesis of stereoisomers **V-83**, **V-87**, and **V-88**

hydrolysis of the ester group gave intermediate **V-94**. Sharpless asymmetric dihydroxylation using AD-mix- β , instead of AD-mix- α in the original synthesis, converted the stereochemistry of C8 and C9. The inseparable epimeric mixture of **V-95** and **V-96** was subjected to the cyclization reaction to form the bis-THF units and these two diastereomers were separated after cyclization. After removing all the protecting groups, compounds **V-83** and **V-88** were obtained. It was found that HF•Py was not efficient to remove TBS groups in the truncated structures. The TBS group in the side chain could not be deprotected even after 48 h using HF•Py, and was finally removed by TBAF in THF at room temperature or under reflux condition. The truncated structure was very stable at various temperatures or under acidic or

basic conditions. In addition, selective deprotection of one TBS group in intermediate **V-97** using optimized condition gave mono TBS ether as desired, which underwent oxidation / reduction and deprotection to afford stereoisomer **V-87**.

All the stereoisomers **V-84**, **V-85**, and **V-86** are derived from the same intermediate **V-36** (Scheme V-24). After cyclization and deacetylation of **V-36**, DMP oxidation followed by 1,2-chelation-controlled reduction (Scheme V-18) provided the major isomer **V-73**, which underwent silyl group deprotection to give the stereoisomer **V-84**. The room temperature TBS deprotection only gave 34% yield of the desired product along with 62% of the mono-TBS ether **V-98**, which suggested that the side-chain TBS group was more stable than that on the THF ring. Moreover, selective deprotection of one TBS group under our optimized conditions afforded



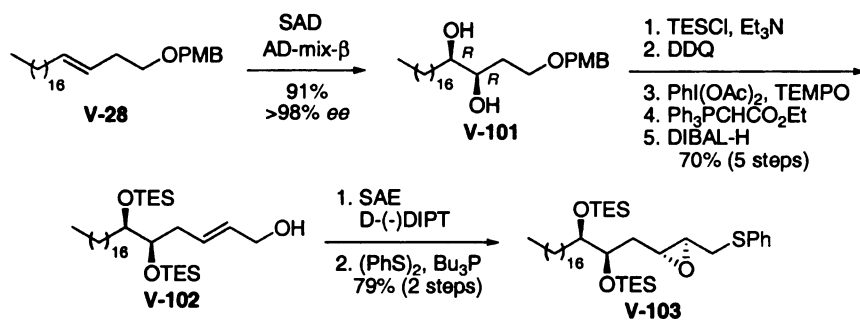
Scheme V-24: Synthesis of stereoisomers **V-84**, **V-85**, and **V-86**

intermediate **V-59**. Acyl protection of the free hydroxyl group followed by the second TBS deprotection under refluxing conditions with TBAF in THF gave compound **V-99**. The higher temperature proved to be helpful in removing the side-chain TBS group. The DMP oxidation / sodium borohydride reduction gave an inseparable 1:1 mixture of two epimers in 80% yield. Even though there was no selectivity in this reaction, the total yield was much higher and the experiment was easier to deal with compared with $\text{Zn}(\text{BH}_4)_2$ reduction. However, it was unfortunate to find that the mixture still could not be separated even after removing the two acyl groups. Considering that the protection of the three hydroxyl groups could change the polarity of the compounds and provide the possibility to separate them, the mixture was treated with excess TESECl. Two epimers of tri-TES ethers were successfully separated via silica gel chromatograph, and we could obtain the desired diastereomer **V-85**. Finally, the DMP oxidation / sodium borohydride reduction of intermediate **V-59** could convert the stereochemistry of C14, which gave two epimers in a 3:2 ratio. The major isomer **V-100** could be separated as a single diastereomer, and was subjected to two continuous deprotection reactions to afford the desired diastereomer **V-86** in good yield (Scheme V-24).

Another series of synthetic targets (**V-89-V-93**) have a *cis*-trisubstituted THF ring as the common structural feature. This structural variation could be derived from the first SAD reaction in the total synthesis.

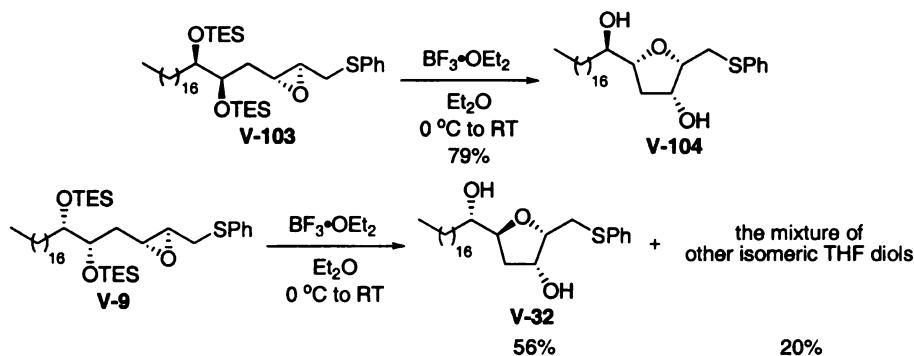
Starting from intermediate **V-28** in the original total synthesis (Scheme V-5), *R,R*-diol **V-101** was formed using AD-mix- β instead of AD-mix- α under the same

SAD conditions in 91% yield and greater than 98% *ee* (Scheme V-25). The same



Scheme V-25: Preparation of intermediate **V-103**

strategy shown in Scheme V-5 could provide the precursor **V-103** after the neighboring group-assisted cyclization. Treatment of compound **V-103** with $\text{BF}_3 \cdot \text{OEt}_2$ in diethyl ether afforded the desired *cis*-trisubstituted THF ring as a single diastereomer in about 80% yield, which was more efficient than the formation of *trans*-THF ring **V-32** (diastereomeric ratio equal to 2.8:1) (Scheme V-26). It seems

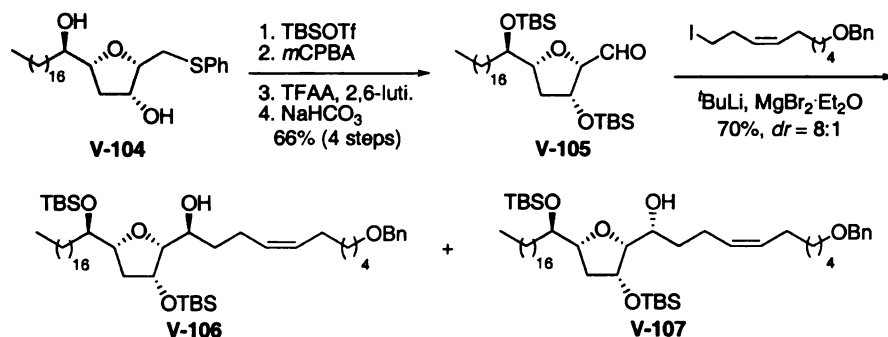


Scheme V-26: Cyclization of two diastereomers of compounds **V-103** and **V-9**

that the absolute stereochemistry of the epoxy diols has a direct effect on this Lewis acid mediated cyclization reaction.

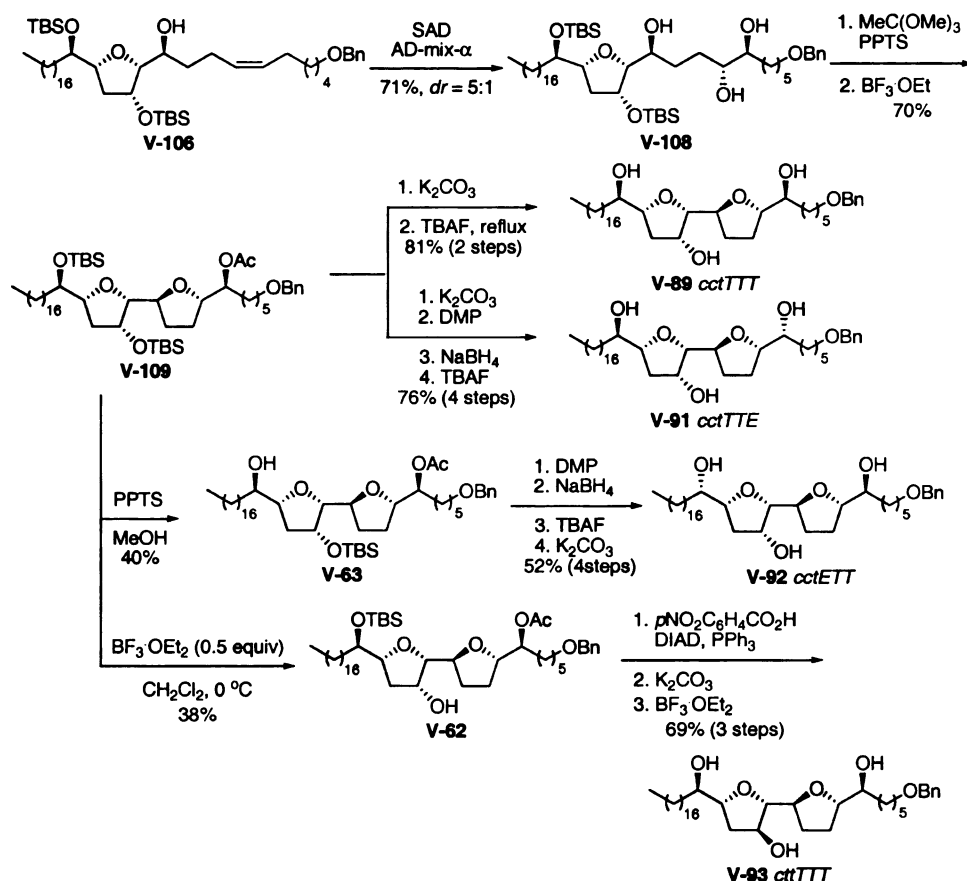
For the synthesis of diastereomers **V-89**, **V-90**, **V-91**, **V-92**, and **V-93** the same strategy as described above was utilized. After converting the thiophenyl group to an aldehyde via the Pummerer rearrangement, 1,2-chelation-controlled nucleophilic

addition with organolithium reagent **V-34** (Scheme V-6) gave the desired secondary alcohol **V-106** as the major product along with its epimer **V-107** in 8:1 diastereomeric ratio (Scheme V-27). These two compounds could be separated via silica gel chromatography and both of them were used in the latter synthesis.



Scheme V-27: Chelation-controlled nucleophilic addition

Compound **V-106** was treated with AD-mix- α under Sharpless asymmetric dihydroxylation conditions to yield triol **V-108** in 5:1 diastereomeric ratio (Scheme V-28). The major isomer **V-108** was separated as a single diastereomer and the following one-pot cyclization reaction provided bis-THF **V-109**. Directly removing both TBS and acyl groups gave diastereomer **V-89** in good yield followed by acyl deprotection to reveal the free hydroxyl group in the right side of the molecule, which underwent the oxidation / reduction sequence to form an epimeric mixture in a 1:1 ratio. The two epimers were separated and the desired isomer was desilylated to give the final diastereomer **V-91**. Based on the previous discussion on selective deprotection in *cis*-trisubstituted THF system, PPTS in methanol removed the TBS group at the left side of the molecule and yielded compound **V-63**. The subsequent oxidation / reduction and deprotection provided diastereomer **V-92**. $\text{BF}_3 \cdot \text{OEt}_2$ in



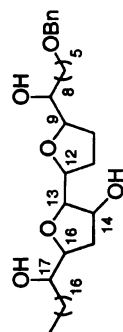
Scheme V-28: Synthesis of stereoisomers **V-89**, **V-91**, **V-92**, and **V-93**

methylene chloride could remove the TBS group on the THF ring to form compound **V-62**, which was subjected to the optimized Mitsunobu conditions to form ester **V-82** as a single diastereomer with inverted stereochemistry (Scheme V-22). The latter two-step deprotection could afford diastereomer **V-93**. It was found that $\text{BF}_3\cdot\text{OEt}_2$ was another efficient reagent for the TBS deprotection.

Compound **V-107** was treated with AD-mix- β under Sharpless asymmetric dihydroxylation conditions to yield triol **V-110** in a 7:1 diastereomeric ratio (Scheme V-29). The ensuing cyclization and deprotection gave diastereomer **V-90** as the desired product.

To summarize Table V-10, generally in every synthesized isomer, some regions of the molecule fit very well with the natural mucosin, suggesting that the relative configurations of these regions might be correct. To this point, the NMR spectral data might reveal useful trends for the relationship between the NMR chemical shift and the relative stereochemistry between two adjacent as well as non-adjacent stereogenic centers.

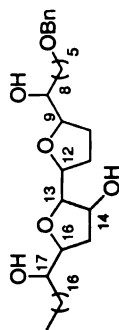
Table V-9: ¹H NMR chemical shifts of different truncated structures^a



proton	tctTTT V-47	tctTET V-83	tctTTE V-84	tctETT V-85	ttTTT V-86	ttTET V-87	ttcTET V-88	cctTTT V-89	cctTET V-90	cctTTE V-91	cctETT V-92	ctTTT V-93
H8	3.41	3.40	3.82	3.41	3.37	3.37	3.40	3.45	3.40	3.86	3.41	3.39
H9	3.95	3.85	4.00	3.92	3.77	3.83	3.79	3.94	3.83	3.97	3.86	3.84
H10	1.71,	1.71,	1.81,	1.64,	1.64,	1.66,	1.74,	1.71,	1.70,	1.87,	1.66,	1.71,
	2.01	2.03	1.90	2.01	1.96	1.99	1.93	2.03	2.01	1.87	1.96	1.99
H11	2.01,	1.84,	1.90,	1.93,	1.96,	1.82,	1.93,	1.86,	1.90,	1.82,	1.64,	1.99,
	2.12	2.21	2.13	2.12	1.96	2.08	2.13	2.21	2.17	2.20	2.21	1.99
H12	4.33	4.22	4.40	4.29	3.95	3.83	4.18	4.26	4.23	4.29	4.22	4.07
	3.80	3.71	3.77	3.87	3.86	3.73	3.69	3.71	3.59	3.66	3.57	3.76
H13	(J = 3.3 Hz)	(J = 3.1, 7.2 Hz)	(J = 3.4, 3.9 Hz)	(J = 3.9 Hz)	(J = 2.4, 3.9 Hz)	(J = 3.4, 6.8 Hz)	(J = 2.9, 7.3 Hz)	(J = 3.4, 4.8 Hz)	(J = 3.3, 7.2 Hz)	(J = 2.3, 2.9 Hz)	(J = 2.7, 6.9 Hz)	(J = 3.5 Hz)
H14	4.43	4.52	4.41	4.44	4.23	4.29	4.50	4.24	4.35	4.19	4.12	4.45
H15	1.83,	1.83,	1.81,	1.84,	1.79,	1.82,	1.93,	1.92,	1.87,	1.87,	1.94,	1.95,
	2.01	2.03	2.02	2.12	2.48	2.41	2.02	2.41	2.36	2.37	2.19	2.10
H16	4.09	4.12	4.07	4.23	4.06	4.00	4.13	4.10	3.98	4.06	4.10	4.12
H17	3.41	3.40	3.41	3.92	3.50	3.52	3.40	3.53	3.52	3.49	3.92	3.39

^a Chemical shift (ppm), reference to ¹H NMR (δ 7.27 ppm for CDCl₃)

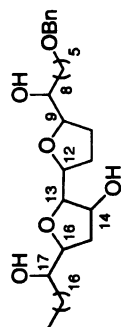
Table V-9 (continued): ¹³C NMR chemical shifts of different truncated structures ^a



carbon	tctTTT V-47	tctTET V-83	tctTTE V-84	tctETT V-85	ttTTTT V-86	ttTET V-87	octTTT V-89	octTET V-90	octTTE V-91	octETT V-92	cttTTT V-93
C8	73.4	73.8	71.5	73.6	73.9	73.9	73.7	74.0	71.3	73.9	73.6
C9	83.9	83.2	83.8	83.9	83.3	83.1	83.6	82.8	83.2	83.5	83.4
C12	79.0	77.8	79.1	79.1	79.7	80.2	78.7	77.0	79.2	78.7	79.2
C13	83.1	84.0	83.3	84.1	89.2	88.1	85.6	85.2	85.8	86.1	87.0
C14	74.4	73.1	74.4	74.2	74.1	73.8	72.5	71.6	72.3	71.6	74.0
C15	38.7	37.5	38.7	34.7	38.1	37.1	38.8	37.8	38.8	34.3	37.9
C16	81.3	81.6	81.4	81.2	81.5	81.1	80.2	80.5	80.2	81.2	81.4
C17	74.1	74.1	74.2	71.6	74.5	74.4	74.1	73.8	74.1	71.7	74.3

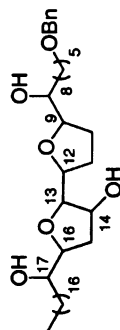
^a Chemical shift (ppm), reference to ¹³C NMR (δ 77.0 ppm for CDCl₃).

Table V-10: Deviation of ^1H NMR chemical shifts of different truncated structures relative to the values reported for the natural mucoxin



proton	$\Delta\delta = \delta$ (Synthetic isomer) – δ (reported natural mucoxin) (ppm)											
	<i>ttTTT</i> V-47	<i>ttTET</i> V-83	<i>ttTTE</i> V-84	<i>ttETT</i> V-85	<i>ttTTT</i> V-86	<i>ttTET</i> V-87	<i>ttTET</i> V-88	<i>ttTTT</i> V-89	<i>ccTTE</i> V-90	<i>ccTTE</i> V-91	<i>ccETT</i> V-92	<i>ctTTT</i> V-93
H8	-0.01	-0.02	+0.40	-0.01	-0.05	-0.05	-0.02	+0.03	-0.02	+0.44	-0.01	-0.03
H9	0.00	-0.10	+0.05	-0.03	-0.18	-0.12	-0.16	-0.01	-0.12	+0.02	-0.09	-0.11
H10	-0.20	-0.20	-0.10	-0.27	-0.27	-0.25	-0.17	-0.20	-0.21	-0.04	-0.25	-0.20
H11	-0.04	-0.02	-0.15	-0.04	-0.09	-0.06	-0.12	-0.02	-0.04	-0.18	-0.09	-0.06
	+0.10	-0.07	-0.01	+0.02	+0.05	-0.09	+0.02	-0.05	-0.05	-0.09	-0.27	+0.08
H12	+0.07	+0.16	+0.08	+0.07	-0.09	+0.03	+0.08	+0.16	+0.12	+0.15	+0.16	-0.06
	+0.02	-0.09	+0.09	-0.02	-0.36	-0.48	-0.13	-0.05	-0.08	-0.02	-0.09	-0.24
H13	+0.09	0.00	+0.06	+0.16	+0.15	+0.02	-0.02	0.00	-0.12	-0.05	-0.14	+0.05
	(<i>J</i> = 3.3 Hz)	(<i>J</i> = 3.1, 7.2 Hz)	(<i>J</i> = 3.4, 3.9 Hz)	(<i>J</i> = 3.9 Hz)	(<i>J</i> = 2.4, 3.9 Hz)	(<i>J</i> = 3.4, 6.8 Hz)	(<i>J</i> = 2.9, 7.3 Hz)	(<i>J</i> = 3.4, 4.8 Hz)	(<i>J</i> = 3.3, 7.2 Hz)	(<i>J</i> = 2.3, 2.9 Hz)	(<i>J</i> = 2.7, 6.9 Hz)	(<i>J</i> = 3.5 Hz)
H14	+0.11	+0.20	+0.09	+0.12	-0.09	-0.03	+0.18	-0.08	+0.03	-0.13	-0.20	+0.13
H15	-0.08	-0.08	-0.01	-0.07	-0.12	-0.09	+0.02	+0.01	-0.04	-0.04	+0.03	+0.04
H16	-0.34	-0.32	-0.33	-0.23	+0.13	+0.06	-0.33	+0.06	+0.01	+0.02	-0.16	-0.25
	+0.05	+0.08	+0.03	+0.19	+0.02	-0.04	+0.09	+0.06	-0.06	+0.02	+0.06	+0.08
H17	-0.12	-0.13	-0.12	+0.29	-0.03	-0.01	-0.13	0.00	-0.01	-0.04	+0.39	-0.14

Table V-10 (continued): Deviation of ¹³C NMR chemical shifts of different truncated structures relative to the values reported for the natural mucoxin



carbon	$\Delta\delta = \delta$ (Synthetic isomer) – δ (reported natural mucoxin) (ppm)											
	<i>tctTTT</i> V-47	<i>tctTET</i> V-83	<i>tctTTE</i> V-84	<i>tctETT</i> V-85	<i>tttTTT</i> V-86	<i>tttTET</i> V-87	<i>cctTTT</i> V-89	<i>cctTET</i> V-90	<i>cctTTE</i> V-91	<i>cctETT</i> V-92	<i>cttTTT</i> V-93	
C8	-0.2	+0.2	-2.1	0.0	+0.3	+0.3	+0.1	+0.4	-2.3	+0.3	0.0	
C9	+0.5	-0.2	+0.4	+0.5	-0.1	-0.3	+0.2	-0.6	-0.2	+0.1	0.0	
C12	-0.1	-1.1	+0.2	+0.2	+0.8	+1.3	-0.2	-1.9	+0.3	-0.2	+0.3	
C13	-0.4	+0.5	-0.2	+0.6	+5.7	+4.6	+2.1	+1.7	+2.3	+2.6	+3.5	
C14	+1.6	+0.3	+1.6	+1.4	+1.3	+1.0	-0.3	-1.2	-0.5	-1.2	+1.2	
C15	+0.7	-0.5	+0.7	-3.3	-0.1	-0.9	+0.8	-0.2	+0.8	-3.7	-0.1	
C16	+1.4	+1.7	+1.5	+1.3	+1.6	+1.2	+0.3	+0.6	+0.3	+1.3	+1.5	
C17	+0.4	+0.4	+0.5	-2.1	+0.8	+0.7	+0.4	+0.1	+0.4	-2.0	+0.6	

V.7. Summary of the NMR Trends

After carefully analyzing Table V-9 and Table V-10, trends that relate relative stereochemistry at the various positions of mucoxin with NMR chemical shifts were summarized as following.

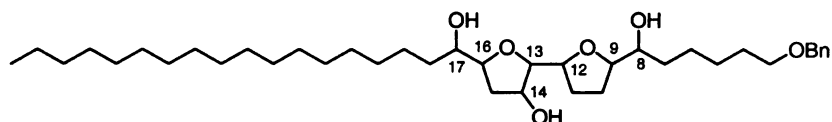


Figure V-12: Truncated structure of mucoxin

1) C8-C9 relationship: The ^1H chemical shift of H8 in the 8,9-*erythro*-isomers is shifted more downfield than in the 8,9-*threo*-isomers. Generally, if the chemical shift of H8 is larger than 3.7 ppm, C8-C9 should be *erythro*. On the contrary, if the chemical shift is smaller than 3.5 ppm, C8-C9 should be *threo*. A similar trend is also shown for the ^{13}C NMR data. If the chemical shift of C8 is smaller than 72 ppm, C8-C9 should be *erythro*. If the chemical shift is larger than 73 ppm, C8-C9 should be *threo*. This trend is in agreement with Born's rule, which explains how to use NMR spectra to predict the relative configuration between the side hydroxyl group and the 2,5-disubstituted THF ring.⁵²

Table V-11 shows the chemical shift of H8 or C8 in both 8,9-*erythro* and *threo* relationship in all the synthesized diastereomers.

Table V-11: Chemical shift of position 8 in all synthesized diastereomers

H/C	<i>erythro</i>		<i>threo</i>									
	V-84	V-91	V-47	V-83	V-85	V-86	V-87	V-88	V-89	V-90	V-92	V-93
H8	3.82	3.86	3.41	3.40	3.41	3.37	3.37	3.40	3.45	3.40	3.41	3.39
C8	71.5	71.3	73.4	73.8	73.6	73.9	73.9	---	73.7	74.0	73.9	73.6

2) C16-C17 relationship: The ^1H chemical shift of the H17 position in the 16,17-*erythro*-isomers is more downfield shifted than in the 16,17-*threo*-isomers. Generally if the chemical shift of H17 is larger than 3.8 ppm, C16-C17 should be *erythro*. On the contrary, if the chemical shift is smaller than 3.6 ppm, C16-C17 should be *threo*. A similar trend is also shown for the ^{13}C NMR data. If the chemical shift of C17 is smaller than 72 ppm, C16-C17 should be *erythro*. If the chemical shift is larger than 73 ppm, C16-C17 should be *threo*. This trend proves that Born's rule could also be applied in the trisubstituted THF systems.⁵²

Table V-12 shows the chemical shift of H17 or C17 in both 16,17-*erythro* and *threo* relationship for all the synthesized diastereomers.

Table V-12: Chemical shift of position 17 in all synthesized diastereomers

H/C	<i>erythro</i>		<i>threo</i>									
	V-85	V-92	V-47	V-83	V-84	V-86	V-87	V-88	V-89	V-90	V-91	V-93
H17	3.92	3.92	3.41	3.40	3.41	3.50	3.52	3.40	3.53	3.52	3.49	3.39
C17	71.6	71.7	74.1	74.1	74.2	74.5	74.4	---	74.1	73.8	74.1	74.3

3) C14-C16 relationship: The difference between the two hydrogens on C15 could be used in the determination of the C14-C16 relationship. If the ^1H chemical shifts of H15 α and H15 β have a large difference (with $\Delta\delta$ larger than 0.4 ppm), C14-C16 should have a *cis*-relationship. If the ^1H chemical shifts of H15 α and H15 β have a small difference (with $\Delta\delta$ smaller than 0.3 ppm), C14-C16 should have a *trans*-relationship.

Table V-13 shows the chemical shifts of the two hydrogens on C15 and the difference between H15 α and H15 β in both 14,16-*trans* and *cis* relationship in all the

synthesized diastereomers.

Table V-13: Chemical shift of H15 α and H15 β in all synthesized diastereomers

H	<i>trans</i>						<i>cis</i>				
	V-47	V-83	V-84	V-85	V-88	V-93	V-86	V-87	V-89	V-90	V-91
H15 α	2.01	2.03	2.02	2.12	2.02	2.10	2.48	2.41	2.41	2.36	2.37
H15 β	1.83	1.83	1.81	1.84	1.93	1.95	1.79	1.82	1.92	1.87	1.87
$\Delta\delta$	0.18	0.20	0.20	0.28	0.09	0.15	0.69	0.59	0.49	0.49	0.50

4) C12-C13 relationship: The splitting pattern and coupling constant of H13 could be used for the determination of the C12-C13 relationship. All of the 12,13-*erythro* compounds have a doublet-doublet splitting pattern of H13 with two dissimilar coupling constants (one is larger than 6.5 Hz and the other is smaller than 3.5 Hz). All the 12,13-*threo* compounds have either a pseudotriplet splitting pattern of H13 with a coupling constant around 3.5 Hz or a doublet-doublet splitting pattern with two similar coupling constants between 2.3-4.8 Hz.

Table V-14 shows the splitting pattern and the coupling constant of H13 in both 12,13-*erythro* and *threo* relationship in all the synthesized diastereomers.

Table V-14: The splitting pattern and the coupling constant of H13 in all synthesized diastereomers

H13	<i>threo</i>							<i>erythro</i>			
	V-47	V-90	V-85	V-86	V-89	V-91	V-93	V-83	V-87	V-88	V-90
splitting	t	dd	t	dd	dd	dd	t	dd	dd	dd	dd
<i>J</i> (Hz)	3.3	3.4	3.9	2.4	3.4	2.3	3.5	3.1	3.4	2.9	3.3
		3.9		3.9	4.8	2.9		7.2	6.8	7.3	7.2

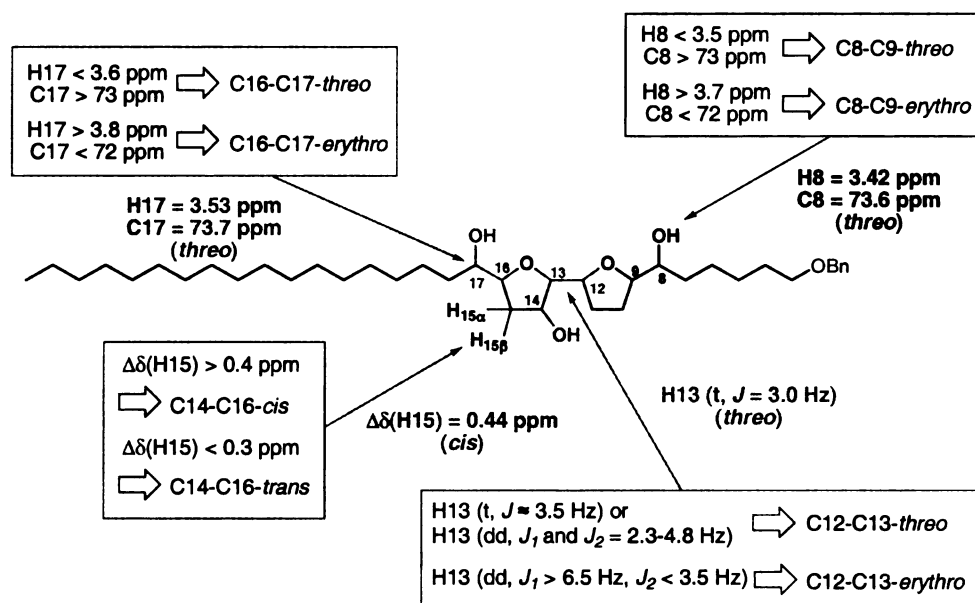
V.8. Revision of the Structure of Natural Mucoxin

The summary of NMR spectral data of reported natural mucoxin² is shown in Table V-15. Using the four trends summarized from the NMR database, some of the

Table V-15: Partial ¹H and ¹³C NMR spectra data of natural mucoxin

H/C	8		17		15		13
	H8	C8	H17	C17	H15 α	H15 β	splitting <i>J</i> (Hz)
chemical shift (ppm)	3.42	73.6	3.53	73.7	1.91	2.35	t 3.0
					$\Delta\delta = 0.44$		

relative stereochemistry of natural mucoxin could be determined. Based on trend (1), since the ¹H chemical shift of H8 is equal to 3.42 ppm (smaller than 3.5 ppm), and ¹³C chemical shift of C13 is equal to 73.6 ppm (larger than 73 ppm), C8-C9 should have a *threo* relationship. Likewise, the ¹H chemical shift of H17 is equal to 3.53 ppm (smaller than 3.6 ppm), and ¹³C chemical shift of C17 is equal to 73.7 ppm (larger than 73 ppm), C16-C17 should also have a *threo* relationship based on trend (2). The ¹H chemical shift of the two hydrogens on C15 in natural mucoxin have a large difference with $\Delta\delta$ larger than 0.4 ppm. Based upon trend (3), the C14-C16 relationship should be *cis* in this molecule. Finally, H13 shows a pseudotriplet with the coupling constant equal to 3.0 Hz. Therefore, C12-C13 should have a *threo* relationship based on trend (4). Figure V-13 shows the summary of these conclusions.



Among all the 64 diastereomers of mucoxin mentioned before (Figure V-7), there are only four possibilities for the correct structure of mucoxin based on the trends summarized (Figure V-13): *tttTTT*, *ttcTTT*, *cccTTT*, and *cctTTT*. These four structures are shown in Figure V-14. Diastereomers *tttTTT* (V-86) and *cctTTT* (V-89) were synthesized amongst the 12 isomers for the NMR study and neither of them matched the NMR data reported for the natural mucoxin. Therefore the new synthetic targets were narrowed to diastereomers *ttcTTT* (V-112) and *cccTTT* (V-113).

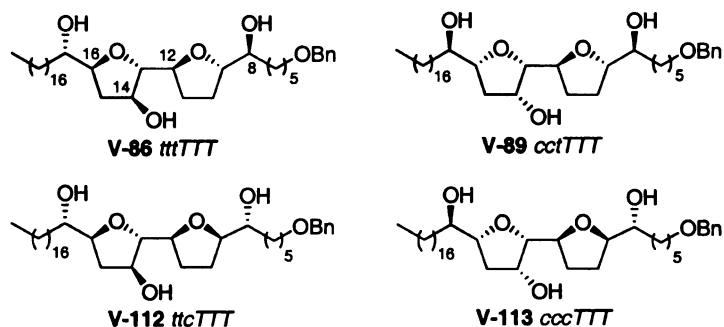
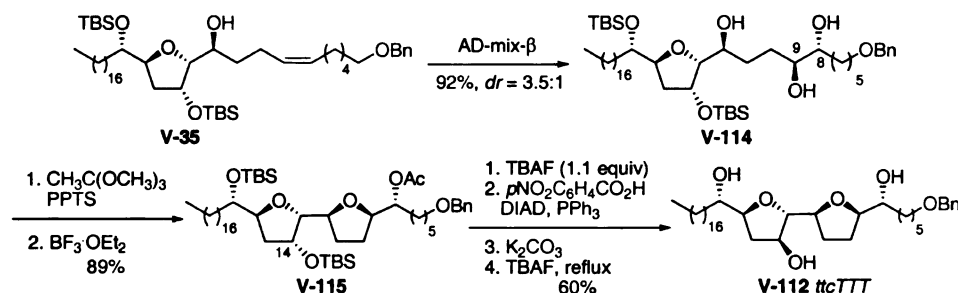


Figure V-14: Four possible structures for natural mucoxin based on the trends

Using the same strategies described before, compound **V-112** was synthesized (Scheme V-30). Treatment of intermediate **V-35** with AD-mix- β instead of



Scheme V-30: Synthesis of diastereomer V-112

AD-mix- α gave triol **V-114** as the major isomer in a 3.5:1 diastereomeric ratio. The asymmetric dihydroxylation reaction set the stereochemistry of C8 and C9. After forming the bis-THF core **V-113** via the one-pot cyclization, selective deprotection using 1.1 equiv TBAF succeeded to remove the TBS group on the THF ring (86% yield). The following Mitsunobu reaction inverted the stereochemistry of C14 and gave the desired ester in excellent yield (93%). Two continuous deprotection reactions to remove both the acetyl and TBS groups yielded the desired diastereomer **V-112**.

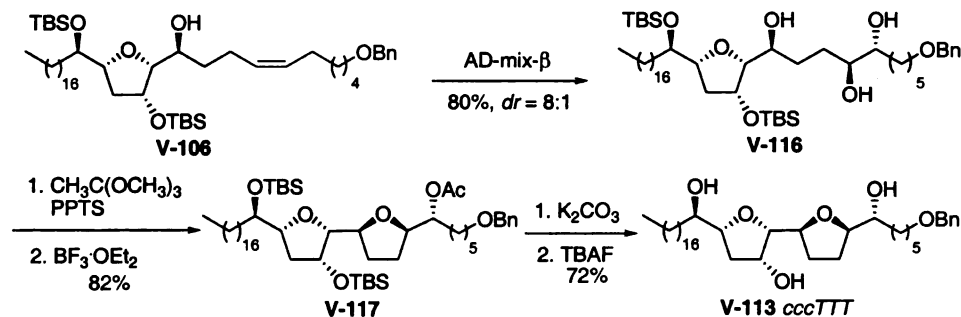
The comparison of NMR spectra between diastereomer **V-112** and the reported natural mucoxin indicated that this compound did not match the natural sample (Table V-16). Large differences in the chemical shift of protons on C10, along with C11, C12, and C13 were observed. Even though this molecule is still not the real structure; the chemical shift data are in accordance with the summarized trends: the ^1H chemical shift of H8 is equal to 3.37 ppm (smaller than 3.5 ppm). ^1H chemical shift of H17 is equal to 3.52 ppm (smaller than 3.6 ppm). The difference of

Table V-16: Comparison of ^1H NMR spectra between **V-112** and natural mucoxin

Proton	V-110	Natural Mucoxin	$\Delta\delta$ (V-112–natural) (ppm)
H8	3.37	3.42	-0.05
H9	3.86	3.95	-0.09
H10	1.84, 1.95	1.91, 2.05	-0.07, -0.10
H11	1.95, 1.95	1.91, 2.05	+0.04, -0.10
H12	4.00	4.31	-0.31
H13	3.88 (t, $J = 3.3$ Hz)	3.71	+0.17
H14	4.27	4.32	-0.05
H15	1.84, 2.44	1.91, 2.35	-0.07, +0.09
H16	4.08	4.04	+0.04
H17	3.52	3.53	-0.01

resonance between two H15 α and H15 β is large with $\Delta\delta = 0.6$ ppm (larger than 0.4 ppm). H13 has a pseudotriplet with a coupling constant equal to 3.3 Hz. All of these observations further prove that it is reasonable to use these trends to predict the relative stereochemistry of the molecule.

Synthesis of compound **V-113** started from intermediate **V-106** (Scheme V-31). The SAD reaction gave a higher diastereomeric ratio for this substrate and the major isomer **V-116** could be separated as a single diastereomer. The following cyclization and deprotection finally gave the desired diastereomer **V-113** in good yield.

**Scheme V-31:** Synthesis of diastereomer **V-113**

Both the ^1H and ^{13}C NMR spectra of diastereomer *cccTTT*, **V-113**, fit the reported data of natural mucoxin very closely (Table V-17). All the deviations in ^1H NMR between compound **V-113** and the reported natural sample are equal to or smaller than 0.02 ppm. For ^{13}C NMR, except C15, which is a little bit larger than the reported data, all the other deviations are equal to or smaller than 0.2 ppm. We checked McLaughlin's NMR data ourselves and found that the large deviation of C15 was possibly due to their mistake in transferring the value from the NMR spectra. The real chemical shift of C15 should be closer to our data. Moreover, H13 has the pseudotriplet splitting pattern with the coupling constant equal to 3.1 Hz. Taken together, it is believed that compound *cccTTT* matches with the natural mucoxin in

Table V-17: Comparison of ^1H NMR spectra between **V-113** and natural mucoxin

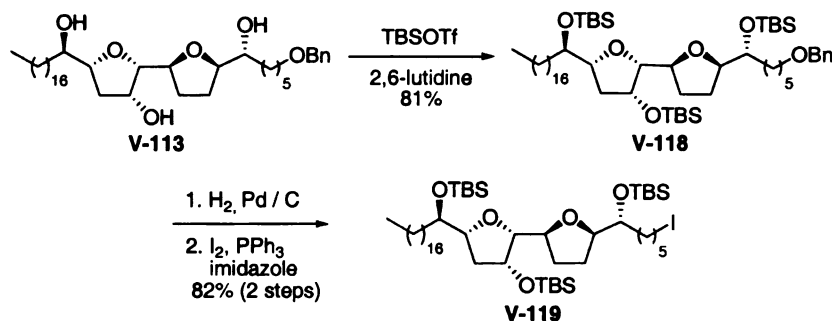
Proton / Carbon	V-113	Natural Mucoxin	$\Delta\delta$ (V-113–natural) (ppm)
H8	3.42	3.42	0.00
H9	3.93	3.95	-0.02
H10	1.91, 2.05	1.91, 2.05	0.00, 0.00
H11	1.91, 2.05	1.91, 2.05	0.00, 0.00
H12	4.31	4.31	0.00
H13	3.71 (t, $J = 3.1$ Hz)	3.71 (t, $J = 3.0$ Hz)	0.00
H14	4.31	4.32	-0.01
H15	1.91, 2.35	1.91, 2.35	0.00, 0.00
H16	4.04	4.04	0.00
H17	3.53	3.53	0.00
C8	73.5	73.6	-0.1
C9	83.5	83.4	+0.1
C12	78.9	78.9	0.0
C13	83.7	83.5	+0.2
C14	72.9	72.8	+0.1
C15	38.8	38.0	+0.8
C16	80.1	79.9	+0.2
C17	73.8	73.7	+0.1

the spectrum and it has the same stereochemistry with the natural sample.

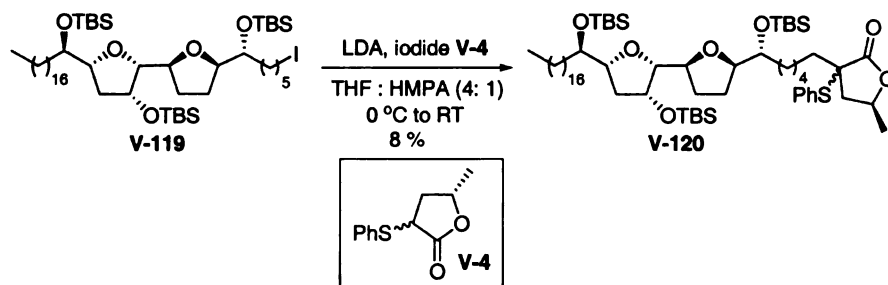
V.9. Total Synthesis of Natural Mucoxin

Since the relative stereochemistry of mucoxin was determined after the library synthesis and NMR database analysis studies, we proceeded with truncated structure **V-113** toward completion of the total synthesis of mucoxin.

The stage now was set for the installation of the terminal γ -lactone moiety. Reprotection of compound **V-113** with TBSOTf followed by debenzylation under hydrogenation conditions afforded the primary alcohol, which upon treatment with I_2 and PPh_3 under basic conditions gave the iodide **V-119** (Scheme V-32).

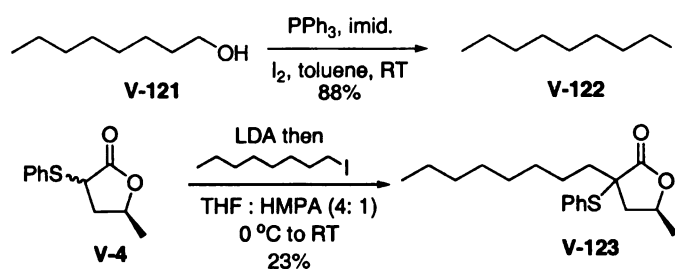


The first attempt to perform the alkylation reaction with α -SPh lactone **V-4** and iodide **V-119** only gave 8% yield of the desired intermediate **V-120**, containing the complete carbon skeleton of mucoxin (Scheme V-33). In order to complete the total



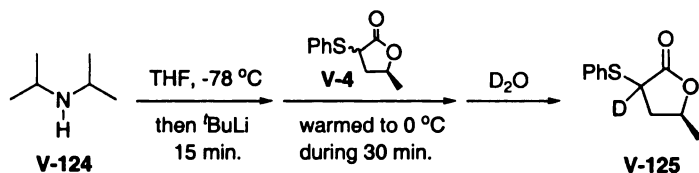
synthesis, this reaction needed to be optimized.

Purification of all the reagents by freshly distilling diisopropylamine (reagent for preparing LDA) and HMPA was done. Also, lactone **V-4** and iodide **V-119** were dried under vacuum for more than 6 hours. n BuLi was titrated in order to know its concentration precisely. By using freshly distilled THF as the solvent, this alkylation reaction was repeated three times and all of them still gave very low yield (< 10%). Thus a simple alkyl iodide was used as the model study for this alkylation reaction. Octane iodide **V-122** was prepared from 1-octanol **V-121** in 88% yield, and was used in the same alkylation reaction (Scheme V-34). However, this reaction still gave low yield of the desired product **V-123**.



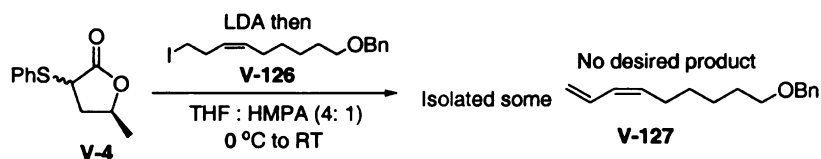
Scheme V-34: Model study of the alkylation reaction

One hypothesis on why this reaction only affords low yield was that the LDA base could not be formed successfully, thus deprotonation of α -proton in **V-4** did not occur. In order to prove this hypothesis, the newly formed LDA was reacted with lactone **V-4** for 30 min, and was quenched with D_2O to yield compound **V-125** (Scheme V-35). The α -proton in **V-4** exhibited 100% deuterated incorporation based on NMR analysis. Thus it was believed that deprotonation of α -proton in **V-4** successfully occurred, which further proved that LDA was formed in the first step.



Scheme V-35: D₂O-quenched experiment to prove the formation of the enolate

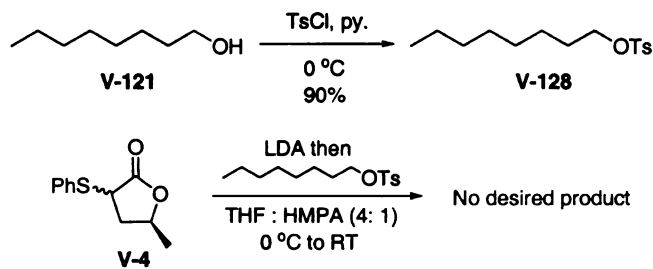
The other iodide **V-126**, which was the intermediate in the previous synthesis, was also used in the model study (Scheme V-36). However, this substrate did not give



Scheme V-36: Another substrate model study in alkylation reaction

any desired product. Instead, some elimination product **V-127** was isolated after the reaction. It seems that the basic conditions led to the elimination of iodide in **V-126** faster than the substitution, due to the formation of the conjugated double bond. Therefore, this was not a compatible substrate for the model study.

Instead of iodide, the tosylate was also used in the alkylation reaction since it is a good leaving group. Preparation of tosylate **V-128** was accomplished by using primary alcohol **V-121** and tosyl chloride (Scheme V-37). The alkylation reaction with **V-128** did not give any desired product. It was believed that the starting



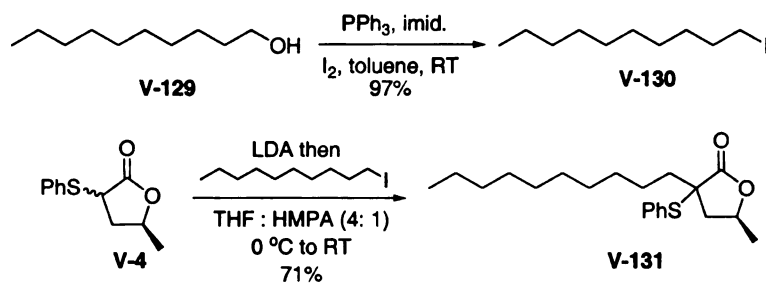
Scheme V-37: Model study using tosylate **V-128**

material decomposed under this condition since TLC showed many spots.

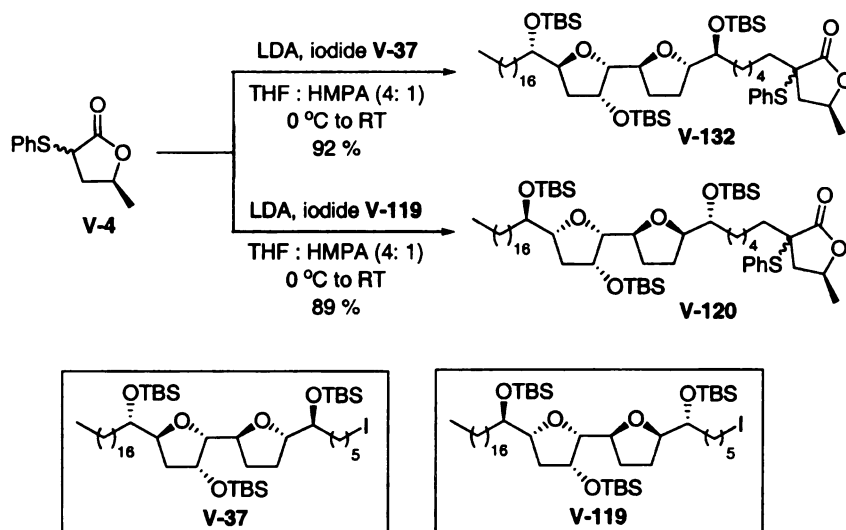
Since all of the model studies were in small scale (the amount of starting material was 0.1 mmol), a larger scale reaction was tried. By using 1.0 mmol of the octane iodide **V-122**, the alkylation reaction under the same conditions provided the desired product **V-123** and the yield increased to 45%. This result indicated that the small scale reaction was much more sensitive to moisture than the large scale reaction. In order to prevent any moisture, all of the glassware was flame-dried just before the reaction including even the microliter syringes. In addition, diisopropylamine and HMPA were newly distilled with CaH_2 and 4Å molecular sieves were added right after distillation. After controlling all these conditions, even the 0.1 mmol scale reaction using octane iodide **V-122** could give 50% yield of the alkylation product.

Another important detail for this reaction was the temperature control. The experiments showed that slowly warming the reaction would decrease the yield. Therefore, after LDA was formed and lactone **V-4** was added, the reaction temperature was increased to 0 °C immediately. Similarly, after iodide was added to the reaction, the temperature was increased to room temperature immediately.

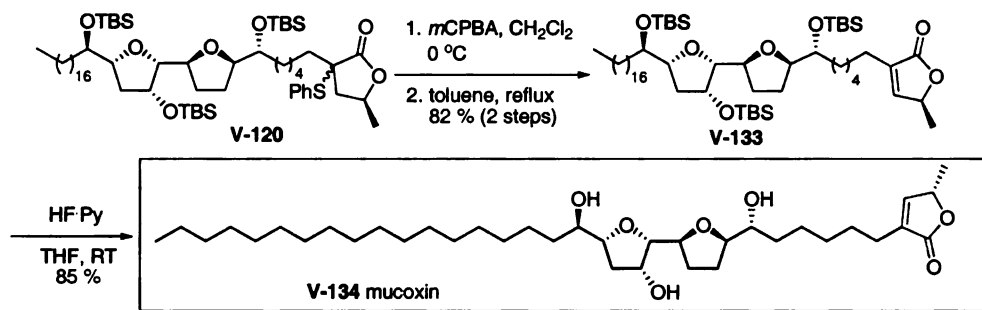
By modifying all of these conditions, the longer decane iodide **V-130** was used in the model study. This time the desired α -alkylated γ -lactone **V-131** was obtained in 71% yield (Scheme V-38). The modified reaction conditions could help to improve the reaction.



Applying the same modified conditions to intermediate **V-37**, the desired product was obtained in 92% yield (Scheme V-39). The modified conditions helped to improve the alkylation reaction in the real system. Finally, the alkylation reaction of α -SPh lactone **V-4** with iodide **V-119** was successful and afforded the intermediate **V-120** in 89% yield.



The last stage of the total synthesis was set for the *syn*- β -elimination and deprotection reactions. Compound **V-120**, when submitted to *m*CPBA oxidation, afforded its corresponding sulfoxide in quantitative yield (Scheme V-40). The crude sulfoxide upon heating in refluxing toluene underwent *syn*- β -elimination to give



Scheme V-40: Final work to afford real structure of mucoxin **V-134**

internal α , β -unsaturated lactone **V-133**. Completion of the total synthesis was achieved by global deprotection after treating compound **V-133** with HF·py to afford mucoxin **V-134**.

We were delighted to find that both ^1H and ^{13}C NMR spectra data of newly synthesized mucoxin **V-134** were in excellent agreement with the reported data for the natural mucoxin (Table V-18). In ^1H NMR spectra, only H13 deviated by 0.04 ppm. The rest of the signals deviated by 0.02 ppm or less. Also, H13 is a pseudotriplet with a coupling constant equal to 3.2 Hz. ^{13}C NMR spectra deviated by 0.2 ppm or less except for C15, which has a slightly larger deviation of 0.8 ppm. We believed that all these deviations are within experimental error and that our synthesized compound matches the structure of the natural product mucoxin. In addition, since only C15 has a slightly larger deviation, we checked McLaughlin's NMR data ourselves and found that this deviation was possibly due to their mistakes in transferring the value of the chemical shift of C15 from the spectra. Since the ^{13}C NMR spectra of our synthesized mucoxin was overlapped with the reported spectra in the same scale, the real chemical shift of C15 should be closer to our data. This detail also supported that the newly synthesized mucoxin has the right structure.

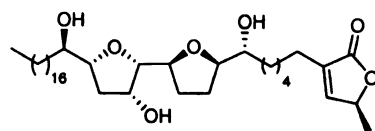
Table V-18: Comparison of ^1H and ^{13}C NMR spectra between newly synthesized mucoxin **V-134** and the natural mucoxin reported by McLaughlin and coworkers²

Proton / Carbon	V-134	Natural Mucoxin	$\Delta\delta$ (V-134–natural) (ppm)
H8	3.42	3.42	0.00
H9	3.95	3.95	0.00
H10	1.93, 2.06	1.91, 2.05	+0.02, +0.01
H11	1.93, 2.06	1.91, 2.05	+0.02, +0.01
H12	4.31	4.31	0.00
H13	3.75 (t, $J = 3.2$ Hz)	3.71 (t, $J = 3.0$ Hz)	+0.04
H14	4.32	4.32	0.00
H15	1.93, 2.35	1.91, 2.35	+0.02, 0.00
H16	4.05	4.04	+0.01
H17	3.54	3.53	+0.01
C8	73.7	73.6	+0.1
C9	83.5	83.4	+0.1
C12	78.9	78.9	0.0
C13	83.7	83.5	+0.2
C14	72.9	72.8	+0.1
C15	38.8	38.0	+0.8
C16	80.1	79.9	+0.2
C17	73.5	73.7	-0.2

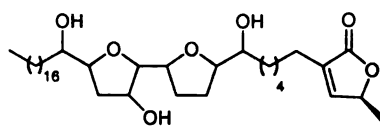
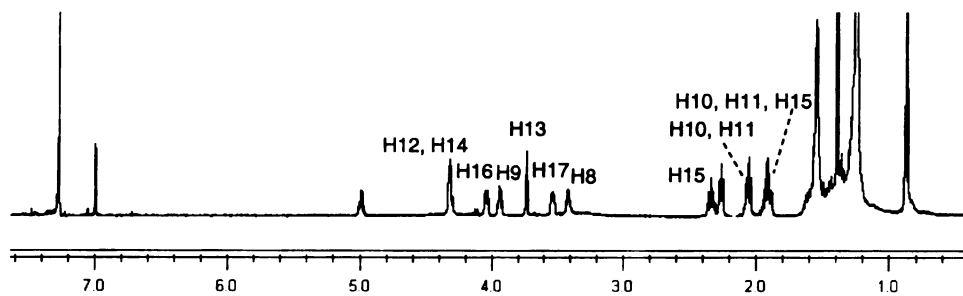
In McLaughlin's original assignment,² they assumed that in order for H13 to maintain the 3 Hz coupling with both H12 and H14, the two THF rings must be *threo* to each other and the OH-14 must be *cis* related to the C13 side chain. This relative stereochemistry was the result of the likely intramolecular hydrogen bonding between OH-14 and the disubstituted THF oxygen, which could freeze the rotation around C12/C13 bond and give the pseudotriplet of H13. This postulate was proved to be reasonable because only *threo* relationship between two THF rings could give the similar coupling constant of H13 with both H12 and H14. They also proposed a *trans*-relationship across both the THF rings due to the lack of nOe correlation peaks

between the respective protons. However, we clearly demonstrated that both the THF rings must bear a *cis* relative configuration in order to fit the spectral data. Actually for 5-membered THF ring, nOe signal is not as conclusive as for 6-membered ring systems. It is dangerous to only use nOe correlation to deduce *cis* or *trans*-relationship in the 5-membered ring system. We found that it was possible to observe the nOe correlations across both of the THF rings of the newly synthesized mucoxin at concentration of 5 mg sample in 1 mL CDCl₃ and above, after degassing the sample. However, if the concentration was lower, it was hard to observe the nOe signal even after overnight scanning. No nOe signal was observed when there was a *trans*-relationship across the THF ring, even if the concentration was high. Therefore, our results showed that in case of a 5-membered ring, nOe experiments ought to be executed and interpreted with great care.

Figure V-15 shows the ¹H NMR spectra of both the newly synthesized mucoxin and the reported natural product. It is clear that except for the free hydroxyl groups, which migrate easily, all the other parts of the spectra are identical.



V-134 newly synthesized mucoxin



V-1 natural mucoxin

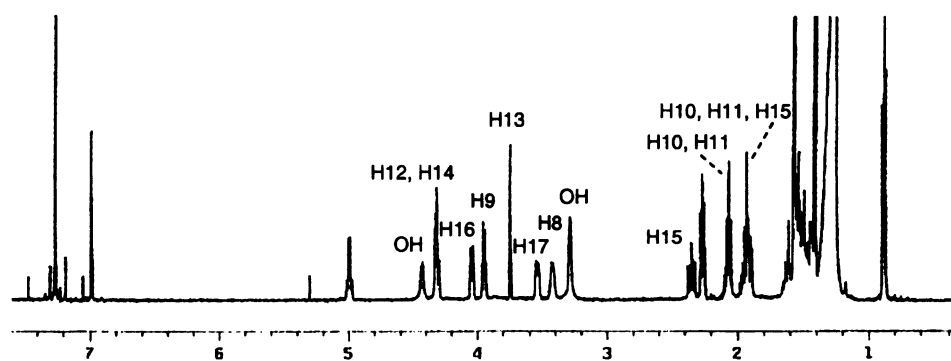


Figure V-15: ^1H NMR spectra of both newly synthesized mucoxin and reported natural mucoxin

V.10. Synthesis of pseudo-Enantiomer of Mucoxin and Comparison of Bioactivity

In McLaughlin's paper,² data on the optical rotation (α_D value) of mucoxin was not reported. Therefore the absolute stereochemistry of natural mucoxin could not be determined based on that information. Since we believed that C36 has *S* configuration, either compound **V-134** or **V-135** could be the natural product (Figure V-16). Our next goal was to evaluate whether compound **V-134** and its

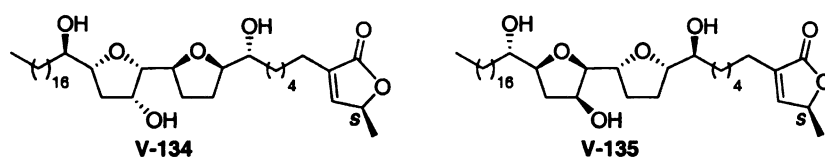
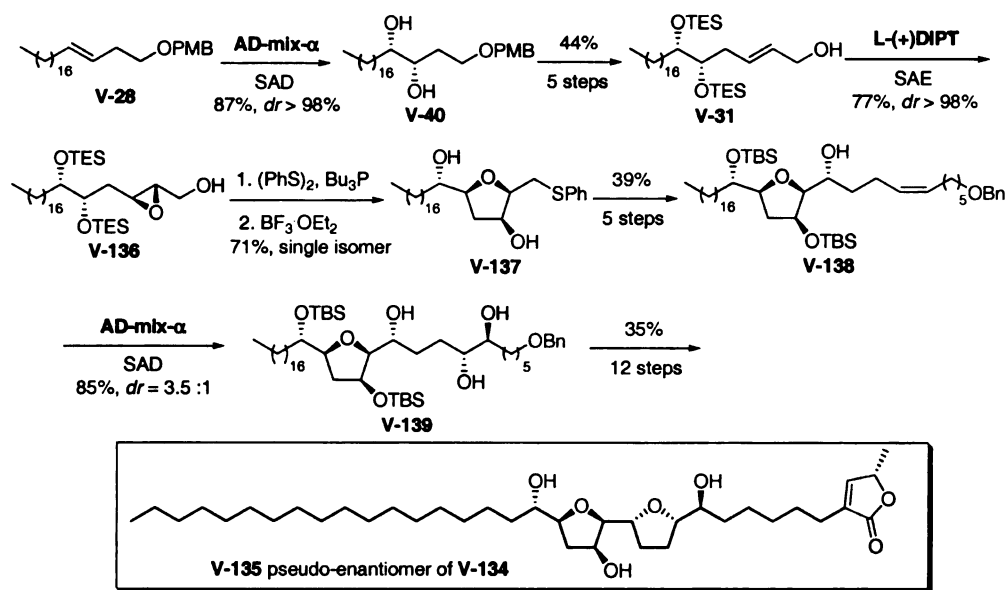


Figure V-16: Two possible structures of the natural mucoxin

pseudo-enantiomer **V-135** had different bioactivity and if we could use that difference to deduce the absolute stereochemistry of the natural product instead of relying on optical rotation. Here, the term 'pseudo-enantiomer' refers to the opposite stereochemistry in bis-THF region (C8-C17) of both compound **V-134** and **V-135**.

Synthesis of compound **V-135** could be achieved with the same sequence as was mentioned before only by changing the chiral reagents in both the asymmetric dihydroxylation and epoxidation reactions (Scheme V-41). The first SAD reaction of intermediate **V-28** gave *S,S*-diol **V-40**, which could be converted to **V-31** in 5 steps. The followed SAE reaction using L-(+)-DIPT instead of D-(-)-DIPT afforded epoxide **V-136** in 77% yield and excellent diastereomeric ratio. Thus the stereochemistry of C13 and C14 was inverted. The neighboring group-assisted cyclization reaction gave compound **V-137**. Here the *cis*-THF ring was formed as a single diastereomer,



Scheme V-41: Total synthesis of pseudo-enantiomer V-135

which was in accordance with the previous observation. Another SAD reaction of intermediate **V-138** provided triol **V-139** as the major isomer in 3.5:1 diastereomeric ratio. The same sequence as previously described finally afforded the pseudo-enantiomer **V-135** as the desired product.

Table V-19: Comparison of ¹H NMR spectra between compounds V-132 and V-133

Proton / Carbon	V-134	V-135	Δδ (V-134–V-135) (ppm)
H8	3.42	3.43	-0.01
H9	3.95	3.95	0.00
H10	1.93, 2.06	1.93, 2.06	0.00
H11	1.93, 2.06	1.93, 2.06	0.00
H12	4.31	4.31	0.00
H13	3.75	3.73	+0.02
H14	4.32	4.32	0.00
H15	1.93, 2.35	1.93, 2.35	0.00
H16	4.05	4.05	0.00
H17	3.54	3.55	-0.01

As predicted, the NMR spectrum of the pseudo-enantiomer **V-135** was identical to that of the newly synthesized mucoxin **V-134** (Table V-19). All the deviations between the two compounds are 0.02 ppm or less. Figure V-17 shows the ^1H NMR

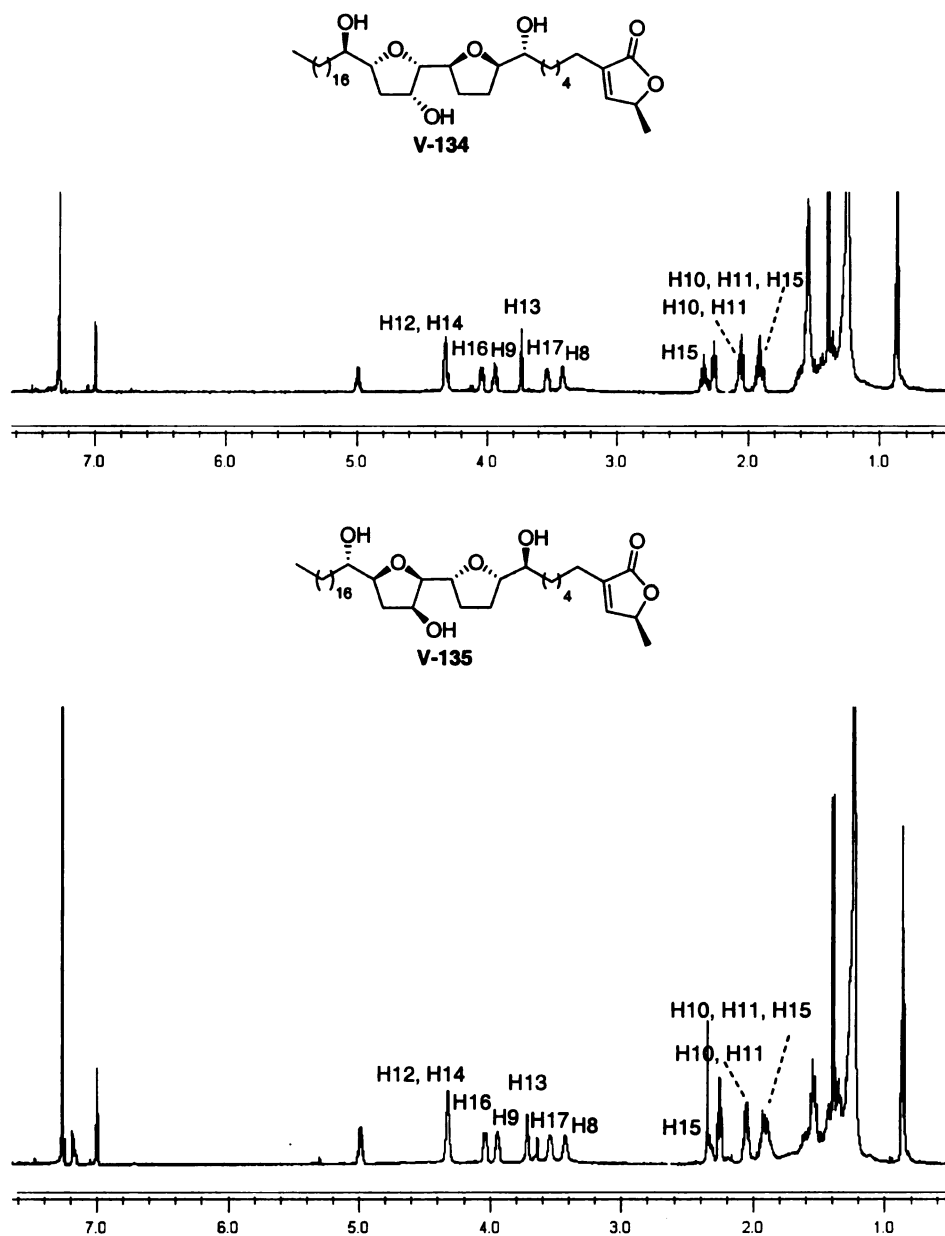


Figure V-17: ^1H NMR spectra of both newly synthesized mucoxin **V-134** and its pseudo-enantiomer **V-135**

spectra of both of these two compounds.

The bioactivity study of newly synthesized mucoxin **V-134** and its pseudo-enantiomer **V-135** showed inhibitory potencies (ED_{50} , $\mu\text{g/mL}$) against a panel of six human cancer cell lines (Table V-20). It was found that the two synthesized

Table V-20: Inhibitory potencies of **V-134** and **V-135** against a panel of six human cancer cell lines^a

ED_{50} ($\mu\text{g/mL}$)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
synthesized mucoxin V-134	0.12	0.039	0.085	0.102	0.11	0.45
synthesized pseudo-enantiomer V-135	0.41	0.079	0.21	0.285	0.092	0.42
reported mucoxin V-1	0.84	0.33	0.31	0.036	0.0037	0.61

^a A-498: renal carcinoma, PaCa-2: pancreas carcinoma, PC-3: prostate adenocarcinoma, A-549: lung carcinoma, MCF-7: breast carcinoma, HT-29: colon adenocarcinoma.

compounds had comparable values of inhibitory potencies against all tumor cells evaluated. Thus the bioactivity comparison could not help to determine the absolute stereochemistry of natural mucoxin. The only method left was to measure the optical rotation value of the natural sample and compare it with the synthesized molecule. However, since we could not obtain the natural isolated mucoxin after repeated inquiries made of the original authors, there was no way for us to determine the absolute stereochemistry of this natural product. Moreover, for A-549 and MCF-7 cancer cell lines, the reported data of inhibitory potencies of natural mucoxin are much lower than the synthesized compounds. The NMR spectra indicated that the synthesized compounds were much more pure than the natural isolated mucoxin.

One of the possible reasons for these suspicious higher activities of natural mucoxin could be the active impurities within the natural isolate, which would make sense since the plants they isolated acetogenins from have many other active ingredients.

All work related to the measurement of bioactivities for the synthesized compounds was performed by Chrysoula Vasileiou, a postdoctoral fellow in the Borhan laboratory.

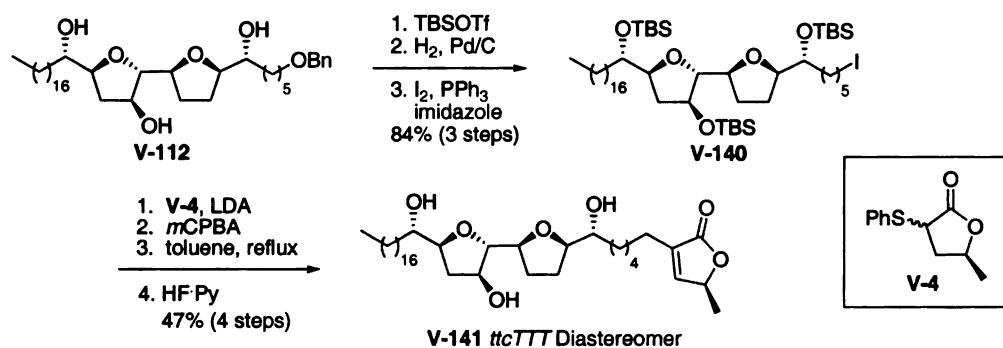
V.11. Structure-Activity Relationship (SAR) Studies of Mucoxin

Up to this point there has been no comprehensive SAR study of acetogenins (discussed in Chapter IV). Several groups only initiated some systematic studies based on their specific interest on particular structures. Specific to mucoxin, no SAR studies has been performed and no conclusions were drawn about its novel structure related to bioactivity. Interested in the cytotoxicities of synthesized mucoxin as well as the previous SAR studies of acetogenins, further SAR studies of mucoxin and its analogs were carried out.

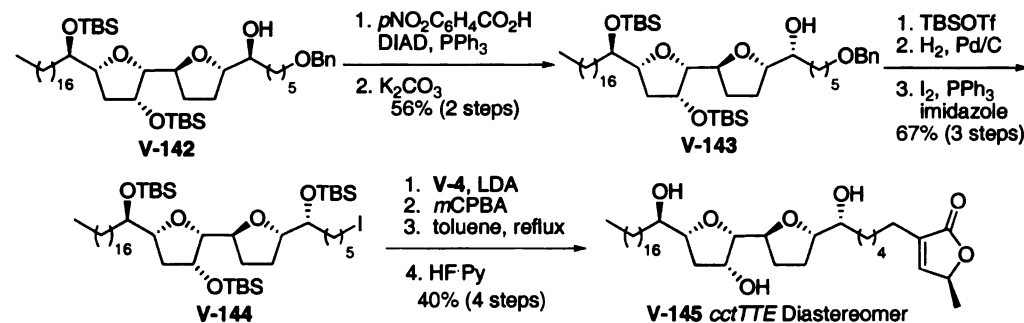
V.11.1. Effect of stereochemistry on the bioactivity

During the structural revision study of mucoxin, a series of different diastereomers of the truncated structures were synthesized. In order to know whether the stereochemistry of these compounds correlates to their bioactivities, the truncated structures could be converted to the full length molecules using the same strategy as was described for the synthesis of the revised structure of mucoxin (Scheme V-42). Mitsunobu reaction succeeded in inverting the stereochemistry in **V-142** (C12) and **V-57** (C14). TBS protection of all the free hydroxyl groups in intermediates **V-112**, **V-143**, **V-83**, and **V-148** followed by debenzylation and iodination afforded iodides

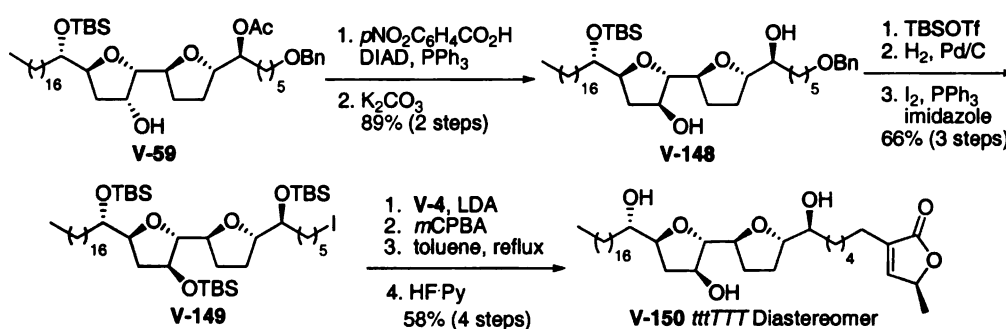
***ttcTTT* Diastereomer:**



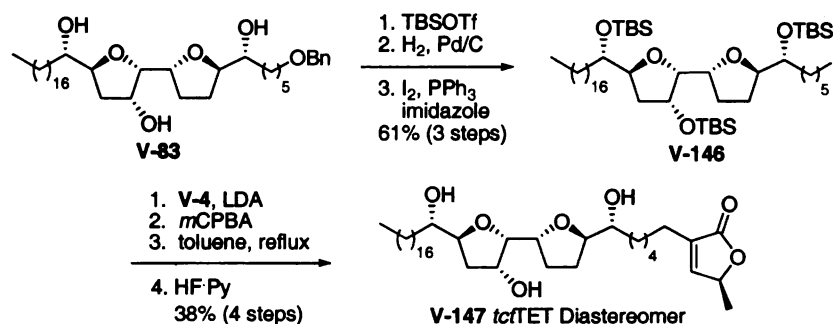
***cctTTE* Diastereomer:**



***tttTTT* Diastereomer:**



***tctTET* Diastereomer:**

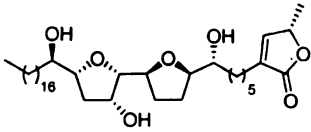
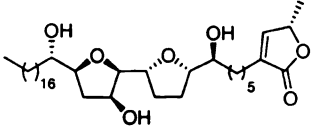
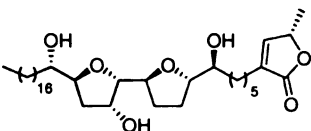
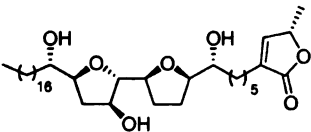
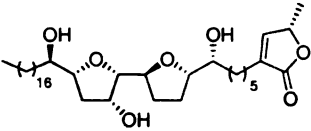
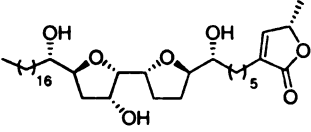
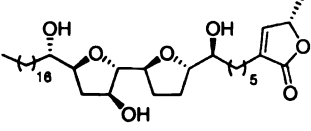


Scheme V-42: Synthesis of four full-length diastereomers of mucoxin

V-140, V-144, V-146, and V-149, which were then subjected to the alkylation reaction to install the terminal γ -lactone ring. Finally four different full length diastereomers **V-141, V-145, V-147, and V-150** of mucoxin were synthesized.

The bioactivity of all the diastereomers examined showed that they have different cytotoxicities against human cancer cell lines. The ED_{50} values of all the diastereomers, synthesized mucoxin, and adriamycin (as a control compound) are listed in Table V-21. Synthesized mucoxin **V-134**, its pseudo-enantiomer **V-135**, *tctTTT* diastereomer **V-2**, and *ttcTTT* diastereomer **V-141** are more active, as compared to other diastereomers. *cctTTE* Diastereomer **V-145** is the most inactive compound. A cursory examination of the data suggested that the relative stereochemistry around the bis-THF moiety had an effect on bioactivity of mucoxin and its analogs. This conclusion is in conflict with previous SAR studies on acetogenins, which considered that the stereochemistry around the THF rings is not an essential structural factor for potent activity (Chapter IV, section 6).

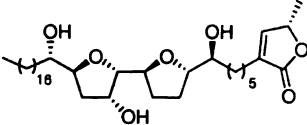
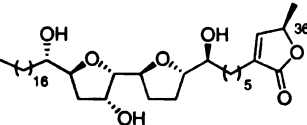
Table V-21: Inhibitory potencies against a panel of six human cancer cell lines

ED ₅₀ (μg/mL)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
reported mucoxin V-1	0.84	0.33	0.31	0.036	0.0037	0.61
	0.12	0.039	0.085	0.102	0.11	0.45
synthesized mucoxin V-134						
	0.41	0.079	0.21	0.285	0.092	0.42
synthesized pseudo-enantiomer V-135						
	0.10	0.037	0.068	0.396	0.070	0.29
<i>tctTTT</i> diastereomer V-2						
	0.060	0.044	0.082	0.19	0.068	0.24
<i>ttcTTT</i> diastereomer V-141						
	1.59	0.18	0.93	2.29	0.45	2.45
<i>cctTTE</i> diastereomer V-145						
	0.79	0.167	0.25	1.43	0.154	0.33
<i>tctTET</i> diastereomer V-147						
	0.64	0.169	0.32	1.22	0.21	1.20
<i>tttTTT</i> diastereomer V-150						
adriamycin	0.145	0.028	0.054	1.375	0.065	0.028

V.11.2. Effect of the terminal γ -lactone moiety on the bioactivity

In previous studies, *tctTTT* diastereomer **V-2** was synthesized as well as its C36 epimer **V-39**.¹⁵ In order to know whether the stereochemistry of the terminal γ -lactone ring has any effect on the bioactivity, the cytotoxicities of these two compounds were tested (Table V-22). From the data tabulated in Table V-22, we

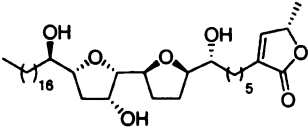
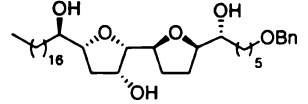
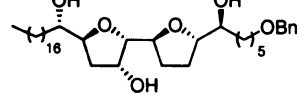
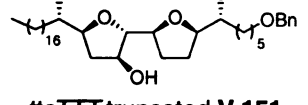
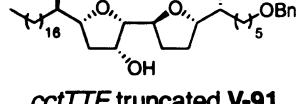
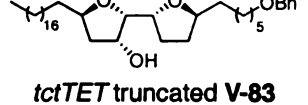
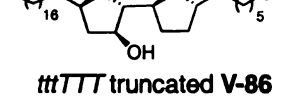
Table V-22: Inhibitory potencies of compound **V-2** and **V-39**

ED ₅₀ (μ g/mL)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
 <i>tctTTT</i> diastereomer V-2	0.10	0.037	0.068	0.396	0.070	0.29
 <i>tctTTT</i> C-36 epimer V-39	0.034	0.049	0.116	0.35	0.095	0.36

concluded that the stereochemistry of the methyl group substituent on the terminal γ -lactone ring does not contribute to the activities.

Moreover, in order to understand the importance of the terminal γ -lactone moiety, the truncated structures with a benzyl ether group instead of the γ -lactone moiety were also subjected to the bioactivity testing (Table V-23). The results show that benzyl ether-containing structures are generally less active than the full length molecules containing the γ -lactone moiety (comparing with Table V-21). However, the stereochemistry of truncated structures has a larger effect on the cytotoxicities. For example, *tctTTT* truncated structure **V-47** does exhibit good activity against some cell

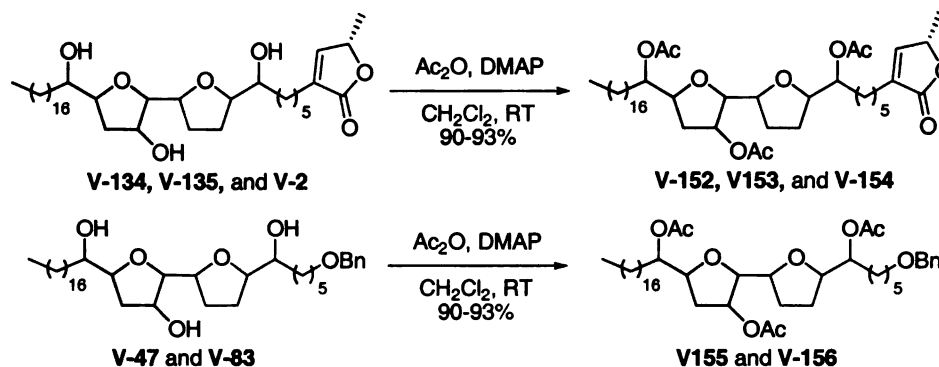
Table V-23: Inhibitory potencies of truncated structures

ED ₅₀ (μg/mL)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
 synthesized mucosin V-134	0.12	0.039	0.085	0.102	0.11	0.45
 cccTTT truncated V-113	5.0	0.50	1.96	>5	>5	>5
 tctTTT truncated V-47	0.48	0.128	0.39	0.59	0.12	1.22
 ttcTTT truncated V-151	0.25	0.22	0.55	3.7	>5	2.48
 cctTTE truncated V-91	1.65	0.56	1.57	>5	4.73	>5
 tctTET truncated V-83	5.6	1.78	>5	>5	>5	>5
 tttTTT truncated V-86	3.1	0.41	2.33	>5	3.2	>5
adriamycin	0.145	0.028	0.054	1.375	0.065	0.028

lines, even better than some of the full length molecules (such as compound **V-145** in Table V-21), while *tctTET* truncated structure **V-83** has lost activity against most of these cell lines. In addition, these analogs are more active against pancreatic carcinoma (PaCa-2) cell line than against other cancer cell lines.

V.11.3. Effect of the side-chain free hydroxyl groups

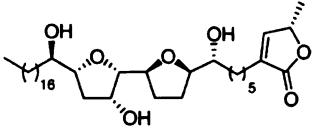
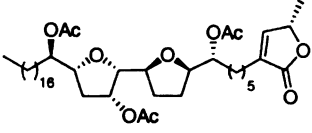
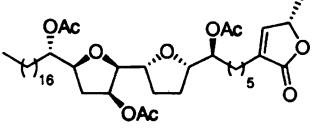
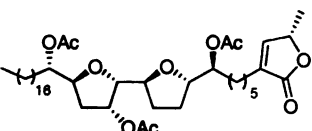
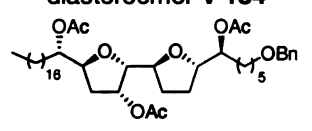
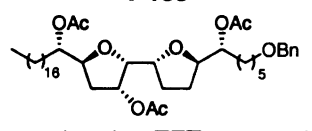
Previous SAR studies showed that the presence of free hydroxyl groups flanking around the THF moiety is important to elicit potent activity (Chapter IV). Protection of the free hydroxyl groups in mucoxin and its analogs could help us to test this observation. Acetylation of all the free hydroxyl groups in synthesized mucoxin **V-134**, its pseudo-enantiomer **V-135**, and its analog **V-2** gave the corresponding acyl derivatives **V-152**, **V-153**, and **V-154** (Scheme V-43). The same procedure was used to synthesize acetylated truncated structures **V-155** and **V-156**.



Scheme V-43: Acylation of full-linked molecules and truncated structures

All these five compounds were used in cytotoxicity assays (Table V-24). Generally acetylation of the free hydroxyl groups diminishes the bioactivity (comparing with Table V-21). This trend is enhanced for the truncated structures: acetylated derivatives **V-155** and **V-156** completely lose their activities. These observations also suggest that the presence of the free hydroxyl groups in acetogenins is important to elicit potent activity. The fact that acetylated derivatives of the full length molecules maintained some cytotoxicities is probably due to the reason that the acetyl groups can be removed with esterases in the cells.

Table V-24: Inhibitory potencies of acetylated derivatives

ED ₅₀ (µg/mL)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
 synthesized mucoxin V-134	0.12	0.039	0.085	0.102	0.11	0.45
 acetylated mucoxin V-152	0.66	0.10	0.47	1.22	0.32	0.65
 acetylated pseudo-enantiomer V-153	0.87	0.125	0.59	1.20	0.49	1.94
 acetylated <i>tctTTT</i> diastereomer V-154	0.39	0.080	0.174	0.38	0.11	0.45
 acetylated <i>tctTTT</i> truncated V-155	>5	3.7	>5	>5	>5	>5
 acetylated <i>tctTET</i> truncated V-156	>5	>5	>5	>5	>5	>5

V.11.4. Effect of the alkyl chain spacer

By comparison, the cytotoxic potency of mucoxin is generally lower than that of other classical acetogenins. Comparing the structure of mucoxin and bullatacin,

which is one of the most potent compounds in the acetogenin family, one of the most significant structural differences is the length of the spacer and tail (Figure V-18).

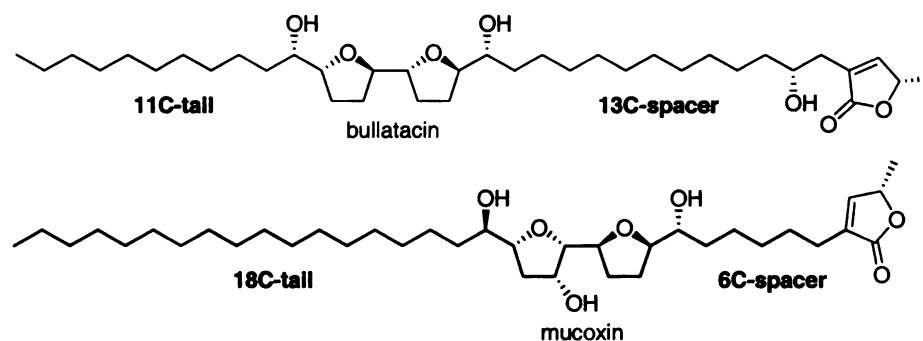


Figure V-18: Bullatacin and mucoxin

Mucoxin has a much shorter spacer and longer tail. Since the previous SAR studies showed that the length of the spacer has a significant effect on the bioactivity,⁵³⁻⁵⁷ we were interested in increasing the length of the spacer in mucoxin and to test the bioactivity of this analog.

The new synthetic target was set to the 13C-spacer analog of mucoxin **V-157**, which has the same spacer length as bullatacin (Figure V-19). Retrosynthetic

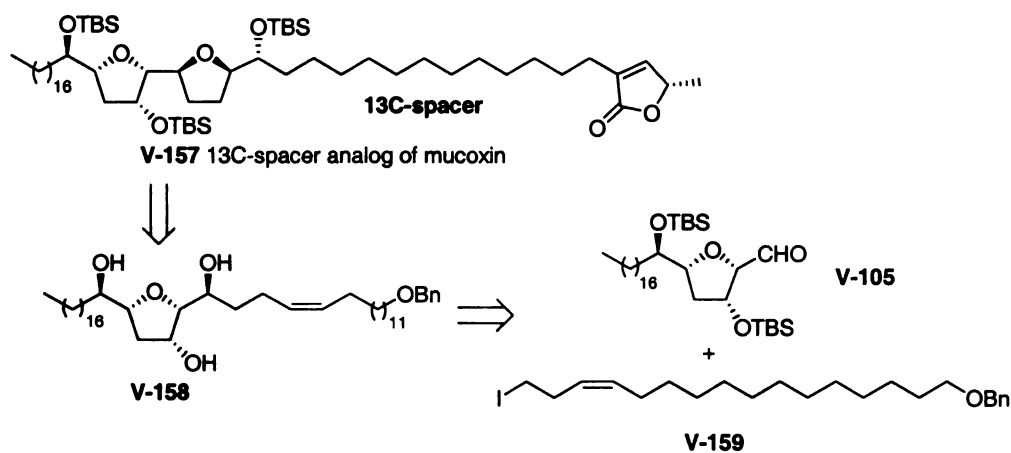
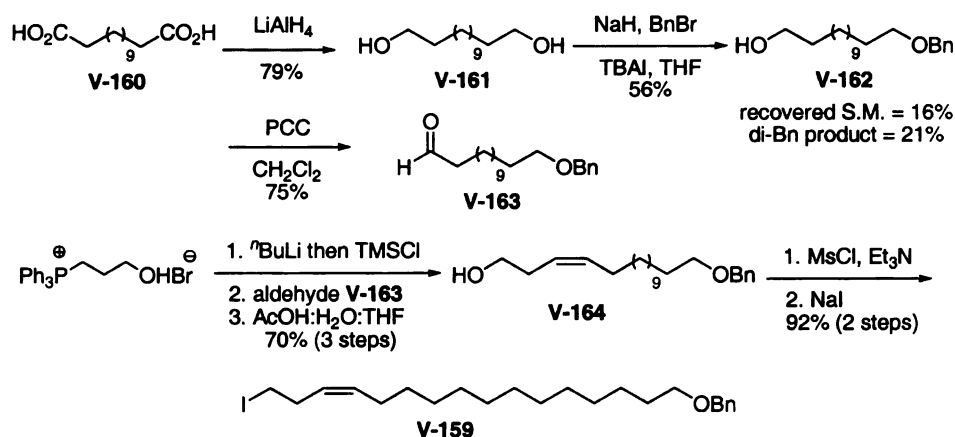


Figure V-19: Retrosynthetic analysis of 13C-spacer analog **V-157**

analysis showed that the length of the spacer in the final structure was determined by the length of the iodide **V-159** used in the alkylation reaction with aldehyde

intermediate **V-105**.

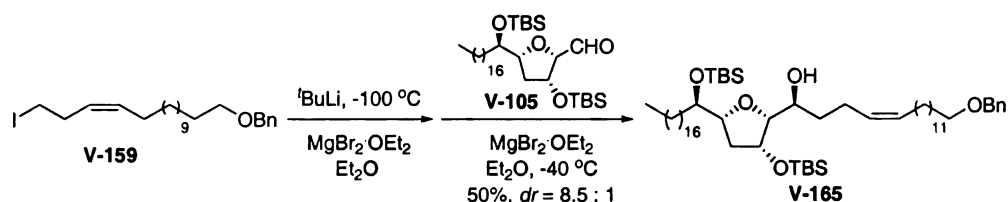
Aldehyde intermediate **V-105** was obtained from the previous library synthesis of truncated structures (Scheme V-27). The new synthetic route started with the LAH reduction of commercially available 1,11-undecanedicarboxylic acid **V-160** to the corresponding 1,11-undecanediol **V-161** (Scheme V-44). Monobenzyl protection of



Scheme V-44: Synthesis of iodide V-159

the diol using NaH and benzyl bromide afforded the primary alcohol **V-162** in 56% yield along with 21% dibenzyl protected diol and 16% recovered starting diol. PCC oxidation of alcohol **V-162** gave 75% yield of the desired aldehyde **V-163**. Wittig olefination using the original conditions (Scheme V-6) by generating the ylide from 3-hydroxypropyltriphenylphosphonium bromide with KHMDS gave 85% recovered starting material. By changing the base to ^tBuLi, the Wittig olefination provided the *cis*-olefin **V-164** as a single diastereomer. Finally, iodide **V-159** was accessed via a two-step iodination via S_N2 displacement of the corresponding mesylate.

Optimization of the 1,2-chelation-controlled nucleophilic addition afforded the intermediate **V-165** in 8.5:1 diastereomeric ratio (Scheme V-45). The two

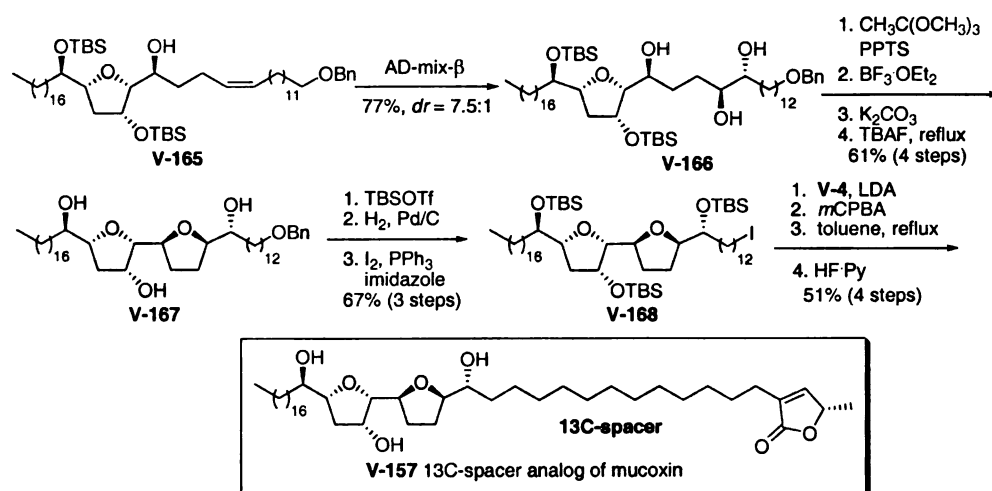


Scheme V-45: 1,2-Chelation-controlled nucleophilic addition to form **V-165**

diastereomers could be easily separated via silica gel chromatography.

From intermediate **V-165**, the synthetic strategy was exactly the same as for the preparation of synthesized mucoxin (Scheme V-46). SAD reaction of olefin **V-165** gave triol **V-166** as the major isomer in 7.5:1 diastereomeric ratio. Cyclization followed by deprotection provided the truncated structure **V-167** with the 13C-spacer. After reprotecting the free hydroxyl groups, iodide **V-168** was prepared, which was subjected to the alkylation conditions to install the butenolide moiety. The final elimination and global deprotection afforded the desired 13C-spacer mucoxin analog **V-157**.

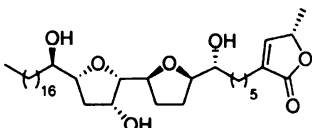
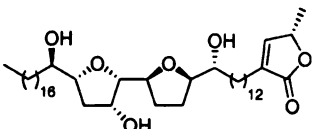
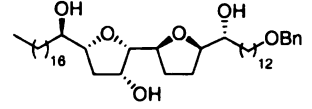
The results of the cytotoxicity assay against a panel of six human cancer cell lines



Scheme V-46: Synthesis of both truncated and full-length 13C-spacer analogs of mucoxin

with the 13C-spacer mucoxin analog is shown in Table V-25. Both the full length

Table V-25: Inhibitory potencies of 13C-spacer analogs

ED ₅₀ (μg/mL)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
 synthesized mucoxin V-134	0.12	0.039	0.085	0.102	0.11	0.45
 13C-spacer analog V-157	>5	0.19	>5	>5	>5	>5
 13C-spacer truncated analog V-167	>5	>5	>5	>5	>5	>5

molecule **V-157** and the truncated structure **V-167** with 13C-spacer lost most their activities as compared to mucoxin. Only analog **V-157** showed potent and selective activity against the PaCa-2 cell line. Structural variation by increasing the length of spacer did not help to improve the bioactivity. Analog **V-157** has a 18C-tail, which is much longer than bullatacin (11C tail). It seems that the length of the whole molecule might be important for maintaining the high activity.⁵³⁻⁵⁵

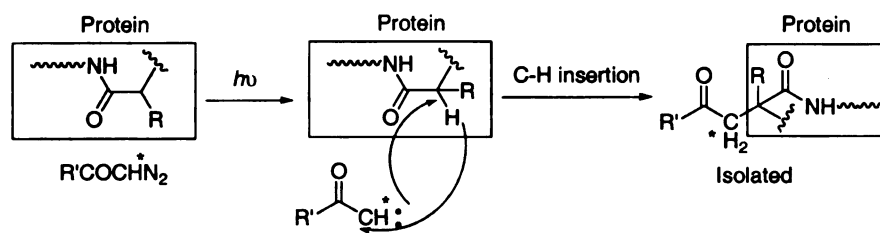
V.11.5. Photoaffinity analogs of mucoxin

The elucidation of molecular interactions leading to biochemical processes is a major objective of chemical and biochemical research. Essential to the understanding of the interactions involved in biological processes at the molecular level is the identification and structural characterization of the components of the

complex systems involved. Studies on the mechanism of action of enzyme-catalyzed reactions require the determination of the amino acids in the active site involved in binding and catalysis. The classical approach for obtaining this information employs reagents for the chemical modification of active site residues, commonly referred to as affinity labeling.⁵⁸⁻⁶¹

Since ideal labeling reagents require both high reactivity as well as *in situ* activation, photogenerated reagents have the potential for these requirements. Thus photoaffinity labeling has become a major technique for studying molecular interactions in biological systems since 1962.^{62, 63} A photolabile reagent is anchored to the macromolecule possibly via a covalent bond. Photolysis of this complex leads to the generation of a highly reactive species that, by reacting rapidly with its immediate environment, labels the macromolecule or specifically the active site.⁶¹ This technique can be applied in identifying complex biological receptors and provides information on their molecular structures.

An example of a general sequence that uses a diazo-compound as the photoaffinity labeling reagent is shown in Scheme V-47. After photogenerating the



Scheme V-47: General sequence of photoaffinity labeling experiment

carbene complex from the diazo-compound, which is labeled with a radioactive atom such as T, C-H insertion of protein by the carbene complex occurs quickly to

covalently attach them together. Subsequent isolation is based on isolation of the radioactive component. Hence photoaffinity labeling studies can assist in clarifying the position of the protein binding site with the molecule.⁶¹

A good photoaffinity labeling group should combine the properties of chemical stability prior to photo-activation, rapid rate of photolysis, and very short half life for the photogenerated reactive species leading to labeling of the environment in which it is generated.⁶¹ Some commonly used photoaffinity groups in labeling studies are shown in Figure V-20.⁶⁴⁻⁷¹

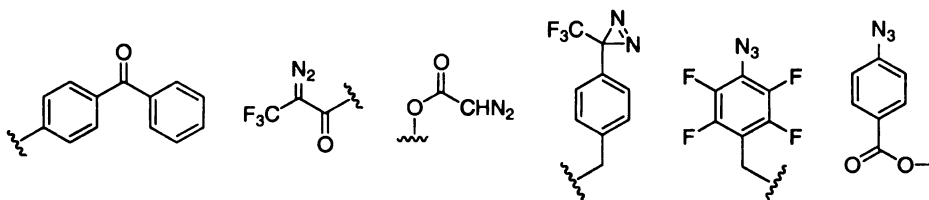


Figure V-20: Commonly used photoaffinity groups

Photoaffinity labeling studies have already been used in understanding the inhibitor binding sites of mitochondrial complex I, the suggested target of *Annonaceous* acetogenins. For example, through photoaffinity labeling using rotenone-derived probes, Ragan and coworkers determined an inhibitor binding site in the ND1 subunit.^{72, 73} Along the same lines, fenpyroximate,⁷⁴ ubiquinone,^{75, 76} and pyridaben derivatives^{77, 78} were also used as either photoaffinity or ¹⁴C-labeling probes indicating that more complex I subunits, such as IP49K, PSST, ND3, and ND5 are part of the binding pocket of these inhibitors.⁷⁹⁻⁸²

However, for acetogenins, the precise mode of complexation with their target proteins in complex I at a molecular level is not known. Also, there are no

photoaffinity labeling studies about acetogenins or their analogs reported, which prompted us to propose the synthesis of photoaffinity analogs of acetogenins. Our goal is to synthesize a series of acetogenins with photoaffinity groups attached in different places and to study the interaction of these compounds and complex I.

Our initial work in this area started from synthesizing an analog **V-169** of mucoxin containing a photoaffinity group in place of the terminal butenolide (**V-169**, Figure V-21). Here, a fluorinated azide group is used in our photoaffinity study due

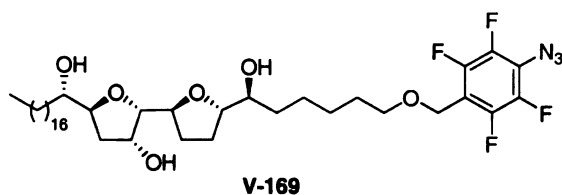
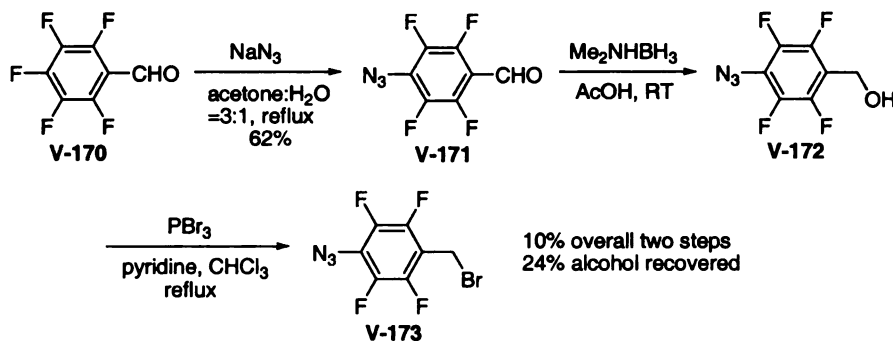


Figure V-21: Mucoxin analog containing a photoaffinity group

to its high efficiency. The major difference between fluorinated and nonfluorinated phenyl azides is that ring expansion of singlet fluorinated phenylnitrenes is much slower than that of singlet nonfluorinated phenylnitrenes.⁷¹ Thus the singlet fluorinated nitrene can be readily trapped with nucleophilic reagents to form adducts in significant yield.

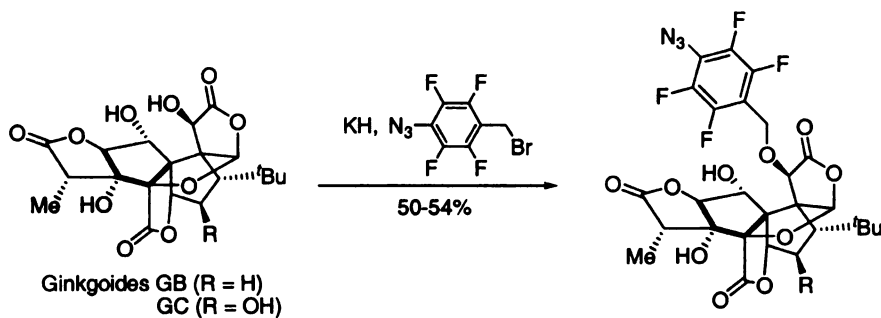
The synthesis of the photoaffinity group **V-173** was achieved from commercially available pentafluorobenzaldehyde **V-170** (Scheme V-48).⁸³ **V-170** was treated with NaN_3 in a solvent mixture of H_2O and acetone and specifically gave the para-substituted azide **V-171** in 62% yield. Pure white solid compound **V-171** could be obtained via subliming the compound under reduced pressure. Reduction of the aldehyde using dimethylamine borane complex afforded primary alcohol **V-172**.



Scheme V-48: Synthesis of 2,3,4,5-tetrafluorophenyl azide **V-173**

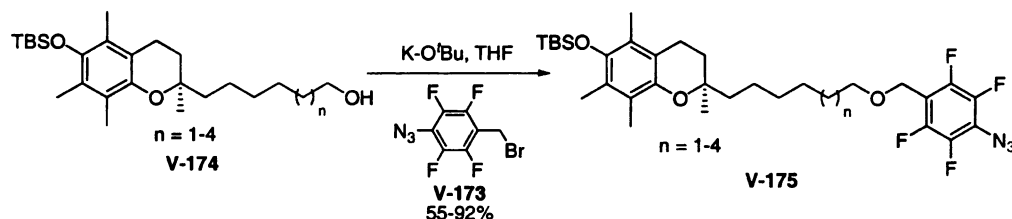
After converting the primary alcohol to bromide using PBr_3 without the purification of **V-172**, the desired azide benzyl bromide **V-173** was formed and purified via silica gel chromatography. The low yield in these two steps could be due to the impurity of compound **V-172**.

Since truncated structure *tctTTT* **V-47** exhibited the highest activity as compared to other truncated structures, it was used as the parent compound. In order to synthesize compound **V-169**, the most important step is the coupling of the photoaffinity group. In the previous studies, Nakanishi and coworkers reported the use of KH while attaching Ginkgolides GB and GC with the same photoaffinity group **V-173** (Scheme V-49).⁸³ Moreover, synthesis of photoaffinity labels based on α -tocopherol was reported by Lei and Atkinson.⁸⁴ During their studies, several bases



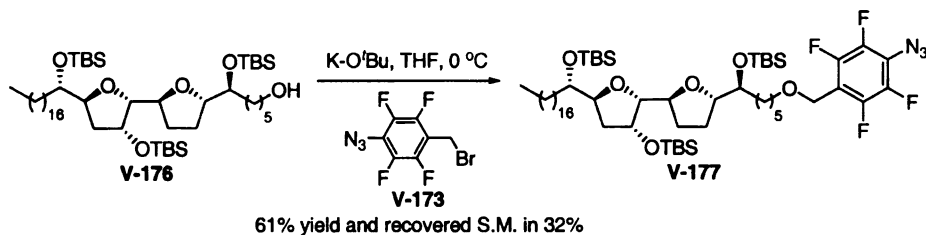
Scheme V-49: Nakanishi's coupling of photoaffinity group **V-173**

were explored for the benzylation of intermediate **V-174**. Aqueous bases such as NaOH with phase transfer catalysts were inappropriate because of the fast substitution of the benzyl bromide by hydroxyl. NaH in ethereal solvents decomposed the azide, apparently by reduction to the aniline and several other products. The best yields for the benzylation were achieved utilizing 4 equiv of potassium *tert*-butoxide in THF at 0 °C (Scheme V-50).



Scheme V-50: Lei and Atkinson's method to couple with photoaffinity group

Because intermediate **V-174** has a primary alcohol with an alkyl chain, which is similar to our truncated structure, the same conditions were used in the coupling of our intermediate **V-176** and photoaffinity group **V-173**. After deprotonation by potassium *tert*-butoxide, benzylation of intermediate **V-176** gave us the desired product **V-177** in 61% yield after 3 h and at the same time we recovered 32% of the starting material **V-176** (Scheme V-51). Increasing the reaction time (more than 12



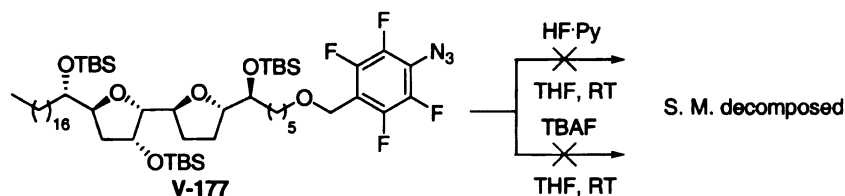
Scheme V-51: Coupling of *tctTTT* truncated structure and photoaffinity group

hours) and temperature (room temperature) did not help to increase the conversion of the starting material to the product. Since the fluorinated benzyl group in compound

V-177 might decompose at higher temperature, other conditions were not tried for this coupling reaction.

The bioactivity study of compound **V-177** showed that it has no cytotoxic effect against any of the cancer cell lines used in the previous SAR studies. It was proven that free hydroxyl groups were very important to maintain good activity. Thus the lost of the activity was most probably due to the TBS protection groups.

However, the initial deprotection of TBS groups under the normal conditions was not successful (Scheme V-52). Using HF•py under the same conditions as was



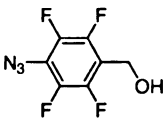
Scheme V-52: The initial deprotection reaction of TBS groups in compound **V-177**

applied in the final step of mucoxin synthesis did not give any desired product. Starting material **V-177** was recovered in 41% yield after 15 h and there were many byproducts as indicated by a complex NMR spectrum. Use of TBAF decomposed the starting material even after 5 h and did not afford any product.

Since the major problem in this deprotection reaction was the decomposition of the photoaffinity group, before optimizing the reaction, we needed to confirm which conditions would not lead the compound's degradation. Therefore, compound **V-172** was treated with several mild TBS deprotection conditions (Table V-26). Alcohol **V-172** instead of bromide **V-173** was used in the stability study because the bromide is known to be unstable under comparable conditions. Alcohol **V-172** was mixed

with other reagents and stirred overnight at RT. All the reactions were worked up and the solvent was removed under reduced pressure. Crude NMR spectra could

Table V-26: Experiments regarding the stability of compound **V-172** under different TBS deprotection conditions^a

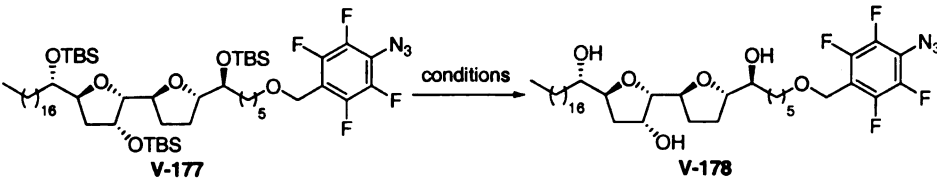
Compound V-172				
conditions	K ₂ CO ₃ , MeOH	PPTS, EtOH	BF ₃ •OEt ₂ , CH ₂ Cl ₂	TsOH (0.1 equiv), THF:H ₂ O = 20 :1
results	decomposed	stable	stable	stable

^a All the reactions were at RT for 15 h.

clearly show whether alcohol **V-172** was stable or decomposed. It was found that only K₂CO₃ in methanol decomposed alcohol **V-172**, and thus the other three conditions could be used in the TBS deprotection reaction.

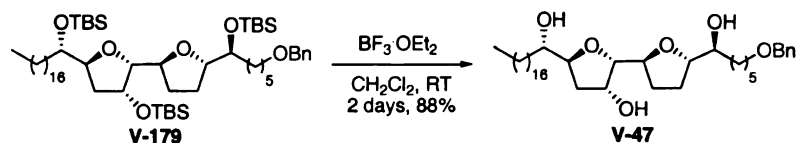
All of the above conditions were applied in the TBS deprotection reaction of compound **V-177** (Table V-27). The reactions mediated by PPTS and TsOH only resulted in recovered starting material. BF₃•OEt₂ could give some product, according to NMR spectral analysis, along with some starting material. The last

Table V-27: Experiments of the TBS deprotection for compound **V-177**^a

				
conditions	PPTS, EtOH, RT	BF ₃ •OEt ₂ , CH ₂ Cl ₂ , RT	TsOH (0.1 equiv), RT, THF:H ₂ O = 20 :1,	TBAF, THF, reflux ^b
results	S.M. recovered 98%	S.M. and some product	S.M. recovered 98%	S.M. decomposed

^a The reactions were stirred for 20 h. ^b The reaction was stirred for 1 h.

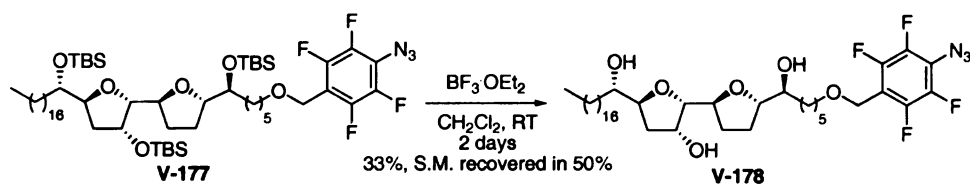
experiments using TBAF under refluxing condition showed that the rate of decomposition of compound **V-177** was faster than the TBS deprotection at high temperature. Based on all these observations, $\text{BF}_3 \cdot \text{OEt}_2$ was chosen for further optimization because it had a comparably faster reaction rate and it did not decompose the photoaffinity group. In order to know how long all of the starting materials could react under these conditions, intermediate **V-179** with normal benzyl group was used for TBS deprotection (Scheme V-53). After 2 days stirring of **V-179**



Scheme V-53: TBS deprotection of **V-179** mediated by $\text{BF}_3 \cdot \text{OEt}_2$

at RT, the reaction gave the desired triol **V-47** in 88% yield with 100% conversion.

Finally the same conditions were used for the compound **V-177** (Scheme V-54). It was found that substrate **V-177** with the photoaffinity group had a slower reaction rate as compared to substrate **V-179** with the normal benzyl group. The reaction gave 33% yield of desired product **V-178** along with 50% starting material after 2 days.

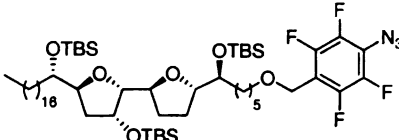
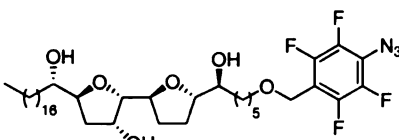


Scheme V-54: TBS deprotection of **V-177** mediated by $\text{BF}_3 \cdot \text{OEt}_2$

However, the bioactivity study showed that compound **V-178** with free hydroxyl groups still had low cytotoxicity against a panel of five human cancer cells (Table V-28).

This photoaffinity analog of mucoxin was only active with the PaCa-2 cell line. It was believed that the loss of activity of mucoxin analog **V-178** was due to the terminal photoaffinity group. Further study of photoaffinity analogs of acetogenins is still ongoing.

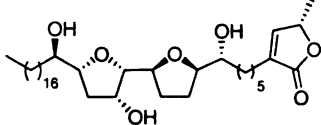
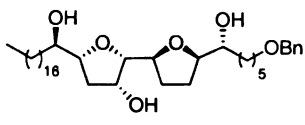
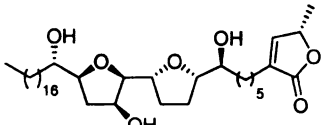
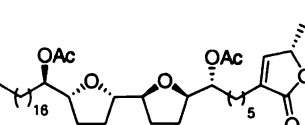
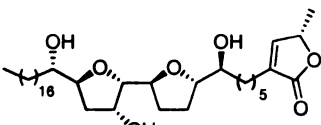
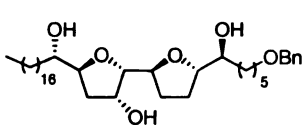
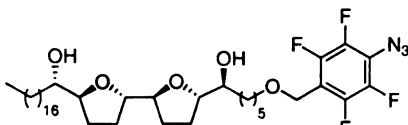
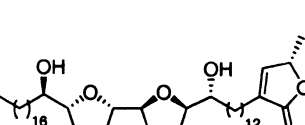
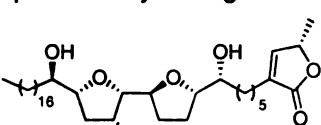
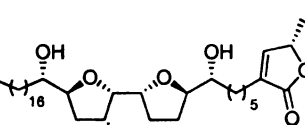
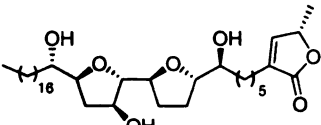
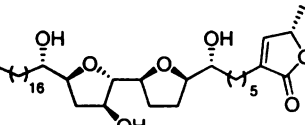
Table V-28: Inhibitory potencies of photoaffinity analogs of mucoxin

ED ₅₀ (μg/mL)	A-498	PaCa-2	PC-3	A-549	MCF-7	HT-29
 TBS-protected photoaffinity analog V-177	>5	>5	>5	>5	>5	>5
 photoaffinity analog V-178	4.1	0.12	0.55	>5	>5	>5

V.11.6. Complex I inhibition study of mucoxin and its analogs

Since acetogenins are one of the most potent inhibitors of complex I, and also since no data has been reported for mucoxin or similar ring hydroxylated acetogenins, our compounds were subjected to the complex I inhibition study (Table V-29).

Table V-29: Inhibition of mitochondrial complex I by mucoxin and its analogs^a

Compound	Complex I Inhibition IC ₅₀ (nM)	Compound	Complex I Inhibition IC ₅₀ (nM)
 synthesized mucoxin V-134	37 ± 2	 cccTTT truncated V-113	>5000
 synthesized pseudo-enantiomer V-135	165 ± 140	 acetylated mucoxin V-152	>5000
 tctTTT diastereomer V-2	~ 1200	 tctTTT truncated V-47	>5000
 photoaffinity analog V-178	>5000	 13C-spacer analog V-157	>5000
 cctTTE diastereomer V-145	879 ± 452	 tctTET diastereomer V-147	~2000
 ttT TTT diastereomer V-150	~1000	 ttT TTT diastereomer V-141	65.2 ± 7.7

^a IC₅₀ (Retenone) = 208 ± 31.

It was interesting to find that there were different trends between the inhibition of complex I and cytotoxicity against cancer cell lines, within the same library of compounds. Synthesized mucoxin **V-134** had the lowest IC_{50} value (37 nM). However, *tctTTT* diastereomer **V-2**, which had the comparable cytotoxicity as **V-134**, was not a good inhibitor for complex I ($IC_{50} = \sim 1200$ nM). Analog *ttcTTT* **V-141** however maintained good inhibition. The stereochemistry of the bis-THF region is still an important factor for the inhibitory ability. All of the truncated structures and the photoaffinity analogs of mucoxin (**V-113**, **V-47**, and **V-178**) exhibited no inhibition for complex I, as well as the ^{13}C -spacer analog **V-157**. Moreover, acetylated analog **V-152**, demonstrated good cytotoxicity, was not a good complex I inhibitor. All these observations suggest that there are different mechanisms of inhibition for complex I and cytotoxicity against cancer cell lines.

V.12. Summary

In summary, combinations of synthesis as well as NMR spectroscopic analyses were used to determine the correct structure of the natural product mucoxin. Since the NMR spectra of the synthesized proposed structure of mucoxin did not match those of the reported natural mucoxin, we attempted to revise the structure. We felt that the correct way to establish the structure was to not only establish a synthetic effort aimed at preparing different diastereomers of mucoxin, but also find the relationship between the NMR spectral data and the relative stereochemistry of these synthesized compounds. Selective deprotection, the Mitsunobu reaction and oxidation / reduction reactions were proven to be efficient and convenient methods to

invert the stereochemistries in the C8-C17 region in order to obtain different diastereomers. Moreover, using the spectroscopic data as a guide, four useful trends were summarized to narrow the possibilities and predict the correct structure. Finally the real structure of mucoxin and its C8-C17 pseudo-enantiomer were synthesized with spectroscopic excellent match to the reported natural mucoxin. Since there was no optical rotation value reported for this natural product, we could not determine which diastereomer had the right absolute stereochemistry.

The related SAR studies of mucoxin and its analogs were also investigated. All the cytotoxicity studies showed that the relative stereochemistry in the bis-THF moiety, the terminal lactone moiety, the free hydroxyl groups, and the length of the molecule are important factors to elicit potent activity. One photoaffinity analog of mucoxin with some bioactivity was synthesized and further photoaffinity labeling study is still ongoing. The complex I inhibition study gave different results as the cytotoxicity study, which suggested the different mechanism for these two processes.

V.13. Experimental Section

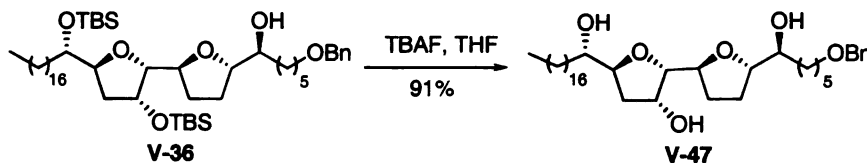
General Information:

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 (Et₂O) were freshly distilled from sodium/benzophenone; methylene chloride (CH₂Cl₂) and toluene (PhCH₃) was dried over calcium hydride (CaH₂) and freshly distilled prior to use; DMF, DMSO, Et₃N, and HMPA were distilled from CaH₂ and stored over 4 Å molecular sieves. 4 Å molecular sieves were dried at 160 °C under vacuum prior to use. Some compounds were prepared as previous reported. 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 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for CDCl₃). ¹³C NMR spectra were measured at 75 MHz on a Varian Gemini-300 or at 125 MHz on a Varian VXR-500 instrument. Chemical shifts are reported relative to the central line of CDCl₃ (δ 77.0 ppm). Infrared spectra were recorded using a Nicolet IR/42 spectrometer FT-IR (thin film, NaCl cells). 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 F₂₅₄ 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 containing Altech SE-54, 30 m × 320 µm × 0.25 µm column.

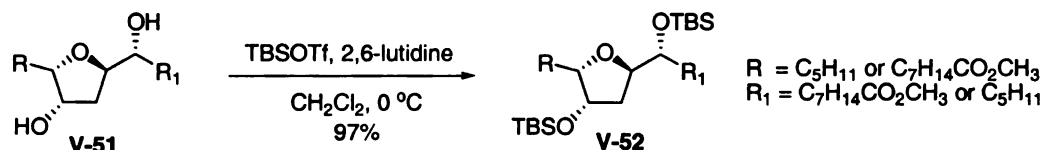
Data for Newly Synthesized Compounds:



To a solution of alcohol **V-36** (16.5 mg, 0.019 mmol) in THF (2 mL), TBAF (1.0 M solution in THF, 38 µL, 0.038 mmol) was added at room temperature. After stirring for 16 h, saturated NH₄Cl (aq.) solution (3 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layers were extracted with EtOAc (3×10 mL). The organic layers were mixed, dried over Na₂SO₄, and the solvent was evaporated to afford a crude product. Purification by column chromatography (EtOAc) gave *tctTTT* truncated structure **V-47** as white wax in 91% yield (11 mg).

Data for *tctTTT* truncated structure **V-47**: $[\alpha]_D^{20}$ -7.3 (c 0.54, CHCl₃), ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.42-4.38 (1H, m), 4.32-4.28 (1H, m), 4.08-4.04 (1H, m), 3.94-3.89 (1H, m), 3.77 (1H, t, *J* = 3.4 Hz), 3.74 (3H, br), 3.44

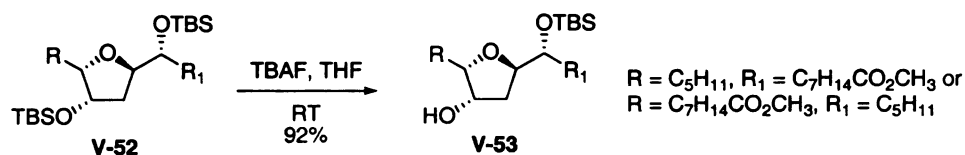
(2H, t, $J = 6.8$ Hz), 3.41-3.35 (2H, m), 2.32-2.29 (3H, m), 2.08-1.95 (4H, m), 1.82-1.78 (1H, m), 1.69-1.58 (6H, m), 1.57-1.23 (32H, m), 0.91-0.80 (3H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.5, 128.3, 127.6, 127.4, 83.9, 83.1, 81.3, 79.0, 74.4, 74.1, 73.5, 72.8, 70.3, 66.8, 38.7, 34.0, 33.8, 33.3, 31.9, 30.4, 29.7, 29.3, 29.2, 28.9, 27.8, 26.2, 25.6, 25.5, 24.5, 23.8, 22.9, 22.7, 14.1, 11.0; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{68}\text{O}_6\text{Na}$, 655.4914 m/z ($\text{M}+\text{Na}$) $^+$; observed, 655.4892 m/z .



To a 0 °C solution of diol **V-51** (154 mg, 0.43 mmol) in CH_2Cl_2 (5 mL), 2,6-lutidine (0.16 mL, 1.4 mmol) and TBSOTf (0.25 mL, 1.08 mmol) were added in that order. After 30 min at the same temperature, saturated NaHCO_3 solution (2 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×8 mL), combined organic layers were dried over Na_2SO_4 , and concentrated under reduced pressure to afford a crude oil. Upon purification of the oil by column chromatography (2% EtOAc in hexanes), di-TBS ether **V-52** was obtained in 97% yield (250 mg).

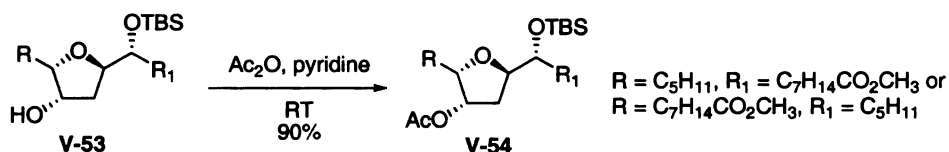
Data for di-TBS ether **V-52**: ^1H NMR (300 MHz, CDCl_3) δ 4.16-4.08 (2H, m), 3.70-3.56 (5H, m), 2.27 (2H, t, $J = 7.4$ Hz), 1.78-1.75 (2H, m), 1.61-1.21 (20H, m), 0.86-0.83 (21H, m), 0.04- -0.01 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 174.3, 82.9, 79.1, 74.6, 73.2, 51.4, 37.6, 34.1, 32.2, 32.0, 29.6, 29.4, 29.2, 29.0, 26.3, 26.0, 25.7, 25.5, 24.8, 22.6, 18.2, 18.0, 14.0, -4.3, -4.5, -4.6, -5.0; IR (thin film) 2930, 2857,

1744, 1591, 1453, 1254, 1113, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{64}\text{O}_5\text{Si}_2\text{Na}$, 595.4190 m/z ($\text{M}+\text{Na}$) $^{+}$; observed, 595.4169 m/z .



To a solution of di-TBS ether **V-52** (71 mg, 0.12 mmol) in THF (5 mL), TBAF (1.0 M solution in THF, 0.15 mL, 0.15 mmol) was added at room temperature. After stirring for 12 h, saturated NH_4Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layers were extracted with EtOAc (3×5 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (20% EtOAc in hexanes) gave the selectively deprotected product **V-53** as colorless oil in 92% yield (66 mg).

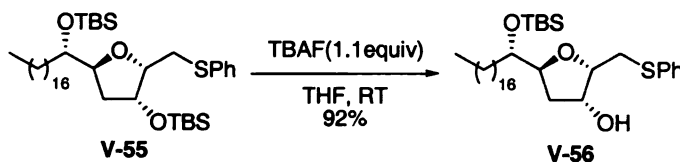
Data for alcohol **V-53**: ^1H NMR (300 MHz, CDCl_3) δ 4.15-4.09 (2H, m), 3.70-3.53 (5H, m), 2.27 (2H, t, $J = 7.4$ Hz), 1.93-1.86 (2H, m), 1.59-1.22 (20H, m), 0.87-0.83 (12H, m), 0.02 (6H, d, $J = 4.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 174.3, 82.4, 82.3, 79.4, 74.8, 73.4, 51.4, 37.2, 34.1, 32.7, 32.1, 32.0, 29.6, 29.5, 29.2, 29.1, 29.0, 28.9, 26.2, 26.0, 25.4, 25.2, 24.9, 22.6, 18.2, 14.0, -4.3, -4.6; IR (thin film) 3430 (br), 2930, 2857, 1742, 1597, 1462, 1252, 1096, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{50}\text{O}_5\text{SiNa}$, 481.3325 m/z ($\text{M}+\text{Na}$) $^{+}$; observed, 481.3319 m/z .



Alcohol **V-53** (52 mg, 0.11 mmol) and acetic anhydride (13 μL , 0.14 mmol) were dissolved in pyridine (5 mL) at room temperature. After 15 h stirring at room temperature, 10% HCl solution (aq., 2 mL) was added to workup the reaction. After stirring for 30 min, EtOAc (5 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford an oil material. Purification of the crude material by column chromatography (10% EtOAc in hexanes) afforded acetate **V-54** (47 mg, 85%) as a colorless oil.

Acetylation was used to determine which TBS group was removed and only ^1H and 2D-COSY NMR were examined.

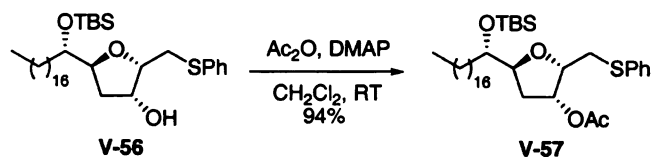
Data for acetate **V-54**: ^1H NMR (500 MHz, CDCl_3) δ 5.24-5.21 (1H, m), 4.08-4.03 (1H, m), 3.89-3.81 (1H, m), 3.63 (3H, s), 3.55-3.47 (1H, m), 2.26 (2H, t, $J = 7.4$ Hz), 2.04 (3H, s), 2.00-1.87 (2H, m), 1.58-1.16 (20H, m), 0.88-0.80 (12H, m), 0.03 (3H, s), 0.01 (3H, s); 174.2, 170.6, 81.1, 79.3, 75.5, 74.7, 51.4, 34.8, 34.0, 32.9, 32.0, 31.8, 29.6, 29.4, 29.1, 29.0, 26.2, 25.9, 25.3, 25.1, 24.8, 22.5, 22.4, 21.0, 18.1, 14.0, 13.9, 1.8, -4.4, -4.6.



To a solution of di-TBS ether **V-55** (310 mg, 0.44 mmol) in THF (10 mL), TBAF

(1.0 M solution in THF, 0.48 mL, 0.48 mmol) was added at room temperature. After stirring for 12 h, saturated NH_4Cl (aq.) solution (10 mL) was added to quench the reaction. EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (10% EtOAc in hexanes) gave the alcohol **V-56** as colorless oil in 92% yield (240 mg).

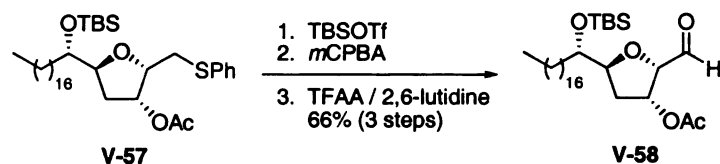
Data for alcohol **V-56**: ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.12 (5H, m), 4.40-4.33 (1H, m), 4.23-4.14 (1H, m), 3.99-3.91 (1H, m), 3.55-3.46 (1H, m), 3.26-3.07 (2H, m), 2.13-2.05 (2H, m), 2.09-2.05 (1H, b), 1.94-1.85 (2H, m), 1.49-1.14 (30H, m), 0.85-0.80 (12H, m), 0.02 (6H, d, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 135.7, 129.2, 128.9, 126.0, 80.9, 80.1, 74.5, 72.4, 60.3, 36.6, 32.8, 32.1, 31.9, 29.8, 29.6, 29.5, 29.3, 25.9, 25.6, 22.6, 20.9, 18.1, 14.1, -4.3, -4.6.



Alcohol **V-56** (186 mg, 0.31 mmol) and acetic anhydride (110 μL , 1.18 mmol) were dissolved in CH_2Cl_2 (6 mL) at room temperature. DMAP (140 mg, 1.18 mmol) was added in one portion. After 12 h of stirring at room temperature, sat. NaHCO_3 solution (aq., 5 mL) was added to workup the reaction. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford an oil material. Purification of the crude material by column chromatography (5% EtOAc in hexanes)

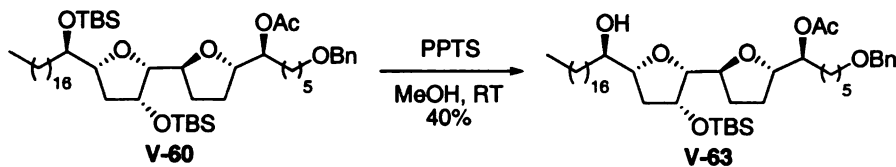
afforded acetate **V-57** (185 mg, 94%) as a colorless oil.

Data for acetate **V-57**: ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.12 (5H, m), 5.38-5.25 (1H, m), 4.18-4.01 (2H, m), 3.56-3.41 (1H, m), 3.24-2.96 (2H, m), 2.07-1.88 (7H, m), 1.38-1.15 (30H, m), 0.90-0.76 (12H, m), 0.02 (6H, d, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 170.2, 135.8, 129.8, 128.9, 126.3, 80.1, 79.8, 74.8, 74.5, 34.8, 32.9, 32.7, 31.9, 29.8, 29.6, 29.5, 29.3, 25.9, 25.4, 22.6, 21.0, 18.1, 14.1, 13.9, -4.4, -4.5.



To a 0 °C solution of sulfide **V-57** (155 mg, 0.25 mmol) in CH_2Cl_2 (3 mL), was added a solution of mCPBA (42 mg, 0.25 mmol) in CH_2Cl_2 (3 mL). After 30 min at 0 °C, the reaction mixture was quenched with sat. NaHCO_3 solution (3 mL) and the aqueous mixture was extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford the sulfoxide as a mixture of stereoisomers. The crude product so obtained was dissolved in CH_2Cl_2 (2 mL), cooled to 0 °C and 2,6-lutidine (0.1 mL, 0.86 mmol) was added. TFAA (0.12 mL, 0.86 mmol) in CH_2Cl_2 (2 mL) was then added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. NaHCO_3 solution and extracted with CH_2Cl_2 . The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to afford a clear oil. This material was taken up in 1:1 acetonitrile-water (9 mL) and solid NaHCO_3 (0.43 g) was added. The reaction mixture was stirred at ambient temperature for 16 h, upon which the solution was diluted with water (5 mL). The aqueous solution was extracted with CH_2Cl_2 (3×5

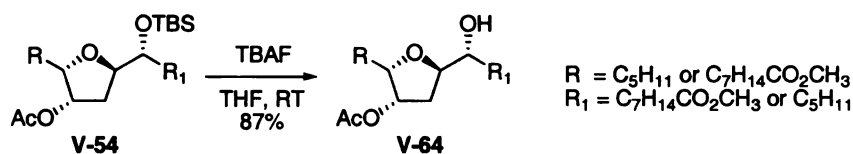
Data for alcohol **V-62**: ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.25 (5H, m), 4.86 (1H, q, $J = 5.8$ Hz), 4.47 (2H, s), 4.20-4.11 (2H, m), 4.10-4.01 (1H, m), 3.96-3.90 (1H, m), 3.76-3.51 (2H, m), 3.42 (2H, t, $J = 6.3$ Hz), 2.20- 2.12 (1H, m), 2.04 (3H, s), 2.00-1.80 (1H, m), 1.78-1.51 (6H, m), 1.42-1.21 (38H, m), 0.87 (12H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 128.3, 127.6, 127.4, 83.8, 80.5, 79.2, 78.9, 75.3, 75.0, 72.9, 70.2, 37.6, 33.3, 31.9, 30.8, 29.8, 29.7, 29.3, 28.5, 27.9, 26.1, 25.9, 25.4, 25.3, 22.7, 21.1, 18.2, 14.1, -4.1, -4.7.



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(5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×6 mL). The organic layers were mixed, dried over Na₂SO₄, and the solvent was evaporated to afford the crude product. Purification by column chromatography (20% EtOAc in hexanes) gave the alcohol **V-63** as colorless oil in 40 % yield (5 mg) and recover S.M. in 22% (3 mg).

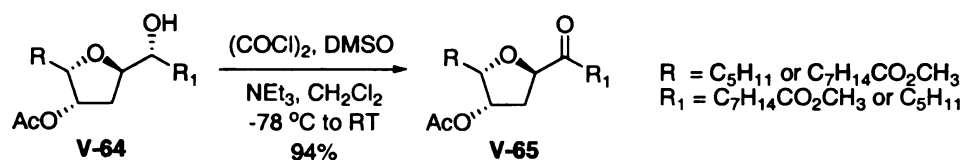
Data for alcohol **V-63**: ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.24 (5H, m), 4.87-4.80 (1H, m), 4.47 (2H, s), 4.37-4.35 (1H, m), 4.18-4.08 (1H, m), 4.11 (1H, q, *J* = 6.3 Hz), 3.89-3.84 (1H, m), 3.59 (1H, dd, *J* = 4.8, 7.3 Hz), 3.48-3.43 (1H, m), 3.43 (2H, t, *J* = 6.6 Hz), 2.13-2.04 (1H, m), 2.04 (3H, s), 2.03-1.90 (2H, m), 1.88-1.59 (1H, m), 1.58-1.48 (6H, m), 1.40-1.21 (36H, m), 0.86-0.83 (12H, m), 0.08 (6H, d, *J* = 9.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 171.0, 138.7, 128.3, 127.6, 127.4, 84.4, 81.1, 79.5, 78.5, 75.5, 73.5, 72.9, 72.8, 70.3, 37.1, 33.8, 31.9, 30.9, 29.8, 29.7, 29.6, 29.3, 28.9, 27.8, 26.1, 25.9, 25.7, 25.3, 22.7, 21.2, 17.9, 14.1, -4.2, -5.2.



To a solution of TBS-ether **V-54** (45 mg, 0.091 mmol) in THF (5 mL), TBAF (1.0 M solution in THF, 0.11 mL, 0.11 mmol) was added at room temperature. After stirring for 15 h, saturated NH₄Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The organic layers were mixed, dried over Na₂SO₄, and the solvent was evaporated to afford the crude product. Purification by column chromatography (20% EtOAc in hexanes) gave the alcohol

V-64 as colorless oil in 81% yield (29 mg).

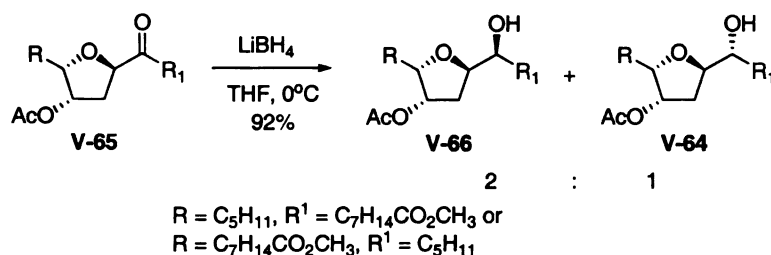
Data for alcohol **V-64**: ^1H NMR (300 MHz, CDCl_3) δ 5.25-5.21 (1H, m), 3.99-3.91 (1H, m), 3.89-3.81 (1H, m), 3.63 (3H, s), 3.40-3.31 (1H, m), 2.26 (2H, t, $J = 7.4\text{Hz}$), 2.02 (3H, s), 1.99-1.89 (2H, m), 1.60-1.14 (20H, m), 0.88-0.81 (3H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 174.1, 170.3, 81.0, 80.2, 75.3, 73.5, 71.9, 70.0, 35.3, 33.8, 33.1, 31.7, 29.2, 28.9, 28.8, 25.9, 25.7, 25.3, 25.1, 24.7, 24.6, 22.4, 22.3, 21.7, 21.5, 20.8, 13.8, 13.9.



To a solution of oxalyl chloride (16 μL , 0.18 mmol) in CH_2Cl_2 (3 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise dry DMSO (26 μL , 0.36 mmol). After 10 min at $-78\text{ }^\circ\text{C}$, a solution of secondary alcohol **V-64** (57 mg, 0.15 mmol) in CH_2Cl_2 (2 mL) was added slowly. The reaction mixture was stirred for another 10 min at $-78\text{ }^\circ\text{C}$ before addition of Et_3N (104 μL , 0.75 mmol). The reaction mixture was allowed to warm to room temperature over 20 min then stirred at the same temperature for 10 min. The reaction was diluted with Et_2O (3 mL) and H_2O (1 mL). The layers were separated and the water layer was washed by Et_2O (3 $\times$ 5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to afford the crude product. Purification by column chromatography (20% EtOAc in hexanes) gave ketone **V-65** (94%, 54 mg) as a colorless oil.

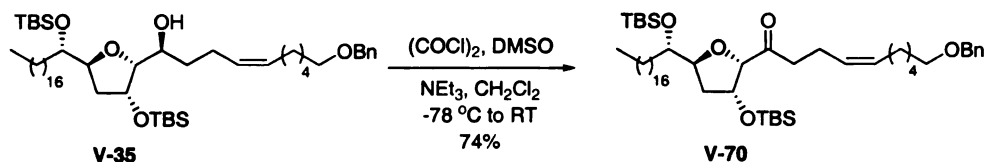
Data for ketone **V-65**: ^1H NMR (300 MHz, CDCl_3) δ 5.34-5.24 (1H, m), 4.54-4.44 (1H, m), 3.91-3.84 (1H, m), 3.62 (3H, s), 2.61-2.47 (2H, m), 2.30-2.18 (4H, m), 2.05

(3H, s), 1.66-1.17 (24H, m), 0.88-0.81 (3H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 174.3, 170.2, 82.9, 82.8, 70.7, 51.5, 36.9, 36.8, 34.0, 33.8, 31.5, 29.7, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 28.5, 25.5, 25.2, 24.8, 24.6, 24.5, 22.4, 20.7, 13.9.



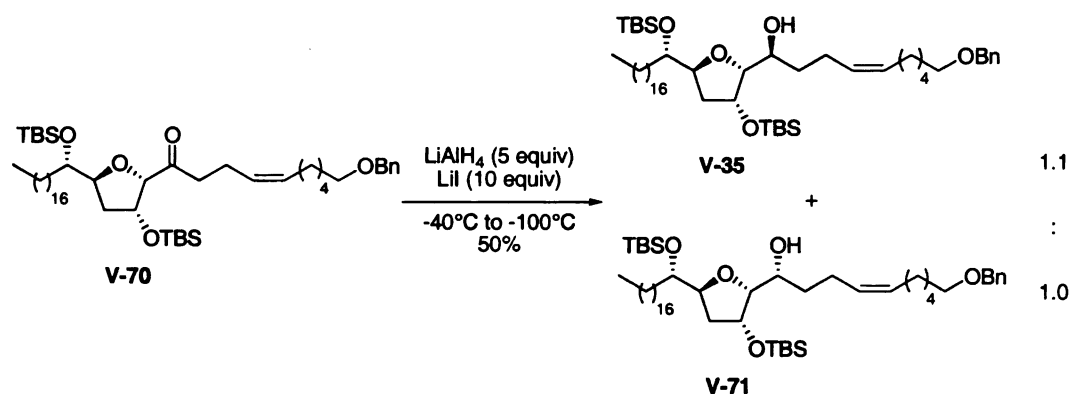
To a solution of ketone **V-65** (39 mg, 0.10 mmol) in THF (5 mL) at 0 °C was added LiBH_4 (2M solution in THF, 0.1 mL, 0.20 mmol). After 2 h at 0 °C, H_2O (2 mL) was added slowly to workup the reaction. The reaction was diluted with Et_2O (3 mL). The layers were separated and the water layer was washed by Et_2O (3×5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to afford the crude product. Purification by column chromatography (20% EtOAc in hexanes) gave the alcohols mixture of **V-66** and **V-64** (92%, 36 mg) as a colorless oil. The diastereomeric ratio was determined by NMR.

Data for the mixture of alcohols of **V-66** and **V-64**: ^1H NMR (500 MHz, CDCl_3) δ 5.27-5.23 (1H, m), 4.96-4.92 (0.33H, m), 4.84-4.78 (0.66H, m), 4.18-4.09 (1H, m), 3.87-3.80 (1H, m), 3.63 (3H, s), 2.26 (2H, t, $J = 7.6$ Hz), 2.11-2.00 (8H, m), 1.66-1.18 (20H, m), 0.84 (3H, t, $J = 6.3$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 174.2, 170.9, 170.5, 170.4, 81.8, 81.7, 81.1, 81.0, 78.0, 77.9, 77.6, 77.4, 77.0, 76.7, 75.1, 75.0, 74.9, 51.4, 35.5, 34.8, 34.0, 31.8, 31.6, 30.8, 30.6, 29.4, 29.2, 29.0, 28.9, 28.8, 26.0, 25.7, 25.2, 25.0, 24.9, 24.8, 22.4, 21.1, 21.0, 13.9.



To a solution of oxalyl chloride (7.4 μL , 0.085 mmol) in CH_2Cl_2 (1 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise dry DMSO (12.1 μL , 0.171 mmol). After 10 min at $-78\text{ }^\circ\text{C}$, a solution of secondary alcohol **V-35** (60 mg, 0.071 mmol) in CH_2Cl_2 (1 mL) was added slowly. The reaction mixture was stirred for another 10 min at $-78\text{ }^\circ\text{C}$ before addition of Et_3N (49.5 μL , 0.35 mmol). The reaction mixture was allowed to warm to room temperature over 10 min. The reaction was diluted with Et_2O (3 mL) and H_2O (1 mL). The layers were separated and the water layer was extracted by Et_2O (3 $\times$ 3 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to afford the crude product. Purification by column chromatography (3% EtOAc in hexanes) gave ketone **V-70** (74%, 44 mg) as a colorless oil.

Data for ketone **V-70**: ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.22 (5H, m), 5.41-5.27 (2H, m), 4.62-4.58 (1H, m), 4.48 (2H, s), 4.40-4.32 (1H, m), 4.27-4.23 (1H, m), 3.65-3.58 (1H, m), 3.44 (2H, t, $J = 6.6\text{ Hz}$), 2.78-2.63 (1H, m), 2.58-2.43 (1H, m), 2.28-2.16 (2H, m), 2.07-1.97 (2H, m), 1.83-1.54 (4H, m), 1.40-1.21 (36H, m), 0.92-0.79 (21H, m), 0.10--0.05 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 211.3, 130.4, 128.3, 127.6, 127.4, 88.4, 82.5, 75.3, 74.5, 72.8, 70.4, 40.7, 37.7, 33.1, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 27.1, 25.9, 25.6, 25.5, 22.6, 20.5, 17.8, 14.1, -4.2, -4.5, -5.0, -5.2.

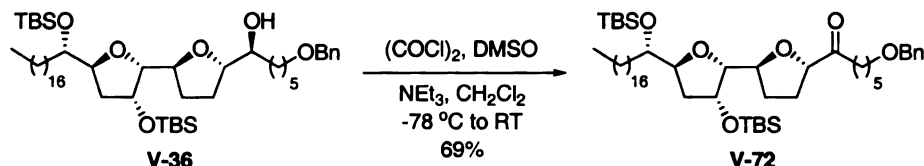


A three-necked flask was charged with ketone **V-70** (43 mg, 0.051 mmol) and Et₂O (3 mL). LiI (68 mg, 0.51 mmol) was added and the resulting mixture was stirred for 5 min at -40 °C before it was cooled to -100 °C and LiAlH₄ (3.9 mg, 0.11 mmol) was added in one portion. After stirring for 1 h, additional LiAlH₄ (5.8 mg, 0.15 mmol) was introduced. The mixture was stirred for 4 h before it was carefully quenched with sat. aqueous Na₂SO₄. The precipitate was filtered off and was carefully washed with EtOAc, the filtrate was evaporated and the residue was purified by column chromatography (3% EtOAc in hexanes) to yield desired chelation-controlled product **V-71** (10 mg, 24%) and its epimer **V-35** (11 mg, 26%) as the colorless oils.

Data for secondary alcohol **V-71**: ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.22 (5H, m), 5.41-5.32 (2H, m), 4.52-4.48 (1H, m), 4.47 (2H, s), 4.16-4.12 (1H, m), 3.82-3.76 (1H, m), 3.64-3.56 (2H, m), 3.43 (2H, t, *J* = 6.6 Hz), 2.66 (1H, d, *J* = 5.1 Hz), 2.29-2.20 (1H, m), 2.18-1.98 (4H, m), 1.88-1.65 (1H, m), 1.62-1.53 (3H, m), 1.52-1.442 (2H, m), 1.39-1.20 (35H, m), 0.93-0.81 (21H, m), 0.10 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 130.1, 129.6, 128.3, 127.6, 127.4, 84.1, 80.1, 74.5, 74.1, 72.8, 70.4, 70.3, 36.8, 34.2, 32.5, 31.9, 29.8, 29.7, 29.6, 29.4,

27.2, 25.9, 25.7, 25.6, 23.4, 22.7, 18.2, 17.9, 14.1, 1.0, -4.2, -4.3, -4.6, -5.1.

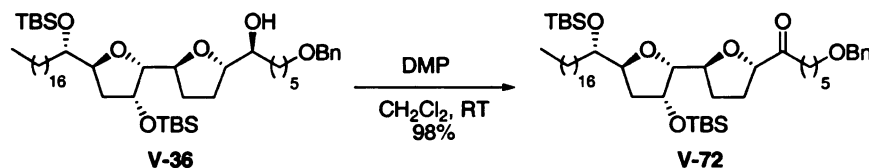
Data for epimer **V-35** was reported in 2006.¹⁵



To a solution of oxalyl chloride (4.9 μL , 0.056 mmol) in CH_2Cl_2 (1 mL) at $-78\text{ }^\circ\text{C}$ was added dropwise dry DMSO (7.9 μL , 0.112 mmol). After 15 min at $-78\text{ }^\circ\text{C}$, a solution of alcohol **V-36** (40 mg, 0.047 mmol) in CH_2Cl_2 (1 mL) was added slowly. The reaction mixture was stirred for another 15 min at $-78\text{ }^\circ\text{C}$ before addition of Et_3N (32.4 μL , 0.23 mmol). The reaction mixture was allowed to warm to room temperature over 10 min. The reaction was diluted with Et_2O (3 mL) and H_2O (1 mL). The layers were separated and the water layer was extracted by Et_2O (3 $\times$ 5 mL). The organic layers were combined, dried over MgSO_4 , and concentrated to afford the crude product. Purification by column chromatography (5% EtOAc in hexanes) gave ketone **V-72** (69%, 27.5 mg) as a colorless oil and starting material **V-36** was recovered in 25% yield (10 mg).

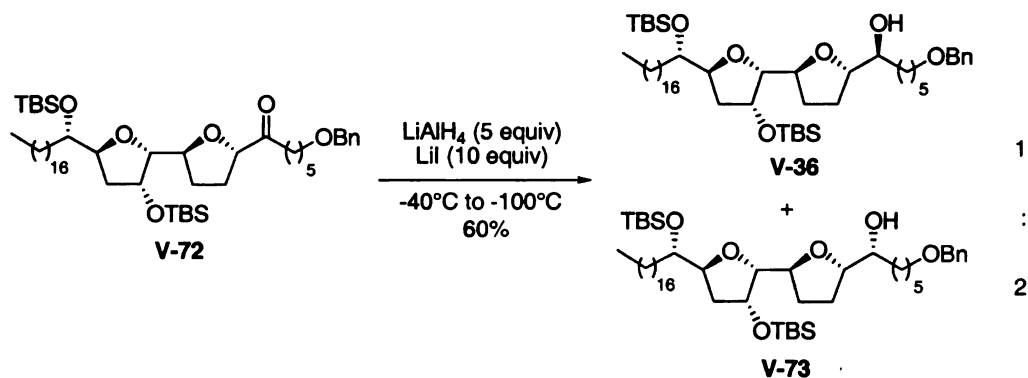
Data for ketone **V-72**: $[\alpha]_{\text{D}}^{20}$ -2.6 (c 2.68, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.38-4.22 (4H, m), 3.80-3.78 (1H, m), 3.67 (1H, dd, J = 7.6, 3.5 Hz), 3.44 (2H, t, J = 6.6 Hz), 2.78-2.49 (2H, m), 2.20-1.93 (2H, m), 1.90-1.81 (3H, m), 1.66-1.51 (5H, m), 1.43-1.21 (34H, m), 0.86-0.84 (21H, m), 0.062-0.032 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 213.5, 138.6, 128.3, 127.6, 127.4, 85.3, 83.6, 80.8, 80.3, 73.9, 73.4, 72.9, 70.2, 37.8, 36.3, 31.9, 31.4, 29.9, 29.7, 29.6, 29.3, 29.2, 28.0, 26.1, 25.9, 25.8, 25.7, 22.8, 22.7, 18.1, 17.9, 14.1, -4.1, -4.3,

-4.6, -5.0; IR (thin film) 3054, 2924, 2851, 1805, 1711, 1603, 1462, 1265, 1057, 837, 738, 704 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{51}\text{H}_{94}\text{O}_6\text{Si}_2$, 876.6927 m/z ($\text{M}+\text{NH}_4$)⁺; observed, 876.6933 m/z .



To a solution of alcohol **V-36** (10 mg, 0.012 mmol) in CH_2Cl_2 (2 mL) at room temperature was added DMP reagent (3.7 mg, 0.014 mmol). After stirring for 15 h at room temperature, sat. NaHCO_3 solution (3 mL) was added to workup the reaction. The layers were separated and the water layer was extracted by CH_2Cl_2 (3×6 mL). The organic layers were combined, dried over Na_2SO_4 , and concentrated to afford the crude product. Purification followed by column chromatography (5% EtOAc in hexanes) gave ketone **V-72** (98%, 9.7 mg) as a colorless oil.

Data for ketone **V-72**: $[\alpha]_{\text{D}}^{20}$ -2.6 (c 2.68, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.38-4.22 (4H, m), 3.80-3.78 (1H, m), 3.67 (1H, dd, J = 7.6, 3.5 Hz), 3.44 (2H, t, J = 6.6 Hz), 2.78-2.49 (2H, m), 2.20-1.93 (2H, m), 1.90-1.81 (3H, m), 1.66-1.51 (5H, m), 1.43-1.21 (34H, m), 0.86-0.84 (21H, m), 0.062-0.032 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 213.5, 138.6, 128.3, 127.6, 127.4, 85.3, 83.6, 80.8, 80.3, 73.9, 73.4, 72.9, 70.2, 37.8, 36.3, 31.9, 31.4, 29.9, 29.7, 29.6, 29.3, 29.2, 28.0, 26.1, 25.9, 25.8, 25.7, 22.8, 22.7, 18.1, 17.9, 14.1, -4.1, -4.3, -4.6, -5.0; IR (thin film) 3054, 2924, 2851, 1805, 1711, 1603, 1462, 1265, 1057, 837, 738, 704 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{51}\text{H}_{94}\text{O}_6\text{Si}_2$, 876.6927 m/z ($\text{M}+\text{NH}_4$)⁺; observed, 876.6933 m/z .

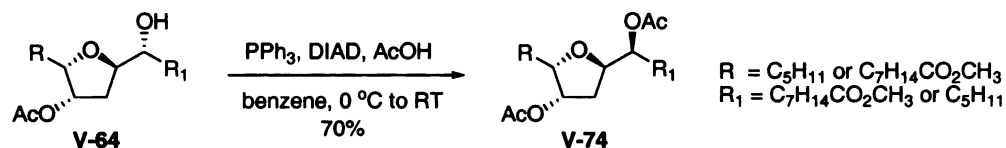


A three-necked flask was charged with ketone **V-72** (57 mg, 0.066 mmol) and Et₂O (3 mL). LiI (89 mg, 0.66 mmol) was added and the resulting mixture was stirred for 5 min at -40 °C before it was cooled to -100 °C and LiAlH₄ (5.0 mg, 0.13 mmol) was added in one portion. After stirring for 1 h, additional LiAlH₄ (7.5 mg, 0.20 mmol) was introduced. The mixture was stirred for 4 h before it was carefully quenched with sat. aqueous Na₂SO₄. The precipitate was filtered off and was carefully washed with EtOAc, the filtrate was evaporated and the residue was purified by column chromatography (10% EtOAc in hexanes) to yield chelation-controlled product **V-73** (21 mg, 36%) and its epimer **V-36** (11 mg, 18%) as the colorless oils.

Data for **V-73**: $[\alpha]_D^{20}$ -31.7 (c 0.42, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.35-4.26 (2H, m), 4.24-4.16 (1H, m), 3.92-3.78 (3H, m), 3.64 (1H, dd, *J* = 7.9, 3.0 Hz), 3.44 (2H, t, *J* = 6.6 Hz), 2.20-2.01 (2H, m), 1.89-1.81 (4H, m), 1.78-1.21 (40H, m), 0.86-0.84 (21H, m), 0.062-0.032 (12H, m); ¹³C NMR (75 MHz, CDCl₃) δ 213.5, 138.6, 128.3, 127.6, 127.4, 86.2, 81.8, 80.6, 79.5, 73.4, 73.2, 72.8, 70.9, 70.4, 36.0, 32.3, 31.9, 30.9, 29.9, 29.7, 29.6, 29.3, 28.6, 26.3, 25.9, 25.7, 22.7, 18.1, 17.9, 14.1, -4.1, -4.4, -4.6, -5.1; IR (thin film) 3418 (br), 2926, 2855, 1464, 1362, 1254, 1076, 939, 835, 775, 696 cm⁻¹; HRMS (ESI) calcd for C₅₁H₉₆O₆Si₂,

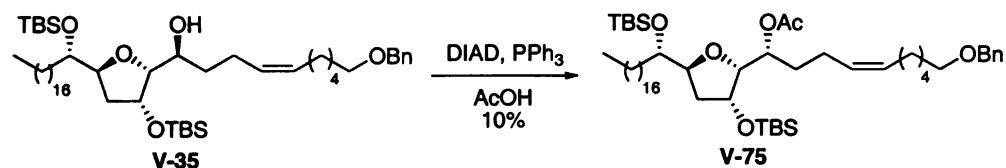
861.6824 m/z ($M+H$)⁺; observed, 861.6828 m/z .

Data for **V-36** was reported in 2006.¹⁵



Alcohol **V-64** (29 mg, 0.075 mmol) was dissolved in benzene (3 mL) followed by the addition of triphenylphosphine (39 mg, 0.15 mmol) and acetic acid (9 μL , 0.15 mmol). The mixture was cooled to 0 $^\circ\text{C}$. Upon addition of diisopropylazodicarboxylate (DIAD) (44 μL , 0.23 mmol) dropwise, the colorless solution turned yellow. After 10 min of stirring at the same temperature, the reaction was brought to room temperature for 15 h. The solvent was removed under reduced pressure to yield a yellow oil. Purification of the crude material by column chromatography (10% EtOAc in hexanes) afforded acetate **V-74** (22 mg, 70%) as a colorless oil.

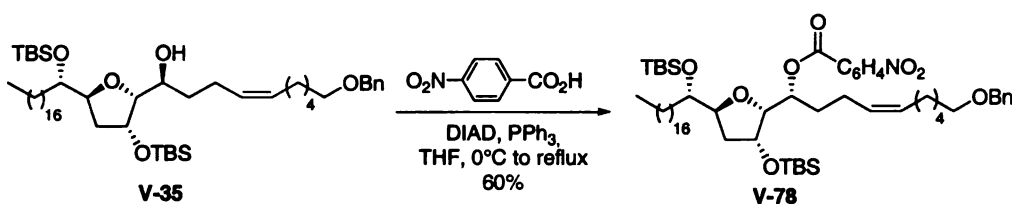
Data for acetate **V-74**: ^1H NMR (500 MHz, CDCl_3) δ 5.28-5.20 (1H, m), 4.56 (1H, dt, $J = 8.6\text{Hz}$, $J = 4.2\text{Hz}$), 4.18-4.08 (1H, m), 3.86-3.78 (1H, m), 3.62 (3H, s), 2.25 (2H, t, $J = 7.4$ Hz), 2.13-1.98 (8H, m), 1.65-1.15 (20H, m), 0.88-0.81 (3H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 174.2, 170.5, 170.4, 81.7, 78.0, 77.9, 75.1, 75.0, 51.4, 34.8, 34.0, 31.7, 31.6, 30.8, 29.3, 29.2, 29.0, 28.9, 26.0, 25.7, 25.2, 24.9, 24.8, 22.4, 21.1, 21.0, 13.9.



Alcohol **V-35** (40 mg, 0.047 mmol) was dissolved in benzene (1 mL) followed by

the addition of triphenylphosphine (18 mg, 0.071 mmol) and acetic acid (5.5 μ L, 0.095 mmol). The mixture was cooled to 0 $^{\circ}$ C. Upon addition of diisopropyl azodicarboxylate (DIAD) (14 μ L, 0.071 mmol) dropwise, the colorless solution turned yellow. After 10 min stirring at the same temperature, the reaction was brought to room temperature for 24 h. The solvent was removed under reduced pressure to give a yellow oil. Purification of the crude material by column chromatography (5% EtOAc in hexanes) afforded acetate **V-75** (4 mg, 10%) as a colorless oil and recover 65% starting material **V-35** (26 mg).

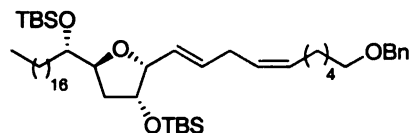
Data for acetate **V-75**: ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.23 (5H, m), 5.37-5.29 (2H, m), 5.03-4.92 (1H, m), 4.50 (2H, s), 4.36-4.30 (1H, m), 4.18-4.08 (1H, m), 3.89-3.80 (1H, m), 3.65-3.58 (1H, m), 3.44 (2H, t, $J = 6.6$ Hz), 2.00 (3H, s), 1.82-1.75 (2H, m), 1.63-1.51 (8H, m), 1.37-1.20 (36H, m), 1.20-0.85 (21H, m), 0.07-0.00 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 171.2, 133.6, 132.8, 130.9, 130.1, 129.6, 129.3, 128.8, 128.4, 80.5, 74.7, 74.4, 72.8, 68.1, 60.4, 38.7, 32.7, 31.9, 30.3, 29.8, 29.7, 29.6, 29.4, 28.9, 25.9, 25.7, 25.6, 25.5, 23.7, 22.7, 21.0, 20.7, 17.9, 14.2, 14.0, 10.9, -3.6, -4.2, -4.5, -4.8.



A solution of alcohol **V-35** (395 mg, 0.47 mmol), *p*-nitrobenzoic acid (0.47 g, 2.81 mmol), and triphenylphosphine (0.74 g, 2.81 mmol) in THF (20 mL) was cooled to 0 $^{\circ}$ C. Diisopropylazodicarboxylate (0.54 mL, 2.81 mmol) was added dropwise over 1

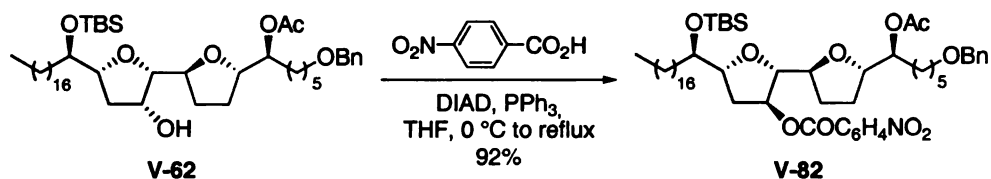
h to keep the reaction temperature at 0 °C. The resulting mixture was heated to reflux for 15 h. After allowing the solution to cool to room temperature, it was diluted with Et₂O (30 mL), and washed with sat. aqueous NaHCO₃ (2×30 mL). The combined aqueous layers were extracted with Et₂O (3×20 mL). The combined organic layers were dried over MgSO₄ and concentrated in reduced pressure. Purification by flash chromatography (3% EtOAc in hexanes) afforded the product **V-78** as a colorless oil (283 mg, 60%).

Data for ester **V-78**: $[\alpha]_D^{20}$ -3.2 (c 3.85, CHCl₃), ¹H NMR (500 MHz, CDCl₃) δ 8.34-8.12 (4H, m), 7.40-7.19 (5H, m), 5.42-5.24 (2H, m), 4.46 (2H, s), 4.45-4.38 (1H, m), 4.24-4.10 (2H, m), 4.06-4.00 (1H, m), 3.64-3.52 (1H, m), 3.39 (2H, t, *J* = 6.6 Hz), 2.25-1.77 (10H, m), 1.37-1.18 (36H, m), 0.95-0.79 (21H, m), 0.07--0.14 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 163.8, 150.4, 136.1, 130.6, 130.1, 128.9, 128.3, 127.6, 127.4, 123.5, 82.8, 80.8, 74.7, 74.5, 72.9, 72.8, 70.3, 37.5, 32.8, 31.9, 30.5, 29.9, 29.7, 29.6, 29.5, 29.3, 27.1, 25.9, 25.7, 25.4, 22.7, 18.2, 17.9, 14.1, -4.2, -4.5, -4.6, -4.9; IR (thin film) 2928, 2857, 1776, 1727, 1531, 1470, 1387, 1348, 1273, 1250, 1103, 949, 835, 775, 721, 698 cm⁻¹; HRMS (ESI) calcd for C₅₈H₉₉NO₈Si₂, 994.6988 *m/z* (M+H)⁺; observed, 994.6993 *m/z*.



Data for elimination byproduct **V-81**: ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.28 (5H, m), 5.62-5.59 (2H, m), 5.41-5.35 (2H, m), 4.48 (2H, s), 4.28-4.16 (3H, m), 3.68-3.62 (1H, m), 3.44 (2H, t, *J* = 6.5 Hz), 2.82-2.76 (2H, m), 2.06-1.75 (3H, m), 1.66-1.50

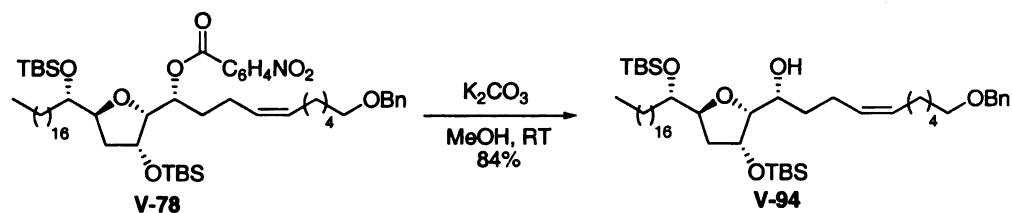
(3H, m), 1.41-1.24 (38H, m), 0.88-0.84 (21H, m), 0.05-0.01 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 132.3, 130.6, 129.7, 128.3, 127.6, 127.4, 126.9, 84.4, 79.8, 75.3, 74.2, 72.8, 70.4, 37.1, 32.1, 31.9, 30.2, 29.9, 29.7, 29.5, 29.4, 27.1, 26.1, 26.0, 25.9, 25.8, 22.7, 18.2, 14.1, -4.3, -4.5, -4.8, -4.9.



A solution of alcohol **V-62** (27 mg, 0.034 mmol), *p*-nitrobenzoic acid (24 mg, 0.14 mmol), and triphenylphosphine (38 mg, 0.14 mmol) in THF (5 mL) was cooled to 0 °C. Diisopropylazodicarboxylate (28 μL , 0.14 mmol) was added dropwise. The resulting mixture was heated to 40 °C for 5 h. After allowing the solution to cool to room temperature, it was diluted with Et_2O (3 mL), and washed with sat. aqueous NaHCO_3 (2 $\times$ 6 mL). The combined aqueous layers were extracted with Et_2O (3 $\times$ 10 mL). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. Purification by flash chromatography (5% EtOAc in hexanes) afforded the product **V-82** as a colorless oil (29 mg, 92%).

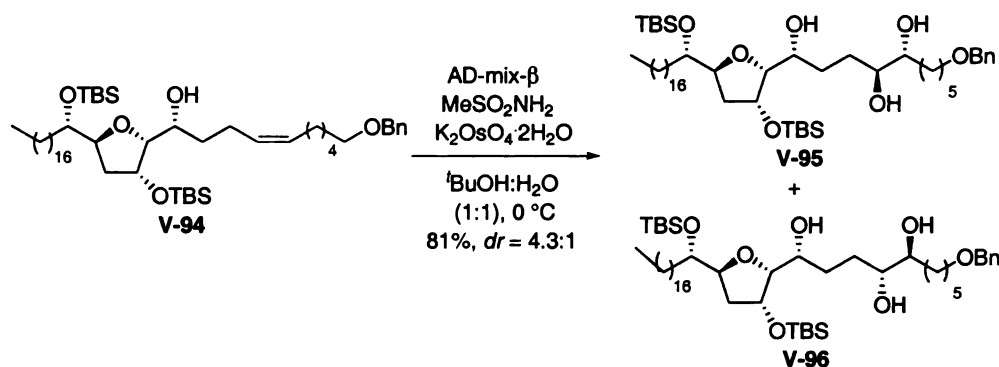
Data for **V-82**: ^1H NMR (300 MHz, CDCl_3) δ 8.26 (4H, dd, J = 32.1, 2.9 Hz), 7.32-7.24 (5H, m), 5.42-5.40 (1H, m), 4.88-4.82 (1H, m), 4.47 (2H, s), 4.23-4.18 (1H, m), 4.11-3.93 (3H, m), 3.65-3.60 (1H, m), 3.43 (2H, t, J = 6.3 Hz), 2.05 (3H, s), 2.00-1.88 (6H, m), 1.62-1.49 (5H, m), 1.42-1.21 (35H, m), 0.88 (12H, s), 0.06 (6H, d, J = 7.1 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 164.2, 150.6, 138.4, 136.4, 135.4, 131.3, 130.7, 128.3, 127.6, 127.5, 123.5, 85.6, 82.5, 80.6, 79.0, 78.6, 75.0, 74.6, 72.9, 70.3, 34.5, 33.3, 31.9, 30.9, 30.4, 29.9, 29.7, 29.6, 29.3, 28.3, 27.6, 26.1, 25.9, 25.3, 25.1,

22.7, 21.1, 14.1, -4.1, -4.7



Ester **V-78** (22 mg, 0.022 mmol) was dissolved in MeOH (1 mL). Solid K_2CO_3 (60 mg) was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with CH_2Cl_2 (2 mL) and washed with sat. NaHCO_3 (3 mL) and H_2O (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried using Na_2SO_4 , the solvent was evaporated, and the crude product was purified by flash column chromatography (5% EtOAc in hexanes). Free alcohol **V-94** was obtained in 84% yield (16 mg) as a clear oil.

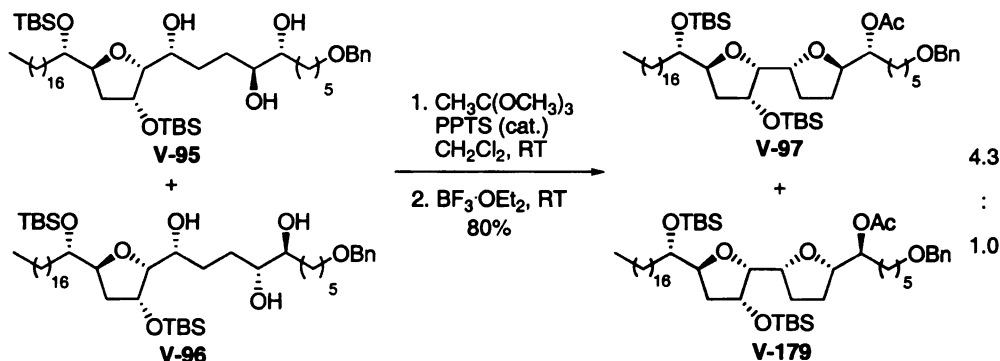
Data for free alcohol **V-94**: $[\alpha]_{\text{D}}^{20}$ -11.3 (c 2.29, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.27 (5H, m), 5.42-5.32 (2H, m), 4.55-4.51 (1H, m), 4.51 (2H, s), 4.20-4.15 (1H, m), 3.84-3.80 (1H, m), 3.66-3.60 (2H, m), 3.47 (2H, t, $J = 6.8$ Hz), 2.65-2.64 (1H, br), 2.31-2.01 (4H, m), 1.89-1.82 (2H, m), 1.80-1.74 (1H, m), 1.66-1.60 (2H, m), 1.58-1.23 (37H, m), 0.96-0.83 (21H, m), 0.13-0.06 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 130.1, 129.6, 128.3, 127.6, 127.4, 84.1, 80.2, 74.6, 74.1, 72.8, 70.5, 70.3, 36.9, 34.2, 32.5, 31.9, 29.9, 29.7, 29.6, 29.4, 27.2, 25.9, 25.7, 25.6, 23.4, 22.7, 18.2, 17.9, 14.1, 1.0, -4.2, -4.6, -5.1; IR (thin film) 3381, 2926, 2855, 1462, 1253, 1063, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{51}\text{H}_{96}\text{O}_5\text{Si}_2$, 845.6875 m/z ($\text{M}+\text{H}^+$); observed, 845.6877 m/z .



AD-mix- β (95.6 mg) was dissolved in 1 : 1 ^tBuOH : H₂O (2 mL). To this clear, orange solution, methane sulfonamide (6.6 mg, 0.069 mmol) and potassium osmate (0.25 mg) were added and stirred until all the solids had dissolved. The solution was then cooled to 0 °C, at which time olefin (52 mg, 0.069 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (0.1 g) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (3 mL) and H₂O (1 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4×5 mL), combined organic layers were dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (15% EtOAc in hexanes). The inseparable mixture of triol **V-95** and its diastereomer **V-96** was isolated in 81% (43.7 mg) combined yield as a colorless oil. The diastereomeric ratio of this SAD reaction was determined after the subsequent cyclization reaction.

Data for the mixture of triols **V-95** and **V-96**: ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.18 (5H, m), 4.52-4.50 (1H, m), 4.46 (2H, s), 4.15-4.09 (1H, m), 3.89-3.82 (1H, m), 3.62-3.52 (4H, m), 3.45 (2H, t, *J* = 6.6 Hz), 1.95-1.82 (4H, m), 1.74-1.52 (8H, m), 1.47-1.18 (34H, m), 0.96-0.84 (21H, m), 0.17-0.02 (12H, m); ¹³C NMR (125 MHz,

CDCl₃) δ 138.6, 128.3, 127.6, 127.5, 83.2, 80.1, 74.6, 74.5, 74.4, 74.1, 72.8, 70.5, 70.3, 36.6, 32.6, 31.9, 31.5, 30.1, 29.8, 29.7, 29.6, 29.3, 27.0, 26.3, 25.9, 25.8, 25.7, 22.7, 18.2, 17.8, 14.1, -4.2, -4.3, -4.6, -5.1; IR (thin film) 3399 (br), 2926, 2855, 1464, 1362, 1254, 1061, 953, 835, 775, 733, 696 cm⁻¹; HRMS (ESI) calcd for C₅₁H₉₈O₇Si₂, 879.6929 *m/z* (M+H)⁺; observed, 879.6912 *m/z*.

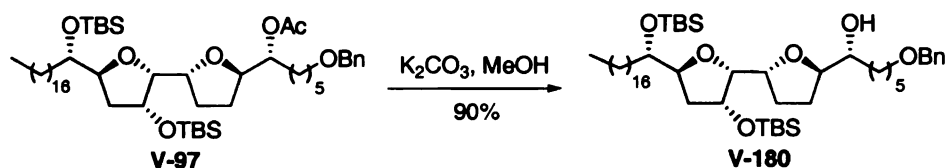


PPTS (4 mg, 0.016 mmol) was added to a solution of triols **V-95** and its diastereomer **V-96** (140 mg, 0.16 mmol) and trimethylortho acetate (21 μL , 0.17 mmol) in CH_2Cl_2 (2 mL) at RT. After complete consumption of the triol (ca. 10 min, as judged by TLC), a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (6 μL , 0.05 mmol) in CH_2Cl_2 (1 mL) was rapidly added to the reaction. After 15 min, the reaction was slowly poured into saturated NaHCO_3 solution (4 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). Combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude product was purified by flash column chromatography (5% EtOAc in hexanes) to furnish bis-THF acetate **V-97** (92 mg, 65%) and its diastereomer **V-179** (21 mg, 15%) as a clear oil.

Major product **V-97**: $[\alpha]_{\text{D}}^{20}$ -5.4 (c 0.75, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.23 (5H, m), 4.81 (1H, dd, J = 11.3, 6.3 Hz), 4.47 (2H, s), 4.36-4.33 (1H, m),

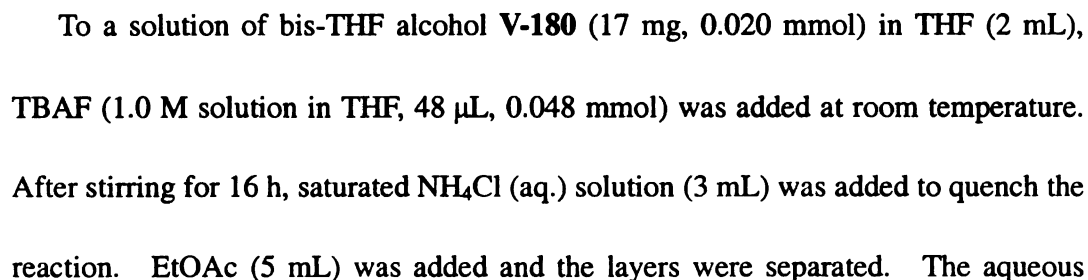
4.13-4.07 (2H, m), 3.97 (1H, dd, $J = 12.4, 7.4$ Hz), 3.59-3.56 (2H, m), 3.43 (2H, t, $J = 6.6$ Hz), 2.02 (3H, s), 1.93-1.70 (4H, m), 1.61-1.54 (6H, m), 1.41-1.24 (36H, m), 0.96-0.84 (21H, m), 0.069-0.033 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 138.6, 128.3, 127.6, 127.4, 85.5, 80.9, 79.4, 77.3, 75.7, 75.0, 72.9, 72.8, 70.3, 37.8, 32.7, 31.9, 31.6, 31.1, 29.8, 29.7, 29.6, 29.3, 28.2, 26.2, 25.9, 25.8, 25.4, 25.2, 22.7, 22.6, 21.2, 18.2, 18.0, 14.1, -4.2, -4.7, -4.9, -5.0; IR (thin film) 2924, 2851, 1740, 1462, 1246, 1061, 835, 777 cm^{-1} ; HRMS (ES) calcd for $\text{C}_{53}\text{H}_{98}\text{O}_7\text{Si}_2$, 903.6929 m/z ($\text{M}+\text{H}$) $^+$; observed, 903.6893 m/z .

Minor product **V-179**: $[\alpha]_{\text{D}}^{20}$ -14.4 (c 1.45, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.81 (1H, dd, $J = 11.4, 6.0$ Hz), 4.47 (2H, s), 4.36-4.33 (1H, m), 4.12-4.05 (1H, m), 4.03-3.96 (1H, m), 3.87-3.80 (1H, m), 3.59-3.41 (4H, m), 2.02 (3H, s), 1.98-1.81 (3H, m), 1.78-1.65 (2H, m), 1.58-1.48 (7H, m), 1.40-1.23 (34H, m), 0.86-0.84 (21H, m), 0.062-0.027 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 138.6, 128.3, 127.6, 127.5, 85.0, 81.0, 79.8, 76.5, 75.9, 75.1, 72.9, 72.8, 70.3, 37.9, 32.7, 31.9, 31.2, 29.9, 29.7, 29.6, 29.4, 29.2, 27.7, 26.2, 25.9, 25.8, 25.4, 25.1, 22.7, 22.6, 21.3, 18.3, 18.1, 14.1, -4.2, -4.7, -5.0, -5.1; IR (thin film) 2927, 2855, 1740, 1462, 1368, 1244, 1067, 939, 835, 775, cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{53}\text{H}_{98}\text{O}_7\text{Si}_2$, 903.6929 m/z ($\text{M}+\text{H}$) $^+$; observed, 903.6943 m/z .



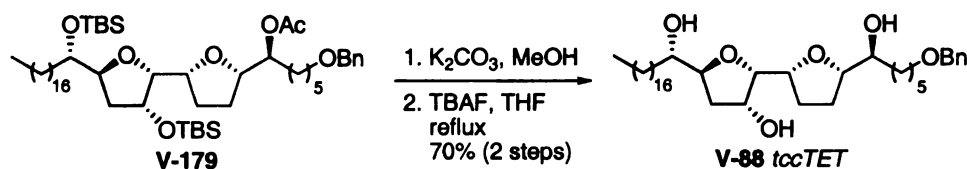
Acetate **V-97** (132 mg, 0.15 mmol) was dissolved in MeOH (3 mL). Solid K_2CO_3 was added to this solution and the heterogeneous mixture was stirred

Data for bis-THF alcohol **V-180**: $[\alpha]_D^{20}$ -7.9 (c 1.05, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.23 (5H, m), 4.47 (2H, s), 4.36-4.33 (1H, m), 4.14-4.07 (2H, m), 3.73 (1H, q, *J* = 6.6 Hz), 3.58-3.54 (2H, m), 3.45 (2H, t, *J* = 6.6 Hz), 3.38-3.33 (1H, m), 2.34 (1H, br), 2.18-2.02 (1H, m), 1.90-1.81 (4H, m), 1.77-1.53 (5H, m), 1.37-1.21 (36H, m), 0.96-0.84 (21H, m), 0.079-0.038 (12H, m); ¹³C NMR (75 MHz, CDCl₃) δ 138.6, 128.3, 127.6, 127.4, 85.3, 82.6, 80.9, 76.5, 75.0, 74.1, 72.9, 72.8, 70.3, 37.9, 33.3, 32.7, 31.9, 31.6, 30.2, 29.8, 29.7, 29.6, 29.3, 28.3, 26.3, 25.9, 25.7, 25.4, 22.7, 22.6, 18.2, 18.0, 14.1, -4.2, -4.6, -4.7, -5.0; IR (thin film) 3347 (br), 2926, 2855, 1736, 1462, 1362, 1256, 1061, 1005, 939, 835, 775, 733, 697 cm⁻¹; HRMS (ESI) calcd for C₅₁H₉₆O₆Si₂, 861.6824 *m/z* (M+H)⁺; observed, 861.6859 *m/z*;



layer was extracted with EtOAc (3×5 mL). The organic layers were mixed, dried over Na₂SO₄, and the solvent was evaporated to afford a crude product. Purification by column chromatography (EtOAc) gave *tctTET* truncated structure **V-83** as white wax in 85% yield (11 mg).

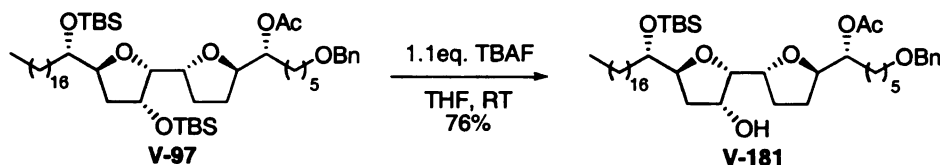
Data for *tctTET* truncated structure **V-83**: ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.42-4.38 (1H, m), 4.32-4.28 (1H, m), 4.08-4.04 (1H, m), 3.94-3.89 (1H, m), 3.77 (1H, t, *J* = 3.4 Hz), 3.74 (3H, br), 3.44 (2H, t, *J* = 6.8 Hz), 3.41-3.35 (2H, m), 2.32-2.29 (3H, m), 2.08-1.95 (4H, m), 1.82-1.78 (1H, m), 1.69-1.58 (6H, m), 1.57-1.23 (32H, m), 0.91-0.80 (3H, m); ¹³C NMR (125 MHz, CDCl₃) δ 138.5, 128.3, 127.6, 127.4, 83.9, 83.1, 81.3, 79.0, 74.4, 74.1, 73.5, 72.8, 70.3, 66.8, 38.7, 34.0, 33.8, 33.3, 31.9, 30.4, 29.7, 29.3, 29.2, 28.9, 27.8, 26.2, 25.6, 25.5, 24.5, 23.8, 22.9, 22.7, 14.1, 11.0; HRMS (ESI) calcd for C₃₉H₆₈O₆Na, 655.4914 *m/z* (M+Na)⁺; observed, 655.4917 *m/z*.



Preparation of *tccTET* truncated structure **V-88** was identical as the preparation of *tctTET* truncated structure **V-83**.

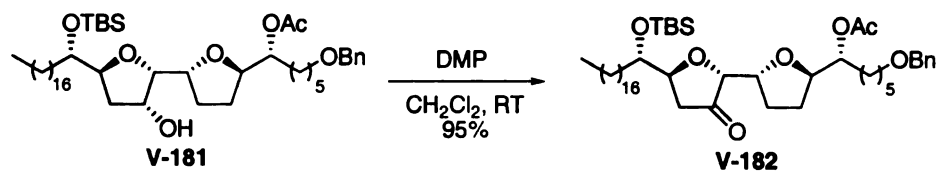
Data for *tccTET* truncated structure **V-88**: ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.25 (5H, m), 4.47-4.17 (3H, m, H14), 4.18-4.08 (2H, m, H12, H16), 3.82-3.73 (1H, m, H9), 3.66 (1H, dd, *J* = 7.3, 2.9 Hz), 3.44 (2H, t, *J* = 6.3 Hz), 3.40-3.34 (2H, m, H17, H8), 3.08-2.92 (1H, br), 2.50-2.41 (1H, br), 2.18-2.04 (1H, m, H11), 2.01-1.98 (1H, m, H15), 1.98-1.79 (3H, m, H10, H11, H15), 1.87-1.61 (1H, m, H10), 1.61-1.57 (2H,

m), 1.57-1.12 (38H, m), 0.85 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 84.4, 83.1, 81.7, 78.1, 74.3, 74.0, 73.2, 72.8, 70.3, 37.3, 33.8, 33.5, 31.9, 29.7, 29.6, 29.5, 29.3, 27.5, 26.2, 25.5, 25.4, 22.7, 14.1; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{69}\text{O}_6$, 633.5094 m/z ($\text{M}+\text{H}$) $^+$; observed, 633.5105 m/z .



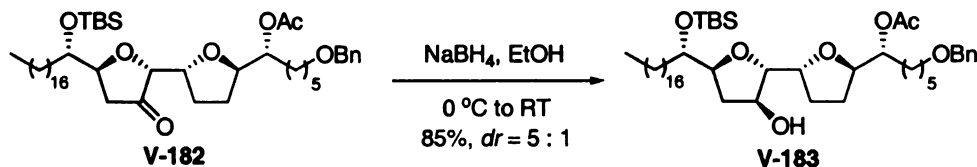
To a solution of bis-TBS ether **V-97** (42 mg, 0.047 mmol) in THF (2 mL), TBAF (1.0 M solution in THF, 49 μL , 0.049 mmol) was added at room temperature. After stirring for 12 h, saturated NH_4Cl (aq.) solution (3 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 6 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (20% EtOAc in hexanes) gave the alcohol **V-181** as colorless oil in 76% yield (28 mg) and recovered starting material **V-97** in 17% (7 mg).

Data for alcohol **V-181**: ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.24 (5H, m), 4.80 (1H, dd, $J = 4.9$ Hz), 4.47 (2H, s), 4.38-4.35 (1H, m), 4.17-4.12 (1H, m), 3.96-3.90 (2H, m), 3.59-3.51 (2H, m), 3.43 (2H, t, $J = 3.8$ Hz), 2.90 (1H, b), 2.20-2.17 (1H, m), 2.06 (3H, s), 2.02-1.89 (2H, m), 1.78-1.56 (4H, m), 1.47-1.23 (36H, m), 0.85-0.84 (12H, m), 0.025 (6H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 172.0, 128.3, 127.6, 127.5, 84.9, 81.4, 80.3, 76.6, 75.6, 75.2, 73.0, 70.2, 53.8, 36.3, 33.0, 31.9, 31.4, 30.2, 29.8, 29.7, 29.6, 29.4, 28.1, 26.0, 25.3, 25.2, 22.7, 21.3, 18.3, 14.1, -4.2, -4.7.



To a solution of alcohol **V-181** (22 mg, 0.028 mmol) in CH_2Cl_2 (5 mL) at room temperature was added DMP reagent (9 mg, 0.034 mmol). After stirring for 15 h at room temperature, sat. NaHCO_3 solution (5 mL) was added to workup the reaction. The layers were separated and the water layer was extracted by CH_2Cl_2 (3×10 mL). The organic layers were combined, dried over Na_2SO_4 , and concentrated to afford the crude product. Purification by column chromatography (20% EtOAc in hexanes) gave ketone **V-182** (95%, 21 mg) as a colorless oil.

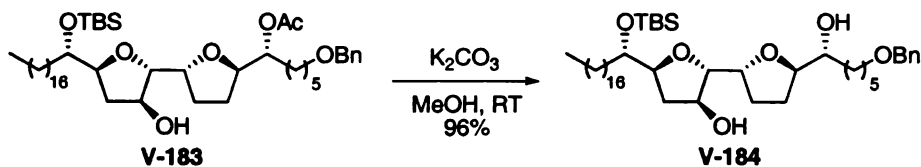
Data for ketone **V-182**: ^1H NMR (300 MHz, CDCl_3) δ 7.32–7.24 (5H, m), 4.84–4.79 (1H, m), 4.46 (3H, s), 4.16 (1H, t, $J = 7.0$ Hz), 4.04 (1H, s), 3.93–3.87 (1H, m), 3.58–3.47 (1H, m), 3.42 (2H, t, $J = 6.6$ Hz), 2.53–2.44 (1H, m), 2.30–2.23 (1H, m), 2.02 (3H, s), 2.00–1.83 (2H, m), 1.70–1.60 (1H, m), 1.59–1.46 (4H, m), 1.45–1.03 (34H, m), 0.95–0.83 (12H, m), 0.05–0.02 (6H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 214.3, 186.4, 128.3, 127.6, 127.5, 81.2, 80.5, 80.2, 75.8, 74.8, 72.9, 70.3, 39.9, 33.1, 31.9, 30.9, 29.8, 29.7, 29.6, 29.3, 27.7, 26.4, 26.1, 25.8, 25.5, 25.2, 22.7, 21.1, 17.9, 14.1, -4.5, -4.7.



A solution of ketone **V-182** (21 mg, 0.027 mmol) in EtOH (2 mL) was added to NaBH_4 (1.5 mg, 0.040 mmol) dissolved in EtOH (2 mL) at -78 $^\circ\text{C}$. Then reaction

Data for alcohol **V-183**: ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.82 (1H, q, $J = 6.6$ Hz), 4.47 (2H, s), 4.20-4.13 (1H, m), 4.00-3.91 (2H, m), 3.76 (1H, q, $J = 7.1$ Hz), 3.56-3.51 (1H, m), 3.43 (2H, t, $J = 6.1$ Hz), 3.0 (1H, b), 2.29-2.22 (1H, m), 2.20-2.05 (1H, m), 2.02 (3H, s), 1.99-1.90 (1H, m), 1.77-1.48 (8H, m), 1.32-1.03 (35H, m), 0.91-0.83 (12H, m), 0.053 (6H, d, $J = 2.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 128.3, 127.6, 127.5, 86.0, 80.5, 80.0, 75.3, 74.7, 72.9, 70.2, 53.8, 35.4, 33.2, 31.9, 30.2, 29.7, 29.6, 29.3, 27.9, 26.1, 26.0, 25.2, 22.7, 21.1, 18.3, 14.1, -4.1, -4.7.

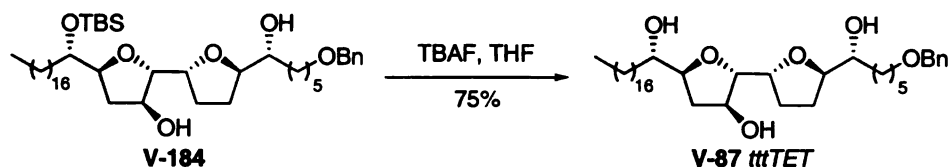
Data for alcohol **V-181**: ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.24 (5H, m), 4.80 (1H, dd, $J = 4.9$ Hz), 4.47 (2H, s), 4.38-4.35 (1H, m), 4.17-4.12 (1H, m), 3.96-3.90 (2H, m), 3.59-3.51 (2H, m), 3.43 (2H, t, $J = 3.8$ Hz), 2.90 (1H, b), 2.20-2.17 (1H, m), 2.06 (3H, s), 2.02-1.89 (2H, m), 1.78-1.56 (4H, m), 1.47-1.23 (36H, m), 0.85-0.84 (12H, m), 0.025 (6H, d, $J = 6.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 172.0, 128.3, 127.6, 127.5, 84.9, 81.4, 80.3, 76.6, 75.6, 75.2, 73.0, 70.2, 53.8, 36.3, 33.0, 31.9, 31.4, 30.2, 29.8, 29.7, 29.6, 29.4, 28.1, 26.0, 25.3, 25.2, 22.7, 21.3, 18.3, 14.1, -4.2, -4.7.



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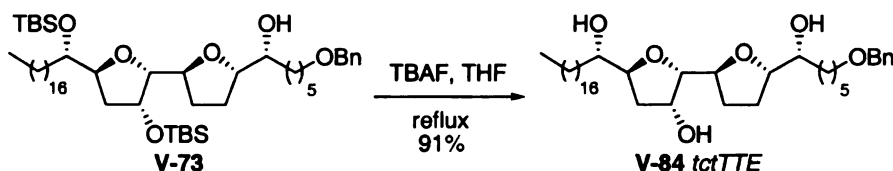
K₂CO₃ was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with CH₂Cl₂ (5 mL) and washed with NaHCO₃ (3 mL) and H₂O (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were dried using Na₂SO₄, the solvent was evaporated, and the crude product was purified by flash column chromatography (30% EtOAc in hexanes). Bis-THF diol **V-184** was obtained in 96% yield (13 mg) as a clear oil.

Data for bis-THF diol **V-184**: ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.24 (5H, m), 4.47 (2H, s), 4.23-4.18 (1H, m), 4.02 (1H, q, *J* = 5.2 Hz), 3.85-3.75 (2H, m), 3.57-3.51 (2H, m), 3.47-3.42 (2H, m), 3.36-3.34 (1H, m), 2.31-2.22 (1H, m), 2.08-2.02 (1H, m), 1.97-1.90 (1H, m), 1.83-1.54 (6H, m), 1.37-1.09 (37H, m), 0.87-0.84 (12H, m), 0.063 (6H, d, *J* = 1.9 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 128.3, 127.6, 127.5, 86.5, 82.9, 80.7, 80.0, 75.3, 74.3, 73.7, 72.8, 70.3, 53.8, 35.9, 33.2, 31.9, 30.1, 29.8, 29.6, 29.3, 27.9, 26.2, 26.0, 25.4, 22.7, 18.3, -4.1, -4.7.



Data for *mTET* truncated structure **V-87**: ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.25 (5H, m), 4.47 (2H, s), 4.26 (1H, quin, *J* = 3.0 Hz, H14), 3.99-3.95 (1H, m, H16), 3.85-3.76 (2H, m, H12, H9), 3.70 (1H, dd, *J* = 6.8, 3.4 Hz), 3.51-3.46 (1H, m, H17), 3.45 (2H, t, *J* = 6.3 Hz), 3.38-3.33 (1H, m, H8), 2.41 (1H, br), 2.40-2.38 (1H, m, H15), 2.11-2.02 (1H, m, H11), 2.00-1.93 (1H, m, H10), 1.81-1.74 (3H, m, H11, H15), 1.68-1.58 (4H, m, H10), 1.52-1.41 (5H, m), 1.39-1.21 (31H, m), 0.86 (3H, t, *J* = 7.3

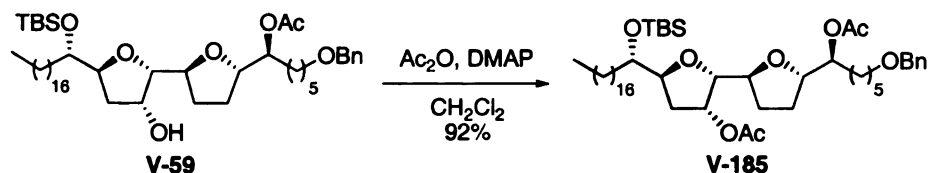
Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 88.0 (C13), 83.1 (C9), 81.1 (C16), 80.2 (C12), 74.4 (C17), 73.9 (C8), 73.8 (C14), 72.9, 70.4, 37.1 (C15), 33.7, 33.4, 31.9, 29.7, 29.6, 29.3, 27.9, 26.2, 25.8, 25.4, 22.7, 14.1; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{68}\text{O}_6\text{Na}$, 655.4914 m/z ($\text{M}+\text{H}$) $^+$; observed, 655.4897 m/z .



To a solution of di-TBS ether **V-73** (20 mg, 0.023 mmol) in THF (2 mL), TBAF (1.0 M solution in THF, 48 μL , 0.048 mmol) was added at room temperature. The reaction temperature was increased to reflux and stirred for 15 h. Saturated NH_4Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (40% EtOAc in hexanes, EtOAc) gave the *tctTTE* truncated structure **V-84** as white wax in 91% yield (13 mg).

Data for *tctTTE* truncated structure **V-84**: ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 4.47 (2H, s), 4.40-4.37 (1H, m), 4.06-4.02 (1H, m), 3.98-3.95 (1H, m), 3.81-3.77 (1H, m), 3.74 (1H, t, J = 3.9 Hz), 3.44 (2H, t, J = 6.6 Hz), 3.40-3.36 (1H, m), 2.11-2.09 (1H, m), 1.99-1.97 (1H, m), 1.95-1.80 (2H, m), 1.80-1.72 (2H, m), 1.64-1.57 (3H, m), 1.52-1.41 (3H, m), 1.40-1.23 (34H, m), 0.86 (3H, t, J = 3.9 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.5, 128.3, 127.6, 127.5, 83.8, 83.3, 81.4, 79.1, 74.4, 74.2, 72.9, 71.5, 70.3, 38.7, 33.1, 32.5, 31.9, 29.7, 29.6, 29.4, 29.1, 26.2, 25.8, 25.6,

24.3, 22.7, 14.1.



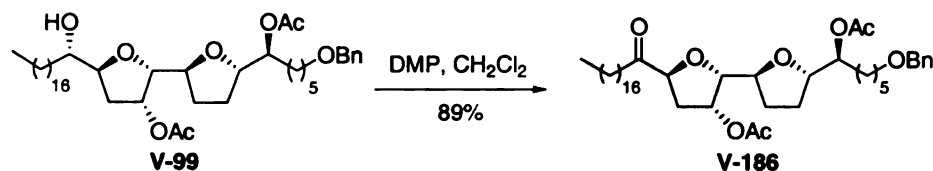
Alcohol **V-59** (33 mg, 0.042 mmol) was dissolved in CH_2Cl_2 (3 mL). DMAP (1.6 mg, 0.013 mmol) was added followed by adding acetic anhydride (4.8 μL , 0.051 mmol) dropwise. The reaction was stirred at room temperature overnight. Saturated NaHCO_3 solution was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (5% EtOAc in hexanes) gave the di-acetate **V-185** as colorless oil in 92% yield (32 mg).

Data for di-acetate **V-185**: $[\alpha]_{\text{D}}^{20}$ -12.3 (c 0.77, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 5.27-5.25 (1H, m), 4.85 (1H, q, J = 5.4 Hz), 4.47 (2H, s), 4.15 (1H, q, J = 5.9 Hz), 4.08-4.05 (1H, m), 3.98 (1H, q, J = 6.3 Hz), 3.82 (1H, dd, J = 6.4, 4.4 Hz), 3.61-3.54 (1H, m), 3.43 (2H, t, J = 6.3 Hz), 2.04 (3H, s), 2.03 (3H, s), 2.00-1.87 (6H, m), 1.71-1.52 (8H, m), 1.48-1.20 (32H, m), 0.98-0.82 (15H, m), 0.046 (6H, d, J = 15.6 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 170.5, 138.6, 128.3, 127.5, 127.4, 82.7, 80.5, 79.6, 78.0, 75.2, 75.0, 74.5, 72.8, 70.2, 34.3, 32.4, 31.9, 30.7, 29.8, 29.6, 29.3, 28.5, 27.7, 26.1, 25.9, 25.6, 25.2, 22.6, 21.1, 18.2, 14.1, -4.3, -4.7; IR (thin film) 2926, 2855, 1742, 1462, 1371, 1242, 1103, 1073, 941, 835, 777, 733, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{49}\text{H}_{86}\text{O}_8\text{Si}$, 831.6170 m/z ($\text{M}+\text{H}$) $^+$; observed, 831.6130 m/z .



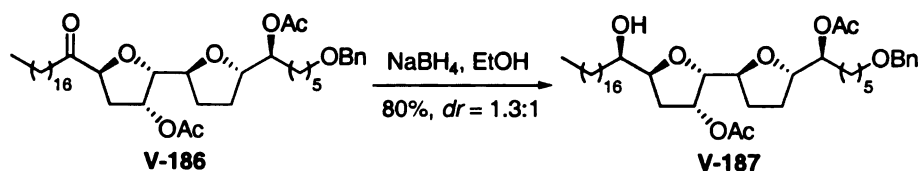
To a solution of TBS ether **V-185** (74 mg, 0.089 mmol) in THF (5 mL), TBAF (1.0 M solution in THF, 0.13 ml, 0.13 mmol) was added at room temperature. The reaction temperature was increased to reflux and stirred for 12 h. Then saturated NH_4Cl (aq.) solution (10 mL) was added to quench the reaction. EtOAc (10 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (30% EtOAc in hexanes) gave alcohol **V-99** as colorless oil in 78% yield (50 mg) and recovered starting material in 7% yield (5 mg).

Data for alcohol **V-99**: $[\alpha]_D^{20}$ -11.4 (c 0.74, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 5.27-5.25 (1H, m), 4.85 (1H, q, $J = 6.0$ Hz), 4.47 (2H, s), 4.18-3.99 (3H, m), 3.88-3.81 (1H, m), 3.43-3.35 (3H, m), 2.04 (3H, s), 2.03 (3H, s), 2.02-1.83 (5H, m), 1.63-1.51 (5H, m), 1.41-1.20 (36H, m), 0.85 (3H, t, $J = 4.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 170.8, 170.3, 138.6, 128.3, 127.6, 127.4, 83.4, 81.4, 79.8, 78.2, 75.1, 73.8, 72.8, 70.2, 35.3, 33.3, 31.9, 30.7, 29.6, 29.5, 29.3, 28.6, 27.8, 26.1, 25.6, 25.2, 22.6, 21.1, 21.0, 14.1; IR (thin film) 3312 (br), 2924, 2855, 1738, 1497, 1466, 1375, 1238, 1111, 1044, 941, 735, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{43}\text{H}_{72}\text{O}_8$, 717.5305 m/z ($\text{M}+\text{H}$) $^+$; observed, 717.5308 m/z .



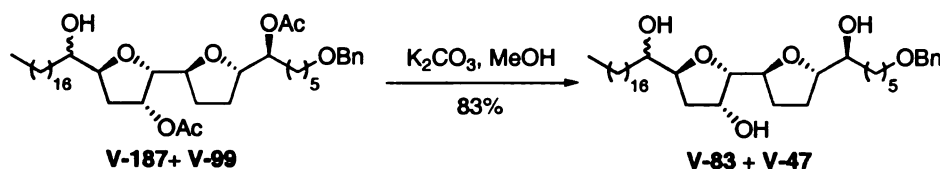
To a solution of alcohol **V-99** (50 mg, 0.070 mmol) in CH_2Cl_2 (5 mL) at room temperature was added DMP reagent (22 mg, 0.084 mmol). After stirring for 15 h at room temperature, sat. NaHCO_3 solution (5 mL) was added to workup the reaction. The layers were separated and the water layer was extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined and dried it over Na_2SO_4 . Removal of solvent followed by column chromatography (20% EtOAc in hexanes) gave ketone **V-186** (89%, 45 mg) as a colorless oil.

Data for ketone **V-186**: $[\alpha]_{\text{D}}^{20}$ -19.0 (c 1.17, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 5.27-5.25 (1H, m), 4.85 (1H, q, $J = 5.5$ Hz), 4.53 (1H, t, $J = 7.9$ Hz), 4.47 (2H, s), 4.21-3.99 (2H, m), 3.93-3.90 (1H, m), 3.44 (2H, t, $J = 6.3$ Hz), 2.62-2.44 (2H, m), 2.31-2.11 (2H, m), 2.04 (3H, s), 2.03 (3H, s), 1.71-1.43 (8H, m), 1.40-1.21 (31H, m), 0.85 (3H, t, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 211.5, 170.8, 170.3, 138.6, 128.3, 127.6, 127.4, 83.8, 82.0, 79.8, 76.6, 75.1, 73.8, 72.8, 70.2, 38.3, 35.5, 31.8, 30.6, 29.6, 29.5, 29.4, 29.3, 29.3, 28.6, 27.7, 26.1, 25.2, 23.0, 22.6, 21.1, 20.9, 14.1; IR (thin film) 2924, 2855, 1805, 1740, 1456, 1372, 1240, 1073, 939, 698 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{43}\text{H}_{70}\text{O}_8$, 715.5149 m/z ($\text{M}+\text{H}$) $^+$; observed, 715.5130 m/z .



A solution of ketone **V-186** (45 mg, 0.063 mmol) in EtOH (2 mL) was added to $NaBH_4$ (3.5 mg, 0.095 mmol) dissolved in EtOH (2 mL) at $-78\text{ }^{\circ}C$. The reaction was slowly warmed to room temperature. After 4 h, the solution was quenched with 10% citric acid (3 mL), partitioned between EtOAc and H_2O , and dried over Na_2SO_4 . The solvent was removed under reduced pressure to give the crude product. Column chromatography (30% EtOAc in hexanes) gave an inseparable alcohol mixture **V-187** and its epimer **V-99** (36 mg) in 80% yield. The diastereomeric ratio was determined after the followed experiments.

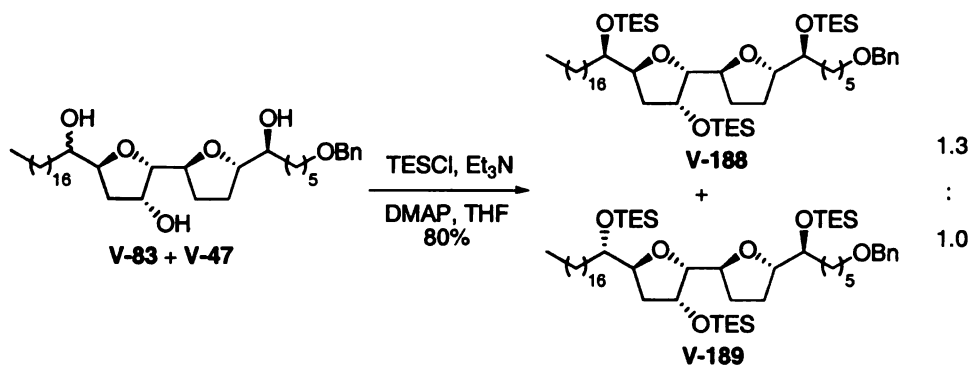
Data for inseparable alcohol mixture **V-187** and its epimer **V-99**: 1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (5H, m), 5.37-5.27 (1H, m), 4.91-4.82 (1H, m), 4.47 (2H, s), 4.20-3.96 (4H, m), 3.84-3.81 (2H, m), 3.48-3.34 (3H, m), 2.30-2.11 (1H, m), 2.045 (3H, s), 2.043 (3H, s), 2.02-1.81 (5H, m), 1.63-1.51 (6H, m), 1.41-1.20 (34H, m), 0.85 (3H, t, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.2, 138.6, 128.3, 127.6, 127.4, 84.1, 83.4, 81.5, 79.7, 78.5, 78.2, 75.1, 73.8, 72.8, 71.1, 70.2, 48.04, 48.02, 35.34, 35.33, 32.1, 31.9, 31.6, 30.5, 29.7, 29.3, 28.6, 28.4, 27.8, 27.7, 26.1, 26.0, 25.6, 25.2, 22.7, 21.2, 21.1, 14.1.



Mixture **V-187** and **V-99** (33 mg, 0.046 mmol) was dissolved in MeOH (3 mL).

Solid K_2CO_3 was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and washed with NaHCO_3 (3 mL) and H_2O (5 mL). The aqueous layer was mixed and extracted with CH_2Cl_2 (3×10 mL). The combine organic layers were dried using Na_2SO_4 , the solvent was evaporated, and the crude product was purified by flash column chromatography (EtOAc). Inseparable truncated structures **V-83** and **V-47** was obtained in 83% yield (25 mg) as a clear oil.

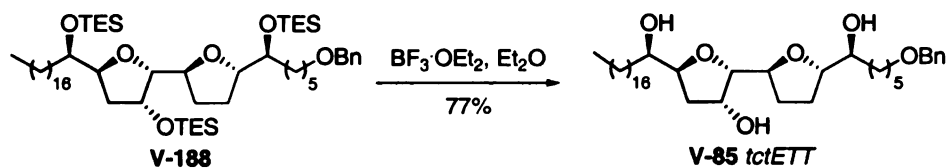
Data for the inseparable truncated structure mixture of **V-83** and **V-47**: ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 4.47 (2H, s), 4.41-4.38 (1H, m), 4.32-4.17 (1.6H, m), 4.09-4.03 (0.4H, m), 3.95-3.84 (1.6H, m), 3.83 (0.6H, t, $J = 3.9$ Hz), 3.76 (0.5H, t, $J = 3.5$ Hz), 3.76 (0.3H, br), 3.44 (2H, t, $J = 6.3$ Hz), 3.39-3.37 (1.5H, m), 3.28 (0.5H, br), 2.16-2.03 (2H, m), 2.00-1.78 (3H, m), 1.71-1.58 (3H, m), 1.57-1.40 (2H, m), 1.40-1.21 (36H, m), 0.86 (3H, t, $J = 6.8$ Hz).



To a solution of the triols mixture **V-83** and **V-47** (24 mg, 0.038 mmol) in THF (5 mL) triethyl amine (0.13 mL) was added followed by triethylsilyl chloride (57 μL , 0.34 mmol) and DMAP (5 mg, 0.019 mol) at ambient temperature. The reaction was stirred under N_2 for 3 h after which time was quenched by adding saturated

NaHCO₃ solution (5 mL). The aqueous layer was extracted with 1 : 5 EtOAc : hexanes (3×10 mL) to afford crude oil which was purified by column chromatography (3% EtOAc in hexanes) providing the separable fully protected triol **V-188** (17 mg, 46%) and its diastereomer **V-189** (12 mg, 34%).

Data for **V-188**: ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.34-4.30 (1H, m), 4.19-4.11 (2H, m), 3.91-3.80 (2H, m), 3.69-3.62 (1H, m), 3.60 (1H, dd, *J* = 7.4, 3.6 Hz), 3.44 (2H, t, *J* = 6.6 Hz), 2.07-1.92 (1H, m), 1.82-1.71 (1H, m), 1.62-1.41 (5H, m), 1.39-1.20 (39H, m), 0.98-0.81 (21H, m), 0.61-0.53 (12H, m); Data for **V-189**: ¹H NMR (300 MHz, CDCl₃) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.32-4.22 (2H, m), 4.18-4.10 (1H, m), 3.94-3.90 (1H, m), 3.78-3.66 (2H, m), 3.60 (1H, dd, *J* = 7.4, 3.8 Hz), 3.44 (2H, t, *J* = 6.6 Hz), 2.02-1.91 (4H, m), 1.71-1.40 (9H, m), 1.38-1.23 (33H, m), 0.98-0.81 (21H, m), 0.61-0.53 (12H, m).



TES ether **V-188** (10 mg, 0.010 mmol) was dissolved into Et₂O (2 mL). BF₃·OEt₂ (0.6 μL, 0.005 mmol) in CH₂Cl₂ (1 mL) solution was added dropwise at room temperature. After 2 h, sat. NaHCO₃ solution was added to quench the reaction. EtOAc was used to extract the aqueous layer (3×5 mL) and the solution was concentrated under reduced pressure. Purification by column chromatography (EtOAc) gave *tctETT* truncated structure **V-85** (77%, 6 mg) as a colorless oil.

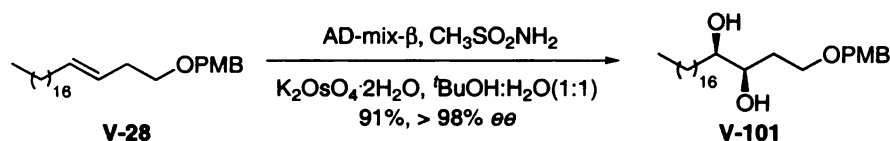
Data for *tctETT* truncated structure **V-85**: ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.23 (5H, m), 4.47 (2H, s), 4.42-4.40 (1H, m), 4.28-4.24 (1H, m), 4.22-4.17 (1H, m),

Data for ketone **V-190**: $[\alpha]_D^{20} +25.6$ (c 0.78, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.28 (5H, m), 4.86-4.82 (1H, m), 4.50 (2H, s), 4.41-4.38 (1H, m), 4.25-4.22 (1H, m), 4.05-4.00 (1H, m), 3.86 (1H, d, $J = 2.2$ Hz), 3.64-3.61 (1H, m), 3.46 (2H, t, $J = 6.6$ Hz), 2.52-2.47 (1H, m), 2.34-2.29 (1H, m), 2.04 (3H, s), 2.04-1.97 (2H, m), 1.70-1.43 (7H, m), 1.40-1.23 (35H, m), 0.93-0.83 (12H, m), 0.065 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 214.1, 170.8, 138.7, 128.3, 127.6, 127.5, 82.0, 80.4, 79.3, 78.0, 75.6, 74.9, 72.9, 70.3, 39.4, 33.2, 31.9, 30.8, 29.8, 29.7, 29.6, 29.4, 28.0, 27.6, 26.1,

Data for **V-59**: $[\alpha]_D^{20}$ -12.2 (c 0.84, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 4.88-4.81 (1H, m), 4.47 (2H, s), 4.40-4.33 (1H, m), 4.31-4.28 (1H, m), 4.19-4.06 (2H, m), 3.79-3.76 (1H, m), 3.58-3.47 (1H, m), 3.44 (2H, t, $J = 6.6$ Hz), 2.04 (3H, s), 2.03-1.88 (2H, m), 1.80-1.62 (1H, m), 1.59-1.43 (4H, m), 1.40-1.21 (39H, m), 0.86-0.79 (12H, m), 0.037 (6H, d, $J = 15.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 138.6, 128.3, 127.6, 127.4, 81.9, 81.3, 80.7, 78.7, 75.1, 75.0, 74.3, 72.8, 70.2, 38.3, 33.2, 31.9, 30.9, 29.8, 29.7, 29.6, 29.3, 28.7, 27.6, 26.1, 25.9, 25.2, 25.1, 22.7, 21.1, 18.2, 14.1, -4.3, -4.6; IR (thin film) 3461 (br), 2926, 2855, 1740, 1464, 1370, 1244, 1103, 1057, 966, 835, 777, 733, 698 cm^{-1} .

Acetate **V-100** (14 mg, 0.018 mmol) was dissolved in MeOH (2 mL). Solid K_2CO_3 was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and washed with $NaHCO_3$ (3 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combine organic layers were dried using Na_2SO_4 , the solvent evaporated, and the crude product was purified by flash column chromatography (30% EtOAc in hexanes). Diol **V-191** was obtained in 98% yield (13 mg) as a clear oil.

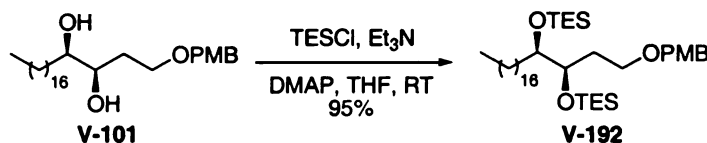
m), 0.86 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.5, 88.1, 83.1, 81.1, 80.2, 74.4, 73.9, 73.8, 72.9, 70.4, 37.1, 33.7, 33.4, 31.9, 29.7, 29.6, 29.4, 27.9, 26.2, 25.8, 25.4, 22.7, 14.1; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{68}\text{O}_6\text{Na}$, 655.4914 m/z ($\text{M}+\text{H}$) $^+$; observed, 655.4891 m/z .



A round flask was charged with AD mix- β (6.5 g). $t\text{BuOH}$ (22 mL) and H_2O (22 mL) were added followed by methanesulfonamide (0.44 g) and $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (9 mg). This mixture was stirred until a orange clear solution was obtained, which was cooled to 0 °C upon which the olefin **V-28** (2 g, 4.65 mmol) was added in one portion. The reaction was vigorously stirred at 0 °C for 20 h after which time sodium sulfite (7 g) was added at the same temperature. The mixture was then warmed to room temperature and stirred for 45 min, then diluted with EtOAc (30 mL) and washed with H_2O (15 mL). The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL), combined organic layers were dried (Na_2SO_4) and concentrated to yield a crude oil which was purified by flash column chromatography (20% EtOAc in hexanes) to yield diol **V-101** (1.01 g, 91%, > 98% ee).

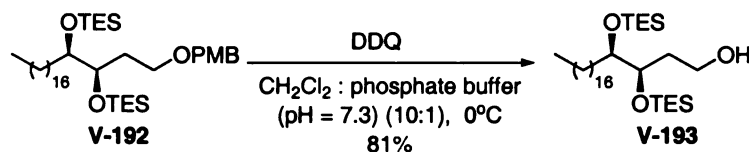
Data for diol **V-101**: $[\alpha]_{\text{D}}^{20} +1.7$ (c 0.70, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.20 (2H, d, $J = 8.0$ Hz), 6.83 (2H, d, $J = 7.7$ Hz), 4.41 (2H, s), 3.75 (3H, s), 3.64-3.58 (3H, m), 3.36-3.34 (1H, m), 3.21 (1H, b), 2.65 (1H, b), 1.78-1.72 (2H, m), 1.42-1.38 (2H, m), 1.24-1.19 (30H, m), 0.84 (3H, t, $J = 6.4$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 129.3, 113.7, 74.2, 72.9, 68.0, 60.3, 55.1, 33.4, 33.1, 31.8, 29.6, 29.3, 25.7, 22.6, 20.9,

14.1; IR (thin film) 3354 (br), 3476, 2918, 2849, 1613, 1514, 1470, 1369, 1250, 1076, 1032 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{52}\text{O}_4$, 487.3763 m/z ($\text{M}+\text{Na}$)⁺; observed, 487.3778 m/z .



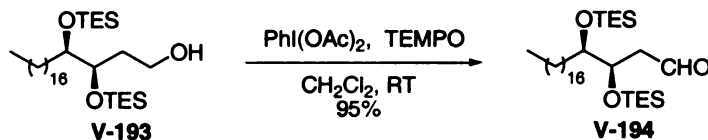
To a solution of the diol **V-101** (1.0 g, 2.16 mmol) in THF (20 mL), triethyl amine (7.4 mL) was added followed by triethylsilyl chloride (2.3 mL, 13.6 mmol) and DMAP (0.11 g, 0.91 mmol) at ambient temperature. The reaction was stirred under N_2 for 3 h after which time it was quenched by adding saturated NaHCO_3 solution (30 mL). The aqueous layer was extracted with 1 : 5 EtOAc : hexanes (3×10 mL) to afford crude oil which was purified by column chromatography (35 : 1 hexanes : EtOAc) providing the fully protected diol **V-192** (1.41 g, 95%).

Data for TES protected diol **V-192**: $[\alpha]_{\text{D}}^{20} +21.8$ (c 1.35, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.23 (2H, d, $J = 7.9$ Hz), 6.84 (2H, d, $J = 8.2$ Hz), 4.40 (2H, s), 3.78 (3H, s), 3.74-3.70 (1H, m), 3.53-3.47 (3H, m), 2.03-1.97 (1H, m), 1.59-1.45 (2H, m), 1.24-1.19 (31H, m), 0.95-0.84 (21H, m), 0.59-0.50 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 129.1, 113.6, 75.2, 72.3, 67.5, 55.2, 53.8, 31.9, 30.5, 30.1, 29.8, 29.7, 29.4, 26.6, 22.7, 14.1, 6.9, 6.8, 5.1, 5.0; IR (thin film) 2955, 2924, 2876, 2855, 1614, 1514, 1464, 1414, 1377, 1302, 1248, 1172, 1100, 1041, 1007 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{41}\text{H}_{80}\text{O}_4\text{Si}_2$, 693.5973 m/z ($\text{M}+\text{H}$)⁺; observed, 693.5667 m/z .



To a 0 °C solution of PMB ether **V-192** (1.5 g, 2.2 mmol) in 52 mL of CH₂Cl₂ : phosphate buffer (10 :1), DDQ (0.76 g, 3.3 mmol) was added in one portion. After stirring the reaction under N₂ at the same temperature for 90 min, saturated NaHCO₃ solution (20 mL) was added. The mixture was warmed to ambient temperature and carefully extracted with CH₂Cl₂ (3×20 mL) so as to avoid emulsions. The combined organic layers were dried (Na₂SO₄), concentrated and the crude oil was purified by flash column chromatography (5% EtOAc in hexanes) to afford 1.04 g (81%) of primary alcohol **V-193**.

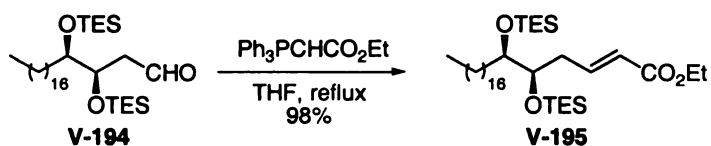
Data for primary alcohol **V-193**: [α]_D²⁰ +24.2 (c 1.09, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 3.77-3.56 (4H, m), 2.96 (1H, b), 1.95-1.91 (1H, m), 1.64-1.60 (2H, m), 1.55-1.23 (30H, m), 0.97-0.91 (18H, m), 0.86 (3H, t, *J* = 6.2 Hz), 0.64-0.52 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 75.7, 75.0, 60.9, 34.5, 31.9, 30.3, 29.8, 29.7, 29.6, 29.4, 26.6, 22.7, 14.1, 6.8, 4.9; IR (thin film) 3405 (br), 2928, 2855, 1458, 1415, 1379, 1265, 1078, 1007, 895 cm⁻¹; HRMS (ESI) calcd for C₃₃H₇₂O₃Si₂, 573.5098 *m/z* (M+H)⁺; observed, 573.5127 *m/z*.



To a solution of alcohol **V-193** (1.0 g, 1.75 mmol) in CH₂Cl₂ (5 mL) at room temperature, bisacetoxyiodo benzene (0.68 g, 2.1 mmol) was added. After addition of TEMPO (28 mg, 0.1 mmol) the clear orange solution was stirred at RT for 2 h.

The reaction was then diluted with CH₂Cl₂ (5 mL) and treated with saturated sodium sulfite solution until it became colorless. Upon separation of the layers aqueous layer was extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (3% EtOAc in hexanes) to furnish aldehyde **V-194** as a colorless oil (0.95 g, 95%).

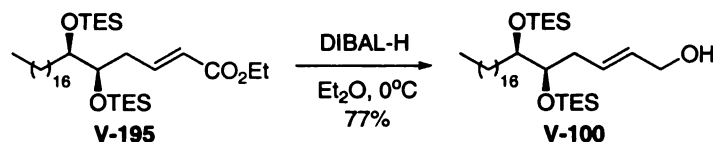
Data for aldehyde **V-194**: $[\alpha]_D^{20} +17.8$ (c 1.14, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 9.76 (1H, s), 4.21-4.15 (1H, m), 3.62-3.58 (1H, m), 2.69-2.62 (1H, m), 2.49-2.40 (1H, m), 1.64-1.60 (1H, m), 1.57-1.45 (1H, m), 1.23-1.13 (30H, m), 0.99-0.83 (21H, m), 0.61-0.52 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 201.9, 74.8, 70.5, 45.8, 31.9, 30.3, 29.8, 29.7, 29.6, 29.4, 26.5, 22.7, 14.1, 6.9, 6.8, 5.0, 4.9; IR (thin film) 3418 (br), 3059, 2926, 2876, 2855, 2255, 1726, 1653, 1636, 1458, 1420, 1375, 1287, 1101, 1009 cm⁻¹; HRMS (ESI) calcd for C₃₃H₇₀O₃Si₂, 571.4942 *m/z* (M+H)⁺; observed, 571.4921 *m/z*.



A solution of aldehyde **V-194** (0.99 g, 1.74 mmol) and (carbethoxymethylene)triphenylphosphorane (1.51g, 4.34 mmol) in THF (16 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 (2% EtOAc in hexanes) to afford α , β -unsaturated *trans*-ester **V-195** as a yellow oil (1.09 g, 98%).

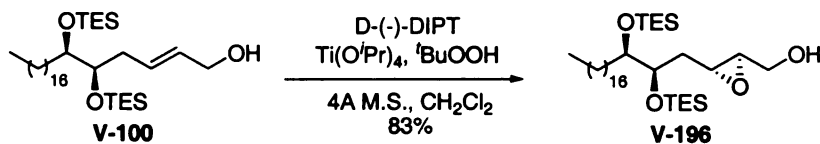
Data for α , β -unsaturated *trans*-ester **V-195**: $[\alpha]_D^{20} +26.8$ (c 1.14, CHCl₃), ¹H NMR

(300 MHz, CDCl₃) δ 6.96 (1H, quartate), 5.80 (1H, d, J = 15.7 Hz), 4.17 (2H, q, J = 6.3 Hz), 3.68-3.62 (1H, m), 3.57-3.53 (1H, m), 2.55-2.47 (1H, m), 2.21-2.14 (1H, m), 1.64-1.59 (1H, m), 1.46-1.12 (31H, m), 0.96-0.83 (24H, m), 0.60-0.50 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 166.5, 147.8, 122.8, 75.3, 74.7, 60.0, 33.9, 31.9, 30.0, 29.8, 29.7, 29.6, 29.4, 26.6, 22.7, 14.2, 14.1, 6.9, 6.8, 5.1, 4.9; IR (thin film) 2955, 2924, 2876, 2855, 1727, 1655, 1458, 1414, 1368, 1318, 1262, 1240, 1167, 1098, 1005, 849 cm⁻¹; HRMS (ESI) calcd for C₃₇H₇₆O₄Si₂, 641.5360 m/z (M+H)⁺; observed, 641.5336 m/z .



To a 0 °C solution of ester **V-195** (1.08 g, 1.69 mmol) in diethyl ether (18 mL), DIBAL-H (5.4 mmol, 3.6 mL of 1.5 M solution in toluene) was added under N₂. After stirring for 30 min. at the same temperature, saturated potassium-sodium tartrate solution (17 mL) was added and the mixture was brought to RT. Et₂O (18 mL), H₂O (4 mL) and glycerol (1 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 (2×10 mL). The combined organic layers were dried (MgSO₄), concentrated and the crude product after chromatographic purification (5% EtOAc in hexanes) afforded allylic alcohol **V-100** as a colorless oil (0.77 g, 77%). Data for allylic alcohol **V-100**: [α]_D²⁰ +28.3 (c 1.12, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 5.73-5.65 (2H, m), 4.10-4.07 (2H, m), 3.58-3.56 (2H, m), 2.42-2.38 (1H, m), 2.06-1.99 (1H, m), 1.61-1.58 (1H, m), 1.46-1.24 (31H, m), 0.97-0.84 (21H, m),

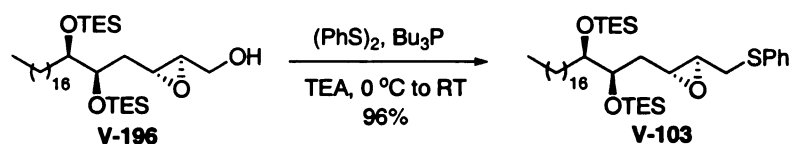
0.61-0.50 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 131.4, 130.6, 75.4, 63.9, 33.6, 31.9, 31.6, 30.1, 29.8, 29.7, 29.6, 29.4, 26.6, 22.7, 14.1, 6.9, 6.8, 5.1, 5.0; IR (thin film) 3328 (br), 2955, 2924, 2876, 2855, 1458, 1238, 1098, 1005, 972, 725 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{75}\text{O}_3\text{Si}_2$, 599.5255 m/z ($\text{M}+\text{H}$) $^+$; observed, 599.5249 m/z .



A two necked round bottom flask charged with 4 Å mol. sieves (0.8 g) and CH_2Cl_2 (7 mL) was cooled to $-20\text{ }^\circ\text{C}$. To this, $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.38 mL, 1.29 mmol) and a CH_2Cl_2 solution of D-(-)-DIPT (0.33 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 $-30\text{ }^\circ\text{C}$, $t\text{BuOOH}$ (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 **V-100** (0.77 g, 1.29 mmol) in CH_2Cl_2 (5 mL) was added via a syringe pump over 45 min. The reaction was warmed to $-20\text{ }^\circ\text{C}$, 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 **V-196** was isolated in 83% yield after purification by column chromatography (5% EtOAc in hexanes).

Data for epoxy alcohol **V-196**: $[\alpha]_{\text{D}}^{20} +42.1$ (c 1.43, CHCl_3), ^1H NMR (300 MHz,

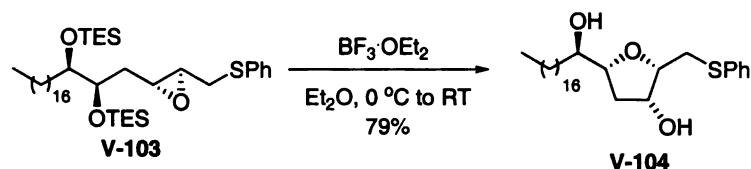
CDCl₃) δ 3.95-3.88 (1H, m), 3.84-3.78 (1H, m), 3.62-3.54 (2H, m), 3.08-3.03 (1H, m), 2.93-2.91 (1H, m), 1.74-1.59 (4H, m), 1.56-1.16 (30H, m), 0.97-0.88 (18H, m), 0.85 (3H, dd, J = 6.6, 3.8 Hz), 0.63-0.52 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 74.9, 72.6, 61.6, 59.2, 53.9, 32.8, 31.9, 31.6, 29.9, 29.8, 29.7, 29.6, 29.3, 26.6, 22.7, 14.1, 6.9, 6.8, 5.1, 5.0; IR (thin film) 3502 (br), 2924, 2876, 2855, 1458, 1238, 1010, 1009, 725 cm⁻¹; HRMS (ESI) calcd for C₃₅H₇₅O₄Si₂, 615.5204 m/z (M+H)⁺; observed, 615.5234 m/z .



To a solution of diphenyldisulfide (0.7 g, 3.2 mmol) in triethylamine (2.5 mL), was added tributylphosphine (0.78 mL, 3.2 mmol) at ambient temperature under N₂. This solution was cooled to 0 °C and to it was cannulated a pre-cooled solution of epoxy alcohol **V-196** (0.65 g, 1.06 mmol) in Et₃N. The reaction was warmed to ambient temperature over 6 h. The reaction mixture was quenched with water (5 mL) and the aqueous layer was extracted with EtOAc (3×15 mL). The combined EtOAc extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes to 2% EtOAc in hexanes) to afford thiophenyl **V-103** as a colorless oil (0.72 g, 96%).

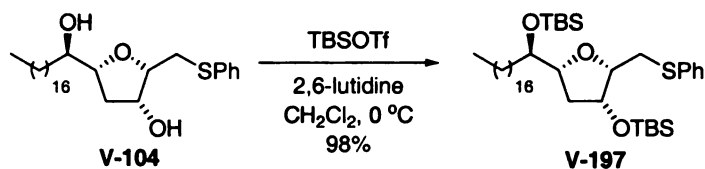
Data for thiophenyl **V-103**: [α]_D²⁰ +26.0 (c 1.22, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.38 (2H, m), 7.30-7.17 (3H, m), 3.81-3.75 (1H, m), 3.62-3.54 (1H, m), 3.12-3.07 (1H, m), 2.99-2.89 (2H, m), 2.84-2.81 (1H, m), 1.61-1.44 (4H, m), 1.24-1.11 (30H, m), 0.96-0.84 (21H, m), 0.61-0.52 (12H, m); ¹³C NMR (125 MHz,

CDCl₃) δ 135.5, 130.3, 128.9, 126.6, 74.9, 72.5, 57.7, 57.1, 36.6, 32.9, 31.9, 31.6, 29.9, 29.8, 29.7, 29.6, 29.4, 26.6, 22.7, 14.1, 6.9, 5.1, 5.0; IR (thin film) 2955, 2924, 2876, 2855, 1653, 1458, 1416, 1238, 1094, 1005, 739 cm⁻¹; HRMS (ESI) calcd for C₄₁H₇₉O₃SSi₂, 707.5289 *m/z* (M+H)⁺; observed, 707.5269 *m/z*.



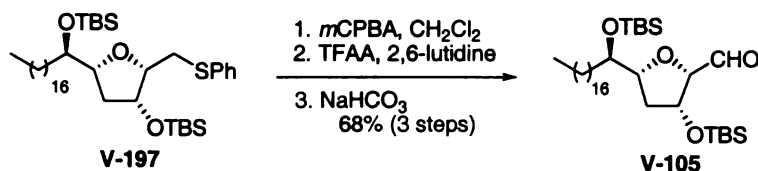
To a solution of epoxy thiophenyl **V-103** (0.7 g, 0.99 mmol) in Et₂O (25 mL) at 0 °C was added BF₃•OEt₂ (0.75 mL, 5.95 mmol) drop wise. After addition was complete, the mixture was slowly allowed to attain room temperature over 5 h. The reaction mixture was quenched with NaHCO₃ solution (5 mL) and extracted with EtOAc (3×10 mL). The combined extracts were dried over MgSO₄ and concentrated under reduced pressure to afford the crude product. Flash column chromatography provided THF diol **V-104** (0.38 g, 80%) as a white solid single product.

Data for THF diol **V-104**: $[\alpha]_D^{20}$ -30.0 (c 1.32, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.10 (5H, m), 4.18-4.15 (1H, m), 3.99-3.94 (1H, m), 3.85-3.79 (1H, m), 3.50-3.40 (3H, m), 3.22-3.19 (2H, m), 2.36-2.26 (1H, m), 1.88-1.82 (1H, dd, *J* = 14.0, 4.6 Hz), 1.57-1.23 (32H, m), 0.85 (3H, t, *J* = 6.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 136.4, 129.0, 128.8, 126.0, 82.6, 79.9, 73.8, 71.2, 38.1, 34.1, 32.2, 31.9, 29.7, 29.3, 26.0, 22.7, 14.1; IR (thin film) 3222 (br), 2917, 2847, 1467, 1088, 1036 cm⁻¹; HRMS (ESI) calcd for C₂₉H₅₁O₃S, 479.3559 *m/z* (M+H)⁺; observed, 479.3577 *m/z*.



2,6-Lutidine (0.28 mL, 2.4 mmol) was added to a 0 °C solution of THF diol **V-104** (0.37 g, 2.4 mmol) in CH₂Cl₂ (4 mL). A solution of TBSOTf (0.44 mL, 1.78 mmol) in CH₂Cl₂ (2 mL) was then added and the reaction mixture was stirred at 0 °C for 30 min. When TLC indicated completion of the reaction, water (5 mL) was added and the aqueous solution was extracted with CH₂Cl₂ (3×10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to afford the crude product as colorless oil. After purification by flash column chromatography, 0.59 g of di-TBS ether **V-197** was obtained (98%).

di-TBS ether **V-197**: $[\alpha]_D^{20}$ -25.9 (c 1.30, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.22 (4H, m), 7.16-7.11 (1H, m), 4.34-4.30 (1H, m), 3.82-3.69 (3H, m), 3.15 (2H, d, *J* = 6.6 Hz), 2.13-2.03 (1H, m), 1.71-1.63 (1H, m), 1.45-1.24 (30H, m), 0.94-0.82 (21H, m), 0.10-0.00 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 136.9, 128.8, 128.4, 125.6, 81.4, 81.2, 74.6, 71.9, 37.0, 32.9, 31.9, 31.6, 29.9, 29.7, 29.6, 29.4, 26.0, 25.8, 25.4, 22.7, 18.3, 18.0, 14.1, -4.0, -4.4, -4.7, -5.0; IR (thin film) 2926, 2855, 1586, 1472, 1362, 1254, 1071, 961, 835, 775, 735, 689 cm⁻¹; HRMS (ESI) calcd for C₄₁H₇₈O₃SSi₂Na, 729.5108 *m/z* (M+Na)⁺; observed, 729.5098 *m/z*.

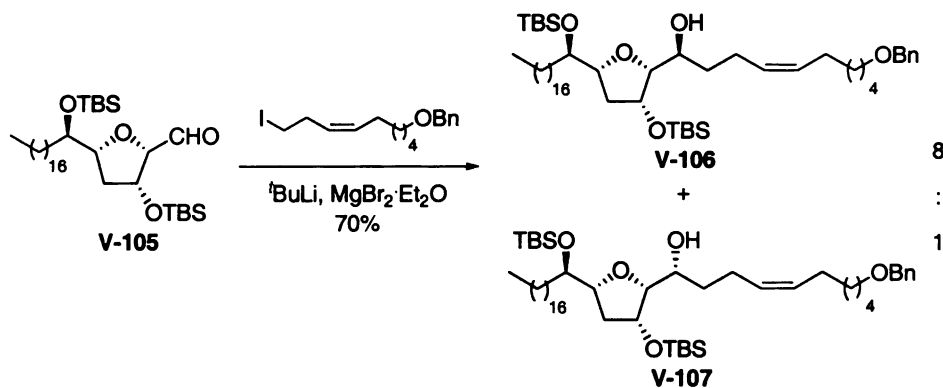


To a 0 °C solution of sulfide **V-197** (0.52 g, 0.74 mmol) in CH₂Cl₂ (8 mL), was

added a solution of *m*CPBA (0.17 g, 0.74 mmol) in CH₂Cl₂ (8 mL). After 30 min at 0 °C, the reaction mixture was quenched with sat NaHCO₃ solution (10 mL) and the aqueous mixture was extracted with CH₂Cl₂ (3×15 mL). The combined extracts were dried over Na₂SO₄ and concentrated under reduced pressure to afford sulfoxide as a mixture of stereoisomers. The crude product so obtained was dissolved in CH₂Cl₂ (6 mL), cooled to 0 °C and 2,6-lutidine (0.30 mL, 2.6 mmol) was added. TFAA (0.36 mL, 2.6 mmol) in CH₂Cl₂ (6 mL) was then added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure to afford a clear oil. This material was taken up in 1:1 acetonitrile-water (28 mL) and solid NaHCO₃ (1.0 g) was added. The reaction mixture was stirred at ambient temperature for 16 h, upon which the solution was diluted with water (10 mL). The aqueous solution was extracted with CH₂Cl₂ (3×15 mL) and the combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. Slow chromatography on wet silica gel containing 10% water (2% EtOAc in hexanes) afforded 0.30 g of aldehyde **V-105** in 66% yield over the three steps.

Data for aldehyde **V-105**: $[\alpha]_D^{20}$ -37.7 (c 0.97, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 9.62 (1H, d, *J* = 2.7 Hz), 4.66-4.62 (1H, m), 4.01 (1H, dd, *J* = 5.5, 3.0 Hz), 3.94 (1H, q, *J* = 6.9 Hz), 3.82-3.81 (1H, m), 2.19-2.10 (1H, m), 1.79-1.71 (1H, m), 1.591-1.23 (30H, m), 0.97-0.78 (21H, m), 0.07-0.01 (12H, m); ¹³C NMR (75 MHz, CDCl₃) δ 202.0, 86.2, 82.9, 75.0, 74.6, 37.5, 33.4, 31.9, 29.9, 29.7, 29.6, 29.4, 26.0, 25.6, 25.2,

22.7, 18.3, 17.9, 14.1, -4.1, -4.6, -4.8, -5.3; IR (thin film) 2919, 2851, 1773, 1653, 1559, 1507, 1486, 1080 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{72}\text{O}_4\text{Si}_2\text{Na}$, 635.4867 m/z ($\text{M}+\text{Na}$) $^{+}$; observed, 635.4846 m/z .

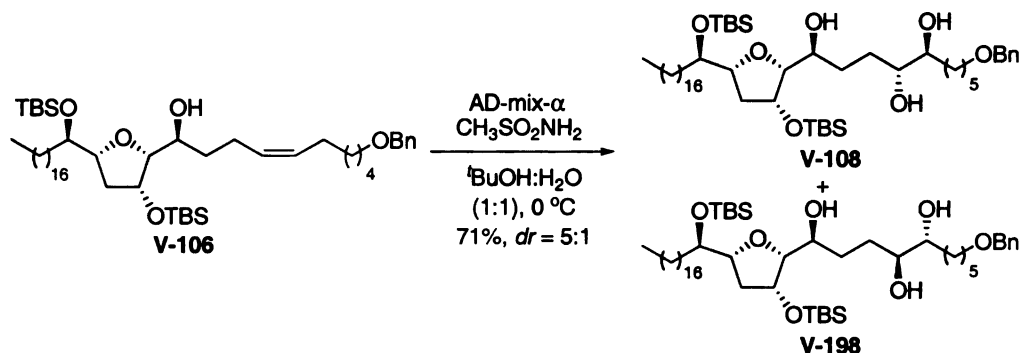


$t\text{-BuLi}$ (1.8 mL of 1.3 M solution in pentane, 3.05 mmol) was added drop wise to pre-cooled ($-100\text{ }^{\circ}\text{C}$) Et_2O (5 mL). To this, a solution of iodide (0.55 g, 1.55 mmol) in Et_2O (4 mL) was added over 10 min. After stirring for 5 min at $-100\text{ }^{\circ}\text{C}$ to $-90\text{ }^{\circ}\text{C}$, $\text{MgBr}_2\cdot\text{OEt}_2$ in Et_2O (4 mL of 1.0 M solution (freshly prepared)), was added and the mixture was warmed to $0\text{ }^{\circ}\text{C}$ over 1 h. Meanwhile, a solution of aldehyde **V-105** (0.31 g, 0.5 mmol) in Et_2O (5 mL) was cooled to $-40\text{ }^{\circ}\text{C}$. $\text{MgBr}_2\cdot\text{OEt}_2$ in Et_2O (1.5 mL of 1.0 M solution) was added and stirred for 10 min. To this pre-complexed aldehyde, solution of the above mentioned Grignard reagent was cannulated at $-40\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred overnight at the same temperature. The reaction was then quenched by slow addition of saturated NH_4Cl solution (5 mL) and H_2O (5 mL). The aqueous layer was extracted with Et_2O ($3\times 10\text{ mL}$). Combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography (2% EtOAc in hexanes) furnished the adduct **V-106** (0.26 g, 62%) and its epimer **V-107** (33 mg, 8%) in 8:1

ratio.

Data for alcohol **V-106**: $[\alpha]_D^{20}$ -5.6 (c 2.42, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.24 (5H, m), 5.38-5.31 (2H, m), 4.48 (2H, s), 4.38-4.34 (1H, m), 3.81-3.71 (3H, m), 3.51-3.42 (3H, m), 2.92 (1H, br), 2.13-2.02 (6H, m), 1.71-1.50 (7H, m), 1.36-1.14 (33H, m), 0.88-0.84 (21H, m), 0.08-0.05 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 130.0, 129.5, 128.9, 127.6, 127.4, 100.5, 83.6, 80.1, 74.5, 73.4, 72.8, 70.4, 69.9, 37.8, 33.4, 31.9, 29.8, 29.7, 29.6, 29.3, 27.2, 25.9, 25.7, 25.3, 22.7, 18.3, 17.8, 14.1, -4.1, -4.4, -4.7, -5.2; IR (thin film) 3424 (br), 2926, 2855, 2099, 1653, 1464, 1254, 1098, 835, 776 cm⁻¹; HRMS (ESI) calcd for C₅₁H₉₆O₅Si₂Na, 867.6694 *m/z* (M+Na)⁺; observed, 867.6686 *m/z*.

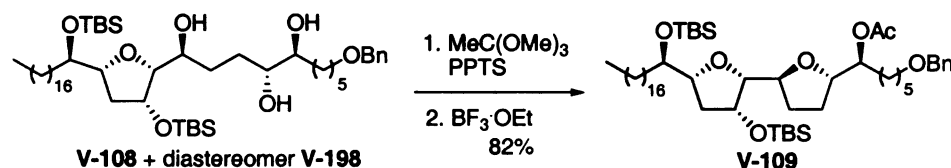
Data for epimer **V-107**: ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.24 (5H, m), 5.37-5.33 (2H, m), 4.53-4.51 (1H, m), 4.48 (2H, s), 3.78-3.72 (2H, m), 3.62-3.60 (1H, m), 3.50-3.42 (3H, m), 2.99 (1H, b), 2.28-2.00 (5H, m), 1.71-1.45 (5H, m), 1.43-1.40 (2H, m), 1.36-1.21 (32H, m), 0.88-0.84 (21H, m), 0.09-0.04 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 129.9, 129.7, 128.3, 127.6, 127.4, 82.4, 80.2, 74.4, 73.9, 72.8, 70.4, 60.4, 36.5, 33.6, 33.2, 31.9, 31.6, 29.8, 29.7, 29.6, 29.3, 27.1, 25.9, 25.7, 25.3, 23.1, 22.6, 21.0, 18.3, 17.8, 14.2, 14.1, -4.2, -4.3, -4.7, -5.3.



AD-mix- α (0.43 g) was dissolved in 1 : 1 $t\text{BuOH} : \text{H}_2\text{O}$ (6 mL). To this clear, orange solution, methane sulfonamide (29 mg, 0.31 mmol) and potassium osmate (1 mg) were added and stirred until all the solids dissolved. The solution was then cooled to 0 $^\circ\text{C}$ at which time olefin **V-106** (260 mg, 0.31 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (0.5 g) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (15 mL) and H_2O (6 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 $\times$ 10 mL), combined organic layers were dried over Na_2SO_4 , concentrated and the crude product was purified by column chromatography (20% EtOAc in hexanes). The inseparable triol **V-108** and its diastereomer **V-198** was isolated in 71% (191 mg) yield as a colorless oil.

Data for the inseparable triols mixture: ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.48 (2H, s), 4.40-4.38 (1H, m), 3.83-3.76 (2H, m), 3.68-3.67 (1H, m), 3.62-3.58 (2H, m), 3.52 (1H, t, $J = 5.2$ Hz), 3.45 (2H, t, $J = 6.6$ Hz), 2.10-2.02 (1H, m), 1.72-1.59 (7H, m), 1.57-1.23 (38H, m), 0.87-0.83 (21H, m), 0.07-0.06 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 83.3, 79.9, 74.4, 74.3, 74.0,

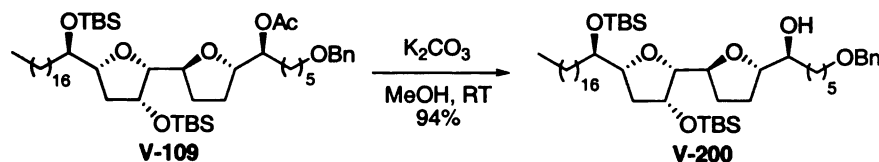
73.3, 72.8, 70.5, 70.3, 37.5, 33.4, 31.9, 31.6, 29.8, 29.7, 29.6, 29.3, 27.4, 26.2, 25.9, 25.7, 25.3, 22.7, 18.3, 17.8, 14.1, -4.2, -4.4, -4.7, -5.2; HRMS (ESI) calcd for $C_{51}H_{98}O_7Si_2Na$, 901.6749 m/z ($M+Na$)⁺; observed, 901.6718 m/z .



PPTS (1.4 mg, 0.006 mmol) was added to a solution of triol **V-108** and its diastereomer **V-198** (50 mg, 0.057 mmol) and trimethylortho acetate (8 μL , 0.063 mmol) in CH_2Cl_2 (3 mL) at RT. After complete consumption of the triol (ca. 5 min, as judged by TLC), a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (2.1 μL , 0.017 mmol) in CH_2Cl_2 (1 mL) was rapidly added to the reaction. After 10 min, the reaction was slowly poured into saturated NaHCO_3 solution (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). Combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude product was purified by flash column chromatography (10% EtOAc in hexanes) to furnish bis-THF acetate **V-109** (36 mg, 72%) and its diastereomer **V-199** (4.8 mg, 9.6%) as a clear oil.

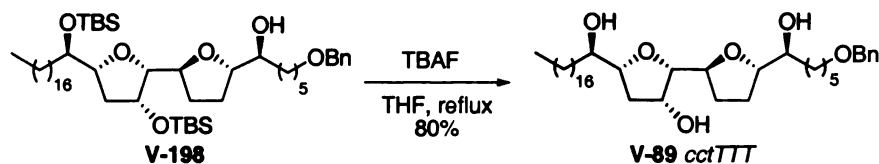
Data for bis-THF acetate **V-109**: ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.85 (1H, q, $J = 4.1$ Hz), 4.47 (2H, s), 4.22-4.18 (2H, m), 4.08-4.04 (1H, m), 3.84-3.72 (2H, m), 3.47-3.40 (3H, m), 2.05-2.02 (2H, m), 2.02 (3H, s), 1.97-1.90 (1H, m), 1.70-1.48 (7H, m), 1.45-1.42 (1H, m), 1.39-1.23 (32H, m), 0.87-0.84 (21H, m), 0.09-0.03 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.1, 128.3, 127.6, 127.4, 85.7, 81.7, 79.1, 78.8, 75.9, 74.7, 72.7, 70.3, 53.8, 48.0, 37.0, 32.7, 31.9, 30.9, 29.9, 29.7, 29.3, 28.5, 27.7, 26.1, 25.7, 25.4, 22.7, 21.1, 17.8, 14.1, -3.9, -4.2, -4.7, -5.3; IR (thin

(ES) calcd for $C_{53}H_{98}O_7Si_2$, 903.6929 m/z ($M+H$)⁺; observed, 903.6884 m/z .



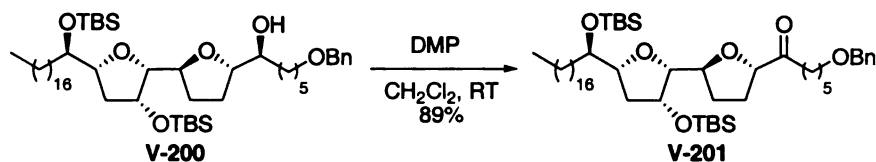
Acetate **V-109** (185 mg, 0.21 mmol) was dissolved in MeOH (3 mL). Solid K_2CO_3 was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with CH_2Cl_2 (6 mL) and washed with $NaHCO_3$ (3 mL) and H_2O (5 mL). The aqueous layer was mixed and extracted with CH_2Cl_2 (3×10 mL). The combine organic layers were dried using Na_2SO_4 , the solvent was evaporated, and the crude product was purified by flash column chromatography (5% EtOAc in hexanes). Bis-THF alcohol **V-200** was obtained in 94% yield (166 mg) as a clear oil.

Data for bis-THF alcohol **V-200**: $[\alpha]_{\text{D}}^{20}$ -5.6 (c 0.64, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.22-4.20 (1H, m), 4.12 (1H, q, $J = 6.3$ Hz), 3.85-3.72 (3H, m), 3.51-3.42 (3H, m), 3.35 (1H, q, $J = 5.2$ Hz), 2.20 (1H, br), 2.09-2.00 (2H, m), 1.93-1.91 (1H, m), 1.71-1.54 (6H, m), 1.40-1.37 (7H, m), 1.36-1.23 (30H, m), 0.86-0.83 (21H, m), 0.09-0.03 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 85.5, 82.4, 81.6, 78.3, 74.7, 73.9, 72.8, 72.6, 70.4, 37.1, 33.3, 32.7, 31.9, 29.9, 29.7, 29.3, 28.9, 28.2, 26.3, 26.0, 25.7, 25.6, 25.5, 22.7, 18.2, 17.8, 14.1, -4.0, -4.1, -4.7, -5.3; IR (thin film) 3584 (br), 2926, 2855, 1462, 1362, 1258, 1084, 937, 837, 806, 775, 733, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{51}\text{H}_{96}\text{O}_6\text{Si}_2$, 861.6824 m/z ($\text{M}+\text{H}$) $^+$; observed, 861.6825 m/z .

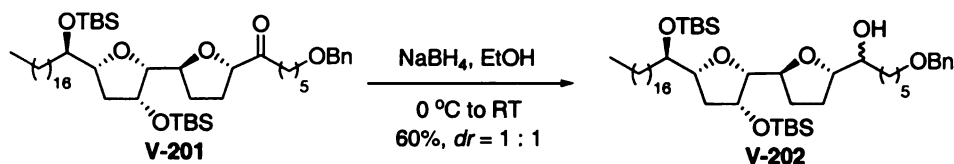


To a solution of bis-TBS ether **V-200** (27 mg, 0.031 mmol) in THF (2 mL), TBAF (1.0 M solution in THF, 78 μL , 0.078 mmol) was added at room temperature. The reaction temperature was increased to reflux and stirred for 12 h. Then saturated NH_4Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 5 mL). The organic layers were mixed, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (EtOAc) gave *cctTTT* truncated structure **V-89** as white wax in 80% yield (14.1 mg).

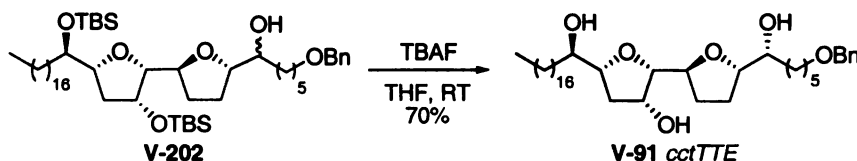
Data for *cctTTT* truncated structure **V-89**: ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.26 (5H, m), 4.51 (2H, s), 4.26-4.22 (1H, m, H12), 4.22-4.18 (1H, m, H14), 4.06 (1H, dt, $J = 8.8, 3.4$ Hz, H16), 3.94-3.88 (1H, m, H9), 3.69-3.65 (1H, dd, $J = 4.8, 3.4$ Hz, H13), 3.52-3.46 (3H, m, H17), 3.44-3.39 (1H, m, H8), 2.61-2.258 (1H, br), 2.41-2.33 (1H, m, H15), 2.22-2.18 (1H, m, H11), 2.03-1.98 (1H, m, H10), 1.91-1.88 (1H, m, H15), 1.88-1.78 (1H, m, H11), 1.71-1.69 (1H, m, H10), 1.69-1.51 (5H, m), 1.50-1.21 (35H, m), 0.89 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 85.6 (C13), 83.6 (C9), 80.2 (C16), 78.7 (C12), 74.1 (C17), 73.7 (C8), 72.8, 72.5 (C14), 70.4, 38.8 (C15), 34.4, 33.4, 31.9, 29.7, 29.6, 29.4, 29.3, 28.0, 26.2, 26.0, 25.5, 22.7, 14.1.



Data for ketone **V-201**: ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.39-4.20 (3H, m), 3.91-3.82 (1H, m), 3.80-3.76 (1H, m), 3.51 (1H, dd, $J = 4.1, 7.7$ Hz), 3.43 (2H, t, $J = 6.6$ Hz), 2.78-2.48 (2H, m), 2.00-1.98 (2H, m), 1.95-1.61 (2H, m), 1.60-1.48 (6H, m), 1.40-1.21 (34H, m), 0.86-0.83 (21H, m), 0.09-0.03 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 186.3, 138.7, 128.3, 127.6, 127.4, 85.3, 83.7, 81.5, 79.8, 74.3, 72.9, 72.6, 70.2, 53.8, 48.1, 37.8, 36.8, 32.4, 31.9, 29.9, 29.7, 29.3, 29.2, 28.2, 26.0, 25.8, 25.7, 22.8, 18.2, 14.1, -4.0, -4.1, -4.7, -5.3.

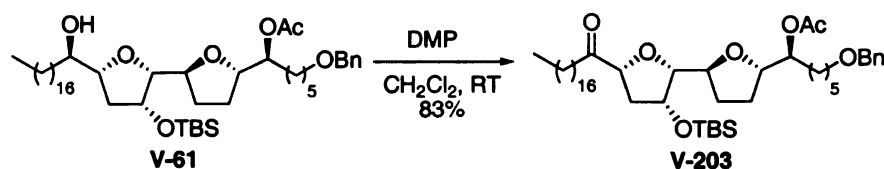


Data for the mixture of two inseparable epimers **V-202**: ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.47 (2H, s), 4.22-4.18 (2H, m), 3.85-3.72 (4H, m), 3.51-3.42 (3H, m), 2.20 (1H, br), 2.09-1.91 (3H, m), 1.71-1.54 (6H, m), 1.40-1.37 (7H, m), 1.36-1.23 (30H, m), 0.86-0.83 (21H, m), 0.09-0.03 (12H, m)

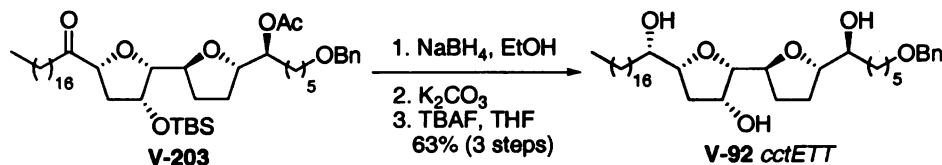


Data for *cctTTE* truncated structure **V-91**: $[\alpha]_{\text{D}}^{20}$ -10.3 (c 1.64, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (5H, m), 4.47 (2H, s), 4.28-4.24 (1H, m, H12), 4.18-4.14 (1H, m, H14), 4.05-4.01 (1H, m, H16), 3.98-3.92 (1H, m, H9), 3.84-3.80 (1H, m, H8), 3.63 (1H, dd, $J = 7.2, 2.3$ Hz, H13), 3.48-3.42 (3H, m, H17), 2.88 (1H, br), 2.38- 2.28

(2H, m, H15), 2.20-2.14 (1H, m, H11), 1.82-1.70 (5H, m, H15, H11, H10), 1.64-1.48 (5H, m), 1.45-1.19 (33H, m), 0.86 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 85.8 (C13), 83.2 (C9), 80.3 (C16), 79.2 (C12), 74.1 (C17), 72.8, 72.3 (C14), 71.3 (C8), 70.3, 38.8 (C15), 34.3, 32.4, 31.9, 29.7, 29.6, 29.3, 29.2, 28.3, 26.2, 26.0, 25.8, 24.3, 22.7, 14.1; HRMS (ESI) calcd for $\text{C}_{39}\text{H}_{69}\text{O}_6$, 633.5094 m/z ($\text{M}+\text{H}$) $^+$; observed, 633.5084 m/z .

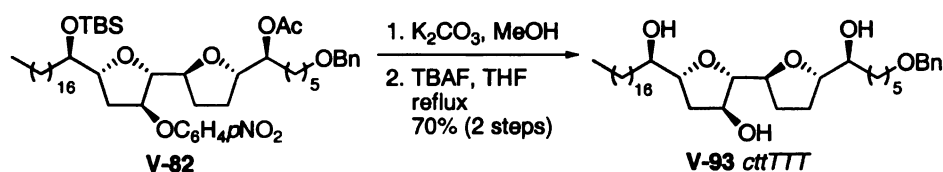


Data for ketone **V-203**: ^1H NMR (300 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.89 (1H, q, $J = 6.3$ Hz), 4.47 (2H, s), 4.37-4.32 (1H, m), 4.24 (1H, q, $J = 7.2$ Hz), 4.11-4.05 (1H, m), 3.63 (1H, dd, $J = 3.0, 8.2$ Hz), 3.43 (2H, t, $J = 6.6$ Hz), 2.79 (1H, q, $J = 7.4$ Hz), 2.32-2.18 (1H, m), 2.04 (3H, s), 2.03-1.90 (2H, m), 1.86-1.42 (8H, m), 1.40-1.21 (34H, m), 0.86-0.83 (12H, m), 0.08 (6H, d, $J = 5.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 215.0, 170.8, 138.7, 128.3, 127.6, 127.4, 87.3, 83.3, 79.4, 78.9, 75.4, 72.8, 72.1, 70.3, 39.8, 38.3, 31.9, 30.9, 29.7, 29.5, 29.3, 28.4, 27.7, 26.1, 25.6, 25.4, 22.8, 22.7, 21.2, 17.8, 14.1, -4.2, -5.4.

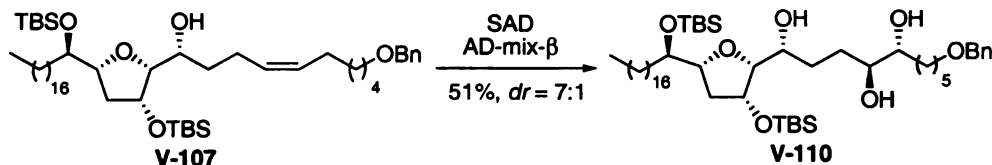


Data for *cctETT* truncated structure **V-92**: ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (5H, m), 4.47 (2H, s), 4.22-4.16 (1H, m, H12), 4.17-4.05 (2H, m, H14, H16), 3.90-3.86 (1H, m, H17), 3.86-3.81 (1H, m, H9), 3.54 (1H, dd, $J = 6.9, 2.7$ Hz, H13),

3.44 (2H, t, $J = 6.6$ Hz), 3.41-3.36 (1H, m, H8), 2.88 (1H, br), 2.22-2.14 (2H, m, H15, H11), 1.96-1.89 (2H, m, H10, H15), 1.66-1.57 (5H, m, H11, H10), 1.56-1.33 (7H, m), 1.32-1.21 (30H, m), 0.86 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.1 (C13), 83.5 (C9), 81.2 (C16), 78.7 (C12), 73.9 (C8), 72.8, 71.7 (C17), 71.6 (C14), 70.4, 34.3 (C15), 33.3, 33.2, 29.7, 29.5, 29.3, 29.2, 28.3, 26.2, 25.9, 25.5, 22.7, 14.1.

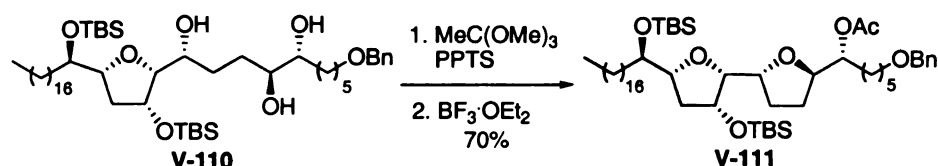


Data for *cttTTT* truncated structure **V-93**: ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (5H, m), 4.47 (2H, s), 4.44-4.41 (1H, m, H14), 4.12-4.07 (1H, m, H16), 4.06-4.02 (1H, m, H12), 3.84-3.78 (1H, m, H9), 3.73 (1H, t, $J = 3.5$ Hz), 3.45 (2H, t, $J = 6.6$ Hz), 3.39-3.32 (2H, m, H8, H17), 2.78 (1H, br), 2.21 (1H, br), 2.11-2.05 (1H, m, H15), 2.00-1.84 (4H, m, H10, H11, H15), 1.71-1.64 (1H, m, H10), 1.64-1.56 (3H, m), 1.52-1.341 (9H, m), 1.30-1.21 (28H, m), 0.86 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 87.0 (C13), 83.4 (C9), 81.4 (C16), 79.2 (C12), 74.3 (C17), 74.0 (C14), 73.6 (C8), 72.9, 70.4, 37.9 (C15), 34.2, 33.5, 31.9, 29.7, 29.5, 29.3, 28.7, 28.4, 26.2, 25.4, 22.7, 14.1.

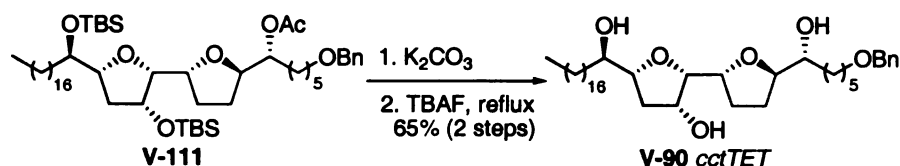


Data for pure triol **V-110**: ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.26 (5H, m), 4.56 (1H, dd, $J = 13.0, 6.7$ Hz), 4.47 (2H, s), 3.87-3.82 (1H, m), 3.78-3.71 (1H, m), 3.61-3.56

(4H, m), 3.44 (2H, t, $J = 6.6$ Hz), 2.04-1.89 (1H, m), 1.89-1.82 (1H, m), 1.75-1.53 (6H, m), 1.51-1.23 (34H, m), 0.92-0.83 (21H, m), 0.10 (6H, s), 0.11 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 80.8, 80.0, 74.5, 74.4, 74.2, 74.1, 72.8, 70.8, 70.4, 36.1, 33.3, 31.9, 31.6, 29.8, 29.7, 29.6, 29.4, 29.3, 26.7, 26.3, 25.9, 25.7, 25.3, 22.7, 18.2, 17.8, 14.1, -4.2, -4.3, -4.6, -5.3.



Data for bis-THF acetate **V-111**: ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.27 (5H, m), 4.90-4.75 (1H, m), 4.47 (2H, s), 4.31-4.25 (1H, m), 4.19-4.13 (1H, m), 4.03-3.96 (1H, m), 3.82-3.73 (2H, m), 3.56-3.38 (3H, m), 2.14-1.90 (5H, m), 2.02 (3H, s), 1.65-1.54 (8H, m), 1.36-1.23 (33H, m), 0.95-0.85 (21H, m), 0.13-0.02 (12H, m).



Data for *cctTET* truncated structure **V-90**: ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (5H, m), 4.47 (2H, s), 4.34-4.30 (1H, m, H14), 4.22-4.17 (1H, m, H12), 3.97-3.93 (1H, m, H16), 3.83-3.78 (1H, m, H9), 3.56 (1H, dd, $J = 7.2, 3.3$ Hz), 3.51-3.47 (1H, m, H17), 3.45 (2H, t, $J = 6.6$ Hz), 3.39-3.35 (1H, m, H8), 2.51 (1H, br), 2.36-2.30 (1H, m, H15), 2.17-2.11 (1H, m, H11), 2.01-1.94 (1H, m, H10), 1.90-1.82 (2H, m, H11, H15), 1.70-1.56 (5H, m, H10), 1.55-1.48 (4H, m), 1.41-1.21 (32H, m), 0.86 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.5, 85.2, 82.8, 80.5, 74.0, 73.8, 72.9, 71.7, 70.4, 37.8, 34.0, 33.4, 31.9, 30.1, 29.7, 29.6, 29.3, 28.2, 26.2,

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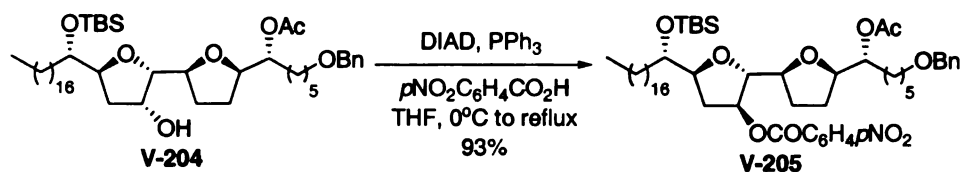
21.4, 18.4, 18.1, 14.4, -3.8, -4.0, -4.4, -4.5, -4.8.



colorless oil in overall 86% yield.

1.42-1.23 (33H, m), 0.92-0.86 (12H, m), 0.07 (3H, s), 0.06 (3H, s); ¹³C NMR (125

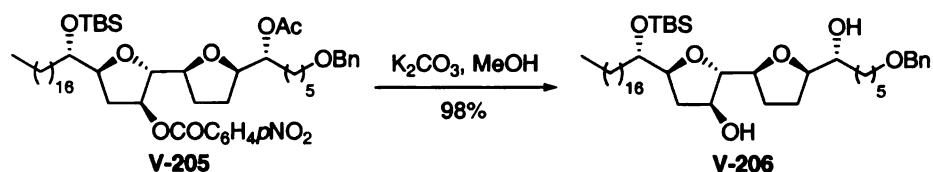
Data for **V-59**: $[\alpha]_D^{20}$ -12.2 (c 0.84, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.23 (5H, m), 4.88-4.81 (1H, m), 4.47 (2H, s), 4.40-4.33 (1H, m), 4.31-4.28 (1H, m), 4.19-4.06 (2H, m), 3.79-3.76 (1H, m), 3.58-3.47 (1H, m), 3.44 (2H, t, $J = 6.6$ Hz), 2.04 (3H, s), 2.03-1.88 (2H, m), 1.80-1.62 (1H, m), 1.59-1.43 (4H, m), 1.40-1.21 (39H, m), 0.86-0.79 (12H, m), 0.037 (6H, d, $J = 15.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 138.6, 128.3, 127.6, 127.4, 81.9, 81.3, 80.7, 78.7, 75.1, 75.0, 74.3, 72.8, 70.2, 38.3, 33.2, 31.9, 30.9, 29.8, 29.7, 29.6, 29.3, 28.7, 27.6, 26.1, 25.9, 25.2, 25.1, 22.7, 21.1, 18.2, 14.1, -4.3, -4.6; IR (thin film) 3461 (br), 2926, 2855, 1740, 1464, 1370, 1244, 1103, 1057, 966, 835, 777, 733, 698 cm^{-1} .



A solution of alcohol **V-204** (96 mg, 0.12 mmol), *p*-nitrobenzoic acid (86 mg, 0.51 mmol), and triphenylphosphine (134 mg, 0.51 mmol) in THF (8 mL) was cooled to 0 °C. Diisopropylazodicarboxylate (0.10 mL, 0.51 mmol) was added dropwise over 30 min to keep the reaction temperature at 0 °C. The resulting mixture was then heated to reflux for 15 h. After allowing the solution to cool to room temperature, it was diluted with Et_2O (15 mL), and washed with sat. aqueous NaHCO_3 (2×15 mL). The aqueous layer was extracted with Et_2O (3×15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc in hexanes) afforded the product **V-205** as a colorless oil (106.3 mg, 93%).

Data for ester **V-205**: $[\alpha]_D^{20}$ +6.5 (c 2.29, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ

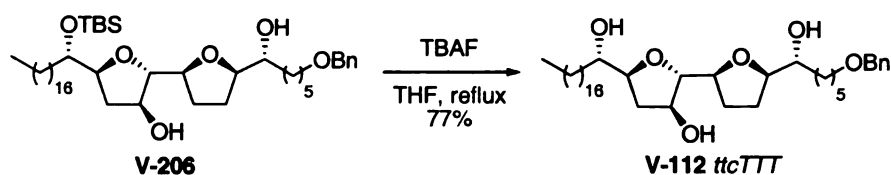
8.30-8.28 (2H, d, $J = 9.0$ Hz), 8.20-8.18 (2H, d, $J = 8.8$ Hz), 7.36-7.27 (5H, m), 5.54-5.51 (1H, m), 4.94-4.90 (1H, q, $J = 6.1$ Hz), 4.50 (2H, s), 4.29-4.24 (1H, dd, $J = 14.2, 6.3$ Hz), 4.12-4.08 (2H, m), 3.94-3.90 (1H, q, $J = 6.4$ Hz), 3.72-3.68 (1H, m), 3.46 (2H, t, $J = 6.6$ Hz), 2.58-2.40 (1H, m), 2.09 (3H, s), 2.00-1.84 (4H, m), 1.73-1.54 (6H, m), 1.42-1.22 (35H, m), 0.92-0.86 (12H, m), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 164.3, 150.6, 138.6, 135.4, 130.6, 128.3, 127.6, 127.4, 123.5, 84.9, 82.8, 80.6, 79.6, 78.6, 75.4, 74.7, 72.9, 70.3, 33.6, 33.1, 31.9, 31.2, 29.9, 29.7, 29.6, 29.3, 27.9, 27.5, 26.1, 25.9, 25.6, 25.2, 22.7, 21.2, 21.0, 18.3, 14.2, -4.1, -4.6.



Ester **V-205** (103 mg, 0.11 mmol) was dissolved in MeOH (5 mL). Solid K_2CO_3 (300 mg) was added to this solution and the heterogeneous mixture was stirred vigorously at room temperature for 17 h. The reaction was then diluted with CH_2Cl_2 (10 mL) and washed with sat. aqueous NaHCO_3 (10 mL) and H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried using Na_2SO_4 , the solvent was evaporated, and the crude product was purified by flash column chromatography (30% EtOAc in hexanes). Free diol **V-206** was obtained in 98% yield (80 mg) as a clear oil.

Data for diol **V-206**: $[\alpha]_{\text{D}}^{20} +9.7$ (c 1.74, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.26 (5H, m), 4.50 (2H, s), 4.26-4.22 (1H, m), 4.16-4.11 (1H, m), 4.04-4.00 (1H, m), 3.88-3.84 (1H, m), 3.77 (1H, t, $J = 3.4$ Hz), 3.63-3.58 (1H, dd, $J = 10.9, 5.9$ Hz),

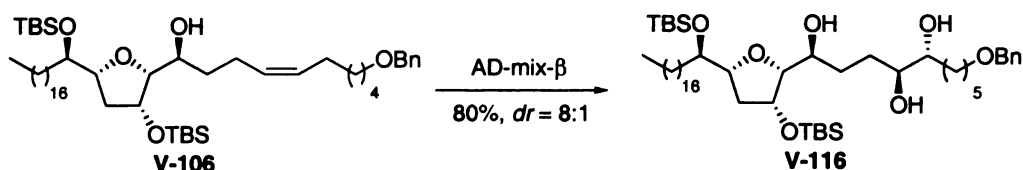
3.47 (2H, t, $J = 6.6$ Hz), 3.39-3.35 (1H, m), 3.24-3.16 (1H, br), 2.86-2.78 (1H, br), 2.38-2.29 (1H, m), 2.02-1.76 (5H, m), 1.74-1.59 (3H, m), 1.56-1.22 (37H, m), 0.92-0.86 (12H, m), 0.11 (3H, s), 0.10 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 87.1, 82.5, 80.2, 79.2, 75.1, 74.4, 73.6, 72.8, 70.4, 36.4, 34.5, 33.3, 31.9, 29.8, 29.7, 29.6, 28.3, 28.1, 26.3, 26.0, 25.6, 25.4, 22.6, 18.2, 14.1, -4.1, -4.6.



To a solution of TBS ether **V-206** (13.4 mg, 0.018 mmol) in THF (3 mL), TBAF (1.0 M solution in THF, 27 μL , 0.027 mmol) was added at room temperature. The reaction temperature was increased to reflux and stirred for 12 h. Saturated NH_4Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 5 mL). The organic layers were combined, dried over Na_2SO_4 , and the solvent was evaporated to afford a crude product. Purification by column chromatography (40% EtOAc in hexanes to EtOAc) gave *ttcTTT* truncated structure **V-112** as colorless oil in 77% yield (8.7 mg).

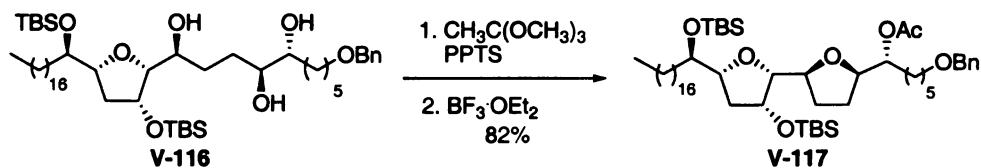
Data for *ttcTTT* truncated structure **V-112**: $[\alpha]_{\text{D}}^{20} +11.5$ (c 0.80, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.27 (5H, m), 4.51 (2H, s), 4.28-4.26 (1H, m, H14), 4.09-4.05 (1H, m, H16), 4.03-3.98 (1H, m, H12), 3.88 (1H, t, $J = 3.3$ Hz, H13), 3.86-3.84 (1H, m, H9), 3.54-3.50 (1H, m, H17), 3.48 (2H, t, $J = 6.6$ Hz), 3.39-3.35 (1H, m, H8), 2.80-2.70 (1H, br), 2.47-2.41 (1H, m, H15), 2.02-1.90 (3H, m, H10, H11, H11),

1.86-1.81 (2H, m, H10, H15), 1.68-1.22 (40H, m), 0.89 (3H, t, $J = 6.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 88.6, 82.6, 81.5, 79.7, 74.6, 74.4, 74.0, 72.9, 70.4, 37.9, 34.5, 33.9, 31.9, 29.7, 29.6, 29.3, 28.3, 28.1, 26.3, 25.8, 25.6, 22.7, 14.1.



SAD reaction using AD-mix- β followed the same procedure as using AD-mix- α for the synthesis of **V-108**.

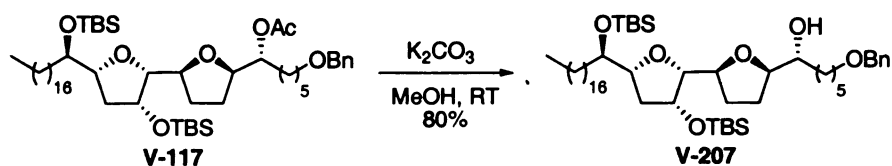
Data for pure triol **V-116**: ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 4.51 (2H, s), 4.43 (1H, dd, $J = 11.5, 5.5$ Hz), 3.84-3.78 (2H, m), 3.72-3.67 (1H, m), 3.65-3.60 (1H, m), 3.55 (1H, t, $J = 5.2$ Hz), 3.52-3.50 (1H, m), 3.48 (2H, t, $J = 6.6$ Hz), 2.20-2.05 (1H, m), 1.80-1.61 (6H, m), 1.60-1.21 (39H, m), 0.98-0.83 (21H, m), 0.08-0.03 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 128.3, 127.6, 127.4, 83.2, 79.9, 74.9, 74.5, 74.4, 73.5, 72.8, 71.3, 70.4, 37.5, 33.5, 31.9, 31.8, 31.2, 29.8, 29.7, 29.6, 29.4, 28.7, 26.3, 25.9, 25.7, 25.3, 22.7, 18.3, 17.9, 14.1, -4.1, -4.4, -4.7, -5.2.



Cyclization reaction of triol **V-116** to prepare bis-THF acetate **V-117** followed the same procedure described above.

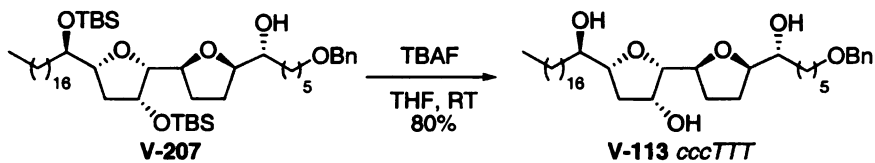
Data for bis-THF acetate **V-117**: $[\alpha]_{\text{D}}^{20} +4.0$ (c 1.43, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 4.91-4.86 (1H, m), 4.47 (2H, s), 4.22-4.18 (1H, m),

4.02-3.90 (2H, m), 3.87-3.68 (2H, m), 3.47-3.38 (3H, m), 2.02 (3H, s), 1.97-1.83 (1H, m), 1.78-1.52 (6H, m), 1.37-1.21 (33H, m), 0.96-0.83 (21H, m), 0.07-0.02 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 170.8, 138.6, 128.3, 127.6, 127.4, 86.3, 81.4, 79.2, 78.9, 75.1, 74.2, 72.8, 70.3, 36.6, 32.0, 31.9, 30.6, 29.9, 29.7, 29.6, 29.3, 27.7, 27.4, 26.1, 25.9, 25.7, 25.3, 22.6, 21.2, 18.2, 17.8, 14.1, -3.9, -4.2, -4.8, -5.4; IR (thin film) 3405, 2926, 2855, 1740, 1462, 1368, 1246, 1082, 936, 837, 775, 733, 696 cm^{-1} .



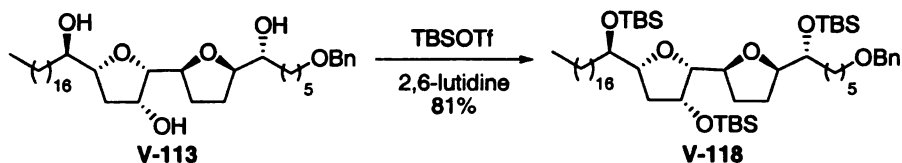
Deprotection of acyl group in bis-THF acetate **V-117** to prepare free alcohol **V-207** followed the same procedure described above.

Data for alcohol **V-207**: $[\alpha]_{\text{D}}^{20} +2.1$ (c 1.24, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 4.47 (2H, s), 4.25-4.12 (2H, m), 3.86-3.68 (3H, m), 3.52-3.40 (3H, m), 3.40-3.32 (1H, m), 2.53 (2H, d, $J = 4.7$ Hz), 2.13-1.82 (2H, m), 1.72-1.18 (44 H, m), 0.96-0.81 (21H, m), 0.09-0.02 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.2, 82.6, 81.6, 78.5, 74.5, 73.9, 72.8, 72.6, 70.4, 37.2, 33.9, 32.5, 31.9, 29.9, 29.7, 29.6, 29.3, 28.4, 27.7, 26.2, 26.0, 25.7, 25.6, 22.7, 18.3, 17.8, 14.1, -4.0, -4.1, -4.8, -5.3; IR (thin film) 3360 (br), 2926, 2855, 1462, 1362, 1254, 1080, 937, 835, 775, 733, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{51}\text{H}_{97}\text{O}_6\text{Si}_2$, 861.6824 m/z ($\text{M}+\text{H}$) $^+$; observed, 861.6818 m/z .



Using the same strategy of TBS deprotection as described above, *cccTTT* truncated structure **V-113** was obtained as white wax.

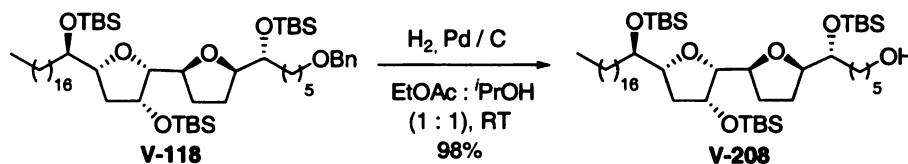
Data for *cccTTT* truncated structure **V-113**: $[\alpha]_{\text{D}}^{20}$ -1.9 (c 1.89, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 4.47 (2H, s), 4.30-4.25 (2H, m, H12, H14), 4.02-3.95 (1H, m, H16), 3.92-3.88 (1H, m, H9), 3.71 (1H, t, $J = 3.1$ Hz), 3.52-3.48 (1H, m, H17), 3.47-3.42 (3H, m), 3.42-3.37 (1H, m, H8), 2.36-2.28 (1H, m, H15), 2.06-2.00 (2H, m, H10, H11), 1.94-1.82 (3H, m, H10, H11, H15), 1.68-1.56 (5H, m), 1.54-1.31 (10H, m), 1.30-1.18 (31H, m), 0.86 (3H, t, $J = 6.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 83.7 (C13), 83.5 (C9), 80.1 (C16), 78.9 (C12), 73.8 (C17), 73.5 (C8), 72.9 (C14), 72.8, 70.4, 65.8, 38.8 (C15), 34.3, 34.0, 31.9, 29.7, 29.6, 29.3, 28.6, 27.6, 26.2, 26.0, 25.7, 22.7, 15.3, 14.1.



To a 0 °C solution of triol **V-113** (150 mg, 0.17 mmol) in CH₂Cl₂ (5 mL), 2,6-lutidine (0.12 mL, 1.04 mmol) and TBSOTf (0.13 mL, 0.52 mmol) were added in that order. After 30 min at the same temperature, saturated NaHCO₃ solution (2 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3×15 mL), combined organic layers were dried over Na₂SO₄, and concentrated under reduced pressure to afford a crude oil. Upon purification of the

oil by column chromatography (1% EtOAc in hexanes), tris-TBS ether **V-118** was obtained in 81% yield (134 mg).

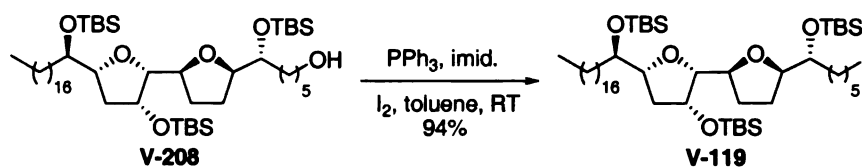
Data for tris-TBS ether **V-118**: $[\alpha]_D^{20} +8.8$ (c 1.79, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 4.47 (2H, s), 4.22-4.18 (1H, m), 4.07-3.81 (4H, m), 3.79-3.71 (1H, m), 3.51-3.39 (3H, m), 2.08-1.69 (3H, m), 1.62-1.11 (39H, m), 0.96-0.79 (30H, m), 0.06- -0.17 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.8, 81.2, 81.0, 79.0, 74.5, 73.4, 72.8, 72.5, 70.5, 36.0, 31.9, 31.2, 30.7, 29.9, 29.8, 29.7, 29.6, 29.3, 28.0, 26.5, 26.2, 26.0, 25.9, 25.8, 25.5, 22.7, 18.1, 17.9, 14.1, -3.8, -4.3, -4.4, -4.7, -5.4; IR (thin film) 2928, 2855, 1653, 1471, 1462, 1361, 1254, 1084, 939, 837, 775, 733, 696 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{57}\text{H}_{111}\text{O}_6\text{Si}_3$, 975.7689 m/z ($\text{M}+\text{H}$) $^+$; observed, 975.7674 m/z .



Benzyl ether **V-118** (133 mg, 0.14 mmol) was dissolved in 1 : 1 EtOAc : $i\text{PrOH}$ (8 mL). To this solution, 10% Pd-C (39 mg) was added and the mixture was stirred vigorously under H_2 (1 atm). The hydrogenolysis was complete in 1 h after which the reaction was filtered through a celite pad. The filtrate was concentrated and the crude product was purified by flash column chromatography (5% EtOAc in hexanes) to furnish primary alcohol **V-208** in 98% yield (119 mg).

Data for primary alcohol **V-208**: $[\alpha]_D^{20} +9.3$ (c 1.14, CHCl_3) ^1H NMR (300 MHz, CDCl_3) δ 4.22-4.16 (1H, m), 4.05-3.81 (4H, m), 3.79-3.72 (1H, m), 3.60 (2H, t, $J = 6.6$ Hz), 3.40 (1H, dd, $J = 7.9, 3.3$ Hz), 2.08-1.68 (4H, m), 1.61-1.15 (38H, m),

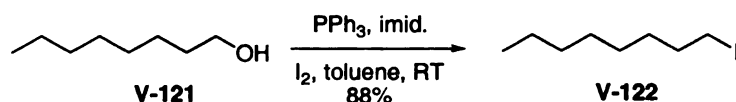
0.96-0.79 (30H, m), 0.05- -0.004 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 86.8, 81.2, 81.0, 78.9, 73.4, 72.5, 72.5, 63.0, 60.3, 36.0, 32.7, 31.9, 31.2, 30.7, 29.9, 29.8, 29.6, 29.3, 28.0, 26.2, 26.0, 25.9, 25.7, 25.4, 22.7, 21.0, 18.1, 18.0, 17.9, 14.1, -3.8, -4.3, -4.4, -4.6, -4.7, -5.4; IR (thin film) 3349 (br), 2928, 2855, 1462, 1361, 1254, 1080, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{50}\text{H}_{105}\text{O}_6\text{Si}_3$, 885.7219 m/z ($\text{M}+\text{H}$) $^+$; observed, 885.7181 m/z .



Primary alcohol **V-208** (120 mg, 0.14 mmol), triphenylphosphine (89 mg, 0.34 mmol) and imidazole (24 mg, 0.35 mmol) were dissolved in toluene (5 mL). Upon addition of iodine (93 mg, 0.37 mmol) the clear, colorless solution turned yellowish brown and turbid. After 1 h vigorous stirring at room temperature, saturated sodium sulfite solution was added to the reaction until the yellowish brown color disappeared. The layers were separated and the aqueous layer was washed with EtOAc (3 $\times$ 10). After evaporation of the solvent form combined and dried (Na_2SO_4) organic layers a gummy material was obtained. Purification of the crude material by column chromatography (3% EtOAc in hexanes) afforded iodide **V-119** (128 mg, 94%) as a colorless oil.

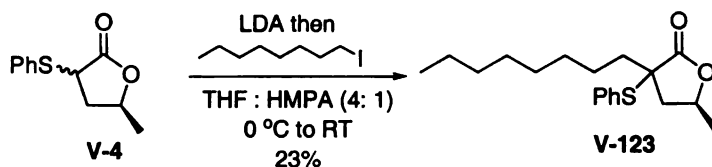
Data for iodide **V-119**: $[\alpha]_{\text{D}}^{20} +7.5$ (c 1.92, CHCl_3) ^1H NMR (300 MHz, CDCl_3) δ 4.24-4.18 (1H, m), 4.06-3.82 (4H, m), 3.80-3.73 (1H, m), 3.42 (1H, dd, $J = 8.2, 3.5$ Hz), 3.16 (2H, t, $J = 6.8$ Hz), 2.09-1.66 (6H, m), 1.61-1.15 (36H, m), 0.96-0.79 (30H, m), 0.06-0.01 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 86.8, 81.2, 81.0, 78.9, 73.4,

73.2, 72.5, 36.0, 33.6, 31.9, 31.3, 30.8, 29.9, 29.7, 29.6, 29.3, 28.0, 26.2, 26.0, 25.9, 25.8, 25.4, 25.1, 22.7, 18.1, 18.0, 17.9, 14.1, 7.2, -3.8, -4.2, -4.4, -4.6, -4.7, -5.4; IR (thin film) 2926, 2855, 1462, 1254, 1080, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{50}\text{H}_{104}\text{O}_5\text{Si}_3$, 995.6236 m/z ($\text{M}+\text{H}$)⁺; observed, 995.6243 m/z .



Primary alcohol **V-121** (0.79 mL, 5.0 mmol), triphenylphosphine (3.3 g, 12.5 mmol) and imidazole (0.89 g, 13.0 mmol) were dissolved in toluene (20 mL). Upon addition of iodine (3.43 g, 13.5 mmol) the clear, colorless solution turned yellowish brown and turbid. After 1 h vigorous stirring at room temperature, saturated sodium sulfite solution was added to the reaction until the yellowish brown color disappeared. The layers were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude product. Purification of the crude material by column chromatography (2% EtOAc in hexanes) afforded octane iodide **V-122** (1.06 g, 88%) as a yellow oil.

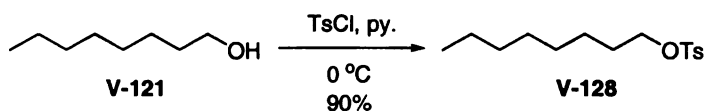
Data for octane iodide **V-122**: ^1H NMR (300 MHz, CDCl_3) δ 3.17 (2H, t, J = 6.9 Hz), 1.80 (2H, quint, J = 7.1 Hz), 1.36-1.25 (10H, m), 0.86 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 33.6, 31.7, 30.5, 29.1, 28.5, 22.6, 14.1, 7.4.



A solution of diisopropylamine (19.6 μL , 0.14 mmol) in THF (0.5 mL) was

cooled to -78 °C and ⁿBuLi (56 μL of 1.9 M solution, 0.14 mmol) was added to it. After 15 min, lactone (29.1 mg, 0.14 mmol) in THF (0.5 mL) was added and stirring was continued for 30 min during which time the solution was warmed to 0 °C. Iodide (16.8 mg, 0.07 mmol) was then added as a solution in 1 : 1 THF : HMPA (1.0 mL). The reaction was allowed to warm up room temperature. After 15 h, H₂O (2 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL), combined organic layers were dried (Na₂SO₄), concentrated and the crude product was purified by column chromatography (2%-5% EtOAc in hexanes) to afford sulfide as a mixture of a pair of epimers **V-123** (5.2 mg, 23%).

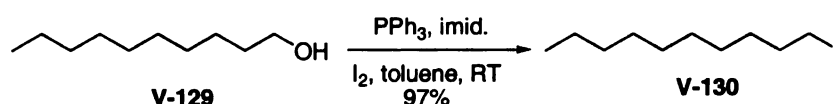
Data for **V-123**: ¹H NMR (300 MHz, CDCl₃) δ 7.58-7.48 (2H, m), 7.41-7.27 (3H, m), 4.51-4.40 (1H, m), 3.17 (3H, t, *J* = 7.1 Hz), 1.85-1.75 (2H, m), 1.43-1.20 (14H, m), 0.86 (3H, t, *J* = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 33.5, 31.8, 30.5, 29.5, 29.4, 29.2, 28.5, 22.6, 14.1, 7.2.



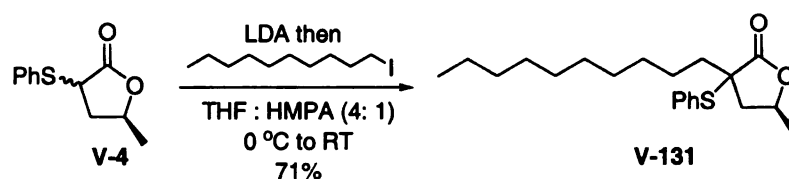
p-Toluenesulfonyl chloride (0.46 g, 2.4 mmol) was added dropwise to a stirred solution of pyridine (0.65 mL, 8.0 mmol) and *n*-octanol (0.31 mL, 2.0 mmol) maintained at 0 °C. The reaction mixture was allowed to stir for 3 h and then quenched with H₂O (4 mL) and extracted with CH₂Cl₂ (3×5 mL), and the combined organic layers were washed with 3 M HCl (3×2 mL) followed by 10% NaHCO₃ (2 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuum and the crude product purified by column chromatography (5% EtOAc in hexanes) to

afford tosylate **V-128** in 90% yield (0.512 g).

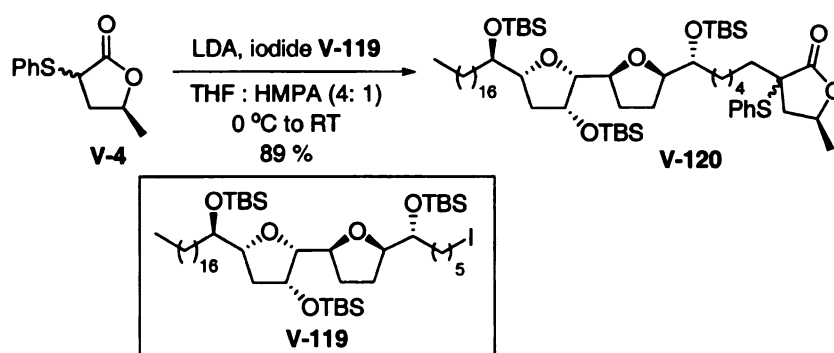
Data for tosylate **V-128**:⁸⁵ ^1H NMR (300 MHz, CDCl_3) δ 7.76 (2H, d, J = 8.3 Hz), 7.31 (2H, d, J = 8.8 Hz), 3.99 (3H, t, J = 6.3 Hz), 2.42 (3H, s), 1.63-1.58 (2H, m), 1.32-1.11 (10H, m), 0.84 (2H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 144.6, 129.8, 127.8, 70.7, 31.6, 29.0, 28.8, 25.3, 22.5, 21.6, 14.0.



Data for decane iodide **V-130**: ^1H NMR (300 MHz, CDCl_3) δ 3.17 (3H, t, J = 7.1 Hz), 1.85-1.75 (2H, m), 1.43-1.20 (14H, m), 0.86 (3H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 33.5, 31.8, 30.5, 29.5, 29.4, 29.2, 28.5, 22.6, 14.1, 7.2.



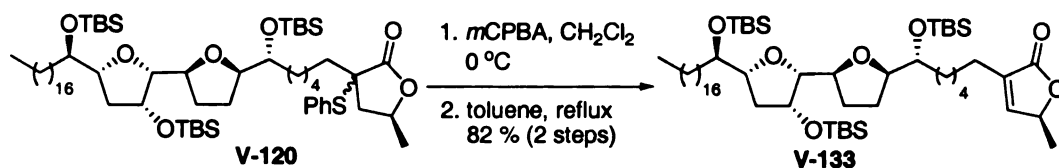
Data for **V-131**: ^1H NMR (300 MHz, CDCl_3) δ 7.58-7.48 (2H, m), 7.41-7.27 (3H, m), 4.51-4.40 (1H, m), 2.53-2.45 (1H, dd, J = 14.0, 7.7 Hz), 1.98-1.91 (1H, dd, J = 14.0, 6.9 Hz), 1.81-1.72 (2H, m), 1.62-1.20 (16H, m), 1.16 (3H, d, J = 6.0 Hz), 0.86 (3H, t, J = 6.6 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 177.1, 137.1, 136.8, 130.5, 129.7, 128.9, 73.2, 56.3, 40.1, 36.5, 34.6, 31.9, 29.6, 29.5, 29.4, 29.3, 24.7, 22.7, 21.5, 14.1.



A solution of diisopropylamine (12.9 μL , 0.09 mmol) in THF (0.5 mL) was

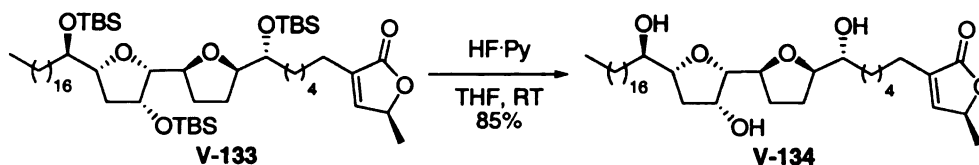
cooled to $-78\text{ }^{\circ}\text{C}$ and $n\text{-BuLi}$ (48 μL of 1.9 M solution, 0.09 mmol) was added to it. After 15 min, lactone (19.1 mg, 0.09 mmol) in THF (0.5 mL) was added and stirring was continued for 30 min during which time the solution was warmed to $0\text{ }^{\circ}\text{C}$. Iodide (45.6 mg, 0.045 mmol) was then added as a solution in 1 : 1 THF : HMPA (1.0 mL). The reaction was allowed to attain room temperature. After 15 h, H_2O (2 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL), combined organic layers were dried (Na_2SO_4), concentrated and the crude product was purified by column chromatography (1%-3% EtOAc in hexanes) to afford sulfide as a mixture of a pair of epimers **V-120** (44 mg, 89%).

Data for the mixture of a pair of epimers **V-120**: ^1H NMR (300 MHz, CDCl_3) δ 7.58-7.43 (2H, m), 7.40-7.28 (3H, m), 4.49-4.40 (1H, m), 4.22-4.17 (1H, m), 4.03-3.81 (4H, m), 3.80-3.73 (1H, m), 3.42 (1H, dd, $J = 8.2, 3.5\text{ Hz}$), 2.55-2.42 (1H, m), 2.09-1.66 (8H, m), 1.61-1.15 (44H, m), 0.96-0.79 (30H, m), 0.06-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 177.1, 136.8, 130.5, 129.7, 129.0, 86.8, 81.0, 79.0, 73.4, 73.2, 72.5, 57.1, 56.2, 40.1, 36.5, 31.9, 29.9, 29.7, 29.6, 29.4, 28.0, 26.3, 26.0, 25.9, 25.8, 24.8, 22.7, 21.5, 18.1, 17.9, 14.1, -3.8 , -4.2 , -4.4 , -4.5 , -4.6 , -5.4 ; IR (thin film) 2926, 2855, 1769, 1471, 1462, 1360, 1254, 1186, 1082, 939, 837, 775, 692 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{61}\text{H}_{115}\text{O}_7\text{SSi}_3$, 1075.7671 m/z ($\text{M}+\text{H}$) $^{+}$; observed, 1075.7659 m/z .



To an ice cold solution of sulfide mixtures **V-120** (15 mg, 0.014 mmol) in CH_2Cl_2 (1 mL), ca. 77% *m*CPBA (3.1 mg, 0.014 mmol) in CH_2Cl_2 (1 mL) was added drop wise. After 20 min, saturated NaHCO_3 solution (1 mL) was carefully added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 5 mL). The combined organic layers were dried and concentrated to afford the corresponding sulfoxide. The crude sulfoxide was taken up in toluene (2 mL) and heated to reflux for 4 h. After cooling the solution to room temperature, the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (5% EtOAc in hexanes) to afford conjugate lactone **V-133** (11.1 mg, 82%).

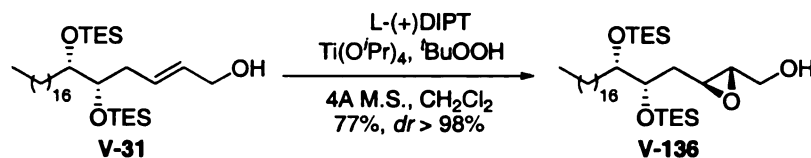
Data for conjugate lactone **V-133**: $[\alpha]_{\text{D}}^{20} +19.6$ (c 1.11, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.01-6.98 (1H, m), 5.01-4.96 (1H, m), 4.22-4.18 (1H, m), 4.03-3.94 (2H, m), 3.92-3.86 (2H, m), 3.80-3.75 (1H, m), 3.43 (1H, dd, $J = 8.0, 3.4$ Hz), 2.24 (2H, t, $J = 7.4$ Hz), 2.09-1.96 (2H, m), 1.86-1.77 (3H, m), 1.61-1.27 (44H, m), 0.93-0.84 (30H, m), 0.08-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 148.9, 134.2, 86.8, 81.2, 81.0, 79.0, 77.4, 73.5, 73.4, 72.5, 31.9, 31.3, 29.9, 29.7, 29.6, 29.5, 29.3, 28.0, 27.5, 26.2, 26.0, 25.9, 25.8, 25.4, 25.2, 22.7, 19.2, 18.1, 17.9, 14.1, -3.8, -4.2, -4.4, -4.6, -4.7, -5.4; IR (thin film) 2954, 2928, 2855, 1761, 1471, 1463, 1360, 1319, 1254, 1082, 1028, 939, 837, 808, 775, 721 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{55}\text{H}_{109}\text{O}_7\text{Si}_3$, 965.7481 m/z ($\text{M}+\text{H}$) $^+$; observed, 965.7465 m/z .



To a solution of conjugate lactone **V-133** (17 mg, 0.018 mmol) in THF (1.5 mL) taken in a polyethylene vial, HF·Py (62 μ L) was added at room temperature. After stirring for 12 h, the reaction was neutralized by saturate NaHCO₃ solution. H₂O (2 mL) and EtOAc (10 mL) were added and the layers were separated. The organic layer was washed with saturated CuSO₄ (2×4 mL) and the combined aqueous layers were extracted with EtOAc (3×10 mL). The organic layers were mixed, dried over Na₂SO₄, and the solvent was evaporated to afford a waxy material. Purification by column chromatography (EtOAc, 10% MeOH in EtOAc) gave synthesized mucoxin **V-134** as a colorless wax (9.6 mg, 85%).

Data for synthesized mucoxin **V-134**: $[\alpha]_D^{20}$ -3.0 (c 0.20, CHCl₃), ¹H NMR (500 MHz, CDCl₃) δ 7.01-6.99 (1H, m), 5.03-4.96 (1H, m), 4.36-4.20 (2H, m, H12/H14), 4.08-4.02 (1H, m, H16), 3.98-3.93 (1H, m, H9), 3.75 (1H, t, J = 3.1 Hz, H13), 3.57-3.52 (1H, m, H17), 3.46-3.40 (1H, m, H8), 2.39-2.32 (1H, m, H15), 2.28 (2H, t, J = 7.5 Hz), 2.11-2.04 (2H, m, H10, H11), 1.98-1.89 (3H, m, H10, H11, H15), 1.62-1.18 (47H, m), 0.89 (3H, t, J = 6.7 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 173.9, 148.9, 134.2, 83.7 (C13), 83.5 (C9), 80.1 (C16), 78.9 (C12), 77.4, 73.7 (C8), 73.5 (C17), 72.9 (C14), 67.9, 38.8 (C15), 34.3, 34.0, 31.9, 29.7, 29.6, 29.3, 29.1, 28.7, 27.7, 27.3, 26.0, 25.5, 25.1, 22.7, 19.2, 14.1; HRMS (ESI) calcd for C₃₇H₆₆O₇Na, 645.4706 m/z (M+Na)⁺; observed, 645.4721 m/z .

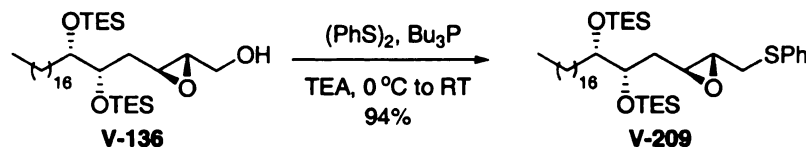
All the procedures to prepare pseudo-enantiomer **V-135** are the same as the preparation of mucoxin **V-134**.



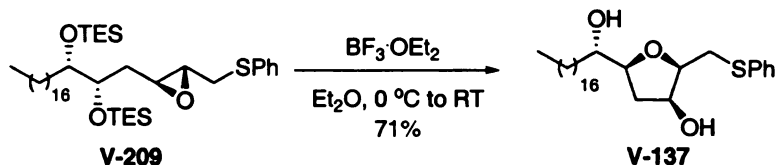
A two necked round bottom flask charged with 4 Å mol. sieves (3.1 g) and CH_2Cl_2 (28 mL) was cooled to $-20\text{ }^\circ\text{C}$. To this, $\text{Ti}(\text{O}^i\text{Pr})_4$ (1.76 mL, 5.95 mmol) and a CH_2Cl_2 solution of L-(+)-DIPT (1.50 mL, 7.14 mmol in 22 mL CH_2Cl_2) were added in that order and stirred at the same temperature under N_2 for 30 min. After cooling the complex to $-30\text{ }^\circ\text{C}$, $^t\text{BuOOH}$ (2.8 mL of 3.6 M solution in toluene, 10.1 mmol) was added dropwise and the mixture was stirred for another 45 min. A solution of allylic alcohol (3.56 g, 5.95 mmol) in CH_2Cl_2 (22 mL) was added via a syringe pump over 45 min. The reaction was warmed to $-20\text{ }^\circ\text{C}$, stirred for 2 h and then quenched by adding saturated Na_2SO_4 and Na_2SO_3 solutions (5.0 mL each). Et_2O (18 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 (14 mL), celite was added and the mixture was filtered through a pad of celite. The filter cake was washed with Et_2O (ca. 180 mL) until it turned dry and granular. The filtrate was concentrated and epoxy alcohol **V-136** was isolated in 77% yield (2.83 g) after purification by column chromatography (5% EtOAc in hexanes).

Data for epoxy alcohol **V-136**: $[\alpha]_D^{20} -39.6$ (c 1.30, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 3.94-3.87 (1H, m), 3.84-3.78 (1H, m), 3.61-3.53 (2H, m), 3.08-3.03 (1H, m), 2.93-2.91 (1H, m), 1.74-1.55 (4H, m), 1.55-1.13 (30H, m), 0.97-0.89 (18H, m), 0.87

(3H, dd, $J = 6.6, 3.5$ Hz), 0.63-0.52 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 74.9, 72.6, 61.7, 59.3, 53.9, 32.8, 31.9, 29.9, 29.8, 29.7, 29.6, 29.3, 26.6, 22.7, 14.1, 6.9, 6.8, 5.1, 5.0.

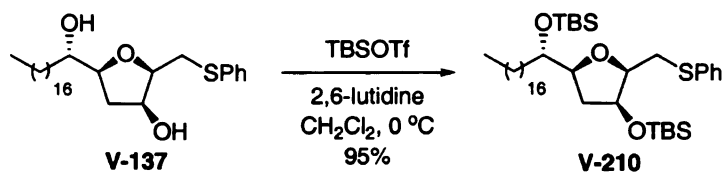


Data for epoxy thiophenyl **V-209**: $[\alpha]_{\text{D}}^{20} -27.7$ (c 1.23, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.16 (5H, m), 3.79-3.73 (1H, m), 3.54-3.51 (1H, m), 3.10-3.05 (1H, m), 2.98-2.87 (2H, m), 2.84-2.79 (1H, m), 1.61-1.40 (6H, m), 1.32-1.04 (28H, m), 0.95-0.82 (21H, m), 0.67-0.50 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 135.5, 130.3, 129.0, 126.6, 74.9, 72.5, 57.8, 57.2, 36.6, 33.0, 31.9, 31.6, 30.0, 29.8, 29.7, 29.3, 26.6, 22.7, 14.1, 6.8, 5.1, 5.0; IR (thin film) 2955, 2924, 2876, 2855, 1458, 1414, 1377, 1238, 1094, 1005, 739 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{41}\text{H}_{79}\text{O}_3\text{Si}_2\text{S}$, 707.5289 m/z ($\text{M}+\text{H}$) $^+$; observed, 707.5306 m/z .

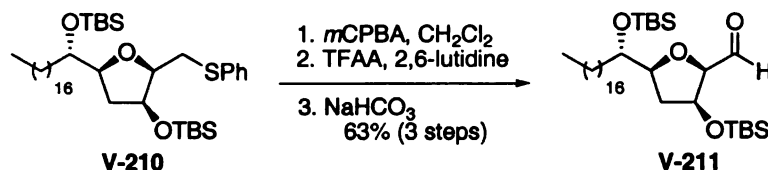


Data for THF diol **V-137**: $[\alpha]_{\text{D}}^{20} +29.6$ (c 1.00, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.10 (5H, m), 4.18-4.15 (1H, m), 3.99-3.94 (1H, m), 3.85-3.79 (1H, m), 3.50-3.40 (3H, m), 3.22-3.19 (2H, m), 2.36-2.26 (1H, m), 1.88-1.82 (1H, dd, $J = 14.0, 4.6$ Hz), 1.57-1.23 (32H, m), 0.85 (3H, t, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 136.4, 128.9, 128.8, 125.8, 82.5, 79.9, 73.6, 71.1, 38.0, 34.0, 32.1, 31.8, 29.6, 29.3, 26.0, 22.6, 14.0; IR (thin film) 3386 (br), 2919, 2849, 1653, 1470, 1086, 1036, 946,

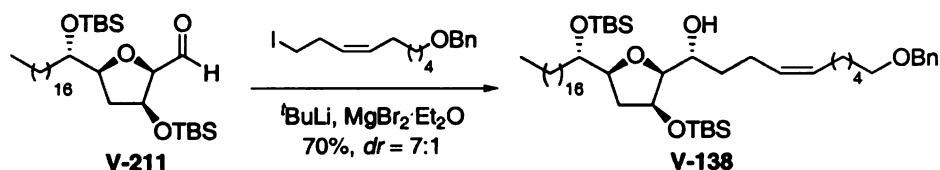
689 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{50}\text{O}_3\text{SNa}$, 501.3378 m/z ($\text{M}+\text{Na}$) $^{+}$; observed, 501.3384 m/z .



Data for TBS protected THF diol **V-210**: $[\alpha]_{\text{D}}^{20} +26.3$ (c 1.26, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.12 (5H, m), 4.33-4.29 (1H, m), 3.81-3.70 (3H, m), 3.14 (2H, d, $J = 6.6$ Hz), 2.12-2.02 (1H, m), 1.70-1.62 (1H, m), 1.45-1.17 (32H, m), 1.02-0.82 (21H, m), 0.19-0.04 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 136.9, 128.8, 128.4, 125.6, 81.5, 81.2, 74.6, 72.0, 37.1, 31.9, 31.6, 29.9, 29.8, 29.6, 29.3, 26.0, 25.8, 25.4, 22.7, 18.3, 18.0, 14.1, -4.0, -4.4, -4.7, -5.0.

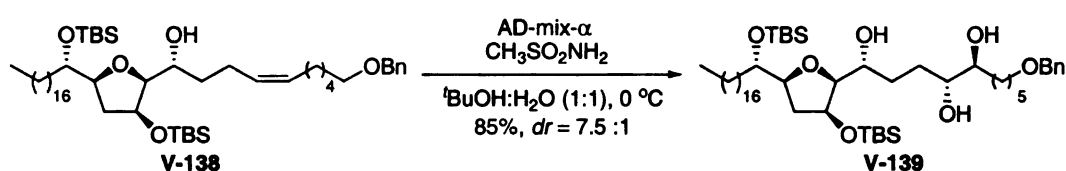


Data for aldehyde **V-211**: $[\alpha]_{\text{D}}^{20} +32.8$ (c 1.09, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 9.62 (1H, d, $J = 2.6$ Hz), 4.66-4.60 (1H, m), 4.04-4.01 (1H, dd, $J = 5.6, 2.7$ Hz), 3.95 (1H, q, $J = 7.1$ Hz), 3.83-3.81 (1H, m), 2.19-2.10 (1H, m), 1.79-1.71 (1H, m), 1.59-1.23 (30H, m), 0.99-0.72 (21H, m), 0.07-0.01 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 202.0, 86.1, 82.9, 75.0, 74.6, 37.5, 33.4, 31.9, 29.9, 29.7, 29.6, 29.3, 26.0, 25.6, 25.2, 22.7, 18.3, 17.9, 14.1, -4.1, -4.6, -4.8, -5.3.

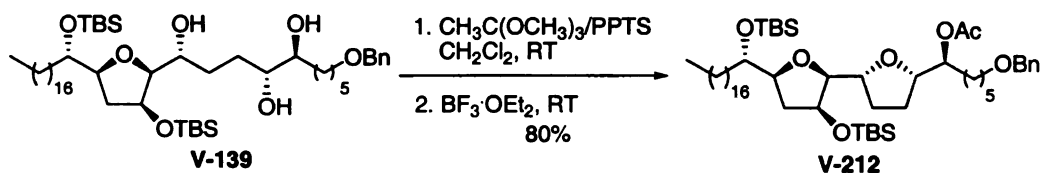


Data for pure alcohol **V-138**: $[\alpha]_{\text{D}}^{20} +5.3$ (c 2.09, CHCl_3), ^1H NMR (300 MHz, CDCl_3)

δ 7.32-7.23 (5H, m), 5.38-5.31 (2H, m), 4.47 (2H, s), 4.38-4.34 (1H, m), 3.80-3.68 (3H, m), 3.50-3.41 (3H, m), 2.11-1.93 (6H, m), 1.69-1.43 (7H, m), 1.35-1.12 (33H, m), 0.87-0.83 (21H, m), 0.07-0.05 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 130.0, 129.5, 128.3, 127.6, 127.4, 100.5, 83.6, 80.1, 74.5, 73.4, 72.8, 70.4, 69.9, 37.8, 33.4, 31.9, 29.8, 29.7, 29.3, 27.1, 26.0, 25.7, 25.3, 22.7, 18.3, 17.9, 14.1, -4.1, -4.6, -4.8, -5.3.

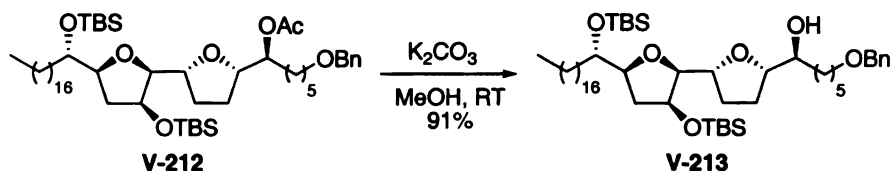


Data for inseparable triol mixtures: ^1H NMR (300 MHz, CDCl_3) δ 7.29-7.21 (5H, m), 4.45 (2H, s), 4.40-4.36 (1H, m), 3.81-3.73 (2H, m), 3.68-3.67 (1H, m), 3.62-3.58 (2H, m), 3.48 (1H, t, $J = 5.5$ Hz), 3.42 (2H, t, $J = 6.6$ Hz), 2.08-2.01 (1H, m), 1.71-1.59 (7H, m), 1.57-1.23 (38H, m), 0.87-0.83 (21H, m), 0.06-0.04 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.6, 128.2, 127.5, 127.3, 83.3, 79.9, 74.4, 74.3, 74.0, 73.4, 72.8, 71.1, 70.3, 37.5, 33.4, 31.8, 30.9, 29.8, 29.7, 29.6, 29.3, 28.6, 26.2, 25.9, 25.6, 25.2, 22.6, 18.2, 17.8, 14.1, -4.2, -4.5, -4.7, -5.2.

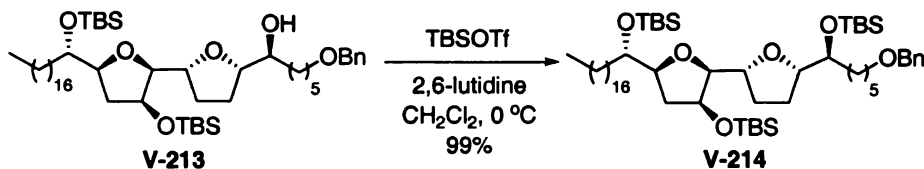


Data for pure bis-THF acetate **V-212**: $[\alpha]_D^{20}$ -5.3 (c 0.95, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.25 (5H, m), 4.90-4.84 (1H, m), 4.46 (2H, s), 4.20-4.17 (1H, m), 4.05-3.89 (2H, m), 3.84-3.78 (2H, m), 3.45-3.39 (3H, m), 2.01 (3H, s), 1.99-1.83 (1H, m), 1.78-1.52 (6H, m), 1.37-1.21 (33H, m), 0.96-0.83 (21H, m), 0.07-0.02 (12H, m);

^{13}C NMR (75 MHz, CDCl_3) δ 170.1, 138.6, 128.3, 127.5, 127.4, 86.2, 81.4, 79.2, 78.9, 75.1, 74.2, 72.8, 70.3, 36.7, 32.1, 31.9, 30.6, 29.9, 29.7, 29.6, 29.3, 27.7, 27.4, 26.1, 25.9, 25.7, 25.3, 22.6, 21.1, 18.2, 14.0, -3.9, -4.2, -4.8, -5.4.

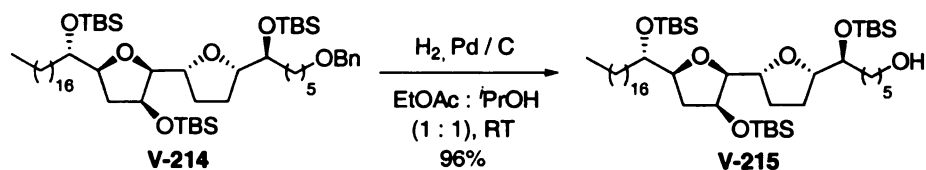


Data for bis-THF alcohol **V-213**: $[\alpha]_{\text{D}}^{20}$ -1.8 (c 1.35, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.23 (5H, m), 4.47 (2H, s), 4.22-4.10 (2H, m), 3.84-3.69 (3H, m), 3.46-3.40 (3H, m), 3.40-3.34 (1H, m), 2.47 (1H, br), 2.10-1.84 (2H, m), 1.67-1.13 (44H, m) 0.95-0.83 (21H, m), 0.08-0.02 (12H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.1, 82.6, 81.6, 78.5, 74.5, 73.9, 72.8, 72.7, 70.4, 37.2, 33.9, 32.6, 31.9, 29.8, 29.7, 29.6, 29.3, 28.4, 27.7, 26.2, 26.0, 25.7, 25.6, 22.6, 18.3, 17.8, 14.1, -4.0, -4.1, -4.8, -5.3; IR (thin film) 3476 (br), 2926, 2855, 1462, 1362, 1254, 1080, 937, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{51}\text{H}_{97}\text{O}_6\text{Si}_2$, 861.6824 m/z ($\text{M}+\text{H}$) $^+$; observed, 861.6819 m/z .

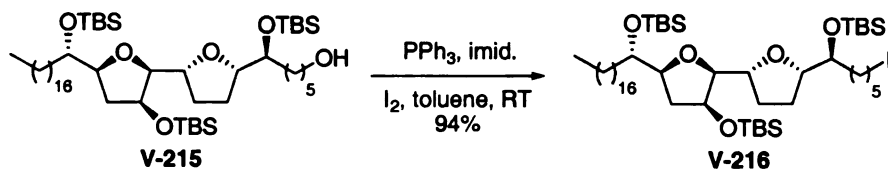


Data for tris-TBS ether **V-214**: $[\alpha]_{\text{D}}^{20}$ -12.2 (c 1.63, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 4.47 (2H, s), 4.22-4.18 (1H, m), 4.03-3.81 (4H, m), 3.79-3.71 (1H, m), 3.51-3.39 (3H, m), 2.08-1.69 (3H, m), 1.62-1.11 (39H, m), 0.96-0.79 (30H, m), 0.06- -0.17 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.8, 81.2, 81.0, 78.9, 74.5, 73.4, 72.8, 72.5, 70.5, 36.0, 31.9, 31.2, 30.7,

29.9, 29.8, 29.7, 29.6, 29.3, 28.0, 26.4, 26.2, 26.0, 25.9, 25.8, 25.5, 22.7, 18.1, 17.9, 14.1, -3.8, -4.3, -4.4, -4.7, -5.4.

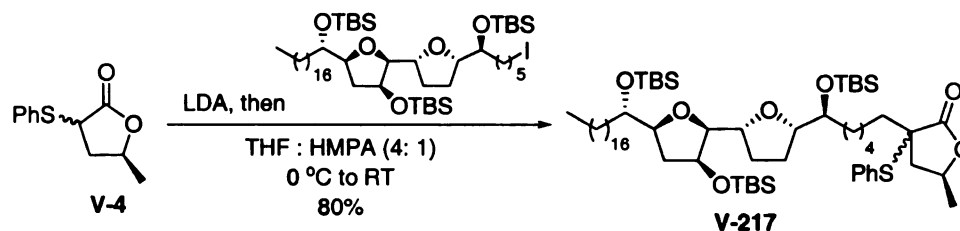


Data for primary alcohol **V-215**: $[\alpha]_D^{20}$ -7.6 (c 2.16, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 4.22-4.17 (1H, m), 4.03-3.81 (4H, m), 3.79-3.72 (1H, m), 3.60 (2H, t, J = 6.6 Hz), 3.40 (1H, dd, J = 7.9, 3.3 Hz), 2.03-1.72 (4H, m), 1.61-1.12 (38H, m), 0.96-0.79 (30H, m), 0.05- 0.00 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 86.8, 81.2, 81.0, 78.9, 73.4, 72.5, 72.5, 63.0, 60.3, 36.1, 32.8, 31.9, 31.4, 30.9, 29.9, 29.8, 29.6, 29.3, 28.0, 26.2, 26.0, 25.9, 25.8, 25.5, 22.7, 18.1, 18.0, 17.9, 14.1, -3.8, -4.3, -4.4, -4.6, -4.7, -5.4; IR (thin film) 3410 (br), 2926, 2855, 1653, 1471, 1462, 1362, 1254, 1082, 937, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{50}\text{H}_{105}\text{O}_6\text{Si}_3$, 885.7219 m/z ($\text{M}+\text{H}$) $^+$; observed, 885.7205 m/z .

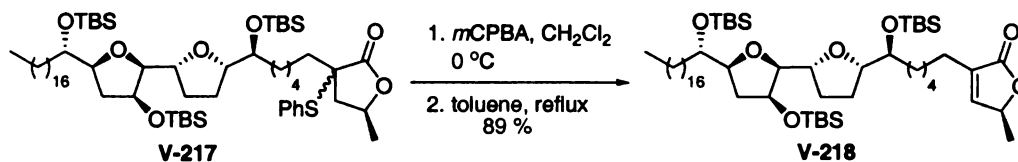


Data for iodide **V-216**: $[\alpha]_D^{20}$ -9.6 (c 2.00, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 4.21-4.18 (1H, m), 4.06-3.82 (4H, m), 3.80-3.73 (1H, m), 3.42 (1H, dd, J = 8.2, 3.5 Hz), 3.15 (2H, t, J = 6.9 Hz), 2.09-1.66 (6H, m), 1.61-1.12 (36H, m), 0.96-0.73 (30H, m), 0.06-0.00 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 86.8, 81.2, 81.0, 78.9, 73.5, 73.2, 72.6, 36.0, 33.6, 31.9, 31.3, 30.8, 29.9, 29.7, 29.6, 29.3, 28.0, 26.2, 26.0, 25.9, 25.8, 25.4, 25.1, 22.7, 18.1, 18.0, 17.9, 14.1, 7.2, -3.8, -4.2, -4.4, -4.6, -4.7, -5.4; IR

(thin film) 2953, 2926, 2855, 1471, 1462, 1362, 1253, 1084, 937, 837, 775 cm^{-1} ;
 HRMS (ESI) calcd for $\text{C}_{50}\text{H}_{104}\text{O}_5\text{Si}_3$, 995.6236 m/z ($\text{M}+\text{H}$)⁺; observed, 995.6255
 m/z .

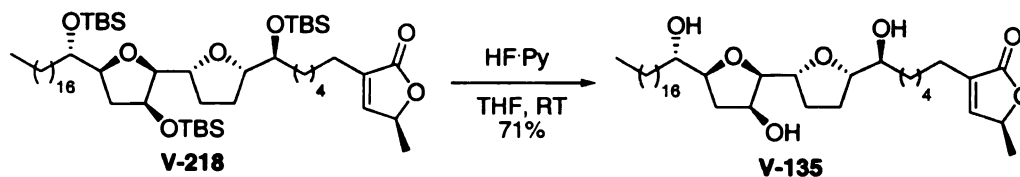


Data for the sulfide mixtures **V-217**: $[\alpha]_{\text{D}}^{20} -22.5$ (c 0.53, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.58-7.43 (2H, m), 7.41-7.34 (3H, m), 4.52-4.47 (1H, m), 4.24-4.22 (1H, m), 4.06-4.00 (1H, m), 4.00-3.93 (1H, m), 3.93-3.87 (2H, m), 3.79-3.77 (1H, m), 3.46 (1H, dd, $J = 8.1, 3.5$ Hz), 2.55-2.50 (1H, m), 2.09-1.95 (3H, m), 1.87-1.74 (5H, m), 1.61-1.20 (44H, m), 0.96-0.79 (30H, m), 0.06-0.00 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 177.0, 136.8, 130.5, 129.7, 129.0, 86.8, 81.2, 81.1, 79.0, 73.5, 73.4, 73.2, 72.6, 56.2, 40.1, 36.6, 36.1, 31.9, 31.4, 30.0, 29.9, 29.7, 29.6, 29.4, 28.1, 26.2, 26.1, 26.0, 25.9, 25.8, 25.5, 24.8, 22.7, 21.5, 18.1, 17.9, 14.1, -3.8, -4.2, -4.3, -4.5, -4.6, -5.4; IR (thin film) 2926, 2853, 1773, 1458, 1252, 1184, 1076, 835, 806, 774 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{61}\text{H}_{115}\text{O}_7\text{SSi}_3$, 1075.7671 m/z ($\text{M}+\text{H}$)⁺; observed, 1075.7677 m/z .



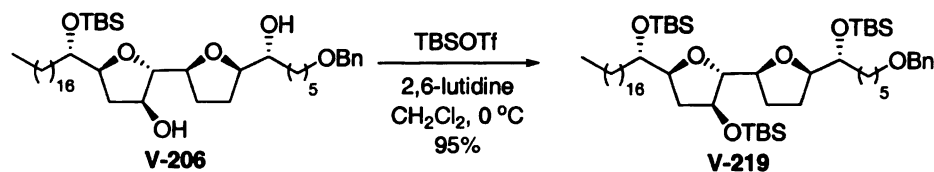
Data for conjugate lactone **V-218**: $[\alpha]_{\text{D}}^{20} -7.5$ (c 0.20, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.01-6.99 (1H, m), 5.01-4.98 (1H, m), 4.25-4.23 (1H, m), 4.06-4.01 (1H, m), 4.01-3.96 (1H, m), 3.94-3.86 (2H, m), 3.81-3.76 (1H, m), 3.45 (1H, dd, $J = 8.0, 3.4$

Hz), 2.27 (2H, t, $J = 7.4$ Hz), 2.08-1.96 (2H, m), 1.86-1.77 (3H, m), 1.61-1.27 (44H, m), 0.93-0.83 (30H, m), 0.08-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 148.9, 134.3, 86.8, 81.2, 81.1, 79.0, 77.4, 73.5, 73.4, 72.6, 31.9, 31.4, 29.9, 29.7, 29.6, 29.5, 29.3, 28.1, 27.6, 26.2, 26.0, 25.9, 25.8, 25.5, 25.2, 22.7, 19.2, 18.1, 17.9, 14.1, -3.8, -4.2, -4.3, -4.5, -4.6, -5.4; IR (thin film) 2926, 2855, 1761, 1462, 1254, 1080, 835, 775 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{55}\text{H}_{109}\text{O}_7\text{Si}_3$, 965.7481 m/z ($\text{M}+\text{H}$) $^+$; observed, 965.7449 m/z .

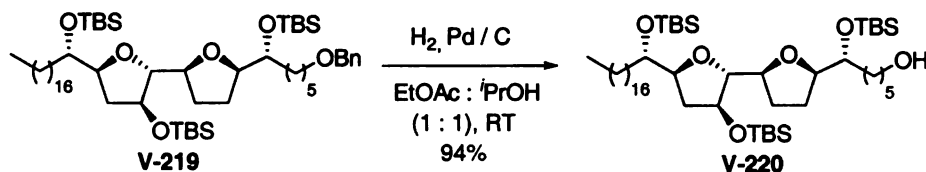


Data for pseudo-enantiomer **V-135**: $[\alpha]_{\text{D}}^{20} +6.3$ (c 0.51, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.01-6.99 (1H, m), 5.03-4.96 (1H, m), 4.36-4.20 (2H, m, H12/H14), 4.08-4.02 (1H, m, H16), 3.98-3.93 (1H, m, H9), 3.75 (1H, t, $J = 3.1$ Hz, H13), 3.57-3.52 (1H, m, H17), 3.46-3.40 (1H, m, H8), 2.39-2.32 (1H, m, H15), 2.28 (2H, t, $J = 7.5$ Hz), 2.11-2.04 (2H, m, H10, H11), 1.98-1.89 (3H, m, H10, H11, H15), 1.62-1.18 (47H, m), 0.89 (3H, t, $J = 6.7$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 173.9, 148.9, 134.2, 83.7 (C13), 83.5 (C9), 80.1 (C16), 78.9 (C12), 77.4, 73.7 (C8), 73.5 (C17), 72.9 (C14), 67.9, 38.8 (C15), 34.3, 34.0, 31.9, 29.7, 29.6, 29.3, 29.1, 28.7, 27.7, 27.3, 26.0, 25.5, 25.1, 22.7, 19.2, 14.1.

All the procedures to prepare different diastereomers are the same as the preparation of mucoxin V-134.



Data for tris-TBS ether **V-219**: $[\alpha]_{\text{D}}^{20} +8.6$ (c 2.87, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.27 (5H, m), 4.51 (2H, s), 4.36-4.32 (1H, dd, $J = 12.3, 6.9$ Hz), 3.94-3.90 (1H, dd, $J = 14.7, 6.7$ Hz), 3.89-3.86 (1H, td, $J = 7.1, 3.4$ Hz), 3.80-3.76 (1H, m), 3.68-3.62 (2H, m), 3.94-3.90 (1H, dd, $J = 5.4, 3.4$ Hz), 3.47 (2H, t, $J = 6.6$ Hz), 2.12-2.06 (1H, m), 1.86-1.80 (2H, m), 1.76-1.60 (5H, m), 1.52-1.22 (38H, m), 0.93-0.86 (30H, m), 0.09-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.5, 82.9, 81.5, 79.0, 74.9, 74.8, 73.7, 72.9, 70.5, 37.3, 33.0, 32.8, 31.9, 29.9, 29.8, 29.7, 29.6, 29.4, 27.9, 27.0, 26.5, 26.0, 25.8, 25.5, 25.3, 22.7, 18.3, 17.9, 14.1, -4.1, -4.2, -4.5, -4.7, -4.8, -4.9.



Data for primary alcohol **V-220**: $[\alpha]_{\text{D}}^{20} +14.8$ (c 1.98, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 4.33-3.94 (1H, dd, $J = 12.2, 6.8$ Hz), 3.94-3.90 (1H, dd, $J = 14.7, 6.8$ Hz), 3.89-3.85 (1H, td, $J = 7.1, 3.4$ Hz), 3.81-3.77 (1H, m), 3.69-3.59 (5H, m), 2.14-2.07 (1H, m), 1.91-1.80 (2H, m), 1.76-1.62 (3H, m), 1.62-1.45 (2H, m), 1.44-1.21 (38H, m), 0.93-0.86 (30H, m), 0.09-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 86.5, 82.9, 81.6, 79.1, 75.1, 74.7, 73.9, 63.0, 37.4, 33.1, 32.8, 32.6, 31.9, 29.9, 29.7, 29.6,

-4.7, -4.9.

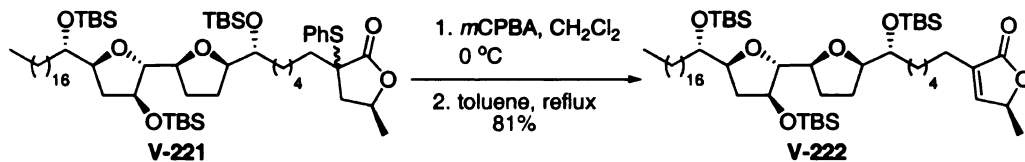


-4.2, -4.5, -4.6, -4.7, -4.8.

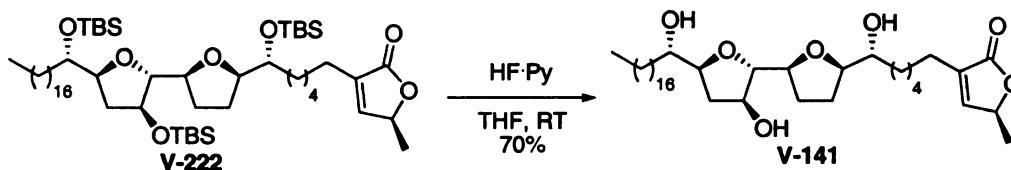


0.94-0.84 (30H, m), 0.12-0.04 (18H, m); ¹³C NMR (125 MHz, CDCl₃) δ 177.0, 137.1,

40.1, 37.3, 36.4, 33.0, 32.8, 31.9, 30.0, 29.9, 29.7, 29.6, 29.3, 27.9, 27.0, 26.0, 25.8, 25.5, 25.2, 24.7, 22.7, 21.5, 18.3, 17.9, 14.1, -4.1, -4.2, -4.5, -4.6, -4.7, -4.9.

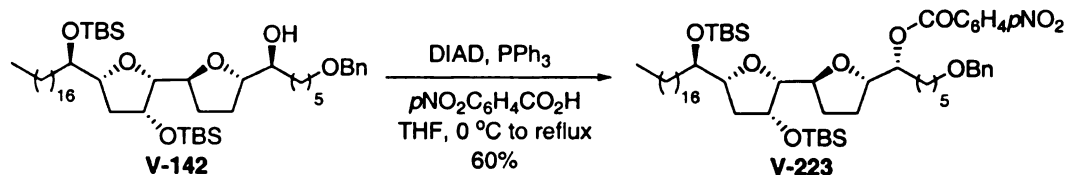


Data for conjugate lactone **V-222**: $[\alpha]_D^{20} +19.8$ (c 2.49, CHCl₃) ¹H NMR (500 MHz, CDCl₃) δ 6.98 (1H, d, *J* = 1.5 Hz), 5.02-4.98 (1H, qd, *J* = 6.6, 1.6 Hz), 4.34-4.30 (1H, q, *J* = 6.9 Hz), 3.93-3.88 (1H, dd, *J* = 14.8, 6.7 Hz), 3.88-3.85 (1H, td, *J* = 6.9, 3.4 Hz), 3.80-3.75 (1H, m), 3.69-3.58 (3H, m), 2.27 (2H, t, *J* = 4.5 Hz), 2.12-2.06 (1H, m), 1.86-1.80 (2H, m), 1.77-1.64 (3H, m), 1.60-1.24 (41H, m), 0.93-0.85 (30H, m), 0.10-0.04 (18H, m); ¹³C NMR (125 MHz, CDCl₃) δ 173.8, 148.8, 134.3, 86.5, 82.8, 81.5, 79.0, 77.4, 74.9, 74.7, 73.7, 37.3, 33.0, 32.7, 31.9, 29.9, 29.7, 29.6, 29.3, 27.9, 27.5, 27.0, 26.0, 25.8, 25.5, 25.2, 22.7, 19.2, 18.3, 18.2, 17.9, 14.1, -4.1, -4.2, -4.5, -4.6, -4.6, -4.8.

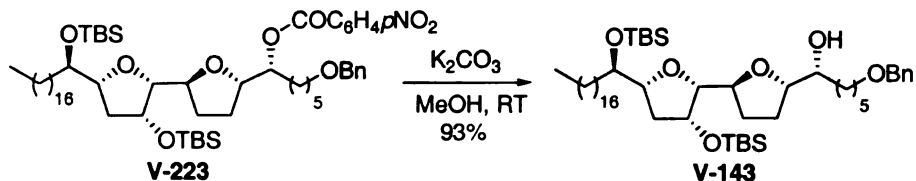


Data for full length *ttcTTT* diastereomer **V-141**: $[\alpha]_D^{20} +10.3$ (c 1.37, CHCl₃) ¹H NMR (500 MHz, CDCl₃) δ 6.99 (1H, d, *J* = 1.7 Hz), 5.02-4.98 (1H, qd, *J* = 6.8, 1.7 Hz), 4.30-4.26 (1H, m, H14), 4.09-4.05 (1H, m, H16), 4.03-3.98 (1H, m, H12), 3.88 (1H, t, *J* = 3.2 Hz), 3.88-3.85 (1H, m, H9), 3.56-3.51 (1H, m, H17), 3.40-3.34 (1H, m, H8), 2.80-2.72 (1H, br), 2.48-2.41 (1H, m, H15), 2.28 (2H, t, *J* = 7.7 Hz), 2.02-1.92 (3H, H10, H11, H11), 1.87-1.81 (2H, m, H10, H15), 1.64-1.50 (6H, m), 1.48-1.22 (37H,

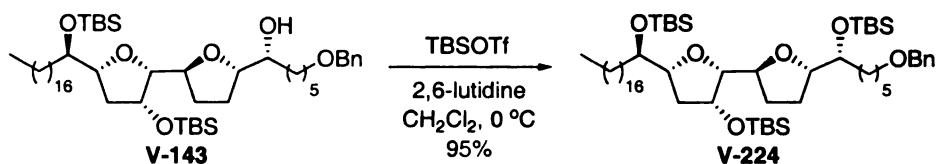
m), 0.88 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 148.9, 134.2, 88.6 (C13), 82.6 (C9), 81.6 (C16), 79.7 (C12), 77.4, 74.5 (C8), 74.4 (C17), 74.0 (C14), 37.9 (C15), 34.3, 33.9, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.3, 28.1, 27.4, 25.8, 25.4, 25.1, 22.7, 19.2, 14.1.



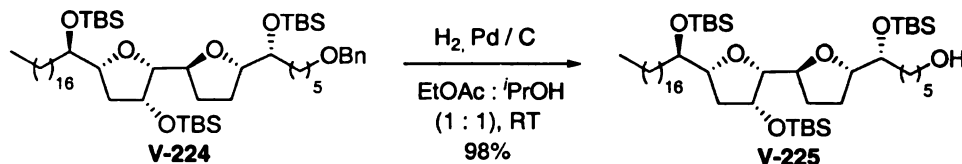
Data for ester **V-223**: $[\alpha]_{\text{D}}^{20}$ -4.3 (c 1.27, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 8.21-8.10 (4H, m), 7.31-7.24 (5H, m), 5.22-5.10 (1H, m), 4.43 (2H, s), 4.21-4.11 (3H, m), 3.82-3.63 (3H, m), 3.51-3.37 (3H, m), 2.12-1.91 (4H, m), 1.88-1.49 (12H, m), 1.42-1.21 (30H, m), 0.91-0.82 (30H, m), 0.06- -0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5, 138.6, 130.8, 130.7, 128.3, 127.6, 127.5, 127.4, 123.5, 109.8, 85.6, 81.6, 79.0, 77.5, 74.9, 74.5, 72.8, 70.2, 33.4, 31.9, 29.9, 29.7, 29.6, 29.3, 28.6, 28.0, 26.0, 25.7, 25.4, 22.7, 18.3, 17.8, 14.1, -3.9, -4.0, -4.7, -5.3.



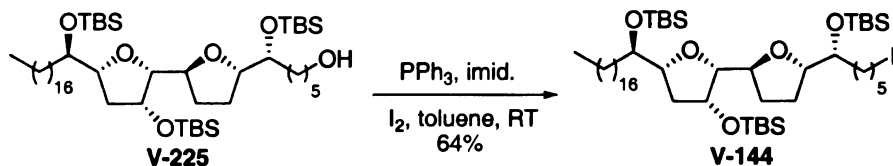
Data for alcohol **V-143**: $[\alpha]_{\text{D}}^{20}$ -4.6 (c 1.91, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.24 (5H, m), 4.47 (2H, s), 4.26-4.18 (1H, m), 3.82-3.70 (5H, m), 3.52-3.41 (3H, m), 2.17-2.00 (1H, m), 1.95-1.80 (2H, m), 1.80-1.65 (1H, m), 1.63-1.49 (7H, m), 1.49-1.21 (36H, m), 0.91-0.82 (30H, m), 0.06-0.02 (18H, m).



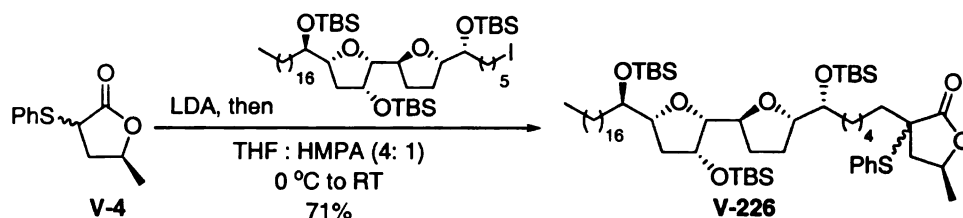
Data for tris-TBS ether **V-224**: ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.27 (5H, m), 4.51 (2H, s), 4.26-4.16 (2H, m), 3.94-3.82 (3H, m), 3.74 (1H, quint, $J = 4.0$ Hz), 3.47 (2H, t, $J = 6.5$ Hz), 3.42 (1H, dd, $J = 8.1, 3.7$ Hz), 2.08-2.01 (2H, m), 1.98-1.72 (2H, m), 1.66-1.20 (42H, m), 0.93-0.86 (30H, m), 0.09-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.7, 128.3, 127.6, 86.3, 81.8, 78.6, 74.1, 73.7, 72.8, 72.5, 70.5, 36.5, 34.9, 32.1, 31.9, 31.5, 29.9, 29.8, 29.7, 29.4, 28.8, 28.6, 26.4, 26.2, 25.9, 25.8, 25.6, 25.1, 22.7, 18.2, 17.9, 14.1, -3.6, -3.9, -4.0, -4.2, -4.6, -5.3.



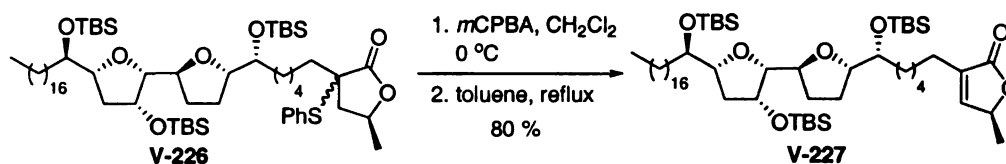
Data for primary alcohol **V-225**: ^1H NMR (300 MHz, CDCl_3) δ 4.22-4.11 (2H, m), 3.91-3.79 (3H, m), 3.63-3.58 (2H, m), 3.45-3.37 (1H, m), 2.09-1.96 (2H, m), 1.92-1.65 (2H, m), 1.63-1.46 (4H, m), 1.45-1.22 (38H, m), 0.91-0.82 (30H, m), 0.09-0.01 (18H, m).



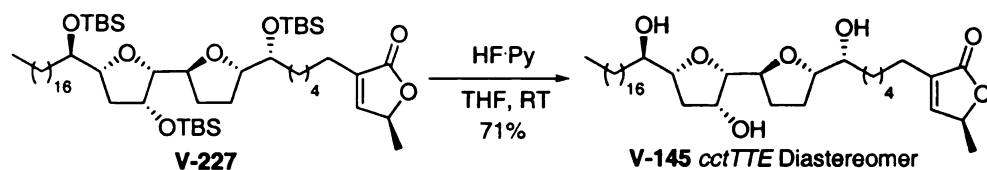
Data for iodide **V-144**: ^1H NMR (300 MHz, CDCl_3) δ 4.25-4.14 (2H, m), 3.95-3.76 (4H, m), 3.47-3.38 (1H, m), 3.22-3.13 (2H, m), 2.03-1.97 (2H, m), 1.88-1.67 (4H, m), 1.58-1.49 (3H, m), 1.44-1.23 (37H, m), 0.86-0.79 (30H, m), 0.08-0.01 (18H, m).



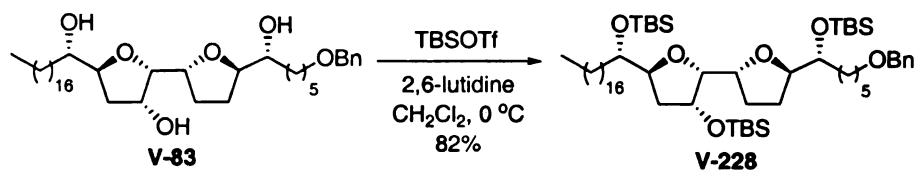
Data for sulfide mixtures **V-226**: $[\alpha]_{\text{D}}^{20}$ -19.6 (c 1.06, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.58-7.52 (2H, m), 7.42-7.33 (3H, m), 4.62-4.46 (1H, m), 4.24-4.16 (2H, m), 3.93-3.80 (4H, m) 3.44-3.41 (1H, dd, J = 8.2, 3.7 Hz), 2.53-2.49 (1H, m), 2.42-2.22 (1H, m), 2.09-2.02 (2H, m), 2.00-1.90 (2H, m), 1.80-1.71 (4H, m), 1.62-1.20 (40H, m), 0.91-0.86 (30H, m), 0.10-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 177.3, 137.3, 137.1, 133.7, 130.7, 129.9, 129.5, 129.2, 128.9, 86.6, 81.9, 81.5, 78.5, 77.5, 74.1, 73.4, 72.8, 56.4, 45.7, 40.4, 37.8, 36.9, 36.7, 35.0, 32.2, 32.1, 30.2, 30.1, 29.9, 29.6, 29.0, 26.3, 26.2, 26.0, 25.6, 25.5, 24.9, 22.9, 21.8, 21.1, 18.4 18.1, 14.4, -3.7, -3.8, -3.9, -4.3, -4.5, -5.1.



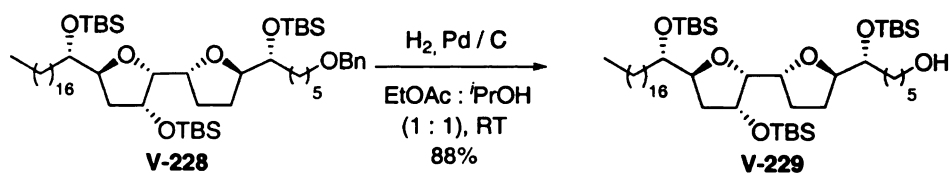
Data for conjugate lactone **V-225**: $[\alpha]_{\text{D}}^{20}$ +2.2 (c 0.74, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 6.98 (1H, d, J = 1.5 Hz), 5.02-4.98 (1H, qd, J = 6.8, 1.7 Hz), 4.24-4.17 (2H, m), 3.94-3.82 (4H, m), 3.43-3.41 (1H, dd, J = 8.2, 3.7 Hz), 2.26 (2H, t, J = 8.2 Hz), 2.09-2.02 (2H, m), 1.96-1.86 (1H, m), 1.81-1.71 (2H, m), 1.60-1.22 (44H, m), 0.90-0.86 (30H, m), 0.10-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 165.6, 148.9, 134.2, 86.4, 81.7, 81.2, 78.2, 77.4, 73.8, 73.1, 72.5, 36.5, 34.8, 31.9, 31.8, 29.9, 29.7, 29.6, 29.4, 28.8, 27.3, 26.0, 25.7, 25.3, 25.2, 22.7, 19.2, 18.2, 17.9, 14.1, -3.9, -4.1, -4.2, -4.6, -4.7 -5.4.



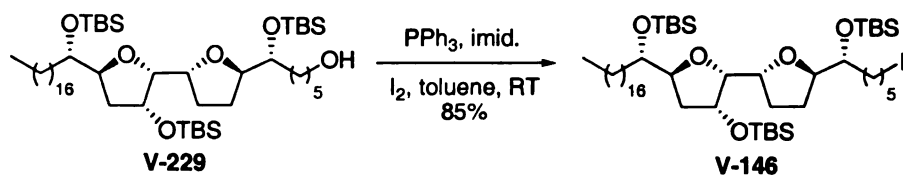
Data for full length *cctTTE* diastereomer **V-145**: $[\alpha]_D^{20} +5.40$ (c 0.53, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 6.99 (1H, d, $J = 1.5$ Hz), 5.02-4.98 (1H, qd, $J = 6.8, 1.5$ Hz), 4.33-4.27 (1H, m), 4.24-4.20 (1H, m), 4.08-4.04 (1H, m), 4.01-3.96 (1H, m), 3.88-3.83 (1H, m), 3.67 (1H, t, $J = 3.7$ Hz), 3.54-3.48 (1H, m), 2.42-2.12 (1H, m), 2.30-2.26 (2H, m), 2.24-2.18 (1H, m), 1.94-1.84 (4H, m), 1.68-1.56 (6H, m), 1.48-1.22 (36H, m), 0.87 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 173.8, 148.9, 134.2, 85.8, 83.3, 80.2, 79.2, 77.4, 74.1, 72.3, 71.2, 38.8, 37.4, 34.4, 33.7, 32.3, 31.9, 30.2, 29.7, 29.4, 29.3, 29.1, 27.3, 27.1, 26.7, 26.0, 25.7, 25.1, 24.4, 22.7, 19.2, 14.1.



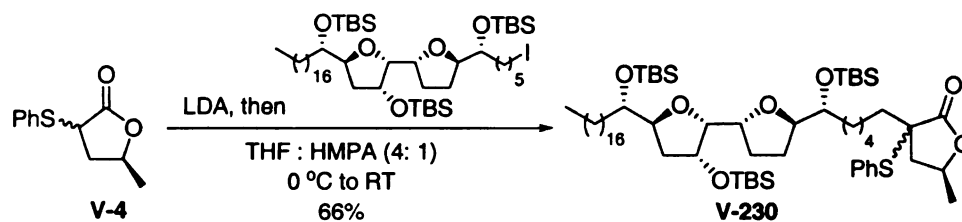
Data for tris-TBS ether **V-228**: $[\alpha]_D^{20} -7.0$ (c 0.57, CHCl_3), ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.24 (5H, m), 4.48 (2H, s), 4.36-4.31 (1H, m), 4.16-4.06 (2H, m), 3.95-3.88 (1H, m), 3.62-3.55 (3H, m), 3.45 (2H, t, $J = 6.6$ Hz), 2.05-1.98 (1H, m), 1.88-1.56 (8H, m), 1.42-1.11 (37H, m), 0.91-0.82 (30H, m), 0.06- -0.03 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 85.6, 81.6, 80.8, 75.0, 74.4, 73.0, 72.9, 70.5, 37.8, 32.7, 32.4, 31.9, 29.9, 29.8, 29.7, 29.6, 29.4, 27.0, 26.4, 26.0, 25.9, 25.5, 22.7, 18.3, 18.2, 18.1, 14.1, 1.0, -4.18, -4.22, -4.52, -4.68, -4.75, -4.79.



Data for primary alcohol **V-229**: $[\alpha]_D^{20}$ -6.6 (c 1.13, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 4.36-4.31 (1H, m), 4.16-4.02 (2H, m), 3.93-3.82 (1H, m), 3.62-3.55 (5H, m), 2.08-1.98 (1H, m), 1.87-1.62 (5H, m), 1.60-1.47 (3H, m), 1.42-1.11 (37H, m), 0.91-0.82 (30H, m), 0.06-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 85.6, 81.5, 80.7, 75.0, 74.3, 73.0, 63.0, 37.8, 32.8, 32.6, 32.4, 31.9, 29.9, 29.7, 29.6, 29.4, 27.0, 26.0, 25.9, 25.8, 25.5, 22.7, 18.3, 18.1, 14.1, -4.18, -4.22, -4.54, -4.70, -4.76, -4.81.

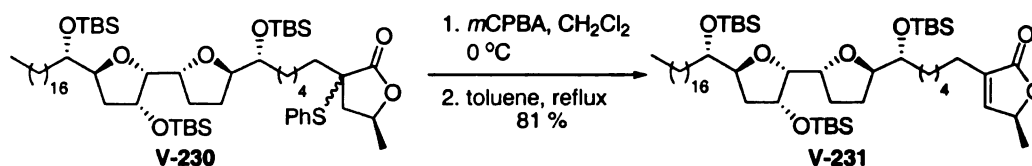


Data for iodide **V-146**: $[\alpha]_D^{20}$ -5.3 (c 2.33, CHCl_3), ^1H NMR (300 MHz, CDCl_3) δ 4.38-4.31 (1H, m), 4.18-4.03 (2H, m), 3.95-3.84 (1H, m), 3.62-3.55 (3H, m), 3.16 (2H, t, $J = 7.0$ Hz), 2.08-1.98 (1H, m), 1.87-1.62 (8H, m), 1.58-1.21 (37H, m), 0.91-0.82 (30H, m), 0.06-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 85.6, 81.5, 80.7, 75.0, 74.2, 73.0, 62.6, 37.8, 33.5, 32.1, 31.9, 30.7, 29.7, 29.6, 29.4, 26.9, 26.0, 25.9, 25.5, 25.0, 22.7, 14.1, 7.1, -4.18, -4.22, -4.52, -4.70, -4.73, -4.78.

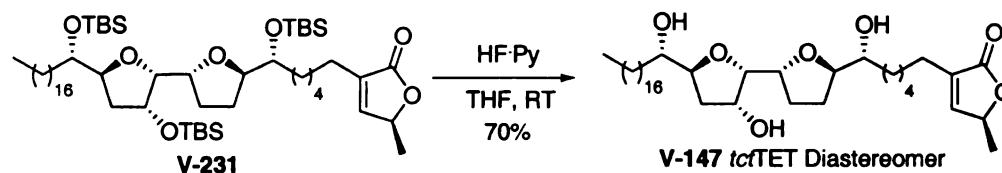


Data for sulfide mixtures **V-230**: $[\alpha]_D^{20}$ -15.4 (c 1.81, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.52 (2H, m), 7.43-7.33 (3H, m), 4.66-4.46 (1H, m), 4.38-4.34 (1H, m),

4.18-4.08 (2H, m), 3.96-3.89 (1H, m), 3.65-3.56 (3H, m), 2.57-2.50 (1H, m), 2.10-1.95 (2H, m), 1.89-1.71 (7H, m), 1.68-1.49 (2H, m), 1.48-1.20 (41H, m), 0.91-0.86 (30H, m), 0.09-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 177.1, 137.1, 136.8, 130.4, 130.0, 129.7, 129.0, 128.9, 85.5, 81.5, 80.8, 75.0, 74.3, 73.6, 73.2, 73.0, 56.2, 42.5, 40.1, 37.8, 36.4, 32.6, 32.3, 31.9, 29.9, 29.7, 29.6, 29.4, 27.0, 26.0, 25.9, 25.5, 24.8, 22.7, 21.5, 20.7, 18.3, 18.1, 14.1, -4.1, -4.2, -4.5, -4.7, -4.7, -4.8.

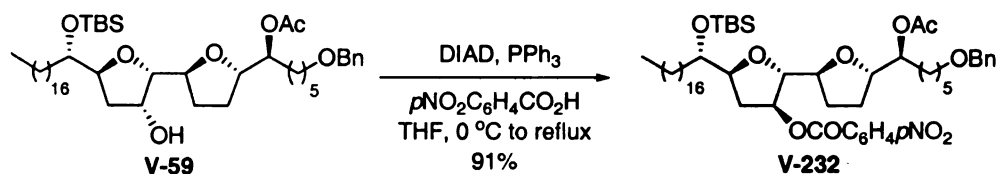


Data for conjugate lactone **V-231**: $[\alpha]_{\text{D}}^{20} +2.9$ (c 0.37, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 6.98 (1H, d, $J = 1.5$ Hz), 5.02-4.98 (1H, qd, $J = 6.8, 1.5$ Hz), 4.37-4.34 (1H, m), 4.17-4.08 (2H, m), 3.94-3.88 (1H, m), 3.64-3.56 (3H, m), 2.30-2.25 (2H, m), 2.09-2.02 (1H, m), 1.88-1.71 (5H, m), 1.68-1.22 (43H, m), 0.90-0.86 (30H, m), 0.10-0.04 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 173.8, 148.8, 134.3, 85.6, 81.5, 80.8, 77.4, 75.0, 74.3, 73.0, 37.8, 32.6, 32.2, 31.9, 29.9, 29.7, 29.6, 29.4, 27.4, 26.9, 26.0, 25.9, 25.8, 25.5, 25.2, 22.7, 19.2, 18.3, 18.1, 14.1, -4.2, -4.5, -4.7, -4.7 -4.8.



Data for full length *tctTET* diastereomer **V-147**: $[\alpha]_{\text{D}}^{20} +3.5$ (c 0.23, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 6.99 (1H, d, $J = 1.5$ Hz), 5.02-4.98 (1H, qd, $J = 6.8, 1.5$ Hz), 4.55-4.51 (1H, m), 4.27-4.21 (1H, m), 4.16-4.00 (1H, m), 3.89-3.84 (1H, m), 3.74-3.72 (1H, dd, $J = 7.1, 3.2$ Hz), 3.44-3.38 (2H, m), 2.31-2.18 (3H, m), 2.07-2.00

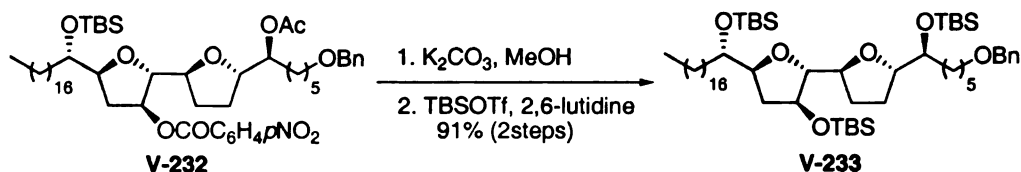
(2H, m), 1.92-1.82 (2H, m), 1.78-1.68 (1H, m), 1.61-1.21 (43H, m), 0.89 (3H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 149.0, 134.2, 84.0, 83.1, 81.6, 77.9, 77.4, 74.1, 73.8, 73.2, 37.5, 33.4, 33.3, 31.9, 30.4, 29.7, 29.6, 29.3, 29.1, 27.9, 27.3, 25.5, 25.2, 25.1, 22.7, 19.2, 14.1.



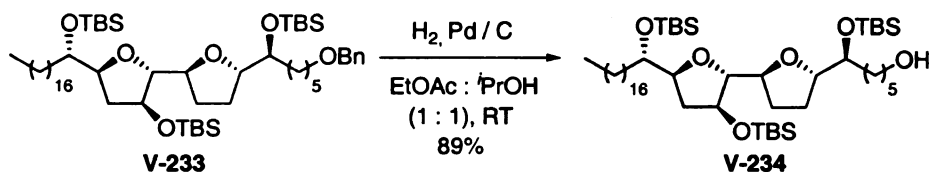
A solution of alcohol **V-59** (55 mg, 0.07 mmol), *p*-nitrobenzoic acid (49 mg, 0.30 mmol), and triphenylphosphine (77 mg, 0.30 mmol) in THF (5 mL) was cooled to 0 °C. Diisopropylazodicarboxylate (57 μL , 0.30 mmol) was added dropwise over 30 min to keep the reaction temperature at 0 °C. The resulting mixture was then heated to reflux for 15 h. After allowing the solution to cool to room temperature, it was diluted with Et_2O (15 mL), and washed with sat. aqueous NaHCO_3 (2 $\times$ 15 mL). The aqueous layer was extracted with Et_2O (3 $\times$ 15 mL). The combined organic layers were dried over Na_2SO_4 and reduced *in vacuo*. Purification by flash chromatography (10% EtOAc in hexanes) afforded ester **V-232** as a colorless oil (59 mg, 91%).

Data for ester **V-232**: $[\alpha]_{\text{D}}^{20}$ -4.6 (c 2.02, CHCl_3) ^1H NMR (300 MHz, CDCl_3) δ 8.31-8.28 (2H, d, J = 9.0 Hz), 8.20-8.18 (2H, d, J = 8.9 Hz), 7.36-7.27 (5H, m), 5.56-5.48 (1H, m), 4.97-4.82 (1H, m), 4.50 (2H, s), 4.24-4.04 (3H, m), 4.00-3.89 (1H, m), 3.74-3.68 (1H, m), 3.46 (2H, t, J = 6.6 Hz), 2.59-2.48 (1H, m), 2.08 (3H, s), 2.02-1.90 (4H, m), 1.67-1.54 (5H, m), 1.44-1.22 (36H, m), 0.92-0.86 (12H, m), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 170.9, 164.4, 150.6, 138.6, 135.4,

130.7, 128.4, 127.6, 127.5, 123.6, 85.0, 82.7, 80.6, 79.4, 78.9, 74.9, 74.5, 72.9, 70.3, 33.8, 32.8, 31.9, 31.0, 30.0, 29.7, 29.4, 28.3, 27.8, 26.1, 26.0, 25.7, 25.3, 22.7, 21.2, 18.3, 14.2, -4.1, -4.5.

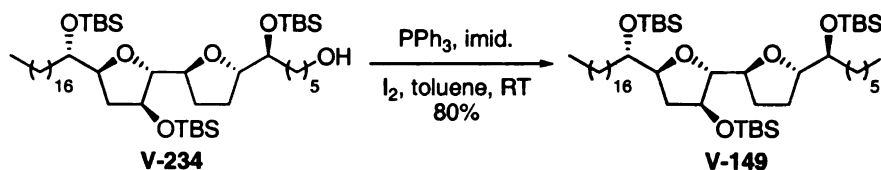


Data for tris-TBS ether **V-233**: $[\alpha]_D^{20} +6.3$ (c 1.895, CHCl_3) ^1H NMR (300 MHz, CDCl_3) δ 7.35-7.27 (5H, m), 4.51 (2H, s), 4.42-4.36 (1H, m), 4.04-3.98 (1H, m), 3.94-3.84 (2H, m), 3.80-3.61 (2H, m), 3.58-3.56 (1H, dd, $J = 5.1, 2.4$ Hz), 3.47 (2H, t, $J = 6.6$ Hz), 2.16-2.06 (1H, m), 1.88-1.79 (3H, m), 1.68-1.58 (4H, m), 1.49-1.22 (38H, m), 0.93-0.86 (30H, m), 0.09-0.04 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.7, 82.7, 81.6, 78.7, 75.2, 74.0, 73.7, 72.9, 70.5, 37.6, 33.1, 32.9, 29.9, 29.7, 29.4, 28.1, 27.3, 26.6, 26.0, 25.8, 25.5, 25.4, 22.7, 18.3, 18.2, 17.9, 14.1, -4.1, -4.2, -4.5, -4.7, -4.8, -4.9.

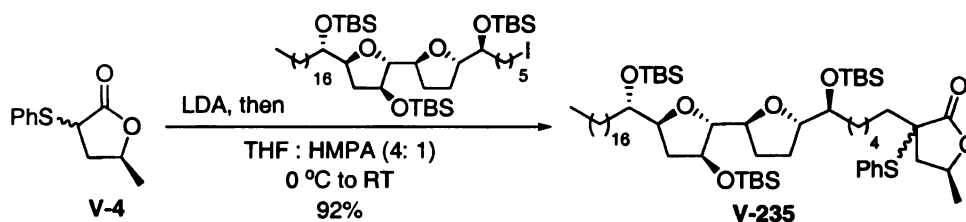


Data for primary alcohol **V-234**: $[\alpha]_D^{20} +6.8$ (c 1.415, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 4.41-4.38 (1H, m), 4.02-3.91 (1H, td, $J = 6.8, 2.3$ Hz), 3.92-3.86 (2H, m), 3.68-3.62 (4H, m), 3.58-3.54 (2H, m), 2.14-2.07 (1H, m), 1.98-1.78 (4H, m), 1.66-1.56 (5H, m), 1.50-1.21 (36H, m), 0.93-0.86 (30H, m), 0.09-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 86.7, 82.6, 81.6, 78.8, 75.2, 75.1, 74.0, 63.0, 37.6, 33.1, 33.0, 32.8, 31.9, 29.9, 29.7, 29.6, 29.3, 28.1, 27.9, 26.0, 25.8, 25.5, 25.3, 22.7, 18.3,

18.2, 17.9, 14.1, -4.1, -4.2, -4.5, -4.6, -4.7, -4.8.

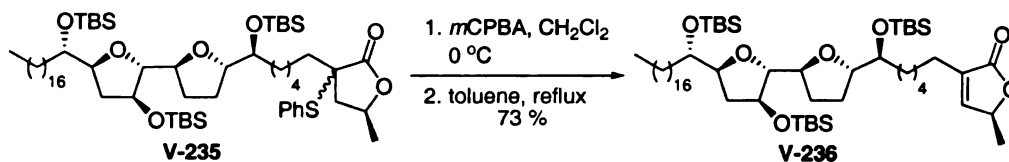


Data for iodide **V-149**: $[\alpha]_D^{20} +4.5$ (c 2.07, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 4.39-4.37 (1H, q, $J = 2.5$ Hz), 4.02-3.99 (1H, td, $J = 6.8, 2.3$ Hz), 3.92-3.86 (2H, m), 3.67-3.62 (1H, m), 3.58-3.54 (2H, m), 3.19 (2H, t, $J = 7.1$ Hz), 2.14-2.09 (1H, m), 1.99-1.81 (5H, m), 1.67-1.57 (2H, m), 1.48-1.21 (38H, m), 0.94-0.84 (30H, m), 0.12-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 86.7, 82.6, 81.6, 78.8, 75.2, 75.0, 73.9, 37.6, 33.5, 33.1, 32.8, 30.8, 29.9, 29.7, 29.6, 29.4, 28.1, 27.9, 26.0, 25.8, 25.5, 24.5, 22.7, 18.3, 18.2, 17.9, 14.1, -4.1, -4.2, -4.5, -4.6, -4.7, -4.8.

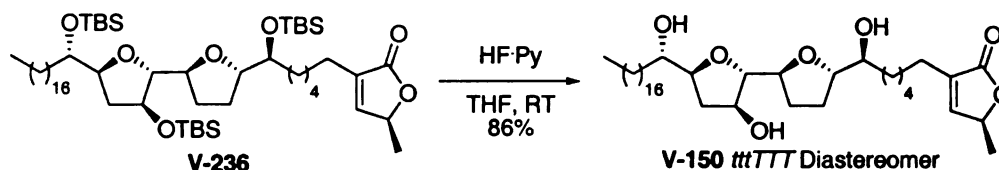


Data for sulfide mixtures **V-235**: $[\alpha]_D^{20} -6.3$ (c 1.97, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.52 (2H, m), 7.42-7.33 (3H, m), 4.52-4.47 (1H, m), 4.40-4.36 (1H, m), 4.03-3.99 (1H, td, $J = 6.8, 3.3$ Hz), 3.92-3.86 (2H, m), 3.67-3.62 (1H, m), 3.58-3.53 (2H, m), 2.55-2.51 (1H, dd, $J = 13.9, 7.6$ Hz), 2.14-2.08 (1H, m), 2.00-1.86 (4H, m), 1.81-1.77 (2H, m), 1.68-1.57 (4H, m), 1.48-1.20 (41H, m), 0.94-0.84 (30H, m), 0.12-0.04 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 177.1, 143.8, 137.1, 136.8, 135.5, 130.4, 130.0, 129.7, 129.6, 129.0, 128.9, 128.8, 128.7, 127.7, 127.6, 127.0, 86.7, 82.6, 81.6, 78.8, 75.1, 73.9, 73.2, 56.2, 40.0, 37.5, 36.5, 33.0, 32.8, 31.9, 31.6, 29.9, 29.7, 29.4, 28.1, 27.9, 26.8, 26.0, 25.8, 25.6, 25.5, 25.4, 24.7, 22.7, 21.5, 18.4, 18.2, 17.9,

14.1, -4.1, -4.2, -4.5, -4.7, -4.8.

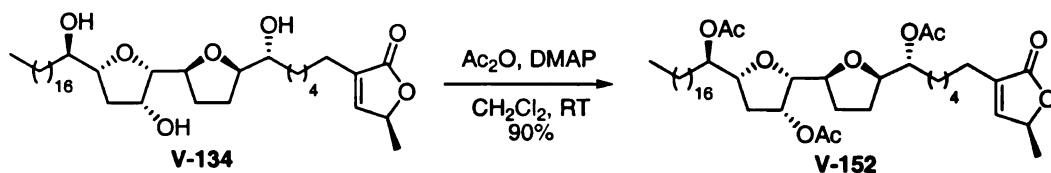


Data for conjugate lactone **V-236**: $[\alpha]_D^{20} +8.3$ (c 1.05, CHCl₃) ¹H NMR (300 MHz, CDCl₃) δ 6.98 (1H, d, J = 1.5 Hz), 5.04-4.96 (1H, m), 4.42-4.34 (1H, m), 4.04-4.89 (1H, m), 3.94-3.84 (2H, m), 3.68-3.61 (1H, m), 3.59-3.53 (2H, m), 2.31-2.24 (2H, m), 2.18-2.06 (1H, m), 1.96-1.84 (3H, m), 1.68-1.22 (45H, m), 0.90-0.86 (30H, m), 0.10-0.04 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ 173.8, 148.8, 134.3, 86.7, 82.7, 81.6, 78.8, 77.4, 75.2, 74.0, 37.6, 33.1, 32.9, 31.9, 29.9, 29.7, 29.5, 29.4, 28.0, 27.9, 27.4, 26.1, 25.9, 25.8, 25.5, 25.2, 22.7, 19.2, 18.4, 18.2, 17.9, 14.1, -4.1, -4.2, -4.5, -4.7, -4.7 -4.8.

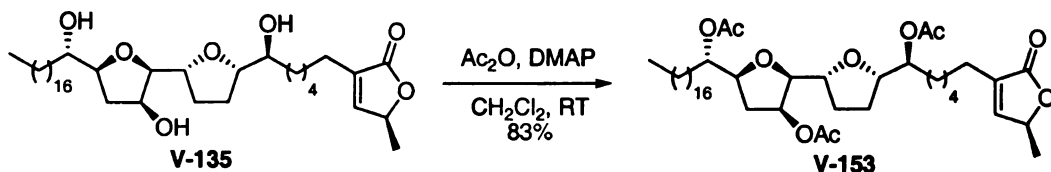


Data for full-linked *tttTTT* diastereomer **V-150**: $[\alpha]_D^{20} +11.9$ (c 0.48, CHCl₃) ¹H NMR (300 MHz, CDCl₃) δ 6.99 (1H, d, J = 1.5 Hz), 5.02-4.98 (1H, qd, J = 6.8, 1.5 Hz), 4.28-4.20 (1H, m), 4.11-4.02 (1H, m), 4.01-3.92 (1H, m), 3.83 (1H, t, J = 3.5 Hz), 3.80-3.71 (1H, m), 3.56-3.49 (1H, m), 3.42-3.31 (1H, m), 2.56-2.39 (1H, m), 2.35-2.21 (2H, m), 2.00-1.88 (2H, m), 1.82-1.68 (1H, m), 1.61-1.21 (45H, m), 0.89 (3H, t, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 148.9, 134.2, 128.0, 89.3, 83.3, 81.5, 79.8, 77.4, 74.5, 74.2, 73.9, 38.2, 34.1, 33.3, 31.9, 29.7, 29.6, 29.4, 29.2, 28.4, 27.4, 25.9, 25.3, 25.1, 22.7, 19.2, 14.1.

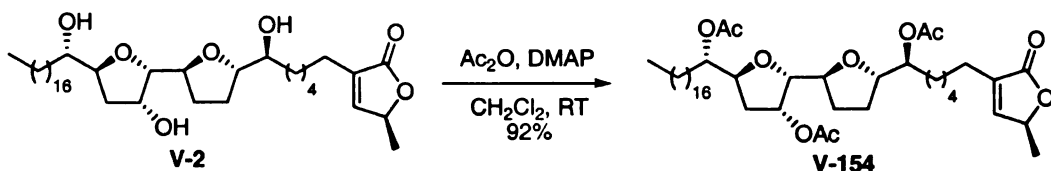
Acetylated diastereomers **V-152** and **V-153** were quickly synthesized for the cytotoxicity study. Only ^1H NMR spectra were obtained since only ~ 1 mg compounds were synthesized.



Data for tris-acetate **V-152** of synthesized mucoxin: ^1H NMR (500 MHz, CDCl_3) δ 7.01-6.99 (1H, m), 5.26-5.22 (1H, m), 5.11-5.06 (1H, m), 5.03-4.98 (1H, m), 4.97-4.92 (1H, m), 4.02 (2H, q, $J = 6.9$ Hz), 3.97 (1H, dd, $J = 11.7, 5.9$ Hz), 3.72 (1H, dd, $J = 6.9, 4.3$ Hz), 2.37-2.07 (4H, m), 2.07 (6H, s), 2.06 (3H, s), 1.95-1.76 (4H, m), 1.72-1.47 (10H, m), 1.43-1.26 (42H, m), 0.89 (3H, t, $J = 6.7$ Hz).

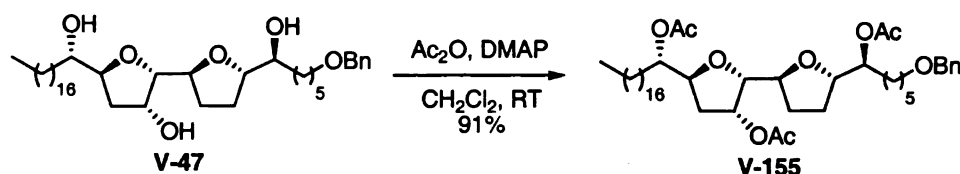


Data for tris-acetate **V-153** of pseudo-enantiomer of mucoxin: ^1H NMR (500 MHz, CDCl_3) δ 7.01-6.99 (1H, m), 5.26-5.22 (1H, m), 5.11-5.06 (1H, m), 5.03-4.98 (1H, m), 4.97-4.92 (1H, m), 4.02 (2H, q, $J = 6.9$ Hz), 3.97 (1H, dd, $J = 11.7, 5.9$ Hz), 3.72 (1H, dd, $J = 6.9, 4.3$ Hz), 2.37-2.07 (4H, m), 2.07 (6H, s), 2.06 (3H, s), 1.95-1.76 (4H, m), 1.72-1.47 (10H, m), 1.43-1.26 (42H, m), 0.89 (3H, t, $J = 6.7$ Hz).

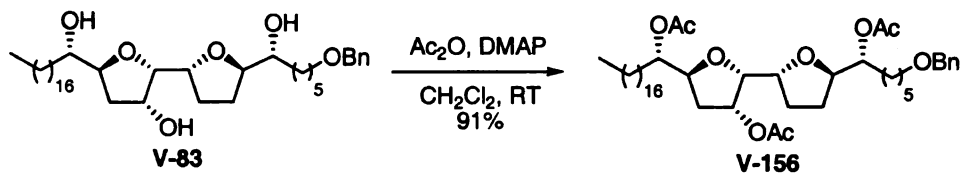


Data for tris-acetate **V-154** of *tctTTT* diastereomer of mucoxin: ^1H NMR (500 MHz, CDCl_3) δ 6.98 (1H, d, $J = 1.5$ Hz), 5.32-5.24 (1H, m), 5.02-4.92 (1H, m), 4.80-4.79

(2H, m), 4.28-4.19 (1H, m), 4.12-3.92 (2H, m), 3.86-3.82 (1H, dd, $J = 3.7, 3.1$ Hz), 2.28 (2H, dt, $J = 7.8, 1.5$ Hz), 2.08-2.00 (9H, m), 1.98-1.82 (2H, m), 1.68-1.43 (6H, m), 1.42-1.21 (41H, m), 0.89 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 173.8, 170.9, 170.5, 149.0, 134.1, 82.5, 79.8, 78.3, 77.8, 77.4, 75.1, 74.8, 74.6, 34.9, 31.9, 30.6, 30.5, 29.7, 29.6, 29.5, 29.3, 29.0, 28.6, 27.7, 27.3, 25.4, 25.1, 25.0, 22.7, 21.1, 21.0, 19.2, 14.1.

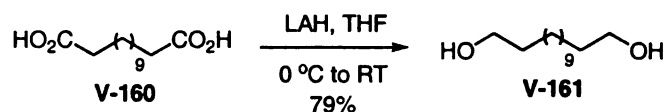


Data for *tctTTT* truncated tris-acetate **V-155**: ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 5.33-5.25 (1H, m), 4.91-4.78 (2H, m), 4.47 (2H, s), 4.23 (1H, ddd, $J = 7.5, 4.9, 2.5$ Hz), 4.09-3.97 (2H, m), 3.86 (1H, t, $J = 4.7$ Hz), 3.43 (2H, t, $J = 6.8$ Hz), 2.06 (3H, s), 2.04 (3H, s), 2.03 (3H, s), 1.95-1.87 (3H, m), 1.68-1.51 (10H, m), 1.38-1.23 (32H, m), 0.86 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 170.6, 170.5, 143.1, 128.3, 127.6, 127.5, 82.4, 79.9, 78.3, 77.8, 75.3, 74.6, 72.9, 70.3, 34.8, 31.9, 30.7, 30.5, 29.7, 29.6, 29.5, 29.3, 28.7, 27.7, 26.1, 25.5, 25.3, 22.7, 21.1, 21.0, 14.1.



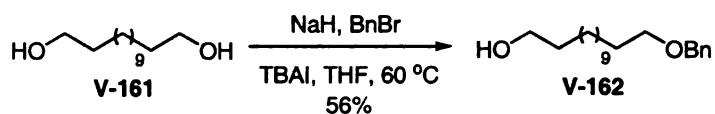
Data for *tctTET* truncated tris-acetate **V-156**: ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 5.50-5.45 (1H, m), 4.90-4.79 (2H, m), 4.49 (2H, s), 4.15 (1H, ddd, $J = 12.6, 8.7, 6.3$ Hz), 4.03-3.99 (1H, m), 3.93 (1H, q, $J = 6.8$ Hz), 3.71 (1H, dd, $J = 8.3, 3.3$

Hz), 3.45 (2H, t, $J = 6.6$ Hz), 2.08 (6H, s), 2.06 (3H, s), 2.03-1.97 (1H, m), 1.93-1.76 (1H, m), 1.65-1.46 (6H, m), 1.43-1.21 (38H, m), 0.88 (3H, t, $J = 6.6$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 170.8, 170.2, 138.6, 128.3, 127.6, 127.5, 83.2, 80.0, 78.8, 76.1, 75.4, 74.8, 74.1, 72.9, 70.3, 35.6, 31.9, 30.8, 30.5, 30.0, 29.7, 29.6, 29.5, 29.4, 29.3, 28.2, 26.1, 25.3, 25.1, 22.7, 21.1, 21.0, 14.1.



Lithium aluminum hydride (0.93 g, 24.5 mmol) was suspended in THF (60 mL). The mixture was cooled to 0 °C. A solution of the diacid **V-160** (1.51 g, 8.2 mmol) in THF (70 mL) was added dropwise over 20 min. The mixture was warmed to room temperature for overnight. 10% HCl solution was added very slowly and the mixture was then stirred until the gray color of unquenched LiAlH_4 has completely disappeared. The mixture was filtered and the inorganic layer was washed with diethyl ether (5×40 mL). The combined organic layer was dried over anhydrous magnesium sulfate and filtered. The solvents were removed under reduced pressure and the residue was purified using column chromatography (35% EtOAc in hexanes to 50% EtOAc in hexanes) to give the white solid diol **V-161** in 79% yield (1.05 g).

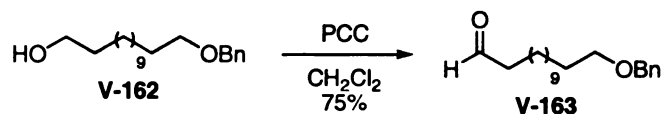
Data for diol **V-161**: ^1H NMR (300 MHz, CDCl_3) δ 3.62 (4H, t, $J = 6.6$ Hz), 1.58-1.50 (4H, m), 1.40-1.21 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 63.1, 32.8, 29.5, 29.4, 25.7.



To a slurry of NaH (0.13 g, 5.4 mmol) in THF (10 mL), diol **V-161** (1.12 g, 5.2

mmol) was added at 0 °C and stirred for 1 h while warming to RT. Benzyl bromide (0.62 mL, 5.2 mmol) was added drop wise followed by TBAI (80 mg). The reaction was heated to 60 °C for 15 h. After cooling to room temperature H₂O (10 mL) was carefully added. The layers were separated, aqueous layer was extracted with Et₂O (3×15 mL) and the combined organic layers after drying (MgSO₄) were concentrated. Monobenzyl ether **V-162** was obtained as white solid (0.89 g, 56%) after chromatographic purification (30% EtOAc in hexanes).

Data for monobenzyl ether **V-162**: ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.22 (5H, m), 4.45 (2H, s), 3.53 (2H, t, *J* = 6.6 Hz), 3.43 (2H, t, *J* = 6.6 Hz), 1.62-1.43 (4H, m), 1.39-1.21 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ 138.4, 128.1, 127.3, 127.2, 72.6, 70.2, 62.4, 32.5, 29.5, 29.4, 29.2, 25.9, 25.6, 13.9.



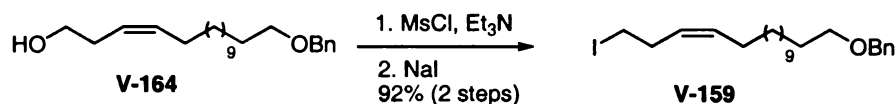
To a slurry of PCC (0.9 g, 4.2 mmol) in CH₂Cl₂ (8 mL), a solution of alcohol **V-162** (0.85 g, 2.8 mmol) in CH₂Cl₂ (3 mL) was added at room temperature under N₂ with vigorous stirring. After 2 h, anhydrous Et₂O (20 mL) was added and the reaction mixture was filtered through a celite pad. The filtrate was concentrated and the crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde **V-163** as a white solid (0.63 g, 75%).

Data for aldehyde **V-163**: ¹H NMR (500 MHz, CDCl₃) δ 9.77 (1H, d, *J* = 1.2 Hz), 7.35-7.27 (5H, m), 4.51 (2H, s), 3.47 (2H, t, *J* = 6.6 Hz), 2.42 (2H, td, *J* = 6.1, 1.2 Hz), 1.65-1.58 (4H, m), 1.40-1.21 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ 202.9, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 43.9, 29.8, 29.5, 29.4, 29.3, 29.1, 26.2, 22.1.



$n\text{BuLi}$ (1.06 mL of 1.9 M solution, 2.02 mmol) was added to a $-20\text{ }^\circ\text{C}$ slurry of 3-hydroxypropyltriphenylphosphonium bromide (404 mg, 1.01 mmol) in THF (2 mL). The mixture was brought to room temperature and stirred for 1 h. After cooling back to $0\text{ }^\circ\text{C}$, TMSCl (0.13 mL, 1.01 mmol) was added and stirring was continued at the same temperature for 15 min. The reaction was then cooled to $-78\text{ }^\circ\text{C}$ upon which a THF solution of aldehyde **V-163** (170 mg, 0.56 mmol in 1 mL THF) was added. The reaction was warmed to $-10\text{ }^\circ\text{C}$ over 1 h and then treated with $\text{AcOH}:\text{H}_2\text{O}:\text{THF}$ (6 : 3: 1, 7 mL). After 15 h stirring at room temperature the reaction mixture was neutralized by saturated NaHCO_3 . The aqueous layer was extracted with EtOAc (3 $\times$ 10 mL), combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography (10% to 20% EtOAc in hexanes) to secure the homoallylic alcohol **V-164** (148 mg, 76%, $Z:E > 10:1$).

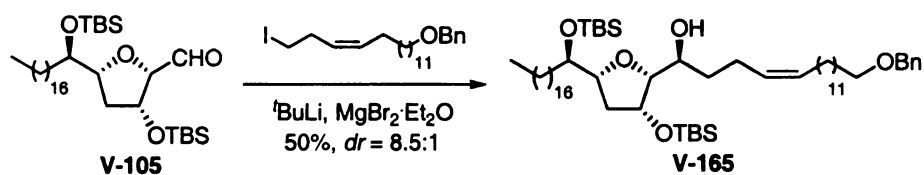
Data for homoallylic alcohol **V-164**: ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.26 (5H, m), 5.61-5.52 (1H, m), 5.42-5.33 (1H, m), 4.52 (2H, s), 3.62 (2H, t, $J = 6.6\text{ Hz}$), 3.48 (2H, t, $J = 6.8\text{ Hz}$), 2.36-2.25 (2H, m), 2.11-2.02 (2H, m), 2.00-1.92 (1H, br), 1.68-1.60 (2H, m), 1.42-1.21 (18H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.6, 133.1, 128.2, 127.5, 127.3, 124.9, 72.7, 70.4, 62.1, 30.7, 29.6, 29.5, 29.4, 29.2, 27.3, 26.1.



A solution of alcohol **V-164** (130 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) was cooled to $0\text{ }^\circ\text{C}$. To this, mesyl chloride (87 μL , 1.13 mmol) and triethyl amine (0.18 mL)

were added and stirring was continued at the same temperature for 30 min. The reaction was quenched with H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3×10 mL) and combined organic layers were concentrated. The residue and sodium iodide (0.26 g, 1.75 mmol) were taken up in acetone (5 mL) and refluxed for 2 h. Upon cooling to room temperature, the reaction was treated with saturated sodium sulfite until it became colorless. The aqueous layer was extracted with EtOAc (3×10 mL). Chromatographic purification (3% EtOAc in hexanes) of the crude product obtained by concentration of the organic portion afforded iodide **V-159** (146.3 mg, 85%) as a pale yellow oil.

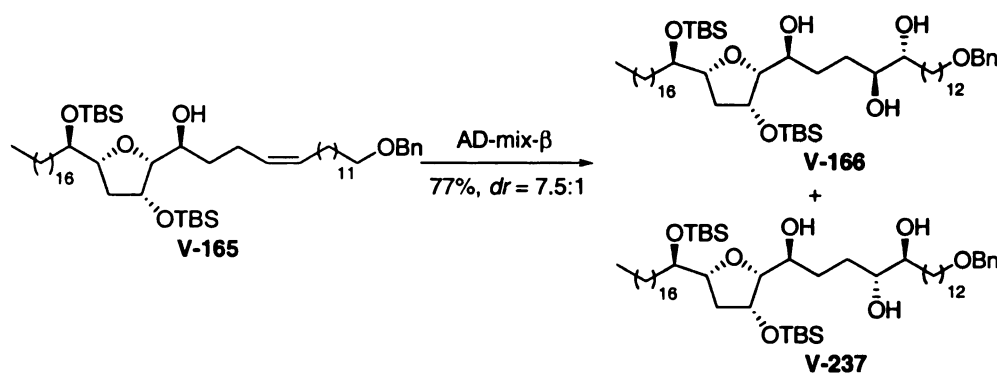
Data for iodide **V-159**: ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.26 (5H, m), 5.61-5.51 (1H, m), 5.42-5.29 (1H, m), 4.52 (2H, s), 3.49 (2H, t, *J* = 6.6 Hz), 3.14 (2H, t, *J* = 7.1 Hz), 2.68-2.61 (2H, m), 2.09-2.00 (2H, m), 1.68-1.59 (2H, m), 1.42-1.22 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 132.7, 128.3, 127.7, 127.5, 127.4, 72.8, 70.5, 31.5, 29.7, 29.5, 29.4, 29.2, 27.4, 26.1.



^tBuLi (1.93 mL of 1.5 M solution in pentane, 2.89 mmol) was added drop wise to pre-cooled (-100 °C) Et₂O (11 mL). To this, a solution of iodide **V-159** (0.66 g, 1.45 mmol) in Et₂O (8 mL) was added over 10 min. After stirring for 5 min at -100 °C to -90 °C, MgBr₂•OEt₂ in Et₂O (8 mL of 1.0 M solution (freshly prepared), was added and the mixture was warmed 0 °C over 1 h. Meanwhile, a solution of aldehyde **V-105** (0.59 g, 0.97 mmol) in Et₂O (10 mL) was cooled to -40 °C. MgBr₂•OEt₂ in

Et₂O (3 mL of 1.0 M solution) was added and stirred for 10 min. To this pre-complexed aldehyde, solution of the above mentioned Grignard reagent was cannulated at -40 °C and the reaction mixture was stirred overnight at the same temperature. The reaction was then quenched by slow addition of saturated NH₄Cl solution (15 mL) and H₂O (20 mL). The aqueous layer was extracted with Et₂O (3×20 mL). Combined organic layers were dried (MgSO₄), concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography (5% EtOAc in hexanes) furnished the adduct **V-165** (0.41 g, 45%) and its epimer (48 mg, 5%) in 8.5: 1 ratio.

Data for alcohol **V-165**: $[\alpha]_D^{20}$ -7.5 (c 3.34, CH₂Cl₂) ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.27 (5H, m), 5.41-5.36 (2H, m), 4.51 (2H, s), 4.42-4.39 (1H, q, J = 5.1 Hz), 3.86-3.72 (3H, m), 3.53 (1H, t, J = 5.0 Hz), 3.48 (2H, t, J = 6.7 Hz), 2.96 (1H, br), 2.31-2.03 (4H, m), 1.78-1.68 (1H, m), 1.66-1.50 (5H, m), 1.42-1.23 (50H, m), 0.94-0.86 (21H, m), 0.14-0.08 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 138.7, 130.2, 129.3, 128.3, 127.5, 127.4, 83.7, 80.1, 74.5, 73.4, 72.8, 70.5, 69.9, 37.8, 33.4, 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 27.2, 26.2, 26.0, 25.9, 25.7, 25.3, 23.6, 22.7, 18.3, 17.9, 14.1, -4.1, -4.4, -4.7, -5.2.

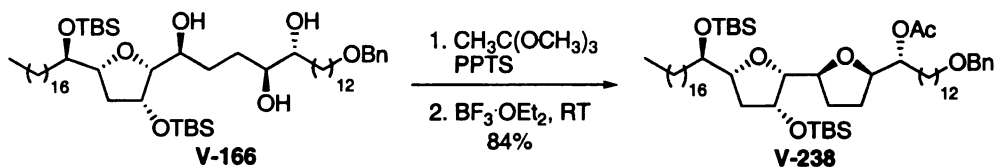


AD-mix- β (0.21 g) was dissolved in 1 : 1 t BuOH : H₂O (2 mL). To this clear, orange solution, methane sulfonamide (14 mg, 0.15 mmol) and potassium osmate (0.75 μ g) were added and stirred until all the solids dissolved. The solution was then cooled to 0 °C upon which olefin **V-165** (138 mg, 0.15 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (0.27 g) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (5 mL) and H₂O (2 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 $\times$ 8 mL), combined organic layers were dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (20% EtOAc in hexanes to 40% EtOAc in hexanes). Triol **V-166** was separted in 68% yield (100 mg) as well as its diastereomer **V-237** (13 mg, 9%) as colorless oil in 7.5:1 ratio.

Data for triol **V-166**: $[\alpha]_D^{20}$ -6.3 (c 1.90, CH₂Cl₂) ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.23 (5H, m), 4.48 (2H, s), 4.42-4.38 (1H, q, J = 5.4 Hz), 4.24 (1H, br), 3.82-3.74 (2H, m), 3.69-3.65 (1H, m), 3.62-3.57 (1H, m), 3.51 (1H, t, J = 5.1 Hz), 3.44 (2H, t, J = 6.6 Hz), 2.17 (1H, br), 2.11-2.05 (1H, m), 1.76-1.56 (6H, m),

1.54-1.46 (2H, m), 1.42-1.38 (2H, m), 1.38-1.22 (49H, m), 0.91-0.84 (21H, m), 0.08-0.05 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 83.3, 79.9, 75.0, 74.6, 74.4, 73.5, 72.8, 71.3, 70.5, 37.6, 33.5, 31.9, 31.1, 29.8, 29.7, 29.6, 29.5, 29.3, 28.6, 26.2, 26.1, 25.9, 25.7, 25.3, 22.7, 18.3, 17.9, 14.1, -4.1, -4.5, -4.6, -5.2.

Data for its diastereomer **V-237**: ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.23 (5H, m), 4.48 (2H, s), 4.42-4.38 (1H, q, $J = 5.4$ Hz), 3.84-3.74 (2H, m), 3.69-3.65 (1H, m), 3.54-3.51 (1H, m), 3.44 (2H, t, $J = 6.6$ Hz), 3.42-3.39 (1H, m), 3.33 (1H, br), 3.28-3.24 (1H, m), 2.44 (1H, br), 2.11-2.05 (1H, m), 1.74-1.41 (12H, m), 1.38-1.20 (48H, m), 0.91-0.84 (21H, m), 0.09-0.05 (12H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 83.3, 79.9, 74.4, 74.3, 74.0, 73.4, 72.8, 70.7, 70.5, 37.6, 33.5, 33.3, 31.9, 30.3, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 26.2, 26.0, 25.7, 25.3, 22.7, 18.3, 17.9, 14.1, -4.1, -4.4, -4.6, -5.2.

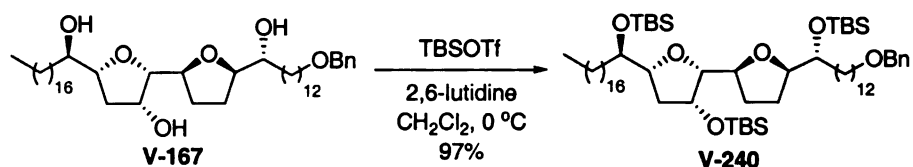


PPTS (2.3 mg, 9.2 μmol) was added to a solution of triol **V-166** (90 mg, 0.092 mmol) and trimethylortho acetate (14 μL , 0.11 mmol) in CH_2Cl_2 (2 mL) at RT. After complete consumption of the triol (ca. 10 min, as judged by TLC), a solution of $\text{BF}_3 \cdot \text{OEt}_2$ (3.5 μL , 0.027 mmol) was rapidly added to the reaction. After 20 min, the reaction was slowly poured into saturated NaHCO_3 solution (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 8 mL). Combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and the crude product was purified by

δ 7.32-7.23 (5H, m), 4.48 (2H, s), 4.23-4.20 (1H, m), 4.17-4.12 (1H, m), 3.83-3.72 (3H, m), 3.44 (2H, t, $J = 6.6$ Hz), 3.38-3.34 (1H, m), 2.52 (1H, d, $J = 4.6$ Hz), 2.10-1.98 (2H, m), 1.92-1.84 (1H, m), 1.68-1.54 (5H, m), 1.50-1.37 (5H, m), 1.36-1.17 (47H, m), 0.90-0.84 (21H, m), 0.10 (3H, s), 0.053 (3H, s), 0.049 (3H, s), 0.026 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 138.8, 128.3, 127.6, 127.4, 86.1, 82.6, 81.6, 78.5, 74.6, 74.0, 72.8, 72.7, 70.5, 37.3, 34.1, 32.7, 31.9, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 28.4, 27.7, 26.2, 26.0, 25.8, 25.6, 22.7, 21.0, 18.3, 17.9, 14.2, 14.1, -4.0, -4.1, -4.8, -5.3.

To a solution of alcohol **V-239** (11.8 mg, 0.012 mmol) in THF (2 mL), TBAF (1.0 M solution in THF, 49 μ L, 0.049 mmol) was added at room temperature. The reaction temperature was increased to reflux and stirred for 12 h. Saturated NH_4Cl (aq.) solution (5 mL) was added to quench the reaction. EtOAc (5 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$ 5 mL). The organic layers were combined, dried over Na_2SO_4 , and the solvent was evaporated to afford the crude product. Purification by column chromatography (40% EtOAc in hexanes to EtOAc) gave the bis-THF triol **V-167** as white solid in 75% yield (6.6 mg).

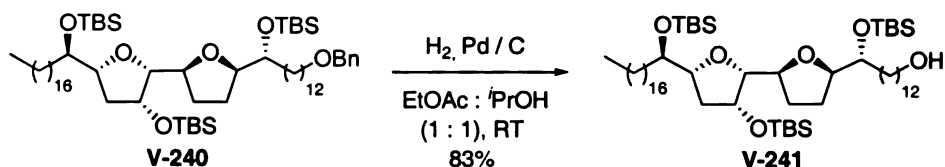
6.6 Hz), 3.42-3.38 (1H, m), 3.30 (1H, br), 2.38-2.26 (1H, m), 2.08-1.99 (2H, m), 1.94-1.84 (3H, m), 1.65-1.14 (54H, m), 0.86 (3H, t, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 83.6, 83.5, 80.2, 78.9, 77.4, 73.8, 73.6, 73.0, 72.8, 70.5, 38.8, 34.5, 34.0, 31.9, 29.7, 29.6, 29.5, 29.4, 28.7, 27.7, 26.2, 26.0, 25.9, 22.7, 14.1.



To a 0 °C solution of bis-THF triol **V-167** (41.3 mg, 0.043 mmol) in CH_2Cl_2 (3 mL), 2,6 lutidine (15 μL , 0.086 mmol) and TBSOTf (21 μL , 0.086 mmol) were added in that order. After 30 min at the same temperature, saturated NaHCO_3 solution (4 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 8 mL), combined organic layers were dried over Na_2SO_4 , and concentrated under reduced pressure to afford a crude oil. Upon purification of the oil by column chromatography (5% EtOAc in hexanes), tris-TBS ether **V-237** was obtained in 97% yield (44.7 mg).

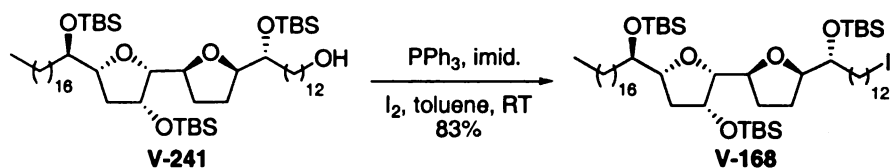
Data for tris-TBS ether **V-240**: $[\alpha]_{\text{D}}^{20} +4.5$ (c 2.23, CH_2Cl_2) ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (5H, m), 4.48 (2H, s), 4.22-4.18 (1H, m), 4.04-3.99 (1H, m), 3.97-3.94 (1H, m), 3.91-3.84 (2H, m), 3.78-3.74 (1H, m), 3.44 (2H, t, $J = 6.6$ Hz), 3.43-3.41 (1H, m), 2.04-1.90 (2H, m), 1.86-1.73 (3H, m), 1.64-1.56 (3H, m), 1.52-1.18 (52H, m), 0.98-0.85 (30H, m), 0.08-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 128.3, 127.6, 127.4, 86.8, 81.3, 81.0, 78.9, 73.6, 73.5, 72.8, 72.6, 70.5, 36.1, 31.9, 31.3, 31.0, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.3, 28.1, 26.2, 25.9,

25.8, 25.5, 22.7, 18.1, 17.9, 14.1, 1.0, -3.8, -4.2, -4.4, -4.6, -4.7, -5.4.



Benzyl ether **V-240** (43 mg, 0.040 mmol) was dissolved in 1 : 1 EtOAc : *i*PrOH (2 mL). To this solution, 10% Pd-C (11 mg) was added and the mixture was stirred vigorously under H₂ (1 atm). The hydrogenolysis was complete in 1 h after which the reaction was filtered through a celite pad. The filtrate was concentrated and the crude product was purified by flash column chromatography (10% EtOAc in hexanes) to furnish alcohol **V-241** in 83% yield (32.5 mg).

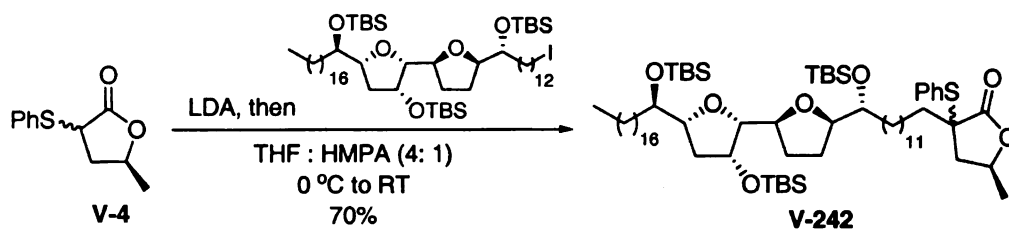
Data for alcohol **V-241**: $[\alpha]_{\text{D}}^{20} +4.5$ (c 1.625, CH₂Cl₂) ¹H NMR (300 MHz, CDCl₃) δ 4.22-4.16 (1H, m), 4.05-3.82 (4H, m), 3.80-3.71 (1H, m), 3.62 (2H, t, *J* = 6.6 Hz), 3.44-3.40 (1H, dd, *J* = 8.1, 3.7 Hz), 2.04-1.70 (4H, m), 1.62-1.15 (56H, m), 0.92-0.82 (30H, m), 0.08-0.01 (18H, m); ¹³C NMR (75 MHz, CDCl₃) δ 86.8, 81.3, 81.0, 78.9, 73.5, 72.5, 63.1, 36.0, 32.8, 31.9, 31.3, 30.9, 29.9, 29.7, 29.6, 29.4, 29.3, 28.1, 26.3, 25.9, 25.8, 25.5, 22.7, 18.1, 17.9, 14.1, 1.0, -3.8, -4.3, -4.4, -4.6, -4.7, -5.4.



Alcohol **V-241** (31.7 mg, 0.032 mmol), triphenylphosphine (21.2 mg, 0.081 mmol) and imidazole (6 mg, 0.084 mmol) were dissolved in toluene (3 mL). Upon addition of iodine (22.1 mg, 0.087 mmol) the clear, colorless solution turned yellowish brown and turbid. After 1 h vigorous stirring at room temperature, saturated sodium sulfite

solution was added to the reaction until the yellowish brown color disappeared. The layers were separated and the aqueous layer was extracted with EtOAc (3×8 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to provide the crude product. Purification of the crude material by column chromatography (5% EtOAc in hexanes) afforded iodide **V-168** (29.1 mg, 83%) as a colorless oil.

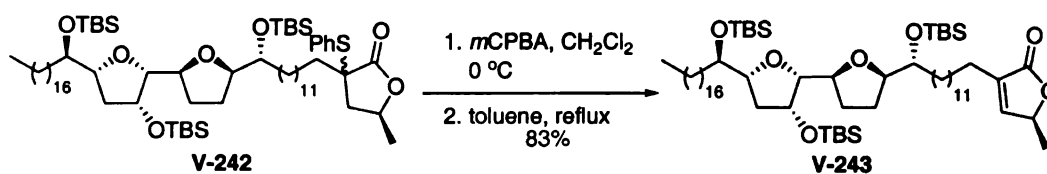
Data for iodide **V-168**: $[\alpha]_D^{20} +3.7$ (c 2.42, CH₂Cl₂) ¹H NMR (500 MHz, CDCl₃) δ 4.22-4.18 (1H, m), 4.05-3.84 (4H, m), 3.78-3.73 (1H, m), 3.43-3.41 (1H, dd, *J* = 8.1, 3.5 Hz), 3.17 (2H, t, *J* = 7.1 Hz), 2.06-1.92 (2H, m), 1.86-1.74 (5H, m), 1.62-1.48 (2H, m), 1.44-1.16 (51H, m), 0.96-0.84 (30H, m), 0.12-0.01 (18H, m); ¹³C NMR (125 MHz, CDCl₃) δ 86.8, 81.3 81.1, 78.9, 73.6, 73.5, 72.6, 36.1, 33.6, 31.9, 31.4, 31.0, 30.5, 30.0, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.5, 28.1, 26.2, 26.0, 25.9, 25.8, 25.6, 22.7, 18.1, 17.9, 7.2, 1.0, -3.8, -4.2, -4.3, -4.6, -4.7, -5.4.



A solution of diisopropylamine (5.7 μ L, 0.04 mmol) in THF (1.0 mL) was cooled to -78 $^\circ$ C and ⁿBuLi (21.3 μ L of 1.9 M solution, 0.04 mmol) was added to it. After 15 min, lactone **V-4** (8.4 mg, 0.04 mmol) in THF (0.5 mL) was added and stirring was continued for 30 min during which time the solution was warmed to 0 $^\circ$ C. Iodide **V-168** (22.1 mg, 0.02 mmol) was then added as a solution in 1 : 1 THF : HMPA (1.0 mL). The reaction was allowed to attain room temperature. After 15 h, H₂O (2 mL)

and EtOAc (8 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3×8 mL), combined organic layers were dried (Na₂SO₄), concentrated and the crude product was purified by column chromatography (5% to 10% EtOAc in hexanes) to afford sulfide **V-242** as a mixture of epimers (16.4 mg, 70%).

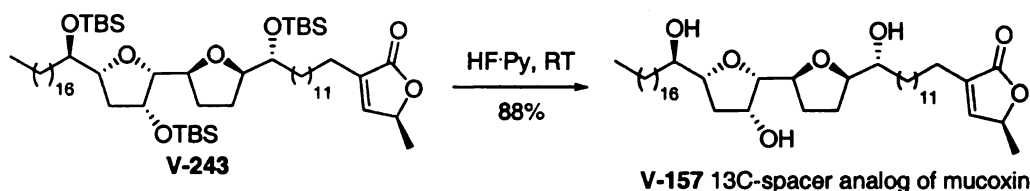
Data for sulfide mixtures **V-242**: $[\alpha]_D^{20}$ -6.9 (c 1.14, CH₂Cl₂) ¹H NMR (500 MHz, CDCl₃) δ 7.55-7.50 (2H, m), 7.39-7.31 (3H, m), 4.60-4.43 (1H, m), 4.22-4.18 (1H, m), 4.04-3.98 (1H, m), 3.97-3.93 (1H, m), 3.91-3.84 (2H, m), 3.78-3.73 (1H, m), 3.43-3.41 (1H, dd, *J* = 8.0, 3.5 Hz), 2.52-2.28 (1H, m), 2.06-1.91 (3H, m), 1.87-1.72 (5H, m), 1.61-1.48 (5H, m), 1.44-1.22 (5H, m), 1.30-1.18 (45H, m), 1.17-1.16 (3H, d, *J* = 4.6 Hz), 0.88-0.82 (30H, m), 0.06-0.01 (18H, m); ¹³C NMR (125 MHz, CDCl₃) δ 177.1, 137.1, 136.8, 130.5, 129.7, 129.0, 128.9, 86.8, 81.3, 81.1, 78.9, 73.6, 73.5, 73.2, 72.6, 56.3, 40.1, 36.5, 31.9, 31.3, 31.0, 30.0, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.1, 26.2, 26.0, 25.9, 25.8, 25.5, 24.7, 22.7, 21.5, 14.1, -3.8, -4.2, -4.4, -4.6, -4.7, -5.4.



To an ice cold solution of sulfide **V-232** (10 mg, 8.5 μ mol) in CH₂Cl₂ (1 mL), ca. 75% *m*CPBA (2.0 mg, 8.5 μ mol) in CH₂Cl₂ (1 mL) was added drop wise. After 20 min, saturated NaHCO₃ solution (2 mL) was carefully added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3×5 mL). The combined organic layers were dried and concentrated to afford the corresponding sulfoxide. The crude sulfoxide was taken up in toluene (2 mL) and heated to reflux for 4 h.

After cooling the solution to room temperature, the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford pure conjugate lactone **V-243** (7.5 mg, 83%).

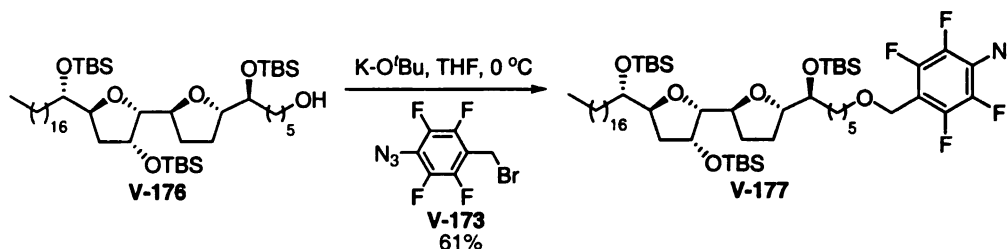
Data for conjugate lactone **V-243**: $[\alpha]_D^{20} +15.7$ (c 0.96, CDCl_3) ^1H NMR (500 MHz, CDCl_3) δ 6.96 (1H, d, $J = 1.5$ Hz), 4.99-4.95 (1H, qd, $J = 6.7, 1.7$ Hz), 4.04-3.83 (4H, m), 3.78-3.72 (1H, m), 3.43-3.41 (1H, dd, $J = 8.1, 3.4$ Hz), 2.26-2.22 (2H, m), 2.06-1.90 (2H, m), 1.84-1.74 (3H, m), 1.69-1.64 (2H, m), 1.60-1.48 (8H, m), 1.46-1.18 (46H, m), 0.92-0.83 (30H, m), 0.08-0.01 (18H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 167.7, 148.8, 134.4, 86.8, 81.3, 81.1, 78.9, 77.4, 73.6, 73.5, 72.6, 38.7, 36.1, 31.9, 31.4, 31.0, 30.4, 30.0, 29.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.9, 28.1, 27.4, 26.2, 26.0, 25.9, 25.8, 25.5, 25.2, 23.7, 23.0, 22.7, 19.2, 18.1, 17.9, 14.1, 11.0, 1.0, -3.8, -4.2, -4.4, -4.6, -4.7, -5.4.



To a solution of **V-243** (7.5 mg, 7.1 μmol) in THF (1.5 mL) taken in a polyethylene vial, $\text{HF}\cdot\text{Py}$ (2.8 μL) was added at room temperature. After stirring for 12 h, the reaction was neutralized by saturate NaHCO_3 solution. H_2O (3 mL) and EtOAc (8 mL) were added and the layers were separated. The organic layer was washed with saturated CuSO_4 (2 $\times$ 5 mL) and the combined aqueous layers were extracted with EtOAc (3 $\times$ 8 mL). The organic layers were combined, dried over Na_2SO_4 , and the solvent was evaporated to afford a waxy material. Purification by

column chromatography (EtOAc, 10% MeOH in EtOAc) gave 13C-spacer analog of mucoxin **V-157** as a colorless wax (4.5 mg, 88%).

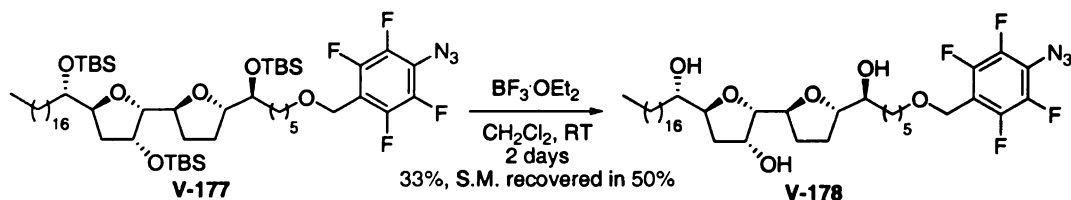
Data for 13C-spacer analog of mucoxin **V-157**: ^1H NMR (500 MHz, CDCl_3) δ 6.99 (1H, d, $J = 1.7$ Hz), 4.99-4.95 (1H, qd, $J = 6.8, 1.7$ Hz), 4.32-4.26 (2H, m), 4.02-3.98 (1H, m), 3.96-3.87 (1H, m), 3.71 (1H, t, $J = 3.2$ Hz), 3.54-3.48 (1H, m), 3.42-3.38 (1H, m), 3.32 (1H, br), 2.35-2.28 (1H, m), 2.26-2.22 (2H, m), 2.06-2.01 (2H, m), 1.96-1.85 (3H, m), 1.64-1.20 (57H, m), 0.83 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 173.9, 148.8, 134.3, 83.6, 83.5, 80.2, 78.8, 73.8, 73.6, 72.9, 38.8, 34.4, 34.0, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 28.7, 27.7, 27.4, 26.0, 25.9, 25.2, 22.7, 19.2, 14.1.



Bis-THF alcohol **V-176** (24.5 mg, 0.028 mmol) was dissolved in dry THF (1.5 mL) and cooled in an ice bath to 0°C under N_2 . Potassium *tert*-butoxide (15 mg, 0.13 mmol) was added in 1 mL of THF. This mixture was stirred at 0°C for another 40 min before adding a solution of aryl bromide (20.5 mg, 0.072 mmol) in dry THF (1 mL) via syringe over a 5 min period. Once addition was completed, the reaction mixture was stirred and allowed to warm to room temperature over a couple hours. The reaction was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The water layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product which was purified by chromatography on silica gel (3% EtOAc in hexanes to 5% EtOAc in hexanes) and

provided compound **V-177** (18.5 mg, 61%) and recovered starting material alcohol **V-176** (8 mg, 32%).

Data for **V-177**: ^1H NMR (300 MHz, CDCl_3) δ 4.62-4.43 (2H, m), 4.31-4.04 (4H, m), 3.91-3.82 (1H, m), 3.81-3.70 (1H, m), 3.67-3.60 (1H, m), 3.47 (2H, t, $J = 6.6$ Hz), 2.38-2.21 (2H, m), 2.07-1.98 (1H, m), 1.96-1.74 (3H, m), 1.64-1.20 (40H, m), 0.98-0.81 (30H, m), 0.89-0.06 (18H, m); ^{19}F NMR (282 MHz, CDCl_3) δ -142.6 (m, 1F), -143.3 (m, 1F), -151.3 (m, 1F), -152.0 (m, 1F); ^{13}C NMR (75 MHz, CDCl_3) δ 129.1, 128.7, 127.7, 126.0, 124.3, 85.2, 81.4, 80.5, 78.7, 77.4, 74.0, 73.7, 73.4, 71.0, 59.6, 36.4, 34.8, 31.9, 31.6, 29.9, 29.7, 29.5, 29.3, 28.6, 28.5, 26.3, 26.1, 26.0, 25.9, 25.7, 25.0, 22.7, 18.1, 17.9, 14.1, 1.0, -4.1, -4.2, -4.3, -4.6, -4.7, -5.1.



Tris-TBS ether **V-177** (6.2 mg, 5.7 μmol) was dissolved in CH_2Cl_2 (3 mL) and $\text{BF}_3 \cdot \text{OEt}_2$ (2.15 μL , 17.1 μmol) was dropwise added. The reaction was stirred at room temperature for two days. 5 mL Sat. NaHCO_3 aq. solution was added to quench the reaction and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 8 mL). The organic layer was washed with brine (2 $\times$ 5 mL), dried over Na_2SO_4 , and evaporated to give a crude product which was purified by chromatography on silica gel (30% EtOAc in hexanes to EtOAc) and provided compound **V-178** (1.4 mg, 33%) and recovered starting material tris-TBS ether **V-177** (3 mg, 50%).

Data for photoaffinity analog **V-178**: ^1H NMR (500 MHz, CDCl_3) δ 4.54 (2H, s), 4.44-4.41 (1H, m), 4.36-4.31 (1H, m), 4.10-4.01 (1H, m), 3.96-3.90 (1H, m), 3.80-3.76 (1H, m), 3.46 (2H, t, $J = 6.6$ Hz), 3.42-3.36 (2H, m), 2.14-1.96 (3H, m), 1.86-1.76 (1H, m), 1.72-1.48 (12H, m), 1.42-1.17 (30H, m), 0.86 (3H, t, $J = 6.8$ Hz); ^{19}F NMR (282 MHz, CDCl_3) δ -143.2 (m, 2F), -152.0 (m, 2F).

V.14. References

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CHAPTER VI

HIGHLY EFFICIENT SYNTHESIS OF BIS-TETRAHYDROFURAN SYSTEMS:

SYNTHESIS OF ETHER LINKED ANALOGS OF *ANNONACEOUS*

ACETOGENINS

VI.1. Introduction

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 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)¹ and bullanin (having much lower ED₅₀ values against a panel of some human cancer cell lines than adriamycin, an anticancer drug currently in clinical use²) (Figure VI-1),

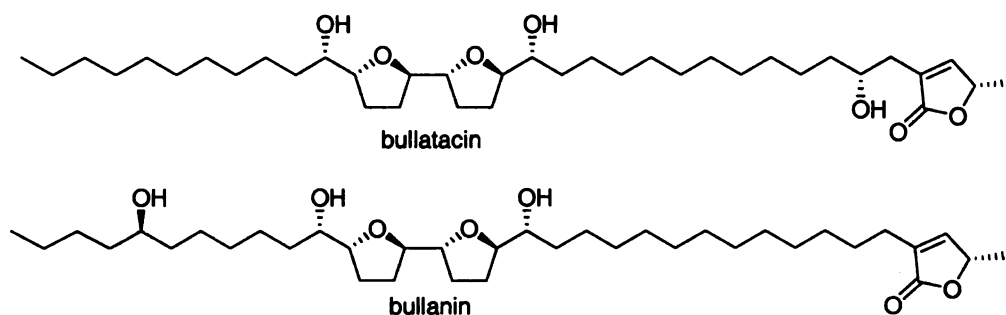


Figure VI-1: Structure of bis-adjacent THF acetogenins bullatacin and bullanin

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 VI-2). Utilization of ether linkages will enable rapid

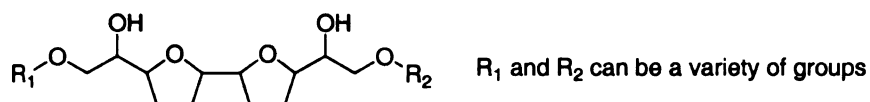


Figure VI-2: Ether linked analogs of bis-adjacent THF acetogenins

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 **VI-1**, 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 **VI-2** and **VI-3** (Figure VI-3). In theory, there is no limitation for the choice of the

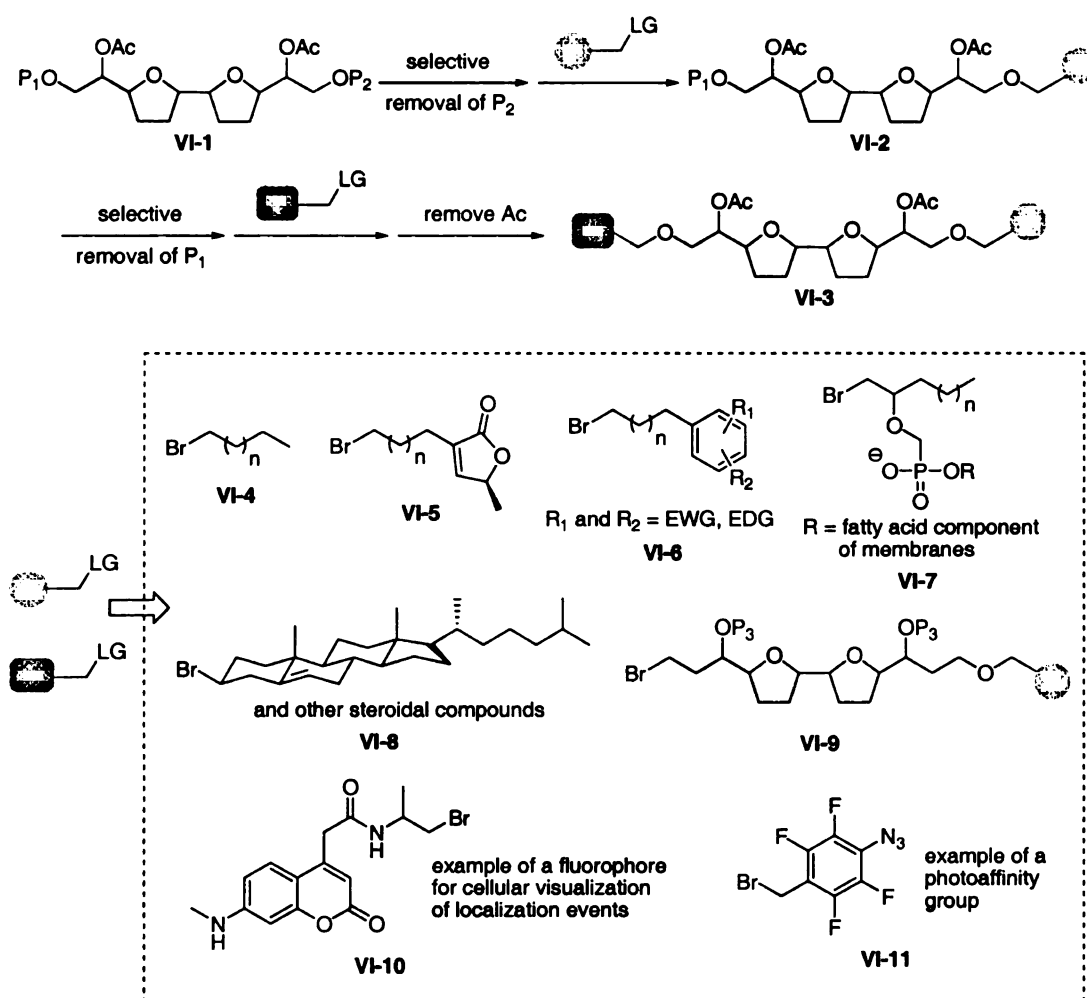
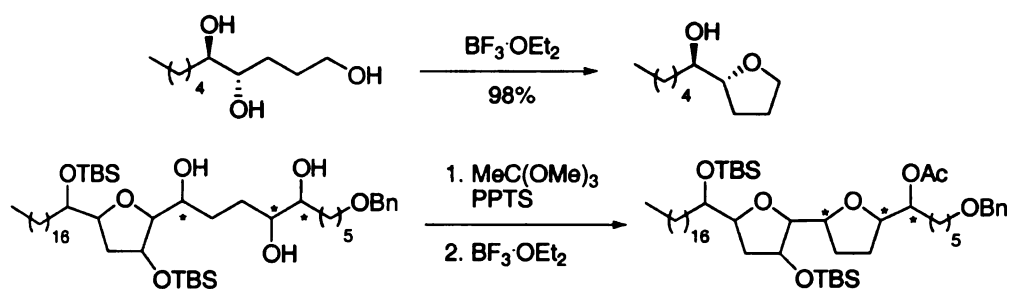


Figure VI-3: Modular synthesis of acetogenin analogs with bis-adjacent THF core

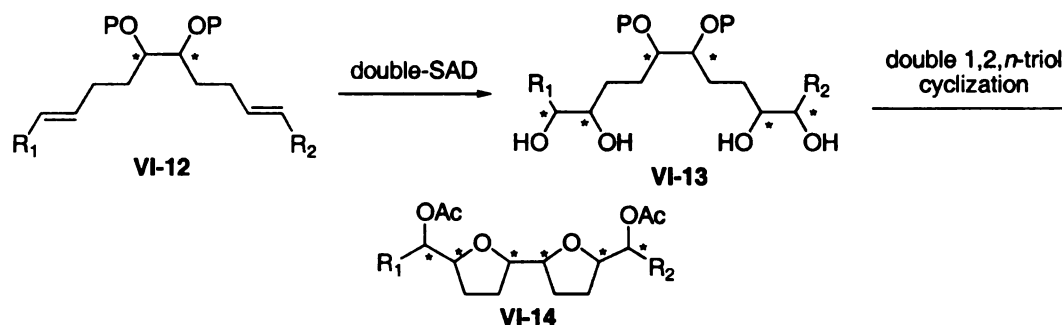
side chains, which could lead to a large library of bis-adjacent THF acetogenin analogs that can be evaluated rapidly for their bioactivities. For example, a variety of hydrophobic tails as well as the spacers with terminal butenolide moiety can be installed with different lengths by using electrophiles **VI-4** and **VI-5** (Figure VI-3). The butenolide functionality can be changed to other groups that could interfere with electron transport in complex I, such as substituted benzenes (**VI-6**) and quinones. Membrane-binding elements such as phosphate esters (**VI-7**) and steroidal compounds (**VI-8**) 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 (**VI-9**). In addition, fluorescent molecules can be attached for sub-cellular localization experiments (**VI-10**) and photoaffinity groups can be attached for photoaffinity labeling experiments (**VI-11**). 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 (Chapter IV). 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 (Scheme VI-1).³ Using Sharpless asymmetric dihydroxylation (SAD)⁴ to control the absolute stereochemistry, 2,5-disubstituted THF rings could be formed in excellent yield. This methodology was successfully



Scheme VI-1: Examples of 1,2,*n*-triol cyclization reaction

used in the total synthesis of mucoxin⁵ and its analogs (Chapter V). 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 VI-2. After preparing intermediate



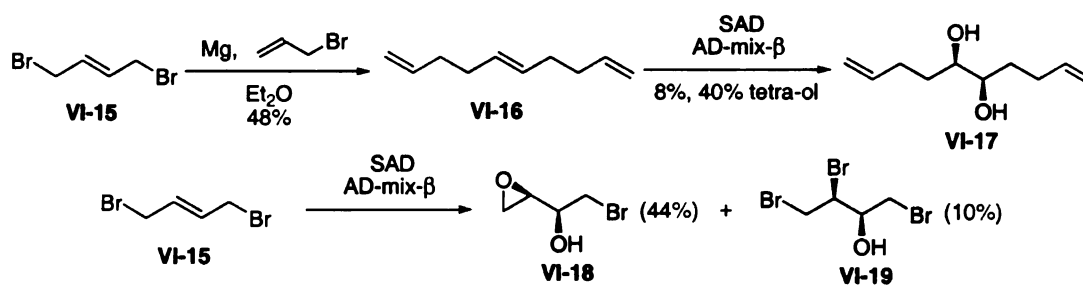
Scheme VI-2: Proposed synthetic plan to form bis-adjacent THF segments

VI-12 containing two double bonds, double SAD reactions can provide tetra-ol **VI-13** 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 **VI-14** 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.

VI.2. Synthesis of Diene Precursor

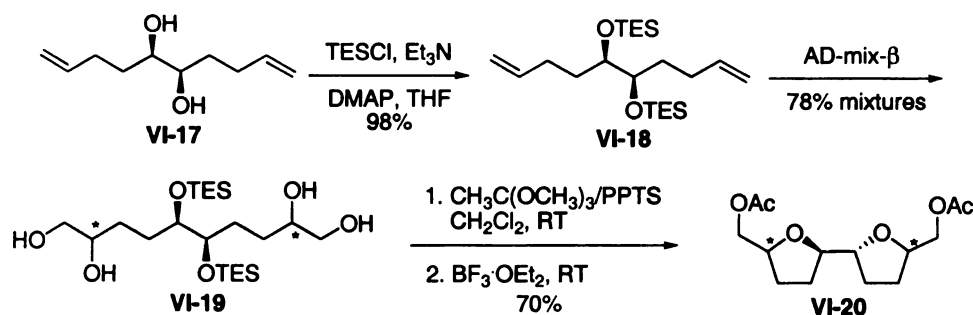
Our studies began with the synthesis of diene precursor **VI-12** for the SAD reaction. The first attempt was to synthesize compound **VI-17**, which contains two terminal double bonds and an adjacent diol moiety. 1,4-Dibromo-2-butene **VI-15** was treated with allylmagnesium Grignard reagent to give triene **VI-16** in 48% yield (Scheme VI-3).⁶ The moderate yield was probably due to the volatility of the



Scheme VI-3: The first synthesis of diene precursor

product. The following SAD reaction using AD-mix- β led to the dihydroxylation of the more substituted double bond to afford compound **VI-17**. However, only 8% yield of diol was isolated after separation, along with 40% tetraol byproduct. Since the regioselectivity of the SAD reaction for compound **VI-16** was not good, the use of compound **VI-15** in the SAD reaction was considered (Scheme VI-3). This reaction did not give any desired diol product, instead, 44% of the monobromohydroxyl epoxide **VI-18** and 10% of the tribromo alcohol **VI-19** were isolated. One possible reason for these two products was the basic reaction conditions. Since the SAD reaction took place under mild basic conditions, newly formed hydroxyl groups could be deprotonated to form alkoxides, which could attack the carbon bearing a good leaving group (bromide) to form epoxide **VI-18**.

Even though this synthetic sequence was not useful due to its low yield and regioselectivity, it did provide the useful intermediate **VI-17** for further study. Protection of the free hydroxyl groups in diol **VI-17** with TESCl followed by double SAD reactions afforded tetra-ol **VI-19** in good yield (Scheme VI-4). The



Scheme VI-4: The first attempt of double cyclization reaction to form bis-adjacent THF

stereoselectivity in this double SAD reaction was not good because of the precursor terminal olefins, which typically show poor stereoselectivity.⁴ Four possible diastereomers were obtained after this reaction, which could not be separated via silica gel chromatography. With our new approach, we investigated the double cyclization reaction of the diastereomeric mixture **VI-19** with trimethylorthoacetate and PPTS followed by BF₃•OEt₂. It was exciting to find that the desired bis-adjacent THF segment **VI-20** was obtained in 70% yield as a diastereomeric mixture. The TES groups were successfully removed under these conditions and the cyclization reaction occurred spontaneously. This result proved that our synthetic strategy of double cyclization of polyhydroxylated systems was an efficient alternative pathway to form bis-adjacent THF cores. The first attempt for the double cyclization methodology was successful to form bis-adjacent THF segment **VI-20** in a good yield.

The following study was to develop a better route to synthesize the diene precursor. Since terminal olefins are not good substrates for the SAD reaction, *trans*-olefins, which normally provide high stereoselectivity, were chosen as the synthetic target (Figure VI-4).

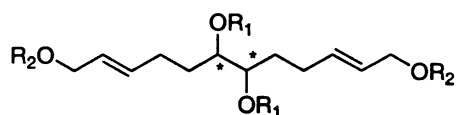
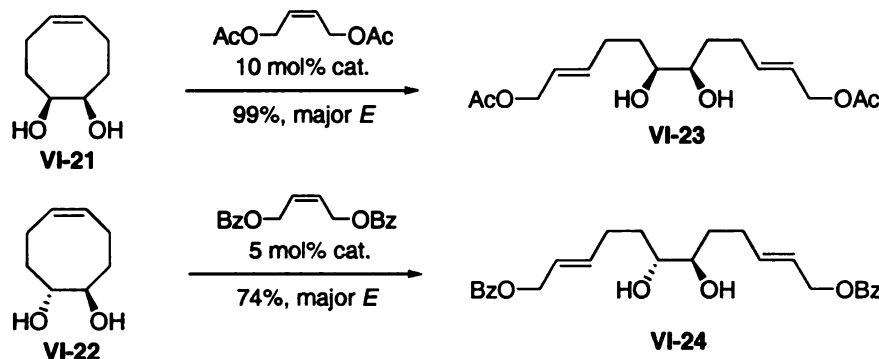


Figure VI-4: Diene precursor for the methodology study

VI.2.1. Ring opening / cross metathesis pathway

In 2006, Burke and coworkers reported an approach to form a series of chiral bis-adjacent THF cores via a Pd(0)-mediated asymmetric double cycloetherification reaction.⁷ During their study, they prepared the diene precursor from known 1,2-dihydroxycyclooctene **VI-21** and **VI-22** (Scheme VI-5).^{8,9} Treatment of **VI-21**



Scheme VI-5: Burke's method to prepare diene precursors **VI-23** and **VI-24**

and **VI-22** with Grubbs' second-generation ruthenium catalyst and 1,4-diprotected-*cis*-2-butene gave the desired diene precursors **VI-23** and **VI-24** through a ring opening/cross metathesis pathway.⁷ The major product of both of these two reactions contained all *E* double bonds, with a small amount of *E/Z* double bond isomers detectable.¹⁰ Also, in order to obtain a good yield, *meso*-compound

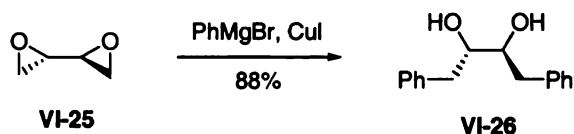
VI-21 and C2-symmetric compound **VI-22** were reacted with *cis*-alkenes with different protecting.

Considering that Grubb's second-generation ruthenium catalyst is expensive (2g / \$405) and this initial step needs to be scaled-up, we did not use this method to synthesize our diene precursors.

VI.2.2. Bis-epoxide ring-opening pathway

Epoxide ring-opening reaction is an efficient route to prepare chiral secondary alcohols since many good methodologies to prepare chiral epoxides such as Sharpless asymmetric epoxidation,¹¹ Jacobsen's epoxidation,¹² and Shi epoxidation¹³ are already well developed. Different organometallic reagents such as organolithium,¹⁴ Grignard,¹⁵ organocuprate,¹⁶ and organoaluminum reagents¹⁵ were successfully used in the ring-opening reaction of chiral epoxides to form secondary alcohols.¹⁷

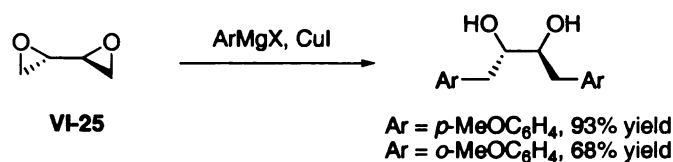
Based on all of these previous studies, in 1999, Robbins and coworkers reported the synthesis of chiral non-racemic vicinal diols such as **VI-26** from (*S,S*)-1,2,3,4-diepoxybutane **VI-25** (Scheme VI-6), which provided an efficient route to prepare chiral vicinal diols.^{18, 19} Later on, different nucleophilic reagents were



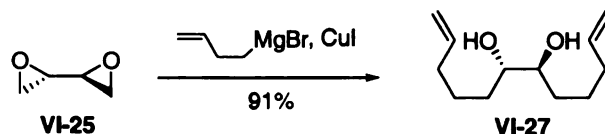
Scheme VI-6: Robbins' synthesis of non-racemic adjacent diol **VI-26**

used, following the same strategy, to open the chiral bis-epoxide. For example, de March and coworkers reported the synthesis of enantiomerically pure monoketals of *p*-benzoquinone with C2-symmetry.²⁰ Their diol precursors were prepared via this

ring-opening reaction of chiral bis-epoxide **VI-25** with different aryl Grignard reagents (Scheme VI-7). Clive and coworkers found that aliphatic Grignard reagents could undergo the same ring-opening reactions to give the desired chiral vicinal diols (Scheme VI-8).²¹ Using 1-butene-4-bromide to generate the corresponding Grignard reagent, chiral diol **VI-27** could be formed via bis-epoxide ring-opening reaction in excellent yield. Besides Grignard reagents, organolithium reagents can also be used

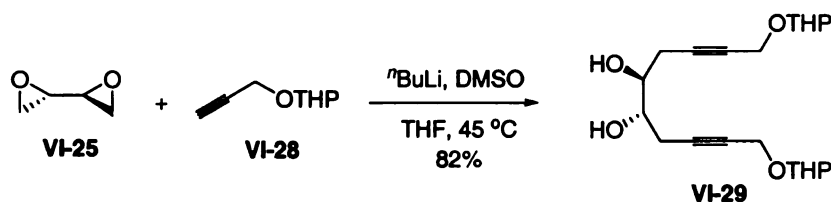


Scheme VI-7: Other aromatic Grignard reagents in bis-epoxide ring-opening reactions



Scheme VI-8: Aliphatic Grignard reagent in bis-epoxide ring-opening reactions

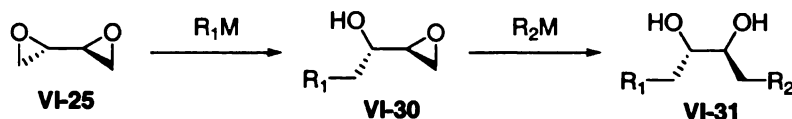
in this strategy. In 2002, König and coworkers used this method to prepare chiral diol **VI-29** by treating chiral bis-epoxide **VI-25** with lithium acetylide derivative **VI-28** in 82% yield (Scheme VI-9).²¹ The bis-epoxide ring-opening pathway



Scheme VI-9: Organolithium reagent in bis-epoxide ring-opening reactions

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.

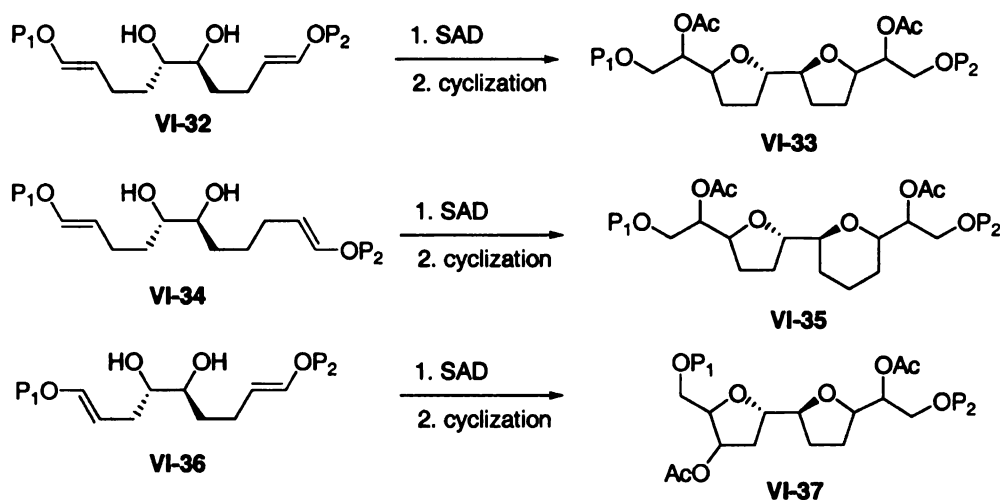
Another advantage for using the bis-epoxide ring-opening pathway is the possibility to form the non-C2-symmetric secondary diols (Scheme VI-10). If only 1



Scheme VI-10: Synthesis of non-C2-symmetric adjacent diols

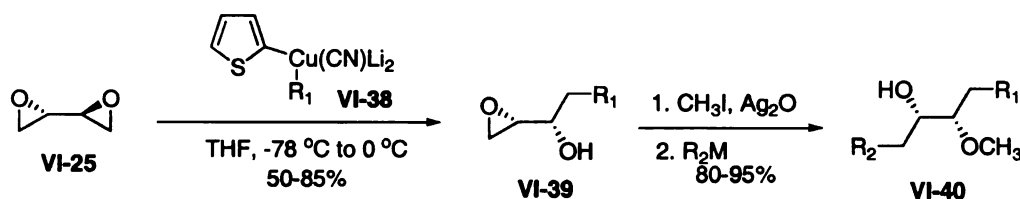
equiv of organometallic nucleophile (R_1M) is used for the mono epoxide ring-opening, epoxyalcohol **VI-30** could be formed, which could be subjected to a second ring-opening reaction using a different organometallic nucleophile (R_2M) to afford the non-C2-symmetric adjacent diol **VI-31**.

The ability to change R_1 and R_2 groups leads to quick access in preparing different classes of acetogenins (Scheme VI-11). For example, if both R_1 and R_2 are allylic organometallic nucleophiles, diol **VI-32** would be formed after the two-step ring-opening reactions, which then leads to the formation of the bis-adjacent THF acetogenins **V-33** with two different terminal protecting groups. If R_1 is allylic and



Scheme VI-11: Preparation of different classes of acetogenins with non-C2-symmetric diol precursors

R_2 is a homoallylic organometallic nucleophile, diol **VI-34** would be formed from which the non-classical THF-THP acetogenin **VI-35** would be obtained. If R_1 is vinyl and R_2 is an allylic organometallic nucleophile, diol **VI-36** is anticipated and the hydroxylated THF acetogenin **VI-37** would be accessed. The monoaddition reaction of chiral bis-epoxide **VI-25** was disclosed in 2002 when Boeckman and Liu reported the controllable monoaddition of carbon nucleophiles to **VI-25** to form non-C2-symmetric diols.²² In their paper, a strategy for the construction of unsymmetrical 1,2-diols bearing various unsaturated appendages was described (Scheme VI-12). The mixed higher-order cyanocuprates $R_1(2\text{-Th})\text{Cu}(\text{CN})\text{Li}_2$ **VI-38**

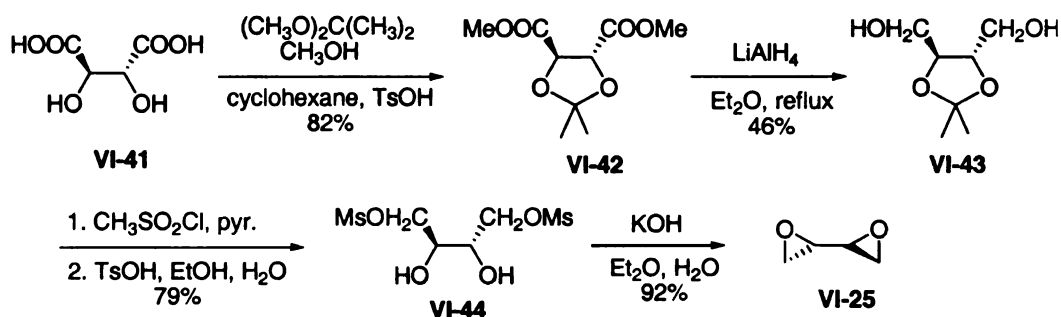


Scheme VI-12: Boeckman and Liu's synthesis of non-C2-symmetrical adjacent diols

bearing either alkenyl or alkyl transferable groups afforded exclusively the monoaddition product epoxy alcohol **VI-39** in good to excellent yield. The differentiation of the two side chains of the bis-adjacent secondary alcohol was accomplished via protection of the free hydroxyl group and the second chain extension using either Grignard or organolithium reagents in the presence of CuI or $\text{BF}_3 \cdot \text{OEt}_2$ was performed. This strategy provided access to unsymmetrical mono-protected diols bearing different side chains and could be used in our new methodology studies.

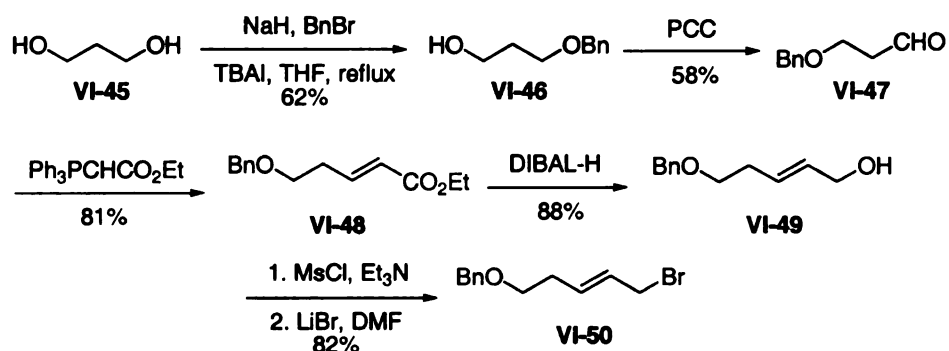
Synthesis of chiral bis-epoxide **VI-25** was carried out from the commercially available L-tartaric acid **VI-41**.^{19, 23} L-tartaric acid was protected by

2,2-dimethoxypropane in methanol to give intermediate **VI-42** in 82% yield (Scheme VI-13). Reduction of the dimethyl ester with LiAlH_4 , followed by mesyl protection and acetonide group deprotection afforded diol **VI-44**. Base-mediated cyclization furnished the (*S,S*)-1,2,3,4-diepoxybutane **VI-25** in 92% yield.



Scheme VI-13: Synthesis of chiral bis-epoxide VI-25

Based on a previous study, 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 an allylic alkyl bromide containing a *trans*-olefin (Scheme VI-14). Mono-benzylation of 1,3-propanediol **VI-45** with



Scheme VI-14: Synthesis of allylic alkyl bromide VI-50

NaH and benzyl bromide at refluxing conditions provided the desired alcohol **VI-46** in 62% yield, along with 23% dibenzylated product. PCC oxidation followed by Wittig reaction using stabilized ylide provided *trans*-olefin **VI-48** as a single diastereomer, which was subjected to DIBAL-H reduction to give allylic alcohol

VI-49. The terminal hydroxyl group was converted to a good leaving group followed by S_N2 displacement with lithium bromide to provide allylic bromide **VI-50** in 82% overall yield after two steps.²⁴

However, attempts to perform the bis-epoxide ring-opening reaction with Grignard reagent generated *in situ* from allylic bromide **VI-50** did not give any desired diol product **VI-52**. Some of the starting material was recovered based on the crude NMR of the reaction.

The unsuccessful reaction was probably due to the difficult formation of the Grignard reagent since some of the allylic bromide was recovered. Optimization of the *in situ* generation of the Grignard reagent followed by epoxide ring-opening reaction under various reaction temperature and solvents did not help (Table VI-1). Even after reflux for 20 h, the reaction still did not work since no desired product was formed.

Table VI-1: Different conditions in bis-epoxide ring-opening reaction by using Grignard reagent

Preparation of Grignard Reagent			Ring-Opening Reaction		
Solvent	Temperature	Time	Solvent	Temperature	Time
Et ₂ O	RT	5 h	THF	-30 °C to 0 °C	more than 20 h
THF	reflux	5 h	Et ₂ O		
THF	reflux	20 h	Et ₂ O		

With the failure of the Grignard approach, we next turned to organolithium reagents. Lithium-halogen exchange using synthesized allylic bromide **VI-50** and lithium reagent should provide the desired organolithium reagent, which could then be

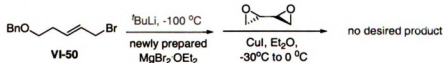
coupled with diepoxide **VI-25**. However, neither $n\text{BuLi}$ nor $t\text{BuLi}$ could facilitate the reaction under different conditions (Table VI-2). After the organolithium reagent was added to the pre-cooled CuI suspension, diepoxide **VI-25** was added dropwise. Even after more than 20 h of reaction, there was still no desired product **VI-52** formed.

Table VI-2: Different conditions in bis-epoxide ring-opening reaction by using organolithium reagent

VI-25 + VI-53 $\xrightarrow{\text{CuI}}$ VI-52

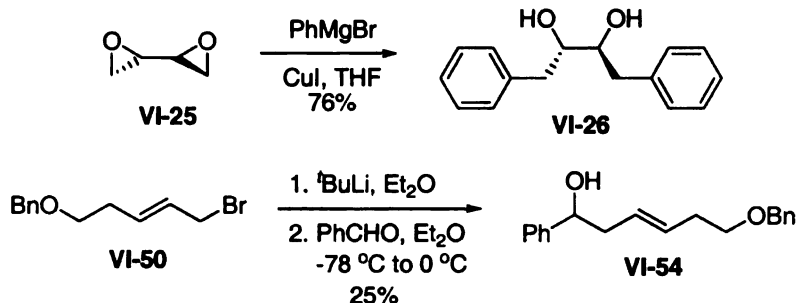
Preparation of Lithium Reagent			Ring-Opening Reaction		
Solvent	Temperature	Lithium Reagent	Solvent	Temperature	Time
	-78 °C	$n\text{BuLi}$	THF		
Et_2O	-78 °C	$t\text{BuLi}$	Et_2O	-30 °C to 0 °C	more than 20 h
	-100 °C	$t\text{BuLi}$	Et_2O		

In situ generation of Grignard reagent was also attempted (Scheme VI-15). Allylic bromide was treated with $t\text{BuLi}$ under very low temperature and the bromide-lithium exchange should provide the corresponding lithium reagent, which reacted with newly prepared $\text{MgBr}_2 \cdot \text{OEt}_2$ to generate Grignard reagent *in situ*. However, this reaction still did not give the desired product.



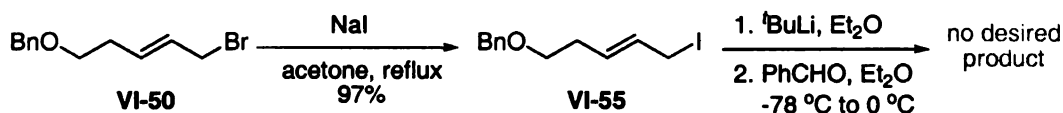
Scheme VI-15: *In situ* generation of Grignard reagent

In order to understand the reason why the reaction failed, two experiments were carried out (Scheme VI-16). Diepoxide **VI-25** was subjected to the common



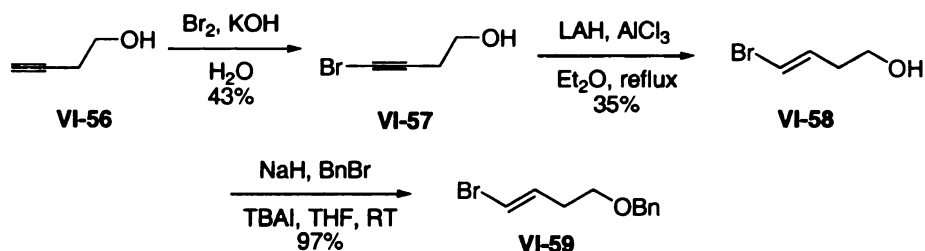
Scheme VI-16: Ring-opening of diepoxide **VI-25** with commercially available PhMgBr and verifying metal-halogen exchange of **VI-50**

ring-opening conditions with phenyl magnesium bromide reagent affording the desired diol **VI-26** in 76% yield, which was comparable as the reported known reaction. This experiment proved that the diepoxide was good and the ring-opening reaction was not the problem. Then allylic bromide **VI-50** was treated with $^t\text{BuLi}$ to generate organolithium reagent, which further reacted with benzaldehyde to do the nucleophilic addition reaction to the carbonyl group. This reaction only gave the desired secondary alcohol **VI-54** in 25% yield. It seemed that the problem was due to the generation of the organolithium reagent. Since bromide is not as efficient in the halogen-lithium exchange as iodide, the corresponding iodide was prepared and subjected to the same nucleophilic addition reaction with benzaldehyde (Scheme VI-17). However, this time the reaction was messy and no desired product was obtained.



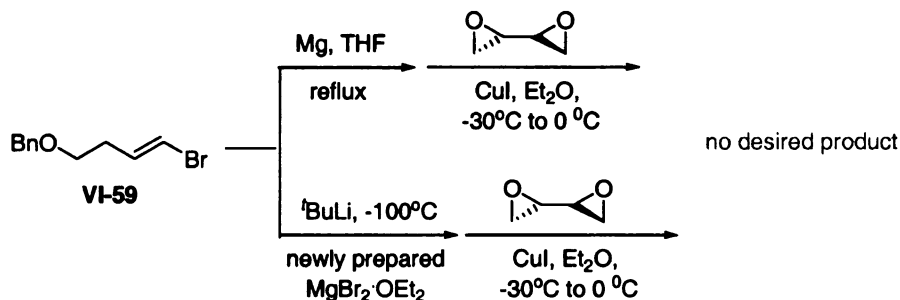
Scheme VI-17: Iodide **VI-55** in nucleophilic addition of benzaldehyde

Because allyl magnesium bromide was known to be unstable and easy to polymerize, vinyl bromide was also synthesized and used in this reaction (Scheme



Scheme VI-18: Synthesis of vinyl bromide **VI-59**

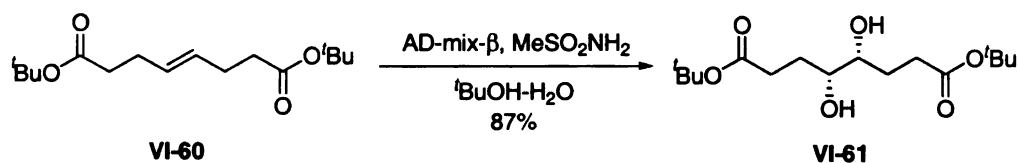
VI-18). The propargylic alcohol **VI-56** was converted to the bromide **VI-57** under basic conditions, which was reduced by LAH to form vinyl bromide **VI-58**. Subsequent benzyl protection of the free alcohol in **VI-58** gave the bromoalkene **VI-59** in excellent yield.^{25, 26} However, the ring-opening reaction using vinyl magnesium bromide failed again and did not afford any desired diol (Scheme VI-19). Neither direct nor transmetallation formation of Grignard reagent could help to improve this diepoxide ring-opening reaction.



Scheme VI-19: Vinyl bromide **VI-59** in diepoxide ring-opening reaction

VI.2.3. Chain-elongation pathway

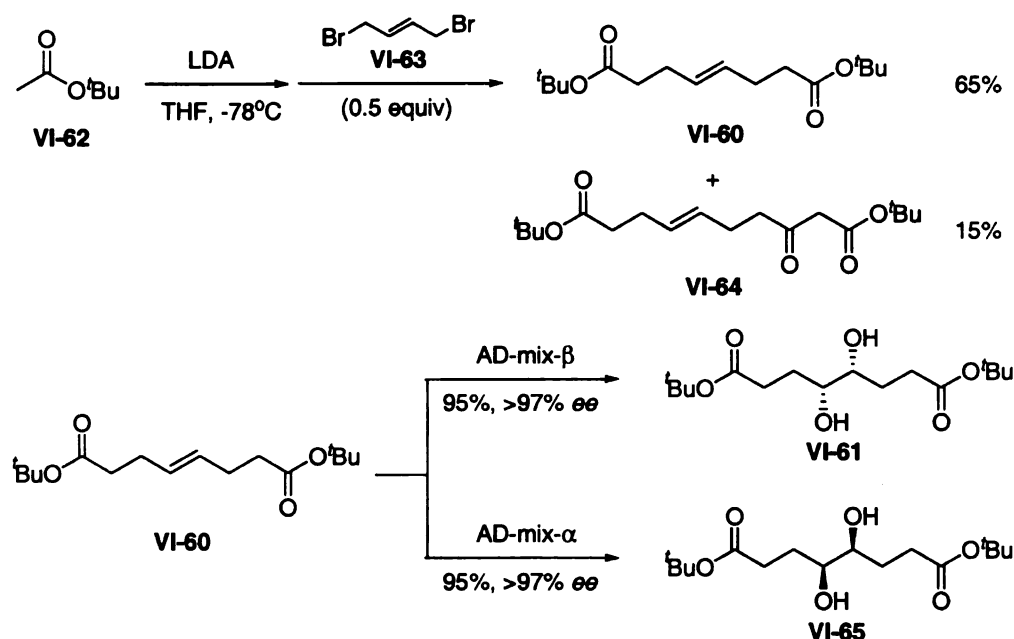
Since the diepoxide ring-opening reaction could not afford the desired diene intermediate, another method was considered. In 2003, Nelson and coworkers reported the desymmetrization of a centrosymmetric diepoxide, which could be efficiently used in the total synthesis of hemibrevetoxin B.²⁷ In their paper, they introduced the reactions to prepare the diol precursor with two ester groups in it



Scheme VI-20: Nelson's method to prepare chiral diol **VI-61**

(Scheme VI-20), which could be used to construct our diene precursor directly through functional group transformations.

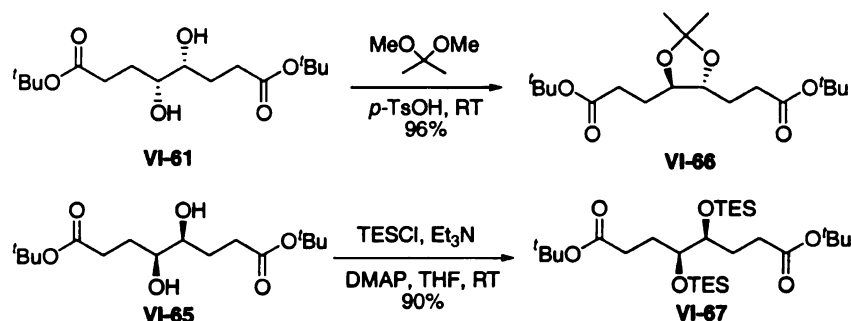
The new synthetic pathway started from the reaction of the lithium enolate of the commercially available *tert*-butyl acetate **VI-62** with 0.5 equiv of (*E*)-1,4-dibromo-2-butene **VI-63** to give the unsaturated diester **VI-60** in 65% yield along with 15% byproduct β -keto ester **VI-64** (Scheme VI-21). Sharpless asymmetric dihydroxylation of the diester **VI-60** with AD-mix- α and β gave the optically active diol **VI-61** and **VI-65** in high yields and high *ees*.



Scheme VI-21: Synthesis of chiral adjacent diol **VI-61** and **VI-65**

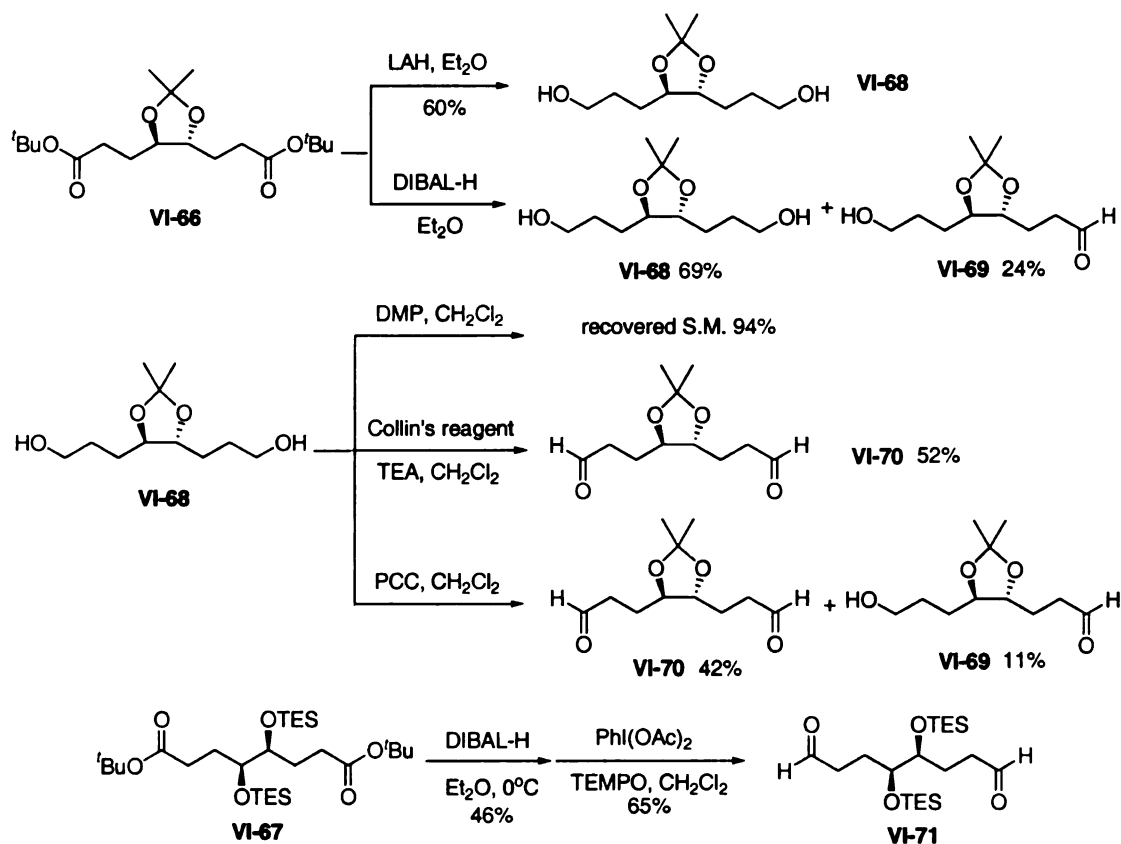
Next, for the protection of the free diol, two different groups were considered. Since these protecting groups should be easily removed under cyclization conditions

($\text{BF}_3 \cdot \text{OEt}_2$), both acetonide and TES groups were used to synthesize compound **VI-66** and **VI-67** in excellent yield (Scheme VI-22).



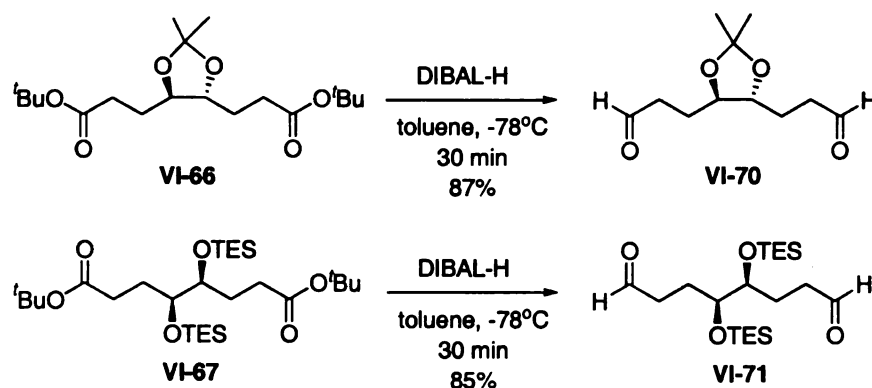
Scheme VI-22: Two different protection reactions of free diols

In order to elongate the alkyl chain and make the diene precursor, Wittig reaction could be used to form the desired *trans*-alkenes. Thus, the ester functional group in **VI-66** and **VI-67** was converted to the corresponding aldehydes. Two-steps reduction/oxidation sequence gave the desired product with moderate yield (Scheme



Scheme VI-23: Synthesis of dialdehydes **VI-69** and **VI-70**

VI-23). LAH reduction of diester **VI-66** gave primary diol **VI-68** as a single product in 60% yield. DIBAL-H reduction of diesters was not complete and afforded the desired diol **VI-68** in 69% yield along with 24% mono-alcohol **VI-69**. The oxidation of the primary diol using a variety of conditions was not efficient. DMP condition did not give any desired product and 94% of the starting material was recovered after the reaction. Using Collin's reagent for the oxidation gave the desired dialdehyde **VI-70** in 52% yield.²⁸ PCC oxidation at RT provided 42% dialdehyde **VI-70** along with 11% of the mono-aldehyde **VI-69**. It was obvious that the oxidation reaction was not easy to be completed. The same observation was found for substrate **VI-67**. DIBAL-H reduction followed by TEMPO initiated radical oxidation with $\text{PhI}(\text{OAc})_2$ gave the corresponding dialdehyde **VI-71** only in moderate yield. However, during the DIBAL-H reduction of diester **VI-66** the byproduct, mono-aldehyde **VI-69**, was isolated after the reaction, which indicated that it was possible to obtain the dialdehyde directly from the reduction reaction. This



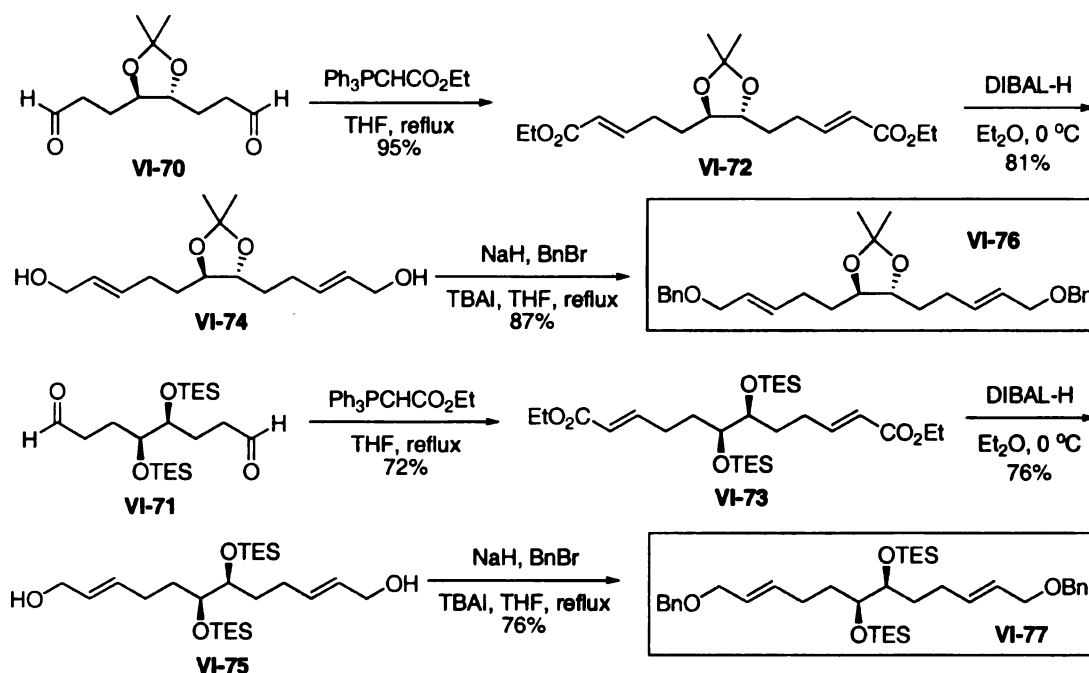
Scheme VI-24: Low temperature reduction to form dialdehyde

was demonstrated via the low temperature reduction experiments (Scheme VI-24).

After treatment of diesters **VI-66** and **VI-67** with DIBAL-H in toluene at -78 °C for

only 30 min, the reduction was complete and the desired dialdehydes **VI-70** and **VI-71** were formed in good yield.

The synthesis of diene precursors was completed via the following three steps (Scheme VI-25). Double Wittig olefination using

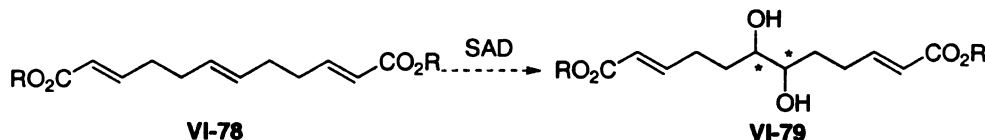


Scheme VI-25: Synthesis of diene precursors **VI-76** and **VI-77**

(carbethoxymethylene)triphenylphosphorane succeeded in forming *E*-olefins **VI-72** and **VI-73**, which were subjected to the DIBAL-H reduction at 0 °C to give allylic alcohols **VI-74** and **VI-75**. After dibenzylation of the primary alcohols, the desired diene precursors **VI-76** and **VI-77** were synthesized in good yield. For the last step, the benzyl protection, it was found that room temperature reaction gave mixtures of dibenzyl ether and mono-benzyl ether. Increasing the temperature to reflux helped to obtain the pure dibenzylation products.

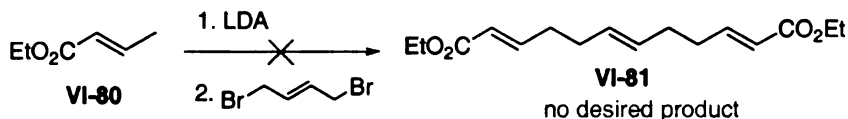
As described before, the chain-elongation strategy was efficient to synthesize the desired diene precursor for the double cyclization methodology. This led us to

consider an alternate strategy; the preparation of a triene followed by a selective SAD reaction (Scheme VI-26). Since the middle double bond in **VI-78** is more



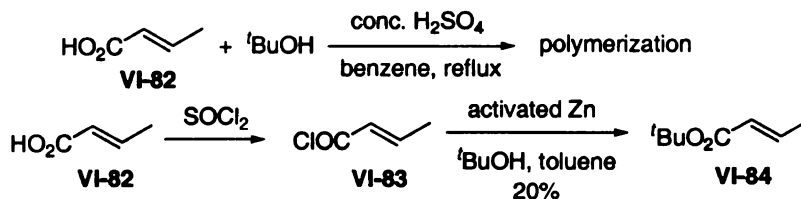
Scheme VI-26: Alternative strategy to form diene precursor

electron-rich than the other two, SAD reaction using 1 equiv AD-mix reagent should prefer to react with it to give the desired diol **VI-79**. If triene **VI-78** could be synthesized via the same process, this pathway would be simpler than the previous strategy. The first attempt to prepare triene **VI-81** using the lithium enolate of ethyl crotonate **VI-80** to (*E*)-1,4-dibromo-2-butene failed and no desired product was formed (Scheme VI-27). In addition, instead of ethyl crotonate, *tert*-butyl crotonate



Scheme VI-27: Elongation reaction of ethyl crotonate

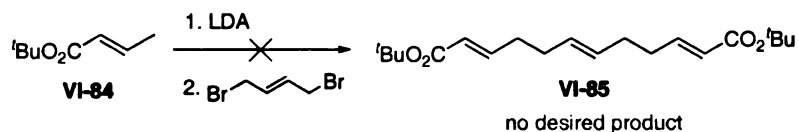
was considered for the same sequence. However, the preparation of *tert*-butyl crotonate was not successful when the benzene solution of crotonic acid **VI-82** and *tert*-butanol was refluxed (Scheme VI-28). A black gel was formed after the reaction



Scheme VI-28: Preparation of *tert*-butyl crotonate **VI-84**

and it is believed that the polymerization of crotonic acid under acidic condition occurred.²⁹ The activated zinc promoted esterification from acid chloride **VI-83** and *tert*-butanol could give low yields of desired *tert*-butyl crotonate **VI-84**.³⁰⁻³²

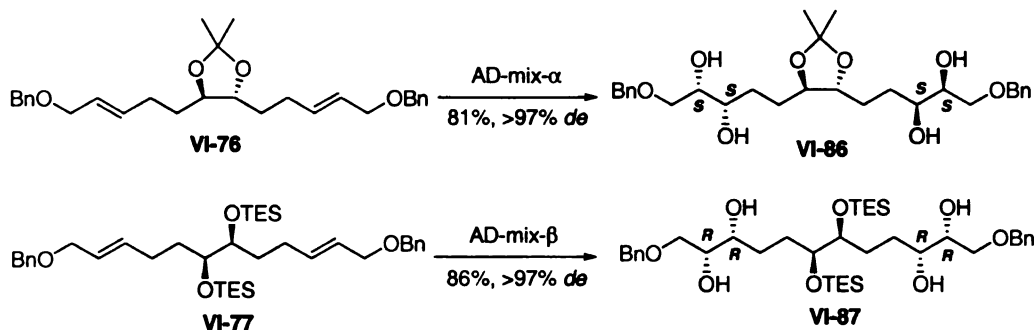
However, similar S_N2 displacement of 1,4-dibromo-2-butene with lithium enolate of *tert*-butyl crotonate failed and gave a messy reaction (Scheme VI-29).



Scheme VI-29: Elongation reaction of *tert*-butyl crotonate

VI.3. Double Cyclization Reaction of the Polyhydroxylated Systems to Form bis-Adjacent THF Moiety

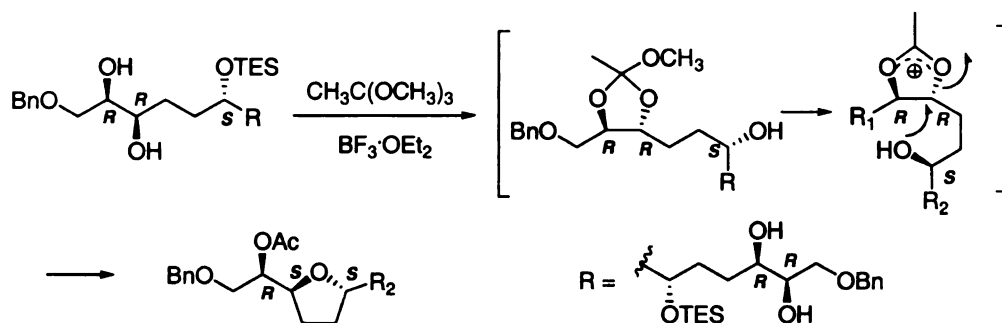
Successful preparation of diene precursors provided the useful intermediates to attempt the double cyclization strategy. First, double SAD reaction of the dienes directly afforded the polyhydroxylated systems in a single step (Scheme VI-30). It was observed that both of the double SAD reactions proceeded in good yield and excellent diastereoselectivities. Tetra-ol **VI-86** and **VI-87** were obtained as single diastereomers. Since both of the substrates were C₂-symmetric, the newly formed



Scheme VI-30: Preparation of polyhydroxylated systems

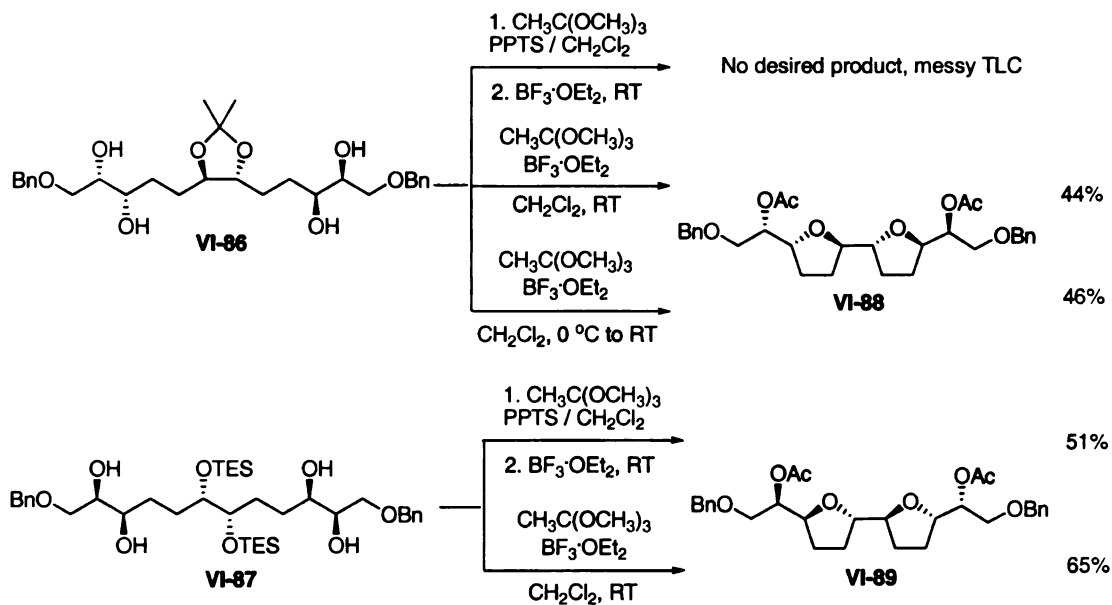
chiral centers had the same absolute configurations. The determination of the absolute configurations was based on the common SAD models (Figure VI-5).⁴ *Trans*-olefins matched with the empirical mnemonic model very well to give excellent diastereoselectivities.

Based on the reported one-pot 1,2,*n*-triol cyclization, the stereochemistry of the desired product is shown in Scheme VI-31.³ The *trans*-THF ring could be formed with the *erythro*-side hydroxyl group flanking on it. The 5-*exo* cyclization converted the stereochemistry of one chiral center and the other two remained the same.



Scheme VI-31: Stereochemistry of the cyclization product

The double cyclization of the polyhydroxylated systems gave the desired bis-adjacent THF moiety in one step under mild conditions (Scheme VI-32). Different protecting groups had an effect on the yield of the reaction. Generally, the

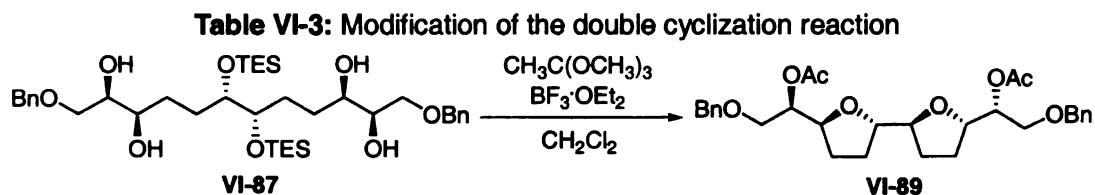


Scheme VI-32: Double cyclization of polyhydroxylated systems to form bis-adjacent THF moiety

reaction of acetonide protected substrate **VI-86** was more difficult than that of TES

protected substrate **VI-87**. The one-pot reaction with PPTS catalyzed *in situ* generation of orthoester followed by $\text{BF}_3 \cdot \text{OEt}_2$ mediated cyclization did not give any desired product of **VI-86** and afforded 51% yield of the desired bis-adjacent THF moiety of **VI-87**. This was probably due to the fact that under cyclization conditions, it is harder to deprotect the acetonide than TES groups. In addition, the one-step reaction using only $\text{BF}_3 \cdot \text{OEt}_2$ promoted both *trans*-ortho esterification and the subsequent cyclization, always gave higher yield than the two-steps reaction. Finally this simplified one-step reaction condition was chosen as the double cyclization condition to form the bis-adjacent THF moiety. In addition, TES groups were considered as more efficient groups than acetonide groups.

Modification of this reaction was carried out by varying the amounts of reagents, reaction temperature, and adding an additive to the reaction mixture (Table VI-3). It



Entry	Equiv of Reagents		Reaction Conditions		Isolated Yield (%)
	$\text{CH}_3\text{C}(\text{OCH}_3)_3$	$\text{BF}_3 \cdot \text{OEt}_2$	Temperature	Additive	
1	2.4	0.1	RT	none	10%
2	2.4	1.0	RT	none	60.6%
3 ^a	2.4	1.0	RT	none	65.4%
4 ^a	2.4	1.5	RT	none	40%
5 ^a	2.4	10.0	RT	none	8%
6 ^a	4.8	1.0	RT	none	61%
7 ^a	2.4	1.0	0 °C to RT	none	19%
8 ^a	2.4	1.0	RT	4 Å M.S.	60%

^a Using newly distilled $\text{BF}_3 \cdot \text{OEt}_2$.

is obvious to see that catalytic amount of $\text{BF}_3 \cdot \text{OEt}_2$ could not efficiently mediate the cyclization reaction (entry 1). More than 1 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ decreased the yield (entry 4, 1.5 equiv) and too much $\text{BF}_3 \cdot \text{OEt}_2$ would shut down the reaction (entry 5, 10 equiv). Varying the amount of trimethyl orthoacetate did not affect the reaction and gave a comparable yield of the desired product (entry 6). Pre-cooling the reaction to 0 °C and after the addition of $\text{BF}_3 \cdot \text{OEt}_2$ warming the solution back to room temperature did not improve the reaction and instead gave a much lower yield of the desired product along with mixtures of acetylated tetra-ols (entry 7). It seemed that low temperature was not good to efficiently remove the TES group and thus the cyclization reaction was much slower than the hydration of the orthoester intermediate to give the byproduct. In order to eliminate moisture, which could lead to the hydration of the orthoester intermediate, 4 Å molecular sieves were added to the reaction (entry 8). However, this additive did not result in better yields. Better results were obtained when newly distilled trimethyl orthoacetate and $\text{BF}_3 \cdot \text{OEt}_2$ were used to prevent the presence of moisture. Finally the best modified conditions for this double cyclization reaction was the use of 2.4 equiv trimethyl orthoacetate and 1.0 equiv $\text{BF}_3 \cdot \text{OEt}_2$ in dichloromethane with the concentration of the tetra-ol substrate equal to 0.02 M. The desired bis-adjacent THF moiety could be formed under mild conditions after about 1 h in moderate yield (65%).

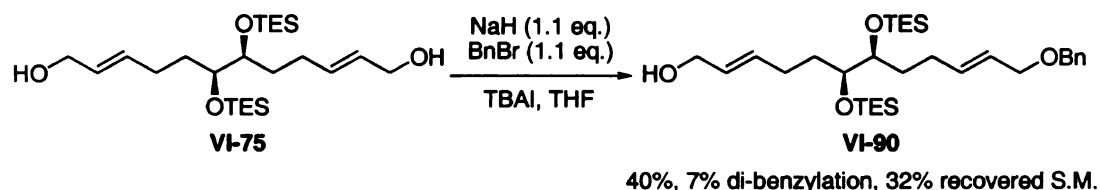
VI.4. Differentiation of the C2-Symmetric bis-Adjacent THF Moiety

Based on the previous strategy, the synthesized bis-adjacent THF moiety had a C2-symmetry. Since *Annonaceous* acetogenins have unsymmetrical side chains in

both sides of the bis-THF moiety, in order to do the library synthesis of the ether-linkage analogs of acetogenins, differentiation of the C2-symmetric molecule needed to be studied.

The initial attempt was to differentiate the two terminal hydroxyl groups. As described before, in order to install different functional groups in either side of the bis-THF moiety, two different protective groups are needed for selective removal.

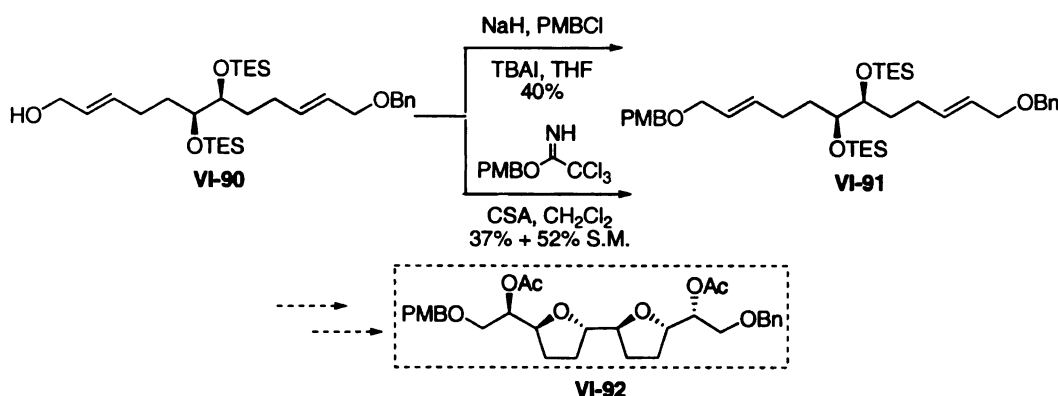
During the synthesis of the diene precursors, it was observed that the benzyl protection was slow at ambient temperature and always gave a mixture of dibenzyl ether and mono-benzyl ether as the product. This experiment provided the possibility to perform a mono-benzylation followed by another protection. It was found that using only 1.1 equiv sodium hydride and 1.1 equiv benzyl bromide, the mono-benzyl ether was formed as the major product (Scheme VI-33). The reaction



Scheme VI-33: Mono-benzylation of diol VI-75

was slow even under refluxing conditions, and after 24 h there was still around 32% recovered starting material. The byproduct dibenzyl ether was only in 7% yield. The selectivity of the mono-benzylation was good and we could easily recover the starting material back.

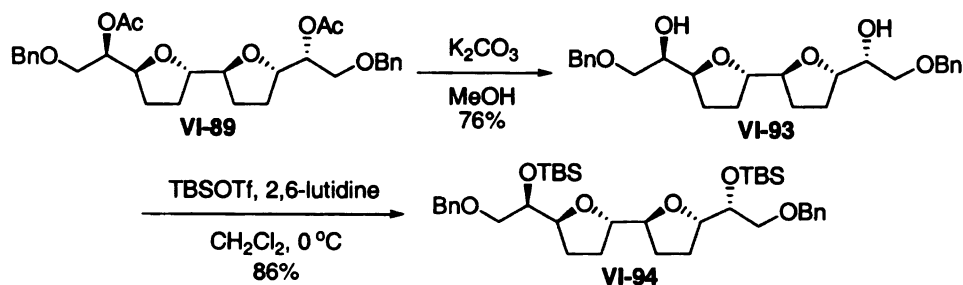
Thus, the second protection with different groups could be achieved. Only the PMB group was used as an example and the differentiation of two terminal hydroxyl groups was successful (Scheme VI-34). Under basic conditions, the reaction was not



Scheme VI-34: PMB protection to accomplish the differentiation of two terminal hydroxyl groups

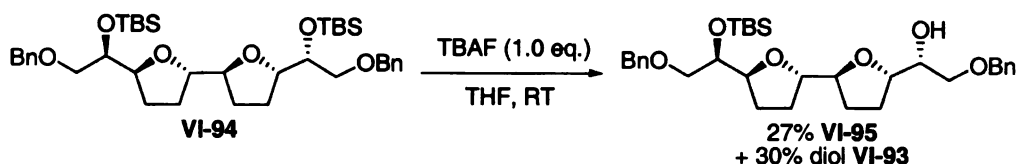
clean and only 40% of the desired PMB ether **VI-91** was isolated. Under acidic conditions, PMB protection using trichloroacetimidate gave PMB ether **VI-91** as the pure product. However, the reaction was very slow and even after 24 h, there were still 52% starting material left. The optimization of this reaction is still ongoing. With diene **VI-91** in hand, double SAD reaction and the subsequent double cyclization strategy formed the bis-adjacent THF core **VI-92**, which contains two different protection groups on two terminal hydroxyl groups.

Next, the desymmetrization of C2-symmetric bis-THF core **VI-89** was carried out. Since there is no chance to selectively deprotect only one of the acyl groups, we converted acyl groups to TBS groups (Scheme VI-35). Basic hydrolysis to remove the acyl groups in **VI-89** afforded diol **VI-93** in good yield, which was reprotected by TBS groups to give **VI-94** in 86% yield.



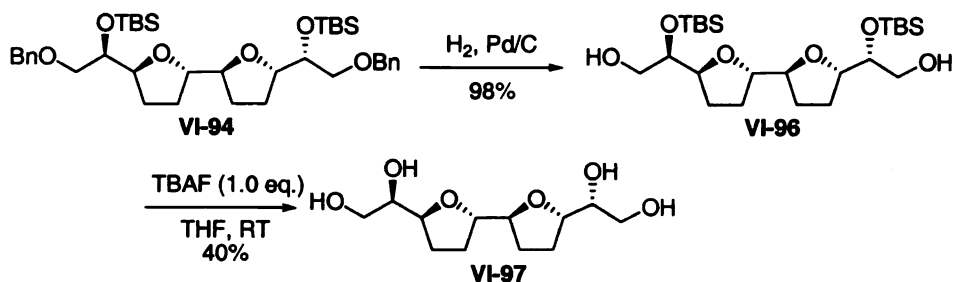
Scheme VI-35: Protecting groups interconversion

The following attempt to remove only one TBS group using 1.0 equiv TBAF showed that there was some mono-TBS product **VI-95** formed during the reaction (Scheme VI-36). However, the diol **VI-93** was separated along with this mono-TBS



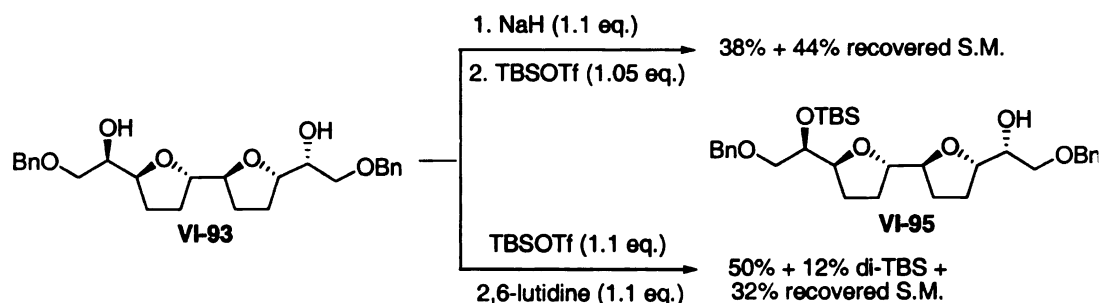
Scheme VI-36: Selective deprotection of bis-TBS ether VI-94

ether almost as an 1:1 ratio. The other substrate diol **VI-96**, which was obtained from the debenzylolation of **VI-94** in 98% yield, was also subjected into the identical conditions (Scheme VI-37). The only product isolated from this reaction was the tetra-ol **VI-97**, there was no mono-desilylation product.



Scheme VI-37: Mono-deprotection of one TBS group in VI-96

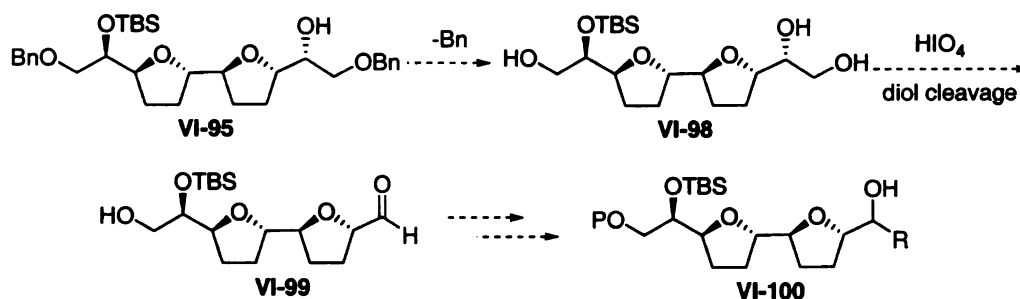
Since the mono-desilylation reaction only gave low yield of the desired product (Scheme VI-35), mono-TBS protection of diol **VI-93** was also carried out under two different conditions (Scheme VI-38). The reaction utilized 1.1 equiv sodium hydride



Scheme VI-38: Mono-TBS protection of diol **VI-93**

and 1.05 equiv TBSOTf at room temperature, was slow and gave mono-TBS ether **VI-95** as the pure product along with about the same amount of recovered starting material. If the base was changed to 2,6-lutidine, the protection reaction at 0 °C gave 50% desired mono-TBS ether along with 12% di-TBS product and recovered diol **VI-93** in 32% yield. It is clear that the mono-TBS protection is more efficient than the deprotection in the desymmetrization sequence. Even though the yield was not very high, the majority of the byproduct was recovered starting material, which could be resubmitted to the reaction.

It is very important to accomplish the desymmetrization of the bis-THF core. Scheme VI-39 shows one proposal of the utilization of this non-C2-symmetric intermediate **VI-95**. 1,2-Diol **VI-98**, obtained from debenzylation of **VI-95**, could be subjected to the oxidative cleavage reaction to provide aldehyde **VI-99**.



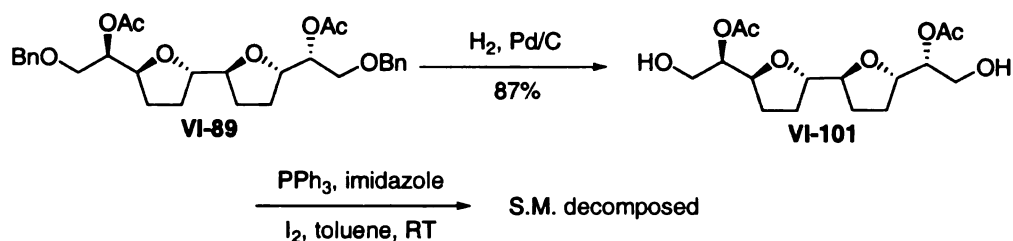
Scheme VI-39: One proposal for the utilization of desymmetrized bis-THF core **VI-95**

Nucleophilic addition on this aldehyde could install one side of the functional group to the bis-adjacent THF core. Based on this proposal, it is easy to use this bis-THF core to synthesize a series of acetogenins as well as their analogs.

VI.5. Etherification of bis-Adjacent THF Core: Synthesis of Ether Linked Analog of Acetogenins

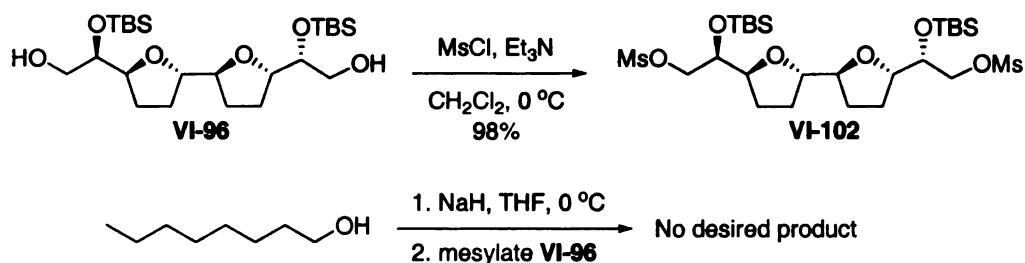
With the double cyclization of polyhydroxylated systems methodology in hand, it is quick and efficient to synthesize the bis-adjacent THF core with different stereochemistries. This sequence can also be easily scaled-up, providing a possibility for the library synthesis of ether linked analogs of acetogenins. However, before we run the library 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.

The first idea for the etherification reaction was to convert the terminal hydroxyl group in the bis-adjacent THF core to a good leaving group such as 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 groups to iodides in substrate **VI-101**, which was formed via hydrogenolysis of the benzyl groups in intermediate **VI-89**, was not successful and the messy crude NMR showed that the starting material decomposed under these conditions (Scheme VI-40). Since acyl groups are not stable under basic conditions, the protecting groups were changed and the alcohols were converted to mesylates (Scheme VI-41). The mesylation of diol **VI-96** using triethylamine and mesyl chloride in



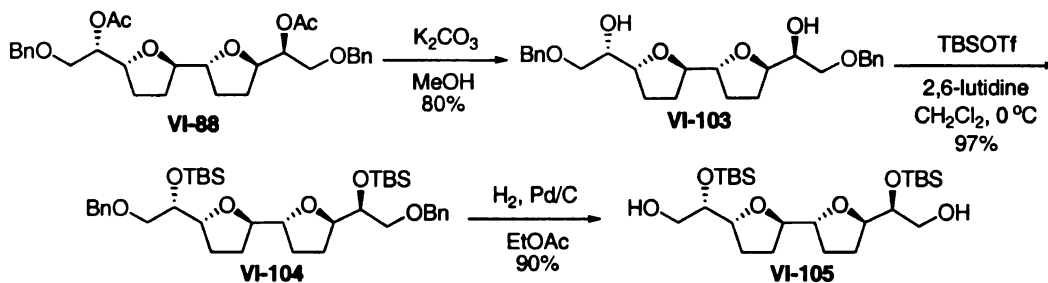
Scheme VI-40: Conversion of primary alcohols to iodides

dichloromethane gave excellent yield of mesylate **VI-102**. However, the subsequent $\text{S}_{\text{N}}2$ displacement with octyl alkoxide did not afford any desired product. There was no reaction at ambient temperature and 78% of mesylate **VI-102** was recovered. Increasing the temperature to reflux decomposed the starting material.



Scheme VI-41: Conversion of primary alcohols to mesylates

An alternate way for the etherification was to use the bis-adjacent THF core as the nucleophile in the etherification reaction. For purposes of a trial reaction, the simple octyl iodide and mesylate were used in the etherification. In addition, different bis-adjacent THF cores were synthesized as the nucleophile. Scheme VI-42 shows the preparation of one intermediate **VI-105**, by following the same sequence as for the



Scheme VI-42: Synthesis of diol **VI-105**

synthesis of **VI-96** (Scheme VI-34 and VI-36).

Some of the experiments and the results for the etherification reactions are summarized in Table VI-4. With sodium hydride as the base, for the substrates **VI-105** and **VI-96** containing TBS protecting groups, no desired products were obtained (entries 1 and 3). Instead, silyl migration of 1,2-diols under basic conditions occurred, which gave the secondary free alcohols as the product (Figure VI-6). However, after changing TBS groups to acyl groups, the same conditions

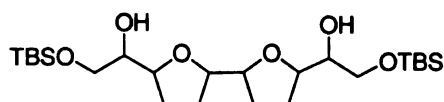
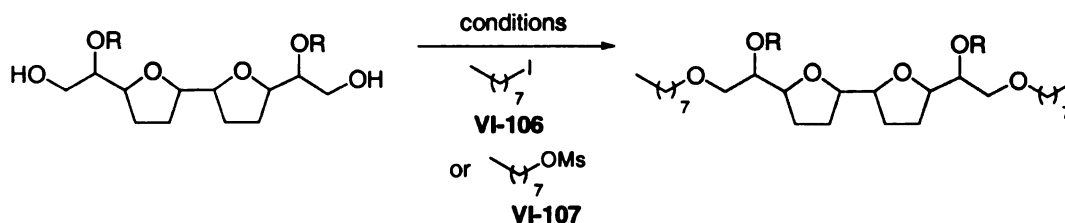


Figure VI-6: Silyl migration product under basic conditions

decomposed the starting material (entry 4). If all the protecting groups were removed, there was no reaction even after 24 h under the same conditions (entry 5). Potassium carbonate in refluxing acetone could not promote the reaction, after

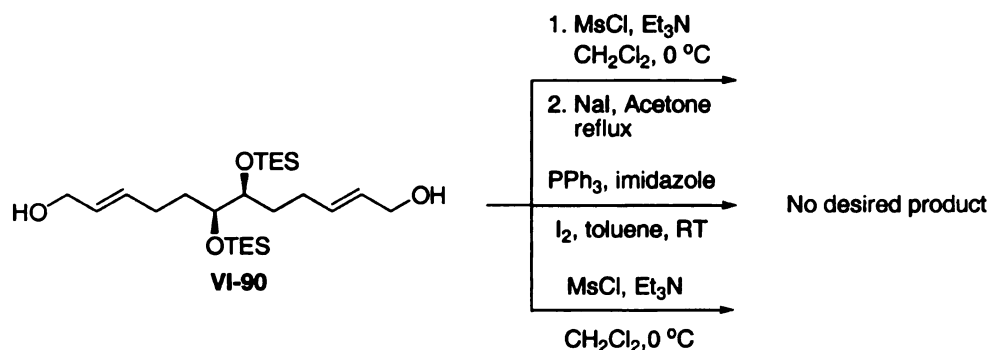
Table VI-4: Experiments for etherification reactions



Entry	Compound	R	Reagents	Temperature	Solvent	Results
1	VI-105	TBS	VI-103 NaH	0 °C to RT	THF	no product 49% S.M.
2	VI-105	TBS	VI-103 K ₂ CO ₃	reflux	acetone	recovered + 35% mono-TBS
3	VI-96	TBS	VI-104 NaH	0 °C to RT	THF	no product S.M.
4	VI-101	Ac	VI-104 NaH	0 °C to RT	THF	decomposed
5	VI-97	H	VI-104 NaH	0 °C to RT	THF	no reaction

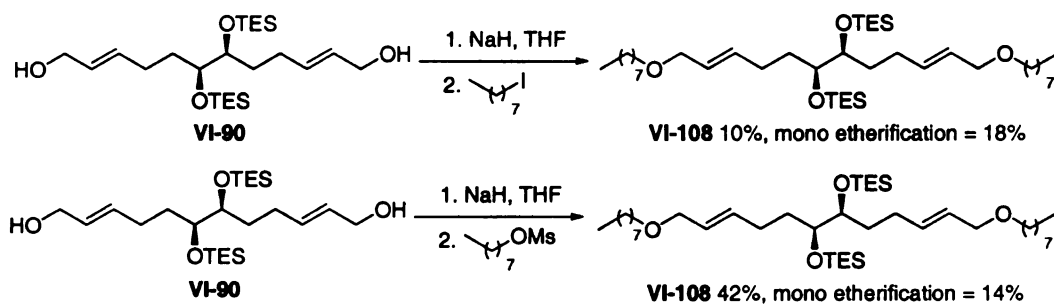
overnight stirring only mono-TBS product along with some starting material were isolated (entry 2). It seems that the major problem in the failed etherification reactions is due to the protecting groups on the secondary alcohols.

Besides all the above attempts, we also considered to first perform the etherification on the diene precursor, and then the subsequent cyclization could give the desired compound directly. It was found that the conversion of diene intermediate **VI-90** to the iodide or mesylate under a variety of conditions did not give the desired product and the starting material decomposed after the reaction (Scheme VI-43).



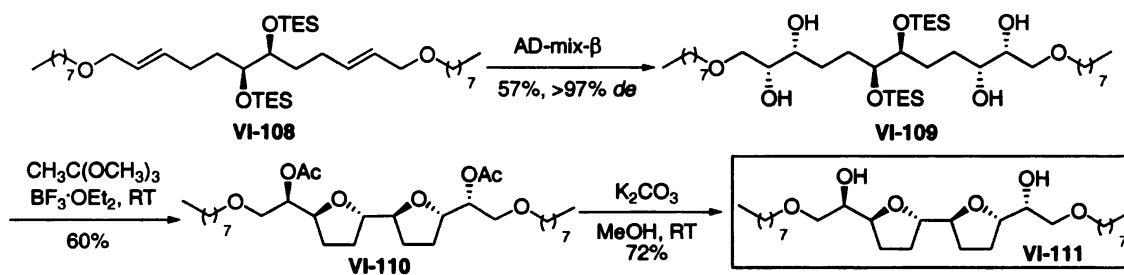
Scheme VI-43: Attempts to synthesize iodide or mesylate from diene intermediate **VI-90**

An alternate way was to use diol **VI-90** as the nucleophile, which could react with octyl iodide **VI-106** or octyl mesylate **VI-107** (Scheme VI-44). The results showed



Scheme VI-44: Etherification of diene intermediate **VI-90**

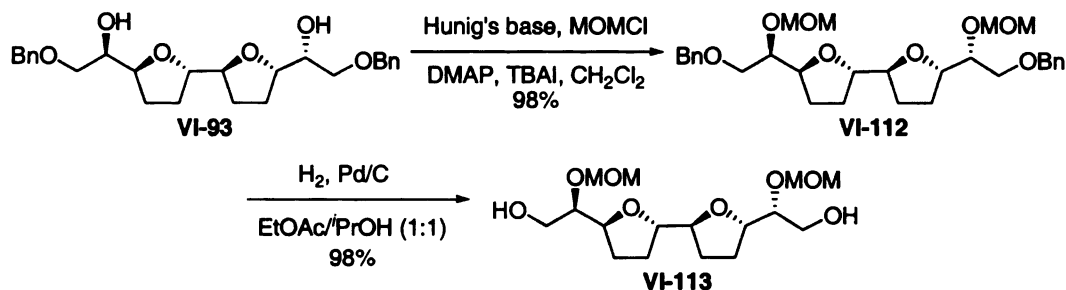
that it was more efficient to use the mesylate than the iodide. Under refluxing conditions, the reaction of alkoxide of diol **VI-90** with octyl iodide **VI-106** gave 10% of the diether **VI-108** along with 18% of the mono-ether. There were more than three other byproducts formed which could not be isolated in pure form. The same conditions with mesylate **VI-107** provided diether **VI-108** in 42% yield and mono-ether in 14% yield. The subsequent double SAD reaction of newly formed diene intermediate **VI-108** afforded the desired tetra-ol **VI-109** in moderate yield and excellent diastereomeric ratio (Scheme VI-45). Double cyclization of this polyhydroxylated system gave bis-adjacent THF moiety **VI-110**, which was subjected to the deacylation reaction to provide the desired ether linked analog **VI-111** of Δ lac-acetogenins.^{33, 34}



Scheme VI-45: Synthesis of ether linked analog VI-111

The success of the etherification of diene precursor **VI-90** led to new attempts for the etherification of the bis-adjacent THF core. Based on the previous experiments, the major problem could be due to the protective groups on the secondary alcohols. It is believed that the steric bulk of the protecting group on the secondary alcohol 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 **VI-113** was achieved via MOM protection of intermediate **VI-93**, followed by debenzylation via hydrogenolysis in excellent yield over two steps (Scheme VI-46).



Scheme VI-46: Synthesis of MOM-protected bis-adjacent THF core **VI-113**

Treatment of intermediate **VI-113** under etherification conditions could give the desired product and the modification of the conditions was also carried out (Table VI-5). Increasing the amount of sodium hydride and mesylate could improve the yield of the etherification (entry 2). DMF was a better solvent under the same conditions than THF, which provided 49% yield of the desired product (entry 3). All these experiments proved that less hindered protecting groups helped to improve the etherification reaction. Therefore, the future work for the optimization of this reaction can be based on changing to other less hindered protecting groups, as well as

Table VI-5: Etherification reactions of intermediate **VI-113**

Entry	NaH	Mesylate or Bromide	Solvent	Temperature	Yield (%)
1	3.0 equiv	3.0 equiv	THF	0 °C to reflux	32
2	8.0 equiv	4.0 equiv	THF	0 °C to reflux	47
3	8.0 equiv	4.0 equiv	DMF	0 °C to 50 °C	49

making other bis-adjacent THF cores. One example is shown in Figure VI-7, which

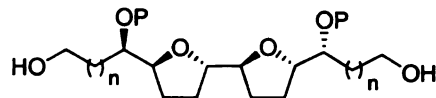


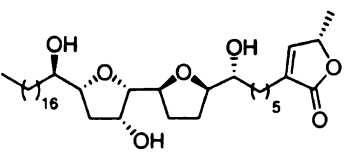
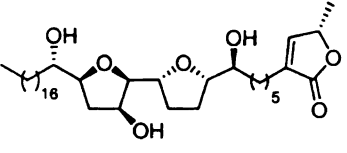
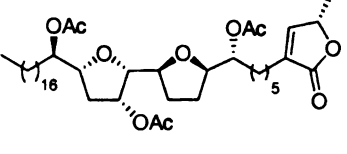
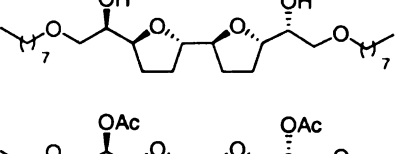
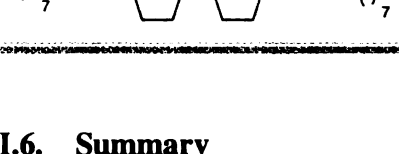
Figure VI-7: New synthetic target of bis-adjacent THF core

contains more methylenes between the secondary hydroxyl groups and the terminal alcohols. In such a case the etherification of the terminal alcohol would be less affected by the size of the protected secondary hydroxyl groups.

The synthesized Δ lac-acetogenin ether-linkage analogs **VI-111** and **VI-110** were subjected to the complex I inhibition study (Table VI-6). It was interesting to find that this newly synthesized analog had good IC_{50} value comparable as the pseudo-enantiomer of mucoxin. Moreover, acetylation of mucoxin made the compound lose all the inhibitory activity against complex I. However, the acetylated ether linked analog **VI-110** retains comparable inhibitory activity as the original compound **VI-111**.

All work related to the measurement of bioactivities for the synthesized compounds was performed by Chrysoula Vasileiou, a postdoctoral fellow in the Borhan laboratory.

Table VI-6: Inhibition of mitochondrial complex I by Δ lac-acetogenin analogs

Compound	Complex I Inhibition IC ₅₀ (nM)
	synthesized mucoxin 37 ± 2
	synthesized pseudo-enantiomer of mucoxin 165 ± 140
	acetylated mucoxin >5000
	Δ lac-acetogenin analog VI-111 193 ± 26
	acetylated analog VI-110 167 ± 43

VI.6. Summary

In conclusion, the new regio- and stereoselective double cyclization of the polyhydroxylated systems is an efficient strategy to form the bis-adjacent THF moiety. Further desymmetrization and etherification of the bis-adjacent THF core can be used to make ether linked analogs of acetogenins. 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.

VI.7. Experimental Section

General Information:

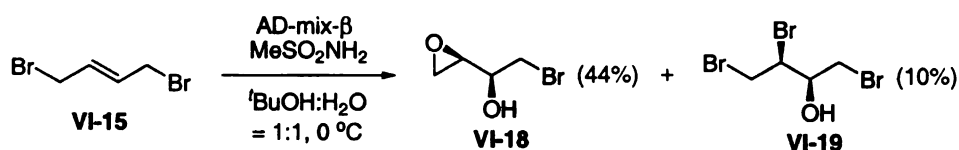
Commercially available starting materials were obtained from Aldrich or Fluka and were used without further purification. Unless otherwise mentioned, solvents were purified as follows: tetrahydrofuran (THF) and diethyl ether (Et₂O) were freshly distilled from sodium/benzophenone; methylene chloride (CH₂Cl₂) and toluene (PhCH₃) was dried over calcium hydride (CaH₂) and freshly distilled prior to use; DMF, DMSO, diisopropylamine, and triethylamine were distilled from CaH₂ and stored over 4 Å molecular sieves. Some compounds were prepared as previous reported. 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 or 500 MHz on a Varian Gemini-300 or a Varian VXR-500 instrument respectively. Chemical shifts are reported relative to residual solvent (δ 7.24 ppm for CDCl₃). ¹³C NMR spectra were measured at 75 MHz on a Varian Gemini-300 or at 125 MHz on a Varian VXR-500 instrument. Chemical shifts are reported relative to the central line of CDCl₃ (δ 77.0 ppm). Infrared spectra were recorded using a Nicolet IR/42 spectrometer FT-IR (thin film, NaCl cells). 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 1mL capacity quartz cell with a 10 cm path length.

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

silica gel 60 F₂₅₄ 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 containing Altech SE-54, 30 m × 320 µm × 0.25 µm column.

Data for Newly Synthesized Compounds:



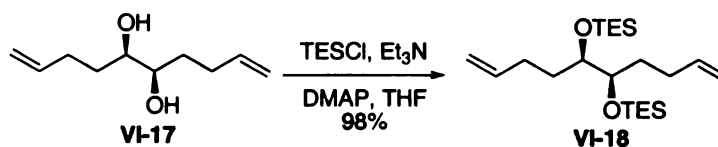
AD-mix-β (7 g) was dissolved in 1 : 1 ^tBuOH : H₂O (50 mL). To this clear, orange solution, methane sulfonamide (0.48 g, 5 mmol) was added and stirred until all the solids dissolved. The solution was then cooled to 0 °C upon which 1,4-dibromo-2-butene **VI-15** (1.07 g, 5 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (8.8 g) was added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (50 mL) and H₂O (30 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4×30 mL), combined organic layers were dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (20% EtOAc in hexanes). Two different products **V-18** (369 mg, 44%) and **V-19** (113 mg, 10%) were obtained.

Data for epoxide **VI-18**: ¹H NMR (300 MHz, CDCl₃) δ 4.00-3.90 (1H, m), 3.58-3.42 (4H, m), 2.85-2.76 (2H, m); ¹³C NMR (125 MHz, CDCl₃) δ 71.0, 70.9, 53.4, 44.8,

33.6, 33.5; LRMS (ES) calcd for $C_4H_8BrO_2$, 166.9708 m/z ($M+H$)⁺; observed, 166.1.

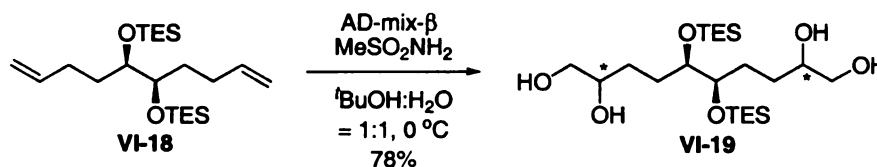
Data for tri-bromide **VI-19**: 1H NMR (500 MHz, $CDCl_3$) δ 4.57-4.56 (2H, m), 4.14-4.11 (2H, m), 3.94-3.91 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.6, 37.9;

LRMS (ES) calcd for $C_4H_8Br_3$, 292.8176 m/z ($M-H_2O+H$)⁺; observed, 292.9.



To a solution of the diol **VI-17** (0.17 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 $\times$ 10 mL) to afford crude oil which was purified by column chromatography (1% EtOAc in hexanes) providing the fully protected diol **VI-18** (0.39 g, 98%) as a colorless oil.

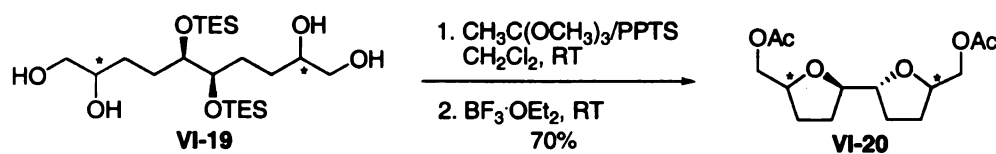
Data for diol **VI-18**: $[\alpha]_D^{20}$ +33.8 (c 3.7, CH_2Cl_2) 1H NMR (500 MHz, $CDCl_3$) δ 5.88-5.80 (2H, m), 5.06-5.04 (2H, dq, J = 17.1, 1.6 Hz), 4.98-4.94 (2H, m), 3.62-3.59 (2H, m), 2.28-2.23 (2H, m), 2.02-1.97 (2H, m), 1.78-1.72 (2H, m), 1.44-1.38 (2H, m), 1.00-0.96 (18H, m), 0.65-0.57 (12H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 114.2, 75.0, 30.9, 29.7, 6.9, 5.2.



AD-mix- β (0.84 g) was dissolved in 1 : 1 $tBuOH$: H_2O (8 mL). To this clear, orange solution, methane sulfonamide (57 mg, 0.60 mmol) and potassium osmate (3.0

μg) were added and stirred until all the solids dissolved. The solution was then cooled to 0 °C upon which terminal diene **VI-18** (116 mg, 0.30 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (1.1 g) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (15 mL) and H₂O (8 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4×15 mL), combined organic layers were dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (50% EtOAc in hexanes to EtOAc). The mixture of four diastereomeric tetraols **VI-19** was isolated in 78% (109 mg) yield as a colorless oil.

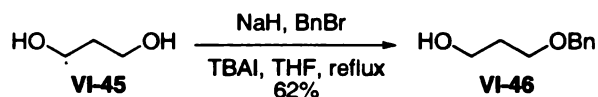
Data for the tetraol diastereomeric mixture **VI-19**: ¹H NMR (500 MHz, CDCl₃) δ 3.68-3.60 (6H, m), 3.49-3.41 (2H, m), 3.42 (2H, br), 2.94 (2H, br), 1.83-1.31 (8H, m), 1.05-0.90 (18H, m), 0.68-0.54 (12H, m); ¹³C NMR (125 MHz, CDCl₃) δ 75.6, 75.5, 75.4, 72.6, 72.55, 72.49, 66.83, 66.79, 66.6, 30.0, 26.4, 6.9, 5.1.



PPTS (5 mg, 20 μmol) was added to a solution of tetraol mixture **VI-19** (46.7 mg, 0.1 mmol) and trimethylortho acetate (31 μL, 0.24 mmol) in CH₂Cl₂ (3 mL) at RT. After complete consumption of the tetraol (ca. 20 min, as judged by TLC), BF₃•OEt₂ (8 μL, 0.06 mmol) was rapidly added to the reaction. After 30 min, the reaction was slowly poured into saturated NaHCO₃ solution (5 mL) and the aqueous layer was extracted with CH₂Cl₂ (3×10 mL). Combined organic layers were dried (Na₂SO₄),

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 **VI-20** (the mixture of diastereomers) (20 mg, 70%) as a clear oil.

Data for bis-THF acetate mixture **VI-20**: ^1H NMR (300 MHz, CDCl_3) δ 4.27-4.12 (4H, m), 4.08-3.91 (3H, m), 3.89-3.84 (1H, m), 2.09 (6H, s), 2.09-1.83 (4H, m), 1.79-1.63 (4H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 82.5, 82.2, 82.0, 81.6, 77.4, 77.2, 66.6, 66.5, 28.4, 28.3, 28.0, 27.5, 27.4, 20.9; LRMS (70 ev, EI) m/z 287 $[\text{M}+\text{H}]^+$, 245 $[\text{M}-\text{CH}_3\text{CO}]^+$.

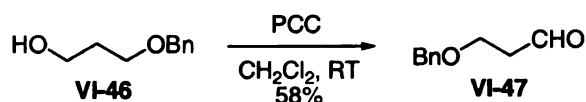


To a slurry of NaH (0.44 g, 11 mmol) in THF (20 mL), 1,3-diol **VI-45** (0.72 mL, 10 mmol) was added at 0 °C and stirred for 1 h while warming to RT. Benzyl bromide (1.24 mL, 10.5 mmol) was added dropwise followed by TBAI (180 mg, 0.05 mmol). The reaction was heated to 60 °C for 15 h. After cooling to room temperature, H_2O (20 mL) was carefully added. The layers were separated, the aqueous layer was extracted with Et_2O (3×25 mL) and the combined organic layers were dried over MgSO_4 and the solvent was removed under reduced pressure. Monobenzyl ether **VI-46** was obtained as pale yellow oil (1.024 g, 62%) after chromatographic purification (20% EtOAc in hexanes) and dibenzyl ether **VI-46'** was obtained as yellow oil (0.521 g, 23%).

Data for monobenzyl ether **VI-46**: ^1H NMR (300 MHz, CDCl_3) δ 7.33-7.28 (5H, m), 4.49 (2H, s), 3.74 (2H, t, $J = 5.8$ Hz), 3.63 (2H, t, $J = 5.8$ Hz), 2.47 (1H, br),

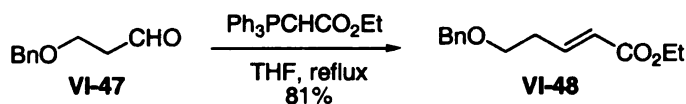
1.87-1.79 (2H, quin, $J = 5.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.0, 128.4, 127.6, 127.5, 73.2, 69.1, 61.5, 32.1.

Data for dibenzyl ether **VI-46'**: ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.28 (10H, m), 4.51 (4H, s), 3.61 (4H, t, $J = 6.3$ Hz), 1.96 (2H, quin, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.5, 128.3, 127.5, 127.4, 72.9, 67.2, 30.1.



To a slurry of PCC (1.99 g, 9.23 mmol) in CH_2Cl_2 (20 mL), a solution of alcohol **VI-46** (1.022 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 celite pad. The filtrate was concentrated and the crude brown oily material was purified by flash column chromatography (10% EtOAc in hexanes) to afford aldehyde **VI-47** as a pale yellow oil (0.583 g, 58%).

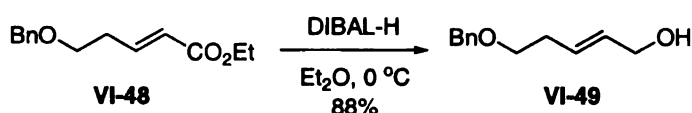
Data for aldehyde **VI-47**: ^1H NMR (300 MHz, CDCl_3) δ 9.78 (1H, t, $J = 1.9$ Hz), 7.38-7.27 (5H, m), 4.52 (2H, s), 3.80 (2H, t, $J = 6.0$ Hz), 2.70-2.03 (2H, td, $J = 6.0$, 1.9 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 201.0, 137.8, 128.4, 127.8, 127.7, 73.2, 63.8, 43.8.



A solution of aldehyde **VI-47** (0.58 g, 3.5 mmol) and (carbethoxymethylene)triphenylphosphorane (2.46 g, 7.07 mol) in THF (18 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 **VI-48** as a colorless oil (0.672 g, 81%).

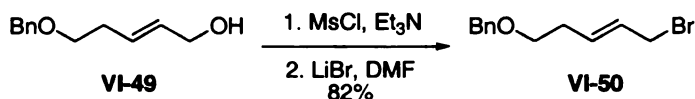
Data for α , β -unsaturated *trans*-ester **VI-48**: ^1H NMR (300 MHz, CDCl_3) δ 7.35-7.22 (5H, m), 7.00-6.90 (1H, m), 5.88-5.83 (1H, dd, $J = 15.6, 1.3$ Hz), 4.46 (2H, s), 4.17-4.10 (2H, q, $J = 7.1$ Hz), 3.54-3.50 (2H, m), 2.48-2.41 (2H, q, $J = 6.6$ Hz), 1.23 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 166.0, 145.3, 137.9, 128.1, 127.3, 127.2, 122.6, 72.7, 68.0, 58.8, 32.3, 14.0.



To a cold (0 °C) solution of ester **VI-48** (0.67 g, 2.86 mmol) in diethyl ether (25 mL), DIBAL-H (7.16 mmol, 2.86 mL of 2.5 M solution in toluene) was added under N_2 . After stirring for 30 min. at the same temperature, saturated potassium-sodium tartrate solution (29 mL) was added and the mixture was brought to RT. Et_2O (30 mL), H_2O (6 mL) and glycerol (1.4 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 (3×20 mL). The combined organic layers were dried (MgSO_4), concentrated and the crude product after chromatographic purification (30% EtOAc in hexanes) afforded allylic alcohol **VI-49** as a colorless oil (0.483 g, 88%).

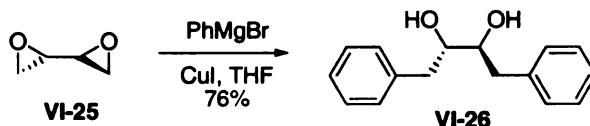
Data for allylic alcohol **VI-49**: ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.23 (5H, m), 5.66-5.63 (2H, m), 4.47 (2H, s), 4.01-3.98 (2H, m), 3.48 (2H, t, $J = 6.6$ Hz), 2.70 (1H, br), 2.39-2.31 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 138.0, 131.0, 128.5, 128.2,

127.5, 127.4, 72.6, 69.4, 63.0, 32.4.



A solution of allylic alcohol **VI-49** (0.47 g, 2.45 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this, mesyl chloride (0.57 mL, 7.34 mmol) and triethyl amine (1.13 mL) were added and stirring was continued at the same temperature for 30 min. The reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL) and combined organic layers were concentrated. The residue was taken up in DMF (10 mL) and cooled to 0 °C. Lithium bromide (0.21 mL, 7.34 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 (3×15 mL). Chromatographic purification (5% EtOAc in hexanes) of the crude product obtained by concentration of the organic portion afforded iodide **VI-50** (0.51 g, 82%).

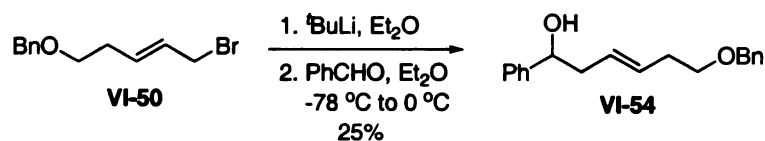
Data for **VI-50**: ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.23 (5H, m), 5.82-5.65 (2H, m), 4.52 (2H, s), 4.05-3.95 (2H, m), 3.55-3.50 (2H, t, $J = 6.6$ Hz), 2.42-2.36 (2H, q, $J = 6.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.2, 132.6, 132.1, 128.1, 127.6, 127.4, 72.7, 69.0, 45.0, 32.4.



A flame-dried round-bottomed flask with copper iodide (17 mg, 0.09 mmol) was pumped under reduced pressure and N_2 atmosphere was introduced. THF (1.5 mL) was added to the flask, stirring was initiated, and the slurry was cooled to -30 °C with

a dry ice-acetone bath. Phenylmagnesium bromide (0.9 mL, 0.9 mmol, 1.0 M solution in THF) was added dropwise, and the stirred slurry was aged for 10 min. (*S,S*)-1,2,3,4-Diepoxybutane (26 mg, 0.3 mmol) in THF (0.5 mL) was added dropwise. After an additional 10 min at -30 °C, the reaction mixture was warmed to 0 °C with an ice bath. After an additional 2.5 h at 0 °C, the reaction was quenched by the slow addition of sat. ammonium chloride solution (10 mL) and warmed to room temperature. The quenched reaction was stirred for 15 min yielding a deep blue color. The reaction mixture was separated and the aqueous layer was extracted with CH₂Cl₂ (4×8 mL), the combined organic layers were dried over Na₂SO₄ and concentrated. The crude product was purified via column chromatography (50% EtOAc in hexanes) to afford the desired diol **VI-26** as a white solid (55 mg, 76%).

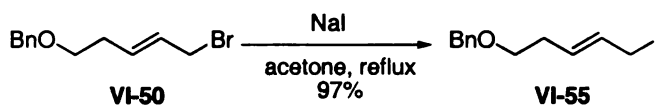
Data for diol **VI-26**: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.18 (10H, m), 3.75-3.70 (2H, m), 2.89-2.78 (4H, m), 2.10-2.00 (2H, br); ¹³C NMR (75 MHz, CDCl₃) δ 138.0, 129.5, 128.7, 126.6, 74.0, 40.3.



A flame-dried round-bottomed flask with 3 mL Et₂O was cooled to -100 °C and ^tBuLi (0.485 mL, 1.7 M in pentane) was added dropwise. A solution of allylic bromide (190.5 mg, 0.75 mmol) in Et₂O (0.5 mL) was added slowly (dropwise) to the flask and the mixture was stirred at -100 °C to -90 °C for 10 min. Benzaldehyde (51 μL, 0.5 mmol) in Et₂O (1.5 mL) was cooled to -78 °C and the newly formed organolithium reagent was cannulated dropwise to this pre-cooled solution. The

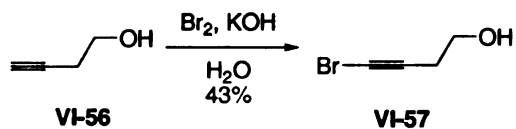
reaction was stirred at -78 °C for 4 h. TLC showed that there was still some starting material left. The reaction was warmed to 0 °C for another 4 h and quenched with sat. NH₄Cl. The quenched solution was extracted with Et₂O (3×5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified via chromatography (10% EtOAc in hexanes) to yield alcohol **VI-54** (35.4 g, 25%) along with starting material PhCHO (25.4 mg, 13%).

Data for alcohol **VI-54**: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.24 (10H, m), 5.60-5.45 (2H, m), 4.73-4.66 (1H, m), 5.51 (2H, s), 3.44 (2H, t, *J* = 6.2 Hz), 2.62-2.26 (4H, m); ¹³C NMR (125 MHz, CDCl₃) δ 138.3, 138.1, 129.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 127.3, 127.2, 127.1, 126.8, 126.7, 126.0, 118.7, 76.4, 73.3, 72.9, 69.2, 68.1, 37.4, 28.0.



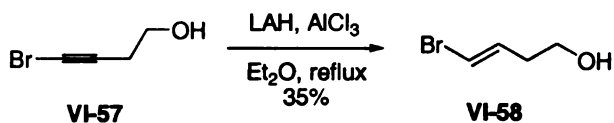
Sodium iodide (1.28 g, 8.6 mmol) was added in one portion to the solution of allylic bromide **VI-50** (1.45 g, 5.7 mmol) in acetone (12 mL). The reaction was refluxed overnight and cooled to room temperature. Newly formed inorganic salt was filtrated and washed with acetone (3×5 mL). The filtrate was concentrated under reduced pressure and purified via column chromatography to yield allylic iodide **VI-55** in 97% yield (1.68 g) as a brown oil.

Data for allylic iodide **VI-55**: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.23 (5H, m), 5.84-5.18 (2H, m), 4.49 (2H, s), 3.85 (2H, d, *J* = 7.0 Hz), 3.48 (2H, t, *J* = 6.7 Hz), 2.33 (2H, q, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 138.3, 131.2, 130.5, 129.6, 128.3, 127.6, 72.8, 69.1, 32.4.



Bromine (1.02 mL, 20 mmol) was added to a vigorously stirred solution of KOH (3 g) in water (8 mL) at -5 °C. The yellow solution was kept at 0 °C and added dropwise for 3 h to a solution of propargyl alcohol **VI-56** (1.6 mL, 21.2 mmol) in water (3 mL) at 0 °C. The reaction mixture was warmed to 10 °C and then extracted with ether (4×10 mL). The organic layer was washed with Na₂S₂O₃ and dried over K₂CO₃. The solvent was removed to provide the crude 1-bromopropyne-3-ol **VI-57** (1.296 g, 43%).

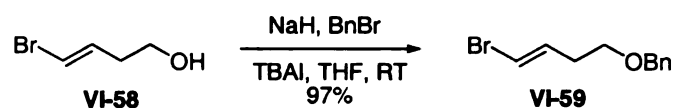
Data for 1-bromopropyne-3-ol **VI-57**: ¹H NMR (300 MHz, CDCl₃) δ 3.73-3.65 (2H, m), 2.46-2.38 (2H, m), 2.20 (1H, br); ¹³C NMR (75 MHz, CDCl₃) δ 70.1, 60.7, 23.9, 22.7.



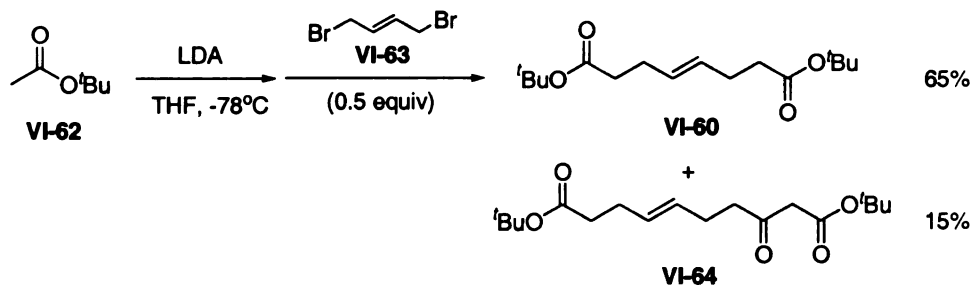
To a 50 mL flask charged with LiAlH₄ (0.61 g, 16.0 mmol) was carefully added anhydrous ether (5 mL) at 0 °C with stirring. A solution of AlCl₃ (1.07 g, 8.0 mmol) in anhydrous ether (5 mL) was added and the solution was stirred. The crude 1-bromopropyne-3-ol **VI-57** was added dropwise and the mixture was refluxed for 4 h. The reaction was quenched with H₂O carefully at 0 °C, followed by 5% NaOH (5 mL). The precipitated was filtered and washed with ether (3×10 mL). The filtrate was extracted with ether (3×10 mL). The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified via chromatography (20%

EtOAc in hexanes) to yield vinyl bromide **VI-58** (0.43 g, 35%).

Data for vinyl bromide **VI-58**: ^1H NMR (300 MHz, CDCl_3) δ 6.21-6.10 (2H, m), 3.65 (2H, t, $J = 6.2$ Hz), 2.31-2.25 (2H, q, $J = 6.2$ Hz), 1.85 (1H, br); ^{13}C NMR (75 MHz, CDCl_3) δ 134.3, 106.6, 61.0, 36.0.



To a slurry of NaH (0.14 g, 3.4 mmol) in THF (3 mL), alcohol **VI-58** (0.43 g, 2.8 mmol) was added at 0 °C and stirred for 30 min. Benzyl bromide (0.4 mL, 3.4 mmol) was added dropwise followed by TBAI (11.5 mg). The reaction was warmed up to room temperature for 4 h. H_2O (10 mL) was carefully added to quench the reaction. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Benzyl ether **VI-59** was obtained as pale yellow oil (0.667 g, 97%) after chromatographic purification (3% EtOAc in hexanes). Data for benzyl ether **VI-59**: ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.25 (5H, m), 6.28-6.14 (2H, m), 4.51 (2H, s), 3.50 (2H, t, $J = 6.6$ Hz), 2.37-2.31 (2H, q, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.1, 134.6, 128.8, 128.4, 127.6, 106.0, 73.0, 68.7, 33.3.

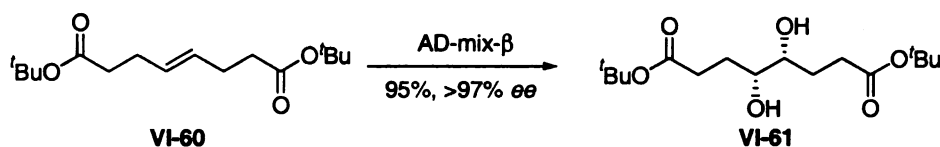


n-Butyllithium (83 mL of a 1.6 M solution in hexanes, 0.13 mol) was added

dropwise to a stirred solution of diisopropylamine (19 mL, 0.136 mol) in dry THF (300 mL) at 0 °C and stirred for 15 min. The reaction mixture was cooled to -78 °C and *tert*-butyl acetate (16.8 mL, 0.125 mol) was added dropwise. The reaction mixture was stirred at -78 °C for 30 minutes and (*E*)-1,4-dibromo-2-butene (10.7 g, 0.05 mol) in dry THF (50 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 13 h and allowed to warm to room temperature, was quenched with saturated aqueous ammonium chloride solution, extracted with ether (3×300 mL), dried over MgSO₄, and evaporated to leave a crude product, which was purified by flash column chromatography (5% EtOAc in hexanes) to give diester **V-60** (18.43 g, 65%) as a white solid along with β -ketoester **VI-64** as a pale yellow oil (2.4 g, 15%).

Data for major product diester **V-60**: ¹H NMR (300 MHz, CDCl₃) δ 5.43-5.41 (2H, m), 2.22 (8H, m), 1.39 (18H, s); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 129.3, 80.1, 35.3, 28.1, 28.0.

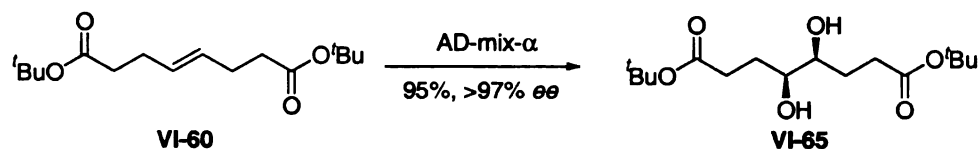
Data for byproduct β -ketoester **VI-64**: ¹H NMR (300 MHz, CDCl₃) δ 5.41-5.38 (2H, m), 3.29 (2H, s), 2.53 (2H, t, *J* = 7.4 Hz), 2.28-2.21 (6H, m), 1.42 (9H, s), 1.39 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ 202.5, 172.4, 166.3, 129.6, 129.1, 81.8, 80.5, 50.6, 42.4, 41.5, 35.2, 28.0, 27.9, 26.3, 26.0, 23.2, 14.0.



AD-mix- β (13.3 g) was dissolved in 1 : 1 *t*-BuOH : H₂O (90 mL). To this clear, orange solution, methane sulfonamide (0.89 g, 9.4 mmol) was added and stirred until all the solids dissolved. The solution was then cooled to 0 °C upon which olefin

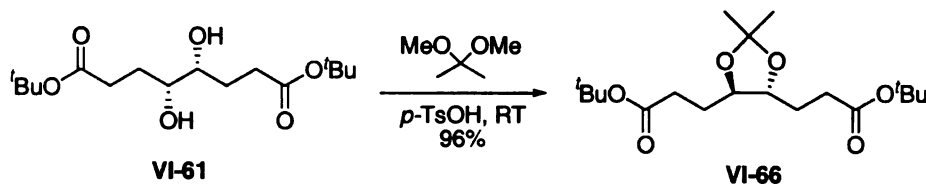
VI-60 (2.67 g, 9.4 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (14 g) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (100 mL) and H₂O (60 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4×60 mL), combined organic layers were dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (30% to 50% EtOAc in hexanes) to yield the diol **VI-61** in 95% yield (2.83 g) and > 97% *ee*.

Data for (*E*)-di-*tert*-butyl-4-octene-1,8-dioate **VI-61**:²⁷ ¹H NMR (300 MHz, CDCl₃) δ 3.44-3.36 (2H, m), 2.89 (2H, d, *J* = 4.9 Hz), 2.40 (4H, t, *J* = 7.0 Hz), 1.84-1.68 (4H, m), 1.42 (18H, s); ¹³C NMR (75 MHz, CDCl₃) δ 173.7, 80.6, 73.7, 31.9, 28.5, 28.0.



Procedure to make diol **VI-65** was the same as the preparation of diol **VI-61** except for using AD-mix-α.

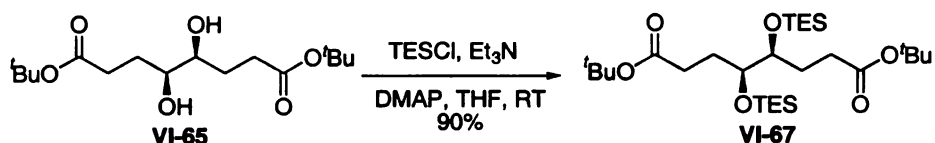
Data for diol **VI-65**: [α]_D²⁰ -6.8 (c 1.15, CH₂Cl₂), ¹H NMR (300 MHz, CDCl₃) δ 3.43-3.36 (2H, m), 3.02-2.94 (2H, br), 2.39 (4H, t, *J* = 7.1 Hz), 1.84-1.68 (4H, m), 1.41 (18H, s); ¹³C NMR (75 MHz, CDCl₃) δ 173.8, 80.7, 73.8, 31.9, 28.5, 28.0.



p-Toluenesulfonic acid (*p*-TsOH, 0.19 g, 0.89 mmol) was added as one portion to the solution of diol **VI-61** (2.83 g, 8.9 mmol) and 2,2-dimethoxypropane (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 (4×60 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification via column chromatography yielded the protected diol **VI-66** in 96% yield (3.05 g).

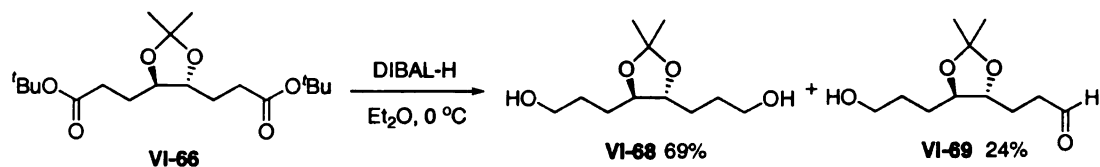
Data for diol **VI-66**: $[\alpha]_D^{20} +22.6$ (c 2.49, CH₂Cl₂), ¹H NMR (300 MHz, CDCl₃) δ 3.61-3.57 (2H, m), 2.44-2.2.28 (4H, m), 1.89-1.83 (2H, m), 1.76-1.69 (2H, m), 1.42 (18H, s), 1.33 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 108.3, 80.2, 79.7, 31.9, 28.1, 27.8, 27.2.



To a solution of the diol **VI-65** (1.38 g, 4.34 mmol) in THF (45 mL) triethyl amine (15 mL) was added followed by triethylsilyl chloride (2.21 mL, 13.0 mmol) and DMAP (0.21 g, 1.74 mmol) at ambient temperature. The reaction was stirred under N₂ for 3 h after which time it was quenched by adding saturated NaHCO₃ solution (45 mL). The aqueous layer was extracted with 1 : 5 EtOAc : hexanes (3×100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to afford crude oil which was purified by column chromatography (2% EtOAc in hexanes) providing the fully protected diol **VI-67** (2.12 g, 90%).

Data for di-TES ether **VI-67**: ¹H NMR (300 MHz, CDCl₃) δ 3.58-3.53 (2H, m), 2.39-2.28 (2H, m), 2.19-2.08 (2H, m), 1.96-1.87 (2H, m), 1.59-1.54 (2H, m), 1.41

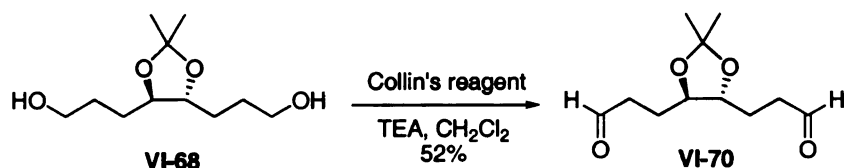
(18H, s), 0.91 (18H, t, $J = 7.8$ Hz), 0.57 (12H, q, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 173.1, 79.9, 74.5, 32.6, 28.1, 26.1, 6.9, 5.1.



To a 0 °C solution of diester **VI-66** (1.14 g, 3.18 mmol) in diethyl ether (35 mL), DIBAL-H (15.9 mmol, 6.4 mL of 2.5 M solution in toluene) was added under N_2 . After stirring for 30 min. at the same temperature, saturated potassium-sodium tartrate solution (80 mL) was added and the mixture was brought to RT. Et_2O (80 mL), H_2O (32 mL) and glycerol (8 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 (2×60 mL). The combined organic layers were dried over MgSO_4 , concentrated under reduced pressure, and the crude product after chromatographic purification (10% to 60% EtOAc in hexanes) afforded diol **VI-68** as a colorless oil (0.50 g, 69%) and aldehyde **VI-69** in 24% (0.16 g).

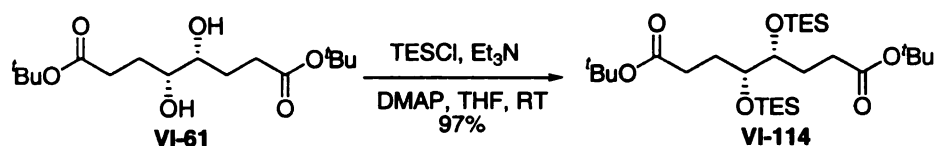
Data for diol **VI-68**: ^1H NMR (300 MHz, CDCl_3) δ 3.57-3.50 (6H, m), 3.34-3.24 (2H, br), 1.66-1.57 (6H, m), 1.52-1.44 (2H, m), 1.30 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 108.0, 80.6, 62.1, 29.1, 29.0, 27.1.

Data for aldehyde **VI-69**: ^1H NMR (300 MHz, CDCl_3) δ 9.73 (1H, s), 3.60-3.56 (4H, m), 2.64-2.50 (2H, m), 1.97-1.47 (6H, m), 1.30 (3H, s), 1.18 (3H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 201.7, 108.3, 80.5, 79.7, 62.3, 40.2, 29.6, 29.2, 27.1, 24.6.

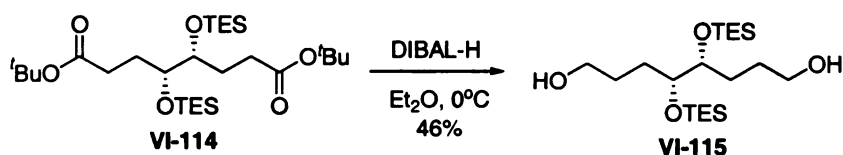


Diol **VI-68** (0.14 g, 0.65 mmol) was dissolved in dry dichloromethane (4.5 mL) and cooled to 0 °C. Triethylamine (0.41 mL, 2.59 mmol) was added, followed by a solution of Collin's reagent (0.35 g, 1.94 mmol) dissolved in dry DMSO (2.4 mL). The reaction was stirred for 1 h and quenched with diethyl ether (9 mL) and hexanes (18 mL). The combined organic solvents were washed with sat. sodium bicarbonate, then 1 M sodium phosphate, monobasic. The water layers were extracted with 2:1 hexanes: Et₂O and the combined organics were washed with brine, dried over Na₂SO₄ and the solvents were removed by rotary evaporation. The residue was purified by column chromatography (50% EtOAc in hexanes) to give the desired di-aldehyde **VI-70** in 52% yield (72 mg).

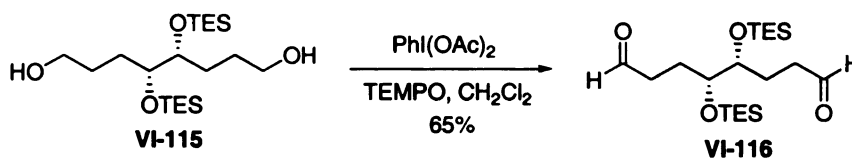
Data for di-aldehyde **VI-70**: ¹H NMR (300 MHz, CDCl₃) δ 9.75 (1H, t, *J* = 1.2 Hz), 3.62-3.54 (2H, m), 2.66-2.48 (4H, m), 1.98-1.87 (2H, m), 1.77-1.65 (2H, m), 1.29 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 201.6, 108.6, 79.5, 40.2, 27.2, 24.8.



Data for bis-TES ether **VI-114**: [α]_D²⁰ +34.99 (c 3.435, CH₂Cl₂), ¹H NMR (500 MHz, CDCl₃) δ 3.57-3.54 (2H, m), 2.38-2.28 (2H, m), 2.19-2.13 (2H, m), 1.97-1.85 (2H, m), 1.62-1.50 (2H, m), 1.41 (18H, s), 0.93 (18H, t, *J* = 7.9 Hz), 0.59 (12H, q, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 173.1, 79.9, 74.5, 32.6, 28.1, 26.0, 6.9, 5.0.

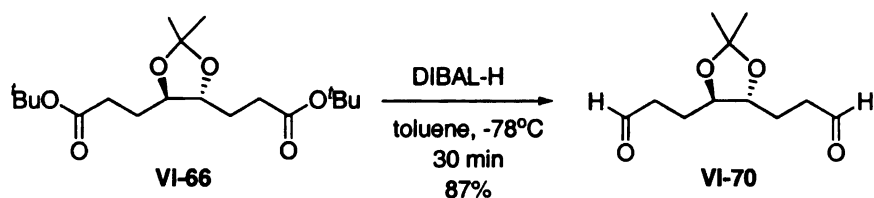


Data for diol **VI-115**: $[\alpha]_D^{20} +33.5$ (c 1.50, CH_2Cl_2), ^1H NMR (300 MHz, CDCl_3) δ 3.63-3.57 (6H, m), 1.71-1.23 (8H, m), 0.94 (18H, t, $J = 8.0$ Hz), 0.57 (12H, q, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 75.4, 63.2, 29.9, 26.6, 6.9, 5.1.



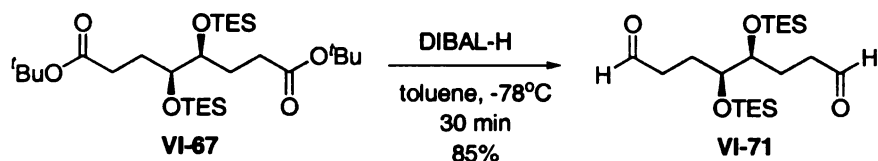
To a solution of diol **VI-115** (20 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) at room temperature, bisacetoxyiodo benzene (35 mg, 0.11 mmol) was added. After addition of TEMPO (1.5 mg, 0.01 mmol) the clear orange solution was stirred at RT for 2 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and treated with saturated sodium sulfite solution until it became colorless. Upon separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3×8 mL). The combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography (5% EtOAc in hexanes) to furnish di-aldehyde **VI-116** as a colorless oil (13 mg, 65%).

Data for di-aldehyde **VI-116**: $[\alpha]_D^{20} +25.9$ (c 2.625, CH_2Cl_2), ^1H NMR (500 MHz, CDCl_3) δ 9.76 (1H, t, $J = 1.5$ Hz), 3.62 (2H, dt, $J = 9.5, 4.3$ Hz), 2.59-2.35 (4H, m), 2.04-1.93 (2H, m), 1.73-1.63 (2H, m), 0.94 (18H, t, $J = 8.2$ Hz), 0.57 (12H, q, $J = 8.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 202.0, 73.9, 40.6, 22.4, 6.4, 4.5.

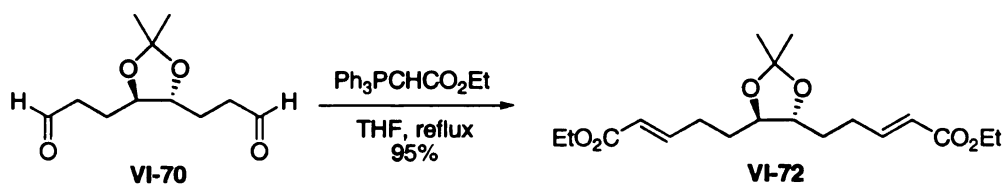


A solution of diester **VI-66** (1.96 g, 5.47 mmol) in toluene (25 mL) was cooled to -78 °C. DIBAL-H (5.53 mL, 2.5 M solution in toluene) was added dropwise and the reaction was stirred at -78 °C for 30 min. Acetic acid (1 mL) was slowly added at -78 °C to quench the reaction and after sat. potassium-sodium tartrate solution (65 mL) was added, the reaction was warmed to RT. Et₂O (65 mL), H₂O (26 mL) and glycerol (6.6 mL) were added and the resultant heterogeneous mixture was stirred for 4 h. The two layers were then separated and the aqueous layer was extracted with diethyl ether (4×80 mL). The combined organic layers were dried (MgSO₄), concentrated and the crude product after chromatographic purification (50% EtOAc in hexanes) afforded dialdehyde **VI-70** in one step (1.02 g, 87%).

Data for di-aldehyde **VI-70**: ¹H NMR (300 MHz, CDCl₃) δ 9.75 (1H, t, *J* = 1.2 Hz), 3.62-3.54 (2H, m), 2.66-2.48 (4H, m), 1.98-1.87 (2H, m), 1.77-1.65 (2H, m), 1.29 (6H, s); ¹³C NMR (75 MHz, CDCl₃) δ 201.6, 108.6, 79.5, 40.2, 27.2, 24.8.

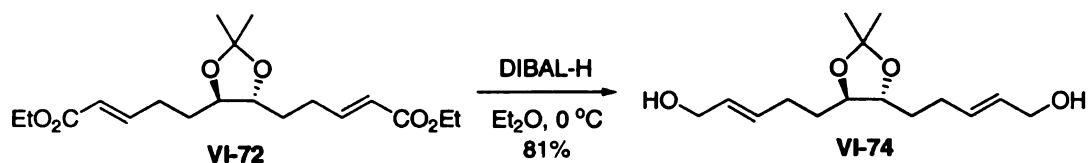


Data for di-aldehyde **VI-71**: ¹H NMR (500 MHz, CDCl₃) δ 9.74 (1H, t, *J* = 1.7 Hz), 3.63-3.60 (2H, m), 2.58-2.49 (2H, m), 2.42-2.35 (2H, m), 2.00-1.93 (2H, m), 1.68-1.62 (2H, m), 0.92 (18H, t, *J* = 8.0 Hz), 0.56 (12H, q, *J* = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 202.4, 74.4, 41.0, 22.9, 6.8, 5.0.



A solution of di-aldehyde **VI-70** (212 mg, 0.99 mmol) and (carbethoxymethylene)triphenylphosphorane (2.07 g, 5.0 mmol) in THF (12 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 (20% EtOAc in hexanes) to afford bis- α , β -unsaturated *trans*-ester **VI-72** (346 mg, 97%).

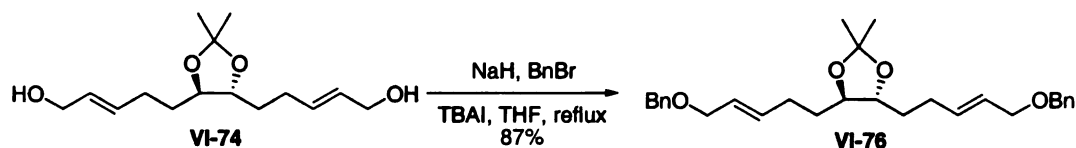
Data for bis- α , β -unsaturated *trans*-ester **VI-72**: ^1H NMR (500 MHz, CDCl_3) δ 6.94 (2H, dt, $J = 15.6, 6.8$ Hz), 5.80 (2H, dt, $J = 15.8, 1.5$ Hz), 4.14 (4H, q, $J = 7.0$ Hz), 3.60-3.56 (2H, m), 2.41-2.35 (2H, m), 2.30-2.21 (2H, m), 1.65-1.61 (4H, m), 1.33 (6H, s), 1.24 (6H, t, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 166.5, 147.9, 121.8, 108.4, 79.8, 60.1, 31.2, 28.6, 27.2, 14.2.



To a 0 °C solution of diester **VI-72** (0.36 g, 1.02 mmol) in diethyl ether (10 mL), DIBAL-H (5.1 mmol, 2.1 mL of 2.5 M solution in toluene) was added under N_2 . After stirring for 30 min. at the same temperature, saturated potassium-sodium tartrate solution (25 mL) was added and the mixture was brought to RT. Et_2O (25 mL), H_2O (10 mL) and glycerol (2.5 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 (2×30 mL). The combined organic layers

were dried (MgSO_4), concentrated and the crude product after chromatographic purification (80% EtOAc in hexanes) afforded allylic diol **VI-74** as a colorless oil (221 mg, 81%).

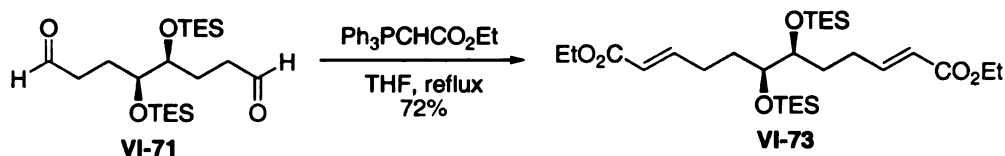
Data for allylic diol **VI-74**: ^1H NMR (500 MHz, CDCl_3) δ 5.68-5.60 (4H, m), 4.03 (4H, d, $J = 4.5$ Hz), 3.59-3.57 (2H, m), 2.22-2.18 (2H, m), 2.11-2.07 (2H, m), 1.88 (2H, br), 1.59-1.55 (4H, m), 1.33 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 131.9, 129.5, 108.0, 80.1, 63.4, 32.2, 28.6, 27.2.



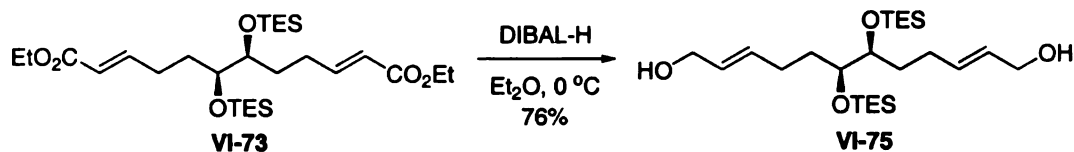
To a slurry of NaH (0.3 g, 7.5 mmol) in THF (8 mL), diol **VI-74** (0.68 g, 2.5 mmol) was added at 0 °C and stirred for 1 h at the same temperature. Benzyl bromide (0.91 mL, 7.5 mmol) was added dropwise followed by TBAI (0.19 g). The reaction was warmed to room temperature and then heated to 60 °C for 15 h. After cooling to room temperature H_2O (10 mL) was carefully added. The layers were separated, the aqueous layer was extracted with Et_2O (3×15 mL) and the combined organic layers after drying (MgSO_4) were concentrated. Dibenzyl ether **VI-76** was obtained (0.99 g, 87%) after chromatographic purification (10% EtOAc in hexanes).

Data for dibenzyl ether **VI-76**: ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.24 (10H, m), 5.76-5.60 (4H, m), 4.49 (4H, s), 3.96 (4H, d, $J = 5.9$ Hz), 3.62-3.60 (2H, m), 2.28-2.12 (4H, m), 1.63-1.59 (4H, m), 1.37 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 138.4, 133.6, 128.3, 127.7, 127.5, 126.8, 108.0, 80.2, 71.9, 70.7, 32.3, 28.8, 27.3.

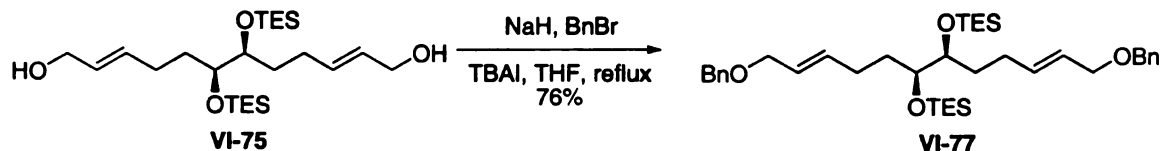
The Preparation of diene precursor **VI-77** was the same as the preparation of diene **VI-76**.



Data for diester **VI-73**: ^1H NMR (500 MHz, CDCl_3) δ 6.96 (2H, dt, $J = 15.6, 6.9$ Hz), 5.79 (2H, d, $J = 15.7$ Hz), 4.15 (4H, q, $J = 7.1$ Hz), 3.61-3.55 (2H, m), 2.38-2.31 (2H, m), 2.14-2.07 (2H, m), 1.81-1.63 (2H, m), 1.46-1.35 (2H, m), 1.26 (6H, t, $J = 7.2$ Hz), 0.93 (18H, t, $J = 6.8$ Hz), 0.56 (12H, q, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 166.6, 149.1, 121.3, 74.7, 60.1, 29.3, 28.8, 14.2, 6.9, 5.1.



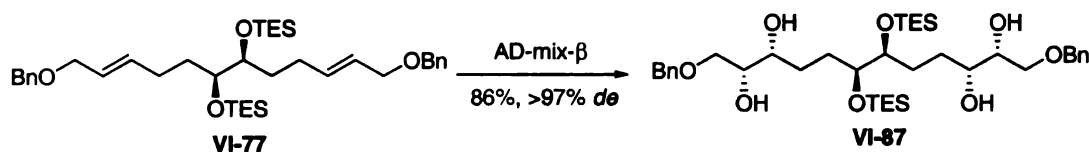
Data for allylic diol **VI-75**: ^1H NMR (500 MHz, CDCl_3) δ 5.71-5.59 (4H, m), 4.05 (4H, d, $J = 5.1$ Hz), 3.56-3.52 (2H, m), 2.23-2.17 (2H, m), 1.98-1.92 (2H, m), 1.72-1.66 (2H, m), 1.38-1.30 (4H, m), 0.93 (18H, t, $J = 8.0$ Hz), 0.56 (12H, q, $J = 7.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 133.4, 128.9, 74.9, 63.8, 29.9, 29.3, 6.9, 5.2.



Data for dibenzyl ether **VI-77**: ^1H NMR (300 MHz, CDCl_3) δ 7.36-7.24 (10H, m), 5.75-5.09 (4H, m), 4.48 (4H, s), 3.95 (4H, d, $J = 5.9$ Hz), 3.57-3.45 (2H, m), 2.23-2.21 (2H, m), 2.09-1.95 (2H, m), 1.72-1.68 (2H, m), 1.37-1.34 (2H, m), 0.94 (18H, t, $J = 8.0$ Hz), 0.56 (12H, q, $J = 8.3$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 138.5, 134.9, 128.3, 127.8, 127.5, 126.3, 75.0, 71.9, 71.0, 29.9, 29.5, 14.9, 7.0, 5.2.

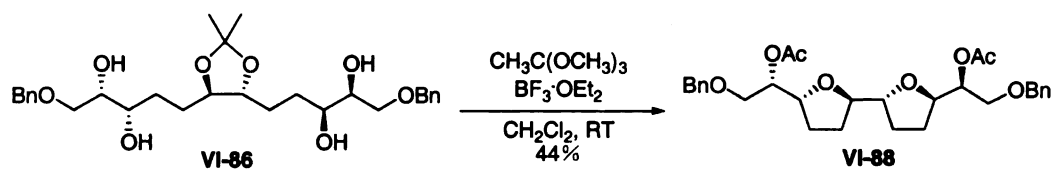
all the solids dissolved. The solution was then cooled to 0 °C upon which diene **VI-76** (87 mg, 0.19 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (1.2 g) was added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (10 mL) and H₂O (6 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4×10 mL), the combined organic layers were dried over Na₂SO₄, concentrated and the crude product was purified by column chromatography (50% EtOAc in hexanes to pure EtOAc) to yield the tetra-ol **VI-86** in 81% yield (80 mg) and > 97% *de*.

Data for tetra-ol **VI-86**: ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.26 (10H, m), 4.53 (4H, dd, *J* = 18.6, 12.0 Hz), 3.67-3.53 (10H, m), 2.81 (2H, br), 2.68 (2H, br), 1.79-1.49 (8H, m), 1.35 (6H, s); ¹³C NMR (125 MHz, CDCl₃) δ 137.7, 128.5, 127.9, 127.8, 108.2, 81.1, 73.6, 72.7, 72.4, 71.9, 30.3, 28.7, 27.3.



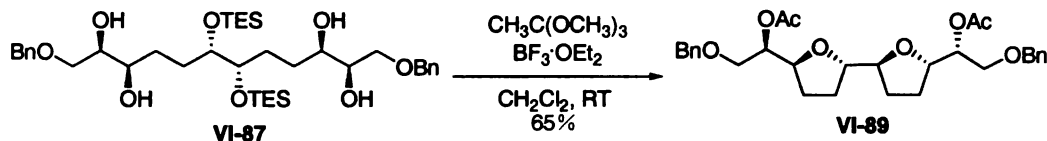
The double SAD sequence, the same as the preparation of tetraol **VI-19**, gave tetraol **VI-87** in 86% yield and > 97% *de*.

Data for tetraol **VI-87**: ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.26 (10H, m), 4.53 (4H, dd, *J* = 14.4, 12.0 Hz), 3.62-3.53 (10H, m), 2.61 (4H, dd, *J* = 17.0, 4.2 Hz), 1.83-1.79 (2H, m), 1.69-1.64 (2H, m), 1.45-1.42 (2H, m), 1.31-1.24 (2H, m), 0.92 (18H, t, *J* = 8.0 Hz), 0.56 (12H, q, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 137.7, 128.5, 127.9, 127.7, 75.7, 73.7, 72.8, 72.6, 72.3, 30.8, 26.6, 6.9, 5.1.



Newly distilled dry $\text{BF}_3 \cdot \text{OEt}_2$ (9.7 μL , 0.077 mmol) was added to a solution of tetraol **VI-86** (40 mg, 0.077 mmol) and trimethylortho acetate (24 μL , 0.185 mmol) in CH_2Cl_2 (2.5 mL) at RT. After 1 h, the reaction was quenched with acetone and the organic layers were concentrated under reduced pressure. The crude product was purified by flash column chromatography (50% EtOAc in hexanes) to furnish the bis-adjacent THF **VI-88** (18 mg, 44%) as a clear oil.

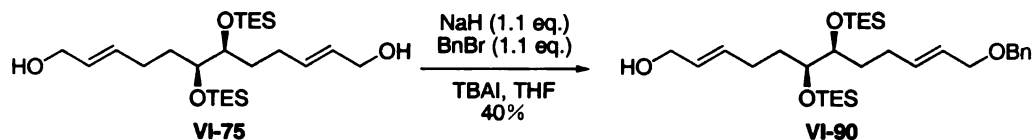
Data for bis-adjacent THF **VI-88**: ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.24 (10H, m), 5.06-5.03 (2H, m), 4.51 (4H, dd, $J = 27.8, 12.2$ Hz), 4.12 (2H, q, $J = 6.6$ Hz), 3.87-3.85 (2H, m), 3.67-3.58 (4H, m), 2.05 (6H, s), 2.02-1.97 (2H, m), 1.93-1.89 (2H, m), 1.77-1.66 (4H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 138.2, 128.3, 127.6, 127.5, 81.9, 77.9, 73.9, 73.1, 69.3, 28.1, 21.2.



Newly distilled dry $\text{BF}_3 \cdot \text{OEt}_2$ (24.4 μL , 0.19 mmol) was added to the solution of tetra-ol **VI-87** (130 mg, 0.184 mmol) and trimethylortho acetate (59 μL , 0.46 mmol) in CH_2Cl_2 (10 mL) at RT. After 1 h, the reaction was quenched with acetone and the organic layers were concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% to 50% EtOAc in hexanes) to furnish the bis-adjacent THF **VI-89** (63 mg, 65%) as a clear oil.

Data for bis-adjacent THF **VI-89**: ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (10H, m),

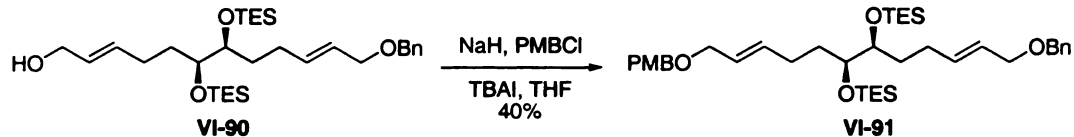
5.06-5.03 (2H, m), 4.50 (4H, dd, $J = 27.9, 12.2$ Hz), 4.12 (2H, q, $J = 6.5$ Hz), 3.88-3.85 (2H, m), 3.67-3.59 (4H, m), 2.05 (6H, s), 2.02-1.89 (4H, m), 1.77-1.65 (4H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 138.2, 128.3, 127.6, 127.5, 81.8, 77.9, 73.9, 73.1, 69.3, 28.1, 21.1.



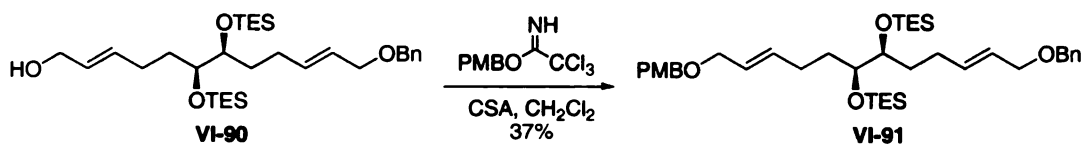
To a suspension of NaH (57 mg, 1.43 mmol, 1.1 equiv) in THF (5 mL), diol **VI-75** (0.59 g, 1.29 mmol, 1 equiv) was added at 0 °C and stirred for 1 h at the same temperature. Benzyl bromide (0.17 mL, 1.43 mmol, 1.1 equiv) was added dropwise followed by TBAI (48 mg, 0.13 mmol, 0.1 equiv). The reaction was warmed to room temperature and then heated to reflux for 15 h. After cooling to room temperature, H_2O (5 mL) was carefully added. The layers were separated, the aqueous layer was extracted with Et_2O (3×10 mL), and the combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. Mono-benzyl ether **VI-90** was obtained (0.282 g, 40%) after chromatographic purification (5% to 10% to 30% EtOAc in hexanes) along with dibenzyl ether **VI-77** (60 mg, 7%) and recovered starting material diol (0.191 g, 32%).

Data for mono-benzyl ether **VI-90**: ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.24 (5H, m), 5.74-5.59 (4H, m), 4.48 (2H, s), 4.06 (2H, d, $J = 5.4$ Hz), 3.96 (2H, d, $J = 5.9$ Hz), 3.58-3.55 (2H, m), 2.24-2.20 (2H, m), 2.00-1.94 (2H, m), 1.74-1.69 (2H, m), 1.39-1.35 (3H, m), 0.95 (18H, m, $J = 7.8$ Hz), 0.57 (12H, q, $J = 7.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 138.5, 134.8, 133.4, 128.9, 128.3, 127.7, 127.5, 126.2, 74.9,

71.8, 70.9, 63.8, 29.9, 29.8, 29.4, 29.2, 6.9, 5.2.



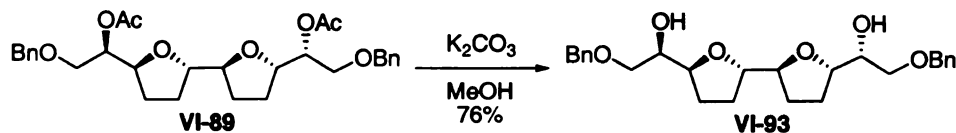
To a suspension of NaH (6.8 mg, 0.17 mmol) in THF (2 mL), a solution of alcohol **VI-90** (31 mg, 0.057 mmol) in 1 mL THF was added at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. PMBCl (12 μ L, 0.086 mmol) was added dropwise followed by TBAI (8.4 mg, 0.023 mmol). The reaction was refluxed for 15 h. After cooling to room temperature sat. NH_4Cl (5 mL) was carefully added to quench the reaction. The layers were separated, the aqueous layer was extracted with Et_2O (3 $\times$ 8 mL), and the combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. PMB ether **VI-91** was obtained (15 mg, 40%) after chromatographic purification (5% to 10% EtOAc in hexanes) along with recovered starting material alcohol **VI-90** (5.1 mg, 16%).



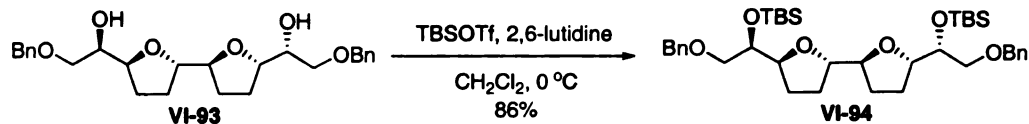
Alcohol **VI-90** (45 mg, 0.082 mmol) and trichloroacetimidate (28 mg, 0.098 mmol) were dissolved in dichloromethane (2 mL). Camphorsulfonic acid (CSA, 2 mg, 0.008 mmol) was added in one portion to the solution and the reaction was stirred at room temperature for 15 h. Sat. sodium bicarbonate (5 mL) was added to quench the reaction and the mixture was separated. The water layer was extracted with

EtOAc (4×5 mL), dried over Na₂SO₄ and concentrated. The residue was purified via column chromatography (10% EtOAc in hexanes) to yield PMB ether **VI-91** (20 mg, 37%) along with recovered starting material alcohol (23.3 mg, 52%).

Data for PMB ether **VI-91**: ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.22 (7H, m), 6.85 (2H, d, *J* = 8.7 Hz), 5.79-5.54 (4H, m), 4.48 (2H, s), 4.40 (2H, s), 3.93 (4H, dd, *J* = 9.4, 6.0 Hz), 3.78 (3H, s), 3.58-3.52 (2H, m), 2.31-2.15 (2H, m), 2.03-1.88 (2H, m), 1.77-1.63 (2H, m), 1.42-1.30 (2H, m), 0.93 (18H, t, *J* = 8.1 Hz), 0.56 (12H, q, *J* = 8.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 135.0, 134.9, 129.4, 128.3, 127.8, 127.5, 126.3, 113.7, 75.0, 71.9, 71.5, 71.0, 70.7, 55.3, 29.8, 29.4, 6.9, 5.2.

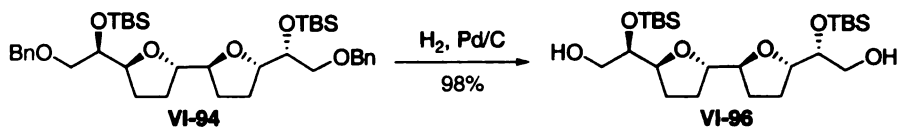


127.6, 127.5, 82.2, 79.9, 73.2, 71.6, 71.4, 28.4, 26.6.



To a 0 °C solution of bis-THF diol **VI-93** (240 mg, 0.56 mmol) in CH₂Cl₂ (11 mL), 2,6 lutidine (0.18 mL, 1.51 mmol) and TBSOTf (0.34 mL, 1.40 mmol) were added in that order. After 30 min at the same temperature, saturated NaHCO₃ solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3×15 mL), combined organic layers were dried over Na₂SO₄, 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 **VI-94** was obtained in 86% yield (312 mg).

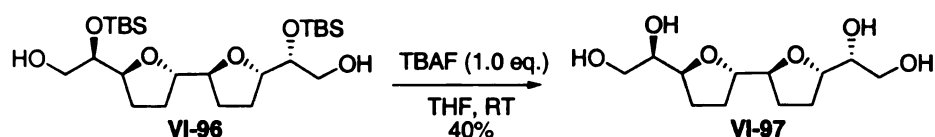
Data for bis-TBS ether **VI-94**: ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.22 (10H, m), 4.48 (4H, dd, *J* = 19.8, 12.0 Hz), 4.01-3.83 (6H, m), 3.49-3.46 (2H, m), 3.38-3.35 (2H, m), 1.88-1.80 (6H, m), 1.66-1.59 (2H, m), 0.86 (18H, s), 0.04 (12H, s); ¹³C NMR (125 MHz, CDCl₃) δ 138.5, 128.2, 127.6, 127.4, 81.7, 80.2, 73.5, 73.3, 73.2, 28.5, 26.8, 25.9, 18.2, -4.5, -4.7.



Dibenzyl ether **VI-94** (271 mg, 0.40 mmol) was dissolved in 1 : 1 EtOAc : ⁱPrOH (5 mL). To this solution, 10% Pd-C (105 mg) was added and the mixture was stirred vigorously under H₂ (1 atm). The hydrogenolysis was complete in 3 h after which the reaction was filtered through a celite pad. The filtrate was concentrated and the

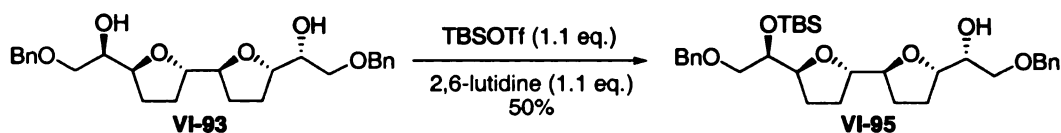
crude product was purified by flash column chromatography (30% EtOAc in hexanes) to furnish diol **VI-96** in 98% yield (194 mg).

Data for diol **VI-96**: ^1H NMR (500 MHz, CDCl_3) δ 3.91-3.87 (2H, m), 3.85-3.80 (2H, m), 3.62-3.50 (6H, m), 2.49 (2H, br), 1.99-1.96 (2H, m), 1.90-1.86 (2H, m), 1.72-1.62 (4H, m), 0.83 (18H, s), 0.03 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 81.5, 81.4, 74.1, 65.6, 28.7, 28.1, 25.7, 17.9, -4.5, -4.7.



To a solution of di-TBS ether **VI-96** (23.4 mg, 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 $\times$ 8 mL). The organic layers were combined, dried over 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 the tetra-ol **VI-97** (6 mg) in 40% yield.

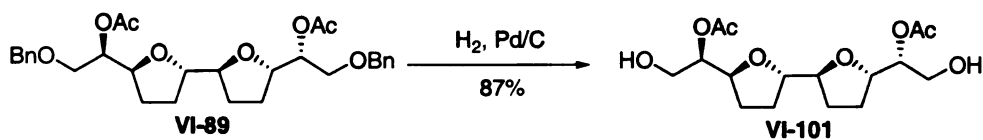
Data for tetra-ol **VI-97**: ^1H NMR (500 MHz, CDCl_3) δ 4.00-3.52 (10H, m), 2.07-1.61 (8H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 82.5, 80.3, 73.1, 63.6, 28.7, 27.0.



To a 0 $^\circ\text{C}$ solution of diol **VI-93** (200 mg, 0.45 mmol) in CH_2Cl_2 (20 mL), 2,6 lutidine (63 μL , 0.54 mmol) and TBSOTf (0.12 mL, 0.50 mmol) were added in that

order. After 30 min at the same temperature, saturated NaHCO₃ solution (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3×20 mL), the combined organic layers were dried over Na₂SO₄, and concentrated under reduced pressure to afford a crude oil. Upon purification of the oil by column chromatography (20% to 30% to 50% EtOAc in hexanes), mono-TBS ether **VI-95** was obtained in 50% yield (125 mg) along with di-TBS ether (36.5 mg, 12%) and recovered starting material diol (64 mg, 32%).

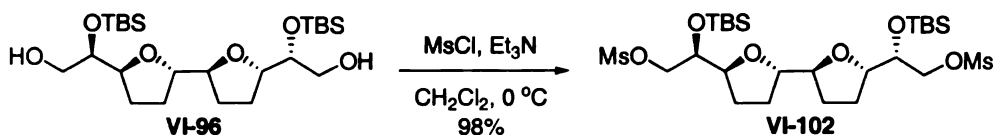
Data for mono-TBS ether **VI-95**: ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.24 (10H, m), 4.57-4.45 (4H, m), 4.04-3.81 (6H, m), 3.60-3.35 (4H, m), 1.95-1.84 (6H, m), 1.62-1.55 (2H, m), 0.87 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 138.3, 138.0, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4, 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, -4.5, -4.8.



Dibenzyl ether **VI-89** (240 mg, 0.34 mmol) was dissolved in 1 : 1 EtOAc : ⁱPrOH (7 mL). To this solution, 10% Pd-C (93 mg) was added and the mixture was stirred vigorously under H₂ (1 atm). The hydrogenolysis was complete in 3 h after which the reaction was filtered through a celite pad. The filtrate was concentrated and the crude product was purified by flash column chromatography (80% EtOAc in hexanes to pure EtOAc) to furnish diol **VI-101** in 87% yield (137 mg).

Data for diol **VI-101**: ¹H NMR (500 MHz, CDCl₃) δ 4.77-4.73 (2H, m), 4.07 (2H, q,

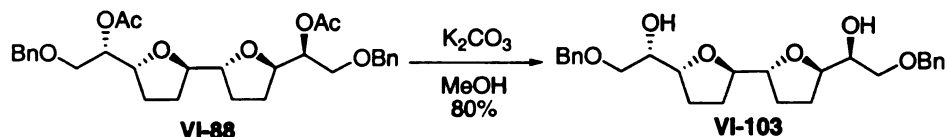
$J = 7.0$ Hz), 3.84-3.66 (6H, m), 3.21 (2H, br), 2.02 (6H, s), 2.02-1.91 (4H, m), 1.70-1.57 (4H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 81.9, 77.9, 75.7, 62.1, 28.5, 27.8, 21.0.



The solution of diol **VI-96** (22.1 mg, 0.033 mmol) in dichloromethane (2 mL) was cooled to 0 °C. Mesyl chloride (10 μL , 0.132 mmol) and triethylamine (30 μL , 0.218 mmol) were added to the solution and the reaction was stirred at 0 °C for 3 h. After adding H_2O (5 mL) to quench the reaction, it was warmed to RT and the layers were separated. The water layer was extracted with CH_2Cl_2 (3 $\times$ 8 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified via column chromatography to yield the dimesylate **VI-102** in 98% yield (26.7 mg).

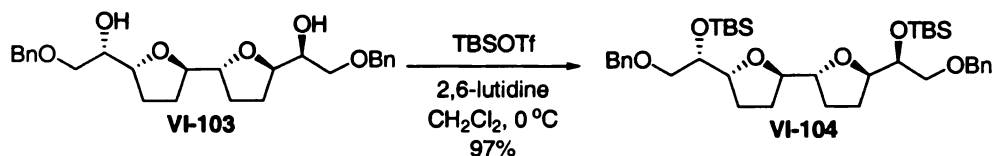
Data for dimesylate **VI-102**: ^1H NMR (500 MHz, CDCl_3) δ 4.27-4.24 (2H, m), 4.09-4.06 (2H, m), 3.89-3.83 (6H, m), 3.00 (6H, s), 2.05-1.88 (4H, m), 1.79-1.58 (4H, m), 0.87 (18H, s), 0.09 (6H, s), 0.06 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 81.7, 79.4, 72.6, 71.5, 37.2, 28.3, 28.1, 25.8, 18.0, -4.4, -4.7.

The preparation of diol **VI-105** was the same as the preparation of diol **VI-96**.

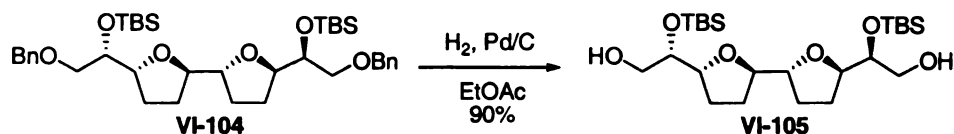


Data for secondary diol **VI-103**: ^1H NMR (500 MHz, CDCl_3) δ 7.35-7.24 (10H, m), 4.53 (4H, dd, $J = 16.1, 12.0$ Hz), 3.99-3.83 (6H, m), 3.60-3.43 (4H, m), 2.46 (2H, br),

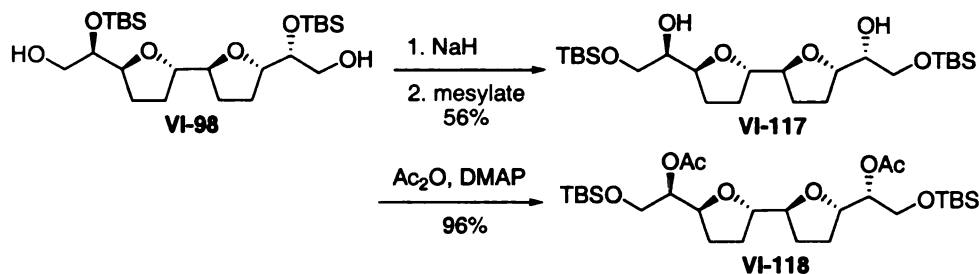
1.97-1.84 (6H, m), 1.62-1.55 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 138.0, 128.4, 127.7, 127.6, 82.4, 80.0, 73.4, 71.6, 28.5, 26.7.



Data for di-TBS ether **VI-104**: ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.23 (10H, m), 4.48 (4H, dd, $J = 15.4, 12.0$ Hz), 3.98-3.83 (6H, m), 3.51-3.34 (4H, ddd, $J = 24.7, 9.8, 4.6$ Hz), 1.88-1.83 (6H, m), 1.68-1.59 (2H, m), 0.86 (18H, s), 0.05 (6H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 138.5, 128.2, 127.6, 127.4, 81.7, 80.2, 73.5, 73.2, 73.1, 28.5, 26.8, 25.9, 18.2, -4.5, -4.7.



Data for primary diol **VI-105**: ^1H NMR (300 MHz, CDCl_3) δ 3.92-3.83 (4H, m), 3.66-3.58 (6H, m), 2.41 (2H, br), 2.03-1.87 (4H, m), 1.77-1.66 (4H, m), 0.86 (18H, s), 0.06 (6H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 81.6, 81.5, 74.1, 65.7, 28.9, 28.1, 25.8, 18.0, -4.4, -4.6.

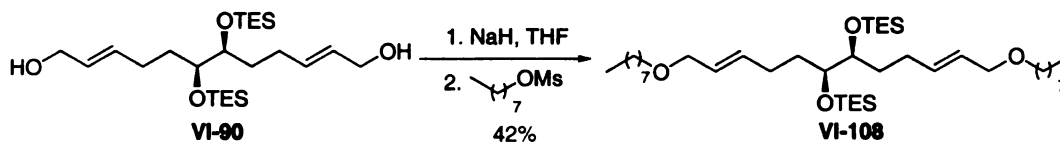


During the etherification of diol **VI-98**, the desired ether product was not obtained. Instead, the silyl migration product **VI-117** was isolated. To a 0 °C suspension of NaH (12 mg, 0.29 mmol, 60%) in THF (3 mL), the solution of diol **VI-98** (48 mg,

0.098 mmol) in THF (1 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 1 h. The solution of octane mesylate (75 mg, 0.353 mmol) in THF (1 mL) was added and the reaction was refluxed for 15 h. After cooling the reaction to RT, sat. NH_4Cl was slowly added to quench the reaction and the layers were separated. The water layer was extracted with EtOAc (3×8 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Secondary diol **VI-117** was isolated via column chromatography (30% EtOAc in hexanes) in 56% yield (26.7 mg). The product was acetylated with acetic anhydride and DMAP in dichloromethane and diacetate **VI-118** was obtained in 96% yield.

Data for secondary diol **VI-117**: ^1H NMR (500 MHz, CDCl_3) δ 3.94-3.81 (4H, s), 3.73-3.58 (6H, m), 2.47 (2H, br), 2.06-1.83 (6H, m), 1.67-1.58 (2H, m), 0.86 (18H, s), 0.06 (6H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 82.2, 79.7, 73.1, 64.5, 28.4, 27.4, 25.9, 18.3, -5.4, -5.3.

Data for diacetate **VI-118**: ^1H NMR (300 MHz, CDCl_3) δ 4.90-4.86 (2H, m), 4.12-4.06 (2H, m), 3.89-3.67 (6H, m), 2.04 (6H, s), 2.04-1.61 (8H, m), 0.86 (18H, s), 0.04 (12H, s).

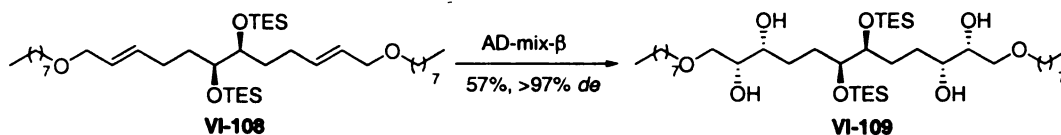


To a suspension of sodium hydride (22 mg, 0.55 mmol, 60%) in THF (2.5 mL) at 0 °C, a solution of allylic diol **VI-90** (84 mg, 0.18 mmol) in THF (1 mL) was added

dropwise. The mixture was brought to RT and stirred for 1 h. A solution of octane mesylate (116 mg, 0.55 mmol) in THF (0.5 mL) was added dropwise and the reaction was refluxed for 15 h. After cooling the reaction to RT, H₂O (10 mL) was added to workup and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified via column chromatography (10% to 20% EtOAc in hexanes) to yield diether **VI-108** (51 mg, 42%) and mono-ether (15 mg, 14%).

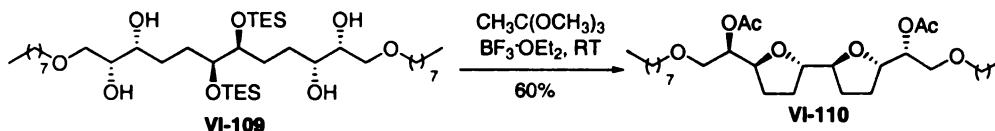
Data for diether **VI-108**: ¹H NMR (500 MHz, CDCl₃) δ 5.68-5.51 (4H, m), 3.86 (4H, d, *J* = 6.1 Hz), 3.54 (2H, d, *J* = 8.8 Hz), 3.37 (4H, t, *J* = 6.7 Hz), 2.27-2.16 (2H, m), 1.99-1.91 (2H, m), 1.75-1.65 (2H, m), 1.60-1.52 (4H, m), 1.37-1.18 (22H, m), 0.93 (18H, t, *J* = 8.0 Hz), 0.85 (6H, t, *J* = 6.8 Hz), 0.56 (12H, q, *J* = 7.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 134.4, 126.6, 75.0, 71.6, 70.3, 31.8, 29.8, 28.5, 29.4, 29.3, 26.2, 22.6, 14.1, 6.9, 5.2.

Data for mono-ether: ¹H NMR (300 MHz, CDCl₃) δ 5.78-5.50 (4H, m), 4.47 (2H, d, *J* = 6.5 Hz), 3.86 (2H, d, *J* = 6.2 Hz), 3.53 (2H, d, *J* = 8.9 Hz), 3.36 (2H, t, *J* = 6.7 Hz), 2.28-2.15 (2H, m), 2.00-1.91 (2H, m), 1.76-1.49 (4H, m), 1.41-1.22 (12H, m), 0.92 (18H, t, *J* = 7.8 Hz), 0.85 (3H, t, *J* = 6.3 Hz), 0.55 (12H, q, *J* = 7.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 134.3, 133.4, 128.9, 126.5, 74.9, 71.5, 70.2, 63.8, 37.3, 31.8, 31.6, 29.8, 29.7, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 26.2, 25.4, 22.6, 22.5, 14.0, 6.9, 5.1.



AD-mix- β (0.21 g) was dissolved in 1 : 1 t BuOH : H_2O (2 mL). To this clear, orange solution, methane sulfonamide (15 mg, 0.14 mmol) and potassium osmate (0.5 mg, 0.0014 mmol) were added and stirred until all the solids had dissolved. The solution was then cooled to 0 $^{\circ}C$ at which time diene **VI-108** (49 mg, 0.072 mmol) was added in one portion. The reaction was vigorously stirred for 16 h after which solid sodium sulfite (0.48 g) was then added at the same temperature. The mixture was warmed to room temperature and stirring was continued for 45 min. EtOAc (8 mL) and H_2O (4 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 $\times$ 10 mL), the combined organic layers were dried over Na_2SO_4 , concentrated under reduced pressure, and the crude product was purified by column chromatography (50% EtOAc in hexanes to pure EtOAc) to yield the tetraol **VI-109** in 57% yield (31 mg) and > 97% *de*.

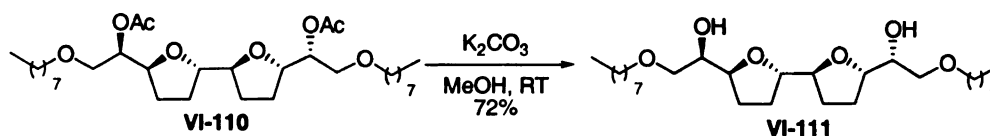
Data for tetraol **VI-109**: 1H NMR (300 MHz, $CDCl_3$) δ 3.58-3.40 (14H, m), 2.70 (2H, br), 2.61 (2H, br), 1.88-1.51 (3H, m), 1.50-1.41 (5H, m), 1.32-1.21 (24H, m), 0.93 (18H, t, J = 8.0 Hz), 0.85 (6H, t, J = 6.8 Hz), 0.57 (12H, q, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.7, 73.5, 72.9, 72.1, 71.9, 31.8, 30.8, 29.6, 29.4, 29.2, 26.6, 26.1, 22.6, 14.1, 6.9, 5.1.



Newly distilled dry $BF_3 \cdot OEt_2$ (4.8 μ L, 0.038 mmol) was added to the solution of

tetraol **VI-109** (28.7 mg, 0.038 mmol) and trimethylortho acetate (12 μ L, 0.096 mmol) in CH_2Cl_2 (2 mL) at RT. After 1 h, the reaction was quenched by acetone and the combined organic layers were concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% EtOAc in hexanes) to furnish ether linked bis-adjacent THF **VI-110** (13 mg, 60%) as a clear oil.

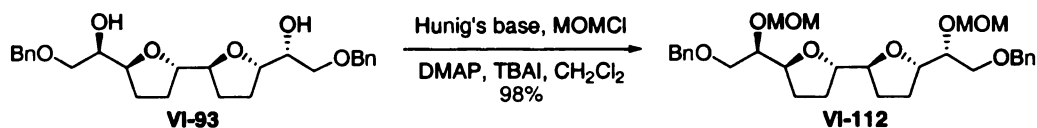
Data for ether linked bis-adjacent THF **VI-110**: ^1H NMR (500 MHz, CDCl_3) δ 5.01-4.98 (2H, m), 4.09 (2H, q, $J = 6.6$ Hz), 3.86 (2H, quint, $J = 5.3$ Hz), 3.61-3.58 (2H, m), 3.55-3.51 (2H, m), 3.45-3.34 (4H, m), 2.05 (6H, s), 2.01-1.91 (4H, m), 1.76-1.62 (4H, m), 1.52-1.48 (4H, m), 1.30-1.24 (20H, m), 0.85 (6H, t, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 81.9, 78.0, 73.9, 71.4, 69.7, 31.8, 29.6, 29.4, 29.3, 28.0, 26.0, 22.6, 21.2, 14.1.



Bis-adjacent THF acetate **VI-110** (11.8 mg, 0.021 mmol) was dissolved in MeOH (3 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 (8 mL) and washed with NaHCO_3 (8 mL) and H_2O (4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 10 mL). The combined organic layers were dried using Na_2SO_4 , the solvent was evaporated and the crude product was purified by flash column chromatography (50% EtOAc in hexanes). Ether linked analog **VI-111** was obtained in 72% yield (7.2 mg).

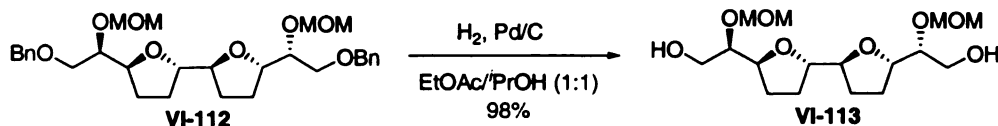
Data for ether linked analog **VI-111**: ^1H NMR (500 MHz, CDCl_3) δ 3.96-3.92 (2H, m),

3.88-3.85 (4H, m), 3.52-3.50 (2H, m), 3.43 (4H, t, $J = 6.7$ Hz), 3.40-3.36 (2H, m), 2.35 (2H, d, $J = 3.2$ Hz), 1.96-1.88 (6H, m), 1.58-1.52 (6H, m), 1.29-1.25 (20H, m), 0.86 (6H, t, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 82.4, 80.1, 72.0, 71.6, 71.5, 31.8, 29.6, 29.4, 29.2, 28.5, 26.8, 26.1, 22.6, 14.1.



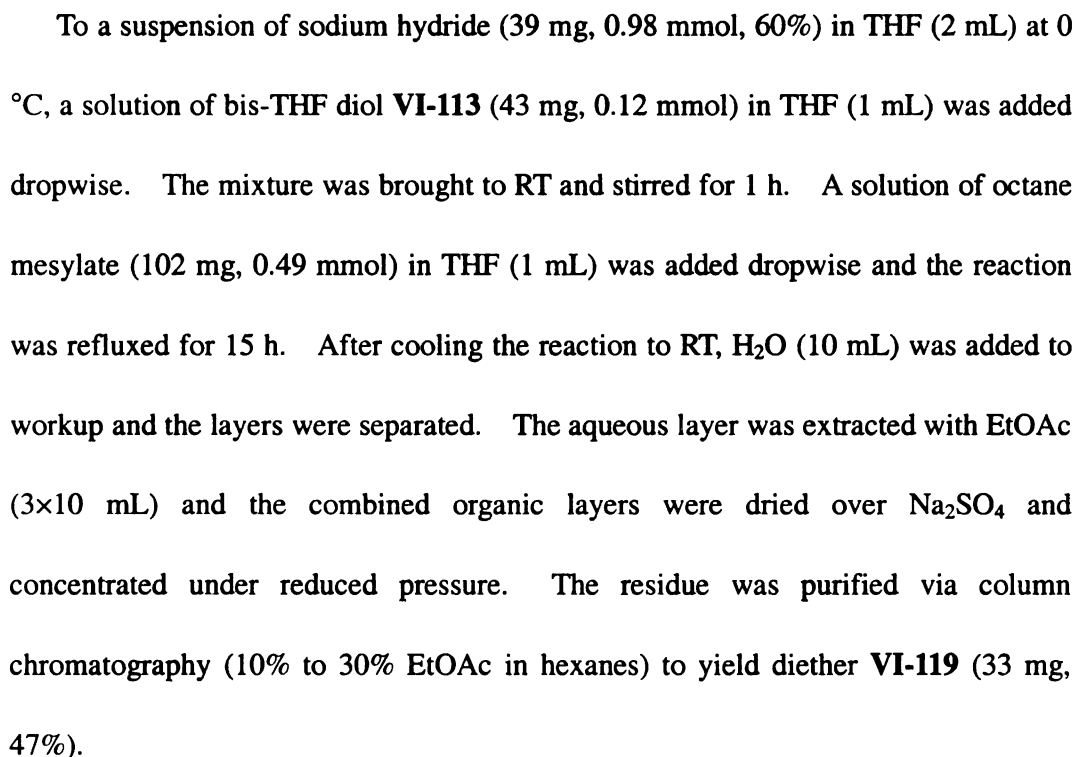
To a solution of diol **VI-93** (124 mg, 0.28 mmol) in dichloromethane (3 mL), DMAP (13.7 mg, 0.11 mmol), Hünig's base (0.59 mL, 3.36 mmol), methoxymethyl chloride (0.13 mL, 1.68 mmol), and TBAI (41.4 mg, 0.11 mmol) were added in that order. The reaction was stirred at room temperature overnight. Sat. 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 Na_2SO_4 and concentrated under reduced pressure. The residue was purified via a fast column chromatography (30% EtOAc in hexanes) to yield the desired fully protected diol **VI-112** in 98% yield (148 mg).

Data for di-MOM ether **VI-112**: ^1H NMR (500 MHz, CDCl_3) δ 4.94-4.91 (2H, m), 4.45-4.42 (2H, m), 4.33 (2H, dd, $J = 11.5, 5.3$ Hz), 4.08-4.02 (2H, m), 3.88-3.85 (2H, m), 3.00 (6H, s), 2.06 (6H, s), 2.06-1.66 (8H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 170.1, 81.9, 72.5, 68.3, 37.5, 28.8, 27.9, 20.9.



Dibenzyl ether **VI-112** (145 mg, 0.27 mmol) was dissolved in 1 : 1 EtOAc :

Data for primary diol **VI-113**: ^1H NMR (500 MHz, CDCl_3) δ 4.64 (2H, dd, $J = 28.0$, 6.8 Hz), 3.95-3.90 (2H, m), 3.82-3.78 (2H, m), 3.65-3.62 (2H, m), 3.54-3.47 (4H, m), 3.33 (6H, s), 3.16 (2H, br), 1.97-1.87 (4H, m), 1.75-1.70 (2H, m), 1.62-1.57 (2H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 96.8, 81.9, 81.6, 79.4, 63.1, 55.5, 28.1, 28.0.



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29.7, 6.5 Hz), 4.02-4.00 (2H, m), 3.86-3.81 (2H, m), 3.79-3.51 (2H, m), 3.54-3.36 (8H, m), 3.36 (6H, s), 1.98-1.82 (6H, m), 1.67-1.60 (2H, m), 1.54-1.49 (4H, m), 1.30-1.26 (20H, m), 0.85 (6H, t, $J = 6.7$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 96.7, 81.7, 79.3, 77.6, 71.7, 71.6, 55.5, 31.8, 29.7, 29.4, 29.2, 28.4, 27.4, 26.1, 22.6, 14.1.

VI.8. References

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