

CONSTRUCTION OF CHIRAL POLYSUBSTITUTED OXACYCLES BY NOVEL JOCIC
REACTIONS AND SYNTHESIS OF A NEW CYTOCHROME-P450
PHOTOAFFINITY LABEL

by

JORDAN THOMAS ENTREKIN

TIMOTHY S. SNOWDEN, COMMITTEE CHAIR

SILAS BLACKSTOCK
DEBRA DOLLIVER
MICHAEL JENNINGS
KEVIN SHAUGHNESSY

A DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy
in the Department of Chemistry
in the Graduate School of
The University of Alabama

TUSCALOOSA, ALABAMA

2016

Copyright Jordan Thomas Entrekin 2016
ALL RIGHTS RESERVED

ABSTRACT

The preparation of a novel cytochrome P-450 photoaffinity label is described. The targeted azidoquinone was to be used as a photo-reactive label to specifically identify peptides associated with the oxidation binding site within cytochrome bc₁, and consequently determine the unique catalytic mechanism of quinol oxidation processes and the intermediates involved. The synthetic route features a Diels-Alder cyclization/alkylation/decyclization approach to prepare the mimic of naturally occurring ubiquinone. The synthesis is accomplished in 6 steps from commercially available 4-methylcatechol and involves incorporation of azide in the final synthetic step to prepare the novel azidoquinone.

(*S*)-Wynberg lactone was used to prepare the potent CERT inhibitor (1*R*,3*S*)-HPA-12. The route featured the preparation of an optically active azidolactone through a Corey-Link reaction accompanied by nucleophilic acyl substitution. The synthesis was accomplished in 5 steps, and proceeded in 33% overall yield from (*S*)-Wynberg lactone.

(*R*)-Wynberg lactone was used to prepare chiral polysubstituted oxacycles through a novel Jovic-type reaction. The route featured a directed 1,3-reduction of a β -hydroxyketone followed by ruthenium-catalyzed cross metathesis and osmium-catalyzed asymmetric dihydroxylation. A modified olefin metathesis procedure to suppress undesired byproduct formation is described in detail. A variety of functionalized olefins were prepared by the modified procedure in yields commonly exceeding 80%. Functionalized tetraols were prepared

by a modified Sharpless asymmetric dihydroxylation reaction with yields commonly exceeding 80%, and diastereomeric ratios typically exceeding 85:15. Stereoselectivity in the dihydroxylation of terminal mono-substituted olefins can be enhanced with a pre-formed phenyl boronic ester adduct. Conditions for enhancing the stereoselectivity with this class of substrates are described in detail. The final synthetic step en route to the targeted tetrahydropyran derivatives involves intramolecular cyclization through a novel Jovic-type reaction, and commonly proceeds in > 80% yield. Work towards the cyclization of all classes of prepared tetraols is currently in progress.

Terminal alkylsulfanyl alcohols were prepared in one step from an aliphatic trichloromethyl carbinol in yields exceeding 85%. These results further demonstrate the utility of *gem*-dichloroepoxide intermediates in Jovic-type reactions, and lay the groundwork for future transformations. Work in this area is currently underway.

DEDICATION

I would like to dedicate this work to my many family and friends. I am especially thankful for my parents Neal and Robin Entrekin for teaching me the value of hard work, and their continued support and encouragement through the years. I would also like to thank my aunt and uncle Gail and Gary Damkoehler for helping make my pursuit of a doctorate degree possible.

LIST OF ABBREVIATIONS AND SYMBOLS

$[\alpha]_{22}^D$	specific rotation (sodium D-line, room temperature)
(<i>R</i>)-	rectus (clockwise)
(<i>S</i>)-	sinister (counterclockwise)
Ac ₂ O	acetic anhydride
AcOH	acetic acid
AD	asymmetric dihydroxylation
AQN	anthraquinone
ATP	adenosine triphosphate
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bu	butyl
<i>t</i> -Bu	<i>tertiary</i> butyl
<i>sec</i> -Bu	<i>secondary</i> butyl
<i>n</i> -BuLi	<i>normal</i> butyl lithium
Calcd	calculated
CAN	ceric ammonium nitrate
CIAT	crystallization-induced asymmetric transformation
<i>Cis</i>	same direction
CM	cross metathesis

COSY	correlation spectroscopy
Cy	cyclohexyl
Cyt	cytochrome
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DI H ₂ O	de-ionized water
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMG	directed metalation group
DMSO	dimethylsulfoxide
<i>E</i> -	entgegen (opposite, <i>trans</i> -)
ee	enantiomeric excess
EI	electron ionization
Et	ethyl
Et ₂ O	diethyl ether
EtOAc	ethyl acetate
FT/IR	Fourier transform

<i>gem-</i>	<i>geminal</i>
HMBC	heteronuclear multiple-bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
IC ₅₀	half maximal inhibitory concentration
IND	indoline
IPA	isopropanol
Ipc-	diisopinocampheyl-
kcal	kilocalories
LDA	lithium diisopropylamide
<i>m-</i>	<i>meta-</i>
Me	methyl
MeCN	acetonitrile
MePh	toluene
Mes-	mesityl-
MHz	megahertz
mol	mole
MTBE	methyl <i>tert</i> -butyl ether
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
Nu	nucleophile

<i>o</i> -	<i>ortho</i> -
OAc	acetate
<i>p</i> -	<i>para</i> -
PHAL	phthalazine
PhH	benzene
<i>pKa</i>	acidity constant
PMB	<i>p</i> -methoxybenzoyl
Pr	propyl
PYR	diphenylpyrimidine
rt	room temperature
SQ	semiquinone
TBAF	tetrabutylammonium fluoride
TBS-	<i>tert</i> -butyldimethylsilyl-
TES-	triethylsilyl-
Tf	trifluoromethanesulfonate
TFAA	trifluoroacetic acid
TFBQ	tetrafluoro-1,4-benzoquinone
TfOH	triflic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS-	trimethylsilyl-
Tol-	toluyl
<i>trans</i>	opposite direction

Ts	4-toluenesulfonyl
UQ	ubiquinone
UQH ₂	ubiquinol
UV	ultraviolet
Z-	zusammen (together, <i>cis</i> -)

ACKNOWLEDGMENTS

I am extremely thankful to have had the opportunity to work under the guidance of Professor Timothy Snowden. Professor Snowden possesses many qualities that I have always admired: His dedication to teaching and mentoring students, his patience, encouragement, and persistence with challenges we met with our research, and his exceptional personality are truly remarkable. I will miss our many conversations about sports, particularly the Green Bay Packers and the University of Alabama football. I will especially miss our scientific conversations and the excitement I felt when solving challenges we faced in our research or discussing new project ideas. I am forever grateful for the knowledge and training I received under Professor Snowden, and I am excited to carry it forward in my professional career.

I would like to thank my dissertation committee members Professor Silas Blackstock, Professor Debra Dolliver, Professor Michael Jennings, and Professor Kevin Shaughnessy for their guidance in my graduate research, and excellent instruction in my course work. I am grateful to have been surrounded by these brilliant individuals, and for the knowledge I received from them.

This research would not have been possible without financial support. I am grateful to the National Science Foundation CAREER program (CHE-0847686), and to the University of Alabama Alumni Association (license tag fellowship) for their support in my research.

I have been fortunate to work with many great people and develop many friendships. I will miss the intellectual and often entertaining conversations I had with them that made my

graduate school experience enjoyable. More specifically, I would like to thank my present group members Yinghui Liu, Brent Wells, Kyle Black, Sydney Marchi, and Amarraj Chakraborty for their support and encouragement. I am also thankful for past group members Akil Foluke and Derek Wells for their support and friendship over the years. Much gratitude goes to former undergraduate researchers Meagan Thomas, Danny Smigielski, Haley Burhans, Christian Smith, Jason Snyder, Saige Miller, and Michael Luebtow for their research contributions. I owe a special note of appreciation to Brent Wells for his contributions toward the tetrahydropyran project. Finally, I would especially like to thank past group member Jesse Li for his help with research related issues, computer software issues, dissertation formatting, presentation formatting, driving me to the airport, letting me in the lab when I locked myself out at midnight..... and the list goes on. It has truly been a privilege to share an office and lab space with such a talented individual who I consider a close friend.

I am greatly appreciative of Dr. Qiaoli Liang for her assistance in collecting mass spectrometry and GC/MS data, and to Dr. Ken Belmore for his help with conducting NMR experiments and analyzing spectra.

I would also like to thank my close friends Adam Milner and Victor Alas for their encouragement and comic relief from my graduate studies, Alex Cruce and Jeff Semmes for listening to my complaints and sharing stories over a round of golf, and especially my beautiful girlfriend Allyson Golden for her unwavering support and encouragement as I have progressed through graduate school.

Finally, my deepest gratitude goes to my mother Robin Entrekin, my father Neal Entrekin, my brothers Shane and Chad Entrekin, and my sisters Ivy and Haley Entrekin. They have been a true inspiration for me to pursue my career aspirations.

TABLE OF CONTENTS

ABSTRACT	ii	
DEDICATION	iv	
LIST OF ABBREVIATIONS AND SYMBOLS	v	
ACKNOWLEDGMENTS	x	
LIST OF SCHEMES.....	xv	
LIST OF FIGURES	xviii	
LIST OF TABLES.....	xx	
CHAPTER 1: SYNTHESIS OF 2-METHOXY-3-AZIDO -5-METHYL- 6-GERANYL- 1,4-BENZOQUINONE	1	1
1.1 Background and Significance	1	
1.2 General Methods for Quinone Formation.....	4	
1.3 Planned Approach for the Synthesis of 2-methoxy-3-azido- 5-methyl-6-geranyl-1,4-benzoquinone	5	
1.3.1 Directed ortho-lithiation/alkylation	6	
1.3.2 Diels-Alder cyclization/alkylation/decyclization.....	7	
1.4 Results and Discussion	7	
1.5 Index of Chapter Compounds and numbers	15	
1.6 Experimental Details.....	15	
CHAPTER 2: SYNTHESIS OF POTENT CERT INHIBITOR (1<i>R</i>,3<i>S</i>)-HPA-12.....	20	
2.1 Background and Significance	20	
2.1.1 CERT Protein Mechanism of Action.....	21	
2.2 Applications of (1 <i>R</i> ,3 <i>S</i>)-HPA-12	22	
2.3 Analysis of Reported Syntheses.....	23	

2.4 Planned Approach for Synthesis of (1 <i>R</i> ,3 <i>S</i>)-HPA-12.....	31
2.5 Results and Discussion	32
2.6 Index of Chapter Compounds and numbers.....	35
2.7 Experimental Details.....	35
CHAPTER 3: CONSTRUCTION OF POLYSUBSTITUTED OXACYCLES BY A NOVEL JOCIC REACTION.....	44
3.1 Background and Significance	44
3.2 General Methods for Tetrahydropyran Formation.....	45
3.3 Relative Rates of Cyclization.....	49
3.4 Planned Approach for Formation of Polysubstituted Oxacycles	51
3.4.1 Olefin Functionalization by Ruthenium-Based Cross Metathesis: Historical Background.....	53
3.4.1.1 Olefin Types and Influencing Their Product Distributions	56
3.4.1.2 Ruthenium Catalysts and Their Reactivities.....	59
3.4.1.3 Undesired Olefin Isomerization.....	62
3.4.1.4 Suppression of Olefin Isomerization	66
3.4.2 Formation of Vicinal 1,2-Diols by Sharpless Asymmetric Dihydroxylation: Historical Background.....	68
3.4.2.1 Glycolate Ester Hydrolysis	74
3.4.2.2 Ligand Choice and Prediction of Stereochemical Outcomes.....	78
3.5 Results and Discussion	81
3.5.1 Formation of <i>syn</i> - and <i>anti</i> -1,3 Diols from (<i>R</i>)-Wynberg Lactone	81
3.5.2 Olefin Functionalization by Cross Metathesis.....	84

3.5.2.1 Use of Additives to Suppress Isomerization	86
3.5.3 Formation of Vicinal 1,2-Diols by Olefin Dihydroxylation	93
3.5.3.1 Enhancing Stereoselectivity in Terminal Mono-substituted Olefins	100
3.5.4 Epoxidation/Azidation of Terminal Mono-substituted Olefins	105
3.5.5 Formation of Polysubstituted Oxacycles by a Novel Jovic Reaction	109
3.6 Index of Chapter Compounds and numbers	118
3.7 Experimental Details	120
CHAPTER 4: REGIOSELECTIVE FORMATION OF TERMINAL ALKYLSULFANYL ALCOHOLS	164
4.1 Background and Significance	164
4.2 Planned Approach for formation of alkylsulfanyl alcohols	165
4.3 Results and Discussion	166
4.4 Future Directions	168
4.5 Index of Chapter Compounds and numbers	168
4.6 Experimental Details	168
Appendix	171
A1: ^1H , ^{13}C , ^{19}F , HSQC, HMBC, COSY, and NOE NMR Spectra of Reported Compounds	171

LIST OF SCHEMES

1.1 Mechanism for the photo-labeling of peptides with azidoquinol	#
1.2 Conceptualized synthetic approaches to azidoquinone 7	#
1.3 Installation of DMG's from 2-methoxy-5-methylphenol	#
1.4 Synthetic approach for the preparation of azidoquinone 7	#
2.1 Formation of 16 by a stereoselective Mannich reaction	#
2.2 Preparation of (1 <i>R</i> ,3 <i>S</i>)-HPA-12 from 16	#
2.3 Preparation of 25 by an enantioselective Mannich-type reaction	#
2.4 Preparation of 28 by an enantioselective Mannich reaction in aqueous media.....	#
2.5 Preparation of 21a through β -amido sulfoxide elaboration	#
2.6 Preparation of (1 <i>R</i> ,3 <i>S</i>)-HPA-12 featuring a CIAT approach.....	#
2.7 Preparation of (1 <i>R</i> ,3 <i>S</i>)-HPA-12 by <i>N</i> -demethylative rearrangement of isoxazolidines	#
2.8 Preparation of (1 <i>R</i> ,3 <i>S</i>)-HPA-12 from keto amino acid derivative 44	#
2.9 Conceptualized approach for synthesis of HPA-12	#
2.10 Preparation of (1 <i>R</i> ,3 <i>S</i>)-HPA-12 from (<i>S</i>)-Wynberg lactone.....	#
3.1 Condensation based approach to Prins-type cyclizations	#
3.2 Dallavalle's approach to (+)-spiroloxine	#
3.3 Oxo-diels alder cyclization to form dihydropyran 56	#
3.4 Oxy-Michael approach to preparation of tetrahydropyran 63	#

3.5 Carbocycle formation from diethyl bromoalkyl malonates	#
3.6 Preferential formation of a 6-membered oxacycle.....	#
3.7 Conceptualized approaches to tetrahydropyran 70	#
3.8 General mechanism for the Jovic reaction	#
3.9 Tetrahydropyran ring construction mechanism with (2 <i>R</i> , 4 <i>S</i> , 6 <i>S</i>) - 2, 4, 6, 7 – tetraol.....	#
3.10 Catalytic cycle in olefin metathesis	#
3.11 Olefin metathesis processes	#
3.12 Statistical distribution of products in a non-selective CM reaction.....	#
3.13 Selective CM reaction between type I and type II/III olefins	#
3.14 Catalytic CM intermediates	#
3.15 Formation of tetrasubstituted alkenes with 79	#
3.16 Proposed mechanism for formation of ruthenium hydride 86	#
3.17 Ruthenium hydride isomerization pathways.....	#
3.18 Phenol used as an additive in preparation of allylic alcohol 97	#
3.19 Osmium catalyzed dihydroxylation mechanism.....	#
3.20 Competing pathways in catalytic olefin dihydroxylation	#
3.21 Dihydroxylation catalytic cycle under biphasic conditions	#
3.22 Electrophilic cleavage mechanism with phenyl boronic acid	#
3.23 Brown allylation approach to olefins of type 67	#
3.24 Directed 1,3 reduction of allyl ketone 72a	#
3.25 Possible pathway leading to truncated byproducts	#

3.26 Alternate approach to preparation of tetraol 75aa	#
3.27 Preparation of pseudo-tetraols 75o from allylic alcohol 73a	#
3.28 Mechanism leading to furan byproduct 75ob	#
4.1 Mechanism leading to terminal alkylsulfanyl alcohols	#

LIST OF FIGURES

1.1 General structures of quinoids, quinones, ubiquinone, and ubiquinol	#
1.2 Isomers of quinone.....	#
1.3 Examples of strong directed metallation groups.....	#
1.4 <i>Ortho</i> lithiation/deuteration of 2a	#
1.5 Self-cyclization of geranyl bromide.....	#
2.1 General structures of ceramide, sphingomyelin where R represents alkyl chains of various fatty acids, and (1 <i>R</i> ,3 <i>S</i>)-HPA-12	#
3.1 Examples of natural products containing tetrahydropyran substructures	#
3.2 Examples of early catalysts featuring late transition metals	#
3.3 Alkylidene metathesis catalysts developed by Schrock and Grubbs	#
3.4 Alkylidene-based metathesis catalysts.....	#
3.5 Ruthenium decomposition products and hydride species	#
3.6 Hemilabile stabilization effect of phenol	#
3.7 Commercially available ligands and linkers used in dihydroxylation reactions.....	#
3.8 Asymmetric dihydroxylation stoichiometry	#
3.9 Asymmetric dihydroxylation in the presence of phenylboronic acid	#
3.10 Mnemonics for predicting enantiofacial selectivity.....	#
3.11 Convenient preparation of 1,3-diols by NaBH ₄ reduction	#

3.12 Nucleophilic addition to Wynberg lactone (R)- 47#	
3.13 Preparation of 74a from phenyl boronic ester 73aa#	
3.14 Attempted preparation of 73b from prenyl adduct 73ab#	
4.1 Examples of biologically active compounds bearing terminal alkylsulfanyl alcohols#	

LIST OF TABLES

1.1 Attempts at forming alkylated product 3	#
1.2 Preparation of <i>para</i> -quinone 9	#
1.3 Optimization of alkylation of 11	#
1.4 Optimization for formation of 7	#
2.1 Optimization studies for formation of lactone 50	#
3.1 Ring-Closing metathesis of diallyl ether	#
3.2 Recommended ligands for each class of olefin where R represents cinchona alkaloids DHQ or DHQD	#
3.3 Preparation of 74a using catalysts 78 or 79	#
3.4 Optimization conditions for preparation of 74a	#
3.5 Preparation of 73b	#
3.6 Preparation of functionalized olefins 74c-74k	#
3.7 Preparation of functionalized olefins 74l-74q	#
3.8 Optimization for dihydroxylation of 74a	#
3.9 Preparation of tetraols 75c-75h	#
3.10 Preparation of 75f under (a) “standard” versus (b) “acidic” conditions	#
3.11 Preparation of tetraols 75j-75m	#
3.12 Preparation of tetraols 75aa and 75ab	#
3.13 Preparation of 75aa and 75ab from boronic ester adduct 73aa	#

3.14 Boronic esters screened in the asymmetric dihydroxylation reaction.....#	#
3.15 Preparation of terminal alcohols from pre-formed boronic ester adducts#	#
3.16 Preparation of 75na and 75nb from 73c#	#
3.17 Preparation of azidotriol 75p#	#
4.1 Optimized preparation of 105 from trichloromethyl carbinol 104#	#

CHAPTER 1

SYNTHESIS OF 2-METHOXY-3-AZIDO-5-METHYL-6-GERANYL-1,4-BENZOQUINONE

1.1 Background and Significance

Quinoids are a family of compounds that possess a specific arrangement of alternating single and double bonds inside and outside of a six-membered ring (Figure 1.1A). Quinones (Figure 1.1B) are the largest class of the quinoid family, and are very common in nature.¹ Some of the more significant quinones in biological systems, such as ubiquinone (Figure 1.1C), contain terpenoid side chains that are anchored in the lipid phase of membranes.² Many biological processes depend on the intrinsic redox potential of quinones which allows transport of electrons between membrane bound components of electron transport chains. The shuttling of electrons creates a proton gradient on the outside of the membrane that serves as the driving force for ATP production.³

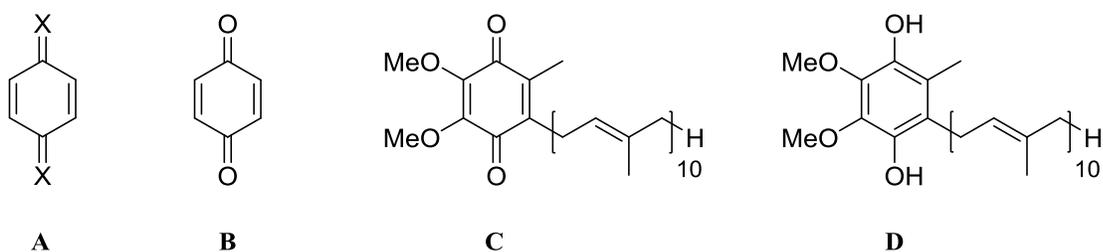


Figure 1.1: A: general structure of quinoids where X = C, N, O, S B: general structure of quinone C: ubiquinone D: ubiquinol

¹ Thompson, R. H. *Naturally occurring quinones. III. Recent Advances*. London. Chapman and Hall; 1987.

² Brunmark, A.; Cadenas, E. *Free Radical Biol. Med.* **1989**, 7, 435-477.

³ Nohl, H.; Gille, L.; Staniek, K. *Ann. N. Y. Acad. Sci.* **1998**, 854, 394-409.

The cytochrome bc1 (cyt bc1) complex is one of the membrane bound components that plays an essential role in establishing the proton motive force necessary for the production of ATP. Two substrate binding sites are within the cyt bc1 complex: Q_o, where ubiquinol (UQH₂) (Figure 1.1D) oxidation to ubiquinone (UQ) occurs, and Q₁, where UQ reduction to UQH₂ occurs.⁴ The transition of UQH₂ to UQ regularly leads to the production of semiquinone (SQ) radicals that, in the presence of oxygen, can potentially form damaging reactive oxygen species.⁵ Failure to inhibit the formation of reactive oxygen species, particularly superoxide, with SQ radicals can lead to oxidative stress and tissue damage.⁶ Due to the potential of superoxide production at the Q_o binding site of cyt bc1, the control of UQH₂ oxidation is of particular interest.⁴

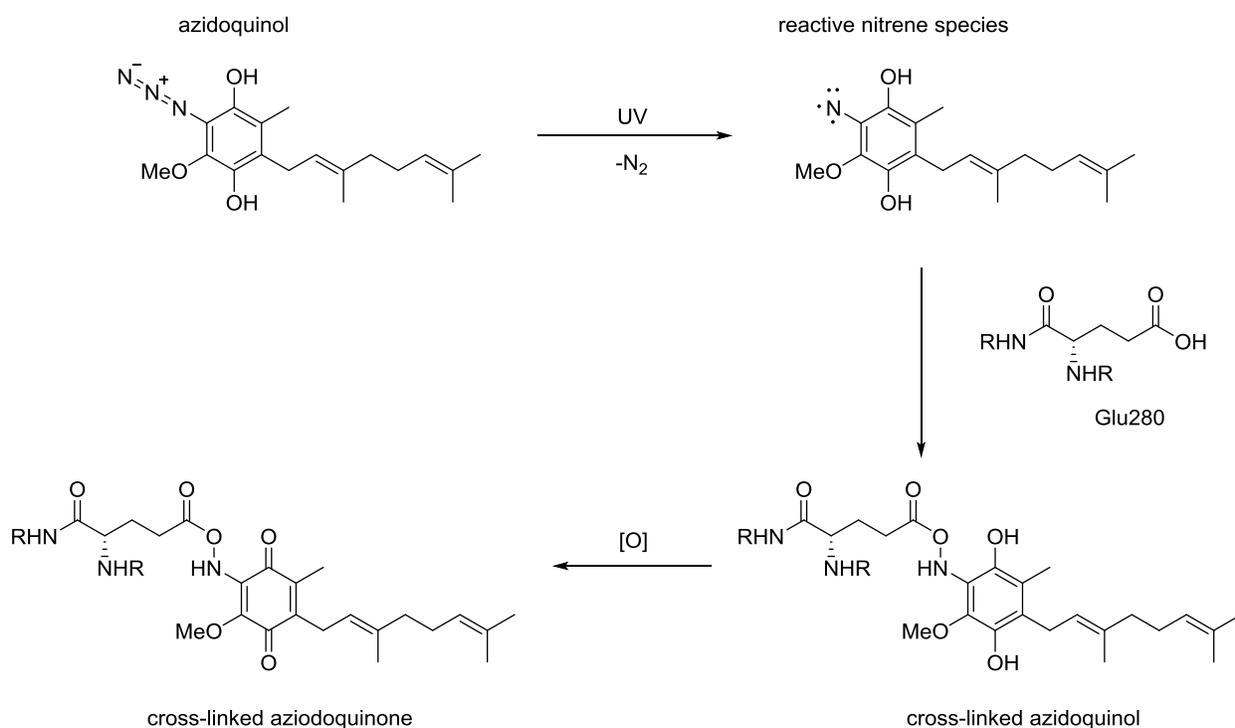
In attempts to gain a better understanding of the unique catalytic mechanism of quinol oxidation and the intermediates involved, the azidoquinone 2-methoxy-3-azido-5-methyl-6-geranyl-1,4-benzoquinone **7** was synthesized. The azidoquinone was to be used as a photo-reactive label to specifically identify peptides associated with the oxidation binding site. It was essential that the synthetic azidoquinone be similar structurally to that of the natural substrate in order to achieve effective labeling. The photo-labeling method involves illuminating high concentrations of the reduced azidoquinol in the presence of the peptide. Illumination causes loss of N₂, and formation of a reactive nitrene species. Subsequently, the nitrene-quinol covalently attaches to peptides located in the binding site. A possible mechanism for the peptide labeling process is shown in Scheme 1.1. The covalently labeled peptides can then be detected and

⁴ Cape, J. L.; Bowman, M. K.; Kramer, D. M. *J. Am. Chem. Soc.* **2005**, *127*, 4208-4215.

⁵ Muller, F. L.; Roberts, A. G.; Bowman, M. K.; Kramer, D. M. *Biochemistry* **2003**, *42*, 6493-6499.

⁶ Panaretakis, T.; Shabalina, I. G.; Grander, D.; Shoshan, M. C.; DePierre, J. W. *Toxicol. Appl. Pharmacol.* **2001**, *173*, 56-64.

analyzed through mass spectrometry.⁷ Being able to identify the peptides associated with the active site will offer insight to where the quinone is binding, and may explain what causes superoxide production. Another application of azidoquinones involves their ability to act as quinone binding site agonists or antagonists to prevent toxic radical generation. For this reason, quinone binding proteins have become attractive putative drug targets. Currently, there are still many cases in which the location and architecture of quinone binding sites are not entirely understood.⁸



Scheme 1.1: Mechanism for the photo-labeling of peptides with azidoquinol

⁷ Matsumoto, Y.; Murai, M.; Fujita, D.; Sakamoto, K.; Miyoshi, H.; Yoshida, M.; Mogi, T. *J. Biol. Chem.* **2006**, *281*, 1905-1912.

⁸ Pei, Z.; Gustavsson, T.; Roth, R.; Frejd, T.; Haegerhaell, C. *Bioorg. Med. Chem.* **2010**, *18*, 3457-3466.

1.2 General Methods for Quinone Formation

It was previously mentioned that quinones are common structural motifs found in a wide variety of naturally occurring compounds. Due to their importance in biological systems, several reactions to form quinones have been developed. One common approach involves the oxidation of phenols or alkyl aryl ethers. Several reagents including nitric acid,⁹ chromic acid, hydrogen peroxide or organic peroxides, ceric ammonium nitrate (CAN),¹⁰ potassium nitrosodisulfonate (Fremy's salt),¹¹ O₂,^{12,13} and others are capable of forming quinones.. The formation of *ortho*- or *para*-quinone isomers (Figure 1.2) is influenced by the presence or absence of substituents para- to the hydroxyl group on the aromatic ring. The *para*- isomer is often preferentially formed, except for cases where the *para*- position relative to the hydroxyl group is substituted. More specifically, *para*-alkyl phenols will form *ortho*-quinones.¹⁴ Having control over which isomer is formed is often desirable due to complications arising from separation of the isomers.

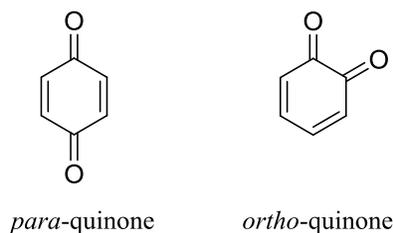


Figure 1.2: isomers of quinone

⁹ Nightingale, D. V. *Chem Rev.*, **1947**, *40*, 117.

¹⁰ Castagnoli Jr, N.; Jacob, P.; Callery, P. S.; Shulgin, A. T. *J. Org. Chem.* **1976**, *41*, 3627-3629.

¹¹ Fremy, E. *Ann. Chem. Phys.* **1845**, *15*, 408.

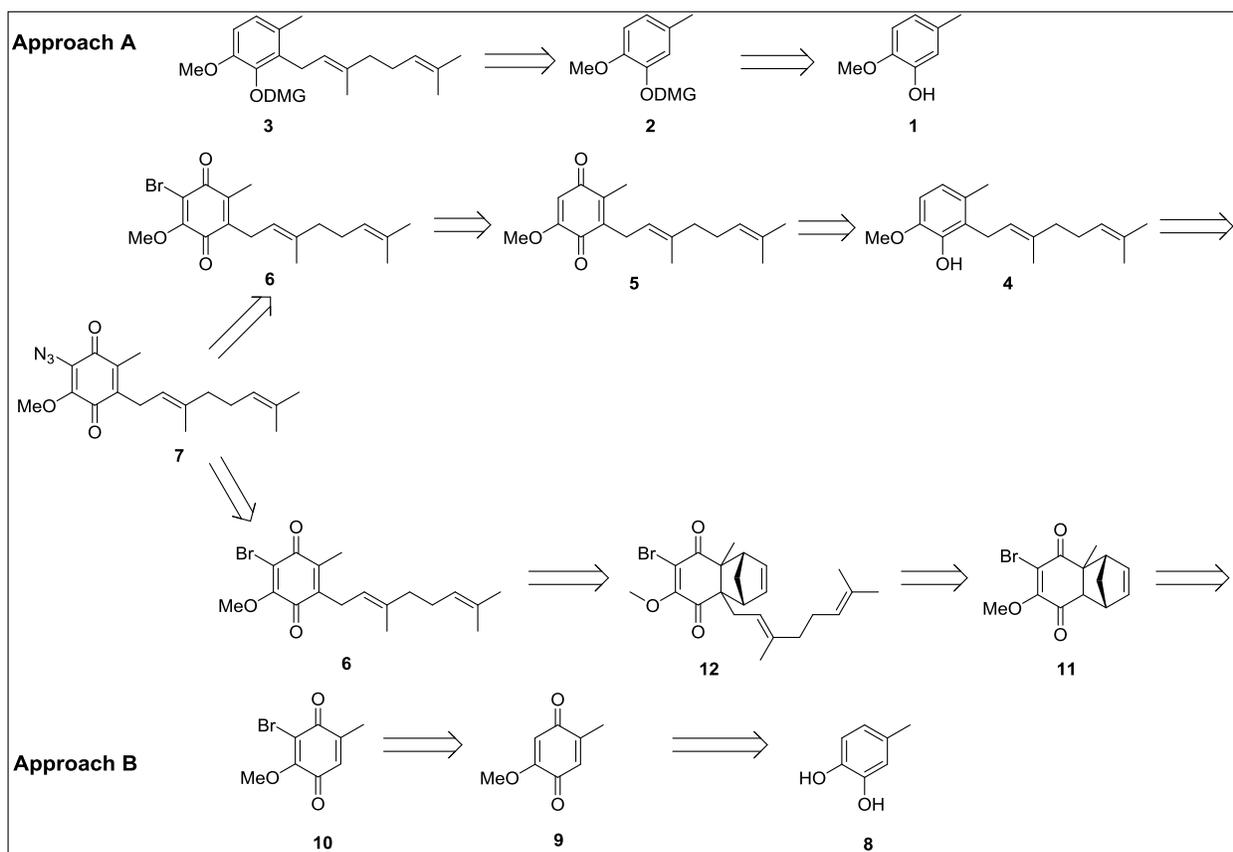
¹² (a) Kita, Y.; Higuchi, K. *J. Am. Chem. Soc.* **2001**, *123*, 3214-3222. (b) Kubo, A.; Saito, N.; Harada, S. Nishida, M.; Inouye, I. *Chem. Pharm. Bull.* **1995**, *43*, 777-782

¹³ Takizawa, Y.; Iwasa, Y.; Suzuki, T.; Miyaji, H. *Chem. Lett.* **1993**, 1863-1864.

¹⁴ Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229-246.

1.3 Planned Approach for the Synthesis of 2-methoxy-3-azido-5-methyl-6-geranyl-1,4-benzoquinone

The synthetic strategy for preparing azidoquinone **7** began with two conceptualized approaches (Scheme 1.2). The key step in the transformation is incorporation of the geranyl substituent on the ring. Approach A involved an ortho-directed lithiation/alkylation reaction. Approach B invoked a Diels-Alder approach, including cyclization, then subsequent alkylation/decyclization.



Scheme 1.2: Conceptualized synthetic approaches to azidoquinone **7**

1.3.1 Directed ortho-lithiation alkylation

Directed ortho-metallation is an alternate approach to traditional electrophilic aromatic substitution that effectively forms the ortho-substituted regioisomer instead of a mixture of ortho- and para- isomers.¹⁵ Aromatic substituents bearing Lewis basic functional groups can serve as ortho-directing groups upon treatment with an alkyl lithium reagent followed by a suitable electrophile. The Lewis basic moiety of the directed metalation group (DMG) coordinates to the lithium cation, resulting in deprotonation of the aromatic ring at the nearby ortho- position. Strong DMG's include amides, carbamate esters, sulfones, sulfoxides, oxazolines, methoxy methyl ethers and many others (Figure 1.3).¹⁶ The DMG's must possess some unique properties including being a good Lewis base capable of coordinating the lithium cation, but also relatively inert toward nucleophilic attack by the alkyl lithium species. Steric and electronic effects can both affect the outcome of the reaction and which regioisomer is formed. The ortho-lithiated arene can be quenched with a variety of electrophiles including aldehydes,¹⁷ ketones,¹⁸ tosyl azides,¹⁹ silyl halides,²⁰ alkyl halides,²¹ and others to furnish the desired regioisomer. Installing a

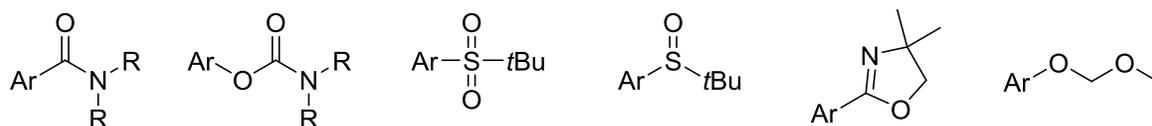


Figure 1.3: Examples of strong directed metalation groups

¹⁵ (a) Bebb, R. L.; Gilman, H. *J. Am. Chem. Soc.* **1939**, *61*, 106-109. (b) Fuhrmann, G.; Wittig, G. *Chem. Ber.* **1940**, *73*, 1197-1218.

¹⁶ Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.

¹⁷ Watanabe, M.; Sahara, M.; Kubo, M.; Furukawa, S.; Billedeau, R. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 742-747.

¹⁸ Pratt, S. A.; Goble, M. P.; Mulvaney, M. J.; Wuts, P. G. M. *Tet. Lett.* **2000**, *41*, 3559-3562.

¹⁹ Reed, J. N.; Snieckus, V. *Tet. Lett.* **1983**, *24*, 3795-3798.

²⁰ Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935-1937.

²¹ Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4386-4390.

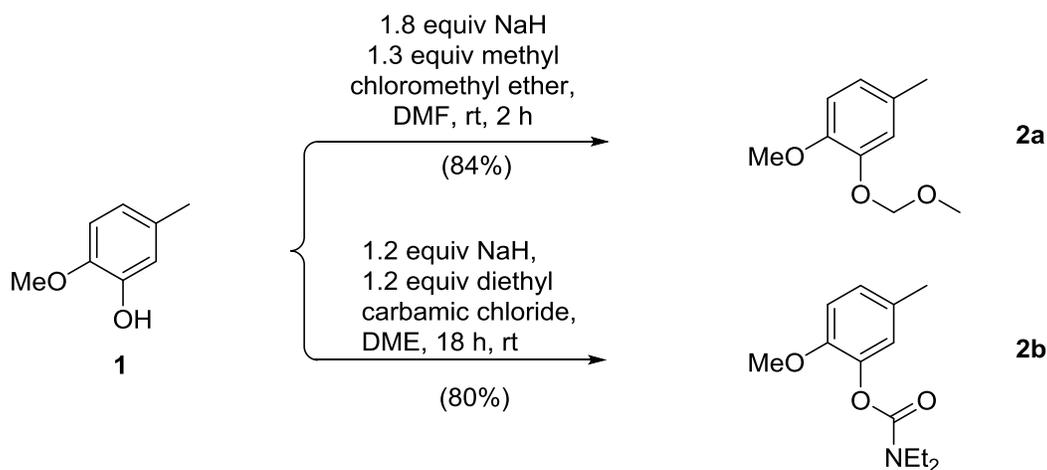
DMG on the phenolic oxygen atom of commercially available **1** (Scheme 1.2) followed by ortho lithiation and alkylation with geranyl bromide should afford the alkylated arene **3** in good yield.

1.3.2 Diels-Alder cyclization/alkylation/decyclization

An alternate approach to the formation of azidoquinone **7** employs a Diels-Alder approach to install the alkyl substituent on the ring (Scheme 1.2, Approach B).²² The formation of the Diels-Alder adduct **11** upon treatment with cyclopentadiene should generate an enolizable ketone at the free bridgehead carbon. Enolization, followed by alkylation and subsequent decyclization should be an effective method for incorporating the alkyl substituent onto the quinone.

1.4 Results and Discussion

Efforts towards the synthesis of azidoquinone **7** began with formation of directed ortho-metalation groups on the commercially available 2-methoxy-5-methylphenol **1**. We chose to install the methoxy methyl, and the *N,N*-diethyl carbamate DMG's because they are robust,



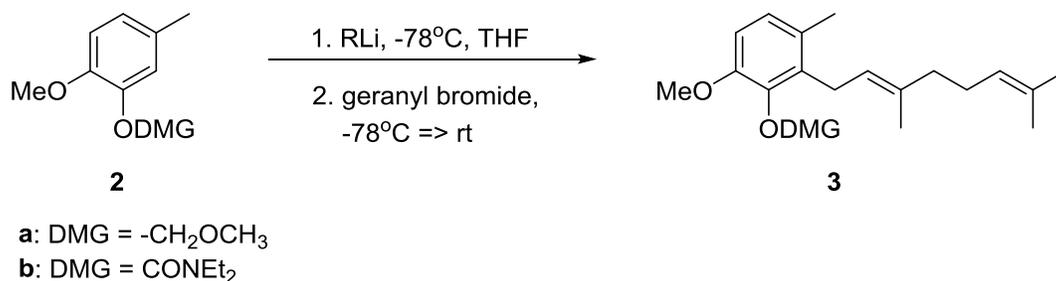
Scheme 1.3: Installation of DMG's from 2-methoxy-5-methylphenol

²² (a) Stowell, M. H. B.; Wang, G.; Day, M. W.; Chan, S. I. *J. Am. Chem. Soc.* **1998**, *120*, 1657-1664. (b) Lu, L.; Chen, F. *Synth. Commun.* **2004**, *34*, 4049-4053. (c) Merz, A.; Rauschel, M. *Synthesis* **1993**, 797-802.

strong ortho- directors, and generally unreactive toward nucleophiles. The two different DMG's were successfully installed as shown in Scheme 1.3. Materials **2a** and **2b** were convenient to handle and were indefinitely stable at room temperature.

Following successful installation of the DMG's, we attempted to form **3** by ortho-lithiation followed by alkylation with geranyl bromide (Table 1.1). Ideally, treatment of **2a** or **2b** at -78 °C with alkyl lithium, followed by addition of geranyl bromide should furnish the desired alkylated product **3**. A variety of conditions were employed, however, all attempts resulted in a complex mixture of products as well as recovered starting material and in some cases, phenol **1** was isolated.

Table 1.1: Attempts at forming alkylated product **3**



Entry	Substrate	RLi (equiv)	Geranyl bromide (equiv)	Yield
1	2a	<i>n</i> -BuLi (2.2)	6	<i>a, b</i>
2	2a	<i>n</i> -BuLi (2.2)	2.2	<i>a</i>
3	2a	<i>n</i> -BuLi (1.1)	1.1	<i>a, c</i>
4	2b	<i>sec</i> -BuLi (1.8)	1.8	<i>a, c</i>
5	2b	<i>sec</i> -BuLi (1.8)	1.8	<i>a, c</i>

^a a complex mixture of products was formed ^b phenol **1** was isolated from the reaction mixture ^c 80-90% of the starting material was recovered

In an attempt to determine why the reaction was unsuccessful, a test reaction was conducted where substrate **2a** was treated with *n*-BuLi at -78 °C and quenched with D₂O (Figure 1.4). The ¹H NMR of the crude mixture revealed that approximately 98% of the substrate had been converted to the deuterated product **3b** at the desired ortho- position. These results suggested that complications with the reaction were most likely related to the geranyl bromide reagent and not to the directed ortho- metallation step.

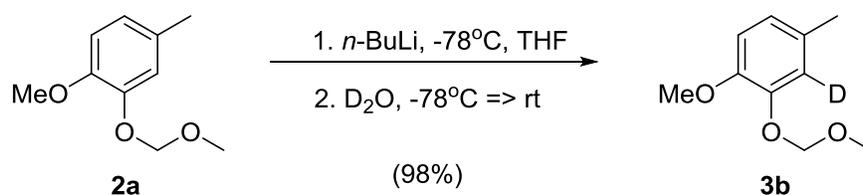


Figure 1.4: *ortho* lithiation/deuteration of **2a**

Work done by Yamamoto et al provided some insight as to what might be happening with geranyl bromide in solution.²³ We reasoned that geranyl bromide might be undergoing an intramolecular cyclization forming limonene and other cyclic byproducts (Figure 1.5). Following cyclization, HBr is generated which can subsequently quench the lithiated arene as well as cleave the aryl ethers. Due to the lack of success of forming azidoquinone **7** with the *ortho* lithiation/alkylation approach, all future efforts were directed at preparing azidoquinone **7** with the alternate Diels-Alder approach (Scheme 1.2, Approach B).

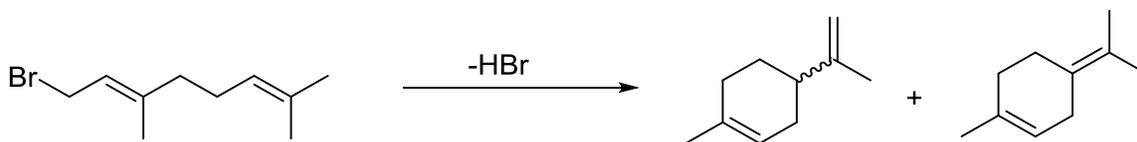
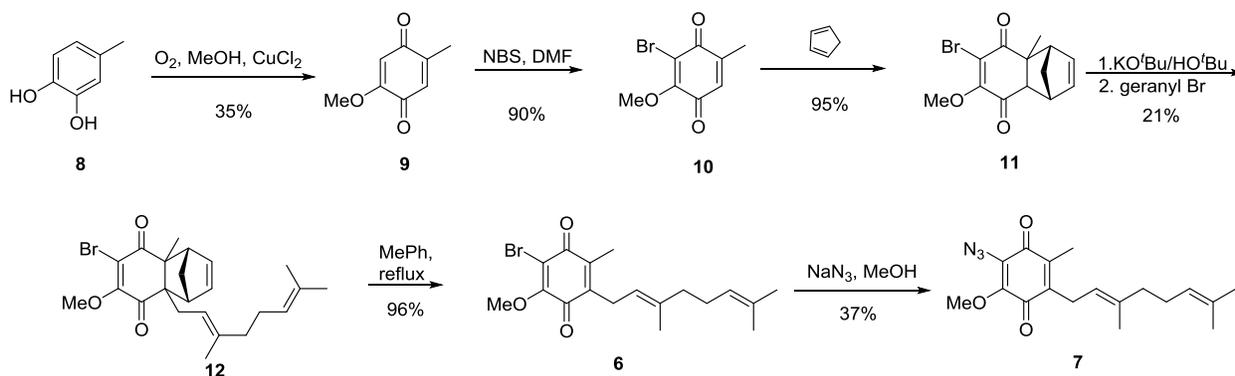


Figure 1.5: self-cyclization of geranyl bromide

²³ (a) Yamamoto, H.; Sakane, S.; Fujiwara, J.; Maruoka, K. *J. Am. Chem. Soc.* **1983**, *105*, 6154-6155.
 (b) Yamamoto, H.; Sakane, S.; Fujiwara, J.; Maruoka, K. *Tetrahedron* **1986**, *42*, 2193-2201.

Approach B led to the successful synthesis of azidoquinone **7** in 6 steps (Scheme 1.4).

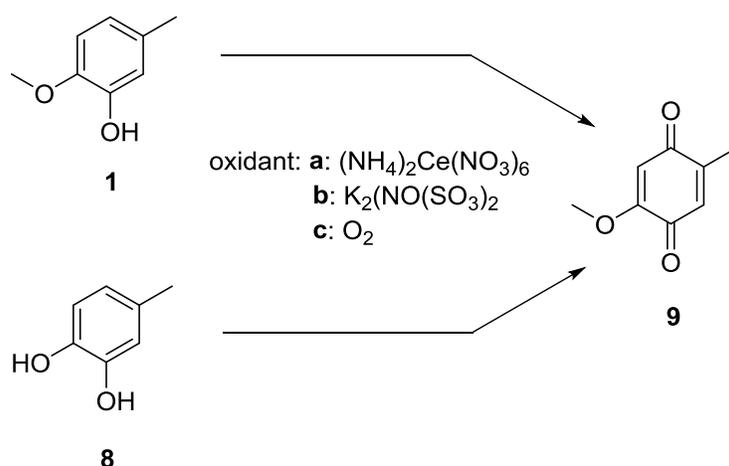
We began by determining optimal oxidation conditions for the preparation of *para*-quinone **9** (Table 1.2). Different reagents including CAN and Fremy's salt were employed following



Scheme 1.4: synthetic approach for the preparation of azidoquinone **7**

procedures described in the literature.²⁴ Unfortunately, all attempts at preparing **9** from **1** resulted in incomplete consumption of starting material, an inseparable mixture of the *ortho* and *para* quinone isomers, or both. A slightly modified approach led to the most successful results. In a $\text{Cu}^{2+}/\text{O}_2$ -catalyzed oxidation of commercially available 4-methylcatechol **8** in methanol, **9** was obtained in 35% yield.¹³ Presumably, the initial oxidation results in formation of the corresponding hydroxy quinone, which undergoes subsequent conjugate addition-elimination with methanol to afford the desired methoxy adduct. The low yield was attributed, at least in part, to problems associated with the work-up; thick, dark emulsions formed while trying to remove the copper salts, making extractions difficult. Fortunately, however, the transformation resulted in only minor amounts of the *ortho*-quinone isomer, and was easily purified by silica gel chromatography.

²⁴ (a) Hua, D. H.; Tamura, M.; Huang, X.; Stephany, H. A.; Helfrich, B. A. *J. Org. Chem.* **2002**, *67*, 2907-2912. (b) Kozikowski, A. P.; Sugiyama, K.; Springer, J. P. *J. Org. Chem.* **1981**, *46*, 2428-2429.

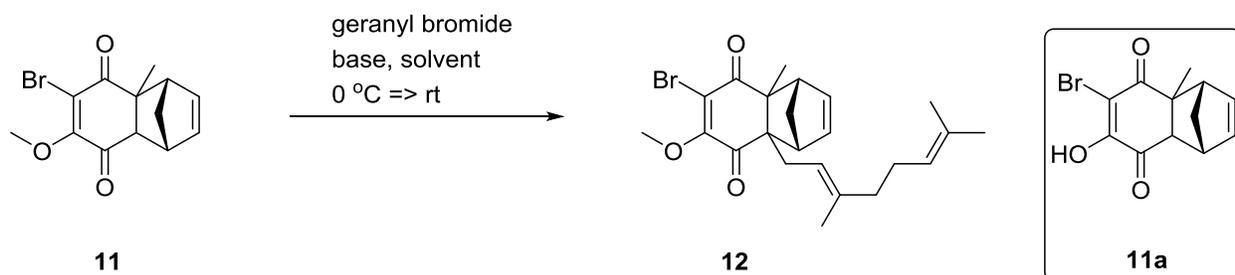
Table 1.2: preparation of *para*-quinone **9**

Entry	Substrate	Oxidant (equiv)	Catalyst (equiv)	Solvent	Isolated yield of 9 (%)
1	1	a (2.5)	-	MeCN/H ₂ O	18
2	1	a (2.5)	-	MeCN/H ₂ O	20
3	1	a (2.5)	-	MeCN/H ₂ O	16
4	1	a (5)	-	MeCN/H ₂ O/dioxane	NR
5	1	a (2.5)	-	MeCN/H ₂ O	15
6	1	b (2.3)	-	Heptane/H ₂ O	3
7	1	b (2.3)	-	MTBE/H ₂ O	NR
8	1	b (3)	-	Acetone/H ₂ O	9
9	8	c (excess)	CuCl ₂ (0.5)	MeOH	35

Bromination of **9** with *N*-bromosuccinimide in dimethylformamide proceeded in 90% yield with high regioselectivity. With brominated quinone **10** in hand, we proceeded with the Diels-Alder approach to install the alkyl substituent on the ring. The approach and methods utilized are similar to those previously reported.²² Formation of the Diels-Alder cycloadduct **11**,

followed by alkylation and subsequent retro-Diels-Alder reaction affords **6** in 19% overall yield. The Diels-Alder adduct **11** was easily prepared by treating **10** with an excess of freshly distilled cyclopentadiene in DCM at room temperature. A variety of different conditions were tested in

Table 1.3: optimization of alkylation of **11**



Entry	geranyl bromide (equiv)	Base (equiv)	Time (h)	Solvent	Isolated yield of 12 (%)
1	1.5	KOtBu (1.5)	48	THF	NR
2	1.5	KOtBu (1.5)	24	THF	NR
3	4	KOtBu (1.5)	24	THF	NR
4	1.5	NaH (1.5)	16	THF	<i>a</i>
5	2	NaH/ <i>t</i> BuOH (2)	72	THF	<i>a</i>
6	allyl bromide (1.2)	NaH (1.2)	40	THF	<i>a</i>
7	allyl bromide (1.2)	NaH/ <i>t</i> BuOH (1.2)	70	THF	<i>a</i>
8	4	NaH/MeOH (1.5)	40	MePh	NR
9	4	neat NaH/MeOH (1.5)	18	MePh	NR
10	4	NaH (1.5)	48	neat	NR
11	1	NaDMSO (1.5)	24	DMSO	<i>b</i>

12	1.5	LiHMDS (1.1)	48	THF	11
13	1.5	KOtBu/ <i>t</i> BuOH (1.1)	24	MePh	9
14	4	KOtBu/ <i>t</i> BuOH (1.1)	3	MePh	21
15	10	KOtBu/ <i>t</i> BuOH (1.1)	3	MePh	20
16	4 ^c	KOtBu/ <i>t</i> BuOH (1.1)	5	MePh	18

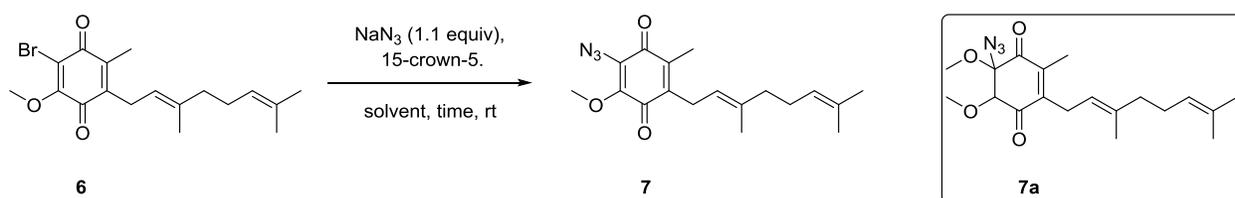
^a **11a** was isolated from the aqueous phase post workup ^b a complex mixture of products was formed ^c geranyl bromide was added drop-wise over 2 hours

the alkylation step (Table 1.3). Interestingly, when NaH was used as the base, a significant amount of byproduct **11a** was isolated following acidification of the aqueous phase during the workup (entries 4-7). The best results were obtained when **11** was treated with KOtBu and 4 equivalents of geranyl bromide in a *tert*-butanol/toluene for 3 hours (entry 14). There appeared to be no advantage to using a larger excess of geranyl bromide, or adding it drop-wise over 2 hours (entries 15 and 16). The low yield in the alkylation was attributed to complications with geranyl bromide that were previously mentioned. Fortunately, we were able to obtain the desired product from the complicated mixture of materials in 21% isolated yield. Heating the alkylated product **12** in refluxing toluene through a retro Diels-Alder reaction afforded the decyclized quinone **6** in 96% yield.

The final step in the synthesis of azidoquinone **7** involved treatment of **6** with sodium azide in methanol. Methanol appeared necessary to solubilize sodium azide, however, it also led to the formation of the byproduct **7a**. Attempts at forming **7** in other polar aprotic solvents were unsuccessful (Table 1.4). It was critical to closely monitor the reaction to achieve maximum yield of product while limiting the amount of byproduct formation. The maximum yield of 37% was obtained when **6** was treated with 1.1 equivalents of sodium azide, a catalytic amount of 15-crown-5, and stirred for 24 hours at room temperature in methanol. It is important to note that

the azidoquinone is to be used as a photo-reactive label in enzyme studies. Logically, installation of the azido group was saved for the last step in the synthesis to limit its light exposure and potential decomposition. Special care had to be taken to ensure that the azidoquinone and the immediate precursors were not exposed to light.

Table 1.4: optimization for formation of **7**



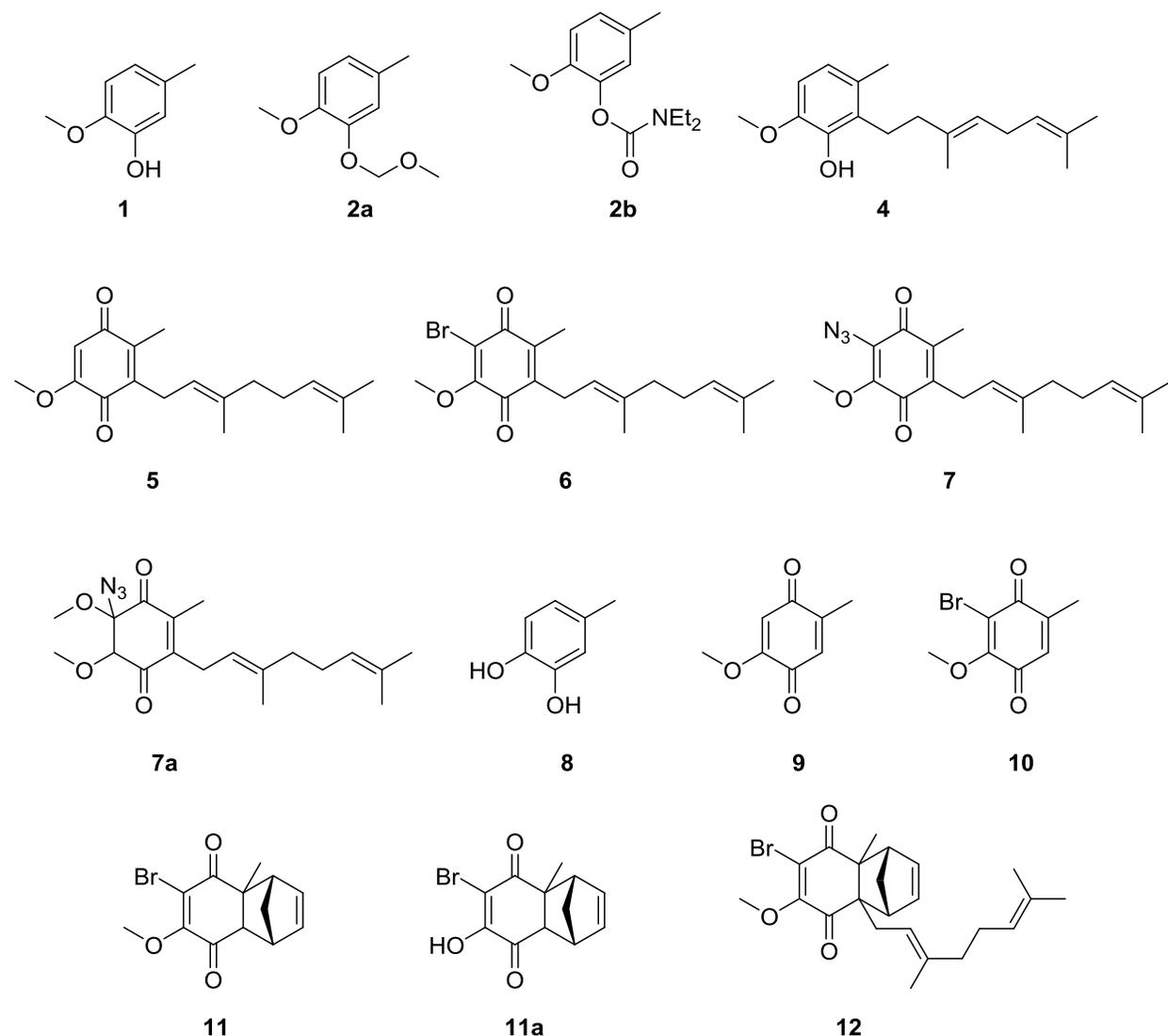
Entry	15-crown-5 (equiv)	Time (h)	Solvent	Isolated yield of 7 (%)
1	0	3	MeOH	25 ^a
2	0	24	DCM/DMF	NR
3	0	24	MeCN/DMF	NR
4	0	24	DMF	NR
5	0	24	CF ₃ CH ₂ OH	NR
6	0.11	6	MeOH	27 ^a
7	0.11	24	MeOH	37 ^a
8	0.22	24	MeOH	31 ^a

^a **7a** was formed as a byproduct

In conclusion, azidoquinone **7** was synthesized in six steps from commercially available 4-methylcatechol. The key step involving incorporation of the alkyl substituent invoked a Diels-Alder approach, including cyclization, then subsequent alkylation/decyclization. Initial studies of

cyt bc1 with azidoquinone **7** by the Michael Bowman research group have been promising, but mass spectrometry results have been inconclusive.²⁵

1.5 Index of Chapter Compounds and Numbers



1.6 Experimental Details

¹H and ¹³C NMR spectra were recorded on Bruker instruments at 360, 500, or 600 MHz and 90 or 125 MHz, respectively. Chemical shifts were referenced to acetone-*d*₆ (δ = 2.05 and 30.83) or CDCl₃ (δ = 7.26 and 77.0). Mass spectra were recorded on an AutoSpec-Ultima_NT

²⁵ Personal communication; Professor Michael Bowman and Preethi Vennam, December, 2012.

mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a MelTemp 1001D capillary melting point apparatus and are uncorrected. Ultrasonication was conducted with a Bransonic 2510R-DTH ultrasonic cleaner. IR samples were prepared by dissolving the pure material in a small amount of a suitable aprotic solvent. A small drop of the concentrated solution was placed on a KBr plate, and the solvent was evaporated completely. A second KBr plate was placed on top of the first plate and rotated by a quarter turn to make an even film of the material between the plates. IR spectra were recorded on a Jasco FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm) or KMnO₄ staining. Commercial cyclopentadiene was distilled immediately before use by following the procedure outlined by Wagner and Hunt.²⁶ Commercially available alkyl lithium reagents were titrated against *N*-benzylbenzamide.²⁷ THF was freshly distilled from a sodium benzophenone ketyl radical solution. All other commercially available reagents were used as received.

2-methoxy-5-methylcyclohexa-2,5-diene-1,4-dione (9)

To a dry 500 mL, 3-neck round-bottom flask was added anhydrous CuCl₂ (1 g, 7.44 mmol) and anhydrous MeOH (100 mL). The solution was purged with oxygen for 30 min. After 30 min, a solution of 4-methylcatechol (2 g, 16.11 mmol) in anhydrous MeOH (40 mL) was added to the reaction flask by cannula, and a reflux condenser was attached. The mixture was heated to 60 °C, and stirred with oxygen bubbling for 20 h. The solution was cooled to rt, and methanol was removed under reduced pressure. The crude mixture was diluted with DI H₂O (100 mL), and extracted with CH₂Cl₂ (5 x 50 mL). The organic layers were then dried (Na₂SO₄) and

²⁶ Wagner, E. C.; Hunt, W. C. *Chem. Commun.* **1951**, 28, 309.

²⁷ Burchat, A. F.; Chong, J. M.; Nielson, N. *J. Organomet. Chem.* **1997**, 542, 281.

concentrated. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 9:1) to obtain **9** (858 mg, 5.64 mmol, 35%) as yellow crystals; mp 169-170 °C. ¹H NMR (360 Hz, CDCl₃): δ = 6.55 (q, *J* = 1.6 Hz, 1 H), 5.93 (s, 1 H), 3.82 (s, 3 H), 2.07 (d, *J* = 1.6 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 187.6, 182.1, 158.7, 146.8, 131.3, 107.6, 56.2, 15.7.

3-bromo-2-methoxy-5-methylcyclohexa-2,5-diene-1,4-dione (10)

To a dry 250 mL, 3-neck round-bottom flask protected from light was added anhydrous *p*-quinone **9** (850 mg, 5.6 mmol) and anhydrous DMF (116 mL). The reaction flask was fit with a reflux condenser, and *N*-bromosuccinimide (1.24 g, 7 mmol) was added. The mixture was heated to 40 °C, and stirred under argon for 24 h. After 24 h, the mixture was cooled to rt, diluted with Et₂O (100 mL), and washed with DI H₂O (5 x 75 mL). The organic layers were then dried (Na₂SO₄) and concentrated. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 9:1) to obtain **10** (1.16 g, 5.02 mmol, 90%) as an orange solid. ¹H NMR (360 Hz, CDCl₃): δ = 6.50 (q, *J* = 1.6 Hz, 1 H), 4.19 (s, 3 H), 2.10 (d, *J* = 1.6 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 181.2, 180.7, 156.8, 145.8, 131.3, 118.2, 61.5, 16.3.

6-bromo-7-methoxy-4a-methyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione (11)

To a dry 25 mL, 2-neck round-bottom flask protected from light was added bromoquinone **10** (900 mg, 3.90 mmol) and CH₂Cl₂ (5 mL). Freshly distilled cyclopentadiene (4.97 mL, 66.2 mmol) was added, and the mixture was stirred under argon at rt for 42 h. After 42 h, CH₂Cl₂ and cyclopentadiene were removed under reduced pressure. The crude product was purified by silica gel chromatography (hexanes–Et₂O, 9:1) to obtain **11** (1.10 g, 3.70 mmol, 95%) as an off-white solid. ¹H NMR (360 Hz, CDCl₃): δ = 6.13 (dd, *J* = 2.9, 5.6 Hz, 1 H), 6.00

(dd, $J = 2.8, 5.6$ Hz, 1 H), 4.10 (s, 3 H), 3.45–3.40 (m, 1 H), 3.13–3.09 (m, 1 H), 2.89 (d, $J = 3.9$ Hz, 1 H), 1.72–1.67 (m, 1 H), 1.56 (dt, $J = 1.7, 9.2$ Hz, 1 H), 1.51 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 194.7, 192.4, 161.7, 138.5, 134.5, 125.5, 60.9, 58.0, 53.8, 53.7, 48.7, 46.3, 27.0$.

(E)-6-bromo-8a-(3,7-dimethylocta-2,6-dien-1-yl)-7-methoxy-4a-methyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione (12)

To a dry 25 mL, 2-neck round-bottom flask protected from light was added Diels-Alder adduct **11** (475 mg, 1.60 mmol) and anhydrous MePh-*t*BuOH (1.33 mL:4.00 mL). Geranyl bromide (1.27 mL, 6.40 mmol) was added, and the mixture was cooled to 0 °C. KO*t*Bu (197 mg, 1.76 mmol) in anhydrous *t*BuOH (1.76 mL) was added drop-wise by syringe. The mixture was warmed to rt, and stirred under argon for 3 h. The reaction was quenched with saturated NH_4Cl (25 mL), and extracted with Et_2O (5 x 25 mL). The organic layers were then dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 20:1) to obtain **12** (146 mg, 0.337 mmol, 21%) as a brown oil. ^1H NMR (360 Hz, CDCl_3): $\delta = 6.06$ (t, $J = 1.8$ Hz, 2 H), 5.15–5.08 (m, 1 H), 5.07–5.01 (m, 1 H), 4.00 (s, 3 H), 3.15–3.11 (m, 1 H), 3.09–3.05 (m, 1 H), 2.72 (dd, $J = 8.1, 15.3$ Hz, 1 H), 2.49 (dd, $J = 5.7, 15.3$ Hz, 1 H), 2.07–1.93 (m, 4 H), 1.82–1.77 (m, 1 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 1.52 (s, 3H), 1.51–1.47 (m, 1 H).

(E)-2-bromo-5-(3,7-dimethylocta-2,6-dien-1-yl)-3-methoxy-6-methylcyclohexa-2,5-diene-1,4-dione (6)

To a dry 10 mL, 2-neck round-bottom flask protected from light equipped with a reflux condenser was added alkylated Diels-Alder adduct **12** (250 mg, 0.58 mmol) and anhydrous MePh (1.92mL). The mixture was heated to reflux for 3 h. After 3 h, the mixture was cooled to

rt, and MePh was removed under reduced pressure. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 100:1) to obtain **6** (204 mg, 0.555 mmol, 96%) as a reddish-brown oil. ¹H NMR (360 Hz, CDCl₃): δ = 5.05–4.99 (m, 1 H), 4.94–4.89 (m, 1 H), 4.16 (s, 3 H), 3.21 (d, *J* = 6.9 Hz, 2 H), 2.09 (s, 3 H), 2.07–1.93 (m, 4 H), 1.73 (s, 3 H), 1.64 (s, 3 H), 1.57 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 181.8, 181.0, 156.9, 142.0, 140.8, 138.0, 131.6, 123.9, 118.5, 117.9, 61.5, 39.6, 26.5, 25.6, 25.4, 17.6, 16.3, 13.0.

(*E*)-2-azido-5-(3,7-dimethylocta-2,6-dien-1-yl)-3-methoxy-6-methylcyclohexa-2,5-diene-1,4-dione (7)

Quinone **6** (96 mg, 0.26 mmol) and 15-crown-5 (11 μl, 58 μmol) were added to a dry 10 mL round-bottom flask and diluted with anhydrous MeOH (0.87 mL). NaN₃ (19 mg, 0.29 mmol) (CAUTION: may explode if ground or contacted by metal surfaces) was added, and the mixture was stirred at rt under argon for 24 h. After 24 h, MeOH was removed under reduced pressure. The crude product was purified by silica gel chromatography (CH₂Cl₂–MePh 2:3) to obtain **7** (32 mg, 0.097 mmol, 37%) as a red oil. IR (KBr): 2524, 2853, 2115, 1652, 1603, 1444, 1292 cm⁻¹. ¹H NMR (360 Hz, CDCl₃): δ = 5.05–4.98 (m, 1 H), 4.94–4.86 (m, 1 H), 4.06 (s, 3 H), 3.18 (d, *J* = 7.1 Hz, 2 H), 2.03 (s, 3 H), 2.06–1.90 (m, 4 H), 1.72 (s, 3 H), 1.64 (s, 3 H), 1.57 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 183.8, 181.7, 144.8, 142.7, 139.1, 137.9, 131.6, 126.9, 123.9, 118.6. MS (EI): *m/z* = 330.2 [*M* + *H*]. HRMS (EI): *m/z* [*M* + *H*] calcd for C₁₈H₂₄N₃O₃: 330.1782; found: 330.178

CHAPTER 2

SYNTHESIS OF POTENT CERT INHIBITOR (1R,3S)-HPA-12

2.1 Background and Significance

The biosynthesis and translocation of lipids are crucial processes for lipid-mediated signaling. In eukaryotic cells, transport vesicles are responsible for trafficking and delivering integral membrane proteins to the correct organelles; however, it has been suggested that various types of lipids synthesized in the endoplasmic reticulum (ER) are delegated to the organelles by non-vesicular mechanisms.²⁸ In mammalian cells, ceramide synthesis occurs in the endoplasmic reticulum and ceramide is transported to the Golgi apparatus for enzymatic conversion to sphingomyelin by an ATP-dependent pathway (Figure 2.1).²⁹ Ceramide is an important contributor in many vital roles in intracellular signaling including cell growth regulation, senescence and apoptosis, and roles related to inflammatory responses.³⁰ The vitality of ceramide analogues to cell signaling processes and autophagy have made them particularly interesting as potential anticancer agents.³¹ Sphingomyelin also plays a part in several vital roles: Sphingomyelin aids in formation of lipid bilayers with unique surface characteristics and

²⁸ (a) Chen, Y. A.; Scheller, R. H. *Nature Rev. Mol. Cell. Biol.* **2001**, *2*, 98-106. (b) Zerial, M.; McBride, H. *Nature Rev. Mol. Cell. Biol.* **2001**, *2*, 107-117.

²⁹ (a) Hanada, K.; Kumagai, K.; Yasuda, S.; Miura, Y.; Kawano, M.; Fukasawa, M.; Nishijima, M. *Nature (London)* **2003**, *426*, 803. (b) Hanada, K.; Kumagai, K.; Tomishige, N.; Kawano, M. *Biochim. Biophys. Acta.* **2007**, *1771*, 644. (c) Merrill, A. H. Jr. *Chem Rev.* **2011**, *111*, 6387.

³⁰ For a review of cell signaling by ceramides, see: (a) Bartke, N.; Hannun, Y. A. *J. Lipid Res.* **2009**, *50* (Suppl), S91 (b) Zeidan, Y. H.; Hannun, Y. A. *Curr. Mol. Med.* **2010**, *10*, 454.

³¹ (a) Ogretmen, B.; Hannun, Y. A. *Nat. Rev. Cancer* **2004**, *4*, 604. (b) Oskouian, B.; Saba, J. D. *Adv. Exp. Med. Biol.* **2010**, *688*, 185. (c) Fox, T. E.; Finnegan, C. M.; Blumenthal, R.; Kester, M. *Cell. Mol. Life Sci.* **2006**, *63*, 1017.

fluidity,³² participates in cellular signaling and membrane dynamics,³³ and helps regulate cell growth and apoptosis among others. Ceramide transport protein (CERT) has been identified as the protein that mediates transportation of ceramide to the Golgi compartment.

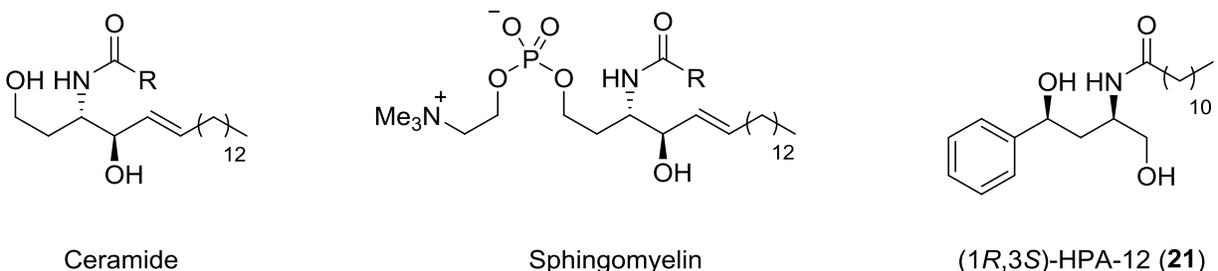


Figure 2.1: General structures of ceramide, sphingomyelin where R represents alkyl chains of various fatty acids, and (1R,3S)-HPA-12

2.1.1 CERT Protein Mechanism of Action

CERT is a hydrophilic 68-kDa protein containing several functional domains including the following: a ~ 120 residue region which forms a pleckstrin homology (PH) domain at the amino terminus, a ~ 230 residue region that forms a steroidogenic acute regulatory protein (StAR)-related START domain at the carboxyl terminus, and a middle region (MR) containing ~ 250 amino acid residues with a critical binding motif (FFAT). The PH domain commonly consists of a seven-stranded β -sandwich moiety and an α -helix at the C-terminus.³⁴ They are well known for effectively binding phosphoinositides through an electrostatic interaction between the phosphoinositides and a positively charged surface of the PH domain. Specifically, CERT is able to bind phosphoinositide phosphates (PIPs) located on the cytosolic side of organelle membrane bilayers in the Golgi apparatus.³⁵ In addition, GTP-binding protein interactions are another factor

³² Hannun, Y. A.; Obeid, L. M. *Nat. Rev. Mol. Cell. Biol.* **2008**, *9*, 139.

³³ Goni, F. M.; Alonso, A. *Biochim. Biophys. Acta.* **2009**, *1788*, 169.

³⁴ Lemmon, M. A.; Ferguson, K. M. *Biochem. J.* **2000**, *350*, 1-18.

³⁵ (a) Auger, K. R.; Serunian, L. A.; Soltoff, S. P.; Libby, P.; Cantley, L. C.; *Cell* **1989**, *57*, 167-175. (b) Bunce, C. M.; French, P. J.; Allen, P.; Mountford, J. C.; Moor, B.; Greaves, M. F.; Michell, R. H.; Brown, G. *Biochem. J.* **1993**, *289*, 667-673.

leading to effective binding of the PH domain with PIPs in the Golgi apparatus.³⁶ START domains contain ~ 210 amino acid residues and are commonly known for mediating cholesterol transportation between the outer and inner membranes in mitochondria for steroid hormone production.³⁷ Ceramide is highly hydrophobic due to the two aliphatic chains it possesses and unsurprisingly, is able to firmly anchor itself in cell membranes. The START domain of CERT is able to efficiently and selectively extract ceramide from cell membranes and facilitate its delivery to other membranes.²⁹ The elucidation of a co-crystal structure of the START domain of CERT complexed with ceramide reveals the overall structure of the domain, and suggests how CERT is able to selectively facilitate the intermembrane transportation of ceramide.³⁸ The middle region of the CERT protein contains an FFAT motif that interacts with the VAP protein of the endoplasmic reticulum. The VAP and FFAT peptides bind primarily through a hydrophobic interaction that allows for effective trafficking of ceramide to the cytosol of the ER.³⁹

2.2 Applications of (1R,3S)-HPA-12

The ceramide analog *N*- [(1R,3S)-3-hydroxy-1-(hydroxymethyl)-3-phenylpropyl]dodecamide (**21**, Figure 2.1) has been used as a valuable tool for determining metabolic pathways and the roles of sphingolipids in cultured cells and animals. (1R,3S)-HPA-12 is a potent inhibitor of the ceramide trafficking protein CERT (IC₅₀ = 50 nM) and was discovered and studied extensively by Kobayashi and Hanada.⁴⁰ The potent effects of (1R,3S)-HPA-12 have

³⁶ Levine, T. P.; Munro, S. *Curr. Biol.* **2002**, *12*, 695-704.

³⁷ (a) Christenson, L. K.; Strauss III, J. F. *Biochim. Biophys. Acta.* **2000**, *1529*, 175-187. (b) Stocco, D. M. *Annu. Rev. Physiol.* **2001**, *63*, 193-213

³⁸ Kudo, N.; Kumagai, K.; Tomishige, N.; Yamaji, T.; Wakatsuki, M.; Nishijima, K.; Hanada, R. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 488-493.

³⁹ Kaiser, S. E.; Brickner, J. H.; Reilein, A. R.; Fenn, T. D.; Walter, P.; Brunger, A. T. *Structure* **2005**, *13*, 1035-1045.

⁴⁰ (a) Yasuda, S.; Kitagawa, H.; Ueno, M.; Ishitani, H.; Fukasawa, M.; Nishijima, M.; Kobayashi, S.; Hanada, K. *J. Biol. Chem.* **2001**, *276*, 43994. (b) Nakamura, Y.; Matsubara, R.; Kitagawa, H.; Kobayashi, S.; Kumagai, K.; Yasuda, S.; Hanada, K. *J. Med. Chem.* **2003**, *46*, 3688. (c) Kumagai, K.; Yasuda, S.; Okemoto, K.; Nishijima, M.; Kobayashi, S.; Hanada, K. *J. Biol. Chem.* **2005**, *280*, 6488.

made it useful for several other applications such as inhibition of hepatitis C secretion in infected cells,⁴¹ studying the role of CERT protein as a ceramide regulator in UVB-irradiated keratinocytes,⁴² and to aid understanding of limonoid-induced inhibition of sphingomyelin metabolism.⁴³ Furthermore, alterations of sphingomyelin metabolism have been associated with many pathologies. Therapeutic strategies have emerged that regulate sphingolipid concentrations, including CERT protein inhibition, for certain cancer and anti-viral treatments.⁴⁴

2.3 Analysis of Reported Syntheses

It was previously mentioned that (1*R*,3*S*)-HPA-12 was originally discovered and studied by Kobayashi and Hanada, and naturally, they reported the first synthesis of the compound.⁴⁵ The route featured a stereoselective Mannich reaction with a chiral zirconium catalyst (Scheme 2.1) as a key step in the synthesis. The three-component reaction included an α -alkoxy aldehyde **13**, 2-amino-*m*-cresol **14**, 1-ethylthio-1-trimethylsiloxyethene **15**, and a chiral zirconium catalyst generated *in situ* from zirconium *tert*-butoxide, (*R*)-6,6'-Br₂BINOL, and *N*-methylimidazole. The alkoxy portion of the aldehyde played a significant role in influencing the stereoselectivity in the reaction. The best selectivity was obtained when the *tert*-butyldimethylsilyloxy group was used (80% ee), and proceeded in 47% overall yield. Selectivity was much lower when a benzyloxy group or a *tert*-butyldiphenyl silyloxy group was used and resulted in ee's of 54% and 16%, respectively.

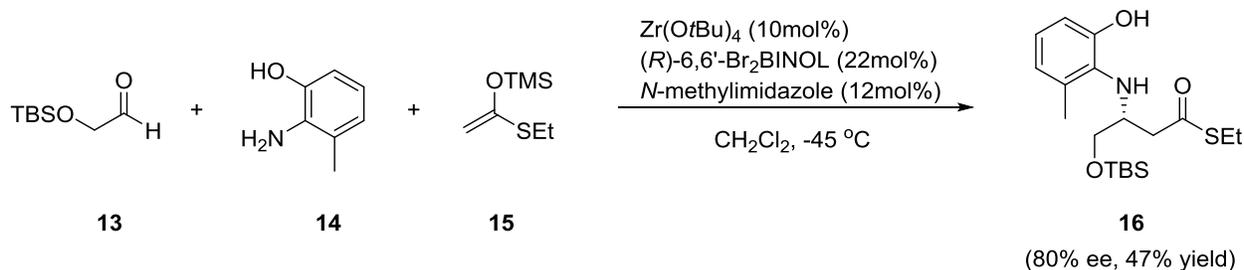
⁴¹ Amako, Y.; Syed, G. H.; Siddiqui, A. *J. Biol. Chem.* **2011**, *286*, 11265.

⁴² Charruyer, A.; Bell, S. M.; Kawano, M.; Douangpanya, S.; Yen, T. Y.; Macher, B. A.; Kumagai, K.; Hanada, K.; Holleran, W. M.; Uchida, Y. *J. Biol. Chem.* **2008**, *283*, 16682.

⁴³ Hullin-Matsuda, F.; Tomishige, N.; Sakai, S.; Ishitsuka, R.; Ishii, K.; Makino, A.; Greimel, P.; Abe, M.; Laviad, E. L.; Lagarde, M.; Vidal, H.; Saito, T.; Osada, H.; Hanada, K.; Futerman, A. H.; Kobayashi, T. *J. Biol. Chem.* **2012**, *287*, 24397.

⁴⁴ Delgado, A.; Fabrias, G.; Bedia, C.; Casas, J.; Abad, J. L. *Anti-Cancer Agents Med. Chem.* **2012**, *12*, 285.

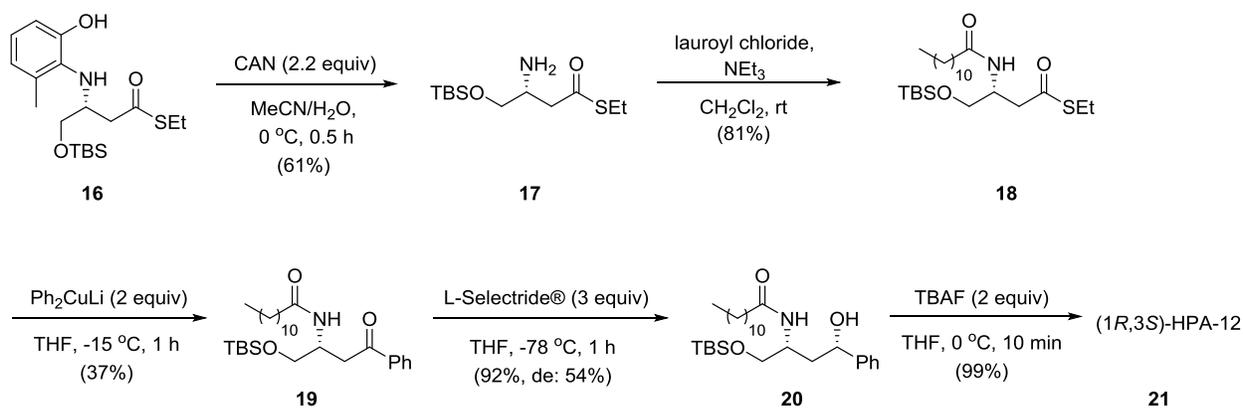
⁴⁵ Ueno, M.; Kitagawa, H.; Ishitani, H.; Yasuda, S.; Hanada, K.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 7863.



Scheme 2.1: Formation of **16** by a stereoselective Mannich reaction

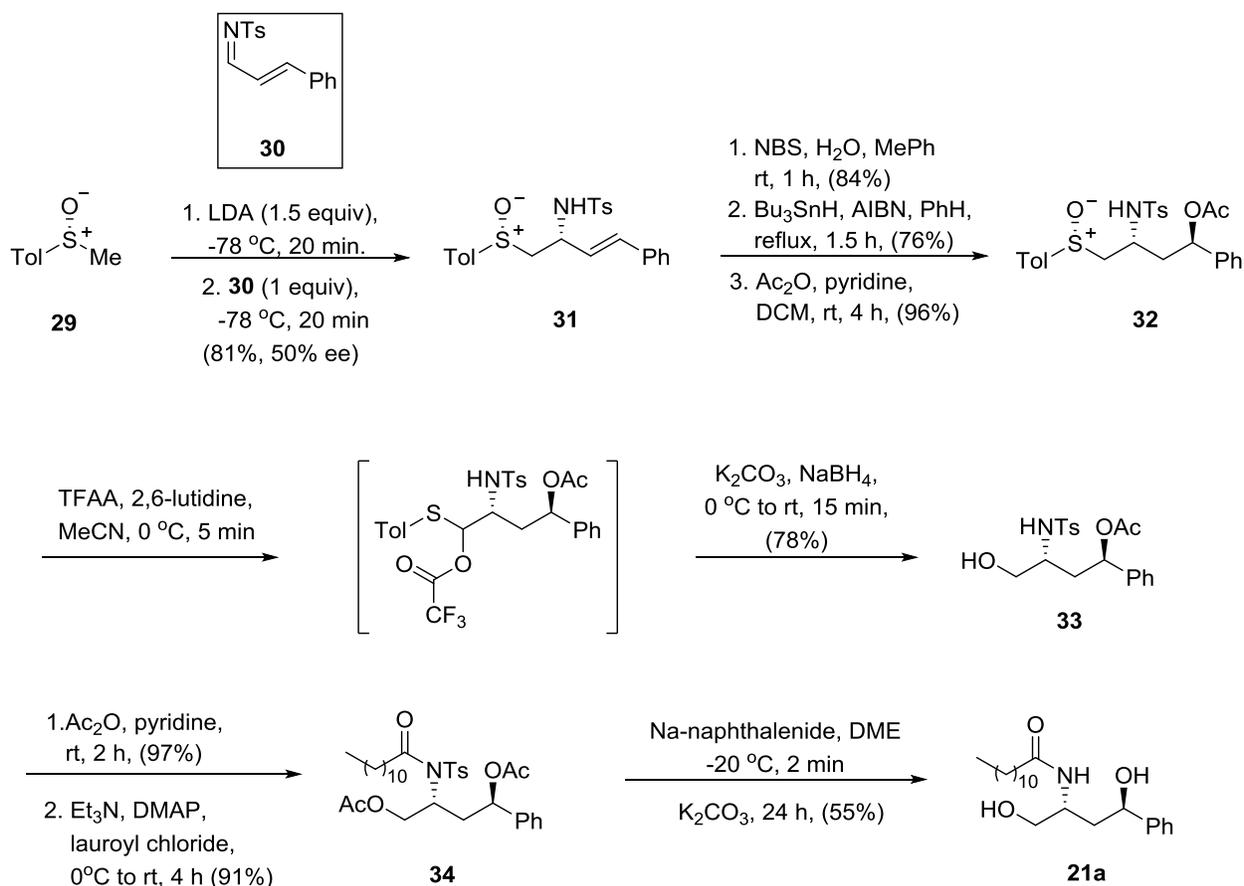
With **16** in hand, (1*R*,3*S*)-HPA-12 (**21**) was prepared in five additional steps (Scheme 2.2). Compound **16** was converted to the free amine **17** in 61% yield by treatment with CAN in acetonitrile/H₂O. Amide **18** was generated in 81% yield by acylation with lauroyl chloride and triethylamine in dichloromethane. Ketone **19** was obtained by treating **18** with a phenyl Gilman reagent at -15 °C in THF. The reaction resulted in only a moderate yield of product (37%); however, 55% of the starting material was recovered. Reduction to the amido alcohol **20** was accomplished with L-Selectride® and proceeded with 54% de and 92% total yield. Desilylation of **20** with tetrabutylammonium fluoride furnished (1*R*,3*S*)-HPA-12 (**21b**) in 99% yield.

Interestingly, the original stereochemical assignment (*anti*-1*R*, 3*R*) of the most potent



Scheme 2.2: preparation of (1*R*,3*S*)-HPA-12 from **16**

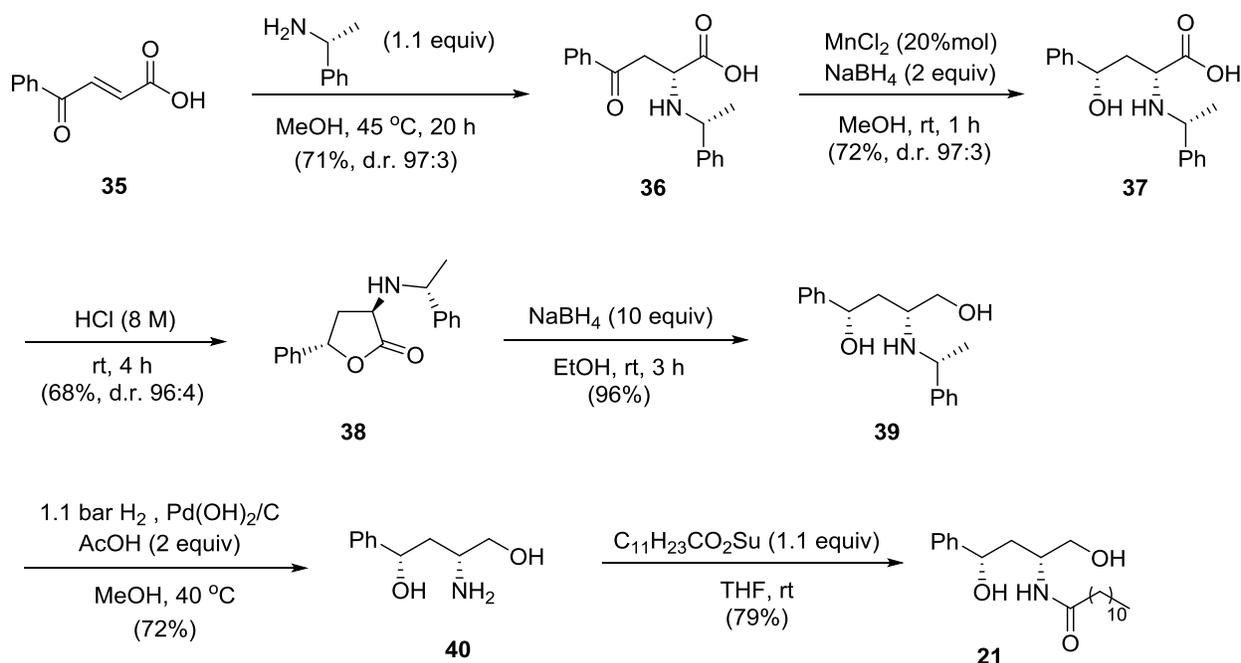
with aqueous K_2CO_3 and $NaBH_4$ without isolation. Acetylation of the terminal alcohol with acetic anhydride, followed by *N*-acylation with lauroyl chloride in the presence of Et_3N and DMAP furnished the product **34**. Reduction of the sulfonamide with sodium naphthalenide, followed by treatment with aqueous K_2CO_3 led to the final product **21a**.



Scheme 2.5: Preparation of **21a** through β -amido sulfoxide elaboration

In 2011, Berkes and co-workers published an expedient stereodivergent synthesis of (1*R*,3*S*)-HPA-12 highlighting a crystallization-induced asymmetric transformation (CIAT) approach from commercially available materials (Scheme 2.6).⁴⁷ The key intermediate **36**, was prepared in 71% yield by an asymmetric Michael-type addition of (*R*)-1-phenylethylamine to

aroylacrylic acid **35** in MeOH.⁵² Michael adduct **36** was reduced to the *syn*-amino alcohol **37** with catalytic MnCl₂ and NaBH₄ in MeOH in 72% yield and 97:3 d.r. Acid-catalyzed lactonization, followed by reduction with NaBH₄ generated intermediate **39** in 65% yield over two steps. Chemoselective *N*-debenzylation to afford **40** was achieved under standard conditions with Pd(OH)₂ and 2 equivalents of AcOH in methanol with excellent diastereomeric purity. *N*-acylation of the (1*R*,3*S*)-HPA-12 precursor **40** with succinimide dodecanoate furnished the final product **21** in 79% yield.



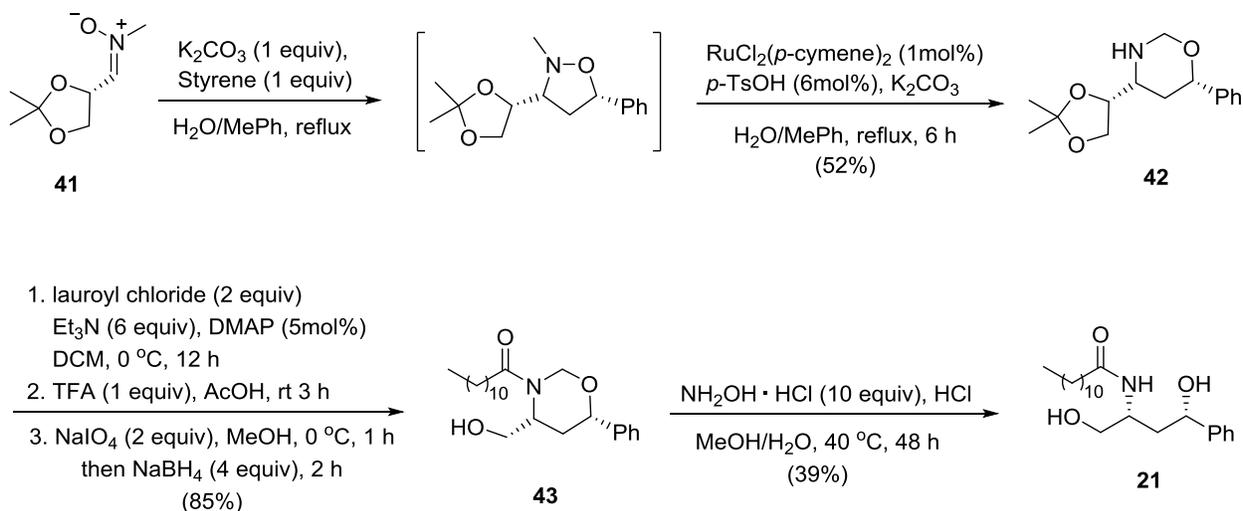
Scheme 2.6: Preparation of (1*R*,3*S*)-HPA-12 **21** featuring a CIAT approach

In 2014, Kang and co-workers reported a synthesis of (1*R*,3*S*)-HPA-12 featuring elaboration of chiral nitron **41** into the chiral 1,3-oxazinane **42** by ruthenium-catalyzed *N*-demethylative rearrangement of the isoxazolidine intermediate generated *in situ* (Scheme 2.7).⁵³ *N*-acylation of **42** with lauroyl chloride, followed by hydrolysis/oxidative cleavage/reduction of

⁵² (a) Berkes, D.; Kolarovic, A.; Manduch, R.; Baran, P.; Povazanec, F. *Tetrahedron: Asymmetry* **2005**, *16*, 1927. (b) Kolarovic, A.; Berkes, D.; Baran, P.; Povazanec, F. *Tetrahedron Lett.* **2001**, *42*, 2579.

⁵³ Xiao, Z.-F.; Yao, C.-Z.; Kang, Y.-B. *Org. Lett.* **2014**, *16*, 6512.

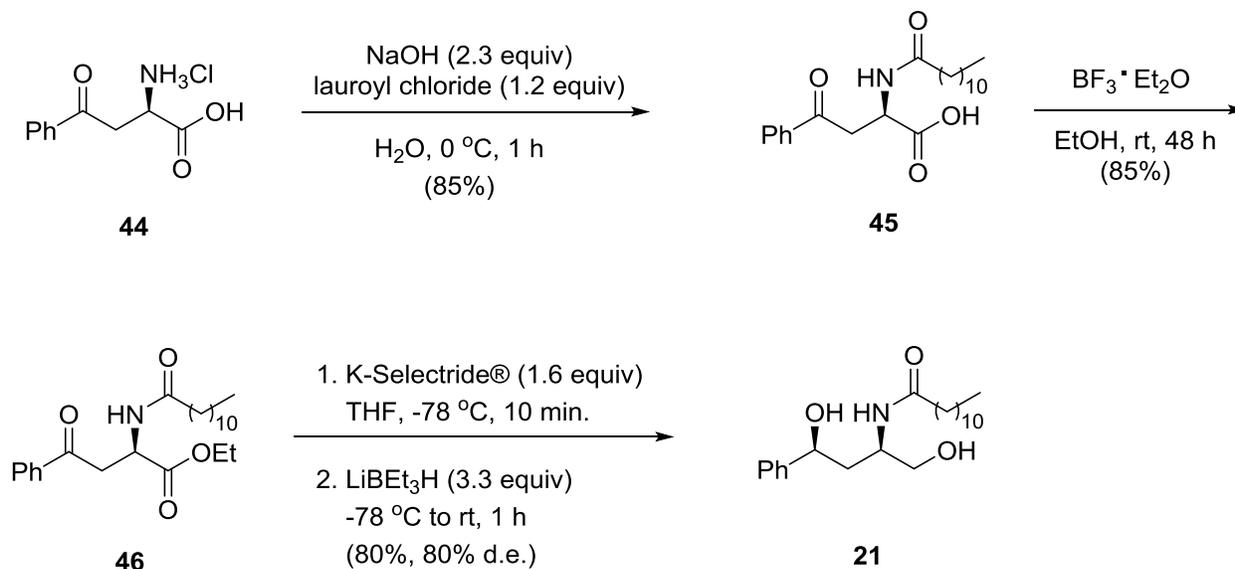
the 1,2-diol afforded product **43** in 85% yield. Hydrolysis of the oxazinane **43** under mildly acidic conditions afforded (1*R*,3*S*)-HPA-12 **21** in 39% yield.



Scheme 2.7: Preparation of (1*R*,3*S*)-HPA-12 by *N*-demethylative rearrangement of isoxazolidines

Recently, Abad and Delgado reported a synthesis of (1*R*,3*S*)-HPA-12 proceeding through the keto amino acid **44** prepared in two steps from D-aspartic acid as the key intermediate (Scheme 2.8).⁵⁴ *N*-acylation of **44** with lauroyl chloride proceeded in 85% yield. Esterification of **45** was achieved by treating **44** with BF_3 diethyl etherate in ethanol for 48 hours. Stereoselective reduction of the ketone with K-Selectride®, followed by reduction of the ester with $LiBEt_3H$ furnished (1*R*,3*S*)-HPA-12 in 80% yield and 80% d.e. Several ester derivatives of **46** were reduced in attempts to increase the selectivity (i.e. methyl, *sec*-butyl, *iso*-butyl, *iso*-propyl esters), however; no increase in selectivity was observed.

⁵⁴ Abad, J.-L.; Armero, I.; Delgado, A. *Tetrahedron Lett.* **2015**, 56, 1706.



Scheme 2.8: Preparation of (1*R*,3*S*)-HPA-12 from keto amino acid derivative **44**

Initial syntheses of (1*R*,3*S*)-HPA-12 reported by Kobayashi and Hanada effectively introduced the C-N bond through an asymmetric Mannich-type reaction; however, reduction to the *syn*-1,3 amidoalcohol was modest. Raghavan was able to improve the selectivity of the C-OH bond formation through stereocontrolled formation of a halohydrin. The key step in the route featured the diastereoselective formation of a β -amino unsaturated sulfoxide. While the reaction proceeded in good yield, only modest selectivity of the C-N bond formation was observed. Arguably the most efficient synthesis of (1*R*,3*S*)-HPA-12 prior to 2013 in terms of efficiency and selectivity was the crystallization-induced approach reported by Berkes. While Berkes was able to prepare (1*R*,3*S*)-HPA-12 in a 6-step approach, the modest efficiency in the synthetic scheme provided a platform for a concise, more efficient approach.

We intended to employ our recent success⁵⁵ with Corey-Link⁵⁶/intramolecular nucleophilic acyl substitution reactions as a featured step in preparation of disubstituted

⁵⁵ Ganta, A.; Shamshina, J. L.; Cafiero, L. R.; Snowden, T. S. *Tetrahedron* **2012**, *68*, 5396.

butyrolactones en route to (1*R*,3*S*)-HPA-12. Reduction of the lactone with LiAlH₄ followed by *N*-acylation of the free amine was expected to furnish the targeted compound. The approach was intended to provide an efficient route to (1*R*,3*S*)-HPA-12 without the need for protection/deprotection steps.

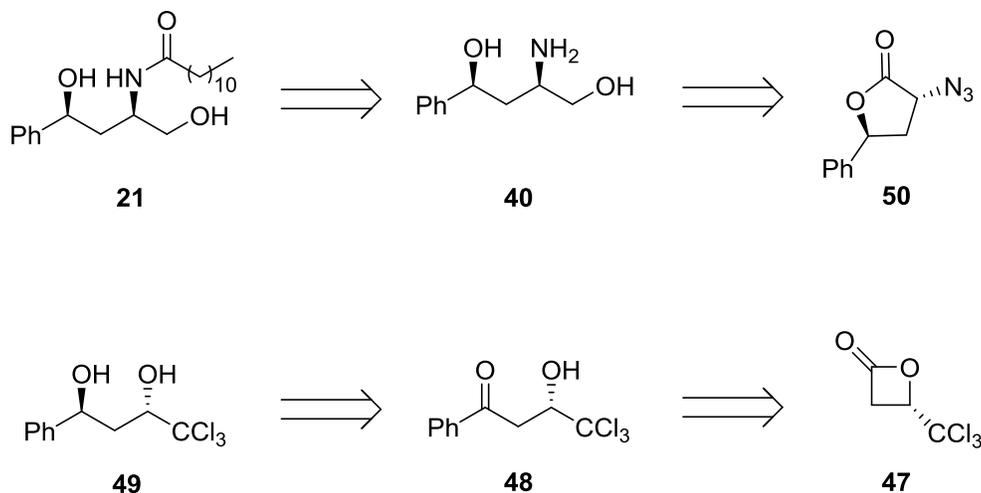
2.4 Planned Approach for Synthesis of (1*R*,3*S*)-HPA-12

For our planned approach to the synthesis of (1*R*,3*S*)-HPA-12, we envisioned expanding upon the aforementioned work proceeding through a reactive *gem*-dichloroepoxide intermediate in the key step (Scheme 2.9). We envisioned that **21** could be prepared by *N*-acylation of **51** with succinimide dodecanoate. The aminodiol **40** should be obtainable by complete reduction of the azidolactone **50** with an excess of LiAlH₄. We expected that **50** could be derived from the *gem*-dichloroepoxide intermediate of **49**, followed by S_N2 substitution with azide, and subsequent lactonization. We conceptualized the *anti*-1,3 diol **49** could be prepared by directed Evans⁵⁷ reduction of ketone **48** with tetramethylammonium triacetoxyborohydrate. Finally, formation of the aryl ketone **48** should be feasible through Friedel-Crafts acylation of (*S*)-Wynberg lactone⁵⁸ **47**, prepared in one step with acetyl chloride, chloral, *N,N*-diisopropylethyl amine and a catalytic amount of quinine.

⁵⁶ (a) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3431. (b) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3435. (c) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.

⁵⁷ Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

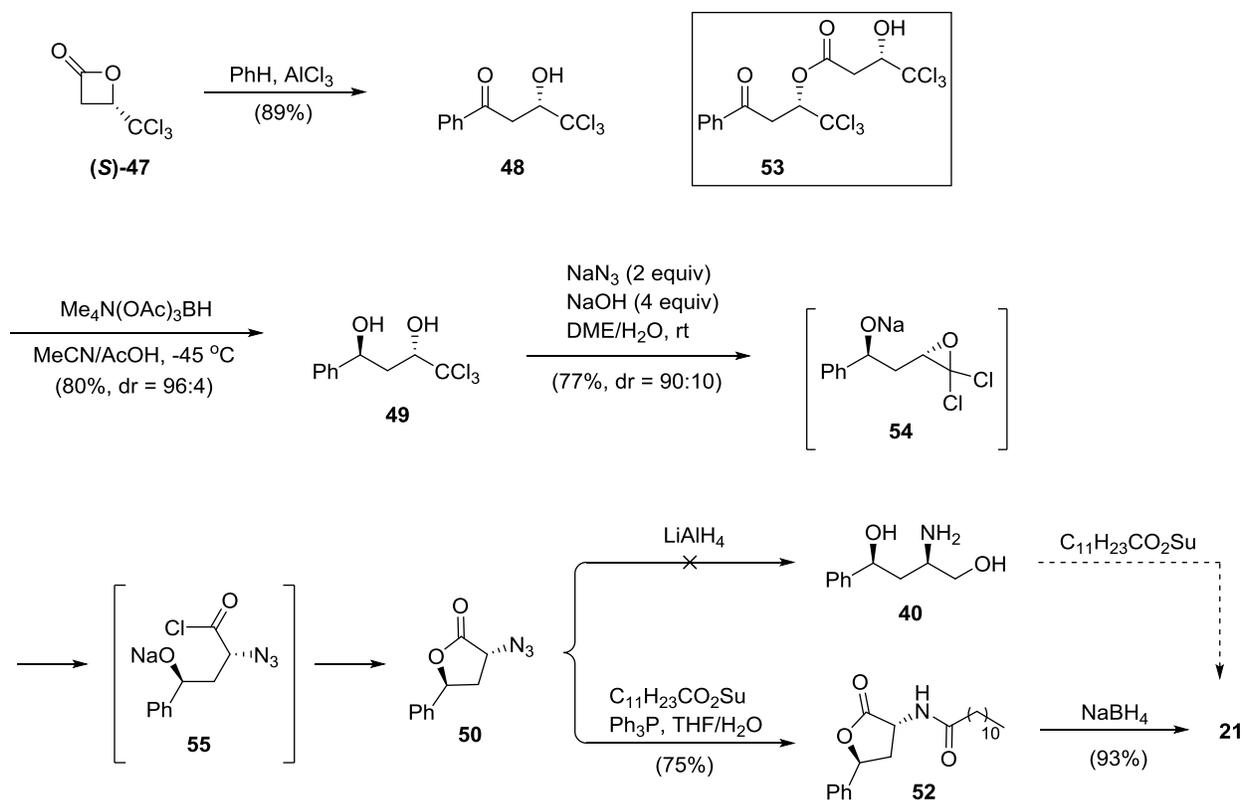
⁵⁸ (a) Wynberg, H.; Staring, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 166. (b) Wynberg, H.; Staring, E. G. *J. Org. Chem.* **1985**, *50*, 1977.



Scheme 2.9: Conceptualized retrosynthetic approach to (1*R*,3*S*)-HPA-12 **21**

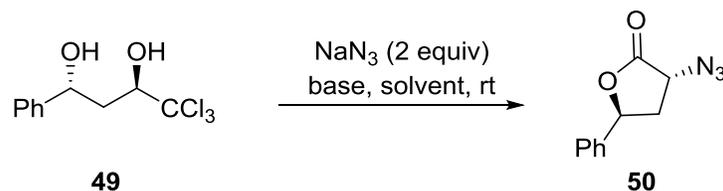
2.5 Results and Discussion

Efforts towards the preparation of (1*R*,3*S*)-HPA-12 began with Friedel-Crafts acylation of (*S*)-Wynberg lactone **47** which smoothly afforded ketone **48** in 89% yield (Scheme 2.10). It was necessary to conduct the reaction at a 0.5 M concentration in order to mitigate the formation of the *O*-acylated byproduct **53**. The best results were obtained when powdered AlCl₃ was sonicated in benzene, creating a fine suspension of the Lewis acid, followed by stirring at room temperature for 12 hours. The *anti*-1,3 diol **49** was successfully obtained in 80% yield and 96:4 d.r. by a directed-1,3 reduction of the β-hydroxy ketone using tetramethylammonium triacetoxyborohydride in MeCN/AcOH at -45 °C. It was prudent to use freshly distilled acetonitrile and acetic acid in a 1:1 ratio to avoid freezing of the solution and to achieve optimal selectivity. Temperatures lower than -45 °C resulted in freezing of the solution, and at higher temperatures, comparable yields were obtained, but stereoselectivity was much lower. Lactone **50** was prepared by Snowden's modified Corey-Link reaction in which diol **49** was treated with four equivalents of sodium hydroxide and two equivalents of sodium azide in a 1:4 mixture



Scheme 2.10: Preparation of (1*R*,3*S*)-HPA-12 **21** from (*S*)-Wynberg lactone

of DME/H₂O at room temperature. The reaction proceeded first through the *gem*-dichloroepoxide intermediate **54** formed following deprotonation of the trichloromethyl carbinol. Azide substitution led to formation of the azidocarboxylic acid chloride intermediate **55**, which underwent *O*-acylation to afford lactone **50**. After completion of the reaction, the crude mixture was stirred in dilute aqueous hydrochloric acid for 2-3 hours to ensure that any hydrolyzed lactone was converted to the product. These conditions provided the target lactone in 77% total yield, in a 90:10 ratio of *trans/cis* epimers. To ensure the reaction had been fully optimized, a series of reactions were conducted with various solvents and bases (Table 2.1). Adjusting the ratio of DME/H₂O resulted in lower yield of product (entry 2), and when less sodium hydroxide was used, hardly any consumption of starting material was observed (entry 3). When sodium

Table 2.1: Optimization studies for formation of lactone **50**

Entry	Base (equiv)	Solvent	[49] (M)	Yield ^a (%)
1	NaOH (4)	DME/H ₂ O (1:4)	0.05	70
2	NaOH (4)	DME/H ₂ O (2:3)	0.05	45
3	NaOH (2.5)	DME/H ₂ O (1:4)	0.05	<i>b</i>
4	TBAH (6.7)	CH ₂ Cl ₂ /TBAH (2:1)	0.05	<i>c</i>
5	DBU (5), 18-crown-6 (cat.)	MeOH	0.05	40

^a Isolated yield of pure *trans*-lactone **50** ^b Reaction showed <5% conversion after 24 hours ^c a complex mixture of products was formed.

hydroxide was substituted with tetrabutylammonium hydroxide (entry 4)⁵⁹ or DBU and 18-crown-6 (entry 5),⁶⁰ conditions that have been successful in other Jocic-Reeve or Corey-Link reactions,⁶¹ there was no observed improvement.

Following successful formation of lactone **50**, we attempted a one-pot reduction of both the azide and the lactone carbonyl with concentrations of lithium aluminum hydride ranging from 6-15 equivalents and at temperatures ranging from 0 to 65 °C. Unfortunately, all attempts resulted in a complex mixture of products, and the desired aminodiol **40** could not be obtained in reasonable yield. As a result, we resorted to a slightly different approach in which a tandem Staudinger reduction and *N*-acylation reaction were employed by adjusting a procedure reported

⁵⁹ Oliver, J. E.; Schmidt, W. F. *Tetrahedron: Asymmetry* **1998**, *9*, 1723.

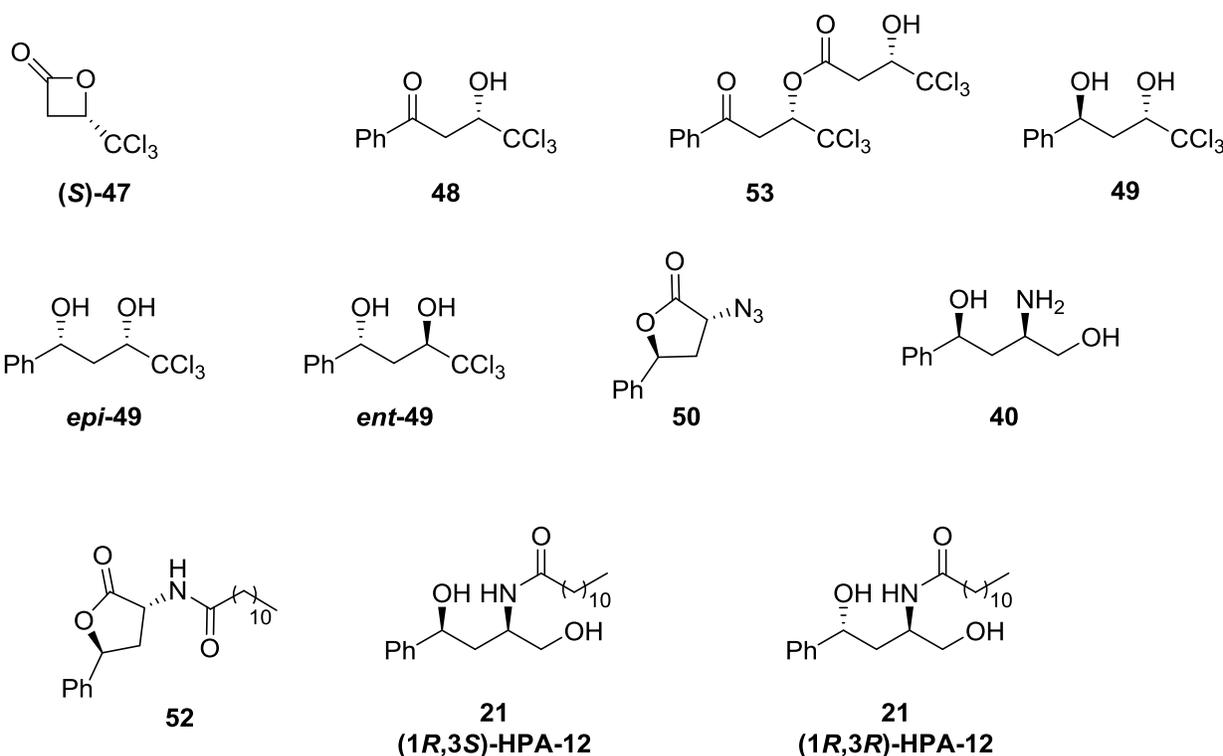
⁶⁰ Dominguez, C.; Ezquerra, J.; Baker, S. R.; Borrelly, S.; Prieto, L.; Espada, C. M.; Pedregal, C. *Tetrahedron Lett.* **1998**, *39*, 9305.

⁶¹ For a recent review of Corey-Link, Jocic-Reeve, or related reactions, see: Snowden, T. S. *ARKIVOC* **2012**, (ii), 24.

by Bittman.⁶² To our delight, treatment of lactone **50** with triphenyl phosphine and succinimide dodecanoate in THF/H₂O afforded the amidolactone **52** in 75% yield. A simple reduction of **52** with sodium borohydride in ethanol provided (1*R*,3*S*)-HPA-12 in 93% yield and 98% ee.⁶³ All characterization data of (1*R*,3*S*)-HPA-12 (**21**) are consistent with those reported by Berkes,⁴⁷ and are in agreement with the most potent HPA-12 stereoisomer (1*R*,3*S*).

In summary, our synthesis of (1*R*,3*S*)-HPA-12 was accomplished in five steps and 33% overall yield starting from (*S*)-Wynberg lactone **47**. The described approach, which features a one-pot Corey-Link/intramolecular acyl substitution reaction, was the shortest and highest yielding synthesis at the time.

2.6 Index of Chapter Compounds and Numbers



2.7 Experimental Details

⁶² He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7627.

⁶³ The ee (%) was determined by preparing the Mosher diester derivative of this compound. The analysis showed the material to have >98% ee.

^1H and ^{13}C NMR spectra were recorded on Bruker instruments at 360, 500, or 600 MHz and 90 or 125 MHz, respectively. ^{19}F NMR spectra were recorded at 338 MHz. Chemical shifts were referenced to acetone- d_6 ($\delta = 2.05$ and 30.83) or CDCl_3 ($\delta = 7.26$ and 77.0). Mass spectra were recorded on an AutoSpec-Ultima_NT mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a MelTemp 1001D capillary melting point apparatus and are uncorrected. Ultrasonication was conducted with a Bransonic 2510R-DTH ultrasonic cleaner. IR samples were prepared by dissolving the pure material in a small amount of a suitable aprotic solvent. A small drop of the concentrated solution was placed on a KBr plate, and the solvent was evaporated completely. A second KBr plate was placed on top of the first plate and rotated by a quarter turn to make an even film of the material between the plates. IR spectra were recorded on a Jasco FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm) or KMnO_4 staining. MeCN and benzene were dried over 4-Å molecular sieves prior to use. THF and Et_2O were distilled from Na/benzophenone ketyl radical. Chloral was purchased from Riedel-de Haën and distilled neat onto 4-Å molecular sieves. Acetyl chloride was distilled from PhNMe_2 (one-tenth volume). Anhydrous acetic acid was prepared by stirring $\text{AcOH}-\text{Ac}_2\text{O}$ (1:1) for 1 h, and then AcOH was distilled onto 4-Å molecular sieves. All other reagents and solvents were used as received from commercial sources.

(S)-4-(Trichloromethyl)oxetan-2-one (47)⁵⁸

A dry 1-L, 3-neck round-bottom flask was fitted with two addition funnels and an argon supply. Quinine (406 mg, 1.25 mmol) and anhydrous Et_2O (165 mL) were added to the round-bottom flask, then anhydrous DIPEA (47.5 mL, 0.273 mol) was transferred to the flask by cannula. Chloral (24.5 mL, 0.251 mol) in anhydrous Et_2O (115 mL) was added to one addition

funnel. AcCl (17.8 mL, 0.250 mol) in anhydrous Et₂O (115 mL) was added to the other addition funnel. While cooling to -15 °C, the chloral and AcCl were added dropwise to the mixture under argon at approximately equal rates over 1.5 h. After the addition was complete, the mixture was stirred at -15 °C for 2 h. Aqueous 1 M HCl (150 mL) was added and the mixture was warmed to r.t. and then filtered through Celite. The layers were separated, and the aqueous layer was extracted with Et₂O (5 × 30 mL). The combined organic layers were washed with 1 M HCl (3 × 25 mL), dried (MgSO₄), and concentrated by rotary evaporation yielding a light tan solid. The solid was placed under vacuum to remove excess volatile components then purified by bulb-to-bulb distillation (82 °C/0.27 mbar) to give **47** as a white solid (mixture of enantiomers). The solid was recrystallized (methylcyclohexane)⁵⁸ yielding pure (*S*)-**47** (23.4 g, 12.4 mmol, 49%) as white, fluffy crystals; mp 52–53 °C. [α]_D²² +15.6 (c 1.0, CH₂Cl₂) (corresponds to >98% ee⁵⁸). IR (KBr): 2972, 1644, 1101, 788 cm⁻¹. ¹H NMR (360 MHz, CDCl₃): δ = 5.01 (dd, *J* = 3.8, 5.7 Hz, 1 H), 3.74 (dd, *J* = 5.7, 17 Hz, 1 H), 3.60 (dd, *J* = 3.8, 17 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 163.9, 96.6, 76.1, 42.5. MS (EI): *m/z* = 71.0 [M – CCl₃]. HRMS (EI): *m/z* [M – CCl₃] calcd for C₃H₃O₂: 71.0133; found: 71.0130.

(*S*)-4,4,4-Trichloro-3-hydroxy-1-phenylbutan-1-one (48)

Powdered AlCl₃ (6.3 g, 47 mmol) in anhydrous benzene (250 mL) was placed in a 1-L round-bottom flask. The system was sonicated for 1.5 h to create a fine suspension of the Lewis acid. The mixture was then cooled to 0 °C, and a solution of (*S*)-Wynberg lactone **47** (2.00 g, 12.5 mmol) in anhydrous benzene (125 mL) was added dropwise. The reaction was warmed to r.t. and stirred until judged complete by TLC analysis (~12 h). The reaction was quenched by slow addition of aqueous sat. NH₄Cl (250 mL) and the aqueous layer was extracted with benzene (4 × 60 mL). The combined organic layers were washed with brine (30 mL), dried (MgSO₄), and

concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc, 9:1) to give **48** (2.99 g, 11.2 mmol, 89%) as white crystals; mp 62–63 °C. $[\alpha]_{22}^D -35.6$ (c 1.0, CH₂Cl₂). IR (KBr): 3448, 3061, 2924, 1683, 1449 cm⁻¹. ¹H NMR (360 MHz, CDCl₃): δ = 8.0 (d, *J* = 7.8 Hz, 2 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.9 Hz, 2 H), 4.88 (ddd, *J* = 1.7, 4.5, 9.1 Hz, 1 H), 3.79 (d, *J* = 4.3 Hz, 1 H), 3.65 (dd, *J* = 0.7, 17.3 Hz, 1 H), 3.50 (dd, *J* = 9.1, 17.3 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 197.1, 136.4, 133.9, 128.8, 128.3, 102.6, 79.1, 40.8. MS (EI): *m/z* = 249.0 [M – OH]. HRMS (EI): *m/z* [M – OH] calcd for C₁₀H₈OCl₃: 248.9641; found: 248.9638.

(1*S*,3*S*)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (**49**)

A solution of tetramethylammonium triacetoxyborohydride (1.57 g, 5.98 mmol) in anhydrous MeCN (3.4 mL) and anhydrous AcOH (3.4 mL) under argon was stirred at r.t. for 1 h. The solution was then cooled to –50 °C. Hydroxy ketone **48** (200 mg, 0.75 mmol) in anhydrous MeCN (1.1 mL) was added to the solution by syringe. The mixture stirred for 30 h at a bath temperature between –45 °C and –50 °C. The reaction was quenched with 0.5 M aqueous sodium potassium tartrate (8 mL) and warmed to r.t. The mixture was diluted with CH₂Cl₂ (6 mL) and the layers were separated. The organic phase was washed with aqueous saturated NaHCO₃ (10 mL). The aqueous phase was back extracted with CH₂Cl₂ (4 × 5 mL), and the combined organic layers were washed with aqueous saturated NaHCO₃ until the aqueous layer reached pH 7. The organic layers were then dried (MgSO₄) and concentrated. The crude product was evaluated by ¹H NMR spectroscopy to establish dr (*anti/syn*) = 96:4 and then purified by silica gel chromatography (hexanes–EtOAc, 8:2) to obtain **49** (155 mg, 0.575 mmol, 77%) as white crystals; mp 104–105 °C. $[\alpha]_{22}^D -65.7$ (c 2.0, CH₂Cl₂). IR (KBr): 3419, 2906, 1641, 1427 cm⁻¹. ¹H NMR (360 MHz, CDCl₃): δ = 7.43–7.29 (m, 5 H), 5.12 (dt, *J* = 3.2, 9.5 Hz, 1 H), 4.44 (ddd, *J* = 1.9, 4.4, 10.0 Hz, 1 H), 3.25 (dd, *J* = 1.2, 4.7 Hz, 1 H), 2.45 (ddt, *J* = 1.4, 9.5, 14.3 Hz, 1 H),

2.27 (d, $J = 3.9$ Hz, 1 H), 2.07 (ddd, $J = 2.6, 9.7, 14.2$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 143.7, 128.7, 127.9, 125.6, 103.8, 79.8, 70.8, 40.1$. MS (EI): $m/z = 268.0$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}]$ calcd for $\text{C}_{10}\text{H}_{11}\text{O}_2\text{Cl}_3$: 267.9825; found: 267.9827.

(3*R*,5*S*)-3-Azido-5-phenyldihydrofuran-2(3*H*)-one (50)

Trichloromethyl carbinol **49** (100 mg, 0.37 mmol) in DME– H_2O (1.5 mL:6.0 mL) was placed in a sample vial with a magnetic stir bar. NaN_3 (48.2 mg, 0.740 mmol) (CAUTION: may explode if ground or contacted by metal surfaces) and freshly powdered NaOH (59.4 mg, 1.49 mmol) were added at once. The reaction was stirred rapidly at r.t. until judged complete by TLC analysis (12–24 h). The mixture was cooled to 0 °C, and the pH was adjusted to pH 2 with 0.5 M HCl. This mixture was stirred for 3 h to promote lactonization of any hydrolyzed product. The aqueous phase was extracted with EtOAc (5×15 mL), dried (MgSO_4), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish dr (*trans/cis*) = 90:10 and then purified by silica gel chromatography (hexanes–EtOAc, 2:1) to obtain **9** (74.0 mg, 0.364 mmol, 70%) as a clear, colorless oil. $[\alpha]_{22}^{\text{D}} +175.4$ (c 1.0, CH_2Cl_2). IR (KBr): 2923, 2852, 1780, 1458 cm^{-1} . ^1H NMR (360 MHz, CDCl_3): $\delta = 7.45\text{--}7.34$ (m, 3 H), 7.30–7.28 (m, 2 H), 5.65 (t, $J = 6.6$ Hz, 1 H), 4.36 (dd, $J = 6.1, 7.9$ Hz, 1 H), 2.60–2.44 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 172.7, 138.0, 129.0, 128.8, 125.0, 79.2, 57.1, 36.8$. MS (EI): $m/z = 203.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}]$ calcd for $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2$: 203.0695; found: 203.0691.

***N*-[(3*R*,5*S*)-2-Oxo-5-phenyltetrahydrofuran-3-yl]dodecanamide (52)**

To a solution of **51** (50 mg, 0.25 mmol) in THF– H_2O (6.6 mL:0.73 mL) were added lauric acid *N*-hydroxysuccinimide ester (183 mg, 0.62 mmol) and Ph_3P (78 mg, 0.30 mmol). The mixture was stirred at r.t. under argon for 48 h. The solvents were then removed by evaporation [*t*-BuOH (3–4 mL) was added to azeotropically remove residual H_2O], and the residue was

dissolved in EtOAc (25 mL) and washed with ice cold 1% K₂CO₃ (4 × 5 mL). The organic phase was dried (Na₂SO₄) and concentrated. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 8:2) to afford **52** (66.2 mg, 0.184 mmol, 75%) as a white solid; mp 96–97 °C. $[\alpha]_{22}^D +38.2$ (c 1.0, CH₂Cl₂). IR (KBr): 3303, 2918, 1648, 1164 cm⁻¹. ¹H NMR (360 MHz, CDCl₃): δ = 7.41–7.27 (m, 5 H), 6.52 (d, *J* = 6.7 Hz, 1 H), 5.73 (dd, *J* = 2.5, 8.5 Hz, 1 H), 4.61–4.54 (m, 1 H), 2.79 (ddd, *J* = 2.8, 9.3, 12.7 Hz, 1 H), 2.67–2.59 (m, 1 H), 2.23 (t, *J* = 7.8 Hz, 2 H), 1.66–1.58 (m, 2 H), 1.35–1.20 (m, 16 H), 0.88 (t, *J* = 6.7 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 175.4, 173.7, 138.9, 128.9, 128.5, 125.0, 78.6, 48.3, 36.9, 36.1, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.2, 25.4, 22.7, 14.1. MS (EI): *m/z* = 359.2 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₂₂H₃₃NO₃: 359.2460; found: 359.2468.

***N*-[(1*R*,3*S*)-3-Hydroxy-1-(hydroxymethyl)-3-phenylpropyl]dodecamide (21)**

To a suspension of **52** (40.0 mg, 0.11 mmol) in absolute EtOH (1.5 mL) was added NaBH₄ (21 mg, 0.55 mmol), and the mixture was stirred at r.t. for 20 h. The reaction was then quenched by the addition of 5% K₂CO₃ soln (2.4 mL), and the EtOH was removed by rotary evaporation. The aqueous phase was extracted with EtOAc (5 × 3 mL), and the resultant organic layers were combined, dried (Na₂SO₄), and concentrated. The product was first purified by silica gel chromatography (EtOAc–hexanes, 4:1). To remove contaminants (presumably grease and/or residual lauric acid from the previous step) from the product, the material was diluted with DCM (10 mL) and transferred to a separatory funnel. The organic layer was washed with saturated aqueous NaHCO₃ (5 x 3 mL), dried with Na₂SO₄, and concentrated. Finally, the organic material was diluted with anhydrous MeCN (5 mL), and transferred to a clean separatory funnel. The MeCN layer was washed with pentanes (8 x 5 mL) and concentrated to obtain **21** (37.6 mg, 0.103 mmol, 93%) as a white crystalline solid; mp 90–91 °C. $[\alpha]_{22}^D -34.8$ (c 1.0, CHCl₃). IR

(KBr): 3417, 3294, 1643 cm^{-1} . ^1H NMR (360 MHz, CDCl_3): δ = 7.36–7.24 (m, 5 H), 6.43 (d, J = 6.6 Hz, 1 H), 4.80 (dd, J = 3.3, 8.9 Hz, 1 H), 4.08–4.01 (m, 1 H), 3.93 (s, 1 H), 3.70–3.62 (m, 2 H), 3.31 (s, 1 H), 2.15 (dd, J = 7.3, 8.0 Hz, 2 H), 2.04 (ddd, J = 3.5, 5.5, 14.6 Hz, 1 H), 1.92 (ddd, J = 7.0, 9.0, 15.8 Hz, 1 H), 1.64–1.55 (m, 2 H), 1.33–1.23 (m, 16 H), 0.88 (dd, J = 6.6, 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 174.3, 144.3, 128.6, 127.7, 125.5, 71.9, 65.6, 50.5, 40.7, 36.8, 31.9, 29.6, 29.6, 29.5, 29.3, 29.3, 29.3, 25.7, 22.7, 14.1. MS (EI): m/z = 363.3 $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}]$ calcd for $\text{C}_{22}\text{H}_{37}\text{NO}_3$: 363.2773; found: 363.2766.

General Procedure for Synthesis of Mosher's Diester Derivatives Using (*R*)-(+)- α -Methoxy- α -trifluoromethylphenylacetic acid

To a flame-dried 10-mL round bottom flask equipped with a magnetic stir bar was added (*R*)-(+)- α -methoxy- α -trifluoromethylphenylacetic acid (61 mg, 0.260 mmol) and 1 mL anhydrous benzene. The solution was concentrated by rotary evaporation to remove adventitious moisture, and then the solid was diluted with DCM (0.1 mL). Freshly distilled oxalyl chloride was added (42.8 mg, 7.33 mmol) followed by 0.15 μL DMF. The solution was stirred rapidly under argon at room temperature for 30 minutes, then cooled to 0 $^\circ\text{C}$ with an ice bath. The solution was concentrated under reduced pressure for 30 minutes then the system was flushed with argon. The crude mixture was diluted with DCM (0.1 mL), and transferred via canula to an ice-cooled solution of diol **49**, *epi*-**49**, *ent*-**49**, or **21** (0.046 mmol), 4-dimethylaminopyridine (2 mg, 0.012 mmol), and triethylamine (64 μL , 0.46 mmol) in DCM (0.2 mL). The resulting solution was stirred rapidly at 23 $^\circ\text{C}$ under argon until deemed complete by TLC analysis. The reaction mixture was transferred to a separatory funnel with the aid of DCM, and sequentially extracted with saturated aqueous ammonium chloride solution (2 x 5 mL), saturated aqueous sodium bicarbonate solution (2 x 5 mL), and 5 mL of water. The organic layer was dried with

Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel chromatography using 4:6 ether/hexanes as the eluent to obtain the products listed below.

Mosher's Diester of (1S,3S)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (49)

The indicated compound was obtained as a light yellow oil in 96% yield (31.2 mg, 44.5 μmol).

¹H NMR (360 Hz, CDCl₃) δ = 7.70 – 7.68 (m, 2H), 7.54 – 7.51 (m, 3H), 7.42 – 7.27 (m, 8H), 7.05 (dd, *J* = 1.9, 7.9 Hz, 2H), 5.80 (dd, *J* = 1.1, 10.1 Hz, 1H), 5.59 (dd *J* = 1.6, 11.8 Hz, 1H), 3.55 (d, *J* = 1.12 Hz, 3H), 3.52 (d, *J* = 0.8 Hz, 3H), 2.85 (ddd, *J* = 1.1, 11.8, 15.2 Hz, 1H), 2.17 (ddd, *J* = 1.8, 10.1, 15.2 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ = 165.6, 165.3, 137.9, 131.8, 130.7, 130.1, 129.5, 128.9, 128.9, 128.7, 128.4, 128.0, 127.6, 126.3, 123.2 (q, *J* = 288.5 Hz), 123.2 (q, *J* = 288.6 Hz), 98.0, 85.1 (q, *J* = 28.5 Hz), 84.8 (q, *J* = 27.9 Hz), 79.5, 74.0, 55.6, 55.4, 38.1. ¹⁹F NMR (360 Hz, CDCl₃) δ = -70.76, -71.14.

Mosher's Diester of (1R,3S)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (*epi*-49)

The indicated compound was obtained as a clear colorless oil in 94% yield (30.5 mg, 43.5 μmol).

¹H NMR (360 Hz, CDCl₃) δ = 7.70 – 7.68 (m, 2H), 7.54 – 7.30 (m, 13 H), 5.89 (dd, *J* = 4.2, 11.4 Hz, 1H), 5.30 (dd, *J* = 1.5, 9.1 Hz, 1H), 3.59 (d, *J* = 1.0 Hz, 3H), 3.41 (d, *J* = 1.0 Hz, 3H), 2.88 (ddd, *J* = 1.6, 11.4, 14.2 Hz, 1H), 2.46 (ddd, *J* = 4.3, 9.1, 14.2 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ = 165.4, 165.3, 135.9, 132.0, 130.0, 129.7, 129.7, 129.0, 128.7, 128.7, 128.4, 127.99, 127.6, 127.3, 124.2 (q, *J* = 287.7), 98.0, 84.5 (q, *J* = 27.8), 84.4 (q, *J* = 28.1), 79.3, 74.8, 55.7, 55.4, 37.3. ¹⁹F NMR (360 Hz, CDCl₃) δ = -70.94, -71.33.

Mosher's Diester of (1R,3R)-4,4,4-Trichloro-1-phenylbutane-1,3-diol (*ent*-49)

The indicated compound was obtained as a light yellow oil in 92% yield (29.9 mg, 42.6 μmol).

^1H NMR (360 Hz, CDCl_3) δ = 7.77 (d, J = 7.5, 2H), 7.55 – 7.46 (m, 5H), 7.39 – 7.28 (m, 6H), 7.04 – 7.02 (m, 2H), 5.63 (dd, J = 0.6, 9.9 Hz, 1H), 5.54 (dd, J = 1.3, 11.8 Hz, 1H), 3.77 (d, J = 1.4, 3H), 3.49 (d, J = 1.0, 3H), 2.81 (ddd, J = 0.8, 11.8, 15.1 Hz, 1H), 2.05 (ddd, J = 1.6, 10.0, 15.1 Hz, 1H) ^{13}C NMR (125 MHz, CDCl_3): δ = 165.5, 165.5, 137.7, 132.6, 131.8, 129.9, 129.6, 129.1, 128.8, 128.8, 128.4, 127.3, 127.3, 126.5, 123.4 (q, J = 289.1 Hz), 123.2 (q, J = 289.5 Hz), 98.1, 84.4 (q, J = 27.8 Hz), 84.3 (q, J = 28.2 Hz), 79.2, 73.5, 56.3, 55.6, 38.0. ^{19}F NMR (360 Hz, CDCl_3) δ = -70.55, -70.95.

Mosher's Diester of (1R,3S)-N-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecamide (21)

The indicated compound was obtained as a clear colorless oil in 85% yield (23.3 mg, 29.3 μmol).

^1H NMR (360 Hz, CDCl_3) δ = 7.48 – 7.26 (m, 13H), 7.18, 7.16 (m, 2H), 5.86 (dd, J = 6.2, 7.9 Hz, 1H), 5.36 (d, J = 8.4 Hz, 1H), 4.35 (dd, J = 4.0, 11.2, Hz, 1H), 4.22 (dd, J = 3.7, 11.2 Hz, 1H), 4.10 – 4.14 (m, 1H), 3.49 (s, 6H), 2.20 – 2.12 (m, 1H), 2.10 – 1.98 (m, 3H), 1.60 – 1.50 (m, 2H), 1.33 – 1.20 (m, 16H), 0.88 (t, J = 7.01 Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ = 172.8, 166.3, 165.7, 137.6, 131.9, 131.7, 129.9, 129.6, 128.9, 128.7, 128.6, 128.4, 127.4, 127.3, 126.8, 84.1 (q, J = 22.4), 84.1 (q, J = 23.7), 76.0, 67.1, 55.5, 55.4, 45.2, 38.0, 36.6, 31.9, 29.7, 29.6, 29.6, 29.5, 29.3, 29.3, 29.2, 25.4, 22.7, 14.1. ^{19}F NMR (360 Hz, CDCl_3) δ = -71.30, -71.57.

CHAPTER 3
CONSTRUCTION OF POLYSUBSTITUTED OXACYCLES BY A NOVEL JOCIC
REACTION

3.1 Background and Significance

Functionalized tetrahydropyrans are common structural motifs found in a wide variety of natural products that show diverse bioactivity. A survey of the literature shows that natural products containing the tetrahydropyran moiety, especially those with 2, 4, 6 connectivity, show anti-bacterial, anti-tumor, and anti-inflammatory activity among many others.⁶⁴ For example, the

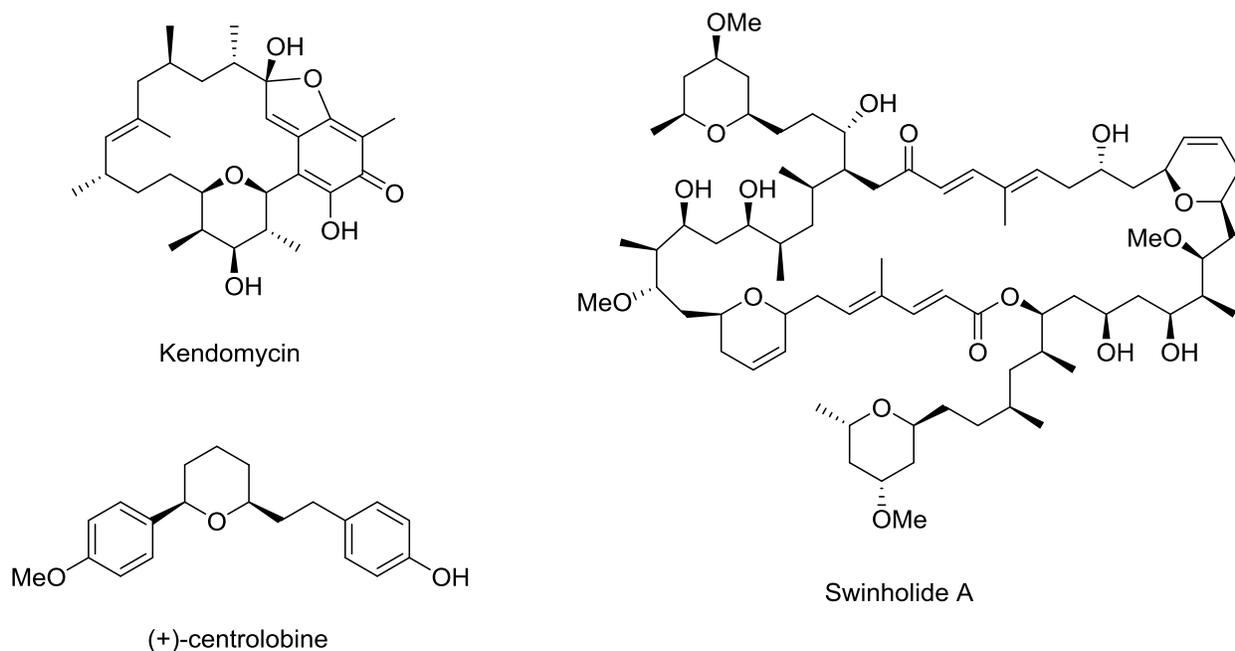


Figure 3.1: examples of natural products containing tetrahydropyran substructures

⁶⁴ (a) Bode, H. B.; Zeeck, A. *Perkin 1* **2000**, 323. (b) Elnakady, Y. A.; Rohde, M.; Sasse, F.; Backes, C.; Keller, A.; Lenhof, H.-P.; Weissman, K. J.; Mueller, R. *Chem. Bio. Chem.* **2007**, 8, 1261. (c) Chan, P. K.; Loh, P. T. *Org. Lett.* **2005**, 7, 4491.

macrocyclic polyketide kendomycin exhibits antibacterial activity against Gram-positive and Gram-negative bacteria as well as cytotoxicity against a number of human tumor cell lines (Figure 3.1). Perhaps most notably, kendomycin shows antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin intermediate *S. aureus* strains. Other examples of natural products bearing a tetrahydropyran substructure include (\pm)-centrolobine, which exhibits antibiotic and antifungal activity,⁶⁵ and swinholide A which exhibits antifungal activity and cytotoxicity to several cancer cell lines.⁶⁶ Due to the diverse biological activity of these types of natural products, a number of reactions have been developed to construct tetrahydropyran rings for their use in natural product synthesis.

3.2 General Methods for Tetrahydropyran Formation

Among the identified reactions for tetrahydropyran construction, those of considerable popularity include the Prins and related cyclization reactions,⁶⁷ the hetero-Diels-Alder cyclization,⁶⁸ intramolecular Michael-type cyclizations,⁶⁹ cyclizations onto epoxides,⁷⁰ and additions to substituted oxocarbenium species.^{71,72}

⁶⁵ Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1984**, *37*, 1127.

⁶⁶ (a) Carmeli, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511. (b) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629. (c) Kobayashi, M.; Kawazoe, K.; Okamoto, T.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 19.

⁶⁷ (a) Gesinski, M. R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2011**, *133*, 9727. (b) Dzedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678.

⁶⁸ (a) Ghosh, A. K.; Gong, G. *Chem. - Asian J.* **2008**, *3*, 1811. (b) Raghavan, S.; Samanta, P. K. *Org. Lett.* **2012**, *14*, 2346.

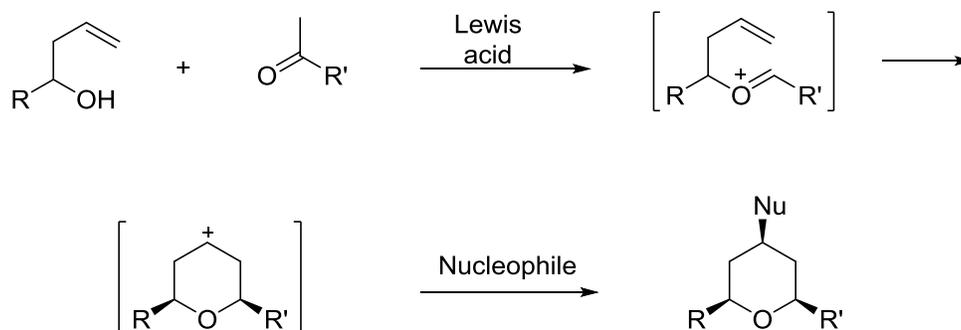
⁶⁹ (a) Evans, P. A.; Andrews, W. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 5426. (b) Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* **2011**, *13*, 1820.

⁷⁰ (a) An, C.; Jurica, J. A.; Walsh, S. P.; Hoye, A. T.; Smith, A. B. *J. Org. Chem.* **2013**, *78*, 4278. (b) Kanemoto, M.; Murata, M.; Oishi, T. *J. Org. Chem.* **2009**, *74*, 8810.

⁷¹ (a) Albury, A. M. M.; DeJoarder, D.; Jennings, M. P. *Tetrahedron Lett.* **2015**, *56*, 3057. (b) Albury, A. M. M.; DeJoarder, D.; Jennings, M. P. *J. Org. Chem.* **2012**, *77*, 6929. (c) Sharpe, R. J.; Jennings, M. P.; *J. Org. Chem.* **2011**, *76*, 8027.

⁷² (a) Beaver, M. G.; Buscagan, T. M.; Lavinda, O.; Woerpel, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 1816. (b) Tran, V. T.; Woerpel, K. A.; *J. Org. Chem.* **2013**, *78*, 6609. (c) Beaver, M. G.; Woerpel, K. A. *J. Org. Chem.* **2010**, *75*, 1107.

The Prins reaction generally refers to a reaction conducted with an alkene and formaldehyde in the presence of an acid catalyst, such as the reaction between styrene and formaldehyde in the presence of aqueous sulfuric acid.⁷³ Products obtained under these conditions include mixtures of 1,3-dioxanes, 1,3-glycols, tetrahydropyrans, and allylic and



Scheme 3.1: Condensation based approach to Prins-type cyclizations

homoallylic alcohols depending on the reaction conditions. More specifically, the Prins cyclization reaction involves a Lewis acid-catalyzed electrophilic addition of an aldehyde or ketone to homoallylic alcohols, and proceeds through intramolecular π -nucleophilic attack on an oxocarbenium cation to generate ring structures through carbon-oxygen and carbon-carbon bond formation (Scheme 3.1). Variations of the reaction have been employed to prepare halogenated tetrahydropyran and dioxane derivatives with predictable and often excellent stereocontrol.^{67, 74, 75} For example, the Prins cyclization was featured in the synthesis of *Helicobacter pylori* inhibitor (+)-spiroloxine reported by Dallavalle and co-workers (Scheme 3.2).⁷⁶ Treatment of homoallylic alcohol **56** with hemiacetal **57** (functioning as a masked aldehyde) under Lewis acidic conditions

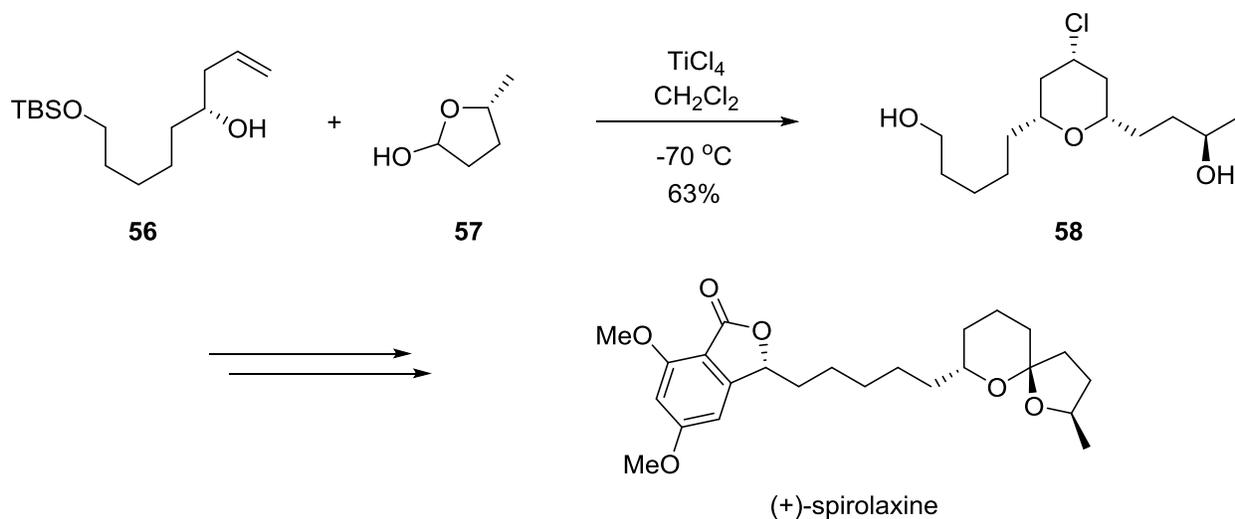
⁷³ (a) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1072. (b) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1510.

⁷⁴ Dziedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678.

⁷⁵ Huang, S.; Du, G.; Lee, C.-S. *J. Org. Chem.* **2011**, *76*, 6534.

⁷⁶ Nannei, R.; Dallavalle, S.; Merlini, L.; Bava, A.; Nasini, G. *J. Org. Chem.* **2006**, *71*, 6277.

at -70 °C generated the tetrahydropyranyl cation intermediate which was quenched by nucleophilic addition of chloride to generate the chlorinated tetrahydropyran **58** in 63% yield.



Scheme 3.2: Dallavalle's approach to (+)-spirolaxine

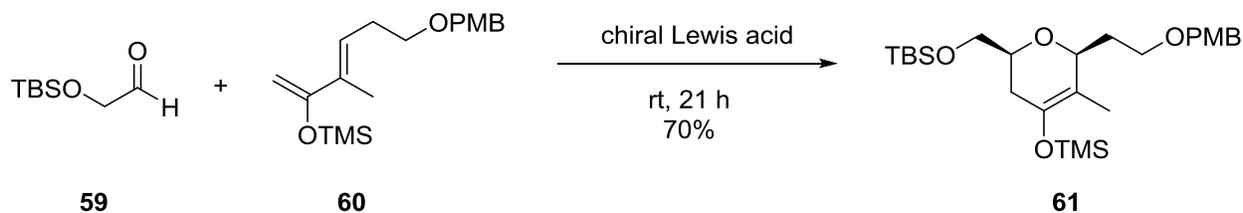
While the Prins cyclization reaction has proven to be an effective method of generating tetrahydropyran derivatives, the reaction requires precursors containing carbonyl and preferentially terminal alkene functional groups. Additionally, Lewis acidic conditions are necessary to generate the desired tetrahydropyran which may not be compatible with certain substrates.

The hetero-Diels-Alder cyclization is another effective method of generating tetrahydropyran derivatives. An oxo-Diels-Alder cyclization is a modification of the traditional Diels-Alder reaction, and involves a reaction between a reactive diene and an aldehyde or ketone. The Sasaki group in route to the natural product (-)-polycavernoside A constructed the dihydropyran ring **61** by a catalytic oxo-Diels-Alder cyclization approach using aldehyde **59** and silyloxy diene **60** mediated by a chiral Lewis acid (Scheme 3.3).⁷⁷ These types of reactions can

⁷⁷ Kasai, Y.; Ito, T.; Sasaki, M. *Org. Lett.* **2012**, *14*, 3186.

often proceed in poor yield unless highly reactive dienes or Lewis acidic catalysts are used.

Additionally, the reactions proceed with poor stereoselectivity unless chiral Lewis acids are used.

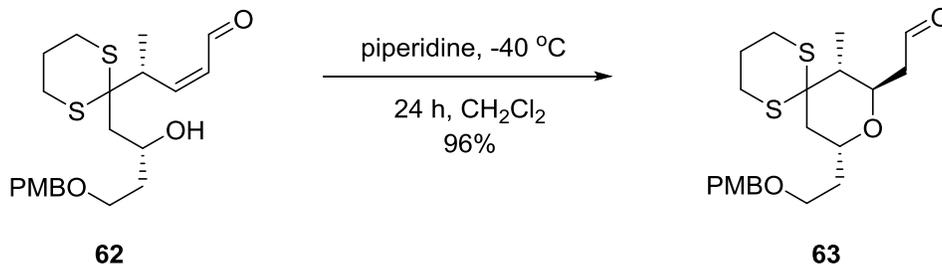


Scheme 3.3: Oxo-diels alder cyclization to form dihydropyran **56**

Another popular method for tetrahydropyran formation invokes an oxy-Michael reaction.

Lee and co-workers highlighted its utility as a key step in the synthesis of leucascandrolide A.⁷⁸

The tetrahydropyran **63** was formed in 96% yield and a 10:1 diastereomeric ratio (dr) from aldehyde **62** and catalytic piperidine at -40 °C (Scheme 3.4).



Scheme 3.4: oxy-Michael approach to preparation of tetrahydropyran **63**

Other methods for tetrahydropyran formation worth recognizing are ring-closing metathesis,⁷⁹ radical cyclizations,⁸⁰ and metal-mediated cyclizations.⁸¹ All published methods for the preparation of chiral polysubstituted tetrahydropyrans are very effective in generating the

⁷⁸ Lee, K.; Kim, H.; Hong, J. *Org. Lett.* **2011**, *13*, 2722.

⁷⁹ Lee, H.-Y.; Lee, S.-S.; Kim, H. S.; Lee, K. M. *Eur. J. Org. Chem.* **2012**, 4192.

⁸⁰ Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047.

⁸¹ Palimkar, S. S.; Uenishi, J.; Ii, H. *J. Org. Chem.* **2012**, *77*, 388.

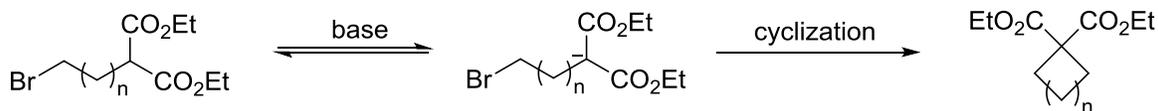
target structures with specific configurations at one or more of the chiral centers in the product. However, no unified approach is available to offer both step economy *and* the ability to form any desired configuration at multiple chiral centers in the preparation of a variety of polysubstituted tetrahydropyrans. Developing a step economic approach with the ability to obtain any desired configuration at multiple chiral centers would expedite the preparation of libraries of polysubstituted tetrahydropyran derivatives with clear advantages for both target-directed synthesis and drug discovery.

3.3 Relative Rates of Cyclization

A key aspect of cyclizations that must be considered is competing rates of cyclization. Competing cyclizations can have major implications on the outcome of a reaction and must be taken into consideration when conceptualizing the approach to a cyclic target. Several factors including entropic and enthalpic factors, transition state energies, substitution patterns, and the nature of the nucleophile can affect the rate and product distribution in a cyclization reaction.

Mandolini and co-workers did an extensive study on the kinetics of base-promoted ring closure of diethyl (ω -bromoalkyl) malonates in DMSO (Scheme 3.5).⁸² As a result of the study, the following trend was established for rate of ring closure: 5 > 6 > 4 > 7 > 8-10, where 5-membered rings form > 100 times faster than 6-membered rings. Interestingly, in the case of carbocycle formation, the difference in the cyclization rates of the 6- and 4-membered rings in the malonate studies were similar, with the 6-member ring formation only being about 1.7 times faster. This suggests that the high strain energy in the transition state for the 4-membered ring only plays a minor role in the overall kinetics of the ring closure. However, in other

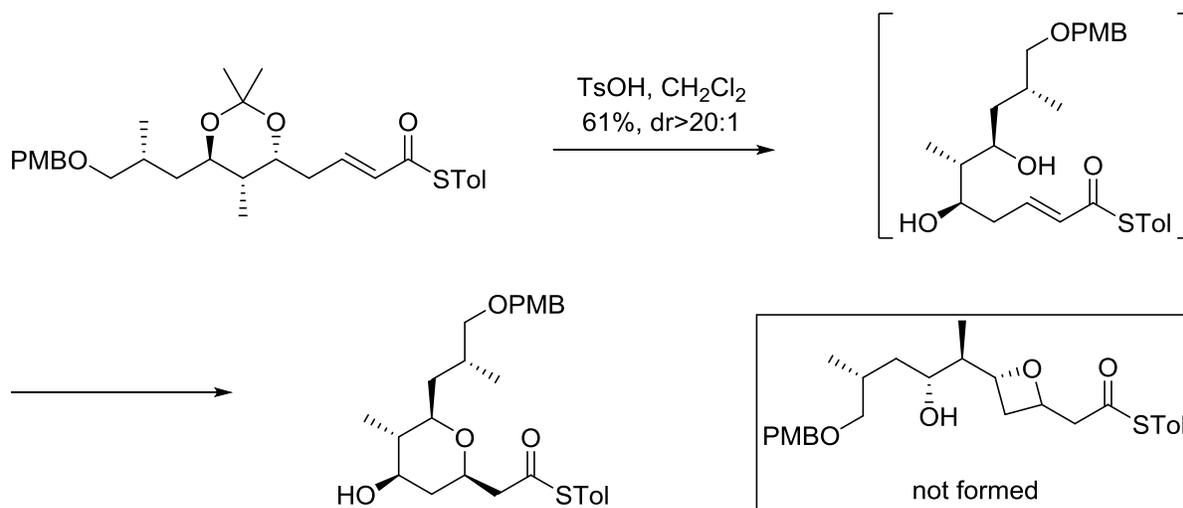
⁸² Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.



Scheme 3.5: carbocycle formation from diethyl bromoalkyl malonates

examples of ring closure (i.e. cyclic ethers, cyclic amines, lactones) the rate of 6-member ring formation can be substantially higher than that of 4-membered rings.⁸³

Synthetic approaches are often designed to take advantage of relative rates of cyclization. Exploiting the difference in ring closure kinetics can often eliminate the need for a protection/deprotection step in a synthetic route. For example, in the synthesis of the C1-C11 subunit of madeirolide A, the 6-membered oxacycle is preferentially formed instead of the 4-membered oxacycle through an oxy-Michael cyclization (Scheme 3.6).⁸⁴



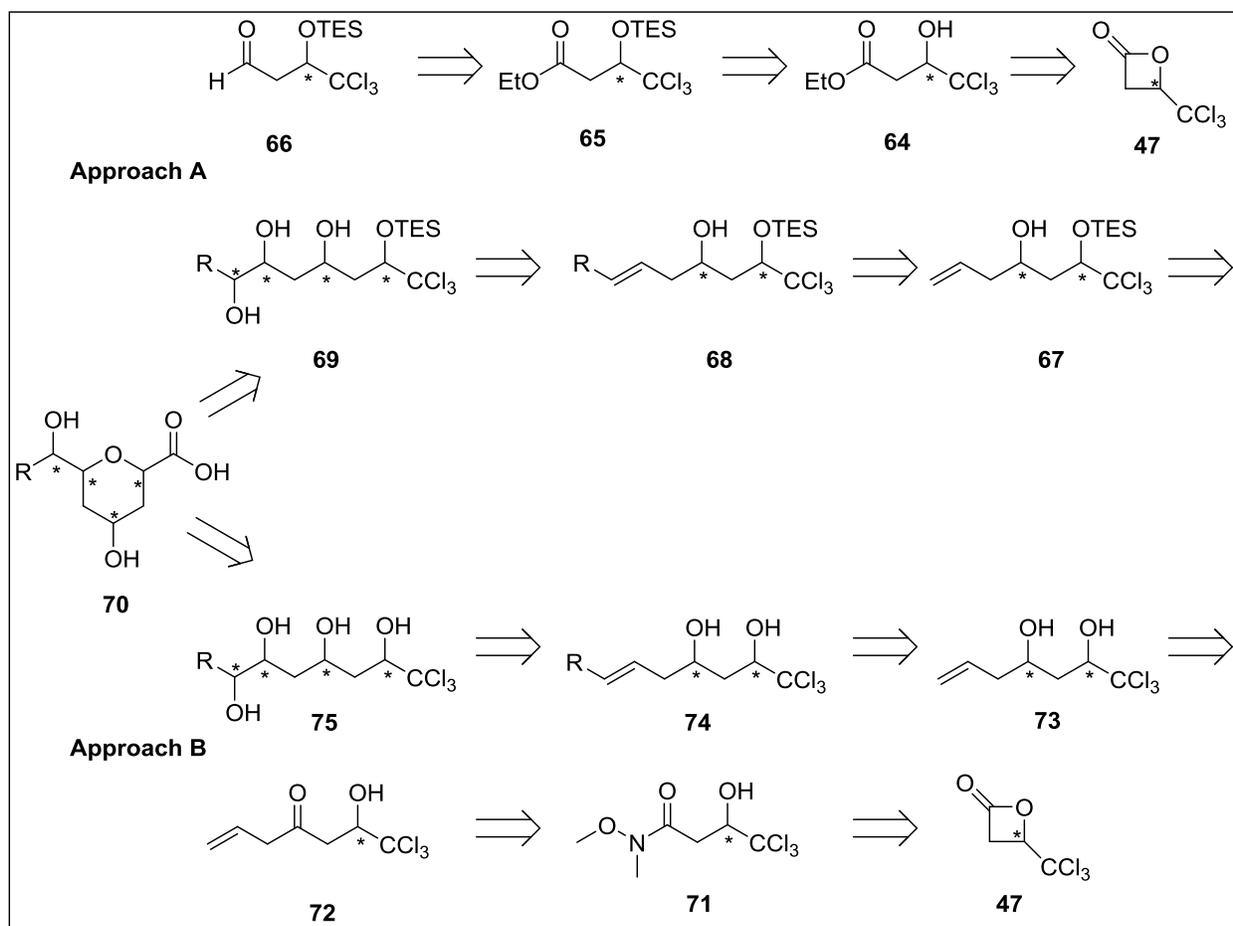
Scheme 3.6: preferential formation of a 6-membered oxacycle

⁸³ (a) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183. (b) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. J. *Am. Chem. Soc.* **1977**, *99*, 2591.

⁸⁴ Paterson, I.; Haslett, G. W.; *Org. Lett.* **2013**, *15*, 1338.

3.4 Planned Approach for Formation of Polysubstituted Oxacycles

Two conceptualized approaches were envisioned for the preparation of the tetrahydropyran derivatives (Scheme 3.7). One key aspect of the synthesis is to be able to obtain the homoallylic diols **67** and **73** in a stereoselective manner. The plan outlined in Approach A was to obtain intermediate **67** from a Brown allylation⁸⁵ of **66**. Approach B aimed to create the homoallylic alcohols by means of a Prasad⁸⁶ or Evans⁸⁷ reduction, following allylation of Weinreb amide **71**. Grubbs cross metathesis⁸⁸ of the resulting homoallylic alcohols in either



Scheme 3.7: Conceptualized approaches to tetrahydropyran **70**

⁸⁵ Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

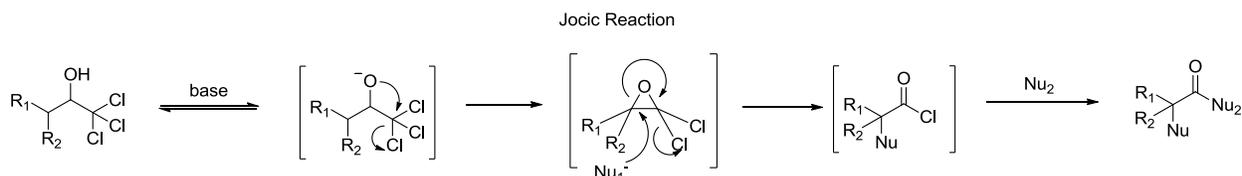
⁸⁶ Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.

⁸⁷ Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

⁸⁸ Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

route allows a library of functionalized olefins to be prepared in a divergent manner. The tetraol precursor to the final product can be prepared stereoselectively from functionalized and unfunctionalized olefins through a modified Sharpless⁸⁹ asymmetric dihydroxylation reaction to establish the desired configuration at two additional chiral centers.

We envisioned the synthesis of disparate tetrahydropyrans of type **70** was possible in 6-7 steps. The key reaction involves a novel Jovic-(Jovic-Reeve)⁹⁰ type reaction in the final step to convert the tetraol **69** or **75** to **70**. The Jovic reaction proceeds through deprotonation of a trichloromethyl carbinol to form a reactive *gem*-dichloroepoxide intermediate (Scheme 3.8). Subsequent nucleophilic substitution to the epoxide occurs regioselectively at the α -carbon (non-chloride bearing carbon) to form α -substituted acid chlorides. The substituted acid chlorides can react further due to their susceptibility to nucleophilic acyl substitution to afford a wide range of acid derivatives.⁹¹ The novel Jovic reaction employed in the synthesis involves intramolecular nucleophilic α -substitution on the *gem*-dichloroepoxide by the alkoxy anion at C-6 to form the



Scheme 3.8: General mechanism for the Jovic reaction

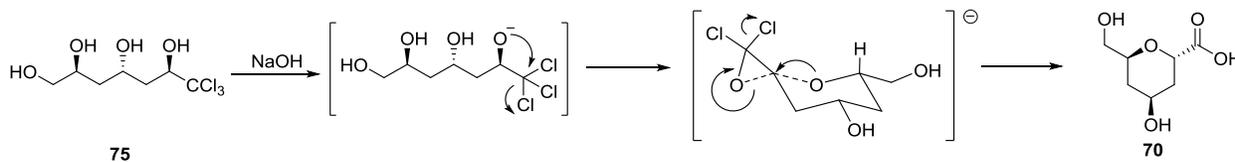
heterocyclic product. The transformation as applied to polysubstituted tetrahydropyran synthesis with a specific diastereomer is depicted in Scheme 3.9. Construction of the heterocycle takes advantage of the relative rates of ring formation, and the ability to form the low energy chair

⁸⁹ Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986.

⁹⁰ Jovic, Z. *Zh. Russ. Fiz. Khim. Ova.* **1897**, *29*, 97.

⁹¹ For a review of applications of Jovic-Reeve reactions, see: Snowden, T. S. *ARKIVOC (Gainesville, FL, U. S.)* **2012**, 24.

conformer demonstrates why the 6-membered ring is preferred. With an excess of sodium hydroxide present, the α -substituted acid chloride can undergo nucleophilic acyl substitution to furnish the carboxylic acid derivatives.



Scheme 3.9: Tetrahydropyran ring construction mechanism with (2*R*,4*S*,6*S*) - 2,4,6,7 – tetraol

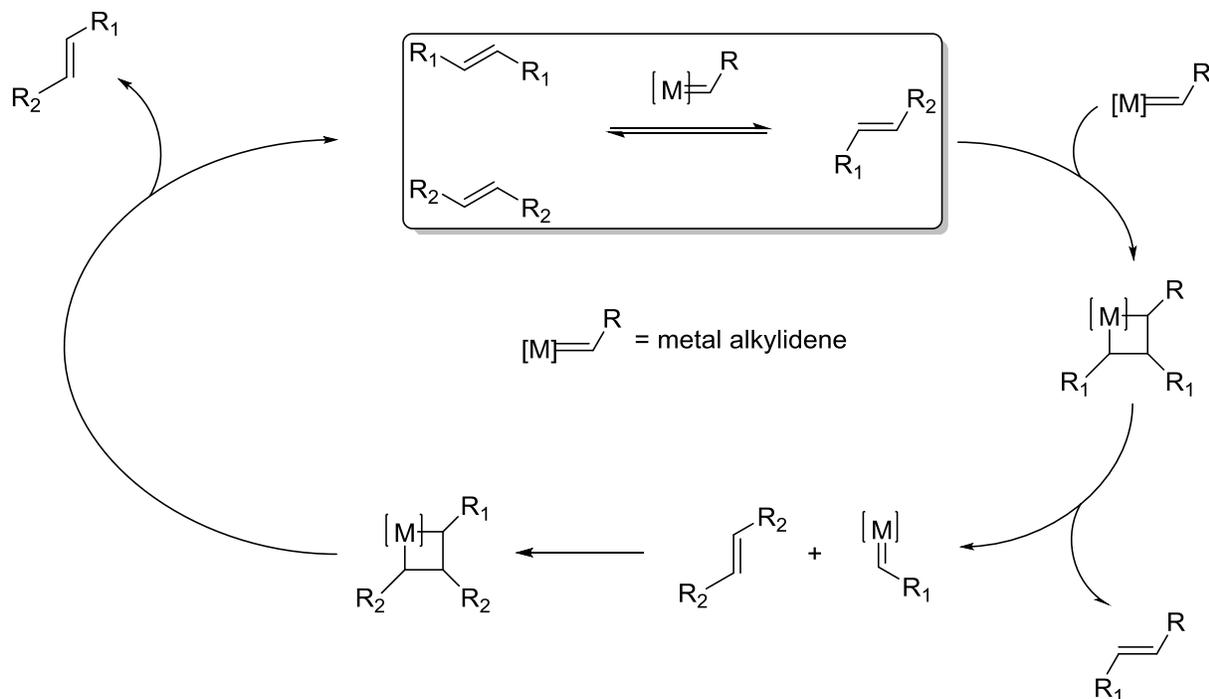
Both routes shown in Scheme 3.7 offer certain advantages and disadvantages. Approach A requires more steps than approach B, but avoids the use of expensive reagents such as the borohydride (tetramethylammonium triacetoxyborohydride) used in the Evans reduction. Another advantage to approach A is the ability to allylate the aldehyde, while stereoselectively generating the homoallylic alcohol. The aldehyde **66** can be prepared by procedures that are described in the literature.⁹² Asymmetric allylation of **66**, however, resulted in only modest diastereoselectivity (dr: 4:1). As a result, approach B was chosen as the primary route (vide *infra*).

3.4.1 Olefin Functionalization by Ruthenium-Based Cross Metathesis: Historical Background

Since its discovery, olefin metathesis has been a widely used method for carbon-carbon bond formation that involves metal-carbene-catalyzed cleavage followed by reconstruction of the carbon-carbon double bonds (Figure 3.2). The first instance of a carbon-carbon double bond rearrangement was reported by Anderson and Merckling in a titanium-catalyzed polymerization

⁹² Tennyson, R. L.; Cortez, G. S.; Galicia, H. J.; Kreiman, C. R.; Thompson, C. M.; Romo, D. *Org. Lett.* **2002**, *4*, 533.

of norbornene.⁹³ Their pioneering work led to a new disproportionation reaction reported years later by Banks and Bailey in which olefins are converted to homologues of various lengths.⁹⁴ Calderon and co-workers later coined the term “olefin metathesis”,⁹⁵ and by the late 60’s, the Phillips’ group highlighted the utility of olefin metathesis in a commercial process.⁹⁶ After extensive research on the metathesis mechanism and its key intermediates,⁹⁷ catalysts could be



Scheme 3.10: catalytic cycle in olefin metathesis

rationally designed and optimized for their use in metathesis processes. The generally accepted mechanism is shown in Scheme 3.10. Tebbe,⁹⁸ Schrock,⁹⁹ and Osborn,¹⁰⁰ made significant

⁹³ Anderson, A. W.; Merckling, N. G. (Du Pont de Nemours & Co.) U.S. Patent 2,721,189, 1955.

⁹⁴ Banks, R. L.; Bailey, G. C. *Ind. Eng. Chem., Prod. Res. Dev.* **1964**, *3*, 170.

⁹⁵ Calderon, N.; Chem, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, *34*, 3327.

⁹⁶ Chen, Z.; Kornfield, J. A.; Claverie, J. P.; Grubbs, R. H. *Polym. Prepr.* **1994**, *35*, 692.

⁹⁷ For a review on the olefin metathesis mechanism, see: Grubbs, R. H.; *Tetrahedron*, **2004**, *60*, 7117.

⁹⁸ Tebbe, F. N.; Parshall, G. W.; Ovenall, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 5074.

⁹⁹ Wengrovius, J.; Schrock, R. R.; Churchill, M. R.; Missert, J. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515.

¹⁰⁰ Kress, J. R. M.; Russell, M. J.; Wesolek, M. G.; Osborn, J. A. *Chem. Commun.* **1980**, 431.

contributions to the movement towards synthesis of well-defined catalysts through the use of high oxidation state, late metal complexes (Figure 3.2). Well-defined catalysts allow the propagating species in a metathesis reaction to be observed and controlled, and represent the basis of modern metathesis catalysts.

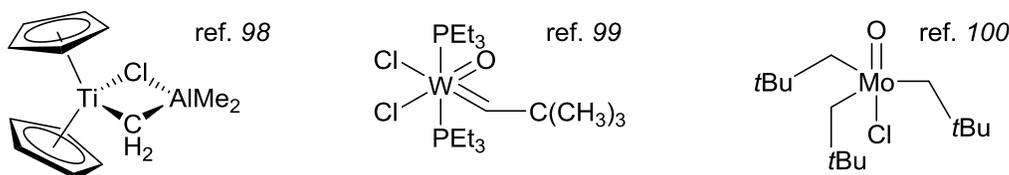


Figure 3.2: Examples of early catalysts featuring late transition metals

Schrock later developed molybdenum-based alkylidene catalysts which were the first example of efficient and controlled catalysts for metathesis reactions (Figure 3.3).¹⁰¹ These catalysts displayed high reactivity and are particularly useful in reactions involving bulky or electron deficient olefins. Despite the tremendous advancements made in metathesis processes and controlled activity of alkylidene catalysts, functional group intolerance and sensitivity to air and moisture make their use impractical in many cases. Many of the concerns related to functional group intolerance and oxophilicity were addressed by Grubbs and co-workers in the development of well-defined ruthenium-based metathesis catalysts (Figure 3.4).¹⁰² Ruthenium based catalysts have proven to be efficient metathesis catalysts due to their thermal stability and functional group tolerance, and their application has been realized in various syntheses reported in the literature.¹⁰³

¹⁰¹ Schrock, R. R.; DePue, R. T.; Feldman, J.; Schaverien, C. J.; Dewan, J. C.; Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 1423.

¹⁰² a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100; b) Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

¹⁰³ a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. b) Sanford, M. S.; Ulman, M.; Grubbs, R. H.; *J. Am. Chem. Soc.* **2001**, *123*, 749. c) Connon, S. J.; Blechert, S.; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

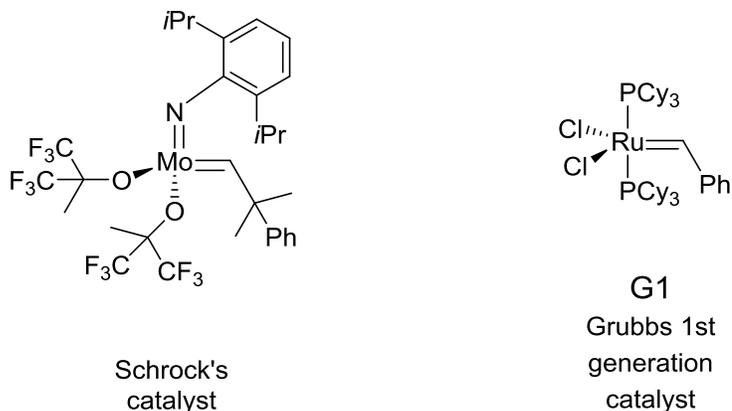


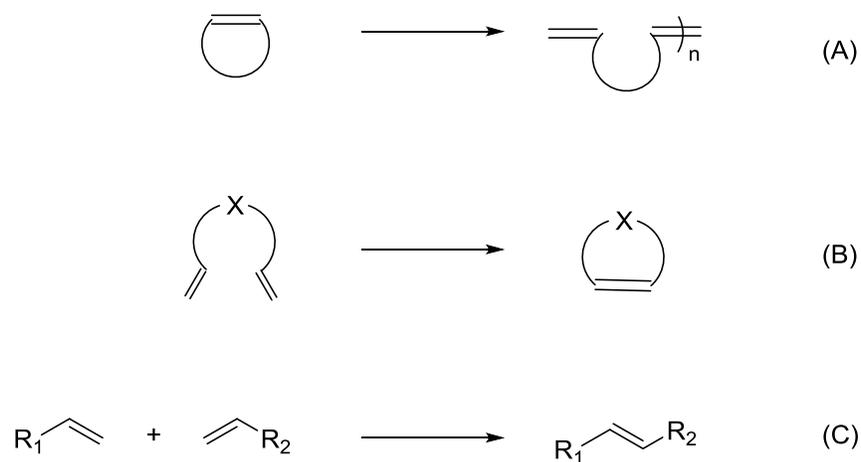
Figure 3.3: alkylidene metathesis catalysts developed by Schrock and Grubbs

3.4.1.1 Olefin Types and Influencing Their Product Distributions

Olefin metathesis can be categorized into three closely-related types of processes (Scheme 3.11): (A), ring-opening metathesis polymerization (ROMP); (B), ring-closing metathesis (RCM); and (C), acyclic cross metathesis (CM).¹⁰⁴ In the case of CM, the ability to predict product distribution and stereoselectivity is crucial for a successful transformation. Following investigation of a wide range of olefins bearing various functional groups and substitution patterns, Grubbs and co-workers developed a general model to predictably determine the product selectivity and stereoselectivity in CM reactions.¹⁰⁵ The model categorizes olefins into types I-IV based on their ability to homodimerize, and the ability of their homodimers to undergo secondary metathesis (direct participation in productive CM to form the desired product).

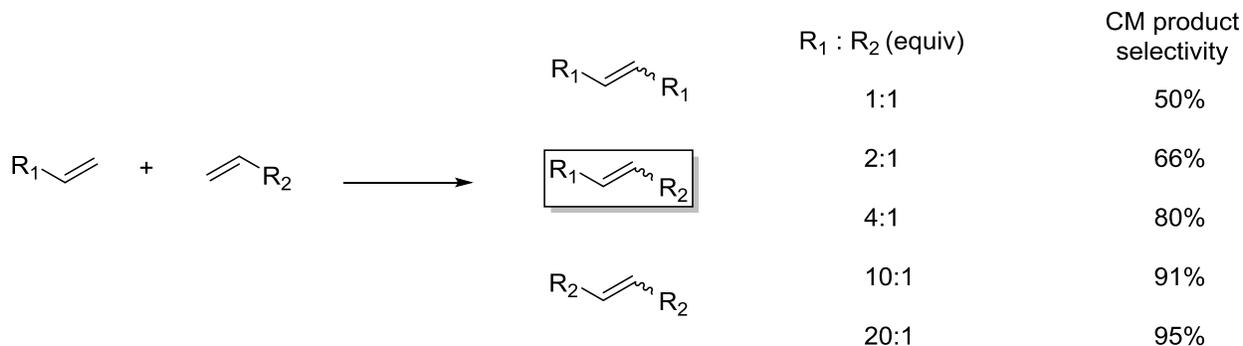
¹⁰⁴ Chang, S.; Grubbs, R. H. *Tetrahedron*, **1998**, *54*, 4413.

¹⁰⁵ Chatterjee, A. K.; Choi, T. -L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.



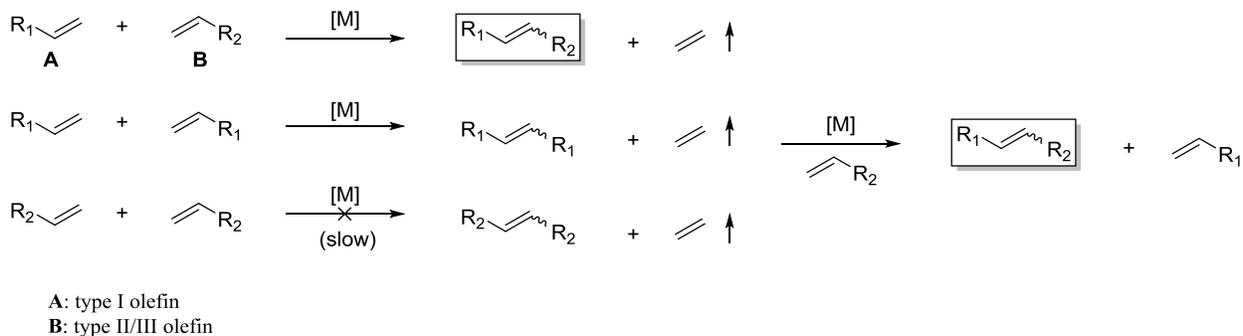
Scheme 3.11: Olefin metathesis processes

Type I olefins are described as those that rapidly undergo homodimerization and whose homodimers as well as the terminal olefin monomer can participate in CM. Olefins of this type generally include terminal, mono-substituted olefins, styrene, 1° allylic alcohols, allyl halides, allyl boronate esters, and allyl silanes. Type II olefins only slowly dimerize, however, unlike type I olefins, the homodimers are generally unreactive and only sparingly participate in productive CM reactions. Examples of type II olefins include acrylates, acrylamides, acrylic acids, acrolein, vinyl ketones, and 2° allylic alcohols. Type III olefins do not undergo homodimerization but can undergo productive CM reactions with type I or type II olefins. Olefins of this type include 1, 1-disubstituted olefins, non-bulky trisubstituted olefins, and 3° allylic alcohols. Type IV olefins are spectators to CM reactions as they do not homodimerize or undergo productive CM with other olefins. Additionally, type IV olefins do not inhibit catalyst activity toward productive CM reactions. In general, unhindered electron rich olefins fall under a type I classification, while sterically hindered and/or electron deficient olefins fall under classes II – IV.



Scheme 3.12: statistical distribution of products in a non-selective CM reaction

Generally, when two olefins of the same type with similar reactivity are combined, a non-selective mixture of products is formed. For example, when two type I olefins are used in a reaction, a statistical distribution of products is formed and only 50% of the desired CM product can be obtained (Scheme 3.12). Type I olefins rapidly homodimerize, and an equilibrium will be established with the desired CM product and the homodimers through secondary metathesis. To increase the percentage of desired CM product, an excess of one of the CM partners must be used. When one CM partner is used in a 10-fold excess, 91% of the CM product can statistically be obtained. To avoid the statistical distribution of products and achieve more selective CM, olefins from two different types must be used. For example, when a type I olefin and a type II or



Scheme 3.13: Selective CM reaction between type I and type II/III olefins

III olefin are combined, the type I olefin will homodimerize initially, but the equilibrium will be entropically driven toward the desired CM product as ethylene leaves the system. This prevents the terminal olefin from regenerating and the type I homodimer will readily undergo secondary metathesis to form the product (Scheme 3.13).

3.4.1.2 Ruthenium Catalysts and Their Reactivities

Among the well-defined alkylidene catalysts used for olefin metathesis reactions, those that are arguably the most popular include the molybdenum-based alkylidene **76**, and ruthenium-based alkylidenes **77-79** (Figure 3.4). The catalysts all share common features including a metal alkylidene, two anionic ligands, and two neutral ligands. Catalyst **76** exhibits remarkably high metathesis activity especially with electron deficient olefins, however, it is incompatible with many functional groups and is sensitive to air and moisture. Ruthenium catalysts **77-79**

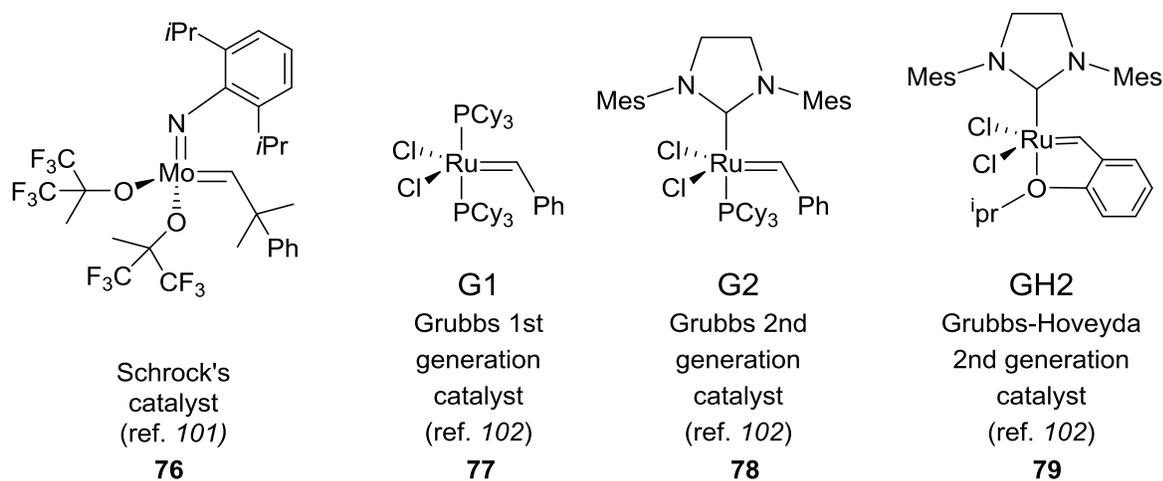
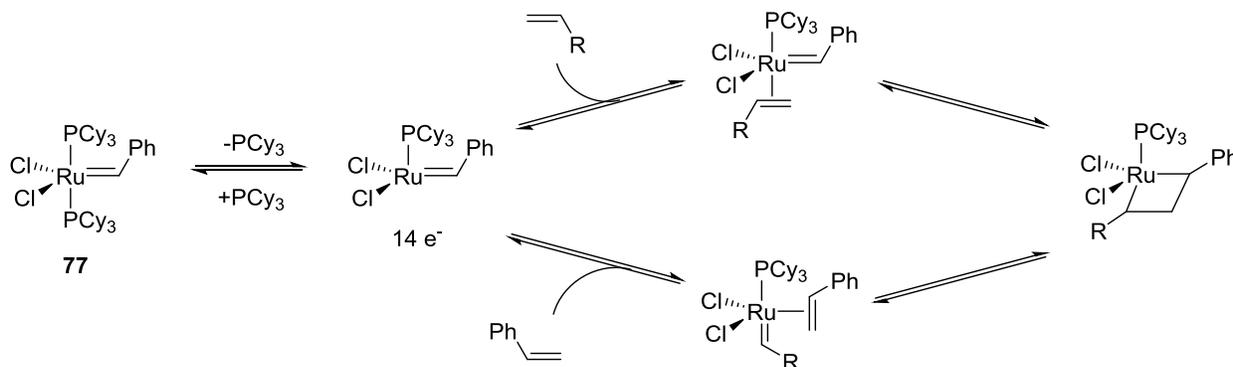


Figure 3.4: alkylidene-based metathesis catalysts

are more functional group tolerant and thermally stable than catalyst **76**. Substitution of the tricyclohexyl phosphine ligand in **77** with stable *N*-heterocyclic carbene (NHC) ligand H₂IMes led to interesting changes in reactivity. Catalyst **78** shows high activity, functional group

tolerance, and higher thermal stability than that of **77**. Substituting the second phosphine ligand with a bidentate alkylidene leads to even higher thermal stability, as well as enhanced oxygen- and moisture-tolerance in **79**.

Crucial to the development and understanding of fundamental catalytic pathways was a key finding that the reaction proceeds through a 14-electron species following dissociation of a neutral phosphine ligand.¹⁰⁶ The catalytic cycle depicted with complex **77** is shown in Scheme 3.14. The tricyclohexyl phosphine ligand provides optimal catalyst activity; less bulky phosphines bind the metal center too strongly and are unable to dissociate effectively, and phosphines with larger cone angles are too labile to produce a stable complex.



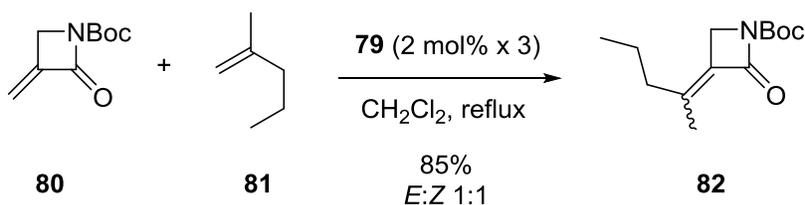
Scheme 3.14: catalytic CM intermediates

The improvement in activity of the NHC catalyst **78** has been attributed to the increased affinity of the NHC ligand for π -acidic olefins. Initially it was believed that the improved activity of **78** stemmed from the trans-influence of the NHC ligands, leading to a faster dissociation rate of the phosphine ligand. However, mechanistic evidence revealed that phosphine dissociation in

¹⁰⁶ Dias, L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

77 was actually 100 times faster than **78**.¹⁰⁷ This result emphasizes the fact that catalyst activity doesn't depend solely on the rate of dissociation. Overall catalyst activity depends on several factors including initiation through phosphine dissociation, phosphine re-association, olefin association with the 14-electron species, and catalyst decomposition rate. NHC ligands are strong σ -donors and poor π -acceptors. The metal-NHC bond is less labile than the corresponding metal-phosphine bond, which may also help explain the increased thermal and oxidative stability of the catalytic intermediates. In short, the NHC ligand is an excellent electron donor that aids in stabilizing the intermediates, and the phosphine provides the labile ligand to initiate the reaction.

Increased thermal catalytic stability can be particularly advantageous in reactions that form a significant amount of the *Z*-alkene isomer. Performing the reaction with a more thermally stable catalyst such as **78** will generate a much higher amount of the more thermodynamically favored *E*-alkene. This is likely due to secondary metathesis on the CM product.¹⁰⁵ The bidentate catalyst **79** proved to be useful in the preparation of the sterically demanding lactams **82** (Scheme 3.15).¹⁰⁸ Treatment of the two type III olefins with catalyst **79** in refluxing CH_2Cl_2 afforded product **82** in 85% yield and *E:Z* ratio of 1:1. Initially, only moderate yields of **82** were obtained, however, yields were dramatically improved with portion-wise addition of the catalyst. Significantly, the report was the first example of CM to form tetrasubstituted alkenes.



Scheme 3.15: Formation of tetrasubstituted alkenes with **79**

¹⁰⁷ (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543. (b) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749.

¹⁰⁸ Liang, Y.; Raju, R.; Le, T.; Taylor, C. D.; Howell, A. R. *Tetrahedron Lett* **2009**, *50*, 1020.

3.4.1.3 Undesired Olefin Isomerization

Despite the tremendous amount of success related to metathesis processes, several problems associated with cross metathesis still remain. In particular, prevention of olefin isomerization and cross metathesis of sterically demanding substrates are challenges that are often encountered.¹⁰⁹ Olefin isomerization/migration is a side reaction often observed in olefin metathesis reactions that can significantly lower the yield of the desired product or alter the product distribution. Additionally, byproducts formed from unwanted isomerization can lead to complications related to isolation of the desired product.

It has been suspected that olefin isomerization in cross metathesis reactions is caused by a ruthenium hydride species either generated by decomposition of the metathesis catalyst *in situ*, or as an impurity formed in the preparation of the commercial reagent. Grubbs reported the observance of a decomposition product **83** in the preparation of catalyst **78** where the Ru metal center inserted into a C-H bond of one of the mesityl groups (Figure 3.5).¹¹⁰ There are also reports of decomposition of catalysts **77** and **78** into hydrido-carbonyl-chloride complexes

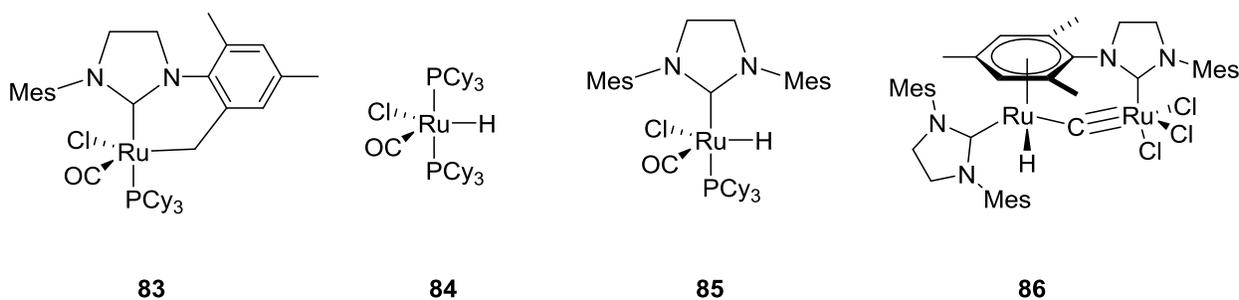


Figure 3.5: Ruthenium decomposition products and hydride species

¹⁰⁹ (a) Pederson, R. L.; Fellows, I. M.; Ung, T. A.; Ishihara, H.; Hajela, S. *Adv. Synth. Catal.* **2002**, *344*, 728. (b) Lehman, S. E.; Schwendeman, J. E.; O'Donnell, P. M.; Wagener, K. B. *Inorg. Chim. Acta.* **2003**, *345*, 190. (c) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865.

¹¹⁰ Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546.

84 and **85** in methanol.¹¹¹ In fact, terminal monosubstituted olefins can be isomerized to the internal crotyl olefin with **78** in the presence of methanol in >80% yield.¹¹² There are also reports that hydride species **85** can be generated upon prolonged heating of **78** in the presence of substrates bearing oxygen atoms such as ethyl vinyl ether.¹¹⁰ The pathway leading to Ru-H formation in aprotic solvents is less apparent; however, Grubbs and co-workers were able to isolate and characterize Ru-H **86** after stirring the methylidene adduct **80** in benzene at 55 °C for 72 hours (Scheme 3.16).¹¹³ Furthermore, **86** was found to promote alkene isomerization of allyl benzene to 2-methylstyrene in 76% yield under normal metathesis conditions in subsequent experiments.¹¹⁴

Following isolation and characterization of **86**, Grubbs proposed a mechanism for its formation by decomposition of the methylidene species **87** (Scheme 3.16). Grubbs reasoned that ruthenium hydride species (**84** or **85**) are not formed under typical metathesis conditions from the parent ruthenium benzylidene complex **78**. However, ruthenium methylidene species are common byproducts formed during a metathesis reaction and studying their decomposition may provide a more revealing pathway for catalyst decomposition. The proposed mechanism was supported by isolation and characterization of the ruthenium hydride **86**, as well as the phosphonium salt **91**. Decomposition begins with nucleophilic attack of the dissociated tricyclohexylphosphine on the 14-electron methylidene **87**. Following elimination of the phosphonium methyl ylide, the 12-electron intermediate **89** binds the pi-system of a neighboring mesityl ring to form the bridged species **90**. HCl abstraction by the phosphonium ylide leads to

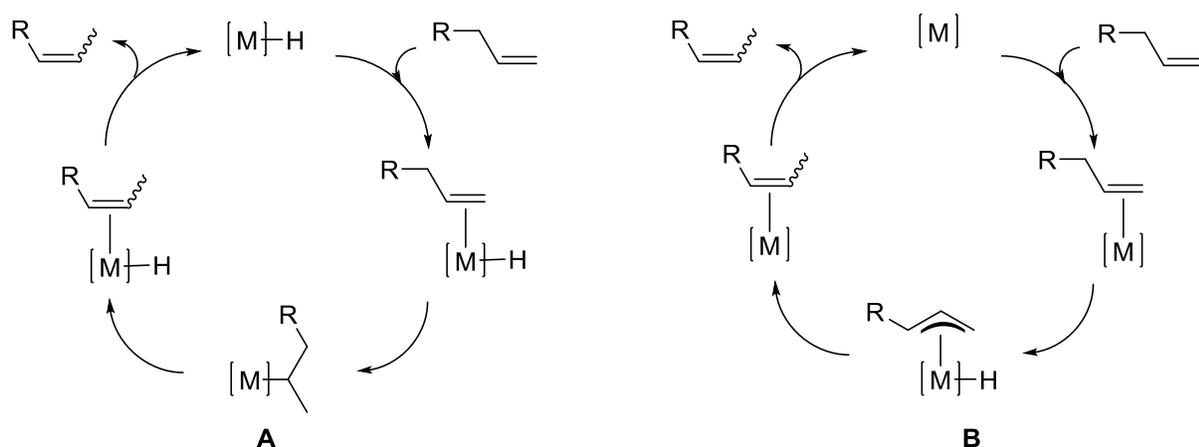
¹¹¹ a) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089. b) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827.

¹¹² Hanessian, S.; Giroux, S.; Larrson, A. *Org. Lett.* **2006**, *8*, 5481.

¹¹³ Hong, S.-H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

¹¹⁴ Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

While the exact mechanism of ruthenium hydride-promoted isomerization is unknown, it can potentially be explained by a metal-based hydride pathway,¹¹⁵ or a π -allyl pathway.¹¹⁶ The two possible mechanisms for isomerization with Ru-H species are shown in Scheme 3.17. Pathway A depicts the hydride addition-elimination pathway in which a secondary metal alkyl is formed, followed by β -hydride elimination to form isomerized olefin. Pathway B involves a π -allyl metal hydride mechanism in which insertion of an allylic C-H to the metal generates a π -allyl metal hydride intermediate. Transfer of hydride to the terminal carbon leads to the isomerized olefin.



Scheme 3.17: Ruthenium hydride isomerization pathways

Experimental evidence seems to suggest that high temperatures and prolonged reaction times can lead to the formation of Ru-H species. Efforts directed toward inhibiting olefin isomerization have focused on using additives to serve as Ru-H scavengers,¹¹⁷ or rate enhancers.¹¹⁸

¹¹⁵ Parshall, G. W. *Homogeneous Catalysis*; Wiley: New York, 1980; p 31-35.

¹¹⁶ Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; Wiley: New York, 1988; p 188-190.

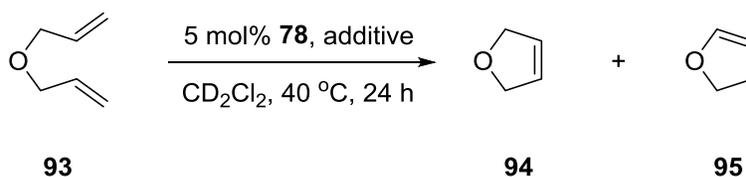
¹¹⁷ Hong, S.-H.; Sanders, D. P.; Lee, C.-W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

¹¹⁸ Hauke, S.; Schmidt, B. *Org. Biomol. Chem.* **2013**, *11*, 4194.

3.4.1.4 Suppression of Olefin Isomerization

While the pathways leading to olefin isomerization are currently not entirely understood, extensive experimental evidence has suggested that ruthenium hydride species are most likely responsible.¹¹³ To suppress unwanted isomerization by ruthenium hydride species, hydride-accepting additives are typically employed. Grubbs and co-workers successfully prevented olefin migration in α,β -unsaturated carbonyl compounds by employing moderate pK_a acids such as acetic acid, and hydride-acceptors such as 1,4-benzoquinone.¹¹⁷ Additionally, they were able to completely suppress olefin isomerization in the ring-closing metathesis of diallyl ether using the 2nd generation Grubbs catalyst **78** with acetic acid, 1,4-benzoquinone, and other electron deficient 1,4-benzoquinones such as 2,6-dichloro-1,4-benzoquinone, and tetrafluoro-1,4-benzoquinone (Table 3.1). Isomerization was more prevalent with electron-rich benzoquinones such as 2,6-dimethyl-1,4-benzoquinone, and 2,6-dimethoxy-1,4-benzoquinone.

Table 3.1: Ring-Closing metathesis of diallyl ether

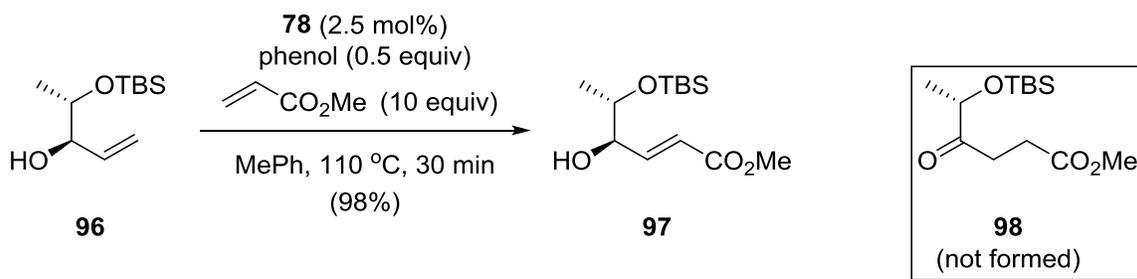


additive	equiv	Product distribution ^a	
	Relative to 93	94	95
None	0.1	< 5%	> 95%
Acetic acid	0.1	> 95%	none
1,4-benzoquinone	0.1	> 95%	none
2,6-dichloro-1,4-benzoquinone	0.1	> 99%	none
tetrafluoro-1,4-benzoquinone	0.1	> 99%	none

2,6-dimethyl-1,4-benzoquinone	0.1	16%	84%
and 2,6-dimethoxy-1,4-benzoquinone	0.1	22%	78%

^a determined from ¹H NMR

Schmidt and co-workers developed a simple and efficient method for inhibiting olefin isomerization of the allylic alcohol **96** using catalyst **78**, methyl acrylate, and phenol as an additive (Scheme 3.18).¹¹⁸ Remarkably, phenol was able to completely inhibit formation of the unsaturated ketone **98** even at 110 °C — conditions that can rapidly lead to catalyst decomposition and byproduct formation. Presumably, coordination of phenol to the 14-electron species retards catalyst decomposition, and in turn suppresses decomposition to a ruthenium hydride species.



Scheme 3.18: phenol used as an additive in preparation of allylic alcohol **97**

The work by Schmidt and co-workers was based on previous success with phenol as an additive in metathesis reactions using the first generation catalyst **77** reported by Forman and co-workers.¹¹⁹ Computational evidence suggests that phenol has a hemilabile stabilization effect where stabilization arises from an equilibrium between the active 14-electron species **99** and the lower energy species **100** (Figure 3.6). The equilibrium favors **100** by 7.8 kcal/mol, ensuring a stabilized intermediate that inhibits decomposition of the parent catalyst. Additionally,

¹¹⁹ G. S. Forman, A. E. McConnell, R. P. Tooze, W. J. van Rensburg, W. H. Meyer, M. M. Kirk, C. L. Dwyer and D. W. Serfontein, *Organometallics* **2005**, *24*, 4528.

coordination of phenol may simultaneously activate the ruthenium species with coordinating olefins for subsequent metathesis reactions.

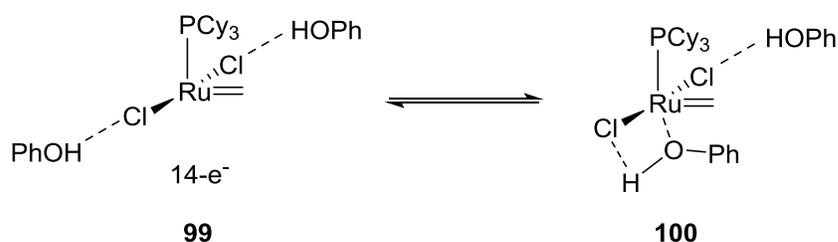


Figure 3.6: Hemilabile stabilization effect of phenol

Examples of other additives that have proven useful for preventing olefin isomerization include phenylphosphoric acid,¹²⁰ chlorodiphenylphosphine, and chlorocatecholborane.¹²¹ While many additives have been effective at preventing olefin isomerization for specific reactions, their effectiveness is often reaction specific. There currently are no general additives that can be used for any metathesis system.

3.4.2 Formation of Vicinal 1,2-Diols by Sharpless Asymmetric Dihydroxylation: Historical Background

Resulting from the need to devise a practical and efficient method for synthesizing biologically active compounds, the development and utilization of asymmetric reactions has become very attractive. Many asymmetric reactions have gained wide acceptance, and some are even used on an industrial scale. The osmium-catalyzed asymmetric dihydroxylation (AD) reaction developed by Sharpless and co-workers is a powerful method for converting olefins into non-racemic vicinal 1,2 diols.⁸⁹ The reaction exhibits enantiofacial selectivity with the olefin by employing chiral cinchona alkaloid ligands dihydroquinine (DHQ) and dihydroquinidine

¹²⁰ Gimeno, N.; Formentin, P.; Steinke, J.; Vilar, R. *Eur. J. Org. Chem.* **2007**, 918.

¹²¹ Moiese, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, 9, 1695.

(DHQD) (Figure 3.7). A variety of ligands have been developed that work with most olefins and yield specific stereoisomers in ee's commonly exceeding 95%.^{122,123}

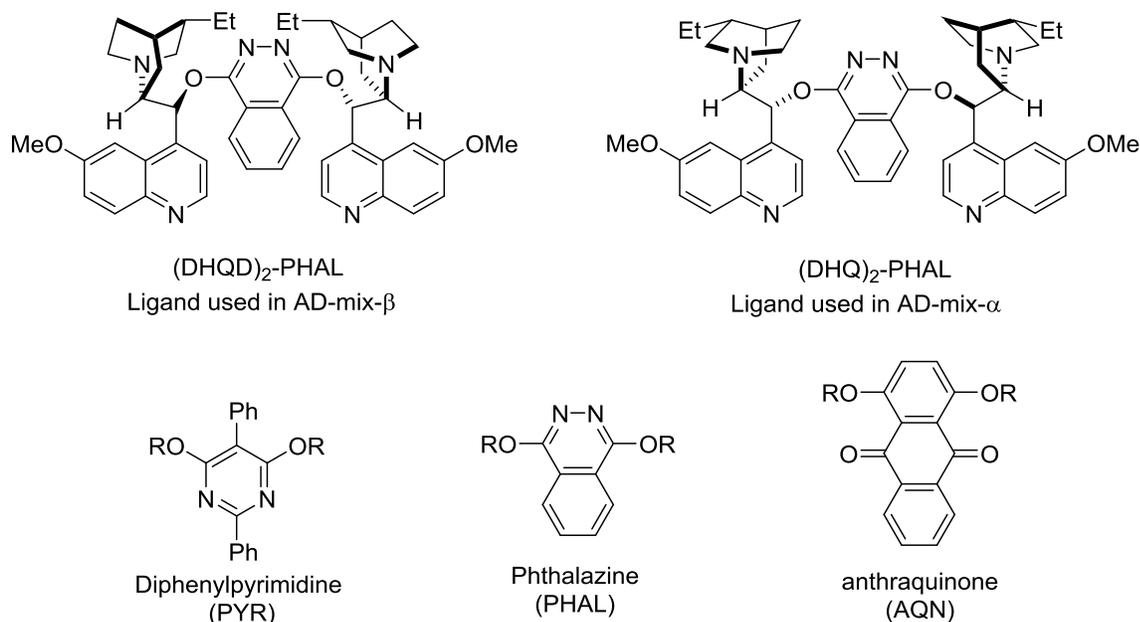


Figure 3.7: Top: commercially available ligands with dihydroquinidine (DHQD), and dihydroquinine (DHQ) alkaloids connected by a phthalazine linker. Bottom: common linkers used in dihydroxylation ligands

Early methods for converting olefins into cis diols employed oxidants such as OsO₄ or KMnO₄ in stoichiometric amounts.¹²⁴ Of the two methods, olefin oxidation with OsO₄ followed by hydrolysis of the osmium(VI) glycolate intermediate (Scheme 3.19) was often the most reliable. Criegee further developed the method by showing that the addition of pyridine

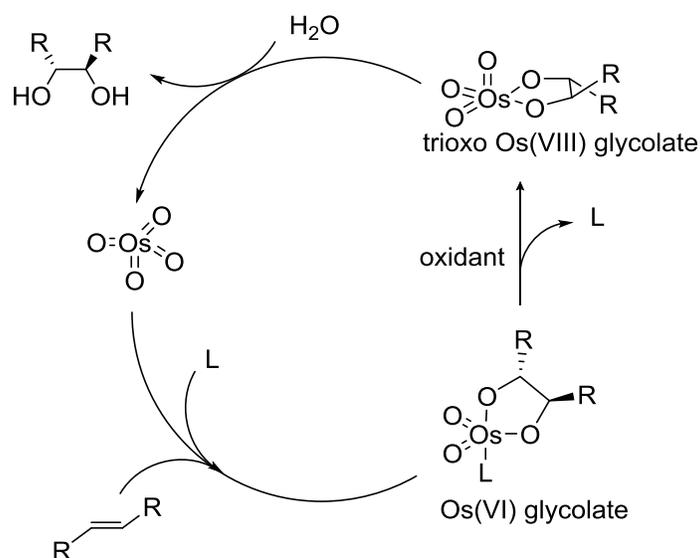
¹²² Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem Rev.* **1994**, *94*, 2483.

¹²³ Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

¹²⁴ (a) Robinson, G. M.; Robinson, R. *J. Chem. Soc.* **1925**, 127, 175. (b) Coleman, J. E.; Ricciuti, C.; Swern, D. *J. Am. Chem. Soc.* **1958**, *78*, 5342.

significantly accelerated the reaction¹²⁵ through a process now known as the ligand acceleration effect.¹²⁶

Although olefin oxidation with a stoichiometric amount of osmium tetroxide was a reliable procedure, the cost and high toxicity of OsO₄ made it impractical, especially for large scale reactions. This prompted the development of osmylation procedures in which OsO₄ could be used catalytically. To achieve catalytic dihydroxylation with OsO₄, the Os(VI) glycolate intermediate must be oxidized to the trioxo Os(VIII) glycolate followed by subsequent hydrolysis to regenerate the OsO₄ catalyst and yield the vicinal diol (Scheme 3.19). Relatively inexpensive co-oxidants such as metal chlorates¹²⁷ or hydrogen peroxide¹²⁸ are capable of



Scheme 3.19: osmium-catalyzed dihydroxylation mechanism

re-oxidizing the osmium (VI) intermediate, however these oxidants often lead to diminished yields due to over oxidation. Sharpless and Akashi attempted to suppress over-oxidation by

¹²⁵ (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, 522, 75. (b) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, 550, 99

¹²⁶ For a review on the ligand accelerated effect, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, 34, 1059.

¹²⁷ Hofmann, K. A. *Chem. Ber.* **1912**, 45, 3329.

¹²⁸ Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, 58,1302.

performing the reaction under basic conditions, and found that catalytic dihydroxylation could be achieved by using the oxidant *tert*-butyl hydroperoxide with OsO₄ in basic media. Oxidation under these conditions gave good yields of vicinal diols with a variety of olefins.¹²⁹ A group from the Upjohn Company later introduced a mild osmium-catalyzed oxidation of olefins to vicinal diols using *N*-methylnmorpholine *N*-oxide (NMO) as the cooxidant. This became known as the Upjohn Process.¹³⁰

The pioneering work of Criegee,¹²⁵ and later work by Griffith and co-workers,¹³¹ revealed that tertiary alkyl amines have a particularly high binding affinity for OsO₄ and form complexes that exhibit high stability. These results inspired Sharpless and Hentges to employ acetate esters of the chiral cinchona alkaloids DHQ and DHQD to determine their usefulness as chiral directors and make the reaction stereoselective.¹³² Experimental results showed that addition of 1 molar equivalent of the DHQ- or DHQD-acetate adduct to olefins with a stoichiometric amount of osmium tetroxide in toluene at room temperature furnished vicinal diol products with fair to high enantiomeric excess (*ee*).

Due to the success of the cinchona alkaloids ligands in achieving enantioselectivity, and the usefulness of the Upjohn Process for the oxidation of the osmate ester intermediate, the olefin dihydroxylation procedure became an increasingly effective catalytic process when the two methods were combined. Sharpless and Marko reported *ee*'s of 62% for styrene, 65% for 1-phenylpropene, and 88% for (*E*)-stilbene under these conditions.¹³³ Interestingly, the *ee*'s under these *catalytic* conditions were lower than those obtained from the *stoichiometric* reaction. These

¹²⁹ Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, 98, 1986.

¹³⁰ VanRheenen, V.; Kelley, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

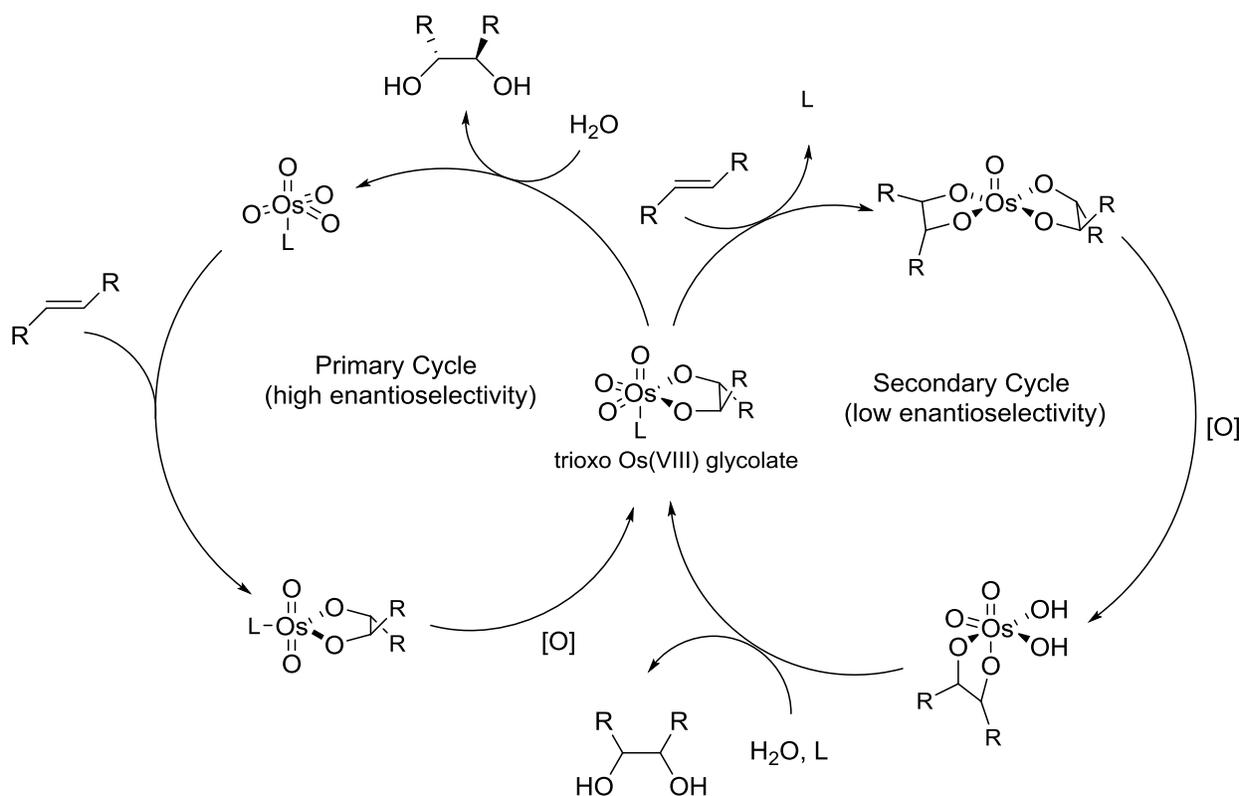
¹³¹ Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941.

¹³² Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, 102, 4263.

¹³³ Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, 110, 1968.

unexplainable results suggested that there may be a competing secondary catalytic cycle exhibiting poor or no enantioselectivity.

Investigations in search of evidence of a secondary cycle led to the significant discovery that there were in fact two diol producing cycles.¹³⁴ The key intermediate in the new proposed mechanism is the trioxo Os(VIII) glycolate (Scheme 3.20). This intermediate is in a vital position at the junction of the two cycles, and consequently determines the production of diol between the



Scheme 3.20: competing pathways in catalytic olefin dihydroxylation

cycles. Experimental results showed that the primary cycle produced diol products with high *ee* and the secondary cycle yielded diol products with low *ee*, presumably because the remote stereochemical information of the primary alcohol does not influence facial selectivity upon

¹³⁴ Wai, J. S. M.; Marko, I.; Svendson, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

oxidation of a second olefin. Slow addition of olefin to the reaction mixture can help minimize the second cycle leading to higher *ee* in the product. Additionally, inclusion of acetate was beneficial for the selectivity – nucleophilic addition of acetate to the trioxo Os(VIII) glycolate helps facilitate regeneration of the catalyst.

Other significant contributions to the development of the AD reaction were made by Hartung and Crispino in the development of ligands with two independent cinchona alkaloid ligands attached to a phthalazine core,¹³⁵ or a diphenylpyrimidine core (Figure 3.7).¹³⁶ These discoveries led to considerably higher selectivity, and significantly broadened the scope of the method. The increase in selectivity and broadened scope can be attributed to the optimal binding affinity of these ligands with the osmium center. The ligands bind strongly enough to OsO₄ to influence olefin coordination and selectivity, but not so strongly that the trioxo Os(VIII) glycolate is inert to hydrolysis.

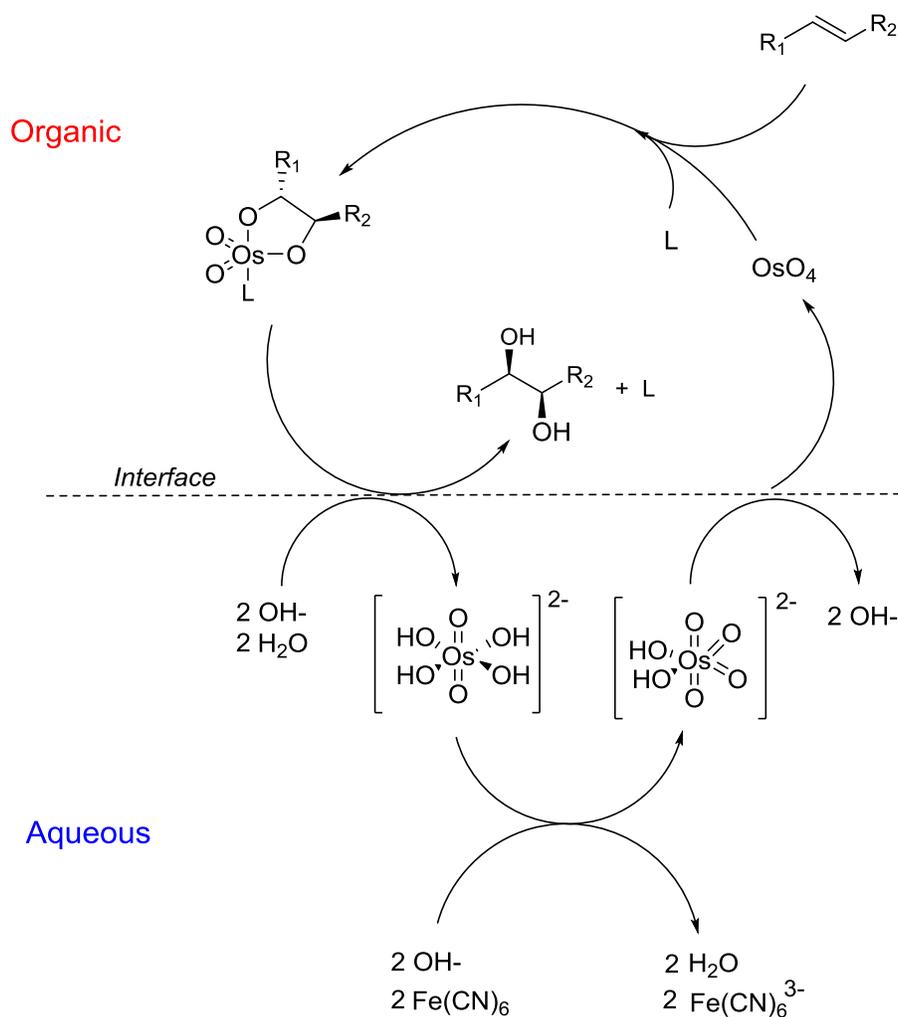
Another key contribution to the method was made by Kwong in 1990 by developing biphasic conditions with K₃Fe(CN)₆ as the co-oxidant.¹³⁷ Under these conditions, participation in the secondary cycle can be essentially eliminated (Scheme 3.21). With biphasic conditions, the only oxidant present in the organic layer is OsO₄ as opposed to the homogeneous NMO solutions. Due to the osmylation taking place in the organic layer, the Os(VI) monoglycolate intermediate undergoes hydrolysis, the diol and ligand return to the organic layer, and Os(VI) returns to the aqueous layer prior to its re-oxidation. This effectively prevents entry of the osmium glycolate intermediate into the secondary cycle. Additionally, potassium carbonate is

¹³⁵ Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K.-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844.

¹³⁶ Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

¹³⁷ Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999.

typically used to increase the pH of the solution and enhance the rate of hydrolysis of the osmium glycolate ester.



Scheme 3.21: dihydroxylation catalytic cycle under biphasic conditions

3.4.2.1 Glycolate Ester Hydrolysis

Since the proposal and discovery of the secondary cycle in the osmium-catalyzed dihydroxylation of olefins,¹³⁴ many methods have been developed to enhance the rate of hydrolysis of the osmium glycolate intermediate, and ultimately avoid its entry into the nonselective secondary cycle. Amberg found that osmium glycolate hydrolysis could be accelerated considerably in the presence of $MeSO_2NH_2$.¹²² Similar to acetate,¹³⁴ $MeSO_2NH_2$

performs nucleophilic addition to the osmium (VIII) glycolate, accelerating regeneration of the catalyst. Additionally, its increased effectiveness as opposed to acetate is attributed to its higher solubility in organic solvents. The reaction rate can be as much as 50 times faster when the additive is included, leading to high catalytic turnovers even with sterically congested substrates. This modification broadened the scope of the reaction to include tetra-substituted olefins. Also, the “sulfonamide effect” allows reactions to be conducted at 0 °C, further enhancing the asymmetric transformation. Methyl sulfonamide is routinely added to reaction mixtures to enhance the rate of glycolate ester hydrolysis with all olefins except for mono-substituted terminal olefins.

Beller and co-workers studied the AD reaction under pH controlled conditions to improve the rate and stereoselectivity.¹³⁸ The dihydroxylation of *trans*-5-decene was examined under typical AD conditions with commercially available AD-mix-β (0.4 mol% K₂[OsO₂(OH)₄], 1 mol% (DHQD)₂PHAL, 3 equiv K₃Fe(CN)₆, 3 equiv K₂CO₃) in *t*-BuOH/H₂O. The initial pH of the solution was 12.2, but decreased to a value of 9.9 after 34 hours. Beller reasoned that two hydroxide ions are consumed for every molecule of *trans*-5-decene that is dihydroxylated which explains the continuous decrease in pH over time (Figure 3.8). Consequently, product formation becomes significantly slower as the pH decreases, presumably due to the slower rate of

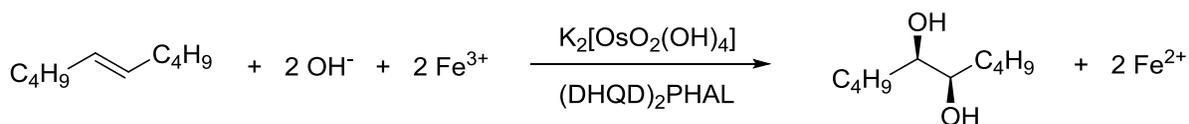


Figure 3.8: asymmetric dihydroxylation stoichiometry

¹³⁸ Mehlretter, G. M.; Dobler, C.; Sundermeier, U.; Beller, M. *Tetrahedron Lett.* **2000**, *41*, 8083.

hydrolysis of the osmium (VIII) glycolate intermediate as the mixture becomes less basic or to protonation of the alkaloid ligand, thereby limiting the ligand-accelerated catalysis. This prompted investigations to determine if maintaining a constant pH of 12 benefitted the reaction, and in fact, this was the case. When the dihydroxylation of *trans*-5-decene was performed at a constant pH of 12 under otherwise identical conditions to the original protocol, full conversion to the diol was obtained *in less than two hours*. The reaction proceeded in an *ee* of 90%, and a 95% isolated yield which was comparable to the results obtained without pH control. The increased reaction rate as a result of maintaining constant pH confirms that the osmium (VIII) glycolate intermediate hydrolysis proceeds much faster at an optimal pH of 12. There is no advantage to conducting the reaction at a pH higher than 12, and in fact, lower selectivity was observed in the enantiomeric ratios. This can most likely be attributed to a competition between hydroxide and the chiral ligand for the osmium metal under strongly basic conditions.

Muniz and co-workers reported another effective modification of the AD reaction.¹³⁹ The modification aimed to generate optically active cyclic boronic esters by including phenyl boronic acid under otherwise unchanged conditions for enantioselective dihydroxylation. The reaction presumably proceeds through olefin oxidation and subsequent cyclic boronic ester formation, and results in high yields of products with excellent enantioselectivity. The free diols could be

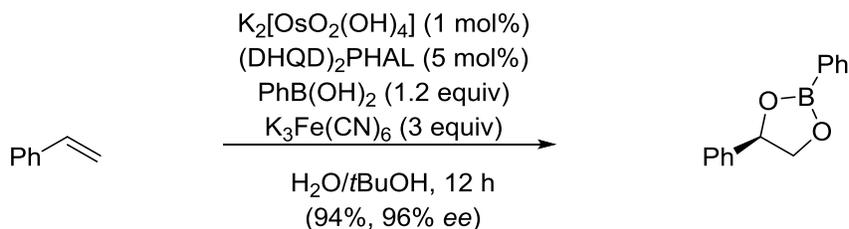
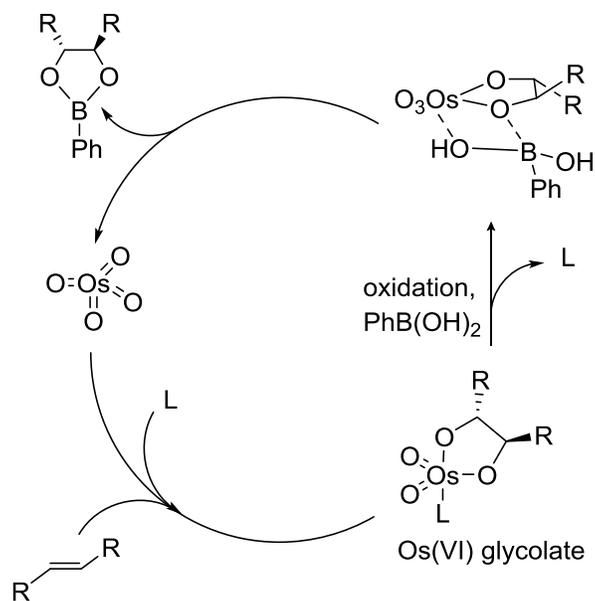


Figure 3.9: asymmetric dihydroxylation in the presence of phenyl boronic acid

¹³⁹ Hovelmann, C. H.; Muniz, K. *Chem. Eur. J.* **2005**, *11*, 3951.

obtained following deprotection of the cyclic boronic esters with hydrogen peroxide, and aqueous NaOH. A representative example with styrene is shown in Figure 3.9. Interestingly, the reaction proceeds in the absence of MeSO_2NH_2 , indicating that the phenyl boronic acid plays a role in the regeneration of OsO_4 following hydrolysis of the osmium (VIII) glycolate intermediate. Muniz proposed an electrophilic cleavage mechanism for the final step in the catalytic cycle to regenerate OsO_4 (Scheme 3.22). The initial stages of the catalytic cycle are identical to the parent Sharpless process. Initial ligation of the chiral ligand to OsO_4 , followed by enantioselective oxidation of the olefin and dissociation of the ligand furnishes the osmium (VI) glycolate ester. Following oxidation to the osmium (VIII) glycolate ester, the catalyst is regenerated by an electrophilic cleavage process with phenyl boronic acid, resulting in the chiral boronic ester adduct. Initial interaction between the Lewis acidic boron center and the Lewis basic oxygen atom of the glycolate ester weakens the osmium-oxygen bond which ultimately



Scheme 3.22: electrophilic cleavage mechanism with phenyl boronic acid

leads to the transesterified boronic ester product. It's worth noting that the addition of phenyl boronic acid does not interfere with the crucial ligation between the chiral ligand and OsO₄. Additionally, higher yields were obtained from the dihydroxylation of styrene, β-methyl styrene, and 2-vinyl naphthalene in the presence of phenyl boronic acid than those obtained from the original Sharpless conditions. This is likely due to unwanted over-oxidation of the products resulting in lower yields obtained under Sharpless conditions.¹⁴⁰ Over-oxidized byproducts were not observed in the presence of phenyl boronic acid.

3.4.2.2 Ligand Choice and Prediction of Stereochemical Outcomes

Following significant development in the AD reaction, Sharpless developed a model to predict the enantiofacial selectivity in the reactions (Figure 3.10 left).^{122, 141} The southwest quadrant in the mnemonic was identified as an “attractive area”, particularly effective at accommodating planar, aromatic substituents, and/or large aliphatic substituents. This can be explained by the electrostatic interaction resulting from a reasonably strong C-H dipole between

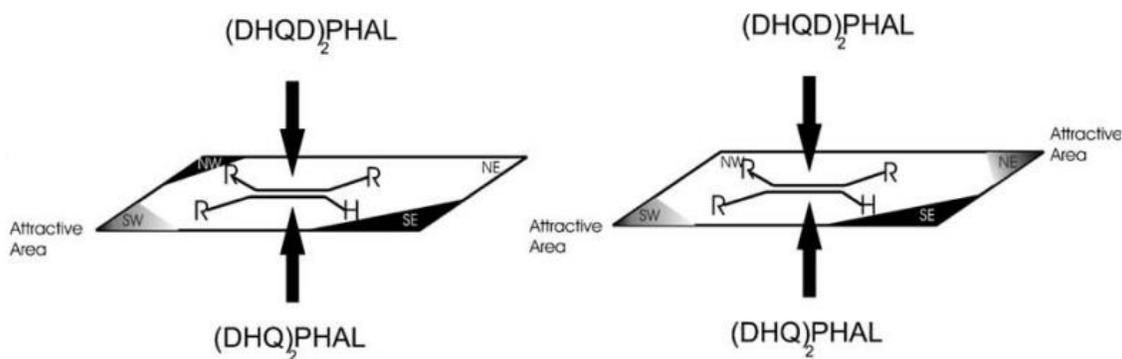


Figure 3.10: left: Sharpless mnemonic predicting enantiofacial selectivity. right: Norrby's revised mnemonic

¹⁴⁰ Dobler, C.; Mehlretter, G.; Sundermeier, U.; Beller, M. *J. Organomet. Chem.* **2001**, 621, 70.

¹⁴¹ (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, 56, 4585.

the aromatic and/or aliphatic substituents and the aromatic moieties in the ligand.¹⁴² When an olefin is positioned in this orientation, it can be attacked from either the top face (β -face) in the presence of DHQD derivatives, or the bottom face (α -face) in the presence of DHQ derivatives. The southeast quadrant can only accommodate small substituents such as hydrogen due to steric crowding by the alkaloid *O*-substituent (PHAL, PYR, etc.). Sharpless originally suggested that the northwest quadrant presents a modest barrier, also only being able to accommodate small substituents. However, Norrby later suggested that the northwest quadrant is an “open” non-interacting quadrant based on extensive computational studies.¹⁴³ Norrby proposed a revised mnemonic where there are actually two “attractive” areas; the southwest quadrant is still the most important for attractive interactions, but is closely followed by the northeast quadrant (Figure 3.10 right). The Sharpless mnemonic is effective at predicting the stereochemical outcomes in the case of *trans*-disubstituted olefins and mono-substituted olefins, while the Norrby mnemonic is arguably more effective when considering *cis*- or tri-substituted olefins.

As it was previously mentioned, the alkaloid *O*-substituent of the cinchona alkaloid plays a major role in influencing the enantioselectivity in AD reactions. While approximately 350 cinchona-based ligands have been studied, three different classes of ligands have emerged as the most effective ligands for the dihydroxylation of almost all olefins (Table 3.2). Although some olefins are more problematic upon dihydroxylation, the ligands PHAL and PYR appear to be the most general over all classes of olefins. PHAL ligands are especially effective when aromatic groups are present, but are less effective with aliphatic olefins or olefins bearing small substituents. The PYR ligand is especially well-suited for olefins bearing sterically demanding

¹⁴² Petterson, I.; Liljefors, T. *J. Comput. Chem.* **1987**, *8*, 1139.

¹⁴³ Fristrup, P.; Tanner, D.; Norrby, P.-O. *Chirality* **2003**, *15*, 360.

substituents, or those bearing large aliphatic groups. The AQN ligand can be particularly effective in the dihydroxylation of olefins bearing aliphatic substituents or those bearing heteroatoms in the allylic position.¹⁴⁴ Only the *cis*-olefin requires the indoline (IND) derived ligand for effective selectivity. Additionally, dimeric ligands bearing phthalazine,¹⁴⁵ pyridazine,¹⁴⁶ and terephthalate¹⁴⁷ linkers have been found to be effective, and in some cases, are superior to PHAL ligands in the reaction. For reasons of availability however, PHAL and PYR ligands remain to be the most popular.

Olefin Class						
Preferred Ligand	PYR PHAL AQN	PHAL	IND	PHAL	PHAL	PYR PHAL
ee range	30-97%	70-97%	20-80%	90-99%	90-99%	20-97%

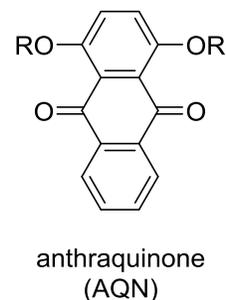
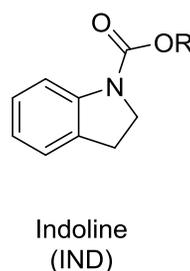
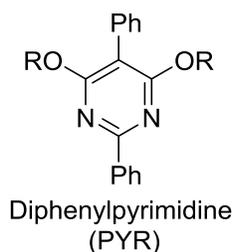


Table 3.2: Recommended ligands for each class of olefin where R represents cinchona alkaloids DHQ or DHQD

¹⁴⁴ Eecker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448.

¹⁴⁵ Becker, H.; King, S. B.; Taniguchi, M.; VanHessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940.

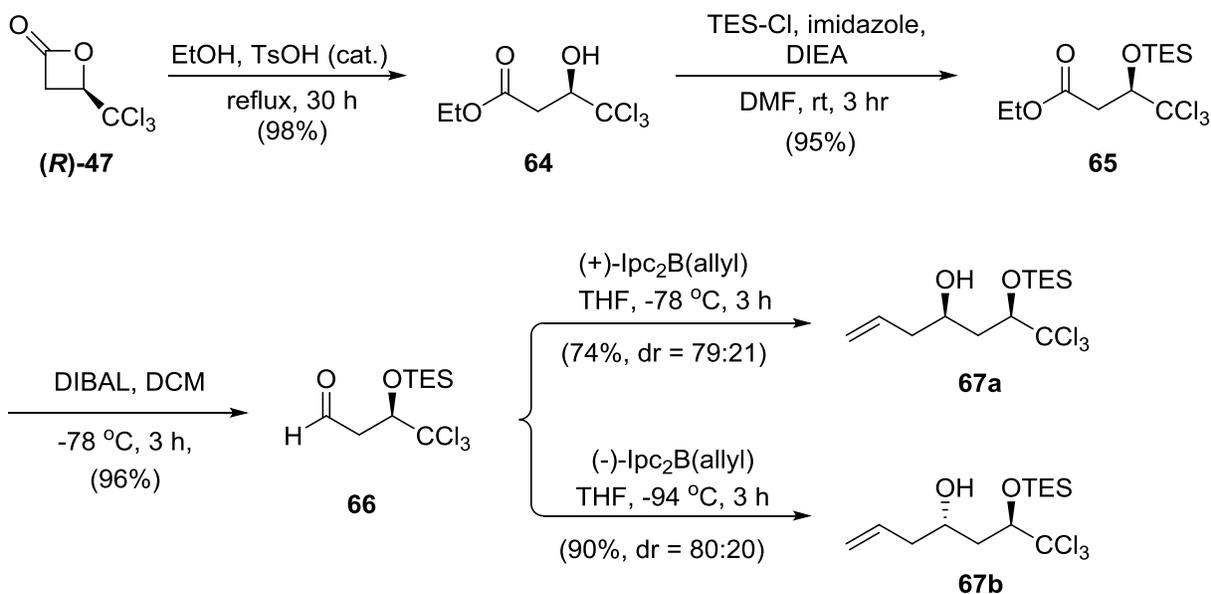
¹⁴⁶ Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828.

¹⁴⁷ (a) Lohray, B. B.; Bhushan, V. *Tetrahedron Lett.* **1992**, *33*, 5113. (b) Lohray, B. B.; Bhushan, V. *Tetrahedron Lett.* **1993**, *34*, 3911.

3.5 Results and Discussion

3.5.1 Formation of *syn*- and *anti*-1,3 Diols from (*R*)-Wynberg Lactone

Efforts toward the preparation of tetrahydropyrans of type **70** were initially directed toward both approaches outlined in Scheme 3.7. The aldehyde **66** can be prepared from Wynberg lactone (*R*)-**47**, which can be prepared by protocols outlined in the literature,⁵⁸ or by following the procedure reported by Romo and co-workers (Scheme 3.23).⁹² Treatment of (*R*)-**47** with a catalytic amount of tosic acid in refluxing ethanol furnished the ethyl ester **64** in 98% yield. To prevent potential retro-aldol side reactions from occurring in subsequent steps, **64** was treated with triethylsilane chloride in DMF to afford the protected triethylsilane adduct **65** in 95% yield. Aldehyde **66** was successfully obtained in 96% yield by reduction of **65** with diisobutylaluminum hydride in dichloromethane at -78 °C. With aldehyde **66** in hand, we attempted to

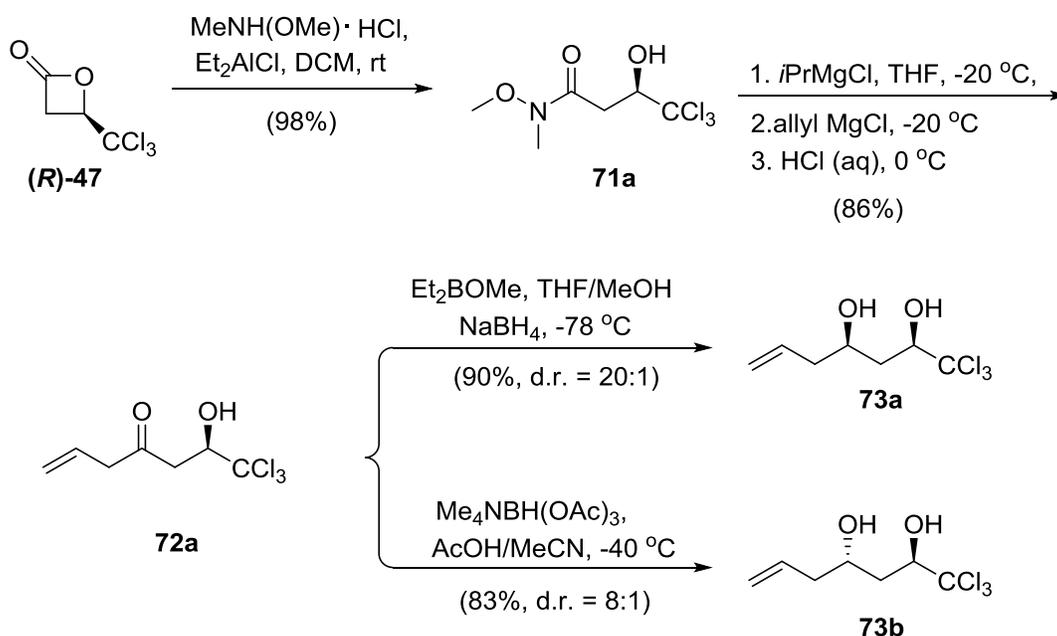


Scheme 3.23: Brown allylation approach to olefins of type **67**

stereoselectively generate the allylated *syn*- and *anti*-1,3 products **67a** and **67b** by employing a Brown allylation with optically active *B*-allyldiisopinocampheyl borane.⁸⁵ The

allylated products were obtained in good yields (74% and 90% respectively); however, only modest diastereoselectivity (dr = 80:20)¹⁴⁸ was obtained for each reaction. As a result, all future efforts were directed towards approach B.

Homoallylic *syn*- and *anti*-1,3 diols **73a** and **73b** were successfully prepared in three steps from (**R**)-**47** (Scheme 3.24). The first step in the synthesis involves Weinreb amidation of (**R**)-**47** under Lewis-acidic conditions to afford **71a** in 98% yield.¹⁴⁹ Allyl ketone **72a** can be obtained in 86% yield by first treating Weinreb amide **71a** with isopropyl magnesium chloride, followed by allyl magnesium chloride at -15 °C. Failure to maintain reaction temperatures below -10 °C, or improper quenching of the allylation reaction can lead to di-addition, isomerization,



Scheme 3.24: directed 1,3 reduction of allyl ketone **72a**

and conjugate-addition byproducts that lower the desired product yield.⁵⁵ Isomerization can also occur on hydrated silica and upon prolonged storage in standard glassware. Oven-dried silica is

¹⁴⁸ The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture

¹⁴⁹ Schimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, 38, 2685.

necessary for the successful isolation of **72a**, and it is prudent that **72a** be used immediately in the next step. The homoallylic *syn*-diol **73a** or *anti*-diol **73b** can be obtained asymmetrically by employing directed 1,3 reduction methods.^{86,87} Treatment of **72a** with diethylmethoxyborane and NaBH₄ in THF generated *syn*-diol **73a** in 90% yield, with a *syn/anti* d.r. = 20:1¹⁴⁸ when the reaction temperature was maintained at -78 °C. Directed reduction of **72a** with tetramethyl ammonium triacetoxyborohydride at -40 °C furnished *anti*-diol **73b** in 83% yield, with an *anti/syn* d.r. = 8:1.¹⁴⁸ It is also worth noting that the *syn*- and *anti*-diols **73a** and **73b** can be quickly and inexpensively prepared on multi-gram scales by NaBH₄ reduction of **72a** in methanol (Figure 3.11). The reactions are complete within 30 minutes and generate roughly equal mixtures (d.r. (*syn/anti*) = 55:45) of the diastereomers that are separable by silica gel chromatography.

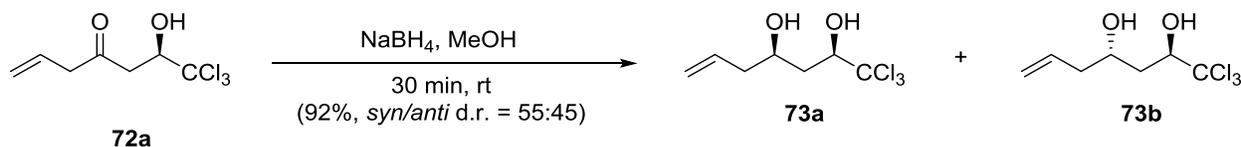


Figure 3.11: Convenient preparation of 1,3-diols by NaBH₄ reduction

Weinreb amide **71a** was crucial to the successful preparation of β -hydroxyketone **72a**. Attempts to prepare β -hydroxyketone **72a** directly from (**R**)-**47** with allyl lithium, magnesium, zinc, or copper reagents generated roughly equal mixtures of **72a**, di-addition product **72aa**, and (**R**)-**47** (Figure 3.12).⁵⁵ Allylation attempts using allyltrimethylsilane BF₃·Et₂O were also unsuccessful. The lack of success is presumably due to premature carbonyl formation following nucleophilic addition to (**R**)-**47** *in situ*. The resulting β -alkoxyketone, likely activated by metal-chelation, undergoes a second nucleophilic addition leading to byproduct **72aa** even at low temperatures. Nucleophilic addition to Weinreb amide **71a** results in a persisting chelated

tetrahedral intermediate when the temperature is kept below $-10\text{ }^{\circ}\text{C}$ and deters regeneration of the carbonyl.

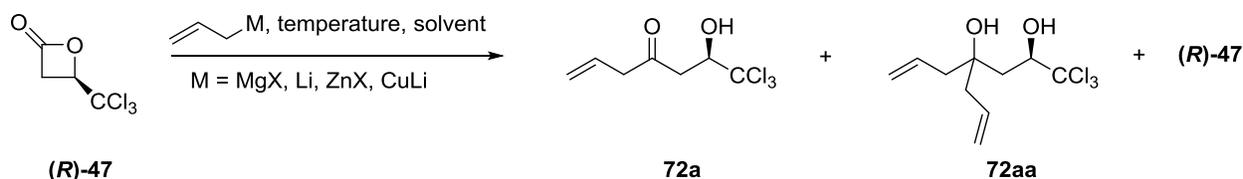
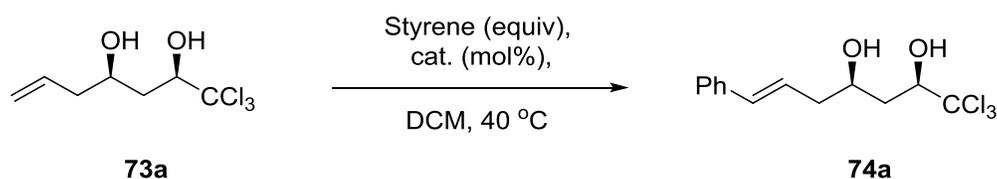


Figure 3.12: nucleophilic addition to Wynberg lactone **(R)-47**

3.5.2 Olefin Functionalization by Cross Metathesis

Terminal olefins **73a** and **73b** were successfully functionalized through olefin metathesis reactions with Grubbs 2nd generation catalyst **78**, and Grubbs-Hoveyda 2nd generation catalyst **79**. Our investigations of optimizing the preparation of functionalized olefins began with attempted formation of the phenyl adduct **74a** from *syn*-diol **73a** (Table 3.3). The optimization results indicated that product yield can be significantly increased by using 10 equivalents of the cross partner styrene (compare entries 1 and 2), and also by adding the catalyst portion-wise throughout the reaction (see entries 4–6). Portion-wise addition of catalyst also significantly increased the rate of product formation; starting material was completely consumed after 6 hours when 1 mol% of the catalyst was present at the outset, and added in 1 mol% portions every hour until 5 mol% was reached (entry 6). Another conclusion drawn from the optimization study was that the Grubbs-Hoveyda 2nd generation catalyst **79** was superior to Grubbs 2nd generation catalyst **78** in terms of product yield. Unfortunately, ¹H NMR analysis of the isolated phenyl derived product revealed that a significant amount of an unexpected byproduct closely resembling the desired product was being formed. We initially reasoned that formation of the *Z*-isomer was possible, however a collection of NMR experiments (¹H, ¹³C, HMBC, HSQC, COSY) confirmed the truncated structure **74aa** (Scheme 3.25). A possible pathway leading to its

Table 3.3: preparation of **74a** using catalysts **78** or **79**



Entry	Styrene (equiv)	Catalyst (mol%)	Time	Yield (%) ^a
1	3	78 (5)	24	24
2	10	78 (5)	24	43
3	10	79 (5)	24	54
4	10	79 (5x2) ^b	24	61
5	10	79 (2x5) ^c	12	65
6	10	79 (1x8) ^d	8	66

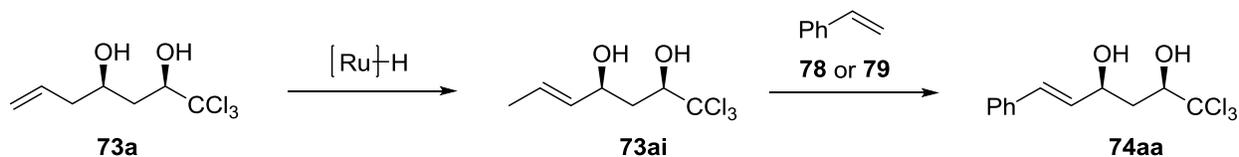
^a Determined from ¹H NMR analysis following isolation of an inseparable mixture of **74a** and a previously unidentified byproduct

^b 5 mol% catalyst was added at the outset, and after 12 hours

^c 2 mol% catalyst was added at the outset, and every 2 hours until 10 mol% was reached, or starting material was consumed.

^d 1 mol% catalyst was added at the outset, and every hour until 10 mol% was reached, or starting material was consumed

formation results from ruthenium hydride promoted isomerization of the terminal olefin **73a** to the internal olefin adduct **73ai**, followed by productive cross metathesis with styrene and loss of propylene. Pathways that proceed through the homodimer of **73a** or through retro-cross metathesis processes are also conceivable.

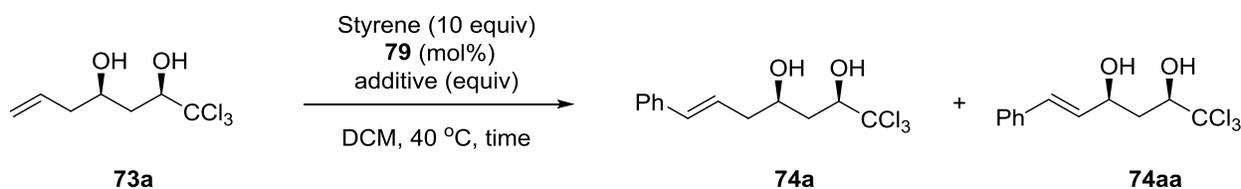


Scheme 3.25: Possible pathway leading to truncated byproducts

3.5.2.1 Use of Additives to Suppress Isomerization

We then directed our efforts toward preventing olefin isomerization in the preparation of **74a** (Table 3.4). It's worth noting that metathesis catalysts were purified by silica gel chromatography immediately before use to remove any potential Ru-H species present in the commercial reagents.¹⁵⁰ Additionally, **74a** and **74aa** are inseparable by silica gel chromatography and other purification techniques. Thus, the ability to form **74a** and other functionalized olefins in >95% purity was prudent for subsequent reactions. Due to its convenient and inexpensive preparation, *syn*-1,3 diol **73a** was used in all cross metathesis optimization reactions. In attempts

Table 3.4: optimization conditions for preparation of **74a**



Entry	79 (mol%)	Additive (equiv)	Time (h)	Yield (%) ^a	
				74a	74aa
1	(5x2) ^b	none	24	61	18
2	(2x5) ^c	none	12	65	19
3	(1x8) ^d	none	8	66	19
4	(5x2) ^b	TFBQ (0.1)	24	63	17
5	(5x2) ^b	TFBQ (1)	24	81	5
6	(2x5) ^c	TFBQ (1)	24	86	< 2
7	(1x5) ^d	phenol (0.5)	5	76	8
8	(2x5) ^c	acetic acid (0.1)	12	67	8
9	(1x5) ^d	acetic acid (0.5)	5	83	5

¹⁵⁰ Upon the recommendation of Professor Robert Grubbs, April 2013.

10	(1x5) ^d	acetic acid (1)	5	89	3
11	(1x5) ^d	acetic acid (2)	5	59	3
12	(1x5) ^d	benzoic acid (0.5)	5	46	6
13	(1x5) ^d	salicylic acid (1)	5	85	3

^a Determined from ¹H NMR analysis following isolation of an inseparable mixture of **74a** and **74aa**

^b 5 mol% catalyst was added at the outset, and after 12 hours

^c 2 mol% catalyst was added at the outset, and every 2 hours until 10 mol% was reached, or starting material was consumed.

^d 1 mol% catalyst was added at the outset, and every hour until 10 mol% was reached, or starting material was consumed

to prevent the formation of truncated byproducts, we employed additives to serve as Ru-H scavengers,¹¹⁷ or rate enhancers.¹¹⁸ In the absence of any additives, the extent of byproduct formation is fairly significant (17–19%). However, using one equivalent of tetrafluoro-1,4-benzoquinone (TFBQ)¹¹⁷ and adding the catalyst in five portions suppressed isomerization substantially (entry 6). Phenol appeared to be useful as a rate enhancer (compare entries 3 and 7); however, formation of **74aa** was still observed. Satisfactory results were also obtained when acetic acid was employed. Using one equivalent of acetic acid limited byproduct formation to 3%, and provided optimal product yields (entry 10). Interestingly, using two equivalents of acetic acid provided no advantage in terms of product yield or purity. The success of using phenol as a rate enhancer and acetic acid as a Ru-H acceptor prompted attempts with benzoic acid and salicylic acid as additives. Benzoic acid provided no advantage compared to AcOH. However, salicylic acid beautifully played *both* roles of rate enhancer, and Ru-H acceptor, and provided satisfactory results (entry 13) but no better than AcOH (entry 10). TFBQ, acetic acid, and salicylic acid all gave satisfactory yields of **74a** and limited formation of **74aa** to < 5%. Acetic acid and salicylic acid proved superior in terms of reaction rate. Reactions with TFBQ required

24 hours for complete consumption of starting material, even with portion-wise addition of catalyst (compare entries 2 and 6). Lastly, in light of reported catalyst decomposition to ruthenium- hydrido-carbonyl species in the presence of methanol,^{111, 112} we attempted preparing **74a** from the phenyl boronic ester adduct **73aa** followed by boronic ester deprotection with H₂O₂ (Figure 3.13). In the absence of any additives, the byproduct **74aa** was formed in fairly significant amounts, suggesting that the alcohol functional groups present in the parent substrate **73a** did not contribute significantly to catalyst decomposition and byproduct formation.

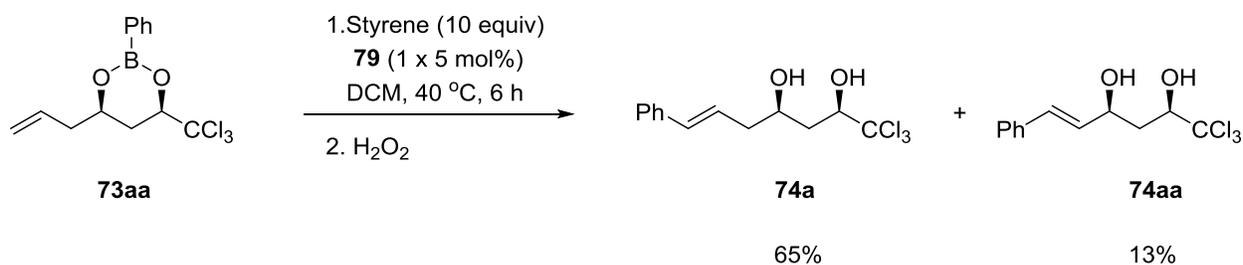
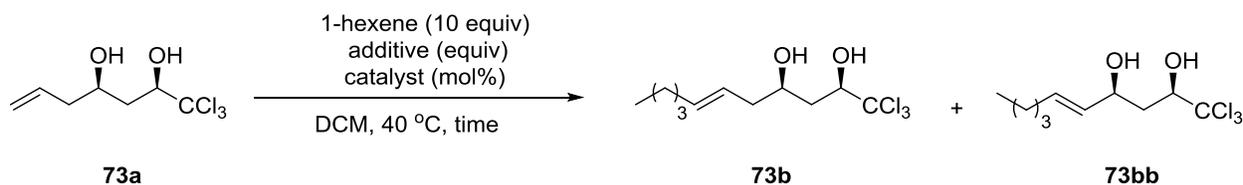


Figure 3.13: Preparation of **74a** from phenyl boronic ester **73aa**

The established cross metathesis conditions from above were applied to other systems to form functionalized olefins **74b-74k**. First, we applied the previously successful conditions in preparation of **73b** (Table 3.5). While including additives did appear to help limit formation of the byproduct **73bb**, we were unable to completely suppress isomerization in the preparation of this substrate. Inclusion of phenol had a significant effect on the reaction rate (compare entries 1 and 3). This prompted attempts with additives similar to phenol, but there was no observed advantage (entries 4 and 5). Salicylic acid appeared to offer the best results in terms of yield and product purity. Additionally, we were interested to see if Oxone® could quench the dissociated tricyclohexylphosphine with catalyst **78**, and potentially inhibit the catalyst decomposition

pathway proposed by Grubbs (Scheme 3.16).¹¹⁴ Unfortunately, the attempt resulted in an unsatisfactory product yield (entry 8).

Table 3.5: Preparation of **73b**



Entry	catalyst (mol%)	Additive (equiv)	Time (h)	Yield (%) ^a	
				73b	73bb
1	79 (2x5) ^b	None	24	54	18
2	79 (2x5) ^b	TFBQ (1)	24	70	12
3	79 (2x2) ^b	phenol (0.5)	5	76	12
4	79 (2x5) ^b	4-nitrophenol (0.5)	24	< 20	-
5	79 (2x2) ^b	thiophenol (0.5)	5	75	15
6	79 (1x5) ^c	acetic acid (1)	6	68	10
7	79 (1x10) ^c	salicylic acid (1)	10	82	11
8	78 (1x10) ^c	Oxone® (0.1)	24	35	-

^a Determined from ¹H NMR analysis following isolation of an inseparable mixture of **74b** and **74bb**

^b 2 mol% catalyst was added at the outset, and every 2 hours until 10 mol% was reached, or starting material was consumed.

^c 1 mol% catalyst was added at the outset, and every hour until 10 mol% was reached, or starting material was consumed

The catalyst decomposition pathway proposed by Grubbs also motivated us to attempt preparation of **73b** from the prenyl adduct **73ab** (Figure 3.14). We envisioned that the 14-electron ruthenium isopropylidene **88a** resulting from productive cross metathesis between **73ab**

and 1-hexene would be less susceptible to nucleophilic attack by free phosphines, or oxidation processes leading to hydrido-carbonyl species.^{119, 151} Unfortunately, we were not able to get the reaction to proceed even at higher temperatures.

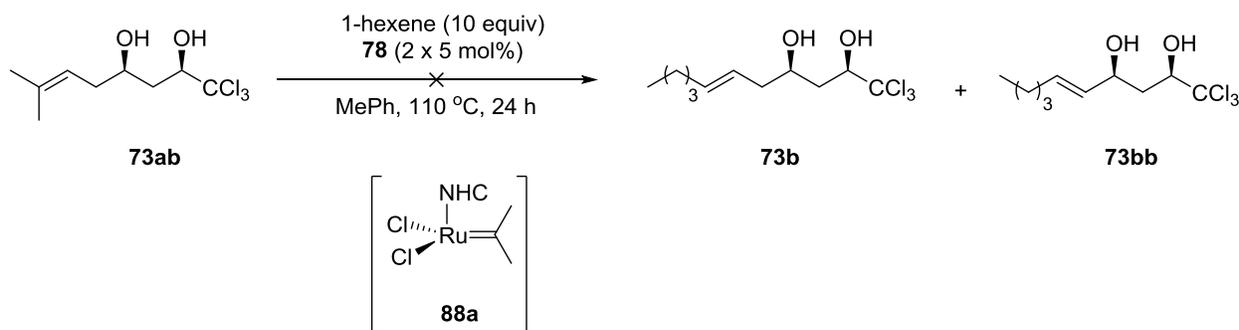
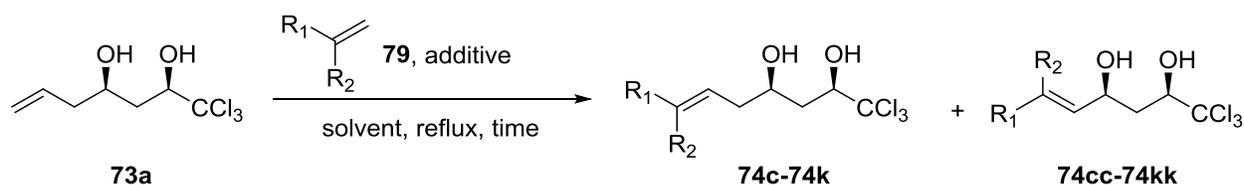


Figure 3.14: Attempted preparation of **73b** from prenyl adduct **73ab**

We were able to successfully prepare olefins **74c-74k** under similar conditions to those described above (Table 3.6). Interestingly, olefin isomerization and truncation was only observed in one other substrate class (entries 18–21). Based on our results, it appeared that isomerization was only observed in cases where the product bears one or more alkyl chains (**74a**, **74b**, **74i**). In cases where the cross partner is further functionalized, particularly with a heteroatom allylic to the olefin, isomerization was not observed. In fact, adding TFBQ to the reaction mixture with these substrates can significantly lower the yield (entries 2, 11). However, salicylic acid was extremely beneficial to the reaction rate (entries 3, 12). Acetic acid and salicylic acid emerged as the most useful additives, and while byproduct formation could not always be completely suppressed, including these additives had a positive effect on the reaction rate in most reactions. We obtained interesting results when attempting to prepare triol **74e**. Comparable yields were obtained when either 3, or 10 equivalents of the type I olefin allyl alcohol was used. These results were slightly unexpected based on Grubbs olefin reactivity model.¹⁰⁵ We were unable to

¹⁵¹ Wang, Z. J.; Jackson, R. W.; Robinson, A. J. *Org. Lett.* **2013**, *15*, 3006.

Table 3.6: preparation of functionalized olefins **74c-74k**

Entry	R ₁ , R ₂ (equiv)	79 (mol%)	Additive (equiv)	Time (h)	Solvent	Isolated Yield (%)	
						74c-74k	74cc-74kk
1	CH ₂ OBn, H (10)	(2x5) ^b	None	24	DCM	74c, 85	74cc, 0
2	CH ₂ OBn, H (10)	(2x5) ^b	TFBQ (1)	24	DCM	74c, 55	74cc, 0
3	CH ₂ OBn, H (10)	(2x4) ^b	salicylic acid (1)	8	DCM	74c, 85	74cc, 0
4	CH ₂ OBn, Me (3)	(2x5) ^b	None	24	DCM	74d, 37	74dd, 0
5	CH ₂ OBn, Me (10)	(1x8) ^c	None	8	DCM	74d, 83	74dd, 0
6	CH ₂ OH, H (10)	(2x5) ^b	None	24	DCM	74e, 47	74ee, 0
7	CH ₂ OH, H (3)	(2x5) ^b	None	24	DCM	74e, 46	74ee, 0
8	CH ₂ OH, H (3)	(2x5) ^b	PhOH (0.5)	24	DCM	74e, 51	74ee, 0
9	CH ₂ OH, H (3)	(2x5) ^b	salicylic acid (1)	24	DCM	74e, 46	74ee, 0
10	CON(Me)OMe, H (2)	(2x5) ^b	None	24	DCM	74f, 88	74ff, 0
11	CON(Me)OMe, H (2)	(2x5) ^b	TFBQ (1)	24	DCM	74f, 20	74ff, 0
12	CON(Me)OMe, H (2)	(2x4) ^b	salicylic acid (1)	8	DCM	74f, 86	74ff, 0
13	COCH ₃ , H (2)	(2x5) ^b	None	12	DCM	74g, 93	74gg, 0
14	Ph, Me (5)	(2x5) ^b	None	24	DCM	74h, NR	-
15	Ph, Me (30)	(2x5) ^b	None	24	DCM	74h, NR	-
16	Ph, Me (30)	(2x5) ^b	None	24	MePh	74h, NR	-
17	propyl, Me (3)	(2x5) ^b	None	24	DCM	74i, <10	-
18	propyl, Me (25)	(2x5) ^b	None	24	DCM	74i, 40 ^a	74ii, 10
19	propyl, Me (25)	(1x10) ^c	None	12	DCM	74i, 78 ^a	74ii, 13
20	propyl, Me (25)	(1x10) ^c	TFBQ (1)	12	DCM	74i, 46 ^a	74ii, 12

21	propyl, Me (25)	(1x10) ^c	AcOH (1)	12	DCM	74i , 58 ^a	74ii , 12
22	CH ₂ OH, Me (3)	(1x10) ^c	None	12	DCM	74j , 56	74jj , 0
23	CH ₂ OH, Me (10)	(1x10) ^c	None	12	DCM	74j , 81	74jj , 0
24	SO ₂ Ph, H (2)	(2x5) ^b	None	24	DCM	74k , 78	74kk , 0

^a Determined from ¹H NMR analysis following isolation of an inseparable mixture of **74i** and **74ii**

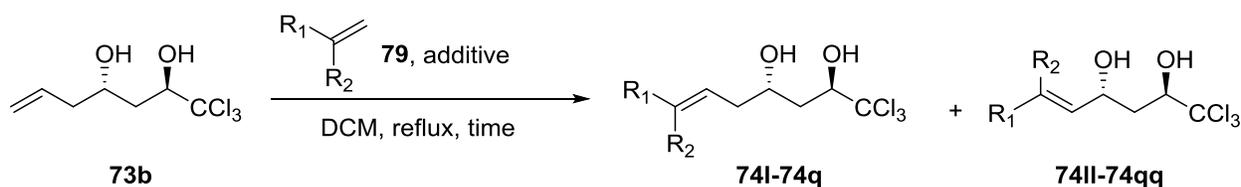
^b 2 mol% catalyst was added at the outset, and every 2 hours until 10 mol% was reached, or starting material was consumed.

^c 1 mol% catalyst was added at the outset, and every hour until 10 mol% was reached, or starting material was consumed

obtain higher than a 51% yield of **74e**; however, preparation of the pseudo-triol **74c** proceeded in satisfactory yield. Given that phenyl derived products of **74a** can be obtained in high purity (see Table 3.4), we attempted to form trisubstituted olefins of type **74h** with α -methylstyrene (entries 14–16). These attempts were not successful unfortunately, even when using 30 equivalents of α -methylstyrene at higher temperatures. Attempts at preparing **74h** through a cross metathesis relay strategy were also unsuccessful.¹⁵² Notably, however, we were able to prepare tri-substituted olefins **74d**, **74i**, and **74j** in satisfactory yields when at least a 10-fold excess of the cross partner was used.

Functionalized olefins **74l-74q** were prepared from *anti*-1,3 diol **73b** under similar conditions (Table 3.7). Comparable yields and product purity was obtained in all cases when **73b** was used as the substrate.

¹⁵² (a) Stewert, I. C.; Douglas, C. J.; Grubbs, R. H. *Org Lett.* **2008**, *10*, 441. (b) Clark, J. R.; French, J. M.; Jecs, E.; Diver, S. T. *Org Lett.* **2012**, *14*, 4178.

Table 3.7: Preparation of functionalized olefins **74l-74q**

Entry	R ₁ , R ₂ (equiv)	79 (mol%)	Additive (equiv)	Time (h)	Yield (%)	
					74l-74q	74ll-74qq
1	Ph, H (10)	(1x5) ^b	salicylic acid (1)	5	74l, 88 ^a	74ll, 3
2	butyl, H (10)	(1x10) ^b	salicylic acid (1)	10	74m, 81 ^a	74mm, 11
3	CH ₂ OBn, H (10)	(1x8) ^b	salicylic acid (1)	8	74n, 84	74nn, 0
4	CH ₂ OBn, Me (10)	(1x10) ^b	None	10	74o, 80	74oo, 0
5	CON(Me)OMe, H (2)	(2x5) ^c	None	24	74p, 88	74pp, 0
6	COCH ₃ , H (2)	(2x5) ^c	None	24	74q, 86	74qq, 0

^a Determined from ¹H NMR analysis following isolation of an inseparable mixture of **74l/74ll** and **74m/74mm**.

^b 1 mol% catalyst was added at the outset, and every hour until 10 mol% was reached, or starting material was consumed

^c 2 mol% catalyst was added at the outset, and every 2 hours until 10 mol% was reached, or starting material was consumed.

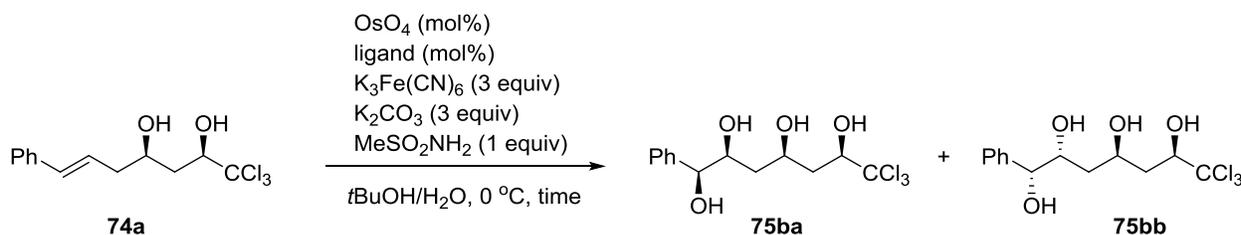
3.5.3 Formation of Vicinal 1,2-Diols by Olefin Dihydroxylation

With a variety of functionalized olefins in hand, we aimed to stereoselectively prepare the tetraol precursors to the final product through a modified Sharpless asymmetric dihydroxylation reaction.⁸⁹ We began by subjecting all olefins to dihydroxylation conditions with commercial AD-mix- α and AD-mix- β . Under these conditions, partial to no starting material consumption was observed after 48 hours at 0 °C. As a result, we moved to a “fortified” AD-mix to obtain a more desirable rate of product formation. It is worth noting that commercial AD-mix contains 0.4 mol% of K₂OsO₂(OH)₄, 1 mol% of the ligand, K₂CO₃ and K₃(FeCN)₆. The ligand/Os molar ratio of 2.5:1 offers optimal enantiofacial selectivity and ligand accelerated catalysis in the

reaction. A 5:1 ligand/Os ratio can further enhance rate and stereoselectivity; however, higher ratios provide no advantage. In fact, too much ligand can inhibit re-oxidation and hydrolysis in the catalytic cycle leading to slow catalyst turnover.^{133,153} We reasoned a higher concentration of osmium, and ligand/Os ratios ranging from 3:1–5:1 would provide satisfactory results.

Our investigations toward finding optimal dihydroxylation conditions began with forming tetraols **75ba** and **75bb** from phenyl derived olefin **74a** (Table 3.8). We were able to achieve complete consumption of starting material in 18 hours at 0 °C when using 10 mol% OsO₄ and 30 mol% ligand. Unsurprisingly, the reaction rate was significantly slower when 2 mol% OsO₄ and 10 mol% was used. Finally, 5 mol% OsO₄ and 20 mol% ligand provided a

Table 3.8: optimization for dihydroxylation of **74a**



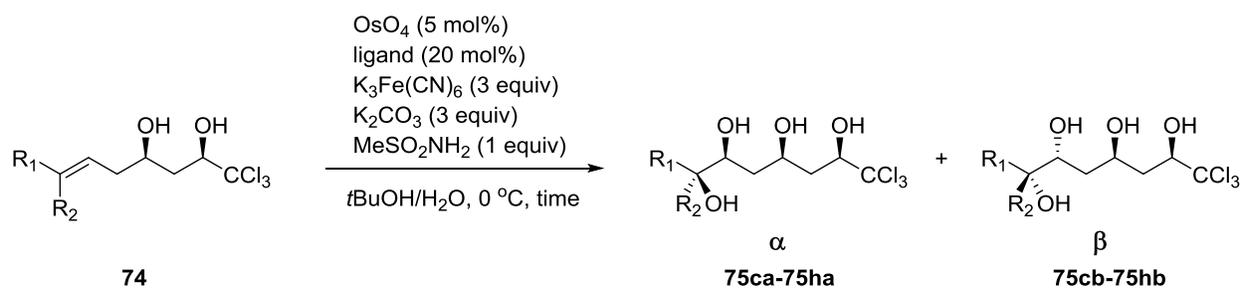
Entry	OsO ₄ (mol%)	Ligand (mol%)	Time (h)	dr ^a 75ba:75bb	Yield (%) 75ba+75bb
1	10	(DHQ) ₂ PHAL (30)	18	91:9	86
2	10	(DHQD) ₂ PHAL (30)	18	10:90	89
3	2	(DHQ) ₂ PHAL (10)	42	95:5	83
4	2	(DHQD) ₂ PHAL (10)	42	7:93	89
5	5	(DHQ) ₂ PHAL (20)	24	95:5	95
6	5	(DHQD) ₂ PHAL (20)	24	6:94	89

^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture

¹⁵³ Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737.

satisfactory reaction rate, and was the most economical approach. Product yields and dr values¹⁴⁸ were comparable among all reactions with the PHAL derived ligands; however, using a 4:1 ligand/Os ratio (entries 5 and 6) offered a slight stereoselective advantage. The substrate **74a** appeared to be perfectly compatible with the PHAL ligand, and stereochemical outcomes were predicted with the selectivity mnemonic (see Figure 3.10).

We then sought to apply our optimized “fortified” AD-mix conditions to prepare tetraols **75c-75h** (Table 3.9). The reaction proceeded nicely with substrates **7b-7d**, and generated tetraols with dr values¹⁴⁸ ranging from 87:13 to 90:10 and yields ranging from 81–97%. We were initially concerned with the successful isolation of tetraols of type **75c** and **75g** from the crude reaction mixtures. The olefin precursors to those tetraols were only ~ 85–88% pure, and contained inseparable truncated byproducts from the previous cross metathesis reaction. Fortunately, we were able to isolate tetraols **75ca** and **75cb** from the crude reaction mixtures, however we weren’t as fortunate with isolation of **75ga** and **75gb**. The Weinreb amide adduct **74f** proved to be a particularly challenging substrate in the AD reaction, and will be discussed in more detail below. Lastly, triol **74j** performed poorly as a substrate in the dihydroxylation reaction, and only minimal to no selectivity was observed in the diastereomeric mixture of products. This was not surprising when compared to the successful results obtained with the analogous benzyl adduct **74d**. The presence of the benzyl substituent in **74d** presumably is well suited for strong interactions with the aromatic moieties in the PHAL ligand. Poor selectivity in the dihydroxylation of **74j** is likely due to the absence of a substituent capable of forming strong interactions within that ligand binding pocket.

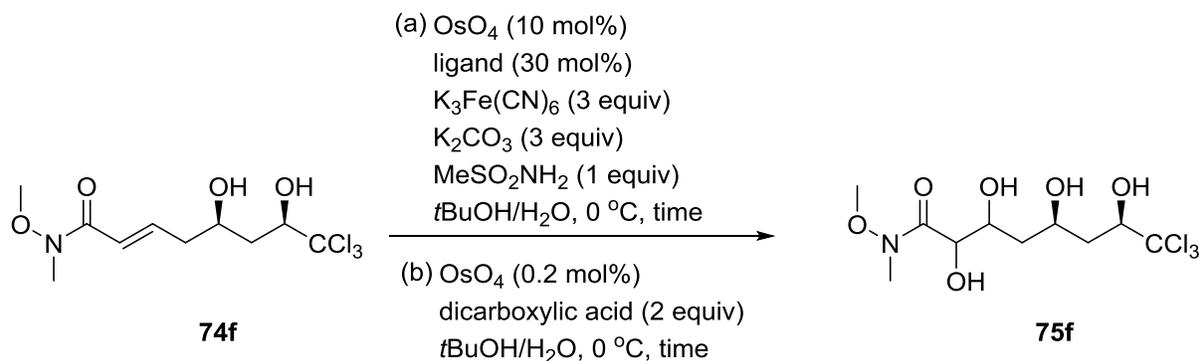
Table 3.9: Preparation of tetraols **75c-75h****74b** $\text{R}_1, \text{R}_2 = \text{butyl, H}$ **74c** $\text{R}_1, \text{R}_2 = \text{CH}_2\text{OBn, H}$ **74d** $\text{R}_1, \text{R}_2 = \text{CH}_2\text{OBn, Me}$ **74f** $\text{R}_1, \text{R}_2 = \text{CON}(\text{Me}), \text{OMe, H}$ **74i** $\text{R}_1, \text{R}_2 = \text{propyl, Me}$ **74j** $\text{R}_1, \text{R}_2 = \text{CH}_2\text{OH, Me}$ **75c** $\text{R}_1, \text{R}_2 = \text{butyl, H}$ **75d** $\text{R}_1, \text{R}_2 = \text{CH}_2\text{OBn, H}$ **75e** $\text{R}_1, \text{R}_2 = \text{CH}_2\text{OBn, Me}$ **75f** $\text{R}_1, \text{R}_2 = \text{CON}(\text{Me}), \text{OMe, H}$ **75g** $\text{R}_1, \text{R}_2 = \text{propyl, Me}$ **75h** $\text{R}_1, \text{R}_2 = \text{CH}_2\text{OH, Me}$

Entry	Substrate	Ligand (mol%)	Time (h)	dr ^a $\alpha:\beta$	Yield (%) $\alpha + \beta$
1	74b	(DHQ) ₂ PHAL	18	88:12	75c , 85 ^b
2	74b	(DHQD) ₂ PHAL	18	13:87	75c , 81 ^b
3	74c	(DHQ) ₂ PHAL	16	87:13	75d , 84
4	74c	(DHQD) ₂ PHAL	16	10:90	75d , 88
5	74d	(DHQ) ₂ PHAL	16	88:12	75e , 97
6	74d	(DHQD) ₂ PHAL	16	13:87	75e , 96
7	74f	(DHQ) ₂ PHAL	72	-	75f , <i>c</i>
8	74f	(DHQD) ₂ PHAL	72	-	75f , <i>c</i>
9	74i	(DHQ) ₂ PHAL	20	80:20	75g , 81 ^d
10	74i	(DHQD) ₂ PHAL	20	18:82	75g , 82 ^d
11	74j	(DHQ) ₂ PHAL	12	50:50	75h , 84
12	74j	(DHQD) ₂ PHAL	12	33:67	75h , 82

^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture. ^b The yield is based on starting material that was ~ 88% pure. ^c NMR analysis of the crude mixture showed 30% consumption of starting material. ^d The starting material was ~ 85% pure. The indicated tetraols could not be obtained as pure compounds from the reaction mixture

After our initial unsuccessful attempts of preparing tetraols of type **75f** from **74f**, we began exploring different reaction conditions to get the reaction to proceed in acceptable yield and diastereoselectivity (Table 3.10). Sharpless noted that unsaturated amides react sluggishly, presumably due to complications with hydrolysis of the osmate ester.¹⁵⁴ However, the rate of catalyst turnover can be drastically improved by increasing the osmium concentration in the

Table 3.10: preparation of **75f** under (a) “standard” versus (b) “acidic” conditions



Method (a)			
Entry	Ligand	Time (h)	Yield (%)
1	(DHQ) ₂ PYR	72	36 ^a
2	(DHQD) ₂ AQN	72	35 ^a
3 ^b	(DHQ) ₂ PHAL	72	42 ^a
4 ^c	(DHQ) ₂ PHAL	72	55 ^a
Method (b)			
Entry	Dicarboxylic acid	Time (h)	Isolated Yield (%)
5	citric acid	14	95
6	L-(–)-malic acid	48	60
7	L-(+)-tartaric acid	48	60

^a Yields were determined from ¹H NMR analysis of the crude reaction mixture. ^b pH was maintained at 10 throughout the reaction by periodic addition of aqueous 1M NaOH and by monitoring with a pH meter. ^c The reaction was buffered with 3 equiv of NaHCO₃

¹⁵⁴ Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079.

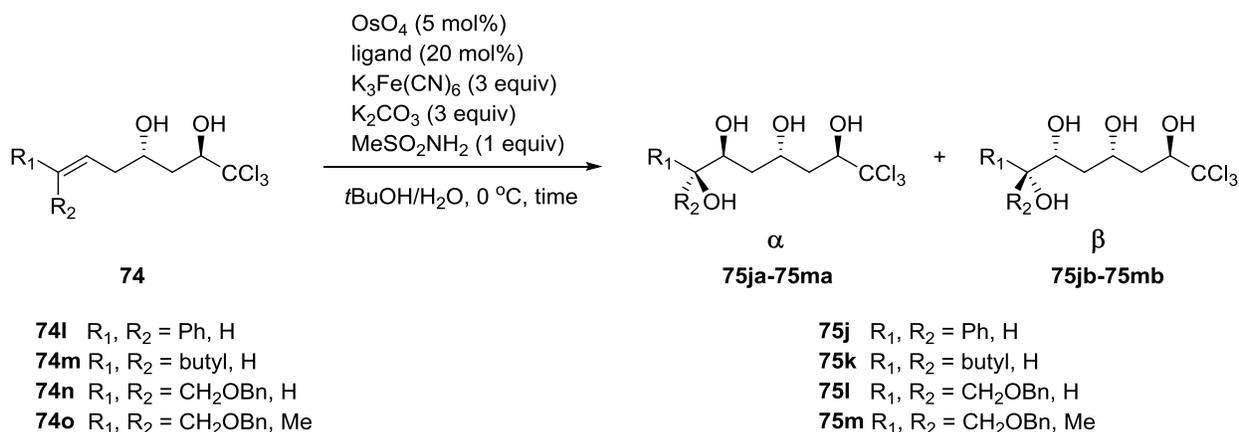
reaction. We first tested all readily available ligands at a higher concentration of osmium in attempts to improve the conversion. There appeared to be only marginal differences between the PHAL, PYR, and AQN ligand with 30 % mol osmium present, and all led to only partial consumption of starting material after 72 hours. Next, we tried to conduct the reaction under pH controlled conditions¹⁵⁸ to improve the rate of hydrolysis of the osmate ester (entry 3). Unfortunately, when the pH was maintained at 10, starting material consumption was only slightly improved. We then reasoned that the osmate ester hydrolysis in this specific reaction might actually be more efficient under more acidic conditions. A few examples in the literature have shown that asymmetric dihydroxylation reactions perform well in carbonate–bicarbonate buffered media.¹⁵⁵ When the reaction was performed in the presence of 3 equivalents of NaHCO₃ under otherwise identical conditions, 55% conversion to product was observed (entry 4). Although modest, the improvement prompted dihydroxylation attempts under even more acidic conditions. According to a report by Sharpless and co-workers,¹⁵⁶ citric acid is an extremely useful additive in the osmium-catalyzed dihydroxylation of electron-deficient olefins. Indeed, in the presence of 2 equivalents of citric acid and *only* 0.2 mol% OsO₄, the reaction was complete in 14 hours. The reaction proceeded in 95% yield, and generated a roughly equal mixture of diastereomers **75f**. Unfortunately, the chiral cinchona alkaloid ligands would be ineffective under acidic conditions and cannot be used to induce stereoselectivity. We were able to modestly influence the selectivity by employing chiral dicarboxylic acids L-(–)-malic acid and L-(+)-tartaric acid (dr = 71:29, 62:38 respectively); however only a 60% yield of the products was obtained in each case.

¹⁵⁵ (a) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1993**, *4*, 133. (b) Arrington, M. P.; Bennani, Y. L.; Gobel, T.; Walsh, P. J.; Zhao, S.-H.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 7375. (c) Ko, S. Y.; Malik, M. *Tetrahedron Lett.* **1993**, *34*, 4675.

¹⁵⁶ Dupau, P.; Epple, R.; Thomas, A. A.; Foki, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.

Tetraols **75i-75m** were prepared from functionalized olefins **74i-74o** using the optimized fortified AD-mix conditions described previously (Table 3.11). The yields and diastereomeric ratios¹⁴⁸ were similar to those obtained from asymmetric dihydroxylation of *syn*-1,3 derived olefins **74b-74e**. The fact that rates and selectivity did not differ much between *syn*- and *anti*-derived olefins in the dihydroxylation reaction is noteworthy. These results suggest that there's negligible substrate-controlled influence on the stereochemical outcomes, *and/or* the 4:1 ligand/Os ratio is optimal for osmium-ligand saturation. The osmium-ligand complex likely mitigates competing substrate-controlled dihydroxylation processes from occurring.

Table 3.11: Preparation of tetraols **75j-75m**



Entry	Substrate	Ligand (mol%)	Time (h)	dr ^a $\alpha:\beta$	Yield (%) $\alpha + \beta$
1	74l	(DHQ) ₂ PHAL	24	94:6	75j , 94
2	74l	(DHQD) ₂ PHAL	24	9:91	75j , 86
3	74m	(DHQ) ₂ PHAL	16	87:13	75k , 84 ^b
4	74m	(DHQD) ₂ PHAL	16	13:87	75k , 88 ^b
5	74n	(DHQ) ₂ PHAL	12	86:14	75l , 88
6	74n	(DHQD) ₂ PHAL	12	14:86	75l , 86

7	74o	(DHQ) ₂ PHAL	20	86:14	75m , 96
8	74o	(DHQD) ₂ PHAL	24	13:87	75m , 95

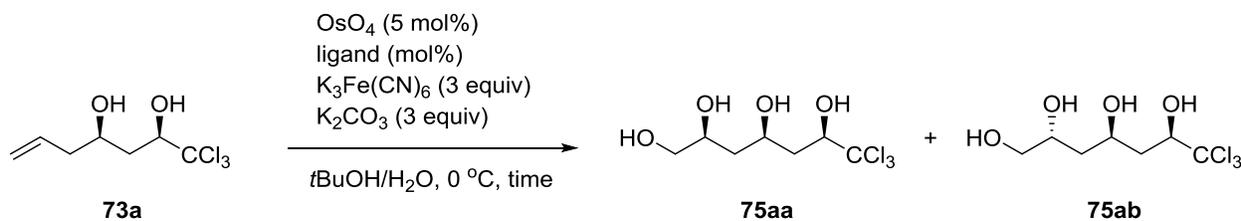
^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture. ^b The yield is based on starting material that was ~ 88% pure.

3.5.3.1 Enhancing Stereoselectivity in Terminal Mono-substituted Olefins

The osmium-catalyzed asymmetric dihydroxylation reaction developed by Sharpless and co-workers is a powerful method for converting olefins into non-racemic vicinal 1,2 diols. A variety of ligands described previously work especially well with *trans*-1,2-disubstituted olefins and trisubstituted olefins to yield specific stereoisomers.¹²² Indeed, this was the case in preparation of *syn*- and *anti*-1,3 derived tetraols **75b-75m**. However, achieving high selectivity in the dihydroxylation of mono-substituted terminal olefins is particularly challenging.¹²²

Our investigation of forming tetraols **75aa** and **75ab** began with asymmetric dihydroxylation of *syn*-diol **73a** (Table 3.12). Different ligands were examined to determine optimal conditions and selectivity. The best results were obtained when the PYR ligand was used, but the selectivity was still only modest (entries 5, 6). After the PYR ligand was identified

Table 3.12: Preparation of tetraols **75aa** and **75ab**



Entry	Ligand (mol%)	Time (h)	dr ^a 75aa:75ab	Yield (%) 75aa + 75ab
1	(DHQ) ₂ PHAL	20	57:43	84
2	(DHQD) ₂ PHAL	16	40:60	86

3	(DHQ) ₂ AQN	72	57:43	73
4	(DHQD) ₂ AQN	60	42:58	78
5	(DHQ) ₂ PYR	16	63:37	88
6	(DHQD) ₂ PYR	16	29:71	90
7 ^b	(DHQD) ₂ PYR	24	30:70	88
8 ^c	(DHQD) ₂ PYR	20	24:76	89

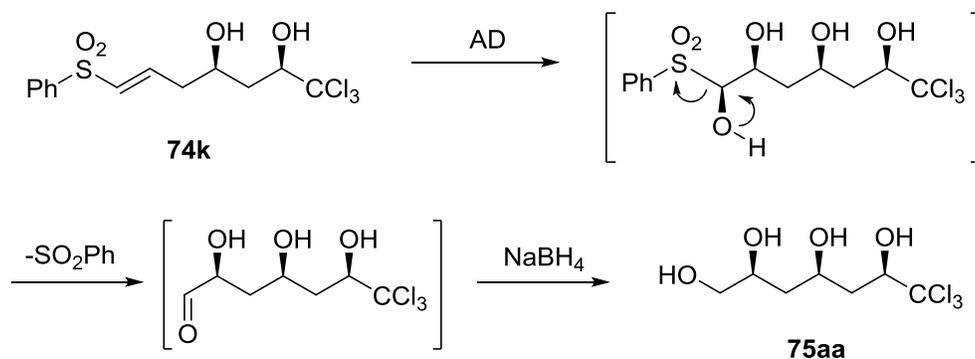
^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture. ^b pH was maintained above 10 throughout the reaction by periodic addition of aqueous 1M NaOH and monitoring with a pH meter. ^c Reaction was run in water–surfactant media (without *t*BuOH) with sodium cholate (0.31 equiv) at a 0.1 M concentration (based on **73a**)

as the optimal ligand for this substrate, it was employed in attempted dihydroxylations under pH controlled conditions,¹²⁰ and in water–surfactant media.¹⁵⁷ There was no advantage to maintaining a pH > 10 (entry 7); however, a slight improvement was observed in the presence of sodium cholate (entry 8).

In hopes of further improving the selectivity in the preparation of **75aa** and **75ab**, we envisioned a slightly different approach proceeding through vinyl sulfone **74k** based on a report by Evans and co-workers.¹⁵⁸ Presumably the lack of selectivity observed when proceeding through the terminal olefin **73a** was due to weak interactions from the relatively small hydrophilic substituent within the ligand binding pocket. We reasoned the vinyl sulfone substituent would be well suited for asymmetric dihydroxylation and would lead to higher selectivity. We hoped subjecting vinyl sulfone **74k** to our established AD conditions would promote formation of the α -hydroxysulfone. This intermediate presumably would undergo base-promoted elimination, followed by rapid NaBH₄ reduction *in situ* to afford the desired tetraol **75aa** (Scheme 3.26). Unfortunately, all attempts resulted in an unidentified mixture of products.

¹⁵⁷ Branco, L. C.; Ferreira, F. C.; Santos, J. L.; Crespo, J. G.; Afonso, C. *Adv. Synth. Catal.* **2008**, *350*, 2086.

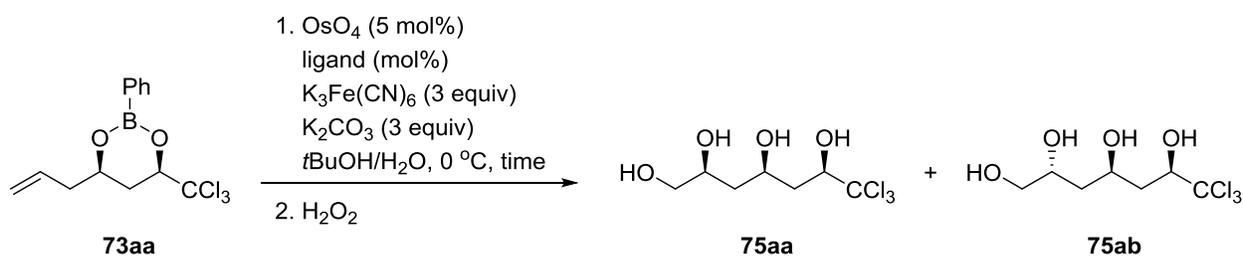
¹⁵⁸ Leffray, M.; Evans, P. *Tetrahedron* **2003**, *59*, 7973.



Scheme 3.26: Alternate approach to preparation of tetraol **75aa**

Next, we envisioned that modifying the steric profile of the substrate to that of a bulkier adduct bearing an aryl group might allow for higher enantiofacial discrimination and stronger interactions in the ligand binding pocket, leading to higher yields of the desired stereoisomer. The phenyl boronic ester adduct **73aa** was prepared by treating diol **73a** with 1.5 equiv phenyl boronic acid in DCM prior to dihydroxylation and proceeded in quantitative yield. Subjecting **73aa** to our established AD conditions, followed by oxidative cleavage of the boronic ester revealed the free tetraol in 94% yield, and 5:1 dr¹⁴⁸ (Table 3.13). Much like with AD of the free

Table 3.13: Preparation of **75aa** and **75ab** from boronic ester adduct **73aa**



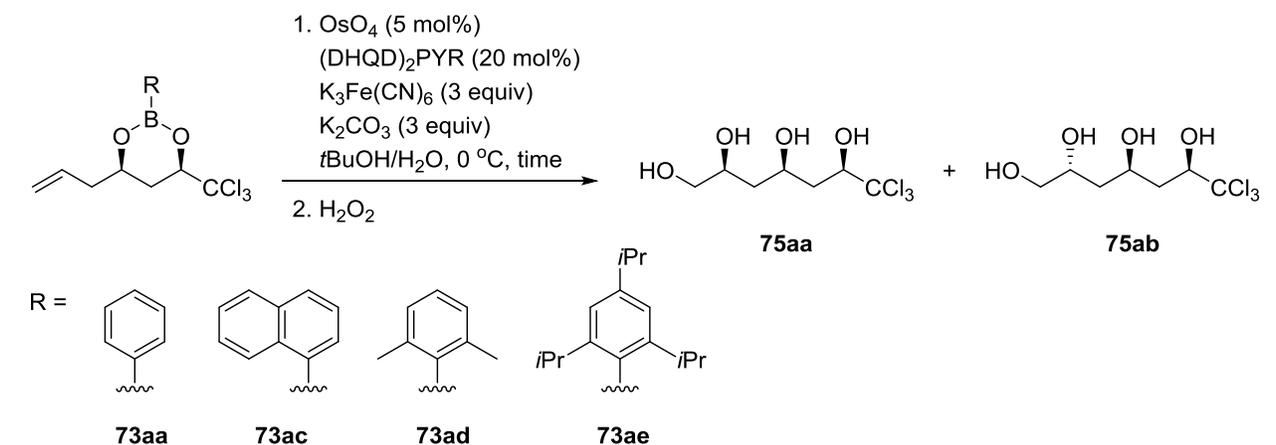
Entry	Ligand (mol%)	Time (h)	dr ^a	Yield (%)
			75aa:75ab	75aa + 75ab
1	(DHQD) ₂ PHAL	24	47:53	78
2	(DHQD) ₂ AQN	30	47:53	86
3	(DHQD) ₂ PYR	24	17:83	94

^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture of boronic ester diols

diol **73a**, the PYR ligand was superior to other ligands with the modified terminal olefin. Along with increasing the steric profile, we believe the phenyl boronic ester has several advantages: First, the increased lipophilicity, and presence of the aromatic ring likely leads to better ligand–substrate interactions and limits potential nonselective dihydroxylation processes. Second, rotational conformers within the ligand binding pocket are limited by formation of the 6-membered ring potentially mitigating substrate-controlled processes. Last, any potential directing effects from the homoallylic alcohol would be effectively eliminated.

As a result of the success of phenyl boronic ester **73aa** in the AD reaction, a variety of aryl boronic esters (Table 3.14) were prepared from their corresponding boronic acids to be

Table 3.14: boronic esters screened in the asymmetric dihydroxylation reaction



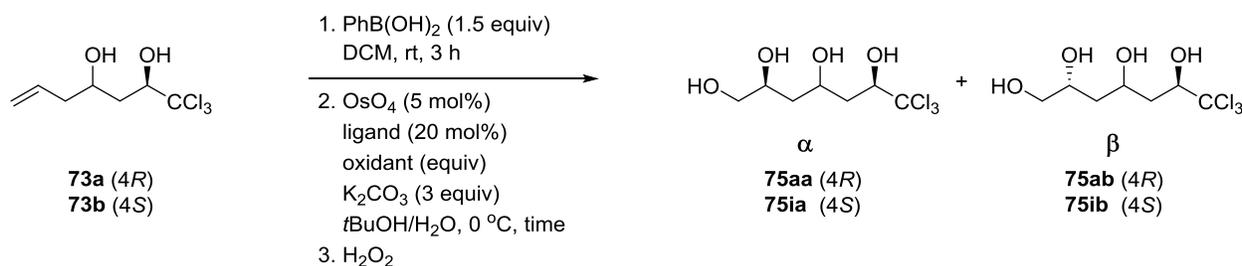
Entry	Substrate	Time (h)	dr ^a 75aa:75ab	Yield (%) 75aa + 75ab
1	73aa	24	17:83	94
2	73ac	24	42:58	45
3	73ad	24	17:83	78
4	73ae	24	40:60	86

^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture of boronic ester diols

screened in the AD reaction. A comparable dr value was obtained from the dimethylphenylboronic ester **73ad**, but resulted in a lower yield than with **73aa**. Other phenyl boronic ester adducts provided no advantage in the stereoselectivity.

After establishing the optimal ligand and boronic ester for the asymmetric dihydroxylation, we prepared tetraols **75aa-75ab** and **75ia-75ib** in a one pot approach from the corresponding *syn*- or *anti*-1,3 diol precursors (Table 3.15). The four stereoisomers were generated in 89–94% yield with diastereomeric ratios¹⁴⁸ ranging from 74:26 – 83:17. The higher degree of selectivity observed in preparation of **75ab** can be explained by examining the substrate-controlled reaction in the absence of the chiral ligands under Upjohn conditions¹³⁰

Table 3.15: Preparation of terminal alcohols from pre-formed boronic ester adducts



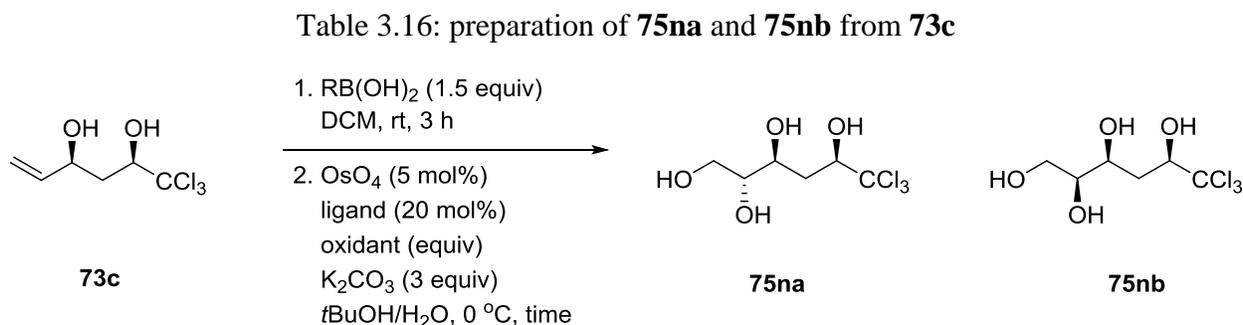
Entry	Substrate	Ligand	Oxidant (equiv)	Time (h)	dr		Yield (%)
					$\alpha:\beta$	$\alpha + \beta$	
1	73a	(DHQ) ₂ PYR	K ₃ Fe(CN) ₆ (3)	24	76:24	75a , 91	
2	73a	(DHQD) ₂ PYR	K ₃ Fe(CN) ₆ (3)	24	17:83	75a , 94	
3	73b	(DHQ) ₂ PYR	K ₃ Fe(CN) ₆ (3)	24	74:26	75i , 94	
4	73b	(DHQD) ₂ PYR	K ₃ Fe(CN) ₆ (3)	24	26:74	75i , 89	
5	73a	none	NMO (1.5)	18	40:60	75a , 88	
6	73b	none	NMO (1.5)	16	48:52	75i , 86	

^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture of boronic ester diols.

(entries 5, 6). Stereoselectivity in **75ab** likely results from being a “matched” pair in which the chiral substrate and the chiral ligand direct dihydroxylation to the same face of the olefin.

3.5.4 Epoxidation/Azidation of Terminal Mono-substituted Olefins

To further expand upon our success in enhancing stereoselectivity in terminal mono-substituted olefins, we attempted formation of tetraols from the corresponding phenyl boronic ester adduct of **73c** (Table 3.16). When **73c** was subjected to standard asymmetric dihydroxylation conditions with chiral ligands (DHQ)₂PYR, and (DHQ)₂AQN, only modest stereoselectivity was observed. Surprisingly, pre-forming the phenyl boronic ester only marginally improved selectivity and yields were modest. Pre-forming the 2,6-dimethylphenyl boronic ester

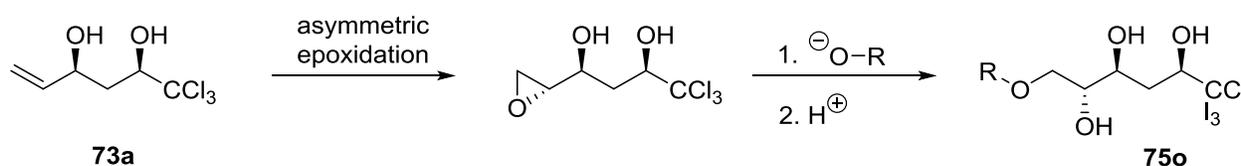


Entry	Boronic acid	Ligand	Time (h)	dr ^a 75na:75nb	Yield (%)
1	none	(DHQ) ₂ AQN	5	62:38	–
2	none	(DHQD) ₂ PYR	8	67:33	–
3 ^b	Phenyl boronic acid	(DHQ) ₂ PYR	24	75:25	50
4 ^b	2,6-dimethylphenyl boronic acid	(DHQD) ₂ PYR	24	60:40	52

^a The diastereomeric ratio was determined from the ¹H NMR spectrum of the crude reaction mixture of boronic ester diols. ^b The crude reaction mixture was treated with aqueous H₂O₂ (30%) for 1 hour to generate the free tetraols

also provided no advantage in stereoselectivity or yield. The low yields were attributed to complications related to oxidative cleavage with H₂O₂, including migration of the boronic ester and some product decomposition.

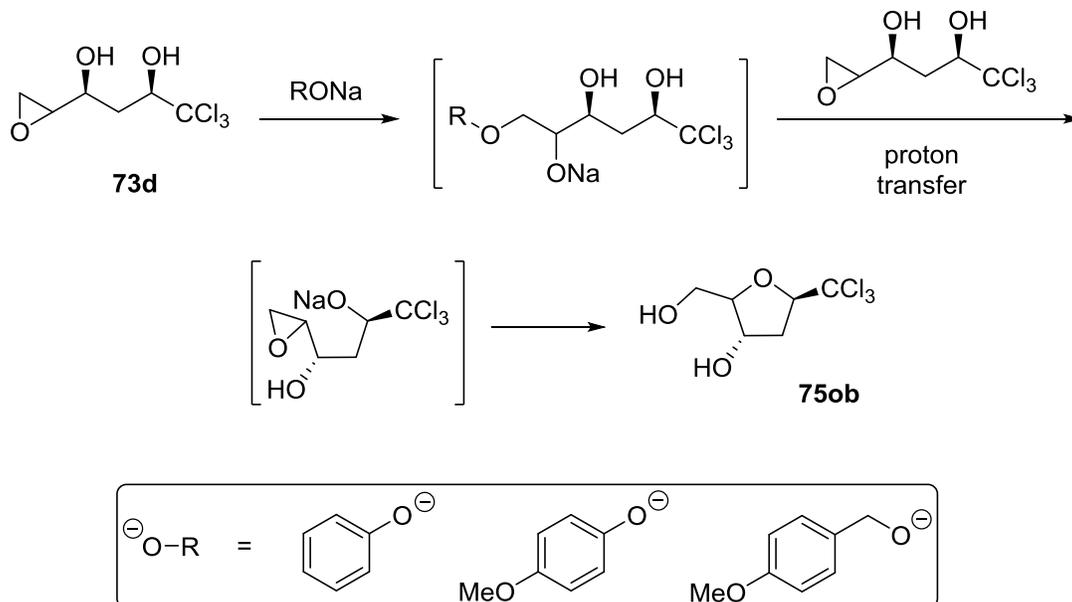
Due to the lack of success in stereoselectively forming tetraols **75na** and **75nb**, we envisioned a slightly modified approach in route to pseudo-tetraols (Scheme 3.27). Asymmetric epoxidation of **73c** followed by subsequent nucleophilic epoxide ring opening *in situ* would lead to pseudo-tetraols of type **75o**. The choice of the oxygen-based nucleophile used in the reaction was crucial; it was necessary that the nucleophile not be basic enough to promote undesired Payne rearrangements,¹⁵⁹ or promote deprotonation of the trichloromethyl carbinol. We imagined phenoxide-type nucleophiles would be well-suited for this transformation.



Scheme 3.27: Preparation of pseudo-tetraols **75o** from allylic alcohol **73a**

To determine if the nucleophilic epoxide addition was feasible, we prepared a diastereomeric (dr = 67:33) mixture of epoxide **73d** by treating olefin **73a** with *m*CPBA in DCM. With epoxide **73d** in hand, we began screening phenoxide nucleophiles under a variety of conditions to prepare **75o**. We quickly realized that the reaction was predominantly generating the furan byproduct **75ob** (Scheme 3.28). Presumably, rapid proton transfer was occurring between the secondary alkoxide anion generated by alkoxide ring opening and the more acidic

¹⁵⁹ Payne, G. B.; *J. Org. Chem.* **1962**, *27*, 3819.



Scheme 3.28: mechanism leading to furan byproduct **75ob**

trichloromethyl carbinol. The generated trichloromethyl alkoxide then undergoes intramolecular cyclization on the internal epoxide carbon electrophile to generate the furan byproduct.

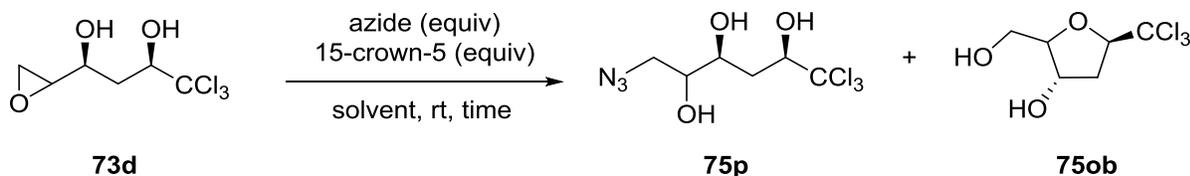
Increasing the nucleophilicity of the alkoxide (i.e. *p*-methoxy phenoxide, *p*-methoxybenzyl oxide) also only resulted in formation of the furan byproduct. Attempts to suppress intramolecular cyclization by adding the conjugate acid of the alkoxide anion were unsuccessful. Also, conducting the reaction with the corresponding protected phenyl boronic ester adduct resulted in byproduct formation and recovery of starting material.

We then directed our attention to more reactive nucleophiles to hopefully out-compete the intramolecular cyclization process. We sought to prepare the azidotriol **75p** by treating the terminal epoxide **73d** with a source of nucleophilic azide (Table 3.17). The azido triol could be an interesting target that may serve as a valuable precursor to nucleoside mimics obtainable through “click” chemistry,¹⁶⁰ or to unnatural deoxyamino sugars. Our initial attempts of treating

¹⁶⁰ Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, 88, 1128.

73d with NaN₃ in polar aprotic solvents were encouraging; however the byproduct was still formed as the major product from the reaction (entries 1–3). Azidation attempts in isopropanol (IPA) resulted in clean conversion to the byproduct. Including 15-crown-5 resulted in a modest improvement, but product yields were still less than desired (entries 2, 3, 4). Finally, the breakthrough came when we treated **73d** with trimethylsilyl azide (TMSN₃) activated by a catalytic amount of tetrabutylammonium fluoride (TBAF) (entry 6). Under these conditions, the resulting C-5 alkoxide anion was silylated by TMSN₃ which inhibited proton transfer/cyclization, and simultaneously propagated activation of the azide anion. After the reaction was complete, the crude reaction mixture was treated with a full equivalent of TBAF to reveal the free azidotriol in 86% yield. Future objectives will focus on a one-pot preparation of **75p** through asymmetric epoxidation, followed by azidolysis with TMSN₃.

Table 3.17: preparation of azidotriol **75p**



Entry	Azide (equiv)	15-crown-5 (equiv)	Solvent	Time (h)	Yield (%)	
					75p	75ob
1	NaN ₃ (1.2)	–	THF	24	23	50
2	NaN ₃ (1.2)	0.2	THF	24	29	52
3	NaN ₃ (1.2)	1	DMF	24	55	24
4	NaN ₃ (1.2)	–	IPA	20	0	81
5	NaN ₃ (1.5)	1	DCM	36	55	21
6 ^a	TMSN ₃ (1.2)	–	DCM	2	86	0

^a TMSN₃ was activated by adding one drop of TBAF (1 M in THF)

3.5.5 Formation of Polysubstituted Oxacycles by a Novel Jocic Reaction

With stereoisomeric tetraol derivatives of type **75** in hand, we aimed to prepare the corresponding tetrahydropyran carboxylic acid derivatives of type **70** by a novel intramolecular Jocic-type reaction.⁹⁰ Previous work related to Jocic-type reactions and formation of *gem*-dichloroepoxide intermediates provided valuable groundwork to establish our reaction parameters. First, protic solvents are necessary to promote formation of the *gem*-dichloroepoxide intermediates. Conducting the reaction in polar aprotic solvents such as anhydrous THF, DMF, or MeCN results in little or no consumption of starting material.¹⁶¹ This indicates an S_N1-type mechanism in which the protic solvent serves as a hydrogen bond donor that likely facilitates the elongation and eventual heterolysis of the carbon-chlorine bond followed by intramolecular attack of the alkoxide anion. Consequently, reactions of this type are often run in alcoholic solvents (i.e. methanol, ethanol, isopropanol), or under aqueous conditions in conjunction with an aprotic organic solvent such as DCM, DME, or acetone.⁶¹ Second, hydroxide has proven to be a convenient and effective base in the formation of *gem*-dichloroepoxide intermediates, and practical for our intended purposes. Other bases that are employed include DBU,¹⁶² and cesium carbonate.¹⁶³

We began our screening studies toward the preparation of the tetrahydropyran derivatives with the phenyl derived tetraol **75ba** (Table 3.18). Naturally, we chose water as our protic solvent to prevent potential formation of unwanted ester byproducts (although preparation of corresponding ester derivatives was also explored), and due to previously successful results in

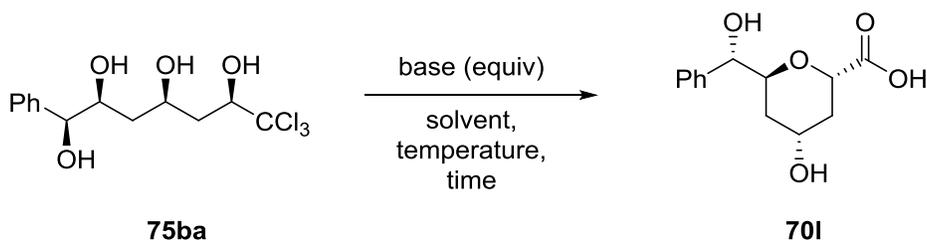
¹⁶¹ (a) Shamshina, J. L.; Snowden, T. S. *Org. Lett.* **2006**, *8*, 5881. (b) Oliver, J. E.; Waters, R. M.; Lusby, W. R. *Synthesis* **1994**, 273. (c) Khimian, A. P.; Oliver, J. E.; Waters, R. M.; Panicker, S.; Nicholson, J. M.; Klun, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 37.

¹⁶² (a) Scaffidi, A.; Skelton, B. W.; Stick, R. V.; White, A. H. *Aust. J. Chem.* **2006**, *59*, 426. (b) Dominguez, C.; Ezquerro, J.; Baker, S. R.; Borrelly, S.; Prieto, L.; Espada, C. M.; Pedregal, C. *Tetrahedron Lett.* **1998**, *39*, 9305.

¹⁶³ Snowden, T. S. unreported results, 2006–2015.

similar Jocic-type cyclization reactions, DCM was initially chosen as the organic co-solvent. When considering the amount of base to use in the reaction, we reasoned that the reaction would require a minimum of 4 equivalents of sodium hydroxide in route to the targeted pyran carboxylic acid (see Scheme 3.8 and 3.9). These conditions provided a reasonable starting point for our studies. Treatment of **75ba** with 4.0 equivalents of NaOH (entry 1) resulted in only partial consumption of starting material after stirring for 96 hours. The substrate was completely consumed when 5.0 equivalents of NaOH was used; however, a more satisfactory rate was observed when **75ba** was treated with 6.0 equivalents of NaOH while stirring at room temperature (compare entries 3–5). Unfortunately and somewhat unexpectedly, when DCM was used as the organic co-solvent even at 0 °C, a complex mixture of products was generated with

Table 3.18: optimization screening toward preparation of **70l**



Entry	Base (equiv)	Solvent (0.1 M)	Temp. (°C)	Time (h)	Yield ^a (%)
1	NaOH (4)	DCM–H ₂ O 5:3	rt	96	<i>b</i>
2	NaOH (5)	DCM–H ₂ O 5:3	0	48	<i>c</i>
3	NaOH (5)	DCM–H ₂ O 5:3	rt	36	<i>c</i>
4	NaOH (6)	DCM–H ₂ O 5:3	rt	22	<i>c</i>
5	NaOH (6)	DCM–H ₂ O 5:3	0	30	<i>c</i>
6	NaOH (6)	DME–H ₂ O 5:3	rt	22	74
7	NaOH (6)	DME–H ₂ O 2:3	rt	24	81

8	NaOH (6)	DME–H ₂ O 1:5	rt	30	83
9	NaOH (6)	DME–H ₂ O 1:10	rt	30	83
10	NaOH (6)	H ₂ O	rt	36	81
11	NaOH (6)	Dioxane–H ₂ O 1:5	rt	24	83

^a Product yields are based off analysis of the ¹H NMR spectrum of the crude reaction mixture and are relative to the amount of **75ba** remaining in the mixture

^b Only partial consumption of the starting material was observed

^c The reaction resulted in a complex mixture of products

70l being present in <60% yield according to the ¹H NMR spectrum of the crude reaction mixture. More encouraging results were obtained after switching to DME as the organic solvent. Analysis of the crude mixture clearly revealed that the targeted carboxylic acid was being generated as the major product of the reaction along with minor amounts of an unidentified byproduct (described in further detail below) and unexpected methoxy signals. We surmised the methoxy signals might be resulting from demethylation of DME by the free alkoxide groups in the substrate. This problem was later solved by switching to 1,4-dioxane as the organic solvent. To our knowledge, this is the first use of 1,4-dioxane as a cosolvent in a reaction involving generation of a *gem*-dichloroepoxide. While screening the reaction conditions with DME as the co-solvent, there was an observed trend that a lower organic solvent/water ratio was beneficial to the yield and purity of the desired product. In fact, comparable yields were obtained when only water was used as the reaction solvent, however, low concentrations of the organic solvent were detrimental to the reaction rate presumably due to limited solubility of the substrate (compare entries 6–10). Finally, the best yield and purity of the desired product was obtained when using a 1:5 ratio of dioxane–H₂O (entry 11). Further optimization studies are ongoing.

We were encouraged by our promising results with the cyclization optimization, but the isolation of the desired product and identification of the unknown byproduct proved to be

extremely challenging. The crude material obtained from cyclization of **75ba** to carboxylic acid **70I** was an oily residue which made re-crystallization difficult, and attempts to isolate **70I** by means of column chromatography on various stationary phases were unsuccessful. Attempts to separate **70I** from the byproduct by acid/base extraction methods were also ineffective. The unsuccessful acid/base extraction attempts along with NMR evidence indicated that the byproduct most likely contained a carboxylic acid functionality whose structure closely resembled the targeted product. We envisioned that converting the crude mixture of carboxylic acids to the corresponding acid fluoride adducts would promote selective lactonization and potentially facilitate separation of the two materials. Indeed, treatment of the crude mixture of products with cyanuric fluoride and pyridine in DCM lead to a meaningful discovery (Figure 3.15). Spectroscopic analysis of the organic product obtained after the aqueous work-up revealed the reaction resulted in clean conversion to the lactone **70II** (86% yield over 2 steps). Successful identification of lactone **70II** offered some clarity pertaining to the products generated from the

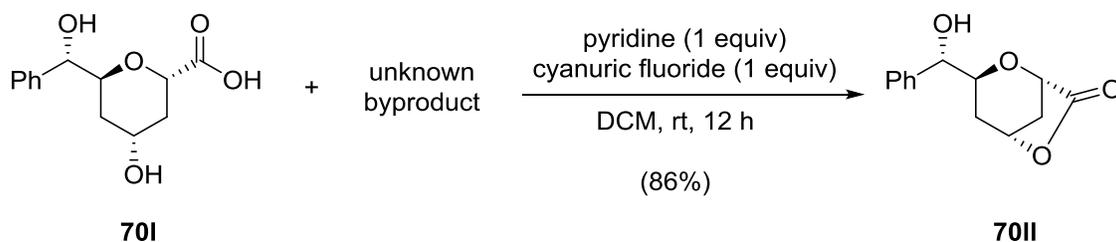


Figure 3.15: preparation of lactone **70II** from **70I**

cyclization reaction in 1,4-dioxane. In fact, comparison of the NMR data from the isolated lactone to the NMR data obtained from the crude reaction mixtures allowed us to determine that the unknown major byproduct was actually the lactone.¹⁶⁴ Identification of **70II** also helps to explain the unfruitful attempts at purification by silica gel chromatography. We reasoned that the

¹⁶⁴ It is possible that other minor, unidentified byproducts may also be generated in <5% yields.

slightly acidic nature of the silica gel was promoting lactonization of **70l** as the material passed through the column, leading to co-elution of the two materials. Somewhat unexpectedly however, simply stirring **70l** over silica gel for 12 hours led to no observed lactonization. We have begun pursuing the preparation of pyran derivatives **70k–70o** (Figure 3.16) following our success with isolating the corresponding lactone of **70l**. Initial results have been promising (**70ll** and **70mm** were obtained in 86% and 81% yields respectively), and work toward the preparation of **70kk**, **70mm**, and **70oo** is ongoing. Future efforts in this area will be directed toward identifying a method for converting lactones **70kk–70oo** to carboxylic acids **70k–70o** and obtaining the carboxylic acids as pure materials.

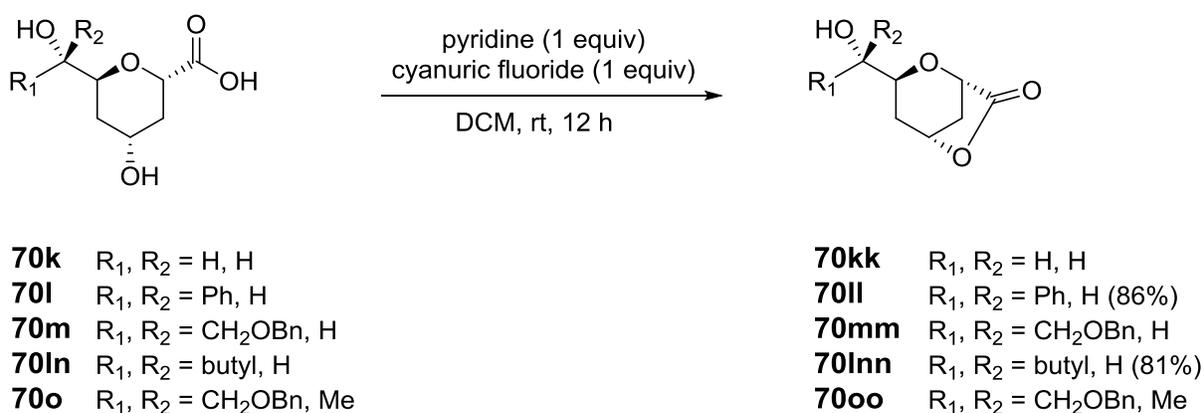
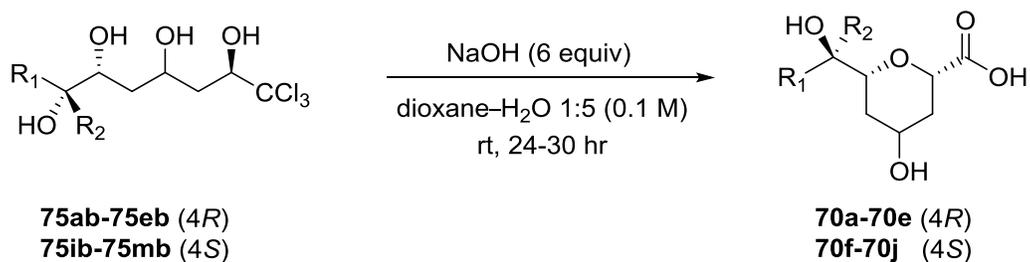


Figure 3.16: preparation of lactones **70kk–70oo**

After determining the optimal conditions for the cyclization reaction, we sought to apply those conditions to other tetraol derivatives of type **75**. To our delight, the cyclizations proceeded as expected and afforded the corresponding pyran carboxylic acids **70a–70j** in yields exceeding 82% (Table 3.19). Interestingly, derivatives **70a–70j** were obtained as amorphous solids following completion of the reaction and were easily purified by recrystallization in DCM. More specifically, in every case where the (*R*)- configuration is observed at the *C*-6 carbon of the tetraol precursor, the corresponding pyran was crystalline regardless of the orientation of the *C*-4

Table 3.19: preparation of pyrans **70a–70j**



Entry	Substrate	Product	Isolated Yield ^a
1	 75ab	 70a	85%
2	 75bb	 70b	93%
3	 75cb	 70c	85%
4	 75db	 70d	93%
5	 75eb	 70e	93%
6	 75ib	 70f	89%

7	<p style="text-align: center;">75jb</p>	<p style="text-align: center;">70g</p>	84%
8	<p style="text-align: center;">75kb</p>	<p style="text-align: center;">70h</p>	86%
9	<p style="text-align: center;">75lb</p>	<p style="text-align: center;">70i</p>	82%
10	<p style="text-align: center;">75mb</p>	<p style="text-align: center;">70j</p>	82%

^a Isolated yield of diastereomerically pure carboxylic acids

hydroxyl group. Perhaps this isn't too surprising when considering the preferred chair conformer of these particular diastereomers, but the consistency of the trend is notable. It's reasonable to assume that when the equilibrium strongly favors one chair conformer over the other that the material can stack in an ordered fashion leading to the crystalline material. In cases where the C-6 carbon of the tetraol is configured in the (*S*)- orientation the opposite is true. The cyclization reaction with these substrates resulted in an oily residue (with the exception of **70p** which formed a crystalline solid) likely due to a lack of preference for one chair conformer over the other. Fortunately, pyrans **70k–70o** with the C-6 (*S*)-configuration have initially shown promising results in the preparation of their corresponding lactones, and we are optimistic that all derivatives from this class of diastereomers can be isolated as the lactone adduct. The class of tetraol diastereomers containing the (4*S*, 6*S*) configuration have shown inconclusive results thus far in the cyclization reaction, and/or in attempting to form the corresponding lactone adducts

(Figure 3.17). Interestingly, tetrahydropyran **70p** was obtained as an amorphous solid from the cyclization reaction, and recrystallization in DCM afforded **70p** in 86% yield. Additionally, the phenyl derived pyran **70q** was purified by silica gel chromatography. We rationalized that silica-promoted lactonization would be much slower in this particular class of stereoisomers due to the relative *anti*- relationship between the carboxylic acid functional group and the 3'-hydroxyl on the pyran ring. We are optimistic that the slower rate of lactonization will simplify purification of this class of pyrans by silica gel chromatography. Alternatively, if column purification is unsuccessful, modified approaches to preparing the corresponding lactone adducts will be explored. Work towards the preparation of pyrans **70r–70t** is currently underway.

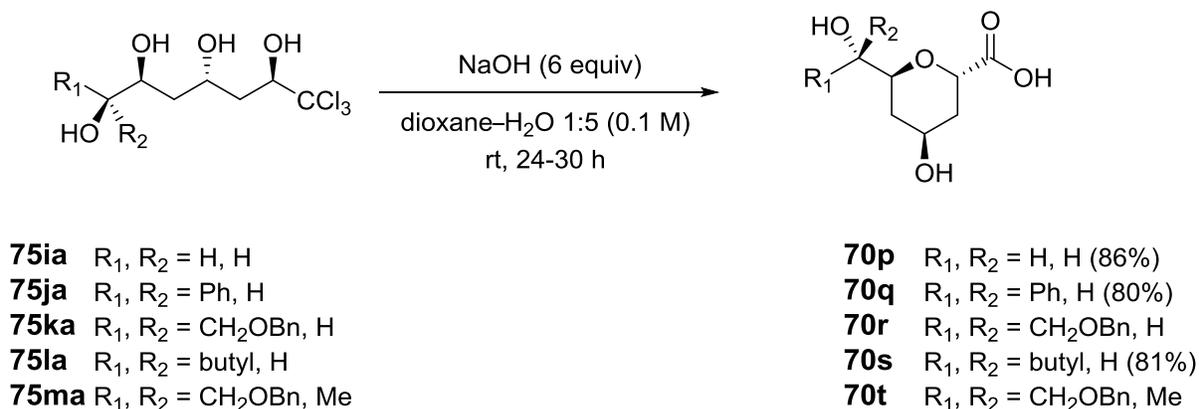


Figure 3.17: preparation of pyrans **70p–70t**

It's worth noting that in all cyclization reactions, there has been no observed formation of 4-member or 7-member rings. These observations have reinforced our hypothesis that we could use the reaction kinetics to our advantage and selectively form the 6-membered oxacycle without the need for additional protection/deprotection steps in the synthetic route. More specifically, we were able to confirm 6-member ring formation from ^{13}C NMR chemical shifts, HMBC, and HSQC NMR experiments. Relative stereochemistry was established by first determining the

chemical shift of each nonequivalent proton (^1H , COSY, HMBC, HSQC NMR), then by NOE experimentation. The NOE correlations are shown in Figure 3.18. These results indicate that the dihydroxylation selectivity mnemonic accurately predicted the stereochemical outcome of the tetraol products. We are pleased that the cyclization reactions have generated the expected 6-membered oxacycles and that the stereochemical outcome is easily predictable. The described method has proven to be a step economic approach to generating a variety of polysubstituted

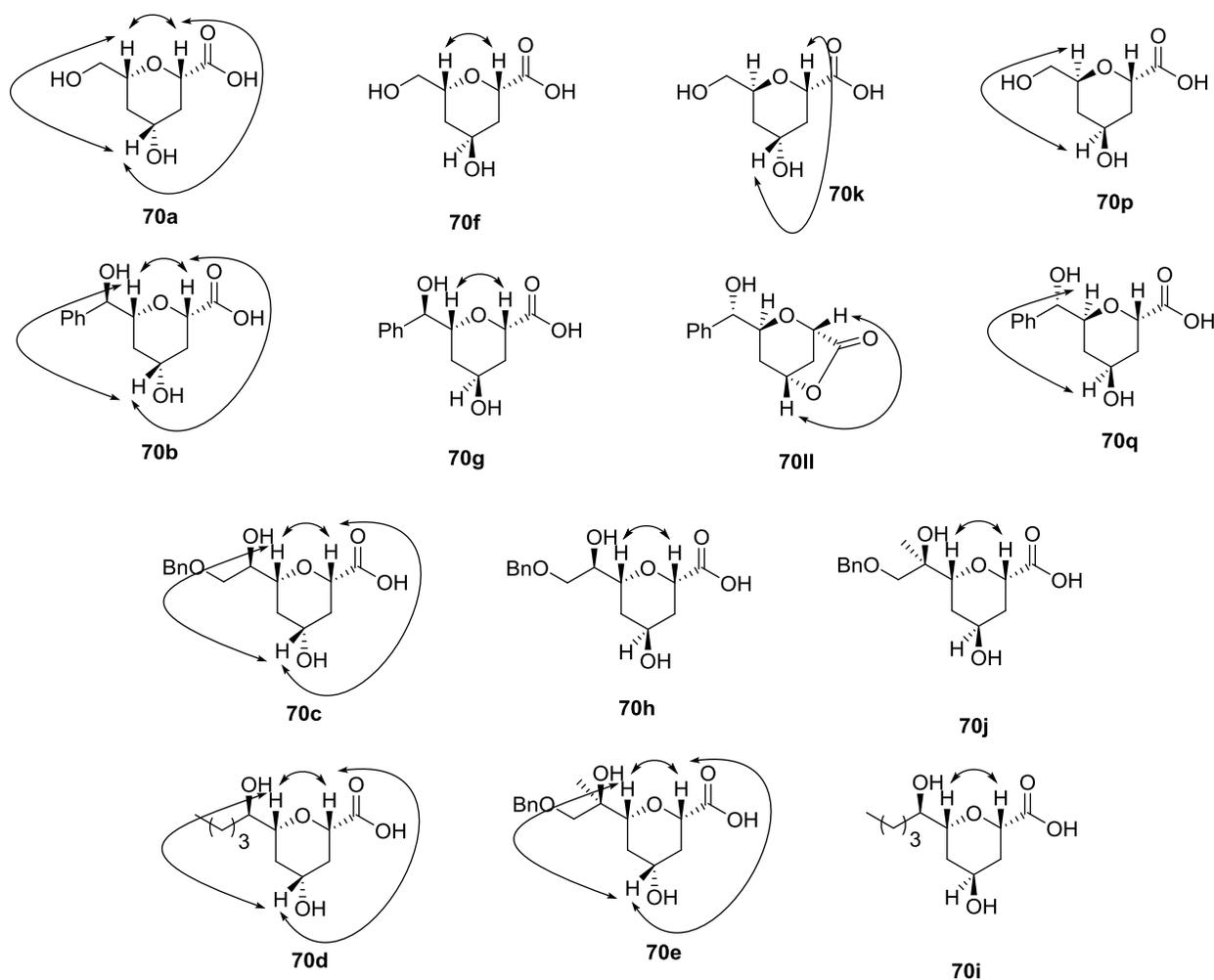
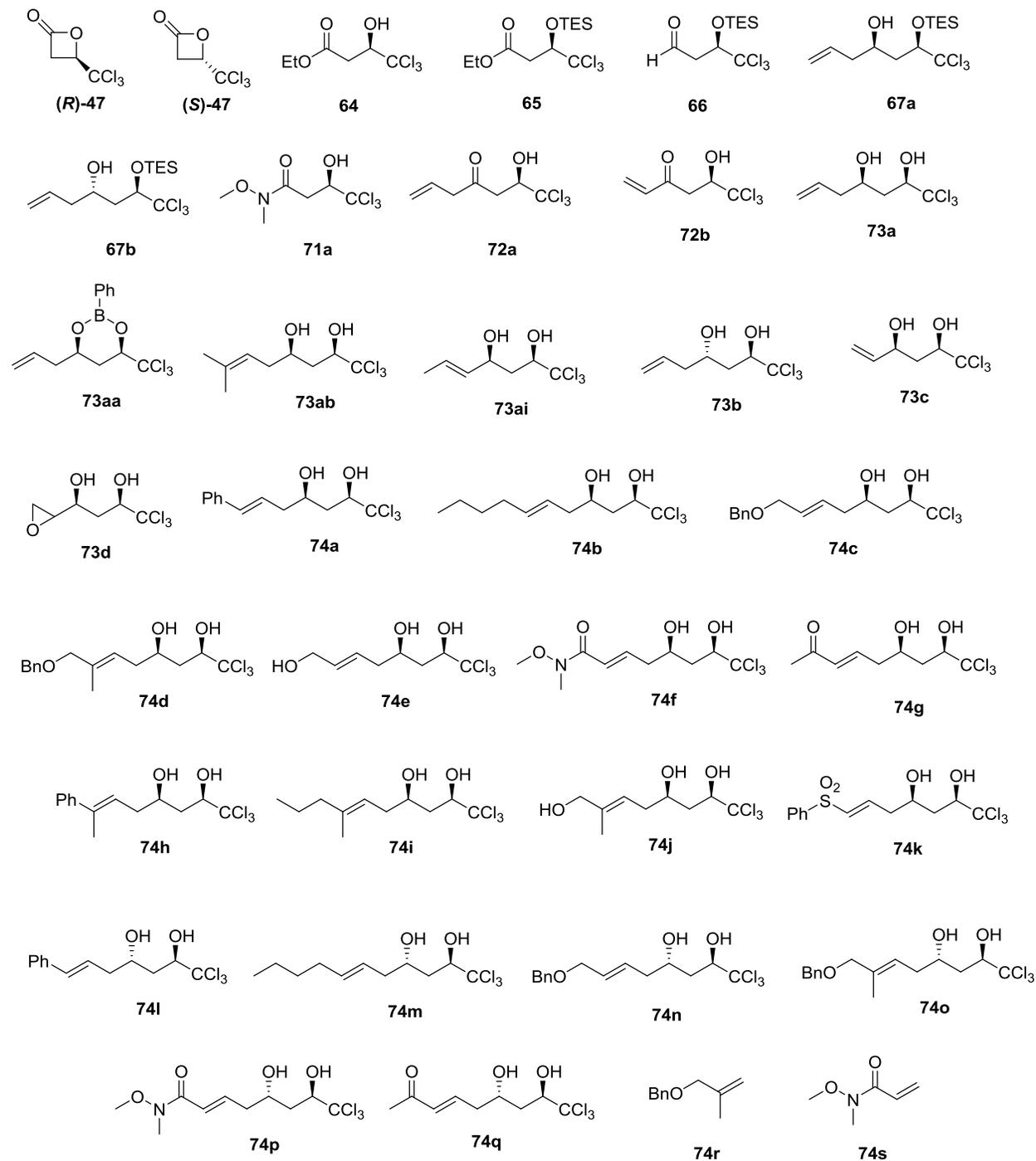
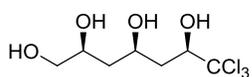


Figure 3.18: NOE correlations showing relative stereochemistry in pyran derivatives of type **70**

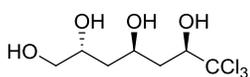
tetrahydropyrans. The ability to form any desired configuration at multiple chiral centers accentuates the appeal and utility of our approach.

3.6 Index of Chapter Compounds and Numbers

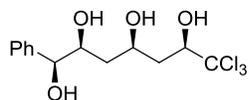




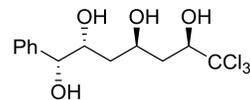
75aa



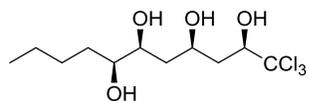
75ab



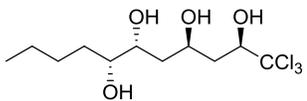
75ba



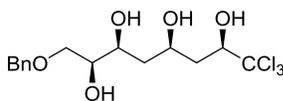
75bb



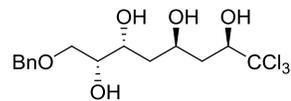
75ca



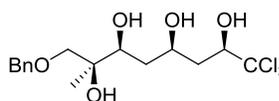
75cb



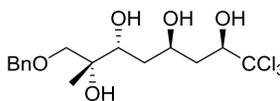
75da



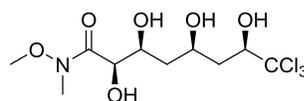
75db



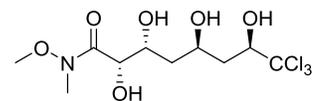
75ea



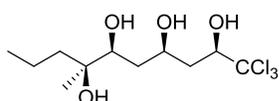
75eb



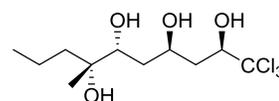
75fa



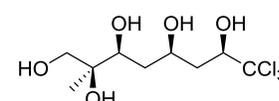
75fb



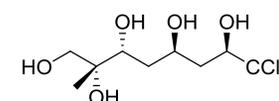
75ga



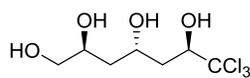
75gb



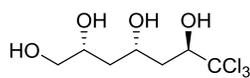
75ha



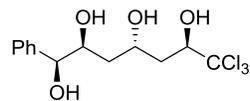
75hb



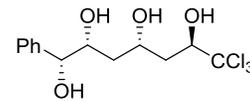
75ia



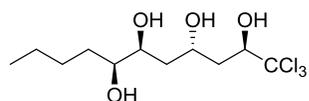
75ib



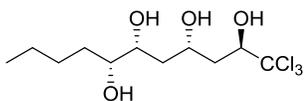
75ja



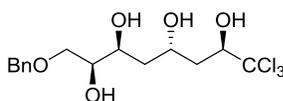
75jb



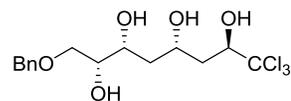
75ka



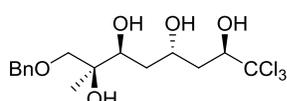
75kb



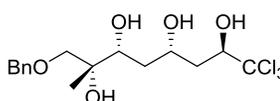
75la



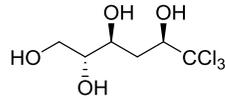
75lb



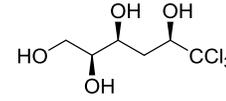
75ma



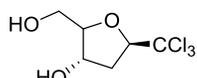
75mb



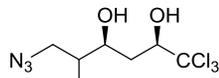
75na



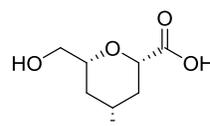
75nb



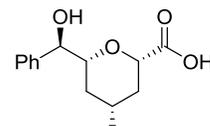
75ob



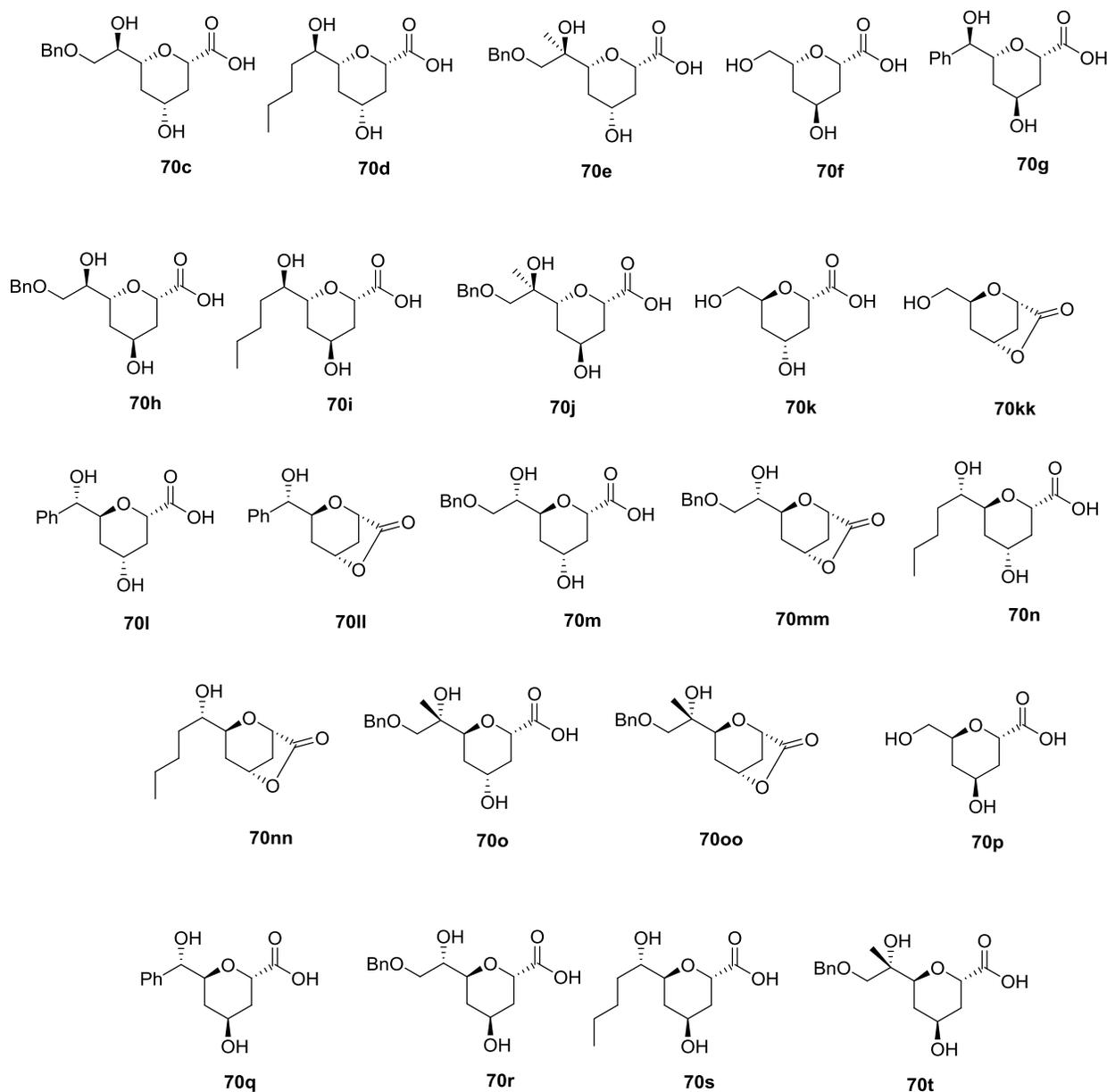
75p



70a



70b



3.7 Experimental Details

^1H and ^{13}C NMR spectra were recorded on Bruker instruments at 360, 500, or 600 MHz and 90 or 125 MHz, respectively. ^{19}F NMR spectra were recorded at 338 MHz. Chemical shifts were referenced to acetone- d_6 ($\delta = 2.05$ and 29.84), CDCl_3 ($\delta = 7.26$ and 77.0), CD_3OD ($\delta = 3.31$ and 49.0), or CD_3CN (1.94 and 1.32). Mass spectra were recorded on an AutoSpec-Ultima_NT

mass spectrometer using electron ionization (EI) at 70 eV and an EBE sector mass analyzer. Melting points were determined with a MelTemp 1001D capillary melting point apparatus and are uncorrected. IR samples were prepared by dissolving the pure material in a small amount of a suitable aprotic solvent. A small drop of the concentrated solution was placed on a KBr plate, and the solvent was evaporated completely. A second KBr plate was placed on top of the first plate and rotated by a quarter turn to make an even film of the material between the plates. IR spectra were recorded on a Jasco FT/IR-4100 instrument. Optical rotations were measured with a Rudolph AUTOPOL IV/6W polarimeter. TLC visualization was achieved by UV light (254 nm), KMnO_4 staining, and *p*-anisaldehyde staining. MeCN was dried over 3-Å molecular sieves prior to use. THF and Et_2O were distilled from Na/benzophenone ketyl radical. Chloral was purchased from Riedel-de Haën and distilled neat onto 4-Å molecular sieves. AcCl was distilled from PhNMe_2 (one-tenth volume). Anhydrous AcOH was prepared by stirring $\text{AcOH}-\text{Ac}_2\text{O}$ (1:1) for 1 h, and then AcOH was distilled onto 4-Å molecular sieves. Commercial ruthenium catalysts were purchased from Aldrich and stored in a reagent bottle under an atmosphere of argon in a dessicator in the freezer. The ruthenium catalysts were purified by silica gel chromatography (hexanes– EtOAc , 9:1) immediately before use.¹⁵⁰ Commercial Grignard reagents were titrated using the procedure described by Paquette and Lin.¹⁶⁵ Dichloromethane was distilled over calcium hydride. DME and 1,4-dioxane were purchased as Drisolv® bottles from EMD Millipore and were used as received. Anhydrous methanol was purchased from Aldrich and was used as received. All other reagents and solvents were used as received from commercial sources.

¹⁶⁵ Lin, H.-S.; Paquette, L. A.; *Synthetic Communications* **1994**, *24*, 2503.

(R)-4-(Trichloromethyl)oxetan-2-one (47)⁵⁸

A dry 1-L, 3-neck round-bottom flask was fitted with two addition funnels and an argon supply. Quinidine (406 mg, 1.25 mmol) and anhydrous Et₂O (165 mL) were added to the round-bottom flask, then anhydrous DIPEA (47.5 mL, 0.273 mol) was transferred to the flask by cannula. Chloral (24.5 mL, 0.251 mol) in anhydrous Et₂O (115 mL) was added to one addition funnel. AcCl (17.8 mL, 0.250 mol) in anhydrous Et₂O (115 mL) was added to the other addition funnel. While cooling to -15 °C, the chloral and AcCl were added dropwise to the mixture under argon at approximately equal rates over 1.5 h. After the addition was complete, the mixture was stirred at -15 °C for 2 h. Aqueous 1 M HCl (150 mL) was added and the mixture was warmed to r.t. and then filtered through Celite. The layers were separated, and the aqueous layer was extracted with Et₂O (5 × 30 mL). The combined organic layers were washed with 1 M HCl (3 × 25 mL), dried (MgSO₄), and concentrated by rotary evaporation yielding a light tan solid. The solid was placed under vacuum to remove excess volatile components then purified by bulb-to-bulb distillation (82 °C/0.27 mbar) to give **(R)-47** as a white solid (mixture of enantiomers). The solid was recrystallized (methylcyclohexane)⁵⁸ yielding pure **(R)-47** (31.3 g, 165 mmol, 70%) as white, fluffy crystals; mp 52–53 °C. $[\alpha]_D^{22} - 15.6$ (*c* 1.0, CH₂Cl₂) (corresponds to >98% ee⁵⁸). IR (KBr): 3006, 1847, 1110, 912 cm⁻¹. ¹H NMR (360 Hz, CDCl₃): δ = 5.01 (dd, *J* = 3.8, 5.7 Hz, 1 H), 3.73 (dd, *J* = 5.7, 17 Hz, 1 H), 3.60 (dd, *J* = 3.8, 17 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 164.1, 96.7, 76.0, 42.3. MS (EI): *m/z* = 71.0 [M – CCl₃]. HRMS (EI): *m/z* [M – CCl₃] calcd for C₃H₃O₂: 71.0133; found: 71.0130.

Ethyl (R)-4,4,4-trichloro-3-hydroxybutanoate (64)⁹²

A dry, 2-neck round-bottom flask was charged with **(R)-47** (500 mg, 2.64 mmol) and diluted with anhydrous EtOH (2 mL). Tosic acid (10.0 mg, 0.020 mmol) was slowly added, a

condenser was attached, and the reaction was heated in a 90 °C oil bath under argon for 30 hours. The reaction mixture was cooled to room temperature, and EtOH was removed under reduced pressure. The crude mixture was diluted with EtOAc (25 mL), and washed with brine (3 x 25 mL). The organic layer was dried (Na₂SO₄), and concentrated to afford **64** (612 mg, 2.60 mmol, 98%) as a clear colorless oil that did not require further purification. ¹H NMR (500 MHz, CDCl₃): δ = 4.62 (ddd, *J* = 2.3, 4.3, 9.2 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.71 (d, *J* = 4.3 Hz, 1 H), 3.07 (dd, *J* = 2.4, 16.3 Hz, 1 H), 2.76 (dd, *J* = 9.2, 16.3 Hz, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 170.8, 102.1, 79.4, 61.4, 37.1, 14.1.

Ethyl (*R*)-4,4,4-trichloro-3-((triethylsilyl)oxy)butanoate (65**)⁹²**

A dry, 2-neck round-bottom flask was charged with **64** (560 mg, 2.38 mmol) and diluted with anhydrous DMF (4.75 mL). The solution was cooled to 0 °C and treated with chlorotriethylsilane (519 μL, 3.09 mmol) and a catalytic amount of imidazole (105 mg, 1.55 mmol). Subsequently, DIEA (455 μL, 2.62 mmol) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred under argon for 3 hours. The reaction was quenched with EtOH (5 mL), and the volatiles were removed under reduced pressure. The crude reaction mixture was diluted with Et₂O (30 mL) and washed with DI H₂O (3 x 30 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc, 33:1) to give **65** (790 mg, 2.26 mmol, 95%) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 4.72 (dd, *J* = 2.4, 8.2 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.11 (dd, *J* = 2.4, 16.4 Hz, 1 H), 2.70 (dd, *J* = 8.2, 16.4 Hz, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.98 (t, *J* = 8.2 Hz, 9 H), 0.71 (q, *J* = 7.7 Hz, 6 H).

(*R*)-4,4,4-trichloro-3-((triethylsilyl)oxy)butanal (66**)⁹²**

A dry, 2-neck round-bottom flask was charged with **65** (200 mg, 0.572 mmol), diluted with DCM (5.70 mL), and cooled to -78 °C. The solution was treated with DIBAL (1 M in DCM, 1 mL, 1 mmol) by dropwise addition. The reaction mixture was stirred at -78 °C for 4 hours, then carefully quenched with dropwise addition of MeOH (0.5 mL) followed by aqueous sodium/potassium tartrate (1M, 3 mL), and DI H₂O (3 mL). The reaction mixture was warmed to room temperature and stirred for 30 minutes. The phases were separated, and the aqueous phase was extracted with DCM (5 x 20 mL). The combined organic layers were washed with brine (25 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography (hexanes–Et₂O , 50:1) to give **66** (168 mg, 0.550 mmol, 96%) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 9.85 (dd, *J* = 0.7, 1.5 Hz, 1 H), 4.78 (dd, *J* = 3.0, 7.0 Hz, 1 H), 3.18 (ddd, *J* = 0.7, 3.0, 18.0 Hz, 1 H), 2.97 (ddd, *J* = 1.5, 7.0, 18.0 Hz, 1 H), 0.98 (t, *J* = 8.1 Hz, 9 H), 0.71 (q, *J* = 8.1 Hz, 6 H). ¹³C NMR (125 MHz, CDCl₃): δ = 198.0, 102.8, 78.3, 48.6, 6.7, 5.0.

(R)-7,7,7-trichloro-6-((triethylsilyl)oxy)hept-1-en-4-one (67a)

A dry, 2-neck round-bottom flask was charged with (+)-*B*-allyldiisopinocampheylborane (1 M soln in pentane, 0.720 mL, 0.720 mmol) and anhydrous THF (2.4 mL). The reaction mixture was cooled to -94 °C, and a solution of aldehyde **66** (146 mg, 0.477 mmol) in THF (0.6 mL) was added dropwise. After stirring for 2 hours at -94 °C under argon, the solution was warmed to room temperature, and quenched with potassium phosphate buffer (1 M in H₂O, pH = 7, 300 μL) followed by slow dropwise addition of 30% aqueous H₂O₂ (650 μL). The mixture was stirred for an additional 12 hours at room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (5 x 10 mL). The combined organics were dried (Na₂SO₄), and concentrated. The crude product was evaluated by ¹H NMR spectroscopy to establish dr (*syn/anti*) = 79:21 and then purified by silica gel chromatography (hexanes–EtOAc ,

9:1) to give a mixture of **67a** and **67b** (123 mg, 0.354 mmol, 74%) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 5.90–5.77 (m, 1 H), 5.23–5.06 (m, 2 H), 4.33 (dd, *J* = 3.9, 6.8 Hz, 1 H), 3.95–3.87 (m, 1 H), 2.38–2.31 (m, 1 H), 2.30–2.16 (m, 2 H), 2.06 (d, *J* = 3.5 Hz, 1 H), 1.86 (ddd, *J* = 6.9, 8.2, 14.9 Hz, 1 H), 1.01 (t, *J* = 7.9 Hz, 9 H), 0.80–0.70 (m, 6 H).

(S)-7,7,7-trichloro-6-((triethylsilyl)oxy)hept-1-en-4-one (67b)

A dry, 2-neck round-bottom flask was charged with (–)-*B*-allyldiisopinocampheylborane (1 M soln in pentane, 0.720 mL, 0.72 mmol) and anhydrous THF (2.4 mL). The reaction mixture was cooled to -94 °C, and a solution of aldehyde **66** (146 mg, 0.477 mmol) in THF (0.6 mL) was added dropwise. After stirring for 2 hours at -94 °C under argon, the solution was warmed to room temperature, and quenched with potassium phosphate buffer (1 M in H₂O, pH = 7, 300 μL) followed by slow dropwise addition of 30% aqueous H₂O₂ (650 μL). The mixture was stirred for an additional 12 hours at room temperature. The layers were separated and the aqueous phase was extracted with EtOAc (5 x 10 mL). The combined organics were dried (Na₂SO₄), and concentrated. The crude product was evaluated by ¹H NMR spectroscopy to establish dr (*syn/anti*) = 20:80 and then purified by silica gel chromatography (hexanes–EtOAc, 9:1) to give a mixture of **67a** and **67b** (149 mg, 0.428 mmol, 90%) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 5.88–5.75 (m, 1 H), 5.23–5.12 (m, 2 H), 4.47 (dd, *J* = 1.6, 9.5 Hz, 1 H), 3.87–3.80 (m, 1 H), 2.38–2.30 (m, 1 H), 2.27–2.17 (m, 1 H), 2.10 (ddd, *J* = 1.6, 10.9, 13.9 Hz, 1 H), 1.80 (ddd, *J* = 1.9, 9.5, 13.9 Hz, 1 H), 1.62 (d, *J* = 3.8 Hz, 1 H), 1.01 (t, *J* = 8.0 Hz, 9 H), 0.81–0.69 (m, 6 H).

(R)-4,4,4-trichloro-3-hydroxy-*N*-methoxy-*N*-methylbutanamide (71a)

A dry, 2-neck round-bottom flask was charged with Et₂AlCl under argon using an oven-dried gas-tight syringe (10.0 mL, 79.8 mmol) and diluted with CH₂Cl₂ (80 mL). Then *N,O*-

dimethylhydroxylamine hydrochloride (7.79 g, 79.8 mmol) was added portionwise over a 15 min period under argon at 0 °C (one-portion was added at the outset, then every 5 minutes). The mixture was warmed to room temperature, and stirred for 1 hour. Then a solution of (**R**)-**47** (7.56 g, 39.9 mmol) in DCM (40 mL) was added dropwise via syringe over 10 min at 0 °C. The reaction was warmed to room temperature, and stirred for 12 hours. After 12 hours, the mixture was cooled to 0 °C, and a saturated aqueous solution of NH₄Cl (250 mL) was *slowly* added. The reaction mixture was diluted with DCM, filtered through a pad of Celite, and then the Celite was thoroughly washed with DCM. The aqueous layer was extracted with DCM (5 x 25 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc, 1:1) to give **71a** (9.83 g, 39.2 mmol, 98%) as a white solid; mp 46–47 °C. [α]₂₂^D + 41.4 (*c* 1.0, CH₂Cl₂). IR (KBr): 3399, 2975, 2941, 1644, 1105, 985 cm⁻¹. ¹H NMR (360 Hz, CDCl₃): δ = 4.74 (d, *J* = 4.2 Hz, 1 H), 4.65 (ddd, *J* = 2.4, 4.6, 9.3 Hz, 1 H), 3.73 (s, 3 H), 3.22 (s, 3 H), 3.12 (dd, *J* = 1.5, 16.4 Hz, 1 H), 2.94 (dd, *J* = 9.3, 16.4 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 171.2, 102.4, 79.3, 61.4, 34.1, 32.1. MS (EI): *m/z* = 249.0 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₆H₁₀Cl₃NO₃: 248.9726; found: 248.9731.

(R)-7,7,7-trichloro-6-hydroxyhept-1-en-4-one (72a)

A dry, 2-neck round-bottom flask was charged with Weinreb amide **71a** (1.25 g, 5 mmol) and diluted with THF (10 mL). The mixture was cooled to –15 °C, and isopropylmagnesium chloride (1.97 M in THF, 2.48 mL, 4.9 mmol) was added dropwise via syringe. The mixture was stirred for 1 h, then allylmagnesium chloride (2.25 M in THF, 2.78 mL, 6.25 mmol) was added, and the mixture was stirred for another 3.5 h. The –15 °C reaction was quenched by rapidly transferring it through a 0 °C 1 M aqueous HCl solution (50 mL) via cannula. The aqueous layer

was extracted with EtOAc (7 x 15 mL). The combined organic layers were dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography (hexanes–Et₂O, 5:1) to give **72a** (1.00 g, 4.32 mmol, 86%) as a clear colorless oil. $[\alpha]_{22}^D + 42.3$ (*c* 1.06, CH₂Cl₂). IR (KBr): 3432, 2984, 2924, 1717, 1638, 1098 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 5.97–5.88 (m, 1 H), 5.26–5.17 (m, 2 H), 4.67 (ddd, *J* = 2.1, 4.6, 9.1 Hz, 1 H), 3.62–3.56 (m, 1 H), 3.29–3.26 (m, 2 H), 3.14–3.09 (m, 1 H), 2.96 (dd, *J* = 9.1, 17.4 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 205.5, 129.4, 119.8, 102.4, 78.7, 48.4, 44.0. MS (EI): *m/z* = 230.0 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₇H₉Cl₃O₂: 229.9668; found: 229.9663.

(R)-6,6,6-trichloro-5-hydroxyhex-1-en-3-one (72b)

A dry, 2-neck round-bottom flask was charged with Weinreb amide **71a** (207 mg, 0.827 mmol) and diluted with THF (1.65 mL). The mixture was cooled to –15 °C, and isopropylmagnesium chloride (2.13 M in THF, 0.372 mL, 0.793 mmol) was added dropwise via syringe. The mixture was stirred for 1 h, then vinylmagnesium chloride (1.15 M in THF, 0.898 mL, 1.03 mmol) was added, and the mixture was stirred for another 4 h. The –15 °C reaction was quenched by rapidly transferring it through a 0 °C 1 M aqueous HCl solution (50 mL) via cannula. The aqueous layer was extracted with EtOAc (7 x 15 mL). The combined organic layers were dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc, 9:1) to give **72b** (89.8 mg, 0.413 mmol, 50%) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ = 6.42 (dd, *J* = 10.4, 17.6 Hz, 1 H), 6.32 (d, *J* = 17.6 Hz, 1 H), 5.97 (d, *J* = 10.4 Hz, 1 H), 4.73 (dd, *J* = 2.0, 9.0 Hz, 1 H), 3.80 (brs, 1 H), 3.26 (dd, *J* = 2.0, 17.4 Hz, 1 H), 3.12 (dd, *J* = 9.0, 17.4 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 197.3, 136.3, 130.0, 102.5, 78.7, 41.5.

(2R,4R)-1,1,1-trichlorohept-6-ene-2,4-diol (73a)

A dry, 2-neck round-bottom flask was charged with β -hydroxyketone **72a** (350 mg, 1.51 mmol), freshly distilled THF (15.2 mL), and anhydrous MeOH (3 mL). Diethylmethoxyborane (238 μ L, 1.81 mmol) was added dropwise via syringe, and the mixture was stirred 30 min at room temperature under argon. Then, the mixture was cooled to -78 $^{\circ}$ C, and sodium borohydride (80.1 mg, 2.12 mmol) was added. The mixture was stirred at -78 $^{\circ}$ C for 16 h then quenched at -78 $^{\circ}$ C by dropwise addition of 30% aqueous H_2O_2 (0.9 mL). The mixture was warmed slowly to room temperature then THF and MeOH were removed under reduced pressure. The residue was dissolved in water (5 mL) and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish dr (*syn/anti*) = 95:5 and then purified by silica gel chromatography (hexanes–EtOAc, 8:2) to give **73a** (319 mg, 1.37 mmol, 90%) as a white solid; mp 34–35 $^{\circ}$ C. $[\alpha]_{22}^{\text{D}} - 3.6$ (*c* 1.00, CH_2Cl_2). IR (KBr): 3398, 2978, 2930, 1643, 1434, 1102 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ = 5.87–5.78 (m, 1 H), 5.22–5.20 (m, 2 H), 5.20–5.16 (m, 1 H), 4.33–4.25 (m, 2 H), 4.04–3.98 (m, 1 H), 2.70–2.63 (m, 1 H), 2.40–2.34 (m, 1 H), 2.33–2.25 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 133.5, 119.1, 102.8, 82.7, 70.1, 42.2, 37.2. MS (EI): m/z = 232.0 [M–OH]. HRMS (EI): m/z [M–OH] calcd for $\text{C}_7\text{H}_{10}\text{Cl}_3\text{O}$: 214.9797; found: 214.9797.

(2R,4S)-1,1,1-trichlorohex-5-ene-2,4-diol (73c)

A dry, 2-neck round-bottom flask was charged with β -hydroxyketone **72b** (530 mg, 2.44 mmol), freshly distilled THF (24.0 mL), and anhydrous MeOH (4.90 mL). Diethylmethoxyborane (384 μ L, 2.92 mmol) was added dropwise via syringe, and the mixture was stirred 30 min at room temperature under argon. Then, the mixture was cooled to -78 $^{\circ}$ C, and sodium borohydride (129 mg, 3.42 mmol) was added. The mixture was stirred at -78 $^{\circ}$ C for 12 h

then quenched at $-78\text{ }^{\circ}\text{C}$ by dropwise addition of 30% aqueous H_2O_2 (1.20 mL). The mixture was warmed slowly to room temperature then THF and MeOH were removed under reduced pressure. The residue was dissolved in water (5 mL) and extracted with EtOAc (5 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish dr (*syn/anti*) = 96:4 and then purified by silica gel chromatography (hexanes–EtOAc, 8:2) to give **73c** (473 mg, 2.03 mmol, 83%) as a white solid. ^1H NMR (500 MHz, CDCl_3): δ = 5.97–5.87 (m, 1 H), 5.38–5.30 (m, 1 H), 5.24–5.17 (m, 1 H), 4.51–4.42 (m, 1 H), 4.33–4.24 (m, 1 H), 4.04 (brs, 1 H), 2.59 (brs, 1 H), 2.30 (ddd, J = 2.0, 4.0, 14.1 Hz, 1 H), 1.94 (ddd, J = 8.9, 9.9, 18.8 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 139.4, 116.1, 102.9, 82.0, 71.9, 37.8.

(2*R*,4*S*)-1,1,1-trichlorohept-6-ene-2,4-diol (73b)

A dry, 2-neck round-bottom flask was charged with tetramethylammonium triacetoxymethylborohydride (3.64 g, 13.8 mmol), anhydrous acetonitrile (8.0 mL), and anhydrous acetic acid (8.0 mL). The mixture was stirred at room temperature for 1 h. The mixture was then cooled to $-45\text{ }^{\circ}\text{C}$, and a solution of β -hydroxyketone **73a** (385 mg, 1.73 mmol) in anhydrous acetonitrile (2.5 mL) was added slowly via syringe. The mixture was stirred at $-45\text{ }^{\circ}\text{C}$ for 48 h. The reaction was quenched with 0.5 N aqueous sodium potassium tartrate (25 mL) and warmed slowly to room temperature. The mixture was diluted with dichloromethane (20 mL) and the layers were separated. The organic phase was then washed with a saturated solution of aqueous sodium bicarbonate. The aqueous phase was back extracted with dichloromethane (5 x 10 mL), and the combined organic layers were washed with a saturated solution of aqueous sodium bicarbonate until pH >7. The combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish dr (*anti/syn*) = 89:11 and then

purified by silica gel chromatography (hexanes–EtOAc, 8:2) to give **73b** (323 mg, 1.38 mmol, 83%) as a white solid; mp 119–120 °C. $[\alpha]_{22}^D + 36.2$ (*c* 1.00, MeOH). IR (KBr): 3384, 3171, 2972, 2932, 1644, 1440, 1042 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): δ = 5.94–5.85 (m, 1 H), 5.57 (dd, *J* = 0.9, 6.6 Hz, 1 H), 5.12–5.01 (m, 2 H), 4.40 (ddd, *J* = 1.6, 6.6, 10.1 Hz, 1 H), 4.00–3.93 (m, 1 H), 3.87 (d, *J* = 5.8 Hz, 1 H), 2.35–2.25 (m, 2 H), 2.04–1.99 (m, 1 H), 1.79–1.72 (m, 1 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 136.2, 117.2, 106.2, 80.6, 67.8, 43.6, 39.9. MS (EI): *m/z* = 232.0 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₇H₁₁Cl₃O₂: 231.9825; found: 231.9829.

Nonselective preparation of *syn*- and *anti*-diols **73a** and **73b**

A dry, 2-neck round-bottom flask was charged with β -hydroxyketone **72a** (4.30 g, 18.6 mmol) and anhydrous methanol (62 mL). The mixture was cooled to 0 °C, and sodium borohydride (1.05 g, 27.9 mmol) was added. The mixture was warmed to room temperature and stirred under argon for 30 min. The solution was cooled to 0 °C, and quenched with a saturated solution of aqueous NaHCO₃ (100 mL). After stirring for 10 min, methanol was removed under reduced pressure. The aqueous phase was extracted with EtOAc (5 x 50 mL). The combined organic layers were dried (Na₂SO₄), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish dr (*syn/anti*) = 55:45 and then purified by silica gel chromatography (hexanes–EtOAc, 8:2) to give **72a** (2.19 g, 9.38 mmol) and **73b** (1.79 g, 7.67 mmol) in a 92% combined yield.

General Procedure for the Preparation of *syn*- and *anti*-1,3 Phenyl Derived Olefins **74a** and **74l**

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the terminal olefin (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Acetic acid (12.3 μL , 0.214 mmol), styrene (246 μL , 2.14 mmol), and Grubbs-Hoveyda 2nd

generation catalyst (1.34 mg, 2.14 μmol) were added, and the reaction mixture was heated in a 45 $^{\circ}\text{C}$ oil bath under a blanket of argon for 5 hours. Grubbs-Hoveyda 2nd generation catalyst (2.14 μmol , 1.34 mg) was added every hour until 5 mol% of the catalyst was present in the reaction mixture. After 5 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography using toluene to remove stilbene then toluene–EtOAc 9:1 to afford the corresponding phenyl derived olefin.

(2*R*,4*R*,*E*)-1,1,1-trichloro-7-phenylhept-6-ene-2,4-diol (74a)

The indicated compound was obtained as a light brown solid in 89% yield (59.0 mg, 0.191 mmol); mp 72–73. $[\alpha]_{22}^{\text{D}} + 6.2$ (*c* 1.0, CH_2Cl_2). IR (KBr): 3364, 3027, 2927, 1495, 1110, 969 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): $\delta = 7.39\text{--}7.36$ (m, 2 H), 7.34–7.30 (m, 2 H), 7.26–7.22 (m, 1 H), 6.52 (d, *J* = 15.8 Hz, 1 H), 6.22 (ddd, *J* = 7.0, 7.7, 16.0 Hz, 1 H), 4.33 (dd, *J* = 2.1, 10.0 Hz, 1 H), 4.24 (brs, 1 H), 4.11–4.05 (m, 1 H), 2.71 (brs, 1 H), 2.56–2.49 (m, 1 H), 2.49–2.41 (m, 1 H), 2.36–2.30 (m, 1 H), 1.93–1.85 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 136.9, 134.1, 128.6, 127.6, 126.2, 124.7, 102.8, 82.7, 70.5, 41.4, 37.4$. MS (EI): *m/z* = 308.0 $[\text{M}]^+$. HRMS (EI): *m/z* $[\text{M}]$ calcd for $\text{C}_{13}\text{H}_{15}\text{Cl}_3\text{O}_2$: 308.0138; found: 308.0134.

(2*R*,4*S*,*E*)-1,1,1-trichloro-7-phenylhept-6-ene-2,4-diol (74l)

The indicated compound was obtained as a light brown solid in 91% yield (60.4 mg, 0.195 mmol); mp 161–162 $^{\circ}\text{C}$. $[\alpha]_{22}^{\text{D}} + 23.0$ (*c* 1.0, MeOH). IR (KBr): 3378, 3086, 3061, 2920, 2871, 1604, 1496, 1081, 1030 cm^{-1} . ^1H NMR (500 MHz, acetone-*d*₆): $\delta = 7.45\text{--}7.38$ (m, 2 H), 7.34–7.27 (m, 2 H), 7.26–7.18 (m, 1 H), 6.52 (d, *J* = 15.9 Hz, 1 H), 6.44–6.34 (m, 1 H), 5.61 (d, *J* = 5.8 Hz, 1 H), 4.48–4.41 (m, 1 H), 4.14–3.99 (m, 2 H), 2.48 (t, *J* = 6.4 Hz, 2 H), 2.15–2.08 (m, 1 H), 1.88–1.81 (m, 1 H). ^{13}C NMR (125 MHz, acetone-*d*₆): $\delta = 138.7, 129.4, 127.9, 126.9, 106.2,$

80.7, 68.2, 42.9, 40.1. MS (EI): $m/z = 308.0$ [M]⁺. HRMS (EI): m/z [M] calcd for C₁₃H₁₅Cl₃O₂: 308.0138; found: 308.0143.

General Procedure for the Preparation of *syn*- and *anti*-1,3 Butyl Derived Olefins **74b and **74m****

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the terminal olefin (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Salicylic acid (29.6 mg, 0.214 mmol), 1-hexene (268 μ L, 2.14 mmol), and Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μ mol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 10 hours. Grubbs-Hoveyda 2nd generation catalyst (2.14 μ mol, 1.34 mg) was added every hour until 10 mol% of the catalyst was present in the reaction mixture. After 10 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 9:1) to afford the corresponding butyl derived olefin.

(2*R*,4*R*,*E*)-1,1,1-trichloroundec-6-ene-2,4-diol (74b**)**

The indicated compound was obtained as an inseparable mixture of **74b** and **74bb** in a 7:1 ratio and 93% total yield (57.5 mg, 0.199 mmol). ¹H NMR (500 MHz, CDCl₃): $\delta = 5.66$ – 5.53 (m, 1 H), 5.47 – 5.33 (m, 1 H), 4.41 (brs, 1 H), 4.30 (dd, $J = 2.1, 10.0$ Hz, 1 H), 4.01 – 3.90 (m, 1 H), 2.58 (brs, 1 H), 2.33 – 2.25 (m, 2 H), 2.25 – 2.17 (m, 1 H), 2.09 – 2.00 (m, 2 H), 1.84 – 1.75 (m, 1 H), 1.38 – 1.26 (m, 4 H), 0.89 (t, $J = 7.1$ Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): (major) $\delta = 136.0, 124.3, 102.9, 82.7, 70.4, 41.1, 37.3, 32.3, 31.5, 22.2, 13.9$. (minor) $\delta = 134.7, 123.6, 102.9, 82.8, 70.9, 35.7, 31.7, 27.2, 22.3, 13.9$.

(2*R*,4*S*,*E*)-1,1,1-trichloroundec-6-ene-2,4-diol (74m)

The indicated compound was obtained as an inseparable mixture of **74m** and **74mm** in a 7:1 ratio and 92% total yield (56.9 mg, 0.196 mmol). ¹H NMR (500 MHz, CDCl₃): δ = 5.65–5.55 (m, 1 H), 5.45–5.35 (m, 1 H), 4.45–4.37 (m, 1 H), 4.05–3.94 (m, 1 H), 3.35 (d, *J* = 4.1 Hz, 1 H), 2.41–2.45 (m, 1 H), 2.26–2.15 (m, 1 H), 2.14–2.00 (m, 3 H), 1.97–1.90 (m, 1 H), 1.87 (ddd, *J* = 2.6, 9.9, 14.1 Hz, 1 H), 1.40–1.27 (m, 4 H), 0.89 (t, *J* = 7.1 Hz, 1 H). ¹³C NMR (125 MHz, acetone-*d*₆): (major) δ = 133.8, 127.3, 106.3, 80.7, 68.2, 42.4, 39.8, 33.0, 32.4, 22.8, 14.2. (minor) δ = 132.5, 126.5, 106.3, 80.7, 68.3, 39.9, 37.0, 32.6, 23.0, 14.3.

General Procedure for the Preparation of *syn*- and *anti*-1,3 Benzyl Ether Derived Olefins 74c and 74n

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the terminal olefin (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Salicylic acid (29.6 mg, 0.214 mmol), allyl benzyl ether (331 μL, 2.14 mmol), and Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μmol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 8 hours. Grubbs-Hoveyda 2nd generation catalyst (4.28 μmol, 2.68 mg) was added at 2 hour intervals until 8 mol% of the catalyst was present in the reaction mixture. After 8 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 4:1) to afford the corresponding benzyl ether derived olefin.

(2*R*,4*R*,*E*)-8-(benzyloxy)-1,1,1-trichlorooct-6-ene-2,4-diol (74c)

The indicated compound was obtained as an inseparable mixture of **74c** and its corresponding *Z*-isomer in a 10:1 ratio and 93% total yield (70.3 mg, 0.199 mmol). ¹H NMR (500 MHz, CDCl₃): δ = 7.39–7.30 (m, 5 H), 5.80–5.71 (m, 1 H), 5.77–5.72 (m, 2 H), 4.52 (s, 2 H), 4.34 (brs, 1 H), 4.28 (d, *J* = 9.2 Hz, 1 H), 4.03–4.00 (m, 2 H), 4.00–3.95 (m, 1 H), 2.80 (brs, 1 H), 2.38–2.28 (m, 2 H), 2.28–2.24 (m, 1 H), 1.83 (dt, *J* = 9.8, 19.5 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): (major) δ = 138.1, 130.6, 128.8, 128.4, 127.8, 127.7, 102.9, 82.6, 72.3, 70.4, 70.3, 40.7, 37.22. (minor) δ = 137.6, 129.4, 129.3, 128.5, 128.0, 127.9, 102.9, 82.6, 72.7, 70.0, 65.2, 37.6, 35.9.

(2*R*,4*S*,*E*)-8-(benzyloxy)-1,1,1-trichlorooct-6-ene-2,4-diol (74n)

The indicated compound was obtained as a white solid in 84% yield (63.7 mg, 0.189 mmol); mp 89–90 °C. [α]_D²² + 26.0 (*c* 1.1, CH₃CN). IR (KBr): 3384, 3136, 2970, 2930, 2851, 1441, 1369, 1106, 1084, 1038 cm⁻¹. ¹H NMR (500 MHz, CD₃CN): δ = 7.40–7.31 (m, 4 H), 7.31–7.26 (m, 1 H), 5.80–5.71 (m, 1 H), 5.71–5.63 (m, 1 H), 4.47 (s, 2 H), 4.45 (d, *J* = 6.4 Hz, 1 H), 4.27 (ddd, *J* = 1.6, 6.4, 10.0 Hz, 1 H), 4.02–3.95 (m, 2 H), 3.89–3.80 (m, 1 H), 2.97 (d, *J* = 5.7 Hz, 1 H), 2.27 (dd, *J* = 0.7, 6.8 Hz, 2 H), 2.02–1.95 (m, 1 H), 1.71 (ddd, *J* = 2.2, 10.1, 13.8 Hz, 1 H). ¹³C NMR (125 MHz, acetone-*d*₆): δ = 139.9, 130.8, 130.2, 129.0, 128.4, 128.1, 106.2, 80.7, 72.2, 71.2, 68.0, 42.1, 40.0. MS (EI): *m/z* = 352.0 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₁₅H₁₉Cl₃O₂: 352.0400; found: 352.0404.

General Procedure for the Preparation of *syn*- and *anti*-1,3 Tri-substituted Benzyl Ether Derived Olefins 74d and 74o

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the terminal olefin (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). 2-

methylallyl benzyl ether **74r** (348 mg, 2.14 mmol), and Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μ mol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 8 hours. Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μ mol) was added every hour until 8 mol% of the catalyst was present in the reaction mixture. After 8 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 4:1) to afford the corresponding tri-substituted benzyl ether derived olefin.

(2R,4R,E)-8-(benzyloxy)-1,1,1-trichloro-7-methyloct-6-ene-2,4-diol (74d)

The indicated compound was obtained as a clear colorless oil in 83% yield (65.4 mg, 0.178 mmol). $[\alpha]_{22}^D + 3.2$ (*c* 1.0, CH₂Cl₂). IR (KBr): 3387, 3031, 2925, 2857, 1653, 1453, 1082, 1069 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.41\text{--}7.29$ (m, 5 H), 5.53–5.46 (m, 1 H), 4.57–4.50 (m, 1 H), 4.48 (s, 2 H), 4.26 (d, *J* = 10.0 Hz, 1 H), 4.00–3.95 (m, 1 H), 3.94 (s, 2 H), 2.94 (brs, 1 H), 2.38–2.28 (m, 2 H), 2.27–2.23 (m, 1 H), 1.87–1.79 (m, 1 H), 1.71 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): $\delta = 138.2, 136.2, 128.4, 127.7, 127.6, 122.3, 102.9, 82.7, 75.8, 72.0, 70.8, 37.2, 36.1, 14.3$. MS (EI): *m/z* = 366.0 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₁₆H₂₁Cl₃O₃: 366.0556; found: 366.0550.

(2R,4S,E)-8-(benzyloxy)-1,1,1-trichloro-7-methyloct-6-ene-2,4-diol (74o)

The indicated compound was obtained as a white solid in 80% yield (63.0 mg, 0.171 mmol); mp 102–103 °C. $[\alpha]_{22}^D + 21.8$ (*c* 1.0, CH₂Cl₂). IR (KBr): 3376, 3031, 2922, 2857, 1454, 1067 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): $\delta = 7.43\text{--}7.31$ (m, 5 H), 5.60–5.50 (m, 1 H), 4.53 (s, 2 H), 4.46 (ddd, *J* = 1.8, 4.7, 9.9 Hz, 1 H), 4.12–4.05 (m, 1 H), 3.98 (s, 2 H), 3.40 (d, *J* = 4.7 Hz, 1 H), 2.45–2.31 (m, 2 H), 2.21–2.13 (m, 1 H), 2.04 (brs, 1 H), 1.93 (ddd, *J* = 2.6, 10.0, 14.1 Hz, 1 H),

1.77 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 138.3, 136.4, 128.4, 127.7, 127.6, 122.5, 104.0, 79.9, 75.8, 72.0, 68.2, 37.9, 36.1, 14.3$. MS (EI): $m/z = 366.0$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}]$ calcd for $\text{C}_{16}\text{H}_{21}\text{Cl}_3\text{O}_3$: 366.0556; found: 366.0550.

2-methylallyl benzyl ether (74r)

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with 2-methylallyl alcohol (1.04 mL, 12.3 mmol), benzyl bromide (1.76 mL, 14.8 mmol), and anhydrous tetrahydrofuran (25.0 mL). The reaction mixture was cooled to 0 °C, and potassium *tert*-butoxide (1.66 g, 14.8 mmol) was added. The reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 8 hours. After 8 hours, the reaction mixture was cooled to room temperature, then a saturated aqueous solution of NH_4Cl (15 mL) was slowly added. The aqueous phase was extracted with Et_2O (5 x 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The crude material was purified by silica gel chromatography (hexanes– Et_2O 9:1) to afford **74r** (1.50 g, 9.25 mmol, 75%) as a clear colorless oil. IR (KBr): 3066, 3031, 2974, 2916, 2853, 1654, 1453, 1097 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): $\delta = 7.40$ – 7.28 (m, 5 H), 5.06–5.01 (m, 1 H), 4.97–4.93 (m, 1 H), 4.52 (s, 2 H), 3.96 (s, 2 H), 1.80 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 142.2, 138.5, 128.3, 127.6, 127.5, 112.2, 74.1, 71.8, 19.5$. MS (EI): $m/z = 162.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}]$ calcd for $\text{C}_{11}\text{H}_{13}\text{O}$: 161.0966; found: 161.0968.

General Procedure for the Preparation of *syn*- and *anti*-1,3 Weinreb Acrylamide Derived Olefins 74f and 74p

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the terminal olefin (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Salicylic acid (29.6 mg, 0.214 mmol), *N*-methoxy-*N*-methylacrylamide **74s** (49.3 mg, 0.429 mmol), and Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μmol) were added, and the

reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 8 hours. Grubbs-Hoveyda 2nd generation catalyst (4.28 μmol, 2.68 mg) was added at 2 hour intervals until 8 mol% of the catalyst was present in the reaction mixture. After 8 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 2:3) to afford the corresponding Weinreb acrylamide derived olefin.

(5*R*,7*R*,*E*)-8,8,8-trichloro-5,7-dihydroxy-*N*-methoxy-*N*-methyloct-2-enamide (74f)

The indicated compound was obtained as a light brown solid in 88% yield (68.7 mg, 0.214 mmol); mp 137–138 °C. $[\alpha]_{22}^D + 7.8$ (*c* 1.0, CH₂Cl₂). IR (KBr): 3382, 3238, 3055, 2979, 2941, 2912, 1660, 1605, 1265, 1025 cm⁻¹. ¹H NMR (360 MHz, CDCl₃): δ = 7.05–6.91 (m, 1 H), 6.51 (d, *J* = 15.4 Hz, 1 H), 5.06 (d, *J* = 3.6 Hz, 1 H), 4.34–4.26 (m, 1 H), 4.17–4.05 (m, 1 H), 3.92 (brs, 1 H), 3.71 (s, 3 H), 3.24 (s, 3 H), 2.55–2.43 (m, 2 H), 2.30–2.20 (m, 1 H), 1.94–1.82 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 166.6, 142.9, 121.8, 103.0, 82.5, 69.7, 61.8, 40.8, 37.5, 32.4. MS (EI): *m/z* = 319.0 [M]⁺. HRMS (EI): *m/z* [M] calcd for C₁₀H₁₆Cl₃O₄: 319.0145; found: 319.0139.

(5*R*,7*S*,*E*)-8,8,8-trichloro-5,7-dihydroxy-*N*-methoxy-*N*-methyloct-2-enamide (74p)

The indicated compound was obtained as a light brown solid in 88% yield (68.7 mg, 0.214). ¹H NMR (500 MHz, CDCl₃): δ = 7.05–6.93 (m, 1 H), 6.50 (d, *J* = 15.5 Hz, 1 H), 4.72 (brs, 1 H), 4.41 (d, *J* = 9.9 Hz, 1 H), 4.18–4.10 (m, 1 H), 3.71 (s, 3 H), 3.25 (s, 3 H), 2.51–2.42 (m, 2 H), 2.14 (ddd, *J* = 1.7, 10.0, 13.8 Hz, 1 H), 1.83 (ddd, *J* = 2.2, 10.2, 13.8 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 167.0, 144.1, 121.3, 104.2, 79.4, 67.2, 61.8, 40.8, 38.7, 32.4.

***N*-methoxy-*N*-methylacrylamide (74s)**

A dry, 2-neck round-bottom flask was charged with freshly distilled acryloyl chloride (404 μ L, 5.00 mmol), *N,O*-dimethoxyhydroxylamine hydrochloride (537 mg, 5.50 mmol), and anhydrous dichloromethane (10.6 mL). The reaction mixture was cooled to 0 °C, and diisopropylethylamine (1.92 mL, 11.0 mmol) was added. The reaction mixture was warmed to room temperature, and stirred under a blanket of argon for 12 hours. The reaction was quenched with 1 N aqueous hydrochloric acid (15 mL) and the layers were separated. The organic layer was washed with a saturated aqueous solution of NaHCO₃ (2 x 10 mL). The organic layer was dried (Na₂SO₄), and concentrated to afford **74s** (503 mg, 4.37 mmol, 87%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ = 6.73 (dd, *J* = 10.3, 17.1 Hz, 1 H), 6.43 (dd, *J* = 1.9, 17.1 Hz, 1 H), 5.75 (dd, *J* = 1.9, 10.3 Hz, 1 H), 3.71 (s, 3 H), 3.26 (s, 3 H).

General Procedure for the Preparation of *syn*- and *anti*-1,3 Methyl Ketone Derived Olefins

74g and 74q

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the terminal olefin (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Methyl vinyl ketone (35.1 μ L, 0.429 mmol), and Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μ mol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 12 hours. Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μ mol) was added at 2 hour intervals until 10 mol% of the catalyst was present in the reaction mixture. After 12 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 2:3) to afford the corresponding methyl ketone derived olefin.

(6R,8R,E)-9,9,9-trichloro-6,8-dihydroxynon-3-en-2-one (74g)

The indicated compound was obtained as a light brown solid in 93% yield (54.9 mg, 0.199 mmol). ¹H NMR (360 MHz, CDCl₃): δ = 6.86 (dt, *J* = 7.2, 16.0 Hz, 1 H), 6.18 (d, *J* = 16.0 Hz, 1 H), 4.50 (brs, 1 H), 4.31 (dd, *J* = 1.6, 9.9 Hz, 1 H), 4.17–4.07 (m, 1 H), 3.55 (brs, 1 H), 2.55–2.41 (m, 2 H), 2.27 (s, 3 H), 2.26–2.20 (m, 1 H), 1.93–1.82 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 198.7, 143.3, 133.6, 102.8, 82.6, 69.6, 40.5, 37.5, 27.1.

(6R,8S,E)-9,9,9-trichloro-6,8-dihydroxynon-3-en-2-one (74q)

The indicated compound was obtained as an off-white solid in 86% yield (50.8 mg, 0.184); mp 125–126 °C. ¹H NMR (500 MHz, CDCl₃): δ = 6.84 (dt, *J* = 7.4, 15.9 Hz, 1 H), 6.20 (d, *J* = 15.9 Hz, 1 H), 4.42 (ddd, *J* = 1.9, 4.6, 10.0 Hz, 1 H), 4.22–4.13 (m, 1 H), 3.39–3.32 (m, 1 H), 2.55–2.43 (m, 2 H), 2.27 (s, 3 H), 2.23–2.11 (m, 2 H), 1.89 (ddd, *J* = 2.6, 10.0, 14.1 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 198.4, 143.1, 133.8, 103.8, 79.7, 67.2, 40.7, 38.2, 27.3.

(5R,7R,E)-8,8,8-trichlorooct-2-ene-1,5,7-triol (74e)

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the *syn*-1,3 diol **73a** (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Allyl alcohol (146 μL, 52.14 mmol), and Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μmol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 20 hours. Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μmol) was added every two hours until 10 mol% of the catalyst was present in the reaction mixture. After 20 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 1:1) to afford **74e** (26.5 mg, 0.101 mmol, 47%) as a light brown oil. ¹H NMR (360 MHz, CDCl₃): δ = 5.84–5.67 (m, 2 H), 4.81 (brs, 1 H), 4.30 (d, *J* = 9.9 Hz, 1 H), 4.13 (d, *J* = 4.6 Hz, 2

H), 4.05–3.96 (m, 1 H), 3.51 (brs, 1 H), 2.38–2.21 (m, 3 H), 1.89–1.79. ¹³C NMR (125 MHz, CDCl₃): δ = 133.1, 127.4, 102.9, 82.6, 70.3, 63.2, 40.6, 37.3.

(2*R*,4*R*,*E*)-1,1,1-trichloro-7-methyldec-6-ene-2,4-diol (74i)

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the *syn*-1,3 diol **73a** (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). 2-methyl-1-pentene (662 μL, 5.36 mmol), and Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μmol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 10 hours. Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μmol) was added every hour until 10 mol% of the catalyst was present in the reaction mixture. After 10 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 4:1) to afford an inseparable mixture of **74i** and **74ii** in a 6:1 ratio and 91% total yield (56.5 mg, 0.195 mmol). ¹H NMR (500 MHz, CDCl₃): δ = 5.21–5.10 (m, 1 H), 4.51–4.41 (m, 1 H), 4.34–4.26 (m, 1 H), 4.01–3.90 (m, 1 H), 2.52 (brs, 1 H), 2.36–2.20 (m, 3 H), 2.05–1.97 (m, 2 H), 1.88–1.76 (m, 1 H), 1.64 (s, 3 H), 1.49–1.37 (m, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃): (major) δ = 140.4, 118.4, 102.9, 82.8, 71.2, 41.9, 37.3, 36.5, 20.9, 16.2, 13.7. (minor) δ = 140.7, 119.1, 102.9, 82.8, 71.2, 36.4, 34.0, 23.6, 21.1, 14.0.

(5*R*,7*R*,*E*)-8,8,8-trichloro-2-methyloct-2-ene-1,5,7-triol (74j)

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the *syn*-1,3 diol **73a** (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). 2-methylallyl alcohol (180 μL, 2.14 mmol), and Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μmol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 12 hours. Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μmol) was added

every hour until 10 mol% of the catalyst was present in the reaction mixture. After 12 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 1:1) to afford **74j** (48.2 mg, 0.174 mmol, 81%) as a light brown oil. ¹H NMR (500 MHz, CDCl₃): δ = 5.52–5.46 (m, 1 H), 4.65 (brs, 1 H), 4.32–4.28 (m, 1 H), 4.04 (s, 2 H), 4.03–3.97 (m, 1 H), 3.24 (brs, 1 H), 2.38–2.28 (m, 2 H), 2.28–2.23 (m, 1 H), 1.90–1.82 (m, 1 H), 1.70 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 138.6, 120.2, 102.9, 82.7, 70.9, 68.4, 37.4, 36.1, 14.1.

(2R,4R,E)-1,1,1-trichloro-7-(phenylsulfonyl)hept-6-ene-2,4-diol (74k)

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with the *syn*-1,3 diol **73a** (50.0 mg, 0.214 mmol) and anhydrous dichloromethane (2.14 mL). Phenyl vinyl sulfone (72.1 mg, 0.429 mmol), and Grubbs-Hoveyda 2nd generation catalyst (1.34 mg, 2.14 μmol) were added, and the reaction mixture was heated in a 45 °C oil bath under a blanket of argon for 24 hours. Grubbs-Hoveyda 2nd generation catalyst (2.68 mg, 4.28 μmol) was added every hour until 10 mol% of the catalyst was present in the reaction mixture. After 24 hours, the reaction mixture was cooled to room temperature, and the volatiles were removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford **74k** (62.5 mg, 0.167 mmol, 78%) as a light brown oil. ¹H NMR (360 MHz, CDCl₃): δ = 7.88 (d, *J* = 7.5 Hz, 2 H), 7.62 (t, *J* = 7.3 Hz 1 H), 7.54 (t, *J* = 7.7 Hz 2 H), 7.11–6.99 (m, 1 H), 6.47 (d, *J* = 15.1 Hz, 1 H), 4.29 (d, *J* = 10.0 Hz, 1 H), 4.08–4.02 (m, 1 H), 3.37 (brs, 1 H), 2.53–2.45 (m, 2 H), 2.24–2.15 (m, 1 H), 1.91–1.78 (m, 1 H), 1.72 (brs, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 142.5, 140.2, 133.5, 133.0, 129.3, 127.6, 102.7, 82.4, 69.1, 39.3, 37.4.

General Procedure for the Preparation of Functionalized Tetraols 75ba-75ha and 75ja-75ma.

A dry round-bottom flask equipped with a stir bar was charged with $K_3Fe(CN)_6$ (98.8 mg, 300 μ mol), K_2CO_3 (41.5 mg, 300 μ mol), (DHQ)₂PHAL (15.6 mg, 20 μ mol), $MeSO_2NH_2$ (9.51 mg, 100 μ mol), and OsO_4 (4% wt. in H_2O , 31.8 μ L, 5 μ mol). The mixture was diluted in a 1:1 mixture of *t*BuOH– H_2O (1 mL), and stirred at room temperature until the mixture was completely homogeneous. Then, the reaction mixture was cooled to 0 °C, and the corresponding olefin (100 μ mol) was added in one portion. The mixture was vigorously stirred at 0 °C for 12–24 hours. After complete consumption of the starting material as indicated by TLC, the reaction was quenched at 0 °C by addition of sodium sulfite (150 mg, 1.19 mmol), then warmed to room temperature and stirred for 30 minutes. The aqueous phase was extracted with EtOAc (5 x 3 mL), and the combined organic layers were washed with saturated aqueous K_2CO_3 (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), and concentrated.

(1*S*,2*S*,4*R*,6*R*)-7,7,7-trichloro-1-phenylheptane-1,2,4,6-tetraol (75ba)

The crude product was evaluated by 1H NMR spectroscopy to establish the dr (**75ba:75bb**) = 95:5 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a colorless clear oil in 95% total yield (32.6 mg, 94.9 μ mol). $[\alpha]_D^{22} + 9.4$ (*c* 1.0, CH_2Cl_2). IR (KBr): 3375, 2921, 1642, 1453, 1428, 1120 cm^{-1} . 1H NMR (360 MHz, $CDCl_3$): δ = 7.45–7.27 (m, 5 H), 4.84 (brs, 1 H), 4.48 (brs, 1 H), 4.45 (d, *J* = 7.0, 1 H), 4.23 (d, *J* = 9.8 Hz, 1 H), 4.15–4.05 (m, 1 H), 4.04–3.94 (m, 1 H), 3.92 (brs, 1 H), 3.21 (brs, 1 H), 2.10–2.01 (m, 1 H), 1.85–1.74 (m, 1 H), 1.71–1.60 (m 1 H), 1.43–1.35 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.4, 128.7, 128.4, 126.9, 102.7, 82.5, 78.0, 76.4, 71.1, 39.0, 38.1. MS (EI): *m/z* = 342.0 [*M*]⁺. HRMS (EI): *m/z* [*M*– H_2O] calcd for $C_{13}H_{15}Cl_3O_3$: 324.0087; found: 324.0097.

(2*R*,4*R*,6*S*,7*S*)-1,1,1-trichloroundecane-2,4,6,7-tetraol (75ca)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ca:75cb**) = 88:12 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 85% total yield (26.5 mg, 81.9 μmol); mp 73–74 $^\circ\text{C}$ $[\alpha]_{22}^{\text{D}} - 5.2$ (*c* 1.0, CH_2Cl_2). IR (KBr): 3360, 2956, 2931, 2871, 2860, 1661, 1455, 1110, 1081 cm^{-1} . ^1H NMR (500 MHz, CD_3CN): $\delta = 4.98$ (brs, 1 H), 4.27 (d, $J = 9.6$ Hz, 1 H), 4.22–4.05 (m, 2 H), 3.66–3.56 (m, 1 H), 3.42 (brs, 1 H), 3.36–3.25 (m, 1 H), 2.84 (brs, 1 H), 2.18 (ddd, $J = 2.0, 4.4, 14.1$ Hz, 1 H), 1.80–1.66 (m, 2 H), 1.63–1.54 (m, 1 H), 1.51–1.40 (m, 2 H), 1.36–1.25 (m, 4 H), 0.91 (t, $J = 6.3$ Hz, 3 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 102.8, 82.6, 74.8, 74.6, 70.9, 40.2, 38.3, 33.2, 27.8, 22.7, 14.0$. MS (EI): $m/z = 322.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}-\text{H}_2\text{O}-\text{CCl}_3]$ calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3$: 187.1334; found: 187.1340.

(2*S*,3*S*,5*R*,7*R*)-1-(benzyloxy)-8,8,8-trichlorooctane-2,3,5,7-tetraol (75da)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75da:75db**) = 87:13 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a clear colorless oil in 84% total yield (32.6 mg, 84.1 μmol). $[\alpha]_{22}^{\text{D}} + 9.2$ (*c* 1.0, MeOH). IR (KBr): 3355, 2922, 2864, 1453, 1314, 1105, 1027 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): $\delta = 7.38$ –7.23 (m, 5 H), 5.80 (brs, 1 H), 4.65 (brs, 1 H), 4.56 (d, $J = 12.1$ Hz, 1 H), 4.53 (d, $J = 12.1$ Hz, 1 H), 4.32 (dd, $J = 2.0, 9.7$ Hz, 1 H), 4.25–4.19 (m, 1 H), 4.05 (brs, 1 H), 3.96–3.92 (m, 1 H), 3.71–3.66 (m, 1 H), 3.64 (dd, $J = 5.0, 9.7$ Hz, 1 H), 3.55 (dd, $J = 6.1, 9.7$ Hz, 1 H), 2.23 (ddd, $J = 2.0, 5.1, 14.0$ Hz, 1 H), 1.88–1.80 (m, 2 H), 1.78–1.70 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 139.7, 129.1, 128.4, 128.2, 105.2, 82.1, 73.7, 73.5, 72.8, 72.0, 70.0, 40.4, 39.9$. MS (EI): $m/z = 386.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}-\text{H}_2\text{O}-\text{CCl}_3]$ calcd for $\text{C}_{14}\text{H}_{19}\text{O}_4$: 251.1283; found: 251.1274.

(2*S*,3*S*,5*R*,7*R*)-1-(benzyloxy)-8,8,8-trichloro-2-methyloctane-2,3,5,7-tetraol (75ea)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ea:75eb**) = 88:12 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a clear colorless oil in 97% total yield (39.0 mg, 97.1 μmol). $[\alpha]_{22}^D + 5.4$ (*c* 1.0, MeOH). IR (KBr): 3381, 2925, 2859, 1651, 1454, 1314, 1090 cm⁻¹. ¹H NMR (500 MHz, acetone-*d*₆): δ = 7.44–7.22 (m, 5 H), 4.57 (d, *J* = 12.1 Hz, 1 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.33 (dd, *J* = 2.0, 9.7 Hz, 1 H), 4.25–4.19 (m, 1 H), 3.89 (dd, *J* = 2.4, 10.2 Hz, 1 H), 3.54 (d, *J* = 9.2 Hz, 1 H), 3.42 (d, *J* = 9.2 Hz, 1 H), 2.24 (ddd, *J* = 2.0, 4.9, 13.9 Hz, 1 H), 1.89–1.79 (m, 2 H), 1.65 (ddd, *J* = 8.7, 10.2, 18.9 Hz, 1 H), 1.15 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 139.8, 129.1, 128.4, 128.3, 105.3, 82.1, 76.5, 75.8, 74.2, 74.0, 70.8, 39.8, 38.0, 21.1. MS (EI): *m/z* = 400.1 [M]⁺. HRMS (EI): *m/z* [M–H₂O] calcd for C₁₆H₂₁O₄Cl₃: 382.0505; found: 382.0487.

(2*R*,4*R*,6*S*,7*S*)-1,1,1-trichloro-7-methyldecane-2,4,6,7-tetraol (75ga)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ga:75gb**) = 80:20 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford an inseparable mixture of **75ga**, **75gb**, and minor impurities as a clear colorless oil in 81% total yield (26.2 mg, 81.0 μmol).

(2*S*,3*S*,5*R*,7*R*)-8,8,8-trichloro-2-methyloctane-1,2,3,5,7-pentaol (75ha)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ha:75hb**) = 50:50 and then purified by silica gel chromatography (hexanes–EtOAc 1:4) to afford the indicated compound in 84% total yield (26.2 mg, 84.1 μmol).

(1*S*,2*S*,4*S*,6*R*)-7,7,7-trichloro-1-phenylheptane-1,2,4,6-tetraol (75ja)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ja:75jb**) = 94:6 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated

compound as a cream colored solid in 94% total yield (32.3 mg, 94.0 μmol); mp 150–151 $^{\circ}\text{C}$. $[\alpha]_{22}^{\text{D}} + 29.8$ (c 1.0, MeOH). IR (KBr): 3410, 2966, 2920, 1644, 1119, 1085, 1018 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 7.41\text{--}7.36$ (m, 2 H), 7.34–7.28 (m, 2 H), 7.25 (tt, $J = 1.4, 6.5$ Hz, 1 H), 5.56 (brs, 1 H), 4.47 (d, $J = 6.7$ Hz, 1 H), 4.37 (dd, $J = 1.6, 10.0$ Hz, 1 H), 4.22–4.16 (m, 1 H), 3.98 (ddd, $J = 2.6, 6.7, 9.6$ Hz, 1 H), 3.97 (brs, 1 H), 2.86 (brs, 1 H), 2.10 (ddd, $J = 1.6, 10.3, 13.7$ Hz, 1 H), 1.66 (ddd, $J = 2.3, 10.0, 13.7$ Hz, 1 H), 1.52 (ddd, $J = 3.0, 10.0, 14.0$ Hz, 1 H), 1.43 (ddd, $J = 2.6, 9.2, 14.0$ Hz, 1 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 143.6, 128.8, 128.1, 128.0, 106.2, 80.7, 78.5, 73.6, 65.4, 41.5, 41.0$. MS (EI): $m/z = 342.0$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}-\text{H}_2\text{O}]$ calcd for $\text{C}_{13}\text{H}_{15}\text{Cl}_3\text{O}_3$: 324.0087; found: 324.0078.

(2R,4S,6S,7S)-1,1,1-trichloroundecane-2,4,6,7-tetraol (75ka)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ka**:**75kb**) = 87:13 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 84% total yield (26.2 mg, 81.0 μmol); mp 154–155 $^{\circ}\text{C}$ $[\alpha]_{22}^{\text{D}} + 3.6$ (c 1.0, MeOH). IR (KBr): 3358, 2926, 2856, 1456, 1140, 1047 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 5.63$ (d, $J = 6.3$ Hz, 1 H), 4.45–4.37 (m, 1 H), 4.24–4.15 (m, 1 H), 4.04 (d, $J = 5.9$ Hz, 1 H), 3.80–3.67 (m, 2 H), 3.61 (d, $J = 4.2$ Hz, 1 H), 3.44–3.33 (m, 1 H), 2.11 (ddd, $J = 1.5, 10.2, 13.6$ Hz, 1 H), 1.73 (ddd, $J = 2.3, 10.0, 16.0$ Hz, 1 H), 1.67–1.62 (m, 2 H), 1.58–1.46 (m, 2 H), 1.43–1.27 (m, 4 H), 0.89 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 106.3, 80.8, 75.2, 72.0, 65.7, 42.1, 41.1, 33.7, 28.9, 23.5, 14.4$. MS (EI): $m/z = 322.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}-\text{H}_2\text{O}-\text{CCl}_3]$ calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3$: 187.1334; found: 187.1338.

(2S,3S,5S,7R)-1-(benzyloxy)-8,8,8-trichlorooctane-2,3,5,7-tetraol (75la)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75la**:**75lb**) = 86:14 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the

indicated compound as a white solid in 88% total yield (34.2 mg, 88.2 μmol); mp 165–166 $^{\circ}\text{C}$. $[\alpha]_{22}^{\text{D}} + 8.6$ (c 1.0, MeOH). IR (KBr): 3336, 2972, 2940, 2925, 1632, 1316, 1131, 1094, 1069, 1040 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 7.42\text{--}7.25$ (m, 5 H), 5.57 (d, $J = 6.4$ Hz, 1 H), 4.58 (d, $J = 12.1$ Hz, 1 H), 4.55 (d, $J = 12.2$ Hz, 1 H), 4.46–4.40 (m, 1 H), 4.27–4.15 (m, 1 H), 4.03–3.91 (m, 2 H), 3.82 (d, $J = 4.3$ Hz, 1 H), 3.70–3.62 (m, 2 H), 3.60 (d, $J = 5.4$ Hz, 1 H), 3.58–3.53 (m, 1 H), 2.18–2.11 (m, 1 H), 1.79–1.71 (m, 2 H), 1.67 (ddd, $J = 3.1, 8.9, 14.1$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 139.8, 129.1, 128.4, 128.2, 106.3, 80.8, 74.1, 73.8, 73.0, 69.6, 65.7, 42.2, 41.1$. MS (EI): $m/z = 386.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}]$ calcd for $\text{C}_{15}\text{H}_{21}\text{Cl}_3\text{O}_5$: 386.0455; found: 386.0453.

(2*S*,3*S*,5*S*,7*R*)-1-(benzyloxy)-8,8,8-trichloro-2-methyloctane-2,3,5,7-tetraol (75ma)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ma**:**75mb**) = 86:14 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 96% total yield (38.6 mg, 96.1 μmol); mp 158–159 $^{\circ}\text{C}$. $[\alpha]_{22}^{\text{D}} + 10.0$ (c 1.0, MeOH). IR (KBr): 3361, 2924, 1453, 1363, 1096, 1069, 1026 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 7.43\text{--}7.21$ (m, 5 H), 5.58 (d, $J = 6.2$ Hz, 1 H), 4.57 (d, $J = 12.2$ Hz, 1 H), 4.54 (d, $J = 12.2$ Hz, 1 H), 4.45–4.38 (m, 1 H), 4.24–4.17 (m, 1 H), 3.99–3.86 (m, 1 H), 3.62 (d, $J = 4.3$ Hz, 1 H), 3.54 (d, $J = 9.2$ Hz, 1 H), 3.53 (brs, 1 H), 3.42 (d, $J = 9.2$ Hz, 1 H), 2.17–2.10 (m, 1 H), 1.77–1.67 (m, 2 H), 1.62–1.55 (m, 1 H), 1.15 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3): $\delta = 139.8, 129.1, 128.4, 128.2, 106.3, 80.9, 76.8, 74.4, 74.0, 72.6, 65.9, 41.1, 39.8, 21.2$. MS (EI): $m/z = 400.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}-\text{H}_2\text{O}]$ calcd for $\text{C}_{16}\text{H}_{21}\text{Cl}_3\text{O}_4$: 382.0505; found: 382.0513.

General Procedure for the Preparation of Functionalized Tetraols 75bb-75hb and 75jb-75mb.

A dry round-bottom flask equipped with a stir bar was charged with $\text{K}_3\text{Fe}(\text{CN})_6$ (98.8 mg, 300 μmol), K_2CO_3 (41.5 mg, 300 μmol), $(\text{DHQD})_2\text{PHAL}$ (15.6 mg, 20 μmol), MeSO_2NH_2 (9.51 mg, 100 μmol), and OsO_4 (4% wt. in H_2O , 31.8 μL , 5 μmol). The mixture was diluted in a 1:1 mixture of *t*BuOH– H_2O (1 mL), and stirred at room temperature until the mixture was completely homogeneous. Then, the reaction mixture was cooled to 0 °C, and the corresponding olefin (100 μmol) was added in one portion. The mixture was vigorously stirred at 0 °C for 12–24 hours. After complete consumption of the starting material as indicated by TLC, the reaction was quenched at 0 °C by addition of sodium sulfite (150 mg), then warmed to room temperature and stirred for 30 minutes. The aqueous phase was extracted with EtOAc (5 x 3 mL), and the combined organic layers were washed with saturated aqueous K_2CO_3 (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), and concentrated.

(1*R*,2*R*,4*R*,6*R*)-7,7,7-trichloro-1-phenylheptane-1,2,4,6-tetraol (75bb)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ba:75bb**) = 6:94 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as an off-white solid in 89% total yield (30.5 mg, 88.8 μmol); mp 151–152 °C [α] $^{22}_{\text{D}}$ + 3.4 (*c* 1.0, MeOH). IR (KBr): 3377, 2917, 1652, 1454, 1416, 1083, 1051 cm^{-1} . ^1H NMR (500 MHz, acetone-*d*₆): δ = 7.41–7.36 (m, 2 H), 7.34–7.28 (m, 2 H), 7.28–7.22 (m, 1 H), 5.82 (brs, 1 H), 4.49–4.46 (m, 1 H), 4.22 (brs, 2 H), 4.24–4.18 (m, 2 H), 4.00–3.95 (m, 1 H), 2.88 (brs, 1 H), 2.18 (ddd, *J* = 2.1, 5.1, 14.0 Hz, 1 H), 1.82 (ddd, *J* = 7.2, 9.7, 16.8 Hz, 1 H), 1.65–1.57 (m 1 H), 1.48 (ddd, *J* = 2.5, 8.6, 14.0 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 143.5, 128.8, 128.1,

128.0, 105.3, 82.2, 78.4, 73.4, 67.9, 40.3, 39.9. MS (EI): $m/z = 342.0$ [M]⁺. HRMS (EI): m/z [M–H₂O] calcd for C₁₃H₁₅Cl₃O₃: 324.0087; found: 324.0094.

(2R,4R,6R,7R)-1,1,1-trichloroundecane-2,4,6,7-tetraol (75cb)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ca:75cb**) = 13:87 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a clear colorless oil in 81% total yield (25.3 mg, 78.2 μmol). $[\alpha]_{22}^D + 38.2$ (*c* 1.0, MeOH). IR (KBr): 3337, 2954, 2929, 2859, 1457, 1314, 1048 cm⁻¹. ¹H NMR (500 MHz, acetone-*d*₆): $\delta = 5.92$ (d, *J* = 3.6 Hz, 1 H), 4.38–4.28 (m, 2 H), 4.24 (brs, 1 H), 3.81–3.72 (m, 2 H), 3.63 (brs, 1 H), 3.45–3.36 (m, 1 H), 2.26 (ddd, *J* = 2.0, 5.3, 14.0 Hz, 1 H), 1.91 (ddd, *J* = 7.0, 9.7, 16.8 Hz, 1 H), 1.78–1.65 (m, 2 H), 1.59–1.47 (m, 2 H), 1.45–1.31 (m, 4 H), 0.91 (t, *J* = 7.0 Hz, 3 H). ¹³C NMR (125 MHz, CDCl₃): $\delta = 104.4, 81.3, 74.2, 70.9, 67.1, 40.1, 39.1, 32.7, 28.0, 22.6, 13.5$. MS (EI): $m/z = 322.1$ [M]⁺. HRMS (EI): m/z [M+H] calcd for C₁₁H₂₂Cl₃O₄: 323.0584; found: 323.0594.

(2R,3R,5R,7R)-1-(benzyloxy)-8,8,8-trichlorooctane-2,3,5,7-tetraol (75db)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75da:75db**) = 10:90 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 88% total yield (34.2 mg, 88.2 μmol); mp 105–106. $[\alpha]_{22}^D + 32.4$ (*c* 1.0, MeOH). IR (KBr): 3362, 2921, 1647, 1454, 1279, 1100, 1091 cm⁻¹. ¹H NMR (500 MHz, acetone-*d*₆): $\delta = 7.41$ –7.20 (m, 5 H), 5.87 (brs, 1 H), 4.56 (d, *J* = 12.1 Hz, 1 H), 4.53 (d, *J* = 12.1 Hz, 1 H), 4.35–4.27 (m, 2 H), 4.26–4.20 (m, 1 H), 4.01–3.93 (m, 1 H), 3.88 (brs, 1 H), 3.72 (brs, 1 H), 3.69–3.65 (m, 1 H), 3.64 (dd, *J* = 4.9, 9.4 Hz, 1 H), 3.54 (dd, *J* = 5.8, 9.4 Hz, 1 H), 2.24 (ddd, *J* = 2.1, 5.2, 14.1 Hz, 1 H), 1.90 (ddd, *J* = 7.1, 9.8, 16.8 Hz, 1 H), 1.82 (ddd, *J* = 3.2, 9.9, 14.1 Hz, 1 H), 1.67 (ddd, *J* = 2.9, 8.8, 14.1 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): $\delta =$

139.8, 129.1, 128.4, 128.2, 105.3, 82.2, 74.0, 73.7, 73.0, 69.4, 68.0, 41.1, 40.1. MS (EI): $m/z = 386.1$ [M]⁺. HRMS (EI): m/z [M] calcd for C₁₅H₂₁Cl₃O₄: 386.0455; found: 386.0439.

(2R,3R,5R,7R)-1-(benzyloxy)-8,8,8-trichloro-2-methyloctane-2,3,5,7-tetraol (75eb)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ea**:**75eb**) = 13:87 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 96% total yield (38.6 mg, 96.1 μmol); mp 142–143 °C. $[\alpha]_D^{22} + 27.2$ (*c* 1.0, MeOH). IR (KBr): 3335, 2966, 2905, 1653, 1417, 1087, 1058 1032 cm⁻¹. ¹H NMR (360 MHz, acetone-*d*₆): δ = 7.39–7.24 (m, 5 H), 5.88 (brs, 1 H), 4.57 (d, *J* = 12.4 Hz, 1 H), 4.54 (d, *J* = 12.4 Hz, 1 H), 4.34–4.18 (m, 3 H), 3.98–3.91 (m, 1 H), 3.73 (d, *J* = 3.7 Hz, 1 H), 3.58–3.51 (m, 3 H), 3.41 (d, *J* = 9.1 Hz, 1 H), 2.25 (ddd, *J* = 2.0, 5.0, 14.0 Hz, 1 H), 1.90 (ddd, *J* = 7.1, 9.8, 16.8 Hz, 1 H), 1.79–1.63 (m, 2 H), 1.14 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 139.8, 129.1, 128.3, 128.2, 105.3, 82.3, 76.8, 74.4, 74.0, 72.4, 68.2, 40.0, 38.7, 21.2. MS (EI): $m/z = 400.1$ [M]⁺. HRMS (EI): m/z [M–CCl₃–H₂O] calcd for C₁₅H₂₁O₄: 265.1440; found: 265.1452.

(2R,4R,6R,7R)-1,1,1-trichloro-7-methyldecane-2,4,6,7-tetraol (75gb)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ga**:**75gb**) = 18:82 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford an inseparable mixture of **75ga**, **75gb**, and minor impurities as a clear colorless oil in 82% total yield (26.5 mg, 81.9 μmol).

(2R,3R,5R,7R)-8,8,8-trichloro-2-methyloctane-1,2,3,5,7-pentaol (75hb)

The crude product was evaluated by ¹H NMR spectroscopy to establish the dr (**75ha**:**75hb**) = 33:67 and then purified by silica gel chromatography (hexanes–EtOAc 1:4) to afford the indicated compound in 82% total yield (25.6 mg, 82.2 μmol). ¹H NMR (500 MHz, acetone-*d*₆): δ

= 5.93 (brs, 1 H), 4.31 (dd, $J = 1.7, 9.7$ Hz, 1 H), 4.27–4.20 (m, 1 H), 3.92 (dd, $J = 3.3, 9.3$ Hz, 1 H), 3.52 (d, $J = 10.8$ Hz, 1 H), 3.49 (d, $J = 10.8$ Hz, 1 H), 2.25 (ddd, $J = 1.9, 5.1, 13.9$ Hz, 1 H), 1.90 (ddd, $J = 6.8, 9.7, 16.9$ Hz, 1 H), 1.77–1.65 (m, 2 H), 1.09 (s, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 105.3, 82.2, 74.5, 72.7, 68.7, 68.2, 39.9, 38.8, 20.7$.

(1R,2R,4S,6R)-7,7,7-trichloro-1-phenylheptane-1,2,4,6-tetraol (75jb)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ja**:**75jb**) = 9:91 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a clear colorless oil in 86% total yield (29.6 mg 86.1 μmol). $[\alpha]_{22}^{\text{D}} + 13.8$ (c 1.0, MeOH). IR (KBr): 3377, 2917, 1652, 1416, 1259, 1084, 977 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 7.42\text{--}7.37$ (m, 2 H), 7.34–7.29 (m, 2 H), 7.27–7.22 (m, 1 H), 5.55 (brs, 1 H), 4.55–4.45 (m, 2 H), 4.40 (brs, 1 H), 4.36–4.30 (m, 2 H), 4.14–4.07 (m, 1 H), 3.96–3.89 (m, 1 H), 1.99 (ddd, $J = 1.6, 9.9, 13.5$ Hz, 1 H), 1.65 (ddd, $J = 2.3, 10.1, 13.5$ Hz, 1 H), 1.61–1.55 (m, 1 H), 1.50–1.45 (m, 1 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 143.4, 128.8, 128.1, 128.0, 106.1, 80.3, 78.1, 76.4, 68.0, 40.6, 40.6$. MS (EI): $m/z = 342.0$ [M] $^+$. HRMS (EI): m/z [M–H $_2$ O] calcd for C $_{13}$ H $_{15}$ Cl $_3$ O $_3$: 324.0087; found: 324.0080.

(2R,4S,6R,7R)-1,1,1-trichloroundecane-2,4,6,7-tetraol (75kb)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ka**:**75kb**) = 13:87 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 88% total yield (27.4 mg, 84.7 μmol); mp 124–125 $^{\circ}\text{C}$ $[\alpha]_{22}^{\text{D}} + 33.8$ (c 1.0, MeOH). IR (KBr): 3357, 2956, 2931, 2860, 1079, 980 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 5.60$ (brs, 1 H), 4.45–4.32 (m, 2 H), 4.21–4.13 (m, 1 H), 4.05 (brs, 1 H), 3.74–3.68 (m, 1 H), 3.61 (brs, 1 H), 3.45–3.37 (m, 1 H), 2.12–2.06 (m, 1 H), 1.76 (ddd, $J = 2.5, 10.1, 13.5$ Hz, 1 H), 1.73–1.67 (m, 1 H), 1.58–1.45 (m, 2 H), 1.45–1.30 (m, 4 H), 0.90 (t, $J = 7.0$

Hz, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 106.2, 80.4, 74.8, 74.7, 68.0, 41.1, 40.7, 33.6, 28.9, 23.4, 14.4. MS (EI): m/z = 322.1 [M] $^+$. HRMS (EI): m/z [M- H_2O - CCl_3] calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3$: 187.1334; found: 187.1334.

(2*R*,3*R*,5*S*,7*R*)-1-(benzyloxy)-8,8,8-trichlorooctane-2,3,5,7-tetraol (751b)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**751a:751b**) = 14:86 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a colorless sticky oil in 86% total yield (33.4 mg, 86.2 μmol); mp 165–166 $^\circ\text{C}$. $[\alpha]_{22}^{\text{D}}$ + 29.3 (c 1.0, MeOH). IR (KBr): 3358, 2928, 2867, 1454, 1087, 1027 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): δ = 7.41–7.22 (m, 5 H), 5.59 (d, J = 4.9 Hz, 1 H), 4.57 (d, J = 12.1 Hz, 1 H), 4.53 (d, J = 12.1 Hz, 1 H), 4.44–4.36 (m, 1 H), 4.29 (brs, 1 H), 4.22–4.12 (m, 1 H), 4.08–3.77 (m, 3 H), 3.71–3.66 (m, 1 H), 3.64 (dd, J = 4.8, 9.6 Hz, 1 H), 3.55 (dd, J = 6.0, 9.6 Hz, 1 H), 2.09 (ddd, J = 1.6, 9.9, 13.7 Hz, 1 H), 1.80–1.71 (m, 3 H), 1.67. ^{13}C NMR (125 MHz, acetone- d_6): δ = 139.8, 129.1, 128.4, 128.3, 128.2, 106.2, 80.4, 73.8, 72.8, 72.2, 67.8, 41.3, 40.7. MS (EI): m/z = 386.1 [M] $^+$. HRMS (EI): m/z [M] calcd for $\text{C}_{15}\text{H}_{21}\text{Cl}_3\text{O}_5$: 386.0455; found: 386.0445.

(2*R*,3*R*,5*S*,7*R*)-1-(benzyloxy)-8,8,8-trichloro-2-methyloctane-2,3,5,7-tetraol (75mb)

The crude product was evaluated by ^1H NMR spectroscopy to establish the dr (**75ma:75mb**) = 13:87 and then purified by silica gel chromatography (hexanes–EtOAc 3:2) to afford the indicated compound as a white solid in 95% total yield (38.2 mg, 95.1 μmol); mp 112–113 $^\circ\text{C}$. $[\alpha]_{22}^{\text{D}}$ + 25.4 (c 1.0, MeOH). IR (KBr): 3372, 2925, 2859, 1454, 1371, 1090, 986 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): δ = 7.41–7.24 (m, 5 H), 5.61 (d, J = 6.3 Hz, 1 H), 4.58 (d, J = 12.1 Hz, 1 H), 4.53 (d, J = 12.1 Hz, 1 H), 4.44–4.36 (m, 2 H), 4.21–4.14 (m, 1 H), 4.12 (d, J = 3.9 Hz, 1 H), 3.92–3.86 (m, 1 H), 3.63 (s, 1 H), 3.53 (d, J = 9.2 Hz, 1 H), 3.43 (d, J = 9.2 Hz, 1 H), 2.08 (ddd,

$J = 1.4, 9.9, 13.6$ Hz, 1 H), 1.80–1.74 (m, 2 H), 1.64 (ddd, $J = 8.6, 10.3, 18.9$ Hz, 1 H), 1.15 (s, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 139.7, 129.1, 128.4, 128.3, 106.2, 76.5, 76.0, 74.3, 74.0, 68.6, 40.7, 38.9, 20.9$. MS (EI): $m/z = 400.1$ $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}+\text{H}]$ calcd for $\text{C}_{16}\text{H}_{24}\text{Cl}_3\text{O}_5$: 401.0689; found: 401.0676.

General Procedure for the Preparation of Unfunctionalized Tetraols 75aa and 75ia

A dry round-bottom flask equipped with a stir bar was charged with terminal olefin **73a** or **73b** (23.3 mg, 100 μmol), phenylboronic acid (18.3 mg, 150 μmol), and anhydrous dichloromethane (1.00 mL). The mixture was stirred for 3 hours at room temperature under a blanket of argon. After 3 hours, dichloromethane was removed under reduced pressure. Then, $\text{K}_3\text{Fe}(\text{CN})_6$ (98.8 mg, 300 μmol), K_2CO_3 (41.5 mg, 300 μmol), and $(\text{DHQ})_2\text{PYR}$ (17.6 mg, 20.0 μmol) were added to the reaction flask. The mixture was diluted in a 1:1 mixture of $t\text{BuOH-H}_2\text{O}$ (1 mL), and stirred at room temperature until the mixture was completely homogeneous. Then, the reaction mixture was cooled to 0 $^\circ\text{C}$, and OsO_4 (4% wt. in H_2O , 31.8 μL , 5.00 μmol) was added. The mixture was vigorously stirred at 0 $^\circ\text{C}$ for 24 hours. The reaction was quenched at 0 $^\circ\text{C}$ by addition of sodium sulfite (150 mg), then warmed to room temperature and stirred for 30 minutes. The aqueous phase was extracted with EtOAc (5 x 3 mL), then the combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish the diastereomeric ratio, then the crude mixture was diluted in a 5:1 mixture of THF–MeOH (1.00 mL). The mixture was cooled to 0 $^\circ\text{C}$, then 30% aqueous H_2O_2 (0.2 mL), and 1 drop of aqueous 1 N NaOH was added. The mixture was slowly warmed to room temperature and stirred for 1 hour. After 1 hour, THF and MeOH were removed under reduced pressure. The residue was dissolved in water (3 mL) and extracted with EtOAc (5 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated.

(2*S*,4*R*,6*R*)-7,7,7-trichloroheptane-1,2,4,6-tetraol (75aa)

Evaluation of the ¹H NMR from the crude reaction mixture established the dr (**75aa:75ab**) 76:24.

The crude mixture was then purified by silica gel chromatography (hexanes–EtOAc–MeOH 10:40:1) to afford the indicated compound as a clear colorless oil in 91% total yield (24.3 mg, 90.8 μmol). $[\alpha]_{22}^D + 15.8$ (*c* 1.0, MeOH). IR (KBr): 3365, 2934, 1428, 1312, 1119, 1114 cm⁻¹. ¹H NMR (360 MHz, acetone-*d*₆): δ = 5.80 (d, *J* = 4.8 Hz, 1 H), 4.62 (d, *J* = 1.8 Hz, 1 H), 4.32 (ddd, *J* = 1.6, 4.4, 9.5 Hz, 1 H), 4.26–4.14 (m, 2 H), 3.95–3.85 (m, 1 H), 3.80 (brs, 1 H), 3.56–3.40 (m, 2 H), 2.23 (ddd, *J* = 1.7, 5.1, 13.9 Hz, 1 H), 1.90–1.77 (m, 2 H), 1.65–1.54 (m, 1 H). ¹³C NMR (125 MHz, acetone-*d*₆): δ = 105.2, 82.0, 72.4, 70.0, 67.2, 40.6, 39.9. MS (EI): *m/z* = 266.0 [M]⁺. HRMS (EI): *m/z* [M+H] calcd for C₇H₁₄Cl₃O₄: 266.9958; found: 266.9953.

(2*S*,4*S*,6*R*)-7,7,7-trichloroheptane-1,2,4,6-tetraol (75ia)

Evaluation of the ¹H NMR from the crude reaction mixture established the dr (**75ia:75ib**) 74:26.

The crude mixture was then purified by silica gel chromatography (hexanes–EtOAc–MeOH 10:40:1) to afford the indicated compound as a white solid in 94% total yield (25.1 mg, 93.8 μmol); mp 109–110 °C. $[\alpha]_{22}^D + 15.8$ (*c* 1.0, MeOH). IR (KBr): 3336, 2950, 1456, 1415, 1362, 1123, 1088, 1016, 945 cm⁻¹. ¹H NMR (360 MHz, acetone-*d*₆): δ = 5.64 (brs, 1 H), 4.41 (d, *J* = 9.7 Hz, 1 H), 4.23–4.16 (m, 1 H), 4.10 (brs, 1 H), 4.01–3.68 (m, 3 H), 3.51 (dd, *J* = 4.8, 10.8 Hz, 1 H), 3.46 (dd, *J* = 4.8, 10.8 Hz, 1 H), 2.11 (ddd, *J* = 1.5, 10.2, 13.6 Hz, 1 H), 1.73 (ddd, *J* = 2.2, 10.1, 13.6 Hz, 1 H), 1.64 (ddd, *J* = 3.4, 8.7, 14.1 Hz, 1 H), 1.58 (ddd, *J* = 3.4, 8.7, 14.1 Hz, 1 H). ¹³C NMR (125 MHz, acetone-*d*₆): δ = 106.2, 80.7, 70.1, 67.6, 65.6, 42.1, 41.0. MS (EI): *m/z* = 266.0 [M]⁺. HRMS (EI): *m/z* [M–CH₂OH] calcd for C₆H₁₀Cl₃O₃: 234.9696; found: 234.9700.

General Procedure for the Preparation of Unfunctionalized Tetraols **75ab** and **75ib**

A dry round-bottom flask equipped with a stir bar was charged with terminal olefin **73a** or **73b** (23.3 mg, 100 μmol), phenylboronic acid (18.3 mg, 150 μmol), and anhydrous dichloromethane (1.00 mL). The mixture was stirred for 3 hours at room temperature under a blanket of argon. After 3 hours, dichloromethane was removed under reduced pressure. Then, $\text{K}_3\text{Fe}(\text{CN})_6$ (98.8 mg, 300 μmol), K_2CO_3 (41.5 mg, 300 μmol), and $(\text{DHQD})_2\text{PYR}$ (17.6 mg, 20.0 μmol) were added to the reaction flask. The mixture was diluted in a 1:1 mixture of *t*BuOH– H_2O (1 mL), and stirred at room temperature until the mixture was completely homogeneous. Then, the reaction mixture was cooled to 0 $^\circ\text{C}$, and OsO_4 (4% wt. in H_2O , 31.8 μL , 5.00 μmol) was added. The mixture was vigorously stirred at 0 $^\circ\text{C}$ for 24 hours. The reaction was quenched at 0 $^\circ\text{C}$ by addition of sodium sulfite (150 mg), then warmed to room temperature and stirred for 30 minutes. The aqueous phase was extracted with EtOAc (5 x 3 mL), then the combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was evaluated by ^1H NMR spectroscopy to establish the diastereomeric ratio, then the crude mixture was diluted in a 5:1 mixture of THF–MeOH (1.00 mL). The mixture was cooled to 0 $^\circ\text{C}$, then 30% aqueous H_2O_2 (0.2 mL), and 1 drop of aqueous 1 N NaOH was added. The mixture was slowly warmed to room temperature and stirred for 1 hour. After 1 hour, THF and MeOH were removed under reduced pressure. The residue was dissolved in water (3 mL) and extracted with EtOAc (5 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated.

(2R,4R,6R)-7,7,7-trichloroheptane-1,2,4,6-tetraol (75ab)

Evaluation of the ^1H NMR from the crude reaction mixture established the dr (**75aa:75ab**) 17:83.

The crude mixture was then purified by silica gel chromatography (hexanes–EtOAc–MeOH 10:40:1) to afford the indicated compound as a white solid in 94% total yield (25.1 mg, 93.8 μmol); mp 102–103 °C. $[\alpha]_{22}^{\text{D}} + 19.8$ (*c* 1.0, MeOH). IR (KBr): 3364, 2933, 1419, 1310, 1119, 1014, 986 cm^{-1} . ^1H NMR (360 MHz, acetone- d_6): δ = 5.87 (d, *J* = 4.9 Hz, 1 H), 4.35 (d, *J* = 4.2 Hz, 1 H), 4.31 (ddd, *J* = 2.0, 4.7, 9.7 Hz, 1 H), 4.27–4.19 (m, 1 H), 3.96–3.85 (m, 2 H), 3.78 (brs, 1 H), 3.53–3.42 (m, 2 H), 2.24 (ddd, *J* = 2.1, 5.2, 14.0 Hz, 1 H), 1.88 (ddd, *J* = 7.0, 9.7, 16.7 Hz, 1 H), 1.71–1.62 (m, 2 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 105.3, 82.2, 70.0, 67.9, 67.6, 41.2, 40.1. MS (EI): *m/z* = 266.0 [M]⁺. HRMS (EI): *m/z* [M–CH₅O₂] calcd for C₆H₈Cl₃O₂: 216.9590; found: 216.9588.

(2R,4S,6R)-7,7,7-trichloroheptane-1,2,4,6-tetraol (75ib)

Evaluation of the ^1H NMR from the crude reaction mixture established the dr (**75ia:75ib**) 26:74.

The crude mixture was then purified by silica gel chromatography (hexanes–EtOAc–MeOH 10:40:1) to afford the indicated compound as a colorless sticky oil in 89% total yield (23.8 mg, 89.0 μmol). $[\alpha]_{22}^{\text{D}} + 33.8$ (*c* 1.0, MeOH). IR (KBr): 3357, 2934, 1419, 1314, 1100, 1016, 988 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): δ = 5.63 (d, *J* = 3.7 Hz, 1 H), 4.44–4.37 (m, 1 H), 4.35 (brs, 1 H), 4.23–4.11 (m, 2 H), 3.94–3.86 (m, 1 H), 3.80 (brs, 1 H), 3.52 (dd, *J* = 4.7, 10.9 Hz, 1 H), 3.46 (dd, *J* = 6.2, 10.9 Hz, 1 H), 2.13–2.06 (m, 1 H), 1.79–1.69 (m, 2 H), 1.65–1.57 (m, 2 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 106.2, 80.4, 72.5, 67.8, 67.3, 41.5, 40.8. MS (EI): *m/z* = 266.0 [M]⁺. HRMS (EI): *m/z* [M–CH₅O₂] calcd for C₆H₈Cl₃O₂: 216.9590; found: 216.9583.

(1*S*,3*R*)-4,4,4-trichloro-1-(oxiran-2-yl)butane-1,3-diol (73d)

A dry, 2-neck round-bottom flask was charged with *syn*-1,3 diol **73c** (40.0 mg, 0.182 mmol) and diluted with dichloromethane (0.910 mL). The reaction mixture was cooled to 0 °C, and *meta*-chloroperoxybenzoic acid (94.0 mg, 0.547 mmol) was added. The mixture was stirred for 8 hours at 0 °C under a blanket of argon. After 8 hours, the reaction mixture was warmed to room temperature, and dichloromethane was removed under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc 3:1) to give a diastereomeric mixture of **73d** (31.3 mg, 133 μmol 73%) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): (major) δ = 4.39–4.33 (m, 1 H), 3.87–3.81 (m, 1 H), 3.15–3.10 (m, 1 H), 2.90–2.86 (m, 1 H), 2.79 (dd, *J* = 2.7, 4.7 Hz, 1 H), 2.38 (ddd, *J* = 2.2, 3.7, 14.5 Hz, 1 H), 2.06–1.97 (m, 1 H). (minor) δ = 4.39–4.33 (m, 1 H), 4.10–4.03 (m, 1 H), 3.10–3.06 (m, 1 H), 2.86–2.81 (m, 2 H), 2.48–2.43 (m, 1 H), 1.96–1.88 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃): (major) δ = 102.8, 81.6, 70.6, 54.7, 44.9, 35.2. (minor) δ = 102.8, 81.9, 68.7, 53.9, 44.2, 34.8.

(3*S*,5*R*)-2-(hydroxymethyl)-5-(trichloromethyl)tetrahydrofuran-3-ol (75ob)

¹H NMR (500 MHz, CDCl₃): (major) δ = 4.91 (dd, *J* = 7.0, 8.1 Hz, 1 H), 4.80–4.65 (m, 1 H), 4.29–4.23 (m, 1 H), 4.15–4.09 (m, 1 H), 4.03 (dd, *J* = 2.8, 12.4 Hz, 1 H), 2.45–2.34 (m, 2 H). (minor) δ = 4.82–4.77 (m, 1 H), 4.54–4.49 (m, 1 H), 4.15–4.09 (m, 1 H), 3.84 (dd, *J* = 4.0, 11.9 Hz, 1 H), 3.73 (dd, *J* = 4.7, 12.1 Hz, 1 H), 2.34–2.24 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃): (major) δ = 101.8, 89.1, 83.3, 74.3, 61.6, 39.8. (minor) δ = 101.8, 88.6, 88.4, 72.2, 62.7, 38.6.

(3*S*,5*R*)-1-azido-6,6,6-trichlorohexane-2,3,5-triol (75p)

A dry round-bottom flask was charged with epoxide **73d** (18.0 mg, 76.0 μmol) and diluted with dichloromethane (380 μL). Trimethylsilyl azide (12.0 μL, 92.0 μmol) was added, and the reaction mixture was cooled to 0 °C. Tetrabutylammonium fluoride (1 M in THF, 1 drop) was

added, and the mixture was slowly warmed to room temperature and vigorously stirred under argon for 2 hours. After 2 hours, tetrabutylammonium fluoride (1 M in THF, 92.0 μL , 92.0 μmol) was added, and the reaction mixture was stirred at room temperature for 30 minutes. Then, the reaction mixture was diluted with aqueous saturated NH_4Cl (3 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (5 x 3 mL), and the combined organics were dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc 3:1) to afford **75p** (17.2 mg, 61.8 μmol , 86%) as a clear colorless oil. IR (KBr): 3399, 2963, 2925, 2877, 2102, 1411, 1260, 1063 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ = 4.39 (dd, J = 1.9, 10.0 Hz, 1 H), 4.03–3.97 (m, 1 H), 3.80 (brs, 1 H), 3.77–3.70 (m, 1 H), 3.54–3.49 (m, 1 H), 3.29 (brs, 1 H), 2.64 (brs, 1 H), 2.39–2.30 (m, 1 H), 2.08–1.99 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 102.8, 82.2, 72.9, 70.6, 53.8, 34.6. MS (EI): m/z = 277.0 $[\text{M}]^+$. HRMS (EI): m/z $[\text{M}-\text{CH}_2\text{N}_3]$ calcd for $\text{C}_6\text{H}_8\text{Cl}_3\text{O}_2$: 220.9539; found: 222.9544.

General Procedure for the Preparation of Tetrahydropyran Derivatives 70a-70j and 70p

To a dry round-bottom flask equipped with a stir bar was added tetraol (50 μmol) and dioxane (83 μL). The reaction mixture was cooled to 0 $^\circ\text{C}$, and an aqueous solution of NaOH (prepared from freshly crushed NaOH pellets) (0.71 M in H_2O , 420 μL) was added dropwise. The reaction mixture was slowly warmed to room temperature, and stirred for 24–30 hours until starting material was consumed as indicated by TLC. The reaction mixture was cooled to 0 $^\circ\text{C}$, diluted with brine (2 mL), and quenched by dropwise addition of 1N HCl until pH 3 was obtained. The aqueous layer was immediately extracted with EtOAc (7 x 5 mL), and the combined organic layers were dried (Na_2SO_4), and concentrated. The carboxylic acid derivatives were obtained by adding hot DCM (2 mL) to the crude residue until complete dissolution of the mixture. The

reaction flask was slowly cooled to room temperature, and then further cooled to 0 °C for 30 minutes. The crystalline solid was filtered, and the solids were washed with ice-cold DCM (3 x 2 mL) to afford the indicated compounds.

(2*S*,4*R*,6*R*)-4-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-carboxylic acid (70a)

The indicated compound was obtained as a white solid in 85% total yield (7.5 mg, 42.6 μmol); mp 184–185 °C. $[\alpha]_{22}^D$ -16.8 (*c* 1.0, MeOH). IR (KBr): 3362, 2928, 2878, 1732, 1268, 1107, 1087, 1022 cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ = 4.06 (d, *J* = 11.7 Hz, 1 H), 3.90–3.81 (m, 1 H), 3.66–3.49 (m, 3 H), 2.29 (d, *J* = 12.1 Hz, 1 H), 1.93–1.82 (m, 1 H), 1.32 (q, *J* = 11.7 Hz, 1 H), 1.22 (q, *J* = 11.7 Hz, 1 H). ¹³C NMR (125 MHz, CD₃OD): δ = 175.1, 77.9, 75.3, 68.1, 66.0, 38.8, 37.2.

(2*S*,4*R*,6*R*)-4-hydroxy-6-((*R*)-hydroxy(phenyl)methyl)tetrahydro-2H-pyran-2-carboxylic acid (70b)

The indicated compound was obtained as a white solid in 93% total yield (11.7 mg, 46.4 μmol); mp 142–143 °C. $[\alpha]_{22}^D$ -21.6 (*c* 1.0, CH₃CN). IR (KBr): 3421, 2957, 2923, 2852, 1716, 1653, 1082 cm⁻¹. ¹H NMR (500 MHz, CD₃CN): δ = 7.40–7.29 (m, 5 H), 4.55 (d, *J* = 6.3 Hz, 1 H), 4.02 (dd, *J* = 2.4, 12.2 Hz, 1 H), 3.72–3.64 (m, 1 H), 3.54 (ddd, *J* = 2.0, 7.1, 11.6 Hz, 1 H), 2.20–2.13 (m, 1 H), 1.44–1.38 (m, 1 H), 1.33–1.23 (m, 1 H), 1.15–1.07 (m, 1 H). ¹³C NMR (125 MHz, CD₃CN): δ = 172.1, 141.8, 129.2, 128.9, 128.2, 81.3, 77.4, 75.0, 67.4, 38.3, 37.4.

(2*S*,4*R*,6*R*)-6-((*R*)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxytetrahydro-2H-pyran-2-carboxylic acid (70c)

The indicated compound was obtained as a white solid in 85% total yield (12.6 mg, 42.5 μmol); mp 168–169 °C. $[\alpha]_{22}^D$ -20.0 (*c* 1.0, MeOH). IR (KBr): 3351, 2951, 2925, 2867, 1726, 1101, 1046 cm⁻¹. ¹H NMR (500 MHz, CD₃OD): δ = 7.36–7.30 (m, 4 H), 7.29–7.25 (m, 1 H), 4.54 (s, 2

H), 4.01 (dd, $J = 1.9, 12.0$ Hz, 1 H), 3.88–3.79 (m, 1 H), 3.68–3.63 (m, 1 H), 3.63–3.59 (m, 1 H), 3.59–3.53 (m, 2 H), 2.29–2.20 (m, 1 H), 1.88–1.81 (m, 1 H), 1.40 (q, $J = 11.4$ Hz, 1 H), 1.30 (q, $J = 11.9$ Hz, 1 H). ^{13}C NMR (125 MHz, CD_3OD): $\delta = 175.2, 139.6, 129.4, 128.9, 128.7, 77.3, 74.4, 73.7, 72.0, 68.1, 38.9, 37.2$.

(2*S*,4*R*,6*R*)-4-hydroxy-6-((*R*)-1-hydroxypentyl)tetrahydro-2H-pyran-2-carboxylic acid

(70d)

The indicated compound was obtained as a white solid in 93% total yield (10.8 mg, 46.5 μmol). ^1H NMR (500 MHz, acetone- d_6): $\delta = 4.05$ (dd, $J = 2.3, 12.0$ Hz, 1 H), 3.93–3.84 (m, 1 H), 3.77–3.73 (brs, 1 H), 3.51–3.44 (m, 1 H), 3.40 (ddd, $J = 2.0, 5.2, 11.5$ Hz, 1 H), 2.28–2.22 (m, 1 H), 1.94–1.88 (m, 1 H), 1.57–1.42 (m, 3 H), 1.41–1.26 (m, 5 H), 0.89 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 171.2, 79.4, 72.9, 66.7, 38.1, 36.5, 32.3, 27.7, 22.5, 13.5$.

(2*S*,4*R*,6*R*)-6-((*R*)-1-(benzyloxy)-2-hydroxypropan-2-yl)-4-hydroxytetrahydro-2H-pyran-2-carboxylic acid

(70e)

The indicated compound was obtained as a white solid in 93% total yield (14.4 mg, 46.4 μmol); mp 183–184 °C. $[\alpha]_{22}^{\text{D}} -29.4$ (c 1.0, MeOH). IR (KBr): 3342, 2958, 2925, 2866, 1717, 1111, 1075 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): $\delta = 11.69$ –10.0 (brs, 1 H), 7.36–7.30 (m, 4 H), 7.28–7.23 (m, 1 H), 4.56 (d, $J = 12.3$ Hz, 1 H), 4.51 (d, $J = 12.3$ Hz, 1 H), 4.14–4.01 (brs, 1 H), 4.05 (dd, $J = 2.0, 12.1$ Hz, 1 H), 3.92–3.85 (m, 1 H), 3.82–3.73 (brs, 1 H), 3.61 (d, $J = 9.0$ Hz, 1 H), 3.33 (d, $J = 9.0$ Hz, 1 H), 2.26–2.20 (m, 1 H), 2.01–1.95 (m, 1 H), 1.40 (q, $J = 11.8$ Hz, 1 H), 1.32 (q, $J = 12.2$ Hz, 1 H), 1.15 (s, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): $\delta = 172.0, 139.9, 129.1, 128.2, 128.2, 79.6, 75.9, 75.3, 73.8, 73.6, 67.9, 39.0, 35.0, 21.5$.

(2*S*,4*S*,6*R*)-4-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-carboxylic acid (70f)

The indicated compound was obtained as a white solid in 89% total yield (7.8 mg, 44.3 μmol); mp 175–176 °C. ^1H NMR (500 MHz, $\text{DMSO-}d_6$): δ = 13.40–11.45 (brs, 1 H), 4.88–4.70 (brs, 1 H), 4.26–4.16 (m, 1 H), 4.10–4.06 (brs, 1 H), 3.79–3.68 (m, 1 H), 3.46–3.26 (m, 3 H), 1.82–1.73 (m, 1 H), 1.57–1.47 (m, 2 H), 1.37–1.28 (m, 1 H). ^{13}C NMR (125 MHz, $\text{DMSO-}d_6$): δ = 173.0, 72.7, 70.5, 64.5, 61.8, 35.5, 34.1.

(2*S*,4*S*,6*R*)-4-hydroxy-6-((*R*)-hydroxy(phenyl)methyl)tetrahydro-2H-pyran-2-carboxylic acid (70g)

The indicated compound was obtained as a white solid in 84% total yield (10.6 mg, 42.0 μmol); mp 204–205 °C. $[\alpha]_{22}^D$ -39.8 (*c* 1.0, MeCN). IR (KBr): 3312, 2920, 2851, 1725, 1455, 1419, 1092, 1065 cm^{-1} . ^1H NMR (500 MHz, CD_3CN): δ = 9.65–9.25 (brs, 1 H), 7.40–7.27 (m, 5 H), 4.50 (d, *J* = 7.3 Hz, 1 H), 4.41 (dd, *J* = 2.6, 12.3 Hz, 1 H), 4.14–4.08 (m, 1 H), 3.92 (ddd, *J* = 2.1, 7.4, 11.9 Hz, 1 H), 3.85–3.60 (brs, 1 H), 2.95–2.83 (brs, 1 H), 1.92–1.87 (m, 1 H), 1.63 (ddd, *J* = 2.5, 12.3, 14.8 Hz, 1 H), 1.43 (ddd, *J* = 2.8, 12.1, 14.6 Hz, 1 H), 1.19–1.13 (m, 1 H). ^{13}C NMR (125 MHz, CD_3CN): δ = 173.1, 141.8, 129.2, 128.8, 128.2, 77.7, 77.7, 71.6, 63.4, 36.0, 34.5.

(2*S*,4*S*,6*R*)-6-((*R*)-2-(benzyloxy)-1-hydroxyethyl)-4-hydroxytetrahydro-2H-pyran-2-carboxylic acid (70h)

The indicated compound was obtained as a white solid in 86% total yield (12.7 mg, 42.9 μmol); mp 181–182 °C. $[\alpha]_{22}^D$ -17.6 (*c* 1.0, MeOH). IR (KBr): 3315, 2919, 2894, 2871, 1715, 1103, 1073 cm^{-1} . ^1H NMR (500 MHz, CD_3OD): δ = 7.37–7.30 (m, 4 H), 7.28–7.24 (m, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.41 (dd, *J* = 2.3, 12.3 Hz, 1 H), 4.28–4.22 (m, 1 H), 4.01–3.95 (m, 1 H), 3.63–3.57 (m, 2 H), 3.56–3.51 (m, 1 H), 2.04–1.95 (m, 1 H), 1.74 (ddd, *J* = 2.8, 12.0, 16.4 Hz, 1 H), 1.68–1.61 (m, 1 H), 1.61–1.55 (m, 1 H). ^{13}C NMR (125 MHz, CD_3OD): δ = 176.5, 139.7, 129.3, 128.9, 128.7, 74.4, 74.3, 73.9, 73.2, 71.9, 64.3, 36.6, 34.6.

(2*S*,4*S*,6*R*)-4-hydroxy-6-((*R*)-1-hydroxypentyl)tetrahydro-2*H*-pyran-2-carboxylic acid

(70i)

The indicated compound was obtained as a white solid in 82% total yield (9.5 mg, 40.9 μmol).

^1H NMR (500 MHz, acetone- d_6): δ = 11.64–9.84 (brs, 1 H), 4.45 (dd, J = 1.9, 12.1 Hz, 1 H), 4.33–4.25 (m, 1 H), 4.15–3.95 (brs, 1 H), 3.86–3.73 (m, 2 H), 3.46–3.36 (m, 1 H), 2.02–1.95 (m, 1 H), 1.69–1.59 (m, 2 H), 1.53–1.25 (m, 7 H), 0.89 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 173.2, 76.5, 74.0, 71.7, 63.6, 36.5, 34.7, 33.2, 28.6, 23.4, 14.4.

(2*S*,4*S*,6*R*)-6-((*R*)-1-(benzyloxy)-2-hydroxypropan-2-yl)-4-hydroxytetrahydro-2*H*-pyran-2-carboxylic acid (70j)

The indicated compound was obtained as a white solid in 82% total yield (12.7 mg, 40.9 μmol);

mp 168–169 $^{\circ}\text{C}$. $[\alpha]_{22}^{\text{D}}$ -14.6 (c 1.0, MeOH). IR (KBr): 3415, 2929, 2868, 1721, 1645, 1090, 1070 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): δ = 12.18–9.45 (brs, 1 H), 7.40–7.29 (m, 4 H), 7.29–7.22 (m, 1 H), 4.57 (d, J = 12.4 Hz, 1 H), 4.51 (d, J = 12.4 Hz, 1 H), 4.46 (dd, J = 2.3, 12.3 Hz, 1 H), 4.35–4.30 (m, 1 H), 4.08–4.00 (m, 2 H), 3.83–3.70 (brs, 1 H), 3.64 (d, J = 8.9 Hz, 1 H), 3.29 (d, J = 8.9 Hz, 1 H), 2.00–1.94 (m, 1 H), 1.74–1.70 (m, 2 H), 1.64 (ddd, J = 2.6, 12.4, 14.9 Hz, 1 H), 1.11 (s, 3 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 173.2, 140.0, 129.1, 128.2, 128.1, 75.8, 75.5, 73.8, 73.7, 72.1, 63.8, 36.6, 32.0, 21.4.

(2*S*,4*S*,6*S*)-4-hydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-carboxylic acid (70p)

The indicated compound was obtained as a white solid in 86% total yield (7.6 mg, 43.1 μmol)

General Procedure for the Preparation of Tetrahydropyran Lactone Derivatives 70ll and 70nn

To a dry round-bottom flask equipped with a stir bar was added tetraol (50 μmol) and dioxane (83 μL). The reaction mixture was cooled to 0 $^{\circ}\text{C}$, and an aqueous solution of NaOH (0.71 M in

H₂O, 300 μmol) was added drop-wise. The reaction mixture was slowly warmed to room temperature, and stirred for 24–30 hours until starting material was consumed as indicated by TLC. The reaction mixture was cooled to 0 °C, diluted with brine (2 mL), and quenched by drop-wise addition of 1N HCl until pH 3 was obtained. The aqueous layer was immediately extracted with EtOAc (7 x 5 mL), and the combined organic layers were dried (Na₂SO₄), and concentrated. The crude residue was added to a dry round-bottom flask equipped with a stir bar, and diluted with DCM (1 mL). The reaction mixture was cooled to 0 °C, then pyridine (50 μmol) was added dropwise followed by dropwise addition of cyanuric fluoride (50 μmol). The reaction mixture was slowly warmed to room temperature and stirred under argon for 12 hours. Solids were observed precipitating from the reaction solution within the first hour, and precipitation continued throughout the entire reaction. The reaction mixture was quenched with ice-cold DI H₂O, filtered, and adequately rinsed on the filter with DCM. The aqueous layer was extracted with DCM (5 x 5 mL), and the combined organic layers were dried (Na₂SO₄), and concentrated. The residue was purified by silica gel chromatography with 3:1 hexanes–EtOAc to afford the corresponding lactone.

(1*S*,3*S*,5*R*)-3-((*S*)-hydroxy(phenyl)methyl)-2,6-dioxabicyclo[3.2.1]octan-7-one (70ll)

The indicated compound was obtained as a white solid in 86% total yield (10.1 mg, 43.1 μmol); mp 153–154 °C. $[\alpha]_{22}^D + 12.8$ (*c* 1.0, DCM). IR (KBr): 3460, 3063, 3032, 2997, 2928, 1778, 1607, 1052 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 7.37–7.29 (m, 5 H), 4.96–4.90 (m, 1 H), 4.57 (d, *J* = 6.7 Hz, 1 H), 4.40 (d, *J* = 3.1 Hz, 1 H), 4.07 (ddd, *J* = 5.7, 6.7, 15.4 Hz, 1 H), 2.92 (brs, 1 H), 2.25–2.17 (m, 1 H), 2.07 (d, *J* = 12.4 Hz, 1 H), 1.74–1.67 (m, 2 H). ¹³C NMR (125 MHz, CDCl₃): δ = 172.9, 138.6, 128.6, 128.5, 127.0, 77.2, 76.4, 76.0, 72.8, 37.4, 32.6.

(1*S*,3*S*,5*R*)-3-((*S*)-1-hydroxypentyl)-2,6-dioxabicyclo[3.2.1]octan-7-one (70nn)

The indicated compound was obtained as a yellow oil in 81% total yield (8.7 mg, 40.6 μmol). ^1H NMR (500 MHz, CDCl_3): δ = 5.06–4.99 (m, 1 H), 4.35–4.31 (m, 1 H), 3.88–3.81 (m, 1 H), 3.48–3.41 (m, 1 H), 2.08–2.02 (m, 2 H), 1.98–1.92 (m, 1 H), 1.51–1.43 (m, 2 H), 1.36–1.28 (m, 5 H), 0.89 (t, J = 8.0 Hz, 3 H).

(2*S*,4*S*,6*S*)-4-hydroxy-6-((*S*)-hydroxy(phenyl)methyl)tetrahydro-2H-pyran-2-carboxylic acid (70q)

The crude mixture was purified by silica gel chromatography with 2:3 hexanes–EtOAc to afford the indicated compound as a yellow oil in 80% total yield (10.1 mg, 40.0 μmol). $[\alpha]_{22}^{\text{D}}$ + 47.4 (c 1.0, MeOH). IR (KBr): 3377, 3034, 2954, 2925, 1716, 1454, 1169, 1112 cm^{-1} . ^1H NMR (500 MHz, acetone- d_6): δ = 12.39–9.78 (brs, 1 H), 7.45–7.41 (m, 2 H), 7.36–7.32 (m, 2 H), 7.31–7.26 (m, 1 H), 4.68 (dd, J = 2.0, 6.4 Hz, 1 H), 4.63 (d, J = 6.7 Hz, 1 H), 3.97 (ddd, J = 2.3, 6.7, 13.6 Hz, 1 H), 3.73–3.66 (m, 1 H), 2.37–2.29 (m, 1 H), 1.64–1.55 (m, 2 H), 1.21–1.13 (m, 1 H). ^{13}C NMR (125 MHz, acetone- d_6): δ = 173.2, 142.1, 128.7, 128.3, 128.2, 77.6, 77.2, 73.0, 64.9, 37.1, 36.5.

CHAPTER 4

REGIOSELECTIVE FORMATION OF TERMINAL ALKYL SULFANYL ALCOHOLS

4.1 Background and Significance

Terminal alkylsulfanyl alcohols are a class of compounds possessing unique medicinal properties. Roots and stems of species isolated from *Salicia* plants have traditionally been used to treat rheumatism, gonorrhoea, and various skin-diseases. The pseudo-sugar sulfonium salts neosalicinol **101** and neokotalanol **102**, also isolated from *Salicia* plants, have been effectively used as remedies for early-stage diabetes (Figure 4.1).¹⁶⁶ The mechanism of action of the sulfonium compounds involves inhibition of α -glucosidases, which catalyze the degradation of carbohydrates.¹⁶⁷ Inhibitors of α -glucosidases delay the digestion of carbohydrates and thus slow the absorption of glucose into the bloodstream. The sulfonium compounds display potent activity toward α -glucosidases inhibition, with IC₅₀ values that are comparable to the widely clinically used acarbose.¹⁶⁸ Terminal alkylsulfanyl alcohols have also found application as alkylating agents toward inhibition of glutathione-S-transferases.¹⁶⁹ Alkylating agents effectively alter replication of DNA, and thus are clinically useful as anti-cancer drugs. Glutathione-S-transferase

¹⁶⁶ Jayaweera D.M.A. Medicinal plants used in ceylon, part 1. National Science Council of Sri Lanka, Columbo, **1981**, 77.

¹⁶⁷ (a) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka O. *Tetrahedron Lett.* **1997**, *38*, 8367. (b) Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem.* **2002**, *10*, 1547.

¹⁶⁸ Yoshikawa, M.; Xu, F.; Nakamura, S.; Wang, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Heterocycles* **2008**, *75*, 1397.

¹⁶⁹ Scheeter, R. L.; Alaoui-Jamali, M. A.; Woo, A.; Fahl, W. E.; Batist, G. *Cancer. Res.* **1993**, *53*, 4900.

inhibitors such as **103** inhibit catalytic activity through a competitive mechanism and display IC_{50} values in the sub-millimolar range.¹⁷⁰

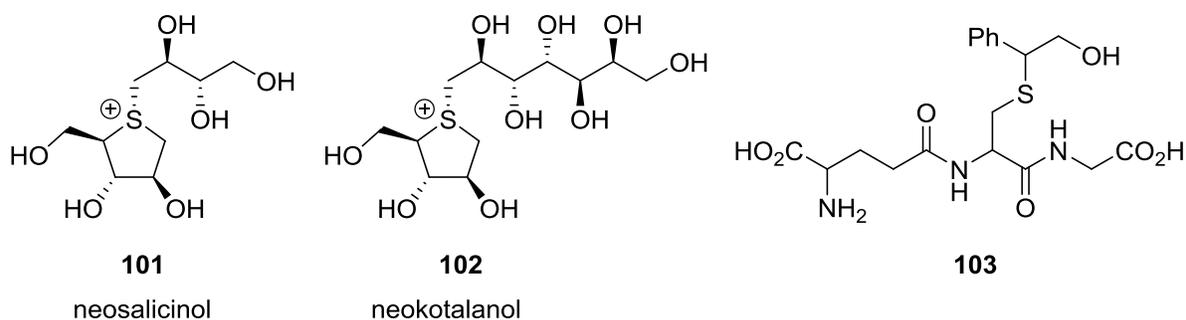


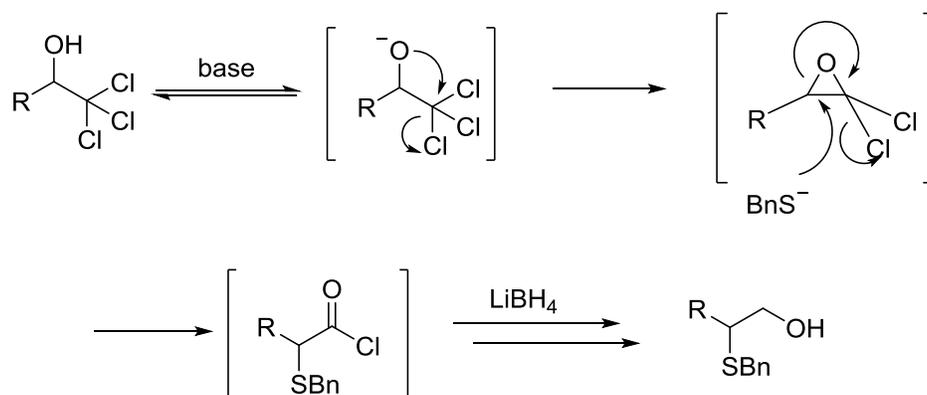
Figure 4.1: Examples of biologically active compounds bearing terminal alkylsulfanyl alcohols

4.2 Planned Approach for Formation of Alkylsulfanyl Alcohols

For the preparation of terminal alkylsulfanyl alcohols, we intended to expand upon our previous success with reactions involving reactive *gem*-dichloroepoxide intermediates (Scheme 4.1).¹⁷¹ We envisioned that treatment of trichloromethyl carbinols with an appropriate base would promote formation of the *gem*-dichloroepoxide intermediate. Nucleophilic substitution with benzyl thiolate to the non-chloride bearing carbon, followed by subsequent acyl chloride reduction would lead to the desired target. We were interested to see if we could establish conditions that would take advantage of the differences in polarizability among the various nucleophiles present in the reaction. We reasoned that the *gem*-dichloroepoxide intermediate would have better interactions with softer nucleophiles (i.e. RS^- or RSH), and the acyl chloride would be better-suited for interactions with harder nucleophiles (i.e. OH^- , $HB(iPr)_3^-$, or $iPrOH$).

¹⁷⁰ Procopio, A.; Alcaro, S.; Cndari, S.; De Nino, A.; Ortuso, F.; Sacchetta, P.; Pennelli, A.; Sindona, G. *J. Med. Chem.* **2005**, *48*, 6084.

¹⁷¹ Gupta, M. K.; Li, Z.; Snowden T. S. *Org. Lett.* **2014**, *16*, 1602.



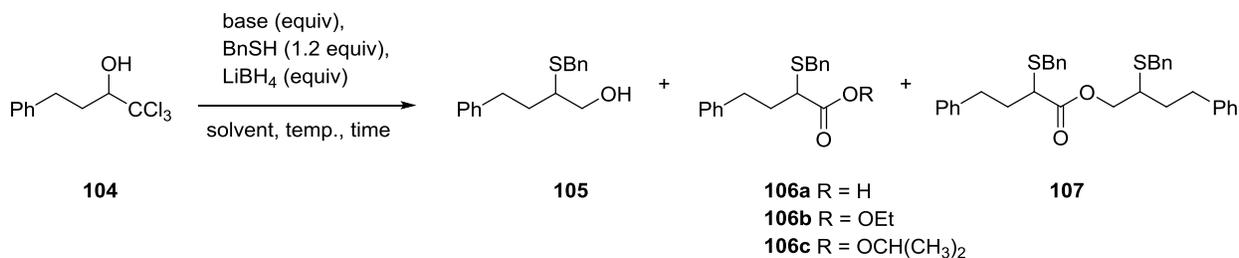
Scheme 4.1: mechanism leading to terminal alkylsulfanyl alcohols

4.3 Results and Discussion

We began our investigations toward the preparation of terminal alkylsulfanyl alcohols with the trichloromethyl carbinol **104** as the test substrate. The trichloromethyl carbinol was prepared in 93% yield from 3-phenylpropanal by following the method reported by Corey and Link.⁵⁶ With **104** in hand, we conducted a series of reactions to explore the preparation of the corresponding benzylsulfanyl alcohol **105** (Table 4.1). When sodium hydroxide was used in the presence of ethanol, the carboxylic acid byproduct **106a** was the major product isolated from the reaction mixture. Switching to IPA as the solvent significantly increased the yield of the desired product **105**; however **106a** was still formed as the major reaction product. We then opted to use cesium carbonate to hopefully avoid the formation of the carboxylic acid byproduct. Indeed, in all reactions where cesium carbonate was used, the carboxylic acid **106a** was not observed. Starting material was consumed within two hours with 3 equivalents of cesium carbonate in refluxing IPA, however a significant amount of the isopropyl ester **106c** and the dimer **107** were formed. We reasoned that higher concentrations of lithium borohydride and longer reaction times would reduce the esters to the primary alcohol, and in fact, this was the case. Conducting the reaction with 4 equivalents of LiBH₄ in refluxing IPA for 5 hours influenced the product ratio

toward the desired product as we had expected (entry 4). In attempts to further improve the yield, **104** was treated with 5 equivalents of LiBH_4 and heated to $60\text{ }^\circ\text{C}$ in IPA. We were able to obtain the product in 86% yield with almost complete reduction of the isopropyl ester after 8 hours (entry 5). Along with a higher concentration of LiBH_4 , the increased product yield can be attributed to the slower rate of thermal decomposition of the reducing agent at lower temperatures. Comparable results were obtained when the reaction was allowed to run for 18 hours under otherwise identical conditions.

Table 4.1: optimized preparation of **105** from trichloromethyl carbinol **104**



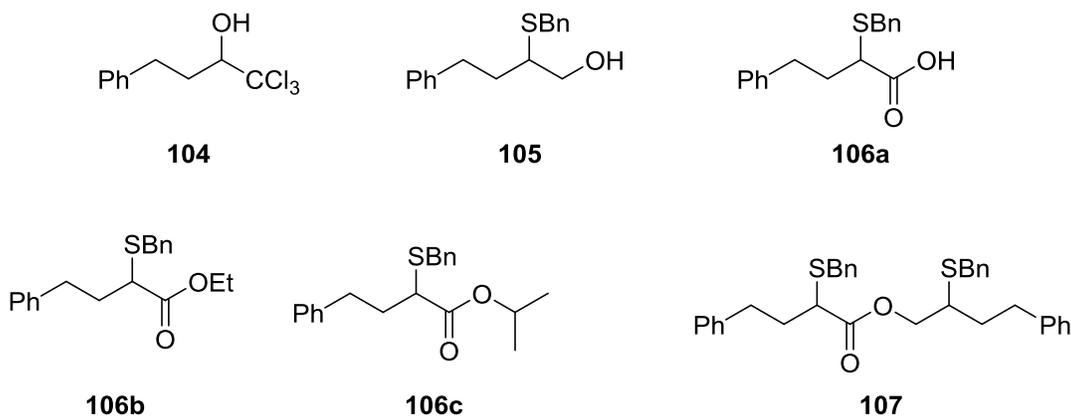
Entry	Base (equiv)	LiBH_4 (equiv)	Time (h)	T ($^\circ\text{C}$)	Solvent	Yield (%)		
						105	106a	106b-c
1	NaOH (4)	2	24	rt	EtOH	9	62	106b, 12
2	NaOH (4)	2	4	85	IPA	38	41	106c, 9
3 ^a	Cs_2CO_3 (3)	3	2	85	IPA	45	0	106c, 39
4	Cs_2CO_3 (3.5)	4	5	85	IPA	67	0	106c, 24
5	Cs_2CO_3 (3.5)	5	8	60	IPA	86	0	106c, 7
6	Cs_2CO_3 (3.5)	5	18	60	IPA	82	0	106c, 12

^a The dimer **107** was also isolated from the reaction in 12% yield

4.4 Future Directions

Due to our encouraging preliminary results in the preparation of terminal alkylsulfanyl alcohols, we are optimistic that the method can be expanded even further by exploring a variety of different nucleophiles to efficiently lead to interesting new targets. The scope of the method can potentially be broadened to prepare biologically interesting compounds such as α -aminoamides, α -thioetheramides and their corresponding sulfones, and aminoalcohols. Work towards the preparation of those compounds is currently underway.

4.5 Index of Chapter Compounds and Numbers



4.6 Experimental Details

^1H and ^{13}C NMR spectra were recorded on Bruker instruments at 360, 500, or 600 MHz and 90 or 125 MHz, respectively. Chemical shifts were referenced to acetone- d_6 ($\delta = 2.05$ and 29.84) or CDCl_3 ($\delta = 7.26$ and 77.0). TLC visualization was achieved by UV light (254 nm), I_2 staining, and *p*-anisaldehyde staining. 3-phenylpropanal was purchased from Aldrich, and was purified by silica gel chromatography with 9:1 hexanes–EtOAc immediately before use. Anhydrous IPA was purchased as a Drisolv® bottle from EMD Millipore and used as received. Anhydrous DMF was purchased as a Sure/Seal™ bottle from Aldrich and was used as received. All other reagents and solvents were used as received from commercial sources.

1,1,1-trichloro-4-phenylbutan-2-ol (104)

A dry, 2-neck round-bottom flask was charged with 3-phenylpropanal (2.40 mL, 18.2 mmol) and diluted with anhydrous DMF (26.6 mL). Trichloroacetic acid (4.47 g, 27.3 mmol), then sodium trichloroacetate (5.07 g, 27.3 mmol) was added, and the reaction was vigorously stirred under a blanket of argon at room temperature. After 6 hours, starting material was still present according to TLC. One equivalent of trichloroacetic acid (2.98 g, 18.2 mmol) and sodium trichloroacetate (3.38 g, 18.2 mmol) were added, and the reaction mixture was stirred an additional 2 hours. The reaction mixture was diluted with Et₂O (75 mL) and washed with saturated aqueous NaHCO₃ (3 x 25 mL). The organic layer was dried with sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (hexanes–EtOAc 20:1) to afford the trichloromethyl carbinol **104** (4.29 g, 16.9 mmol, 93%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.31 (m, 2 H), 7.30–7.23 (m, 3 H), 4.02 (dd, *J* = 2.7, 9.8 Hz, 1 H), 3.08–2.98 (m, 1 H), 2.85–2.75 (m, 2 H), 2.47–2.37 (m, 1 H), 2.06–1.97 (m, 1 H). ¹³C NMR (125 MHz, CDCl₃): δ = 140.7, 128.6, 128.5, 126.3, 104.1, 82.0, 32.9, 32.0.

2-(benzylthio)-4-phenylbutan-1-ol (105)

A dry, 2-neck round-bottom flask equipped with a reflux condenser and stir bar was charged with trichlorocarbinol **104** (100 mg, 0.394 mmol), and diluted with anhydrous IPA (3.20 mL). Benzyl mercaptan (55.5 μL, 0.473 mmol) was added, followed by lithium borohydride (42.9 mg, 1.97 mmol). Cesium carbonate (450 mg, 1.38 mmol) was added, and the reaction flask was heated in a 65 °C oil bath for 8 hours. The reaction mixture was cooled to room temperature, then quenched with a saturated aqueous solution of NH₄Cl (15 mL). The aqueous phase was extracted with EtOAc (5 x 15 mL). The combined organic layers were dried with sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel

chromatography (hexanes–EtOAc 7:1) to afford **105** (92.4 mg, 339 μ mol, 86%) as a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ = 7.37–7.27 (m, 5 H), 7.25–7.15 (m, 3 H), 7.12–7.07 (m, 2 H), 3.72 (dd, J = 13.4, 16.9 Hz, 1 H), 3.67–3.61 (m, 1 H), 3.54–3.48 (m, 1 H), 2.77 (ddd, J = 5.6, 9.0, 14.1 Hz, 1 H), 2.71–2.67 (m, 1 H), 2.67–2.61 (m, 1 H), 2.11–2.03 (m, 1 H), 1.92–1.85 (m, 1 H), 1.85–1.75 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 141.5, 138.3, 128.8, 128.6, 128.4, 128.4, 127.2, 125.9, 64.0, 48.0, 34.9, 33.2, 32.9.

2-(benzylthio)-4-phenylbutanoic acid (106a)

The indicated compound was obtained as a white solid. ^1H NMR (500 MHz, CDCl_3): δ = 11.01 (brs, 1 H), 7.37–7.21 (m, 8 H), 7.07–6.98 (m, 2 H), 3.94–3.78 (m, 2 H), 3.20–3.06 (m, 1 H), 2.76–2.56 (m, 2 H), 2.23–2.08 (m, 1 H), 2.01–1.85 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 179.0, 140.5, 137.3, 129.1, 128.6, 128.4, 128.4, 127.3, 126.1, 44.5, 36.0, 32.9, 32.2.

isopropyl 2-(benzylthio)-4-phenylbutanoate (106c)

The indicated compound was obtained as a yellow oil. ^1H NMR (360 MHz, CDCl_3): δ = 7.35–7.27 (m, 8 H), 7.09–7.01 (m, 2 H), 5.14–4.99 (m, 1 H), 3.81 (dd, J = 13.2, 21.5 Hz, 2 H), 3.11 (t, J = 7.4 Hz, 1 H), 2.71–2.55 (m, 2 H), 2.21–2.07 (m, 1 H), 1.98–1.85 (m, 1 H), 1.32–1.27 (m, 6 H).

2-(benzylthio)-4-phenylbutyl 2-(benzylthio)-4-phenylbutanoate (107)

The indicated compound was obtained as a yellow oil. ^1H NMR (360 MHz, CDCl_3): δ = 7.34–7.00 (m, 20 H), 4.29 (ddd, J = 5.2, 6.7, 11.4 Hz, 1 H), 4.10 (ddd, J = 2.5, 7.2, 11.2 Hz, 1 H), 3.81–3.71 (m, 4 H), 3.12 (q, J = 7.4 Hz, 1 H), 2.81–2.70 (m, 2 H), 2.67–2.55 (m, 3 H), 2.17–2.08 (m, 1 H), 2.01–1.87 (m, 2 H), 1.79–1.71 (m, 1 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 172.2, 141.3, 140.7, 138.2, 137.5, 129.1, 129.0, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 127.2, 127.1, 126.1, 125.9, 67.0, 45.2, 42.7, 35.8, 35.5, 35.5, 33.4, 33.0, 32.6.

APPENDIX

A1: ^1H , ^{13}C , ^{19}F , HSQC, HMBS, COSY, and NOE NMR Spectra of Reported Compounds

