

Method Development for the Stereoselective Synthesis of Medium-Sized Cyclic Ethers
and Application to Natural Product Synthesis: Part I. Organocatalytic Oxa-Conjugate
Addition for α,α' -*trans*-Oxepanes Part II. Gold(I)-Catalyzed Alkoxylation for α,α' -*cis*-
Oxocenes Part III. Studies toward the Synthesis of (+)-Intricenyne

by

Megan L. Lanier

Department of Chemistry
Duke University

Date: _____

Approved:

Jiyong Hong, Supervisor

Ross A. Widenhoefer

Qiu Wang

Katherine J. Franz

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 Duke University

2015

ABSTRACT

Method Development for the Stereoselective Synthesis of Medium-Sized Cyclic Ethers and Application to Natural Product Synthesis: Part I. Organocatalytic Oxa-Conjugate Addition for α,α' -*trans*-Oxepanes Part II. Gold(I)-Catalyzed Alkoxylation for α,α' -*cis*-Oxocenes Part III. Studies toward the Synthesis of (+)-Intricenyne

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Abstract

Medium-sized cyclic ethers are challenging synthetic targets due to enthalpic and entropic barriers. Methods for the stereoselective synthesis of α,α' -disubstituted medium-sized cyclic ethers began to appear with the discovery of naturally-occurring, ladder-shaped polycyclic ethers, such as brevetoxin B, and monocyclic ethers, such as (+)-laurencin. Despite the progress made in this field, limitations remain including competing formation of smaller ring sizes and scarcity of catalytic methods. Our aim has been to develop stereoselective syntheses for 7- and 8-membered cyclic ethers which have potential for application in natural product synthesis. The C–O bond disconnection was selected for the methods described within because cyclization and stereoinduction could be achieved simultaneously. In the case of 7-membered cyclic ethers, an organocatalytic oxa-conjugate addition reaction promoted by the *gem*-disubstituent (Thorpe–Ingold) effect has been developed to stereoselectively provide α,α' -*trans*-oxepanes. A gold(I)-catalyzed alkoxylation reaction has also allowed access to α,α' -*cis*-oxocenes. This method has been probed for feasibility in the stereoselective synthesis of (+)-intrincenyne, an 8-membered cyclic ether belonging to the C₁₅ nonterpenoid acetogenin natural product class. These methods have the potential to become general and efficient routes to highly functionalized oxepanes and oxocenes.

Dedication

To my parents, Andrew D. Lanier and Cecilia A. Lanier, for their constant support and encouragement. To Ryan L. Hanna for waiting for me to come home to you. To Professor Debra D Dolliver and Professor David Norwod for mentoring me. To my family and friends, for bringing meaning to my life.

Contents

Abstract	iv
List of Tables	ix
List of Figures	x
List of Schemes	xiii
List of Abbreviations	xvii
Acknowledgements	xxi
1. Introduction.....	1
1.1 Natural Product Synthesis	1
1.2 Significance of Medium-Sized Cyclic Ether Synthesis.....	3
1.3 Challenges of Medium-Sized Cyclic Ether Synthesis.....	7
1.4 General Approaches to the Synthesis of Medium-Sized Cyclic Ethers	8
1.5 Numbering System for Entire Dissertation	9
1.6 Summary.....	10
2. Stereoselective Synthesis of α,α' - <i>trans</i> -Oxepanes via an Organocatalytic Oxa-Conjugate Addition Promoted by the <i>gem</i> -Disubstituent Effect.....	11
2.1 Background	11
2.1.1 Stereoselective Synthesis of α,α' - <i>cis</i> -Oxepanes.....	15
2.1.2 Stereoselective Synthesis of α,α' - <i>trans</i> -Oxepanes.....	22
2.1.3 Oxa-Conjugate Addition as a Method for Oxacycle Synthesis	30
2.1.4 Organocatalytic Activation of α,β -Unsaturated Aldehydes.....	35
2.1.5 Previous Studies	41

2.1.6 Summary of Background	46
2.2 Results and Discussion	47
2.2.1 Optimization of Organocatalyzed Oxa-Conjugate Addition Conditions	47
2.2.2 Development of the Tandem Organocatalytic Oxa-Conjugate Addition/ α -Oxidation Reaction.....	61
2.3 Attempts to Extend Methodology to the Preparation of Eight-Membered Cyclic Ethers.....	66
2.4 Summary.....	76
2.5 Experimental Section	77
3. Stereoselective Synthesis of α,α' - <i>cis</i> -Oxocenes via Gold(I)-Catalyzed Alkoxylation .	123
3.1 Background	123
3.1.1 Stereoselective Synthesis of α,α' -Disubstituted Oxocenes.....	125
3.1.2 Gold(I)-Catalyzed Alkoxylation as a Method for Oxacycle Synthesis	142
3.1.3 Summary of Background	147
3.2 Results and Discussion	148
3.2.3 Preliminary Studies.....	148
3.2.3 Optimization of the Gold(I)-Catalyzed Alkoxylation Reaction for α,α' -Disubstituted-Oxocenes	161
3.2.4 Determination of the Relative Configuration of α,α' -Disubstituted Oxocene 3.101.....	166
3.3 Summary.....	171
3.4 Experimental Section	171
4. Studies toward a Stereoselective Total Synthesis of (+)-Intricenyne	178

4.1 Background	180
4.1.1 Isolation and Structural Elucidation of (+)-Intricenyne	180
4.1.2 Similar Oxocene Natural Products	181
4.1.2.1 Total Syntheses of (+)-Laurencin.....	185
4.1.2.2 Background.....	186
4.1.2.3 Previous Syntheses of Laurencin.....	187
4.1.3 Summary of Background	220
4.2 Results and Discussion	221
4.2.1 Retrosynthetic Analysis of (+)-Intricenyne	221
4.2.2 Preparation and Coupling of the Epoxide and Alkyne Fragments.....	223
4.2.3 Selection of a suitable protecting group for the C12 alcohol.....	234
4.2.4 The Gold(I)-Catalyzed Alkoxylation for α,α' - <i>cis</i> - Δ 9-Oxocene Formation	242
4.2.5 Proposed Plan to Complete the Total Synthesis of (+)-Intricenyne.....	258
4.3 Summary.....	259
4.4 Experimental Section	261
References	285
Biography.....	310

List of Tables

Table 1: Preparation of α,β -unsaturated aldehydes <i>ent</i> -2.102A-E.....	53
Table 2: Substrate scope for the organocatalyzed oxa-conjugate addition reaction.....	55
Table 3: Optimization of the organocatalyzed α -oxidation of oxepane aldehyde 2.121...	63
Table 4: Gold-catalyzed alkoxylation of Δ 10 monoallylic diol 3.98	151
Table 5: Preparation of simple hydroxy allene 3.108 and testing under gold(I)-catalyzed alkoxylation conditions	156
Table 6: Preparation of chiral Δ 9-hydroxy allene 3.115 and testing under gold(I)-catalyzed alkoxylation conditions	158
Table 7: Screening of silver salts for the gold(I)-catalyzed alkoxylation of Δ 9 monoallylic diol 3.100	162
Table 8: Screening of solvents for the gold(I)-catalyzed alkoxylation of Δ 9 monoallylic diol 3.100	163
Table 9: Temperature and catalyst loading effects on the gold(I)-catalyzed alkoxylation of Δ 9 monoallylic diol 3.100 using AgClO_4	164
Table 10: Temperature and catalyst loading effects on the gold(I)-catalyzed alkoxylation of Δ 9 monoallylic diol 3.100 using AgOTf	165
Table 11: Optimization of conditions for the gold(I)-catalyzed alkoxylation of monoallylic diol 4.263.....	252

List of Figures

Figure 1: A selection of naturally occurring medium-sized cyclic ethers.....	6
Figure 2: General methods for medium-sized cyclic ether synthesis.....	9
Figure 3: Numbering system for dissertation based on (+)-intrincenyne.....	10
Figure 4: Examples of monocyclic C ₁₅ non-terpenoid, marine natural products with a 7-membered cyclic ether skeleton.....	12
Figure 5: Regioselectivity issues in oxepane synthesis.....	14
Figure 6: Murai's Lewis acid directing reductive or allylative cleavage of dioxabicyclo[3.2.1]octanes	25
Figure 7: Crimmins' asymmetric alkylation/RCM method for α,α' -trans-oxepane synthesis.....	28
Figure 8: Martin's oxa-conjugate addition reaction	33
Figure 9: Fall's oxa-conjugate addition reaction.....	34
Figure 10: Organocatalyzed α -oxyaminations of aldehydes	40
Figure 11: Importance of the 1,3-dithaine moiety in intramolecular conjugate additions.....	43
Figure 12: ¹ H NMR kinetic study for the organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehyde <i>ent</i> -2.102A	51
Figure 13: ¹ H NMR kinetic study for the organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehydes <i>ent</i> -2.102A-E with (<i>R</i>)-amine catalyst 2.78.....	54
Figure 14: ¹ H NMR kinetic study for the organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehydes <i>ent</i> -2.102A-E with (<i>S</i>)-amine catalyst 2.78	57
Figure 15: Examples of monocyclic C ₁₅ non-terpenoid, marine natural products with an 8-membered cyclic ether skeleton.....	123
Figure 16: Key inspirational gold(I)-catalyzed functionalization of allylic alcohols	125
Figure 17: Kotsuki's stereoselective reduction of bicyclic ketals.....	127

Figure 18: Governing variables in Synder's ring-expanding bromoetherification.....	136
Figure 19: Suzuki's Lewis acid promoted cyclizations of model hydroxyl epoxide 3.72139	
Figure 20: Suzuki's Lewis acid promoted cyclizations of hydroxyl epoxides	140
Figure 21: Key inspirational gold(I)-catalyzed fuctionalization of allylic alcohols	145
Figure 22: (A) Gagné's gold(I)-catalyzed cascade cyclization of allenyl alcohols (B) She's gold-catalyzed 1,2-acyloxy migration/intramolecular [3+2] 1,3-dipolar cycloaddtion cascade reaction.....	147
Figure 23: Attempts to cyclize dithiane-containing monoallylic diol 3.94.....	149
Figure 24: Attempts to cyclize dithiane-containing monoallylic diol 3.96.....	150
Figure 25: Gold(I)-catalyzed alkoxylation of Δ^9 monoallylic diol 3.100	152
Figure 26: Potential substrates for gold(I)-catalyzed cyclizations.....	160
Figure 27: ^1H - ^1H COSY spectra of oxocene 3.101.....	168
Figure 28: ^1H - ^1H NOESY spectra of oxocene 3.101	170
Figure 29: Three dimensional conformation of oxocene 3.101	170
Figure 30: Monocyclic oxocene-containing natural products.....	185
Figure 31: Holmes's attempts to stereoselectively install the C12 alcohol using oxaziridines.....	195
Figure 32: Proposed methods for installation of the C7 enyne side chain.....	223
Figure 33: Attempts to prepare terminal alkyne 4.220	225
Figure 34: Model studies for epoxide/alkyne coupling reaction.....	227
Figure 35: Attempts to prepare hydroxy epoxide (<i>R,R</i>)-4.240.....	230
Figure 36: Attempts to prepare epoxide (<i>R,R</i>)-4.240 via Suzuki's route	232
Figure 37: Acetate and TBDPS protecting groups for C12 alcohol	237

Figure 38: Summary of protecting group compatibility with synthetic route to (+)-intrincenyne	242
Figure 39: Isolation and determination of target α,α' - <i>cis</i> -oxocene	244
Figure 40: ^1H - ^1H COSY NMR spectra of α,α' - <i>cis</i> -oxocene 4.270.....	248
Figure 41: ^1H - ^1H NOESY NMR spectra of α,α' - <i>cis</i> -oxocene 4.270.....	249
Figure 42: Possible three deminsional configuration of α,α' - <i>cis</i> -oxocene 4.270.....	249
Figure 43: Kim's ^1H NMR of cyanoketone 4.281.....	257
Figure 44: Lanier's ^1H NMR of cyanoketone 4.281.....	257

List of Schemes

Scheme 1: Experimental evidence establishing α,α' - <i>cis</i> -oxepanes as the more thermodynamically stable diastereomer	12
Scheme 2: Bartlett's iodocyclization/oxonium ion formation method to prepare <i>trans-syn-trans</i> 6,7-fused cyclic ethers	16
Scheme 3: Holmes' ring expansion method employing Baeyer–Villiger oxidation, Tebbe methylenation, and sterically controlled hydroboration/oxidation	18
Scheme 4: Evan's acyl radical cyclization method	19
Scheme 5: Furman's silyl Prins cyclization for oxepane synthesis	20
Scheme 6: Kumar's reductive cyclization for α,α' - <i>cis</i> -oxepane synthesis.....	22
Scheme 7: López-Herrera's carbenoid method for α,α' - <i>trans</i> -oxepane synthesis	23
Scheme 8: Sugita's ring expansion method to prepare α,α' - <i>trans</i> -4-oxepanones via cyclopropapyranone Lewis acid-generated 1,3-zwitterions.....	27
Scheme 9: Piccialli's RuO ₄ catalyzed oxidative and stereoselective preparation of α,α' - <i>trans</i> -oxepanes	30
Scheme 10: Organocatalyzed asymmetric synthesis of chiral benzopyranes.....	38
Scheme 11: One-pot organocatalytic synthesis of chiral 2,5-disubstituted cyclohex-2-enones	39
Scheme 12: Attempts to induce oxa-conjugate addition in the absence of a 1,3-dithiane moiety	44
Scheme 13: Summary of our lab's initial studies.....	46
Scheme 14: Preparation of α,α' - <i>trans</i> -oxepane 2.103A	49
Scheme 15: Chiral catalyst induced stereoselective switch and substrate controlled stereoselectivity for α,β -unsaturated aldehyde <i>ent</i> -2.102A.....	58
Scheme 16: Preparation and organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehyde 2.119	60

Scheme 17: Tandem organocatalyzed oxa-conjugate addition/ α -oxidation of α,β -unsaturated aldehyde <i>ent</i> -2.102A and attempts to further functionalize	65
Scheme 18: Preparation of 2.134 and attempts to cyclize under organocatalytic oxa-conjugate addition conditions.....	67
Scheme 19: Attempts to cyclize α,β -unsaturated methyl ester 2.137.....	68
Scheme 20: Preparation of 2.141 and attempts to cyclize under organocatalytic oxa-conjugate addition conditions.....	69
Scheme 21: Preparation of 2.154 and attempts to cyclize under organocatalytic oxa-conjugate addition conditions.....	71
Scheme 22: Preparation of 2.161 via Wittig route.....	73
Scheme 23: Coupling of alkyne 2.167 and iodide 2.165.....	75
Scheme 24: Alkyne/iodide coupling route for preparation of 2.160.....	76
Scheme 25: Martín's strategy for the synthesis of ciguatoxin's IJK ring framework.....	129
Scheme 26: De Voss's <i>O,S</i> -acetal ring expansion/ring contraction method for oxocene formation.....	131
Scheme 27: Li's ring expansion method for stereoselective oxocene synthesis	133
Scheme 28: Inspiration for Snyder's regio- and stereocontrolled brominium induced ring expansion method	134
Scheme 29: Murai's unanticipated ring contraction method for α,α' - <i>trans</i> -oxocene synthesis	138
Scheme 30: Preparation of simplified monoallylic diol 3.104 and reaction under gold(I)-catalyzed conditions	154
Scheme 31: Direct comparison of the reactivity of Δ^9 and Δ^{10} monoallylic diols 3.100 and 3.98 under optimized gold(I)-catalyzed alkoxylation conditions	166
Scheme 32: Determination of the absolute configuration of (+)-intrincenyne.....	181
Scheme 33: Synthesis of (+)-laurencin by Masamune	189

Scheme 34: Synthesis of (+)-laurencin by Murai.....	191
Scheme 35: Synthesis of 12 <i>epi</i> -(+)-laurencin by Holmes.....	194
Scheme 36: Synthesis of (+)-laurencin by Holmes.....	198
Scheme 37: Synthesis of (+)-laurencin by Overman.....	202
Scheme 38: Formal synthesis of laurencin by Palenzuela.....	204
Scheme 39: Formal synthesis of laurencin by Hoffmann.....	206
Scheme 40: Formal synthesis of laurencin by Crimmins.....	208
Scheme 41: Synthesis of (+)-laurencin by Crimmins.....	210
Scheme 42: Synthesis of (+)-laurencin by Fujiwara.....	213
Scheme 43: Synthesis of (+)-laurencin by Kim.....	215
Scheme 44: Formal synthesis of laurencin by Pansare.....	217
Scheme 45: Formal synthesis of laurencin by Hoffmann.....	219
Scheme 46: Initial retrosynthetic analysis of (+)-intriceyne.....	222
Scheme 47: Optimized route to terminal alkyne 4.220.....	226
Scheme 48: Preparation of terminal alkyne 4.236 and coupling with model epoxide 4.230.....	228
Scheme 49: Optimized route to epoxide 4.248 and coupling with alkyne 4.236.....	233
Scheme 50: Attempts to protect model homoallylic alcohol 4.237 with PMB group.....	235
Scheme 51: Optimized route to C12 PMBz protected alcohol 4.263.....	239
Scheme 52: Optimized route to C12 Bn protected alcohol 4.266.....	240
Scheme 53: Functionalization of α,α' - <i>cis</i> -oxocene 4.267.....	255
Scheme 54: Gold(I)-catalyzed alkoxylation of monoallylic alcohol 4.266 and further functionalization of α,α' - <i>cis</i> -oxocene 4.279.....	256

Scheme 55: Proposed route for final steps in the synthesis of (+)-intricenyne259

List of Abbreviations

BDSB	Et ₂ SBr·SbBrCl ₅
BF ₃ ·OEt ₂	boron trifluoride diethyl etherate
Bn	benzyl
br s	broad singlet
CM	cross metathesis
CNS	central nervous system
COSY	correlation spectroscopy
Cu(hfacac) ₂	copper(II) hexafluoroacetylacetonate hydrate
d	doublet
dd	doublet of doublet
ddd	doublet of doublet of doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPA	diisopropyl amine
DMAP	4-(<i>N,N</i> -dimethylamino)-pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
<i>ee</i>	enantiomeric excess
eq.	equivalent

Et ₃ N	trimethylamine
EtOAc	ethyl acetate
GCA	gold(I)-catalyzed alkoxylation
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
i.p.	intraperitoneal injection
IAEA	intramolecular amide enolate alkylation
LAH	lithium aluminium hydride
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
MeOH	methanol
min	minute
MnO ₂	manganese dioxide
MPM/PMB	<i>p</i> -methoxybenzyl
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOSEY	nuclear Overhauser effect spectroscopy
OTf	trifluoromethanesulfonate

pH	negative logarithm of hydrogen ion concentration
PMBz	<i>para</i> -methoxybenzoyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
PTSA	<i>p</i> -toluenesulfonic acid
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
RCM	ring closing metathesis
SEM	[2-(trimethylsilyl)ethoxy]methyl
S _N 2	bimolecular nucleophilic substitution
S _N 2'	bimolecular nucleophilic substitution with allylic rearrangement
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -BuLi	<i>tert</i> -butyllithium
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

TPS

tripropylsilyl

Ts

para-toluenesulphonyl

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1. Introduction

1.1 *Natural Product Synthesis*

Of the many applications for organic synthesis, the total synthesis of natural products has undeniably captured the attention of numerous synthetic chemists throughout history. Often times, the structural complexity of natural products allows exceptional demonstrations of current methods and even drives the development of new synthetic methodologies.¹ Furthermore, the selectivity with which nature constructs the vast array of natural products continues to peak interest and challenges synthetic chemists to pursue biomimetic total syntheses. Additionally, the potential therapeutic applications of these natural products has greatly impacted modern medicine with many pharmaceutical companies investing in natural product discovery programs.² However, the past several decades have resulted in a decline in natural product research in the industrial sector for a number of reasons, including the advent of new technologies (high throughput screening), financial factors and the belief that continued natural product elucidation would result in little to no new structural diversity.³

Justifiably, traditional natural product discovery programs have been hindered by several factors. Biological screening of natural product extracts eventually requires isolation of the single molecule responsible for the observed biological activity and often suffers from low isolatable amounts. Thus, further comprehensive biological investigations are limited. In these cases, total synthesis would be necessary to continue developing the

natural product as a marketable drug. The structural complexity of many natural products which has traditionally attracted the attention of synthetic chemists is often the very reason pharmaceutical companies have deemed them a financial risk. In a profit-driven setting, the time and cost required to elucidate and synthesize a natural product which may or may not become an FDA approved drug is too high. Additionally, the natural product itself is often a lead molecule and enhanced potency or minimization of off target effects is accomplished through structure–activity relationship (SAR) studies.

Despite these limitations, natural products have proven to be privileged molecular scaffolds for drug discovery because of their structural complexity. Continued natural product isolation and elucidation in the academic realm has also demonstrated continued discovery of novel molecular scaffolds with biological activity.⁴ Thus, natural products cannot be completely eliminated as a source of new therapeutics.⁵ Therefore, the scientific community has been challenged by the need to develop highly accurate technologies and instrumentation for structure elucidation. Additionally, synthetic chemists are confronted with a demand for time and cost efficient, as well as scalable, total syntheses. New methodologies are also emerging to address site selective functionalization of natural product entities or late stage intermediates to expedite SAR studies.⁶ Hence, natural product synthesis and methodologies for their construction continue to be relevant topics in synthetic chemistry.

1.2 Significance of Medium-Sized Cyclic Ether Synthesis

Cyclic hydrocarbons have a long standing history in organic chemistry. Their physical properties have been well characterized over the years, especially those of cyclohexane.⁷ The ring size can have significant impacts on reactivity and stability due to torsional, steric and angle strains of various three dimensional conformations.⁸ For example, cyclopropane derivatives can undergo electrophilic addition of bromine,⁹ a reaction typically observed with π -bonds. Heterocycles of certain sizes have also been studied; however investigations are often complicated by the nature of the heteroatom. The bond lengths are no longer equivalent, lone pairs of electrons are often present and the number of discrete conformations increases. Thus, the limited understanding of physical properties for certain heterocycles can hinder predictable method development for their construction and subsequent reactions. For example, there are only a handful of reports on the conformational analysis of medium-sized cyclic ethers (7 to 10 members) and in these cases, substituent effects are not investigated.¹⁰ Furthermore, investigations into cyclization rates for oxacycles indicate that this size range is particularly sluggish.¹¹ Thus, the feasibility of proposed methods for the construction of medium-sized cyclic ethers (MSCEs) are often unknown prior to experimental investigations. For these reasons, the synthesis of single oxygen-containing, medium-sized cyclic ethers has been a neglected topic until the discovery of their presence in natural products.

Naturally-occurring MSCEs are typically isolated from marine organisms and can have interesting biological activity. Marine organisms have and continue to provide an extensive collection of diverse metabolites for drug discovery.¹² A selection of naturally-occurring MSCEs with a wide range of complexities are shown in Figure 1. Of this class of natural products, the ladder-shaped polycyclic ethers such as gymnocin-A (**1.1**),¹³ maitotoxin (**1.7**)¹⁴ and brevetoxin B (**1.5**)¹⁵ have received a great deal of attention due to their structurally complex, fused 6-, 7- and 8-membered cyclic ether skeleton and high biological activities. For example, gymnocin-A has in vitro cytotoxicity against P388 murine leukemia cells with an IC₅₀ value of 1.3 μM.¹⁶ Maitotoxin and brevetoxin B are both highly potent neurotoxins and maitotoxin is believed to regulate Ca²⁺ channels.¹⁷ Many methods for MSCEs have emerged during synthetic studies of this natural product class.

A second sub-class of naturally-occurring MSCEs include the C₁₅ non-terpenoid, acetogenins. This class is represented in Figure 1 by (+)-chlorofucin (**1.6**),¹⁸ (+)-intricenyne (**1.8**),¹⁹ obtusenyne (**1.13**),²⁰ rogioloxepane A (**1.9**),²¹ (+)-poiteol (**1.14**)¹⁸ and isolaurefucin (**1.10**).²² Although this natural product class has a high number of MSCE-containing members, other scaffolds are included. In fact, more than 140 members belong to the C₁₅ non-terpenoid, acetogenin natural product class and most contain a 4- to 12-membered cyclic bromoether core.²³ Of the 140 members, approximately 50 contain MSCEs. The diversity within this natural product class is quite unique considering biogenesis studies indicate they are derived from common linear precursors, such as laurediol (**1.15**) which is

shown in Figure 3.²⁴ Therefore, several structural features are typically conserved in this natural product class. For example, all members are comprised of 15 carbon units and typically contain a cyclic ether core with either α,α' -*cis*- or α,α' -*trans*-disubstitution. One of the side chains typically contains either an enyne or allene functionality. Most members are monocyclic with a skeletal *cis*-alkene; however bicyclic members do exist and likely are biological derivatives of their monocyclic counterparts arising from nucleophilic addition to the skeletal olefin. Despite the relatively small number of carbon units, members often contain 4–7 stereocenters, making them densely functionalized. Although this class of natural products is not known for any remarkable biological activity, they have been utilized to demonstrate methodology for MSCE synthesis. In fact, the majority of current methods available for monocyclic MSCE synthesis have arisen because of this class of natural products.

Other naturally-occurring MSCEs which do not fall into either the ladder-shaped polycyclic ether or C₁₅ non-terpenoid acetogenin natural product classes include cladiellisin (**1.2**),²⁵ nakorone (**1.3**),²⁶ crellastatin A (**1.4**), microcladallene B (**1.12**)²⁷ and cucurbitacin S (**1.11**). Crellastatin A (**1.4**) is a nonsymmetric dimeric steroid with an α,α' -*trans*-oxepane as the central component that has no total syntheses to date. Crellastatin A exhibits in vitro cytotoxic activity against non-small cell lung cancer (NSCLC-N6) cells (IC₅₀ of 1.5 μ g/mL).²⁸ Cucurbitacin S (**1.11**) is one of few MSCE containing natural products which has been isolated from non-marine sources.²⁹ Cucurbitacin S was isolated from *Bryonia dioica*, a vine which is native to Central and Southern Europe. It should be

noted that **1.11** is suspected to be in a natural state of equilibrium with its hemiacetal derivative which arises from nucleophilic attack of the tertiary alcohol on the oxepane carbonyl. This is likely the reason biological studies have not been completed for **1.11** despite the fact that many cucurbitacins have biological applications.

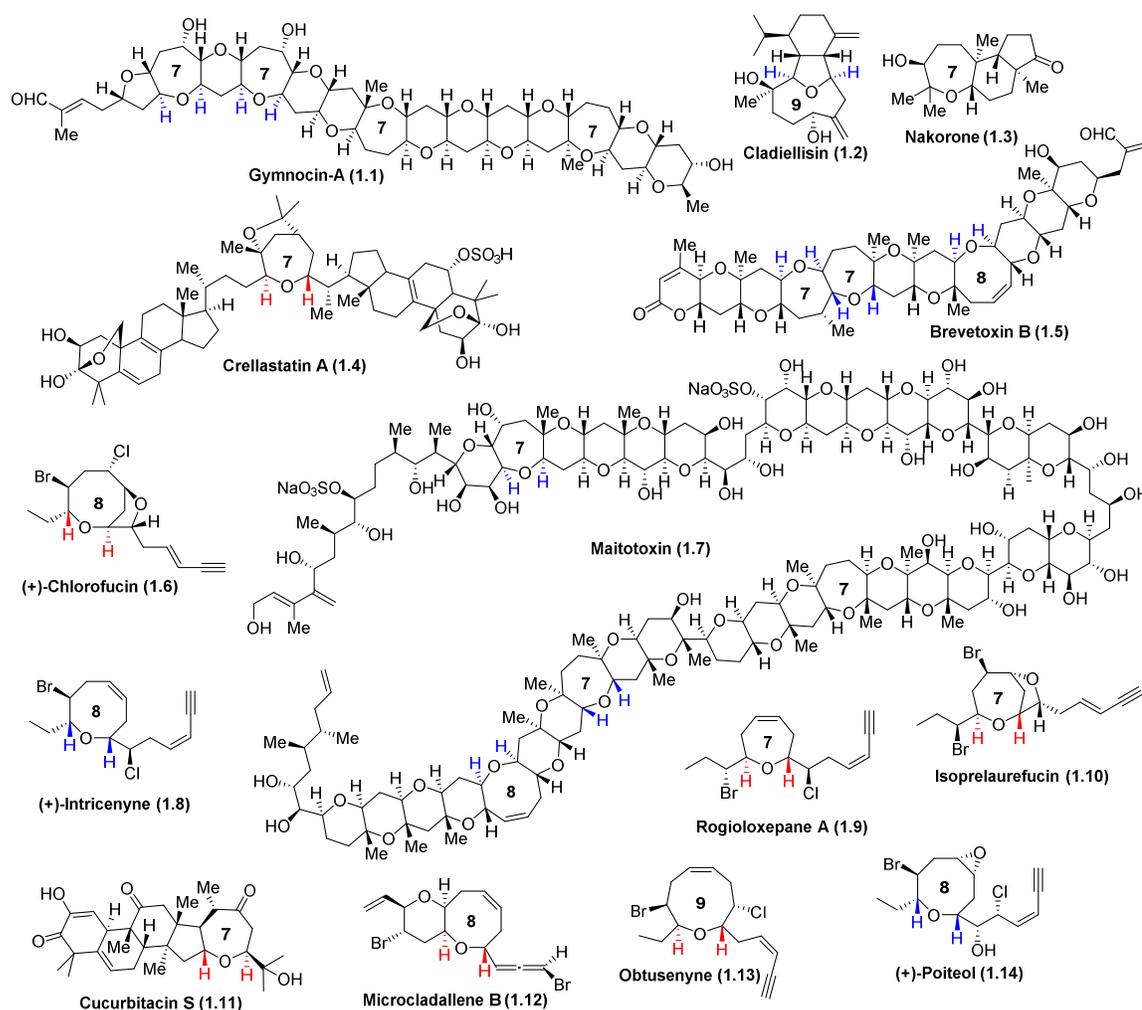


Figure 1: A selection of naturally occurring medium-sized cyclic ethers

1.3 Challenges of Medium-Sized Cyclic Ether Synthesis

Despite the growing interest in method development for monocyclic, single oxygen-containing MSCEs, there remain several limitations in the field. The stereoselective synthesis of either the α,α' -*cis*- or α,α' -*trans*-disubstituted cyclic ether is the greatest challenge. This challenge has been answered through various methods and many utilize functionalized linear ethers in which the relative stereochemistry of the α and α' positions is set prior to cyclization. Fewer methods are available which selectively introduce the relative stereochemistry in a single step during ring formation. Access to substrates for the synthesis of MSCEs often requires several synthetic steps; thus, easy preparation of starting materials is an important consideration when developing a new method. If an asymmetric route is desired, then access to chiral substrates is an added factor. Also, regioselectivity can sometimes be problematic as smaller ring sizes can form according to Baldwin's rules. Furthermore, the 8- and 9-membered cyclic ethers are more difficult to form via cyclization routes; thus, fewer methods for their preparation exist compared to 7-membered cyclic ethers. The generality and predictability of a method is often limited because few reports disclose a broad substrate scope. Specific examples of these limitations in the context of 7-membered cyclic ether synthesis are discussed in detail in chapter 2. A similar detailed discussion for 8-membered cyclic ethers is not provided in an effort to prevent repetitive discussion; however, it is important to realize that these limitations are even more extreme in this case.

1.4 General Approaches to the Synthesis of Medium-Sized Cyclic Ethers

Over the years, various bond disconnections and approaches for the construction of medium-sized cyclic ethers have been developed. Each method has its own set of beneficial and limiting aspects; thus, one superior approach does not exist. However, certain approaches have been utilized more often than others. Five general categories have been established for MSCE synthesis and they are represented in Figure 2.³⁰ C–C and C–O bond disconnections are likely the most apparent retrosynthetic approaches. Ring-expansion has also developed as a general category due to the general hypothesis that smaller ring systems are likely easier to form initially. Within this category, methods which utilize oxonium ion intermediates are common. More recently, complementary ring-contraction methods have also begun to appear in the literature with the same foundational thinking that certain ring sizes are more accessible than others. Metal-catalyzed annulations, often referred to as ring-closing metathesis, is arguably the most commonly used method due to the high efficiency and reliability of these well studied catalyst systems. Lastly, lactone formation and functionalization is an early approach that has lost momentum in recent years. This is likely due to the need to replace the carbonyl oxygen with a carbon-containing functional group and convert the sp^2 carbon to an asymmetric sp^3 carbon. Thus, multistep synthesis is required to install functionalities that can be more directly access by the methods within the other main general categories. These five general categories for MSCE synthesis will be referenced throughout the body of this dissertation.

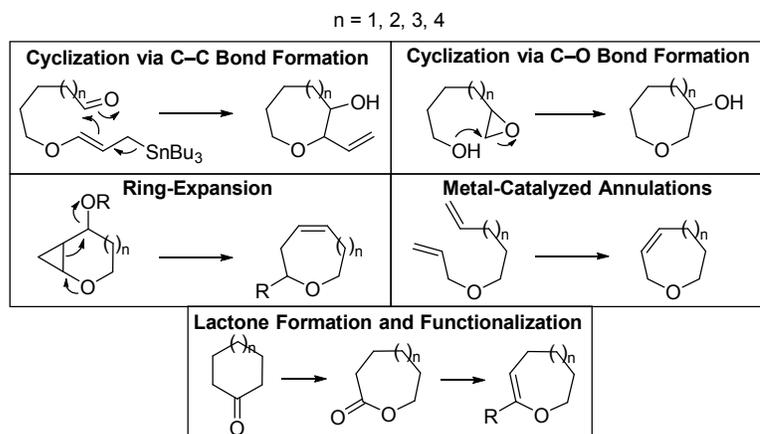


Figure 2: General methods for medium-sized cyclic ether synthesis

1.5 Numbering System for Entire Dissertation

Because the methodology presented herein is most directly applicable to the C₁₅ non-terpenoid, acetogenin natural product class and, indeed, we have made attempts to prepare (+)-intricenyne (**1.8**), the numbering system commonly adapted for this natural product class will be utilized throughout this document. As shown in Figure 3, (+)-intricenyne is numbered beginning from the terminal enyne resulting in numbers 7 and 13 being assigned to the flanking ether carbons (α and α'). It should be noted that a variety of other 7-, 8- and 9-membered cyclic ethers from this natural product class arise from different regioselective nucleophilic alcohol attacks at the Δ ₁₂ alkene. For example, 7-membered cyclic ethers can be obtained via C–O bond formation between carbon 12 and

the C7 alcohol. Similarly, the 9-membered cyclic ethers are derived by C–O bond formation between carbon 13 and the C6 alcohol.

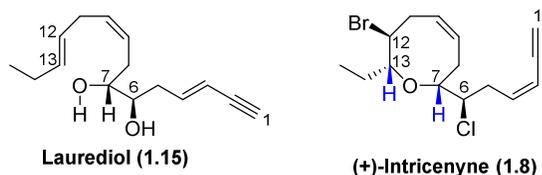


Figure 3: Numbering system for dissertation based on (+)-intricynyne

1.6 Summary

In this introduction chapter, the significance of the research presented in the following chapters has been outlined. Namely, single oxygen-containing medium-sized cyclic ethers is a class of molecules which continue to pose challenges for the synthetic chemist. Limited knowledge of physical properties for only the most basic structures is available and highly predictable and reliable methods for their synthesis has yet to be obtained. Furthermore, their occurrence in nature and potentially useful biological properties requires efficient synthetic access. The unique scaffolds found in these natural products add to the biodiversity that drug discovery programs deem essential. A brief description of the challenges associated with the synthesis of MCSEs and an overview of the general methods developed thus far have been provided. Lastly, a numbering system for this dissertation is included for clarity.

2. Stereoselective Synthesis of α,α' -*trans*-Oxepanes via an Organocatalytic Oxa-Conjugate Addition Promoted by the *gem*-Disubstituent Effect

2.1 Background

Seven-membered cyclic ethers (oxepanes) are found in a wide range of natural products, including ladder-shaped, polycyclic ether-containing marine natural products such as brevetoxin B and gymnocin A shown in Section 1.2. Another subclass of cyclic ether-containing marine natural products includes members such as rogioloxepane A (**2.1**)²¹, isoprelaurefucin (**2.2**)³¹, rogiolenyne A (**2.3**)³², and isolaurepinnacin (**2.4**)³³ (Figure 4). This group of C₁₅ non-terpenoid, marine natural products are characterized by a monocyclic oxepane or oxepine skeleton, either a *cis* or *trans* relationship between the two carbons flanking the ether bond (α and α' positions) and a C7 enyne-containing side chain. Members of this natural product class have received less attention from the synthetic community compared to the more complex ladder-shaped, polycyclic ether-containing marine natural products. Despite their lack of any known biological activity³⁴ and moderate complexity, monocyclic oxepane-containing natural products offer several attractive synthetic challenges. For instance, the absence of fused rings increases the conformational flexibility of any proposed acyclic substrate for either a C–C or C–O bond forming cyclization method. The C7 and C12 side chains, as well as substitution within the oxocycle skeleton, provide a platform for a diverse set of synthetic methods to be utilized within a single natural product synthesis. In addition to the challenges nature offers, 7-membered

cyclic ethers have inherent enthalpic and entropic barriers that make their preparation more difficult than their tetrahydropyran and tetrahydrofuran siblings.³⁵ Therefore, the number of methods for 7-membered cyclic ether synthesis have continued to increase.^{30, 36}

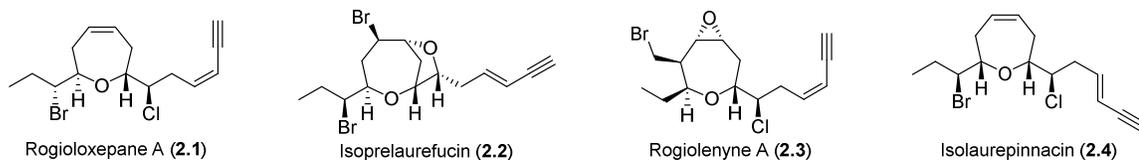
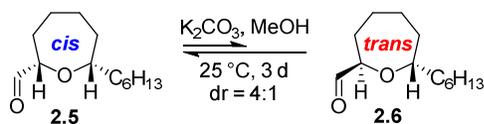


Figure 4: Examples of monocyclic C₁₅ non-terpenoid, marine natural products with a 7-membered cyclic ether skeleton

Although progress has been made in this area, several limitations still exist. One of the major challenges is to stereoselectively synthesize α,α' -*trans*-oxepanes, which are thermodynamically less stable than their α,α' -*cis* counterparts. Holmes and co-workers demonstrated this concept when they treated a pure sample of α,α' -*cis*-oxepane **2.5** with basic conditions for three days. Upon isolation they found that the sample contained a 4:1 mixture of α,α' -*cis*-oxepane **2.5** and α,α' -*trans*-oxepane **2.6** (Scheme 1).³⁷



Scheme 1: Experimental evidence establishing α,α' -*cis*-oxepanes as the more thermodynamically stable diastereomer

Another limitation of current methods to prepare oxepanes is the competitive formation of smaller ring sizes based on Baldwin's rules. For example, Tachibana and co-workers reported a significant amount of tetrahydrofuran formation while attempting to complete an intramolecular epoxide opening under basic conditions (Figure 5A).³⁸ Although the competing tetrahydropyran formation was still observed, the regioselectivity was reversed in their studies toward the preparation of the KLM ring fragment of ciguatoxin. The change in product distribution is likely caused by the conformational constraints introduced by the *trans* fused tetrahydrofuran or the electronic properties of the functionalities neighboring the internal epoxide. Similarly, the bicyclic acetal ring cleavage investigated by Fujiwara and co-workers also suffered from regioselectivity issues.³⁹ In their system, Lewis acid promoted cleavage and reductive hydride addition of **2.10A** gave a 74:26 mixture of oxepane and tetrahydropyran. Use of diastereomeric **2.10B** as the substrate nicely gave the target oxepane **2.11B** in high yield and regioselectivity (Figure 5B). Thus, conformational considerations appear to be a key factor when planning 7-*endo* cyclizations that have a potential competing 6-*exo* pathway.

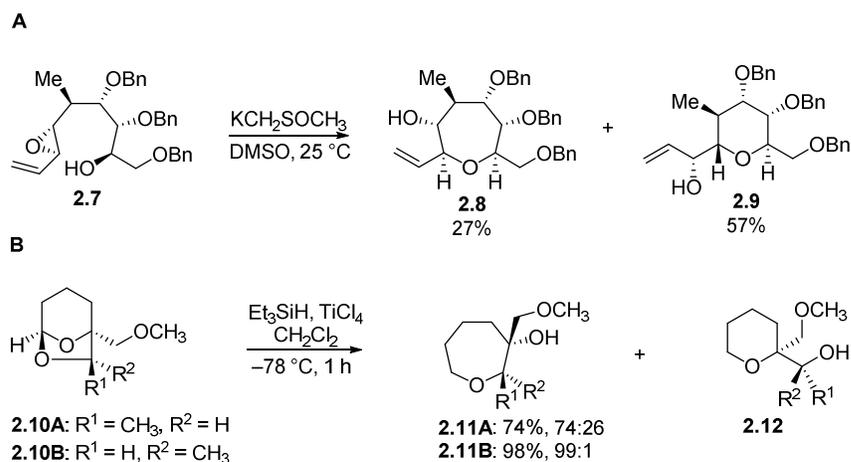


Figure 5: Regioselectivity issues in oxepane synthesis

(A) Tachibana's epoxide opening (B) Fujiwara's Lewis acid promoted cleavage and reductive hydride addition

Many current methods for oxepane synthesis also lack a broad substrate scope to demonstrate functional group tolerance or probe effects on reactivity and regio- or stereo-selectivity. Thus, few methods allow predictable application to new substrates, which would be useful for the synthetic community. Another limitation is the need to prepare substrates with preinstalled stereocenters. Often times, the strategy for oxepane synthesis is to cyclize linear ethers with predetermined chiral centers. Very few methods generate a new chiral center during the oxepane formation. Additionally, few catalytic methods are available with the exception of ring closing metathesis.

With these current limitations in mind, it was our aim to develop a method for the stereoselective synthesis of either α,α' -*cis*- or α,α' -*trans*-oxepanes. If initial testing was promising, an investigation of the substrate scope would be conducted. Should the method

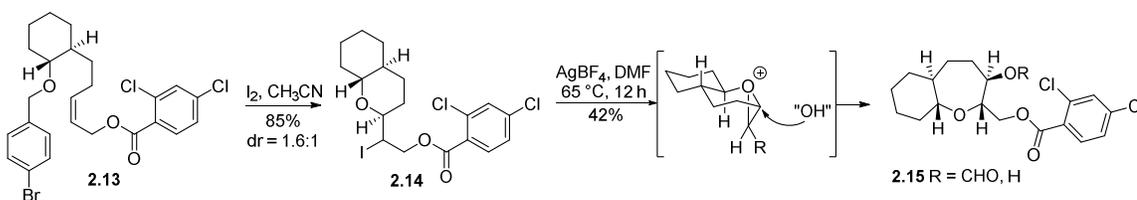
development be successful, we also aimed to demonstrate the method's utility in a natural product synthesis. Since the class of C₁₅ non-terpenoid, marine natural products was of interest to us, we wished to prepare functionalized monocyclic ethers that could be potential advanced intermediates in a formal or total synthesis.

Initially, it was not known whether stereoselective access to either the α,α' -*cis*- or α,α' -*trans*-oxepanes would be possible. Thus, it was imperative to have an understanding of current selective methods for both diastereomers. In the following sections, the more notable methods for stereoselective synthesis of either the α,α' -*cis*- or α,α' -*trans*-oxepanes will be discussed. Special attention will be given to installation of the α and α' chiral centers, bond disconnections for formation of the 7-membered cyclic ether and any governing factors for the reactivity or selectivity.

2.1.1 Stereoselective Synthesis of α,α' -*cis*-Oxepanes

One of the earliest examples of a stereoselective α,α' -*cis*-oxepane synthesis was reported by Bartlett and co-worker during their studies on construction of brevetoxins (Scheme 2).⁴⁰ Because members of the brevetoxin family contain *trans-syn-trans* fused polycyclic ethers, their goal was to develop an iterative method which would reliably build 6-, 7- and 8- membered polycyclic ethers with the correct configurations. Initially, model substrates containing (*Z*)-1,2-*trans*-alkenylcyclohexanols were employed to build 6,6- and 6,7-fused ring systems. From their studies on the construction of *trans-syn-trans* 6,6-fused rings, it was anticipated that analogous (*Z*)-1,2-*trans*-alkenylcyclohexanols would give

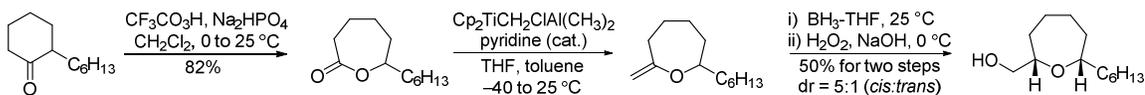
trans-anti-trans 6,7-fused rings upon treatment with I₂ in CH₃CN followed by solvolysis of the oxonium ion intermediate. Thus, a method to generate the less thermodynamically stable *trans-anti* 6,6-fused iodoether **2.14** was developed. Due to the energetics of the cyclization, a steric auxiliary was essential to push the equilibrium toward **2.14**. Therefore, standard iodocyclization of alkenyl benzyl ether **2.13** was completed giving **2.14** in slight excess of the *trans-syn* 6,6-fused iodoether. Of the steric auxiliaries tested, the 4-bromobenzyl group was found to give the highest diastereomeric ratio favoring **2.14**. Treatment of **2.14** with AgBF₄ promoted the oxonium ion formation and subsequent regioselective opening upon solvolysis to give the *trans-syn-trans* 6,7-fused cyclic ether **2.15** in 42% yield.



Scheme 2: Bartlett's iodocyclization/oxonium ion formation method to prepare *trans-syn-trans* 6,7-fused cyclic ethers

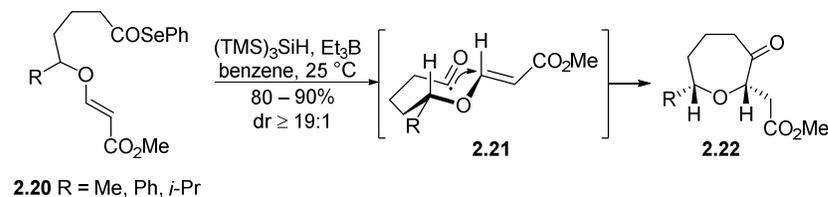
As demonstrated in Bartlett's iodocyclization/oxonium ion formation method, ring expansions are a common method to prepare 7-membered cyclic ethers since tetrahydropyrans are easier to access. Within this category, Baeyer–Villiger ring expansions followed by lactone functionalization are a traditional subclass as seen in Holmes's 1992 report described herein.³⁷ Holmes and co-workers proposed a Baeyer–

Villiger oxidation, Tebbe methylenation, and hydroboration/oxidation sequence to prepare MSCEs ranging in size from 7- to 9-membered rings. To begin their studies, racemic hexanone **2.16** was treated with trifluoroacetic acid in the presence of a phosphate buffer (Scheme 3). The Baeyer–Villiger ring expansion successfully gave the 7-membered lactone **2.17** in good yield. The Tebbe methylenation gave the target enol ether **2.18**, which was sensitive to hydrolytic cleavage. Thus, the hydroboration/oxidation was carried out promptly, giving the hydroxy α,α' -*cis*-oxepane **2.19** in 50% yield for two steps. The moderate yield was attributed to sensitivity of the enol ether **2.18**. Optimal yields required careful removal of any Lewis acids from the previous methylenation step and a low temperature during hydroboration/oxidation to prevent degradation of **2.18**. Although complete stereoselectivity was not observed, the moderate 5:1 diastereomeric ratio favoring hydroxy α,α' -*cis*-oxepane **2.19** was rationalized by a steric approach control during the hydroboration step. Interestingly, when the targets were 8-membered cyclic ethers, the diastereoselectivity improved to 8:1 – 14:1 (*cis:trans*) and use of a bulky borane reagent (disiamylborane) further improved the selectivity (120:1). It is worth noting that the diastereoselectivity was reversed in the case of the 9-membered enol ether, further supporting the argument that substrate conformation directs the facial hydroboration approach. It would have been worthwhile to test the hydroboration/oxidation sequence of enol ether **2.18** with disiamylborane to determine if any improvement in stereoselectivity could be made.



Scheme 3: Holmes' ring expansion method employing Baeyer–Villiger oxidation, Tebbe methylation, and sterically controlled hydroboration/oxidation

Among the C–C bond forming cyclizations for 7-membered cyclic ether synthesis, very few utilize radical based chemistry. Evans and co-workers proposed that an acyl radical could undergo addition to an intramolecular vinylogous carbonate for the construction of 5-, 6- and 7-membered cyclic ethers.⁴¹ After minor optimizations of the protocol developed for the 5- and 6-membered cyclic ethers, Evans was able to obtain high yields of oxepan-3-ones **2.22** in reliably high diastereoselectivity ($\geq 19:1$) favoring the α, α' -*cis* isomer in each case (Scheme 4). It was essential to maintain the reaction temperature at 25 °C to prevent decarbonylation of the acyl radical and subsequent alkyl radical cyclization to form tetrahydropyrans. This undesired reaction pathway was only observed in the case of the 7-membered cyclic ethers, indicating that the enthalpic and entropic barriers to cyclization were beginning to play a significant role. The otherwise regioselective exo cyclizations for 5-, 6- and 7-membered cyclic ethers was indicative of a nucleophilic acyl radical addition to the LUMO of the vinylogous carbonate. Intermediate **2.21** was proposed to explain the high diastereoselectivity. Evans and co-workers later used this method in an iterative fashion to construct the BC ring fragment of gamberic acids, another class of ladder-shaped polycyclic ethers.⁴²



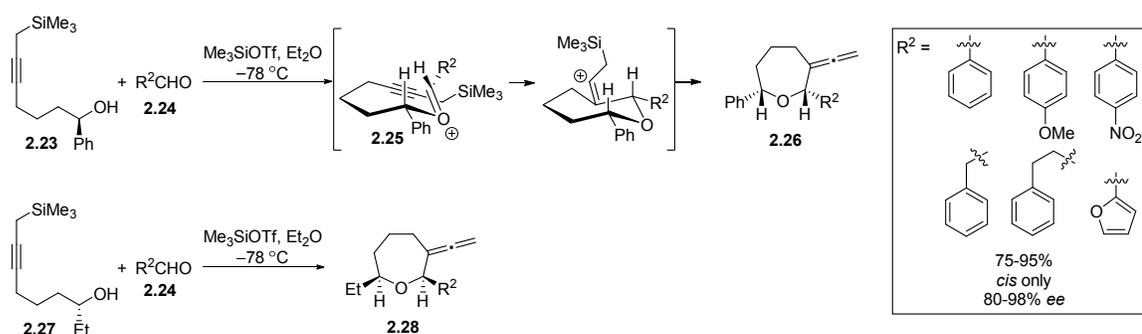
Scheme 4: Evan's acyl radical cyclization method

Furman and co-workers reported a unique C–C bond forming silyl-Prins cyclization for the preparation of α,α' -*cis*-oxepanes **2.26** and **2.28**.⁴³ The Prins reaction typically consists of an acid-catalyzed addition of an aldehyde to an alkene and can give a variety of products depending on the reaction conditions. Furman chose to use a propargylic silane functionality as the source of pi electrons. A tethered chiral secondary alcohol served to generate the necessary carbocation upon addition of TMSOTf and activate the aldehyde toward nucleophilic attack to generate intermediate **2.25**. Formation of the allene functionality completed the transformation giving α,α' -*cis*-oxepanes **2.26** and **2.28** in good to high yields (75-95%). Furthermore, the α,α' -*cis* isomer was the only observed product in all cases examine.

This example is one of few methods that have provided a significant substrate scope. Furman examined the relative bulkiness of the C12 substituent by testing both **2.23** and **2.27** (Scheme 5). The electronic effects of the aldehyde reagent were also examined, as well as the side chain length and type of aromatic ring. Notably, aldehyde **2.24** with R²

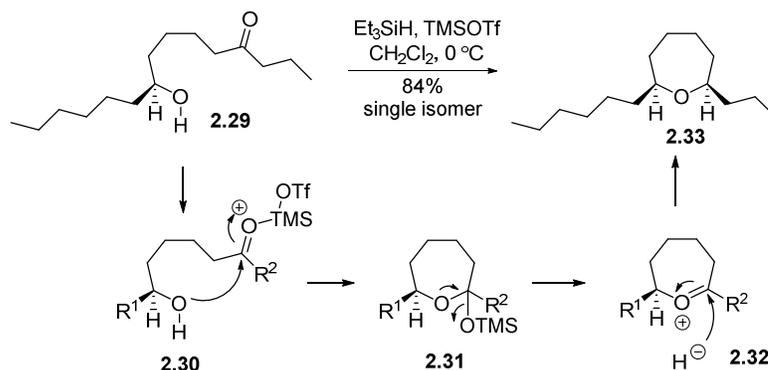
= *p*-NO₂Ph consistently gave the lowest yield when reacted with either secondary alcohol substrate **2.23** or **2.27**. These results are in agreement with the proposed mechanistic route in which an electron deficient aldehyde **2.24** would be expected to display a lower propensity to form the oxonium intermediate. The diastereoselectivity was proposed to arise from intermediate **2.25** in which R¹ and R² are opposite of each other, thus reducing steric interactions. The conserved high diastereoselectivity indicates that the reduced steric interactions in **2.25** plays a pivotal role even for moderately bulky substrates.

In the context of monocyclic, C₁₅ non-terpenoid natural products, one would be concerned with the ability to functionalize oxepanes **2.26** and **2.28**. Specifically, the C8 allene would need to be converted to a more useful functional handle. Furman and co-workers did in fact transform the allene functionality by subsection to ozonolysis conditions and selective hydride reductions to give C8 chiral alcohols. However, the C7 and C12 substituents examined do not have the potential to be functionalized into more reactive groups.



Scheme 5: Furman's silyl Prins cyclization for oxepane synthesis

An interesting C–O bond forming method for oxepane synthesis came from Kumar and co-workers attempts to prepare (+)-isolaurepan (**2.33**), the fully saturated skeleton of (+)-isolaurepinnacin (**2.4**).⁴⁴ The simplicity of their method which utilized linear hydroxy ketone **2.29** is, in part, responsible for the impressiveness with which the results invoke. Treatment of **2.29** with TMSOTf and Et₃SiH gave α,α' -*cis*-oxepane (**2.33**) as a single diastereomer in 84% yield (Scheme 6). The ketone was activated by TMSOTf for nucleophilic attack of the tethered secondary alcohol. Oxonium ion formation was prompted by the loss of the silyl ether and hydride addition selectively occurred from the axial approach via a twist chair conformation. The flexibility of **2.29** makes the yield and diastereoselectivity even more surprising. Kumar and co-workers also tested this method in their preparation of (–)-lauthisan, the fully saturated skeleton of 8-membered cyclic ether (+)-laurencin. Unfortunately, the yield of (–)-lauthisan was much lower (42%) compared to the yield for **2.33**, which is likely caused by the increased enthalpic and entropic barriers for preparation of 8-member cyclic ethers compared to oxepanes. It would be interesting to determine if similar reactivity and stereoselectivity could be obtained in more functionalized substrates which could potentially lead to one of the naturally occurring oxepanes.

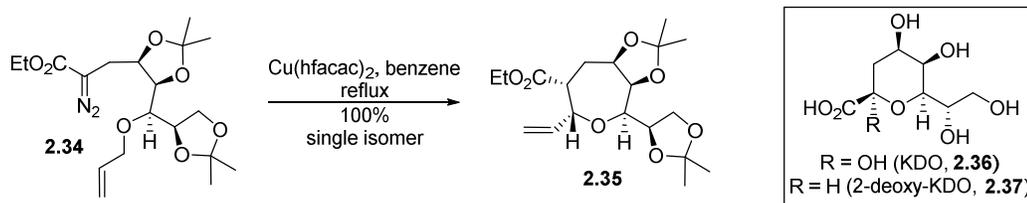


Scheme 6: Kumar's reductive cyclization for α,α' -*cis*-oxepane synthesis

2.1.2 Stereoselective Synthesis of α,α' -*trans*-Oxepanes

One interesting selective α,α' -*trans*-oxepane synthesis materialized from efforts to prepare biologically important sugar derivatives. López-Herrera and co-worker aimed to prepare analogs of 3-deoxy-D-*manno*-2-octulosonic acid, also known as KDO (**2.36**).⁴⁵ KDO (Scheme 7) is an essential component of the lipopolysaccharides contained in the outer membrane of Gram-negative bacteria. Ironically, the 2-deoxy-KDO analog (**2.37**) has been identified as a potent inhibitor of CMP-KDO synthetase, an enzyme required for incorporation of **2.36** into the bacteria's lipopolysaccharides. López-Herrera proposed a transition metal catalyzed insertion reaction using diazo compound **2.34** for the preparation of KDO analogs; however, they were aware that this method had several competing reaction pathways. The mechanistic pathway for synthesis of **2.35** involves C–H insertion into the highly reactive carbenoid species; whereas, the desired pathway is characterized by an oxonium ylide formation and sigmatropic rearrangement. Fortunately, they were able

to control the reactivity based on the nature of transition metal or solvent used. While Rh(II) catalysts favored tetrahydropyran formation, Cu(II) catalysts gave high yields of the 7-membered cyclic ether. Benzene was also found to be the optimal solvent for selectively obtaining the tetrahydropyran or oxepane, while CH₂Cl₂ gave a mixture of products. Thus, α,α' -*trans*-oxepane **2.35** was obtained quantitatively as a single isomer when treated the Cu(hfacac)₂ in refluxing benzene. It would be intriguing to test the cyclization on a substrate that did not have the 1,2-acetal group built into the carbon skeleton since its presence likely provides some conformational constraints that aid the process.



Scheme 7: López-Herrera's carbenoid method for α,α' -*trans*-oxepane synthesis

Fujiwara, Murai and co-workers reported a Lewis acid directing reductive or allylative cleavage of dioxabicyclo[3.2.1]octanes for selective oxepane formation.⁴⁶ They proposed that the C–O bond cleavage of bicyclic acetals such as **2.38** (Figure 6A) could be selective for the C12–O2 bond if a Lewis acid-chelating alkoxy group was positioned β to O2. In their initial studies using reductive cleavage conditions (TiCl₄, Et₃SiH), they found that the presence of a C7 methyl substituent was essential to obtain high selectivity for C12–O2 bond cleavage and thus, oxepane formation. Furthermore, the configuration of the

C7 methyl also had an effect on the ratio of oxepane to tetrahydropyran products. Use of a dioxabicyclo[3.2.1]octane that lacked a Lewis acid-chelating alkoxy group only gave the tetrahydropyran product. Thus, three factors were important for the exclusive formation of oxepanes.

A silyl allylative cleavage was then examined with dioxabicyclo[3.2.1]octane **2.41** which contained the key (*7S*)-methyl substituent and Lewis acid-chelating benzyl ether (Figure 6B). α,α' -*trans*-Oxepane **2.42** was obtained in 90% yield as a single isomer. In contrast, **2.43** with a (*7R*)-methyl substituent gave a mixture of products including a 7:3 ratio of oxepanes to tetrahydropyrans (Figure 6C). Interestingly, a 3.2:1 mixture of α,α' -*trans*- and α,α' -*cis*-oxepanes were obtained from dioxabicyclo[3.2.1]octane **2.43**. A rationale for the regioselectivity can be made from examination of structure **2.44** in which minimal bicyclic steric interactions are achieved in (*7S*)-**2.41**. The release of such strain in an analogous conformation of (*7R*)-**2.43** is likely driving force for tetrahydropyran formation. The cause of the high stereoselectivity observed with (*7S*)-**2.41** compared to (*7R*)-**2.43** is less obvious and was not commented on in the original publication.

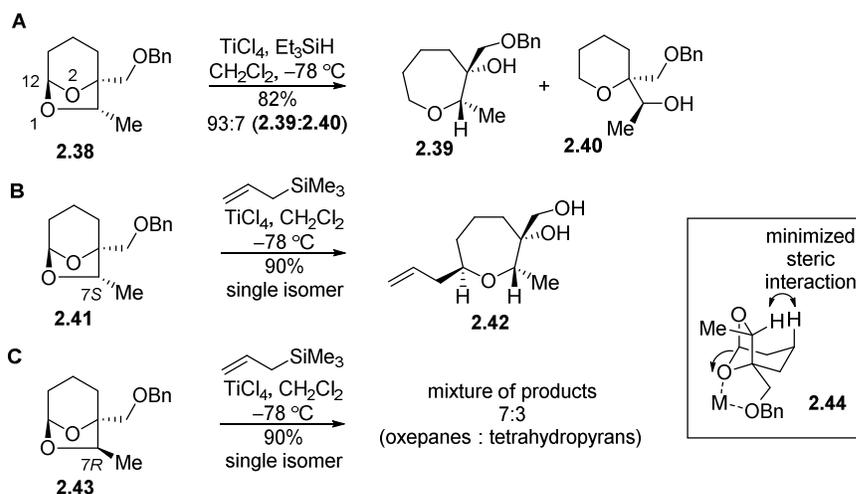


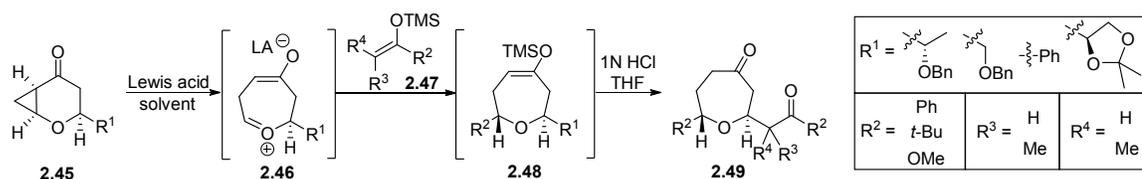
Figure 6: Murai's Lewis acid directing reductive or allylative cleavage of dioxabicyclo[3.2.1]octanes

Sugita and co-workers published a unique ring expansion method for the preparation of α, α' -*trans*-4-oxepanones via cyclopropapyranone Lewis acid-generated 1,3-zwitterions.⁴⁷ Their method relied on the observation that cyclopropanes **2.45** with oxygen donor and carbonyl acceptor substituents vicinal to the bridging carbons are equivalent to the ring-opened 1,3-zwitterion. Thus, simple treatment of **2.45** with a Lewis acid was proposed to access the 1,3-zwitterion and subsequent nucleophilic attack of silyl enol ether followed by an acidic workup would provide 4-oxepanones (Scheme 8). In fact, their hypothesis was correct.

Initial screening of Lewis acids revealed that $\text{BF}_3 \cdot \text{OEt}_2$ and TMSOTf served to provide either optimal yield or diastereoselectivity of the target 4-oxepanone **2.49** ($\text{R}^1 = \text{CH}_2\text{OBn}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3, \text{R}^4 = \text{H}$). A variety of cyclopropapyranones and silyl enol ethers were

used to determine the substrate scope of the method. Typically, use of $\text{BF}_3 \cdot \text{OEt}_2$ conditions gave moderate to good yields (64 – 85%); however, TMSOTf conditions gave higher diastereoselectivity (92:8 – 96:4 *trans:cis*) and lower yields (24 – 46%) of **2.49** when compared to $\text{BF}_3 \cdot \text{OEt}_2$ conditions. When fully substituted silyl enol ether ($\text{R}^2 = \text{OMe}$, $\text{R}^3, \text{R}^4 = \text{Me}$) was used as the nucleophile, neither $\text{BF}_3 \cdot \text{OEt}_2$ nor TMSOTf conditions gave optimal results. Instead, SnCl_4 had to be utilized as the Lewis acid in each of those cases often giving moderate yields (48 – 88%) and diastereoselectivities (68:32 – 81:19 *trans:cis*). The need to carefully select a Lewis acid based on substrate structure and sacrifice high diastereoselectivity for moderate to good yields are the major drawbacks of this method.

There still remains a lack of understanding regarding the factors which govern the stereoselectivity in this method. It is interesting to note that the 7-membered cyclic oxonium ion generated in this method gives the same diastereoselectivity as observed in Murai's Lewis acid directing allylative cleavage method.⁴⁶ Additionally, a similar Lewis-acid induced 7-membered cyclic oxonium ion intermediate in Kumar's reductive hydride method⁴⁴ showed similar facial preference for nucleophilic hydride addition, giving the α, α' -*cis*-oxepane **2.32**. Hence, it is likely that all three stereoselective methods are governed by the same principles and that Lewis acid induced 7-membered cyclic oxonium ions could be employed in a method to preferentially access either α, α' -*cis*- or α, α' -*trans*-oxepanes.



Scheme 8: Sugita's ring expansion method to prepare α,α' -*trans*-4-oxepanones via cyclopropylidene acyl ketone Lewis acid-generated 1,3-zwitterions

A common method for the construction of MSCEs is ring closing metathesis of chiral linear ethers. Since many of the MSCE-containing C_{15} non-terpenoid marine natural products contain an internal *cis* double bond, RCM has been used extensively to access members of this natural product class. Due to the ease and reliability of RCM, the key challenge then is to stereoselectively prepare either the desired α,α' -*cis*- or α,α' -*trans*-linear ether. Crimmins's and co-workers' total synthesis of rogioloxepane A (**2.1**) exemplifies this method nicely.⁴⁸

After constructing the left hemisphere of **2.1**, Crimmins diastereoselectively alkylated oxazolidinone glycolate **2.50** using non-chelating enolate conditions in the presence of allyl iodide (Figure 7A), a method which was developed earlier in his lab⁴⁹ based on Evan's previous asymmetric alkylations of *N*-acyl oxazolidones.⁵⁰ Crimmins found that allyl iodide reacted more readily than allyl bromide which was used in Evan's reported alkylations. It was also noted that excess allyl iodide and warming the reaction temperature to -40 °C were necessary to obtain optimal reactivity. The stereoselectivity of the alkylation was completely dictated by the chirality of the oxazolidinone auxiliary as

demonstrated when oxazolidinone glycolates **2.53** and **2.55**, differing only in the chirality of the auxiliary, was treated with standard alkylation conditions to give α,α' -*cis*- and α,α' -*trans*-dienes **2.54** and **2.56**, respectively (Figure 7B and 7C). With good yield and high diastereoselectivity for α,α' -*trans*-diene **2.51**, the key RCM was completed with 10 mol% Grubbs 1st generation catalyst. Advanced intermediate **2.52** was, thus, obtained in 95% yield and further transformed into rogioloxepane A (**2.1**).

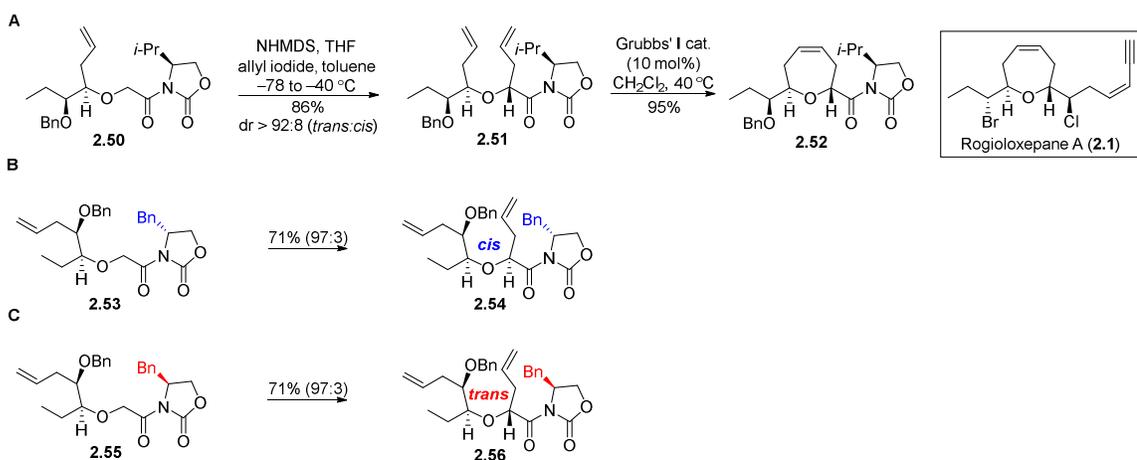
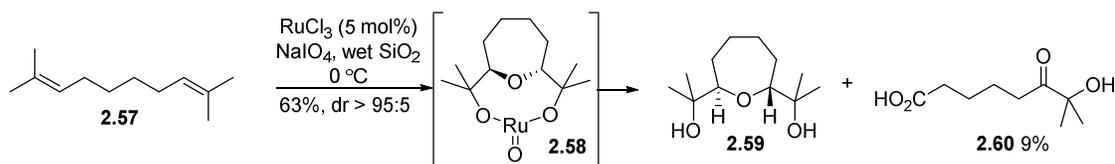


Figure 7: Crimmins' asymmetric alkylation/RCM method for α,α' -*trans*-oxepane synthesis

As a final example, Piccialli and co-workers reported a catalytic C–O bond forming cyclization of hydrocarbon **2.57** (Scheme 9).⁵¹ Previous reports of RuO₄ catalyzed oxidative and stereoselective formations of tetrahydrofurans and tetrahydropyrans prompted their investigation into applying similar chemistry to the preparation of

oxepanes. Initial testing using $\text{RuO}_2 \cdot \text{H}_2\text{O}$ as a precatalyst and NaIO_4 as a co-oxidant gave α, α' -*trans*-oxepane **2.59** in poor yield (26%). Changing the precatalyst to RuCl_3 and employing wet SiO_2 were sufficient alterations, giving **2.59** in high diastereoselectivity (>95:5) and in improved yield (63%). The authors attempted to use the method on two similar diene substrates without much success. In one case, no desired reactivity was observed under any attempted reaction conditions. The proposed catalytic pathway involves an initial [3+2] cycloaddition of RuO_4 to one of the two alkenes, a second intramolecular [3+2] cycloaddition occurs setting the α, α' -*trans* relationship as in **2.58** and hydrolysis releases oxepane **2.59** and low-valent Ru species for reoxidation. Despite the limited success of this method, it serves as a potential platform for further development. It is one of a few examples employing a double C–O bond forming method, thus installing the stereochemistry of both α and α' positions simultaneously. Additionally, the ruthenium oxidative mechanism is a catalytic process that differs from the traditional catalytic method (RCM) employed in the preparation of MSCEs, such as Crimmins' synthesis of rogioloxepane A shown in Figure 7. As mentioned, further improvement would be necessary prior to considering this method for the synthesis of oxepane-containing C_{15} non-terpenoid marine natural products. Specifically, the method is not enantioselective and the α and α' side chains are not easily amendable to further elaboration.



Scheme 9: Piccialli's RuO_4 catalyzed oxidative and stereoselective preparation of α,α' -*trans*-oxepanes

2.1.3 Oxa-Conjugate Addition as a Method for Oxacycle Synthesis

As mentioned in Section 2.1, our aim was to develop a method for the stereoselective synthesis of either α,α' -*cis*- or α,α' -*trans*-oxepanes. We wished to contribute to the current methods for stereoselective preparation of these molecules, at least in part, by addressing some of the unmet needs in the field. Specifically, there have been few stereoselective methods that disconnect the 7-membered cyclic ether at either of the C–O bonds, likely because it would require stereinduction in addition to the already challenging cyclization. Competing tetrahydropyran formation is another common issue, especially seen in Tachibana's epoxide opening by an intramolecular nucleophilic alcohol (Figure 5A, Section 2.1).³⁸ This regioselectivity issue could be eliminated by employing a reactive functionality that contains a single electrophilic carbon. Another requirement we wished to fulfill in our method was easy access to chiral substrates, thus allowing rapid construction of enantiomerically pure oxepanes for natural product synthesis. As part of our method development, we also aimed to complete a brief substrate scope and provide a rationale for any reactivity or stereoselectivity observed. Based on these requirements and

the previous literature discussed herein, the oxa-conjugate addition reaction was selected for our method development.

Although the parent Michael addition is a versatile, well developed C–C bond forming method typically characterized by high yields and stereoselectivity, the analogous conjugate addition of alcohols to α,β -unsaturated carbonyl compounds (oxa-conjugate addition reaction) has attracted less attention.⁵² Reasons for this include decreased reactivity of nucleophilic alcohols compared its carbanion counterparts in the Michael addition, reversibility of the reaction and a lack of stereocontrol. Despite these traditional drawbacks, the oxa-conjugate addition reaction has several advantages. With the development of organocatalysts, especially amine catalysts, improvements in the reactivity and stereoselectivity of the oxa-conjugate addition reaction have been accomplished. Surprisingly, the potential for the oxa-conjugate addition reaction as a method to prepare oxepanes and other MSCEs has not been fully investigated.

Of the handful of publications describing the synthesis of oxepanes via the oxa-conjugate addition reaction, the report by Martin and co-workers was the only example in which a monocyclic α,α' -disubstituted oxepane was prepared.⁵³ Their earlier work involving the synthesis of tetrahydropyrans from an intramolecular oxa-conjugate addition to α,β -unsaturated esters caused them to extend the methodology to oxepane synthesis. Initial testing with hydroxy α,β -unsaturated ester **2.61** under basic conditions did not yield any of the target oxepane (Figure 8A). Instead, the only observed product was the tetrahydropyran obtained from nucleophilic attack at the C8 position followed by benzoyl

migration. Installation of an internal *cis* double bond β to the alcohol was expected to promote the cyclization due to a favorable preorganization of the substrate conformation. During the desilylation of **2.62** with TBAF, the target oxepine **2.63** was obtained as a single isomer in 75% yield (Figure 8B). It was reasoned that the nucleophilic oxygen anion generated under TBAF conditions readily underwent the oxa-conjugate addition reaction. The stereoselectivity of the reaction was proposed to arise from the α,β -unsaturated ester geometry. To confirm, (*E*)- α,β -unsaturated ester **2.64** was prepared. Treatment of **2.64** with TBAF gave 7,8-*trans*-oxepine **2.65** as a single isomer (Figure 8C). The method was then extended to a diastereomeric mixture of **2.66** which contained a chiral secondary alcohol. In this case, the reaction proceeded without complication giving a mixture of oxepines **2.67** in 72% yield (Figure 8D). The stereoselectivity was also conserved giving the 7*S* configuration exclusively based on the double bond geometry. Furthermore, the C12 configuration did not have an effect on the reactivity as each diastereomer contributed to the product mixture in a ~1:1 ratio.

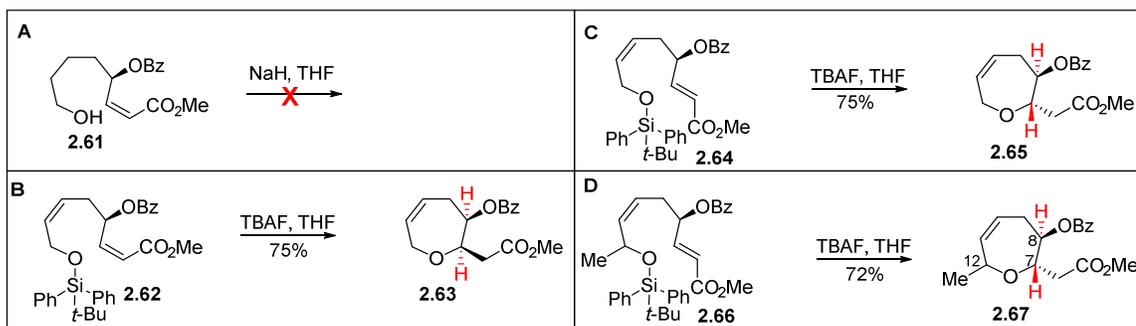


Figure 8: Martin's oxa-conjugate addition reaction

Fall and co-workers later reported a similar silyl deprotection/oxa-conjugate addition reaction for the synthesis of oxepanes.⁵⁴ In this case, an α,β -unsaturated 5-membered lactone tethered to a silyl ether **2.68** was treated with TBAF yielding the 5,7-fused polycyclic ether **2.69** (Figure 9). The 5-membered lactone is likely responsible for providing sufficient conformational preorganization to favor oxepane formation. Fall and co-workers did not report any attempts to cyclize a α,β -unsaturated 5-membered lactone tethered to a secondary silyl ether, which would have been relevant for our purposes.

Instead, attempts were made to prepare the analogous 8- and 9-membered cyclic ethers. Unfortunately, no reaction was observed in these cases, indicating that the 5-membered lactone did not provide enough structural bias for the synthesis of all MSCEs.^{54a} Fall and co-workers later extended this methodology to the synthesis of 5,7,7-fused polycyclic ethers since some naturally occurring ladder-shaped polycyclic ethers contain the 7,7-fused polycyclic ether motif.⁵⁵ When oxepane-containing 5-membered lactone **2.70**

was treated with TBAF, the target 5,7,7-fused polycyclic ether **2.71** was obtained in 25% yield as a single isomer. If the 1:1 diastereomeric mixture of **2.70** is taken into account, then 50% of the reactive diastereomer was converted to **2.71**. Similarly, oxepane-containing 5-membered lactone **2.72** gave 15% of **2.73** as a single isomer. From these examples, it can be concluded that the three existing stereocenters in both **2.70** and **2.72** have a significant impact on the reactivity.

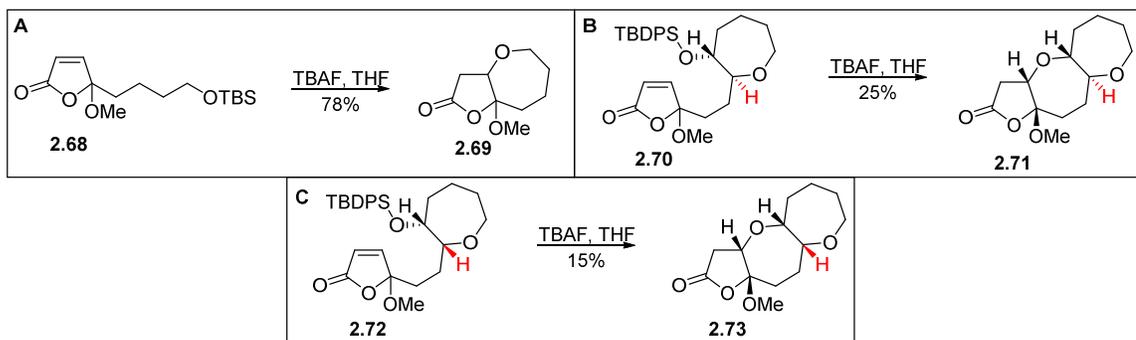


Figure 9: Fall's oxa-conjugate addition reaction

These reports exemplified the feasibility of an oxa-conjugate addition reaction for the preparation of α,α' -disubstituted oxepanes and prompted us to pursue the development of such a method. Martin and Fall's publications also suggested that several factors would be essential to develop a successful oxa-conjugate addition. Namely, a structural element to induce substrate preorganization would be required. Also, enhancement of the alcohol's nucleophilicity would likely be necessary to obtain high yields of the oxepane. There are

several aspects of the oxa-conjugate addition reaction method that Martin and Fall did not fully investigate. There was an obvious lack of a versatile oxa-conjugate addition reaction for the synthesis of a variety of α,α' -disubstituted oxepanes. Moreover, attempts to extend their methods to the synthesis of monocyclic oxepane-containing natural products were not made; thus, the applicability of an oxa-conjugate addition reaction to such natural products remained unanswered. Encouraged by these reports and keeping the current gaps in knowledge in mind, it was concluded that we could make a significant contribution to this field.

2.1.4 Organocatalytic Activation of α,β -Unsaturated Aldehydes

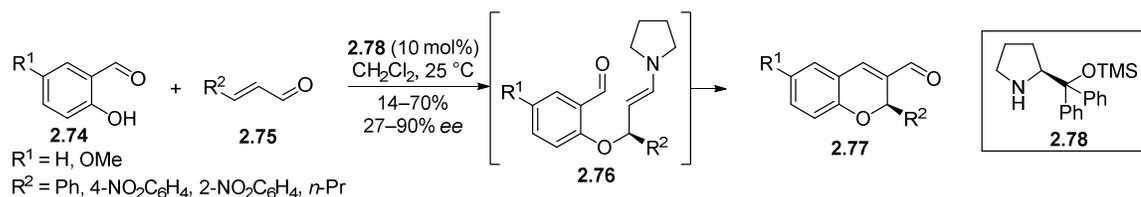
Since Martin and Fall both used silyl deprotection conditions to generate a nucleophilic oxygen anion, we suspected that the reactivity of our oxa-conjugate addition would need to be enhanced either by activating the nucleophilic alcohol or increasing the electrophilicity of the α,β -unsaturated carbonyl. With the recent development of organocatalysts and amine catalysts in particular, the later approach was chosen for our system due to the benefits associated with this class of catalysts (*vide infra*). Because our main goal was to develop a general method for the preparation of monocyclic oxepane-containing natural products, we chose the α,β -unsaturated aldehyde motif as our electrophilic α,β -unsaturated carbonyl. The C₁₅ non-terpenoid natural products shown in Figure 4 (Section 2.1) contain a methylene unit at C5 which is typically conserved throughout this natural product class. Thus, use of an α,β -unsaturated aldehyde motif would

generate an aldehyde upon treatment with oxa-conjugate addition reaction conditions. The aldehyde could be reduced to a primary alcohol or used directly in further elaborations of the C7 side chain. Use of organocatalysts to activate α,β -unsaturated aldehydes for β -functionalization has been documented and good to high levels of stereoselection and yields have been obtained.⁵⁶

The advent of organocatalysts, or the use of small organic molecules to catalyze organic transformations, occurred in the late 1990's with rapid development due to several advantages.⁵⁷ Compared to the asymmetric catalytic standards of that time (organometallic and enzymatic catalysts), organocatalysts represented a safe and relatively inexpensive alternative due to their fully organic nature and biological sources. Since early organocatalysts, such as L-proline, were biologically derived, large quantities of both enantiomers could be obtained. Additionally, their stability to aerobic & aqueous conditions and non-toxic properties made them easy to handle. Their modes of activation are often amenable to tandem (also termed domino or cascade) reactions resulting in the construction of multiple bond types without the need to isolate intermediates, change reaction conditions or add reagents.⁵⁸ Tandem reactions offer several attractive features including high atom economy, time saving elimination of protection/deprotection steps and minimal generation of chemical waste. However, tandem reactions must be carefully designed as the presence of multiple reaction pathways could lead to high yields of side products. The modes of activation induced by organocatalysts are also typically complementary to traditional organometallic catalysts,⁵⁹ resulting in the recent

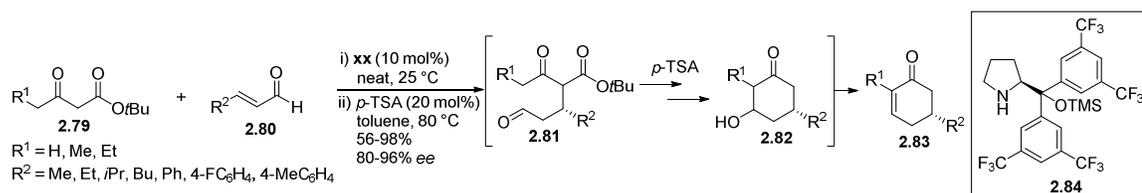
development of cooperative tandem or sequential multicatalyst systems which typically use organo and metallic catalysts.⁶⁰ The application of new methodology to the synthesis of pharmaceutically and biologically important molecules can be used as a gauge to determine its usefulness; in fact, organocatalytic methods have been used in innumerable syntheses of this type.⁶¹

Two examples of organocatalyzed β -functionalization of α,β -unsaturated aldehydes are shown in Schemes 10 and 11 to highlight the utility of organocatalyzed conjugate additions employing α,β -unsaturated aldehydes in other synthetic applications. In Scheme 10, α,β -unsaturated aldehyde **2.75** was treated with chiral amine catalyst **2.78** to induce iminium activation. A second substrate **2.74** was used as the nucleophilic source; thus, allowing oxa-conjugate addition to the iminium activated aldehyde intermediate generating acyclic intermediate **2.76**. The tethered aldehyde in **2.76** was positioned to allow enamine promoted C–C bond formation, leading to the final unsaturated tetrahydropyran product **2.77**. Unfortunately, the reaction was highly influenced by the electronic nature of the R groups resulting in a wide range of yields and enantiomeric excess. However, this example shows that alcohols can be used as nucleophilies in conjugate additions to α,β -unsaturated aldehydes which have been activated by amine catalysts. It also demonstrates the ability of the reactive enamine intermediate to undergo α -functionalization, a characteristic which will prove valuable in later discussions (*vide infra*).



Scheme 10: Organocatalyzed asymmetric synthesis of chiral benzopyranes

The example in Scheme 11 was chosen to demonstrate the good to high yields and stereoselectivity that can be obtained in organocatalytic conjugate additions. In this case, a β -ketoester was chosen as the nucleophile. Iminium activation of α,β -unsaturated aldehyde **2.80** resulted in Michael addition of β -ketoester **2.79** gave **2.81** as the first reaction intermediate. Addition of PTSA then catalyzed the remaining hydrolysis, decarbonylation and aldol reaction steps to provide cyclohexanone **2.82**. Lastly, dehydration gave cyclohexenones **2.83** in moderate to high yield (56–98%) and in good to high enantioselectivity (80–96%). It is noteworthy that the β -ketoesters did not require base addition to generate the reactive carbanion; instead, resonance access to the reactive species was sufficient. It is possible that the moderate yields in certain cases could be improved by employing a two step sequence in which base promoted anion generation followed by addition to premixed α,β -unsaturated aldehyde and amine catalyst was performed.



Scheme 11: One-pot organocatalytic synthesis of chiral 2,5-disubstituted cyclohex-2-enones

As mentioned earlier, enamine activation of aldehydes and α,β -unsaturated aldehydes (in tandem reactions) is a trait that could be used to our advantage. Our primary goal of developing a general method to access oxepane-containing natural products as shown in Figure 4, prompted us to consider the possibility of using iminium/enamine activation in a tandem fashion to produce α -functionalized oxepane aldehydes. Many of the natural products in our target class contain substitution at C6 with either an oxygen or chlorine atom. Developing a tandem organocatalytic oxa-conjugate addition/ α -functionalization method would be beneficial in this context as it would allow rapid construction of advanced intermediates in the syntheses of these natural products. Additionally, the formation of two new chiral centers would be accomplished, hopefully, in a stereoselective fashion.

A literature search of organocatalyzed α -functionalization of aldehydes revealed several reports for α -oxidation,⁶² α -chlorination,⁶³ and α -bromination.⁶⁴ Since methods exist to convert alcohols to halogens, we choose to focus our attention on developing a tandem organocatalyzed oxa-conjugate addition/ α -oxidation method for the preparation of

α -oxidized oxepane aldehydes. Three reports were found for the organocatalyzed α -oxidation of aldehydes which appeared simultaneously in 2003; thus, the methodology presented in each is very similar (Figure 10). For example, all three reports used L-proline as the organocatalyst and nitrosobenzene (PhNO) as the oxygen source. The range of yields and enantioselectivities were conserved throughout the publications despite having examined different substrates under slightly different conditions. The methods did differ in the catalyst loading, solvent and reaction time & temperature. Close examination of these reports indicate that the catalyst loading and reaction temperature were likely responsible for the differences in reaction rate but had little effect on the yield and stereoselectivity. Based on these three reports, we hypothesized that we could potentially apply this methodology to our oxepane system.

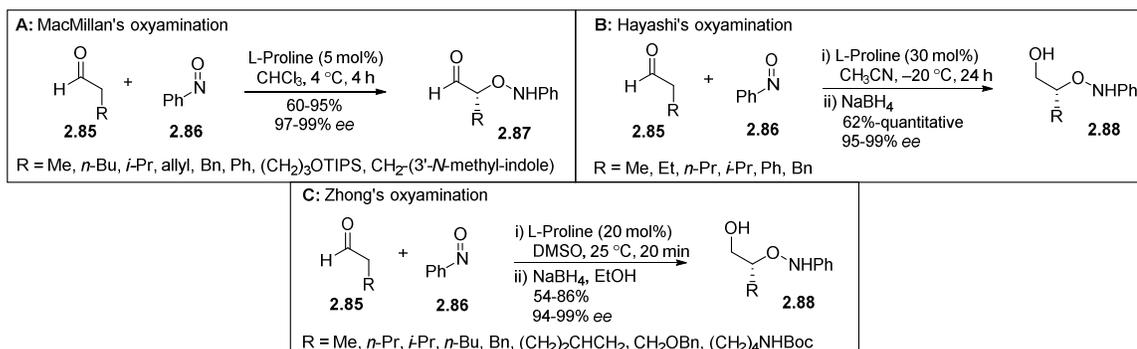


Figure 10: Organocatalyzed α -oxyaminations of aldehydes

2.1.5 Previous Studies

The intramolecular oxa-conjugate addition reaction has previously been studied in our lab for the stereoselective synthesis of α,α' -*cis*- and α,α' -*trans*-tetrahydropyrans⁶⁵ and has resulted in the application of this method to several natural product syntheses.⁶⁵⁻⁶⁶ A similar intramolecular aza-conjugate addition reaction was also developed by our lab for the synthesis of α,α' -*cis*- and α,α' -*trans*-piperidines and resulted in two natural product syntheses.⁶⁷ Therefore, key results from these publications that impacted the development of our organocatalytic oxa-conjugate addition for α,α' -disubstituted oxepane synthesis will be discussed. Initial results for this method obtained by other group members will also be reviewed here as they significantly impacted the experimental results discussed in Section 2.2.⁶⁸

As previously mentioned, we suspected that a structural element within the substrate would be essential for high yields of the target oxepanes. In fact, we knew from our prior work^{65b, 67} that a 1,3-dithiane moiety was essential to induce cyclization through the *gem*-disubstituent (Thorpe–Ingold) effect.⁶⁹ When monoallylic diol **2.89** with an unsubstituted skeleton was treated with MnO₂, the α,α' -*cis*-tetrahydropyran **2.90** was obtained as a mixture with **2.91** (3:1) and α,α' -*trans*-tetrahydropyran (7:1). When the monoallylic diol **2.89** containing a 1,3-dithiane moiety was subjected to the same conditions, a significant improvement was made in the product distribution giving only the α,α' -*cis*-tetrahydropyran **2.90** in 96% yield (Figure 11A). Similarly, amino α,β -unsaturated aldehyde **2.92** without a dithiane moiety was treated with organocatalyst **2.78** and BzOH the α,α' -*cis*-piperidine

2.93 was obtained as the major product (dr = 11:1); however, the yield was low (<15%). When the dithiane moiety was installed and **2.92** was treated with **2.78**, the α,α' -*cis*-piperidine **2.93** was obtained as the major product (dr = 11:1) in 92% yield (Figure 11B). It should be noted that the tosyl-protected amino α,β -unsaturated alcohols only underwent oxidation of the α,β -unsaturated alcohol when treated with MnO₂ due to the poor nucleophilicity of sulfonamide. It was necessary to activate the α,β -unsaturated aldehyde with a secondary amine catalyst to induce aza-conjugate addition. Hence, the 1,3-dithiane was also chosen as the structural element responsible for substrate preorganization in the development of our oxepane synthesis method.

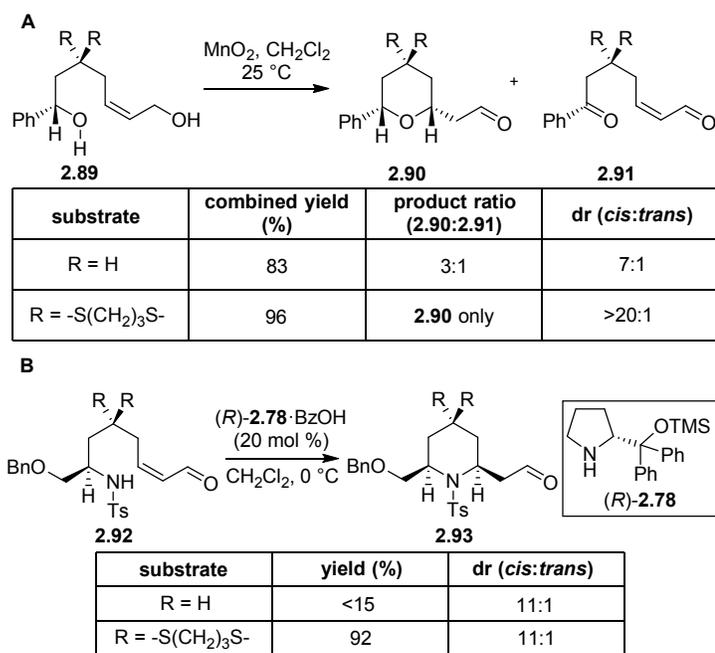
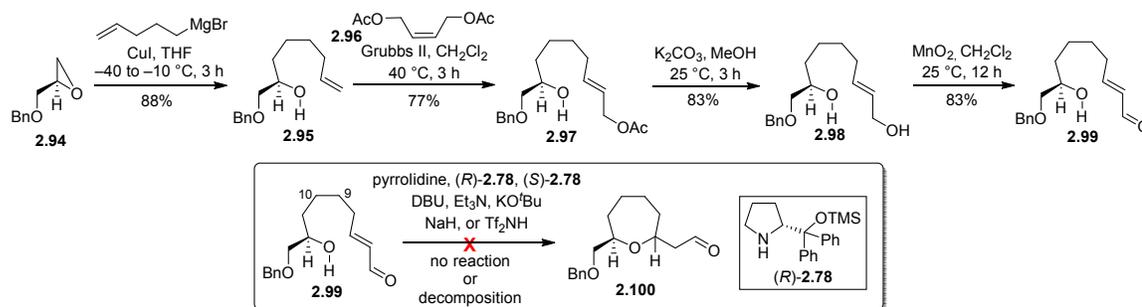


Figure 11: Importance of the 1,3-dithiane moiety in intramolecular conjugate additions

Initially, members of our lab prepared monoallylic diol **2.98** and attempted both the tandem allylic alcohol oxidation/oxa-conjugate addition reaction and base or organocatalyzed oxa-conjugate addition (Scheme 12). To synthesize **2.98**, (*S*)-benzyl glycidol ether (**2.94**) was subjected to a copper mediated nucleophilic addition giving hydroxy alkene **2.95** in 88% yield. Cross metathesis with diacetate **2.96** using Grubbs's 2nd generation catalyst gave the protected allylic alcohol **2.97**. Deacetylation provided monoallylic alcohol **2.98**, which was treated with MnO₂. As expected, only the α,β -unsaturated aldehyde **2.99** was obtained. In the absence of a 1,3-dithiane moiety, **2.99** could not be cyclized to oxepane **2.100**. Use of various basic or organocatalytic conditions to

enhance the alcohol nucleophilicity or α,β -unsaturated aldehyde electrophilicity resulted in either decomposition of the substrate or no reaction. Thus, installation of the 1,3-dithiane moiety would be essential for cyclization to occur.



Scheme 12: Attempts to induce oxa-conjugate addition in the absence of a 1,3-dithiane moiety

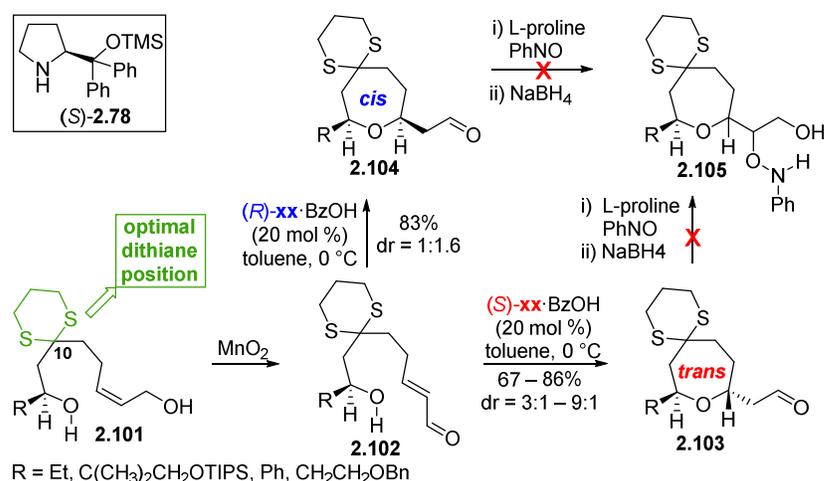
Unlike the 6-membered oxygen and nitrogen analogs, the optimal location for the dithiane moiety in the carbon skeleton was not obvious. Typically, the *gem*-disubstituent effect is greatest when the *gem*-disubstituent is located 180° from the site of cyclization. In the case of 7-membered rings, a *gem*-disubstituent could be positioned at either C9 or C10. It was unclear at the time which position would induce a substrate conformation favorable for oxa-conjugate addition; additionally, the feasibility of a tandem allylic oxidation/oxa-conjugate addition aided by the *gem*-disubstituent effect was unknown.

Monoallylic alcohols containing either a C9 or C10 1,3-dithiane were prepared in a similar manner as described in Section 2.2.1 and extensive cyclization studies were

completed. From our lab's early studies, it was concluded that allylic oxidation with MnO₂ could only produce the α,β -unsaturated aldehydes (Scheme 13). Fortunately, the proposed iminium activation did in fact give the α,α' -disubstituted oxepanes in moderate to good yield but in typically low diastereoselectivity. Interestingly, the diastereoselectivity could be switched to favor either the α,α' -*cis*- or α,α' -*trans*-oxepanes **2.104** and **2.103** depending on the configuration of the chiral amine catalyst. The optimization studies revealed chiral amines (*S*)- and (*R*)-**2.78** as the organocatalysts of choice, toluene as the preferred solvent and 0 °C as the best temperature. Also, positioning the dithiane moiety at C10 gave higher yields of the target oxepanes.

When the substrate scope was complete, variable results were obtained. Of most concern was the wide range of diastereoselectivities for the α,α' -*trans*-oxepanes **2.103** (3:1 to 9:1). Moreover, the diastereoselectivity of specific reaction conditions using the same substrate varied from trial to trail indicating some inconsistency in an important unidentified variable. Efforts were also made in our lab to develop an organocatalytic α -oxidation of oxepane aldehydes using conditions separately reported by MacMillan, Zhong, and Hayashi.⁶² Unfortunately, the target α -oxidized oxepane alcohol **2.105** could not be obtained using L-Proline and PhNO. To demonstrate the applicability of this method in the context of natural product synthesis, our lab prepared (–)-isolaurepan, a fully saturated analog of (+)-isolaurepinnacin (**2.4**). The synthesis was successfully completed; however, elaboration of the oxepane aldehyde **2.104** was completed via Wittig reaction to extend the C7 side chain and Raney Ni hydrogenation of the alkene and dithiane units.

Although appropriate for the synthesis of (–)-isolaurepan, this method of removing the dithiane moiety would not be amendable to syntheses of the natural products shown in Figure 4 since an internal *cis* double bond is typically present. A method to convert the dithiane moiety to a ketone or other functional handle would be necessary if natural product synthesis was to be pursued.



Scheme 13: Summary of our lab's initial studies

2.1.6 Summary of Background

In this section, a brief description of the importance of stereoselective oxepane synthesis has been provided. The challenges associated with oxepane synthesis have been described in detail and several examples of stereoselective α,α' -*cis*- and α,α' -*trans*-oxepanes have been reviewed. The organocatalyzed oxa-conjugate addition for the synthesis of

oxepanes has been proposed. A discussion of previous reports disclosing use of the oxa-conjugate addition for preparation of oxepanes has been given. An introduction to organocatalysis has been provided detailing the benefits of this catalysis class and its ability induce iminium activation of α,β -unsaturated aldehydes. Furthermore, enamine activation via organocatalysis is possible and can be employed to α -functionalize aldehydes. It has been proposed that the iminium/enamine catalyst activation mode could be used to develop a tandem organocatalyzed oxa-conjugate addition/ α -oxidation. Our lab's efforts toward these goals have been summarized and areas in need of improvement have been identified. The next sections will describe my efforts to address the limitations of our organocatalyzed oxa-conjugate addition which had been encountered in our lab's preliminary studies. Specifically, it was my aim to 1) determine the cause of the variable diastereoselectivities and optimize conditions, 2) attempt and potentially optimize the tandem organocatalytic oxa-conjugate addition/ α -oxidation and 3) develop general strategies to elaborate the oxepane aldehydes **2.103** into advanced intermediates for natural product syntheses.

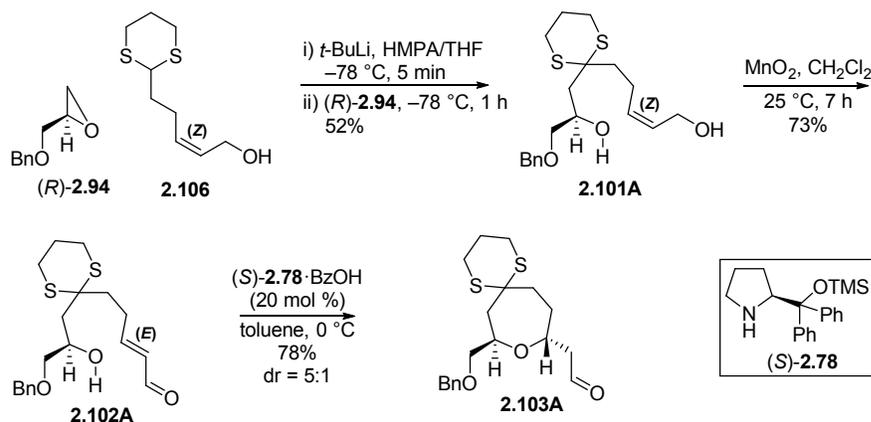
2.2 Results and Discussion

2.2.1 Optimization of Organocatalyzed Oxa-Conjugate Addition Conditions

Based on our lab's previous studies, it was suspected that the variable diastereoselectivities might be due to a retro oxa-conjugate addition which would eventually establish a thermodynamic equilibrium between the α,α' -*cis*- and α,α' -*trans*-oxepanes.

Thus, my initial task was to confirm that an equilibrium did exist between the two diastereomers. If the hypothesis was correct, then it would be necessary to develop a method to monitor the formation of both diastereomers *in situ*. Monitoring the reaction in this way would allow more insight to the dynamics of the reaction and optimization of the reaction conditions could be conducted in a more reliable manner. To address this aim, it was first necessary to prepare a substrate with which to complete the experiments.

To prepare dithiane-containing hydroxy α,β -unsaturated aldehyde **2.102**, known monosubstituted dithiane **2.106** was lithiated and treated with (*R*)-benzyl glycidol ether (**2.94**). The resulting monoallylic diol **2.101** was obtained in 52% yield. As previously observed, treatment of **2.101** with MnO₂ gave only the α,β -unsaturated aldehyde **2.102**. During the oxidation, the (*Z*)-alkene was isomerized to the (*E*)-alkene which was consistent with the results previously obtained in our lab. Upon treatment of α,β -unsaturated aldehyde **2.102** with 20 mol% (*S*)-**2.78** a mixture of oxepanes **2.103** (5:1 *trans:cis*) was obtained in 78% yield. Although the yield was consistent with our previous results, the diastereoselectivity had dropped significantly (9:1 *trans:cis*). To determine if an equilibrium existed between the α,α' -*cis*- and α,α' -*trans*-oxepanes, the mixture of oxepanes (5:1 *trans:cis*) was resubmitted to identical organocatalytic conditions. Isolation of the oxepane mixture after 24 hours showed that the diastereoselectivity had decreased to 1.2:1 (*trans:cis*), confirming that a retro oxa-conjugate addition and subsequent cyclization was occurring over time.



Scheme 14: Preparation of α,α' -*trans*-oxepane **2.103A**

Several spectroscopic methods, including HPLC, LC/MS, GC/MS and ^1H NMR, were initially tested to monitor the formation of both α,α' -*cis*- and α,α' -*trans*-oxepanes **2.104** and **2.103** during the organocatalyzed oxa-conjugate addition reaction. HPLC or LC/MS were not acceptable methods since baseline separation of the diastereomers could not be achieved. Interestingly, when α,β -unsaturated aldehyde **2.102A** was injected into a GC/MS, spontaneous cyclization occurred giving a small percentage of the oxepane. Although this did not render a reliable method, it indicates that heating the organocatalyzed oxa-conjugate addition reaction could provide access to high diastereoselectivities of the more thermodynamically stable α,α' -*cis*-oxepanes. Proton NMR proved to be the best method for monitoring the formation of α,α' -*cis*-**2.104** and α,α' -*trans*-**2.103** for several reasons. Primarily, base line separated peaks characteristic of each diastereomer and the starting α,β -unsaturated aldehyde could be distinguished. Another benefit was the ability

to regulate the sample temperature. Many NMR instruments have a temperature control element, allowing reactions to be completed in the NMR tube while acquiring spectra at variable temperatures. Since the cyclization was being conducted at 0 °C, it was essential to maintain the sample temperature at 0 °C to prevent any thermodynamic shift in the equilibrium prior to spectral acquisition. Use of HPLC or LC/MS, even if baseline separation could be obtained, would have required slight warming of the aliquoted sample prior to injection. Additionally, “snap shoots” of the reaction mixture could be obtained within a matter of seconds, permitting spectra to be obtained every 1-2 minutes if desired.

Therefore, α,β -unsaturated aldehyde *ent*-**2.102A** was dissolved in deuterated toluene and treated with (*R*)-**2.78** and BzOH. While maintaining the temperature at 0 °C, ¹H NMR spectra were obtained every 15 minutes for the three hours (Figure 12). This series of spectra showed that the diastereomeric ratio fluctuated between 5:1 and 7:1 (*trans*:*cis*) and that the substrate was nearly consumed at 1.5 hours. Since the diastereomeric ratio did not change significantly in the first three hours, spectra were acquired at the 4 and 24 hour time points. At 4 h, the diastereomeric ratio began to decrease to 4.5:1 (*trans*:*cis*) and continued to decrease over the remaining reaction time until a 1:1 mixture of diastereomers was observed at 24 h. It was also noted that a small amount of the substrate remained present throughout the reaction. This experiment not only confirmed the presence of a reaction equilibrium, but also showed that higher diastereoselectivities could be obtained at earlier time points. Previously, the reaction time had not been specified and were typically carried out “overnight”, likely because consumption of the substrate was not

observed on TLC. This kinetic study showed that the previous satisfactory yields could be preserved while increasing the diastereoselectivity simply by quenching the reaction earlier.

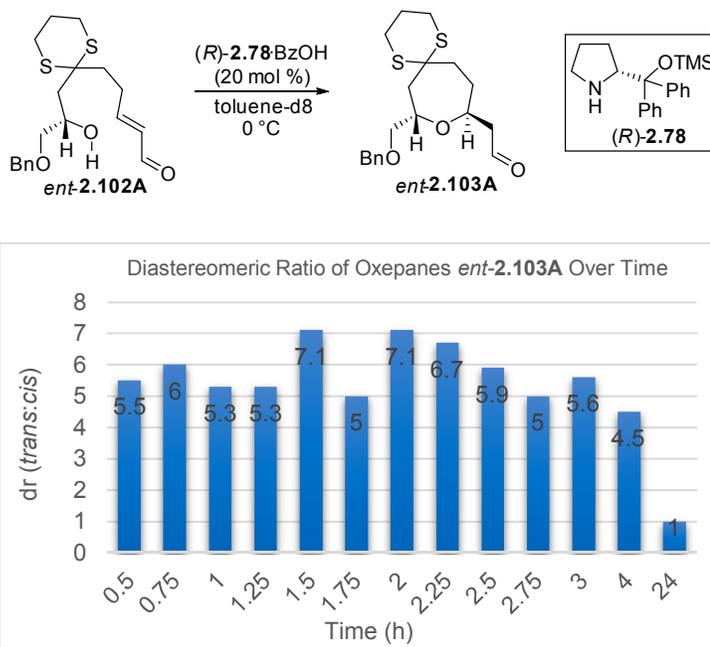
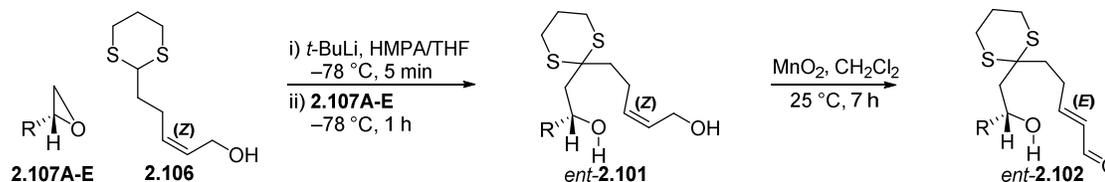


Figure 12: ¹H NMR kinetic study for the organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehyde *ent*-2.102A

At the time, it was unclear whether these results would be conserved throughout the substrate scope. Hence, several α,β -unsaturated aldehydes *ent*-2.102B-E were prepared via epoxide/dithiane coupling and allylic alcohol oxidation. Yields for each of these reactions are shown in Table 1. Similar ¹H NMR kinetic studies were completed for each of the α,β -unsaturated aldehydes *ent*-2.102B-E using (R)-amine catalyst 2.78. The data

from these experiments are summarized in Figure 13. Data from the first ^1H NMR kinetic study using *ent*-**2.102A** is included for comparison. From these experiments, we concluded that the highest diastereomeric ratio for each substrate was obtained at early reaction times and that the ratio deteriorated over the 24 hour period typically reaching ratios of 2:1 to 1:1 (*trans:cis*). It was also noted that the majority of the substrate was consumed within 1–1.5 h with a small portion of unreacted starting material remaining throughout the entire 24 h period. Thus, it was recommended that the oxa-conjugate addition reactions stir for 1.5 hours prior to quenching to obtain optimal yields and diastereoselectivities. It should be noted that *ent*-**2.102B** had an earlier optimal reaction time of one hour with near consumption of substrate and a diastereomeric ratio of 8.3:1 (*trans:cis*). However, consistency was desired for the substrate scope to allow direct comparison of isolated yields and diastereomeric ratios.

Table 1: Preparation of α,β -unsaturated aldehydes *ent*-2.102A-E



entry	R	yield of 2.101 (%)	yield of 2.102 (%)
1	CH ₂ OBn	63	74
2	Et	70	78
3	Ph	48	75
4	C(CH ₃) ₂ CH ₂ OBn	62	83
5	CH(<i>R</i>)-OPMB)CH ₂ OBn	49	76

Each of the α,β -unsaturated aldehydes *ent*-2.102A-E were treated with (*R*)-amine catalyst **2.78** and the oxa-conjugate addition reactions were stirred for 1.5 hours prior to quenching. Several trials indicated that isolation of the oxepane aldehydes *ent*-2.103A-E was not trivial. Often times, the yield suffered; thus, a reductive workup using NaBH₄ was required. However, ¹H NMR of the crude oxepane alcohols **2.110A-E** was not conducive to calculating the diastereomeric ratio since characteristic peaks in the ¹H NMR of the crude oxepane aldehydes *ent*-2.103A-E were no longer distinguishable. Therefore, it was necessary to complete two sets of experiments per substrate. In the first set of experiments, the crude oxepane aldehydes *ent*-2.103A-E were analyzed by ¹H NMR to calculate a diastereomeric ratio (Table 2). In the second experiment, the oxa-conjugate addition reaction was diluted with EtOH and treated with NaBH₄. Standard aqueous workup and

column chromatography gave a mixture of oxepane alcohols **2.110A-E** to determine the isolated yields.

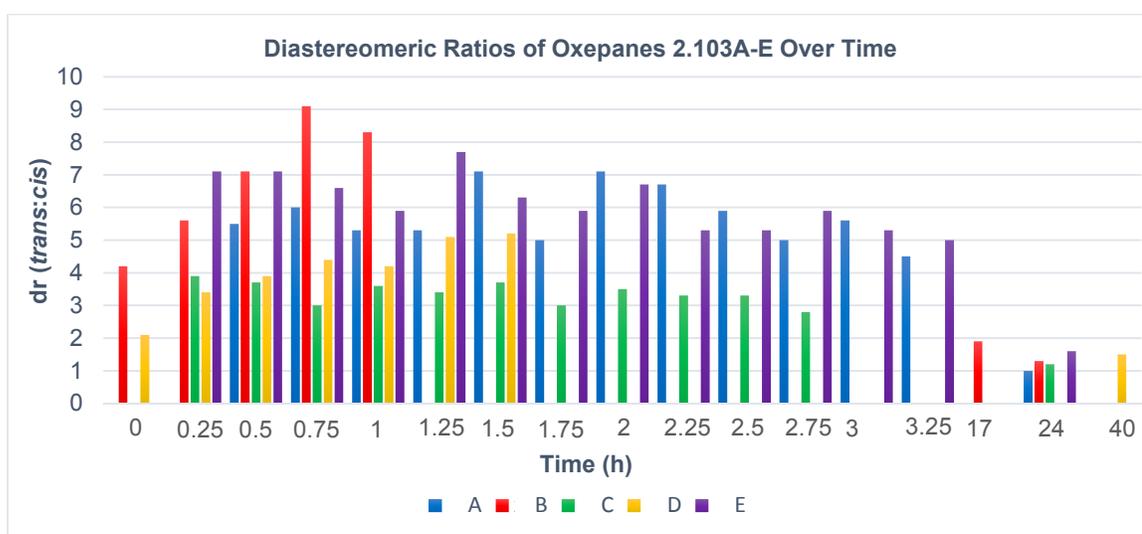
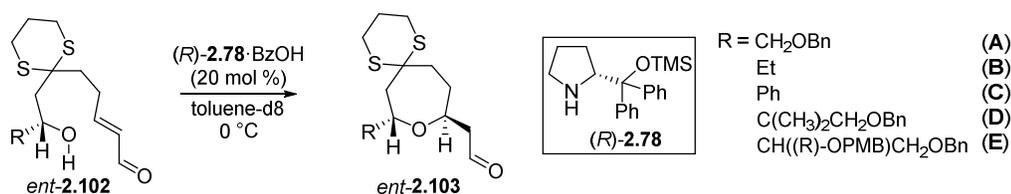
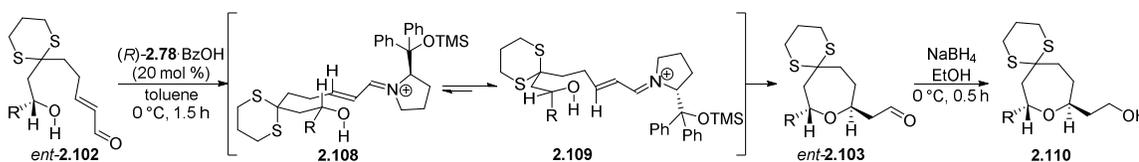


Figure 13: ^1H NMR kinetic study for the organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehydes *ent*-**2.102A-E** with (*R*)-amine catalyst **2.78**

The yields for oxepane alcohols **2.110A-E** were moderate to good (56 – 87%). The lowest yielding substrate was *ent*-**2.102C**. This result was not surprising as our ^1H NMR kinetic study for *ent*-**2.102C** showed a larger amount of unreacted substrate at 1.5 hours compared to other substrates. The diastereoselectivities ranged from 6:1 to 20:1 (*trans*:*cis*)

with higher selectivities being obtained for bulkier R groups (Table 2, entries 4 & 5). The stereoselectivity for the less thermodynamically stable α,α' -*trans*-oxepanes can be rationalized by the transition state equilibrium shown above Table 2. Based on the current understanding of pyrrolidine-catalyzed β -functionalization of α,β -unsaturated aldehydes,^{56a} the iminium intermediate is expected to sterically direct nucleophilic approach from the less hindered Si face as in **2.109**.

Table 2: Substrate scope for the organocatalyzed oxa-conjugate addition reaction



entry	R	yield (%) ^a	dr ^b
1	CH ₂ OBn	67	8:1
2	Et	87	6:1
3	Ph	56	6:1
4	C(CH ₃) ₂ CH ₂ OBn	82	17:1
5	CH((<i>R</i>)-OPMB)CH ₂ OBn	64	20:1

^aCombined yield of the isolated α,α' -*trans*- and α,α' -*cis*-oxepane alcohols after NaBH₄-reduction of the corresponding oxepane aldehydes. ^bThe diastereomeric ratio (α,α' -*trans*/ α,α' -*cis*) was determined by integration of relevant ¹H NMR spectroscopic signals of the crude oxepane aldehydes.

The success of the ¹H NMR kinetic studies prompted us to complete similar studies for the mismatched α,β -unsaturated aldehydes *ent*-**2.102A-E** and (*S*)-amine catalyst **2.78** which had already been shown to give the α,α' -*cis*-oxepanes as the major diastereomer.

Our aim was to determine if improved diastereoselectivities could be obtained by simply quenching the cyclizations at early reaction times. Thus, α,β -unsaturated aldehydes *ent*-**2.102A-E** was dissolved in toluene- d_8 and treated with (*S*)-amine catalyst **2.78**. While maintaining the temperature at 0 °C, ^1H NMR spectra were obtained every 15 minutes. The data obtained from these experiments are shown in Figure xx. The ^1H NMR kinetic studies with *ent*-**2.102A-E** and (*S*)-**2.78** revealed that the diastereomeric ratios were often low and ranged from (1:4 to 1:1 *trans:cis*) and did not change significantly over time. Because the diastereomeric switch was not completely shifted to match the ratios for the matched substrate and catalyst systems, it was concluded that the α,β -unsaturated aldehydes *ent*-**2.102A-E** did in fact have an inherent preference for formation of the α,α' -*trans*-oxepanes. This conclusion was confirmed with certainty when duplicate trials of the ^1H NMR kinetic studies with *ent*-**2.102D** and (*S*)-**2.78** revealed that the α,α' -*trans*-oxepane **2.103D** was the major diastereomer despite using the amine catalyst expected to yield the α,α' -*cis*-oxepane as the major stereoisomer.

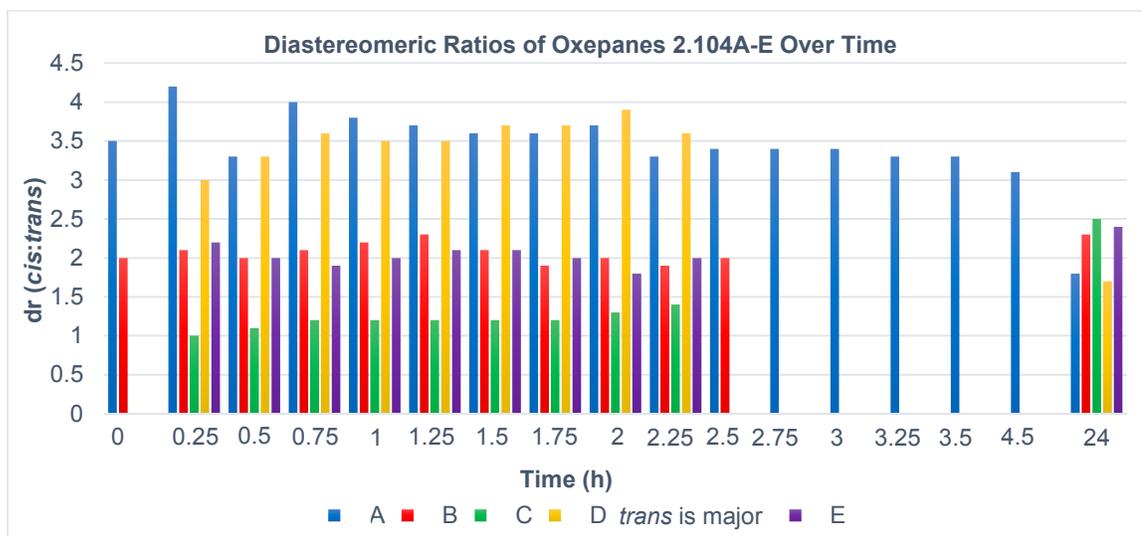
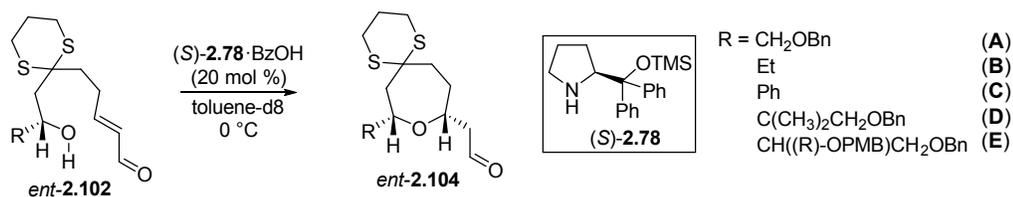
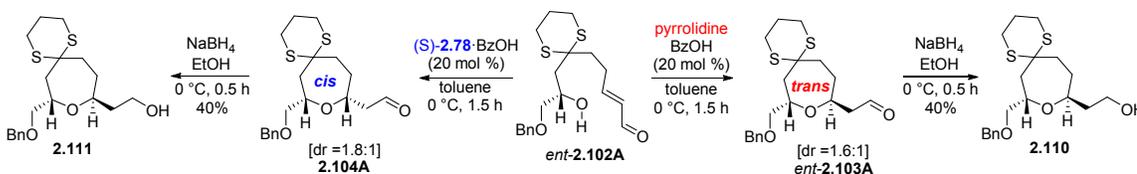


Figure 14: ^1H NMR kinetic study for the organocatalyzed oxa-conjugate addition of α,β -unsaturated aldehydes *ent*-2.102A-E with (*S*)-amine catalyst 2.78

For publication purposes, the conclusion that α,β -unsaturated aldehydes *ent*-2.102A-E exhibit substrate controlled stereoselectivity was demonstrated by subjecting *ent*-2.102A to an achiral amine catalyst (pyrrolidine) as shown in Scheme 15. After 1.5 hours, the reaction mixture was quenched and a 1.6:1 (*trans*:*cis*) mixture of oxepane aldehydes were obtained. Because the diastereomeric ratios obtained from the mismatched kinetic experiments shown in Figure 14 were low, additional experiments to obtain isolated yields and diastereomeric ratios were not completed. To demonstrate the chiral amine

induced stereoselective switch, an isolated yield and diastereomeric ratio was obtained for *ent*-**2.102** using the mismatched (*S*)-amine catalyst **2.78** (Scheme 15). When *ent*-**2.102A** was treated with (*S*)-**2.78**, the oxepane alcohol mixture **2.111** was obtained in 40% yield and the crude oxepane aldehyde mixture *ent*-**2.104A** gave a diastereomeric ratio of 1:1.8 (*trans*:*cis*).



Scheme 15: Chiral catalyst induced stereoselective switch and substrate controlled stereoselectivity for α,β -unsaturated aldehyde *ent*-2.102A****

Although it had already been determined by members of our lab that positioning the dithiane group at C10 gave optimal results, it became necessary for us to repeat and verify those experiments in light of the kinetic studies. To prepare α,β -unsaturated aldehyde **2.119** with dithiane positioned at C9, known chiral alcohol (**2.112**) was protected with TBS and subjected to ozonolysis conditions followed by a reductive work up (Scheme 16). The primary alcohol **2.114** was obtained in 91% for two steps. Alcohol **2.114** was then converted to the iodide **2.115** in 93% yield. Iodide **2.115** was then coupled with known dithiane (**2.116**) via generation of the lithium ion and S_N2 displacement of the iodide in **2.115**. Silyl deprotection and allylic alcohol oxidation gave α,β -unsaturated aldehyde **2.118**

without double bond isomerization. When α,β -unsaturated aldehyde **2.118** was treated with (*R*)-**2.78** in toluene at 0 °C for 20 h, only 19% of α,α' -*trans*-oxepane **2.120** (dr = 7:1) was obtained. The decrease in yield was significant compared to the yield obtained for α,α' -*trans*-oxepane *ent*-**2.103A** (67%) containing a dithiane moiety at C10. This result was consistent with our lab's previous studies and can be explained by observations of decomposition, a significant amount of unreacted substrate and formation of unidentified side products. Despite the low yield, the diastereoselectivity was comparable to that obtained for α,α' -*trans*-oxepane **2.103A** (dr = 8:1). This result was interesting since the oxa-conjugate addition of *ent*-**2.102A** had been stirred for 20 hours, a reaction time that would have given little to no diastereoselectivity for *ent*-**2.103A**. Therefore, a ¹H NMR kinetic study was completed for the oxa-conjugate addition of **2.119** using (*R*)-**2.78**. The data obtained from this experiment was expected to provide an explanation for the observed diastereoselectivity and low yield and allow a more informed comparison to be made with cyclization of *ent*-**2.102A**.

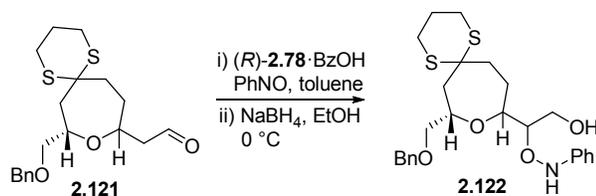
substrate's decreased ability to form the α,α' -*cis*-oxepane. Thus, it can be reasoned that the substrate conformation after iminium ion formation is unlike that of **2.109** and is not energetically favorable toward cyclization pathways.

2.2.2 Development of the Tandem Organocatalytic Oxa-Conjugate Addition/ α -Oxidation Reaction

Having met the challenges posed by the first aim, our attention was redirected to developing the tandem organocatalyzed oxa-conjugate addition/ α -oxidation reaction. Initially, diastereomeric mixtures of oxepane aldehyde **2.121** were treated with (*R*)-amine catalyst **2.78** and PhNO under various conditions (Table 3). Because the aldehydes are not easily isolated in optimal yield, the reaction mixture was diluted with EtOH and treated with NaBH₄. As a first attempt, the optimized solvent, catalyst loading, and temperature from our organocatalyzed oxa-conjugate addition reaction were used, along with 1.1 eq of PhNO (entry 1). Upon addition of PhNO, the reaction mixture gradually became green in color. As Zhong and co-workers reported, this color change is typical and should eventually become orange in color once PhNO is consumed.^{62a} However, TLC analysis revealed a significant amount of decomposition over time and the reaction never changed colors from green to orange. Thus, the desired product **2.122** was not formed under these conditions. Because the solvents (DMSO, CHCl₃, and CH₃CN) used in the literature organocatalyzed oxyaminations⁶² were polar, it was hypothesized that PhNO was not being fully dissolved in our first attempt using toluene as the only solvent. Therefore, PhNO was dissolved in

small amount of DMSO as a co-solvent prior to addition to the reaction mixture containing oxepane **2.121** and (*R*)-amine catalyst **2.78** (entry 2). It was ensured that PhNO was fully dissolved in DMSO prior to addition. Although the substrate had not been consumed at 4.5 h, a new product formed on TLC which required isolation and identification. The product was confirmed to be α -oxyaminated **2.122** by ^1H NMR and mass spectroscopy; additionally, **2.122** was obtained as a single isomer. Increasing the initial reaction temperature to 25 °C increased the isolated yield to 42%. However, warming the reaction to 90 °C over 5.5 hours did not have any effect on the yield (entry 4). As shown in entry 5, maintaining the temperature at 0 °C while increasing the catalyst loading to 40 mol% of (*R*)-amine catalyst **2.78** displayed the same improvement in yield that was observed in entry 3. Using a higher catalyst loading while maintaining the temperature at 0 °C was preferred since our aim was to develop a tandem reaction with the organocatalyzed oxa-conjugate addition reaction. As a last attempt to improve the stepwise formation of **2.122**, the equivalents of PhNO were increased (entry 6); however, no improvement was observed. With these preliminary results in hand, we could attempt the tandem organocatalyzed oxa-conjugate addition/ α -oxidation reaction using α,β -unsaturated aldehyde *ent*-**2.102A**.

Table 3: Optimization of the organocatalyzed α -oxidation of oxepane aldehyde **2.121**

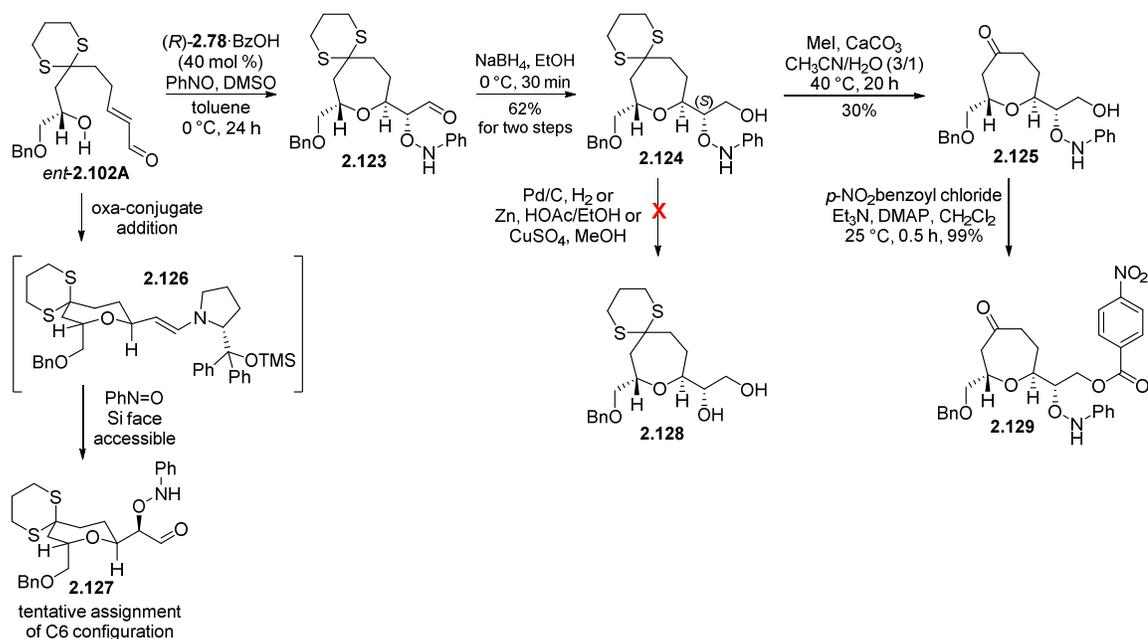


entry	co-solvent	catalyst loading (mol%)	PhNO (eq)	T (° C)	time for step i (h)	yield (%)
1	N/A	20	1.1	0 to 25	4	N/A
2	DMSO	20	1.2	0	4.5	23
3	DMSO	20	1.2	25	3	42
4	DMSO	20	1.2	0 to 90	5.5	46
5	DMSO	40	1.2	0	23	45
6	DMSO	40	2.2	0	24	43

The α,β -unsaturated aldehyde *ent*-**2.102A** was treated with 40 mol% (R) -**2.78** followed by addition of PhNO in DMSO (Scheme 17). After 24 hours, the reaction was diluted with EtOH and reduced with NaBH₄ providing α -oxidized oxepane alcohol **2.124** in 62% yield for two steps. The success of the tandem reaction required that the configuration at C6 be determined. To do this, the O–N bond would first need to be cleaved. The free C6 alcohol could then be used to determine the configuration via Mosher ester analysis. At that time, there were several methods in the literature for this type of transformation including Pd/C in H₂,^{62b, 70} Zn in HOAc/EtOH,⁷¹ Cu(OAc)₂ in MeOH or EtOH,⁷² CuSO₄ in MeOH,⁷³ and PtO₂, H₂.^{73e, 73f, 74} Initially, Pd/C in H₂ was tested for the O–N bond cleavage in **2.124**; however, no reaction was observed under these conditions

even after prolonged reaction time. It was suspected that the dithiane moiety in **2.124** rendered the Pd catalyst inactive. Next, Zn in HOAc/EtOH was tested. Unfortunately, no reaction was also observed in this case after stirring at 25 °C for 16 h. Lastly, CuSO₄ in MeOH was examined for the O–N bond cleavage. Although two new products were formed and isolated, ¹H NMR of both samples was inconclusive.

At this point, we hypothesized that the dithiane moiety in **2.124** was incompatible with both the Zn and CuSO₄ conditions. Therefore, attempts to hydrolyze the dithiane moiety in **2.124** were completed. When **2.124** was treated with I₂ in saturated aqueous NaHCO₃ and CH₃CN, two products were formed and isolated. Unfortunately, ¹H NMR spectrum of both of these products were not consistent with the anticipated spectrum of our target molecule, **2.125**. Next, MeI and CaCO₃ conditions were tested for hydrolysis of dithiane-containing **2.124**. These conditions gave target ketone **2.125** in 30% yield as a single isomer. Regrettably, our simultaneous efforts to extend the organocatalyzed oxoconjugate addition to the synthesis of oxocanes (Section 2.3) demanded increased attention and prevented any attempts to cleave the O–N in the absence of the dithiane moiety using **2.125**. However, one attempt was made to crystallize **2.125** via conversion to *p*-NO₂benzoyl **2.129**. If this molecule had been crystalline, then X-ray crystal analysis could have been performed to determine the configuration at C6. Unfortunately, all efforts to crystallize the sample were unsuccessful. Thus, a tentative assignment of the C6 configuration of (6*S*) was made based on the conformational model **2.126** in which PhNO would add from the less sterically hindered *Si* face.



Scheme 17: Tandem organocatalyzed oxa-conjugate addition/ α -oxidation of α,β -unsaturated aldehyde *ent*-2.102A** and attempts to further functionalize**

To summarize our efforts toward the three aims of Section 2.2, ¹H NMR kinetic studies were completed for several α,β -unsaturated aldehydes *ent*-**2.102A-D** with matched and mismatched amine catalysts. An optimal reaction time for the matched substrate/catalysts system was determined from these studies. Isolated yields and diastereomeric ratios for the matched systems were obtained. A ¹H NMR kinetic study was also completed for α,β -unsaturated aldehyde **2.119** containing a C9 dithiane moiety. A tandem organocatalyzed oxa-conjugate addition/ α -oxidation was also developed using PhNO as the oxygen source and (*R*)-amine catalyst **2.78** giving α -oxidized oxepane alcohol

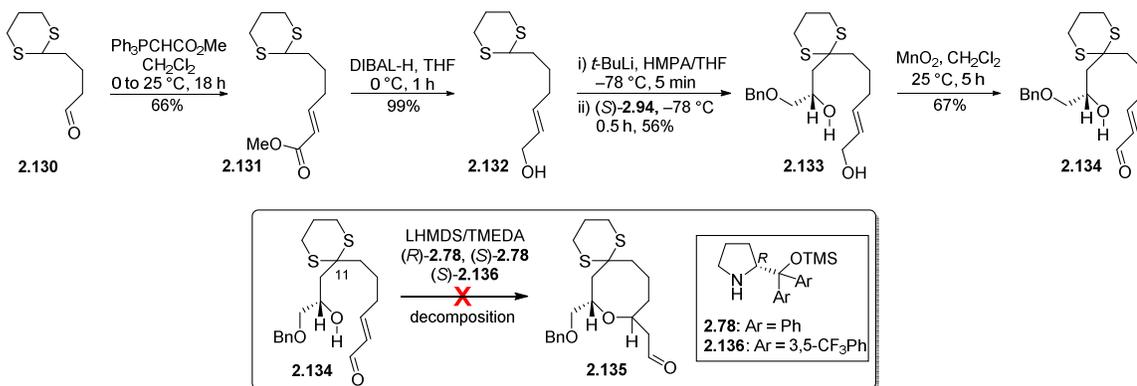
2.124 in 62% for two steps. All efforts to determine the C6 configuration were unsuccessful; therefore, a tentative assignment of (*S*)-configuration has been made. Additional efforts were not made to further functionalize α -oxidized oxepane alcohol **2.124** for potential application to natural product synthesis.

2.3 Attempts to Extend Methodology to the Preparation of Eight-Membered Cyclic Ethers

Due to our success with the organocatalytic oxa-conjugate addition for the stereoselective synthesis of α,α' -*trans*-oxepanes, we wanted to determine the feasibility of the method in the context of 8-membered cyclic ether (oxocanes) synthesis. A review of current methods for the stereoselective synthesis of 8-membered cyclic ethers will be provided in Section 3.1.1. As with the organocatalytic oxa-conjugate addition for oxepane synthesis, the optimal location of the 1,3-dithiane moiety was unknown. Since the synthesis of 7-membered cyclic ethers required iminium activation, in addition to the presence of the dithiane group, to promote cyclization, we anticipated that similar reactivity would be observed for oxocane synthesis. Namely, treatment of dithiane-containing monoallylic alcohol **2.133** or **2.140** with MnO₂ would lead only to allylic alcohol oxidation and that oxa-conjugate addition would need to be induced by organocatalysis. Because positioning the dithiane moiety at C10 gave higher yields of oxepanes *ent*-**2.103A-E**, we thought that placing the dithiane moiety at C11 would also give better results. Both of these carbons are located slightly more than 180° from the proposed C–O bond formation. Therefore,

monoallylic diol **2.133** with a C11 dithiane was prepared and studied first with the anticipation that analogous monoallylic diol **2.140** with a C10 dithiane would also need to be prepared and examined.

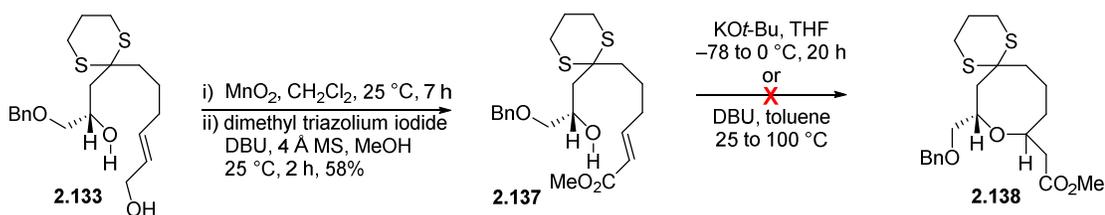
To prepare **2.133**, known dithiane-containing aldehyde (**2.130**) was treated with methyl (triphenylphosphoranylidene)acetate to yield the α,β -unsaturated methyl ester **2.131** (Scheme 18). DIBAL-H reduction gave the allylic alcohol which was then coupled with epoxide (*S*)-**2.94** to generate the monoallylic diol **2.133** in 56% yield. The monoallylic diol was then treated with MnO₂ resulting in exclusive formation of the α,β -unsaturated aldehyde **2.134** in 67% yield.



Scheme 18: Preparation of 2.134 and attempts to cyclize under organocatalytic oxa-conjugate addition conditions

Attempts were made to cyclize **2.134** under various organocatalyzed conditions using diphenyl and diaryl amine catalysts (*R*)-**2.78**, (*S*)-**2.78** and (*S*)-**2.136**. Various

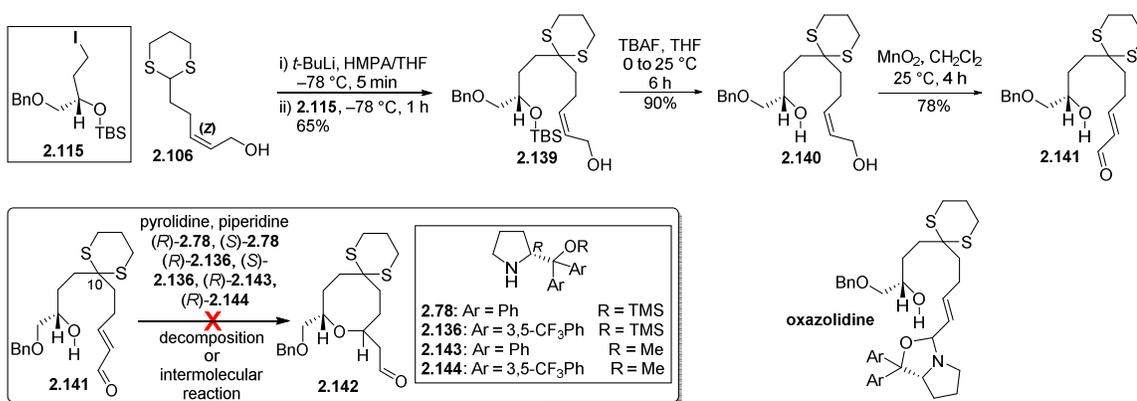
temperatures (0 to 50 °C) and catalyst loadings (20-50 mol%) were used; however, all conditions resulted in decomposition of the substrate. An attempt to induce oxa-conjugate addition via a base catalyzed method⁷⁵ was also attempted. After stirring under the LHMDS/TMEDA conditions at 25 °C for 3 h without any conversion, the reaction was warmed to 100 °C and stirred for 19 h. Unfortunately, decomposition of the substrate was observed during this time.



Scheme 19: Attempts to cyclize α,β -unsaturated methyl ester 2.137

The α,β -unsaturated methyl ester **2.137** was prepared from monoallylic alcohol **2.133** via tandem allylic alcohol oxidation/NHC catalyzed esterification (Scheme 19).⁷⁶ It was thought that **2.137** would be more stable toward base promoted oxa-conjugate addition. However attempts to obtain the oxocane **2.138** using KO t -Bu or DBU were not successful. A significant amount of decomposition was observed in both cases. Therefore, we shifted our attention to the oxa-conjugate addition of **2.140** which contained a C10 dithiane.

To prepare **2.140**, the monosubstituted dithiane **2.106**, previously used to prepare oxepanes *ent*-**2.103A-E** and *ent*-**2.104A**, was lithiated and coupled with iodide **2.115** to give the disubstituted dithiane **2.139** in 65% yield (Scheme 20). The secondary silyl ether was then cleaved upon treatment with TBAF. Monoallylic diol **2.140** was treated with MnO₂ providing α,β -unsaturated aldehyde **2.141** as the sole product. As with similar substrates *ent*-**2.102A-E** for oxepane synthesis, the (*Z*)-alkene was isomerized to the (*E*)-alkene.



Scheme 20: Preparation of 2.141 and attempts to cyclize under organocatalytic oxo-conjugate addition conditions

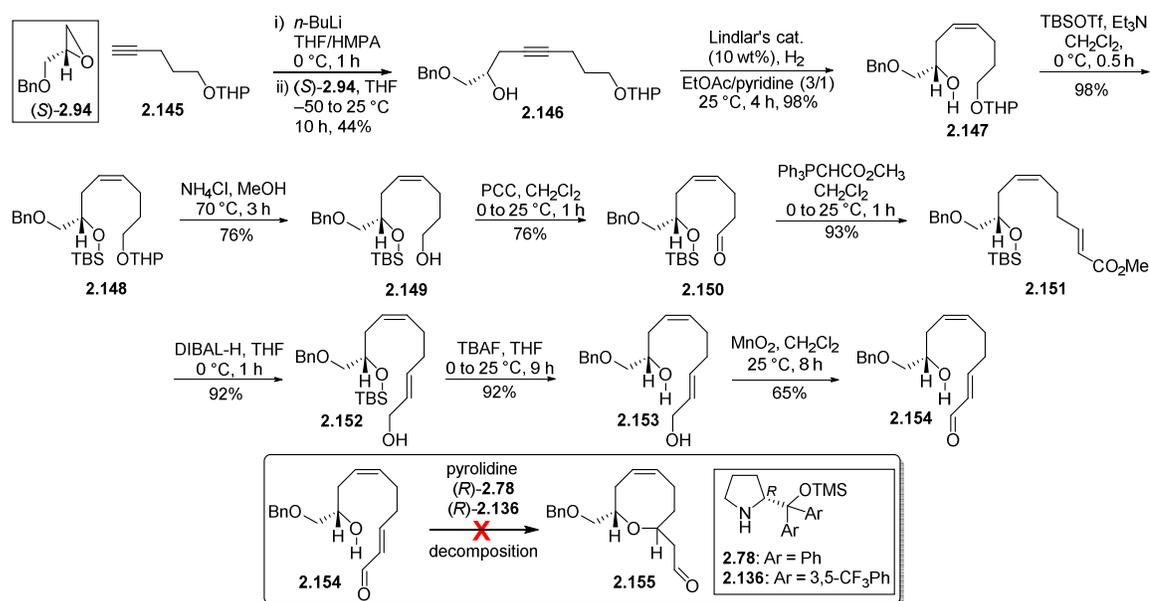
When α,β -unsaturated aldehyde **2.141** was treated with (*R*)- or (*S*)-diphenyl amine catalysts **2.78**, only decomposition of **2.141** was observed. More reactive (*R*)- or (*S*)-diaryl amine catalysts **2.136** were also tested. In these cases, a product was formed that was not stable to purification by silica gel. Hence, several attempts were made to identify the

product. Eventually, LC/MS indicated that a parasitic oxazolidine had formed due to silyl deprotection.⁷⁷ Therefore, the tertiary alcohol in amine catalysts **2.143** and **2.144** was protected with a less liable methyl group. When α,β -unsaturated aldehyde **2.141** was treated with either (*R*)-**2.143** or **2.144**, decomposition was observed on TLC. In a final set of attempts to cyclize **2.141**, achiral amine catalysts, pyrrolidine and piperadine, were employed. Use of pyrrolidine produced three products; one of these products was identified as the aldol product from intermolecular reaction while the other two products could not be identified. Similar results were obtained with piperadine, along with a significant amount of decomposition.

At this stage, we hypothesized that the dithiane moiety might be too rigid for cyclization to occur. Therefore, we decided to install a *cis* alkene into the carbon skeleton based on Martin's success with similar alkene-containing oxa-conjugate addition substrates.⁵³ As with the dithiane moiety, optimal positioning of the *cis* alkene within the carbon skeleton was unknown. Thus, we anticipated the need to prepare *cis* alkene-containing monoallylic diols **2.153** and **2.161**. We suspected that **2.161** could potentially undergo double bond isomerization upon treatment with MnO₂ to give the fully conjugated $\alpha,\beta,\gamma,\delta$ -unsaturated aldehyde **2.163**. Therefore, we prepared and examined **2.153** and **2.161** simultaneously.

To prepare **2.153**, commercial alkyne (**2.135**) was lithiated and treated with epoxide (*S*)-**2.94** to yield disubstituted alkyne **2.146** (Scheme 21). In retrospect, the poor yield of **2.146** could have potentially been improved by using *n*-BuLi/BF₃·OEt₂ conditions instead

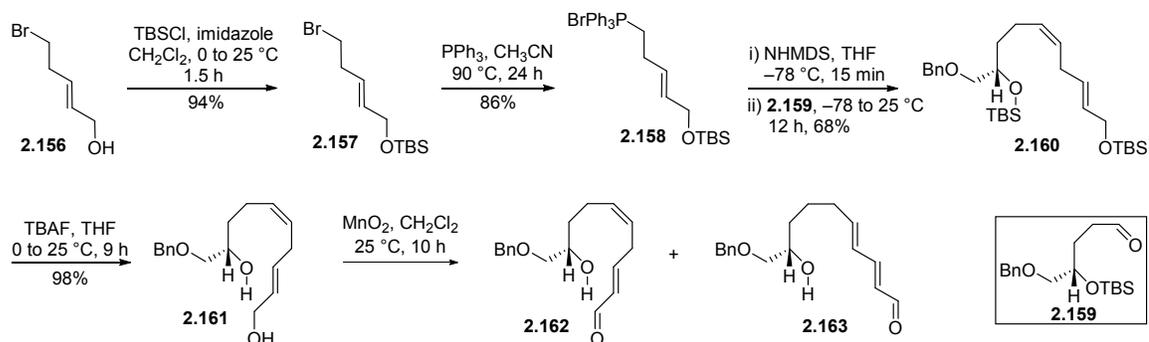
of *n*-BuLi/HMPA.⁷⁸ Hydrogenation of the alkyne to the *cis*-alkene **2.147** was then completed with Lindlar's catalyst. A series of protection and deprotection reactions were carried out including TBS protection of the C13 alcohol and THP cleavage using refluxing NH₄Cl in MeOH. The free primary alcohol **2.149** was then oxidized with PCC in CH₂Cl₂ to give the aldehyde **2.150**. Wittig reaction with methyl (triphenylphosphoranylidene) acetate gave the α,β -unsaturated methyl ester **2.151** in 93% yield. DIBAL-H reduction and desilylation provided the monoallylic diol **2.153** which was then treated with MnO₂ giving α,β -unsaturated aldehyde **2.154** as the sole product.



Scheme 21: Preparation of **2.154** and attempts to cyclize under organocatalytic oxa-conjugate addition conditions

Treatment of α,β -unsaturated aldehyde **2.154** with either pyrrolidine or (*R*)-**2.78** resulted in significant decomposition of the substrate without any potential desired product formation. Use of (*R*)-**2.136** as the amine catalyst did yield a minor product, along with a significant amount of decomposition, which was potentially the desired product. In attempts to isolate and identify this minor product, higher catalyst loadings were employed; however, analysis of the minor product by ^1H NMR was inconclusive. The purified sample of the minor product was then analyzed by mass spectroscopy and the results were promising with a mass ion peak corresponding with the mass of the target molecule. Use of stoichiometric amounts of (*R*)-**2.136** did not improve the yield and clear ^1H NMR spectra could not be obtained to confidently assign the structure. Although the investigation was not extensive, we concluded that pursuing this methodology with substrate **2.154** was not worthwhile.

Due to the *cis* alkene location of monoallylic diol **2.161**, a different synthetic route was devised. In this route, the *cis* alkene was selectively installed via Wittig reaction instead of being prepared from an alkyne precursor. As shown in Scheme 22, preparation of **2.161** began with TBS protection of known bromine-containing alcohol (**2.156**). Treatment of **2.156** with triphenylphosphine gave the phosphine bromide salt **2.157** in 86% yield. Upon exposure to NHMDS, **2.158** produced an ylide for Wittig reaction with known aldehyde (**2.159**).⁷⁹ This Wittig reaction was problematic due to the variability in isolated yields. Thus, a second route to **2.161** was investigated later (Scheme 24). Bis-TBS cleavage with TBAF gave monoallylic diol **2.161** in 98% yield.



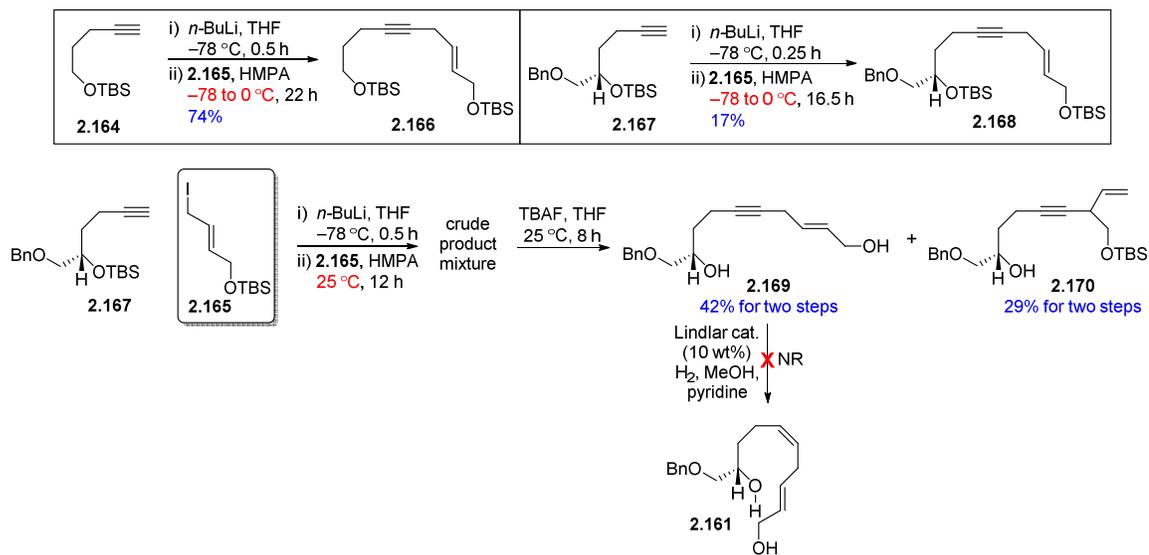
Scheme 22: Preparation of 2.161 via Wittig route

Treatment of monoallylic diol **2.161** with MnO_2 gave the target α,β -unsaturated aldehyde **2.162** in addition to fully conjugate aldehyde **2.163**. This was a problem that we anticipated prior to preparation of **2.161**. Oxa-conjugate addition of this substrate **2.161** was not pursued further due to our simultaneous efforts to probe the potential for 8-membered cyclic ether formation via gold(I)-catalyzed alkoxylation, the topic of chapter 3. However, it did become important to address the problems that the Wittig route posed for the preparation of monoallylic alcohol **2.161** as it was a key substrate for the gold(I)-catalyzed alkoxylation reactions we were studying.

The Wittig route to monoallylic alcohol **2.161** was mainly hindered by the irreproducible and often low yields obtained for the pivotal Wittig reaction. Furthermore, purification of the triphenylphosphonium bromide salt **2.158** was problematic. Therefore, it was hypothesized that an alkyne/iodide coupling using known substrates (**2.167**)⁷⁹ and

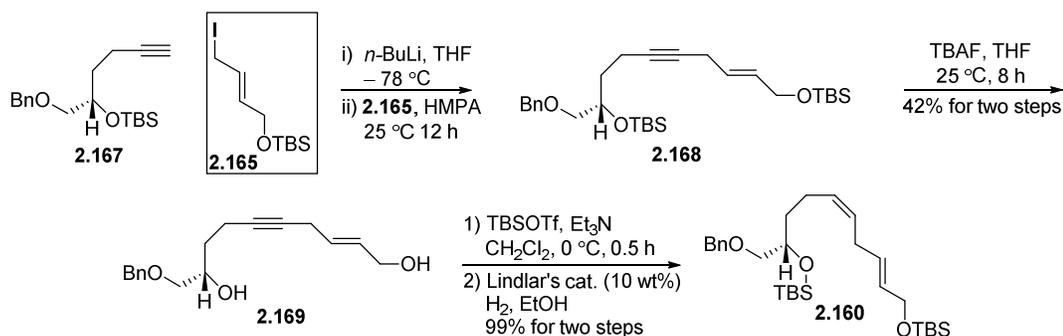
(**2.165**)⁸⁰ could be employed as an alternative route. A model study for this alkyne/iodide coupling was completed using alkyne **2.164** (Scheme 23) which gave high selectivity for the S_N2 product (74%). However, when alkyne (**2.167**) was lithiated and treated with allylic iodide (**2.165**), both the S_N2 and S_N2' products were obtained in 1.4:1 ratio. It was later suspected that the S_N2' pathway was temperature dependent and this was confirmed. When the temperature was maintained at 0 °C, the desired S_N2 product **2.168** was obtained as the sole coupling product but in low yield (17%).

Unfortunately, the isomeric mixture was difficult to purify as the bis-TBS ether; thus, desilylation was necessary to cleanly separate products **2.169** and **2.170**. Hydrogenolysis of **2.169** was then required to install the *cis* alkene; however, efforts to reduce to the alkene were unsuccessful. Protection of the monoallylic diol **2.169** with TBS groups, followed by hydrogenolysis with Lindlar's catalyst was accomplished in 99% for two steps. The bis-TBS ether could then be deprotected using TBAF as shown in Scheme 22. The optimized alkyne/iodide coupling route to **2.160** is given in Scheme 24.



Scheme 23: Coupling of alkyne **2.167** and iodide **2.165**

Although effective, this route was not efficient. Thus, development of an improved route to **2.161** was not accomplished and the alternative alkyne/iodide route could be considered more problematic than the original Wittig route. In retrospect, the variable and low yield in the Wittig reaction could have been addressed by generating the ylide at 0 °C instead of –78 °C since consumption of aldehyde **2.159** was never observed. With time, purification of the triphenylphosphine bromide salt **2.158** could have also been optimized.



Scheme 24: Alkyne/iodide coupling route for preparation of 2.160

2.4 Summary

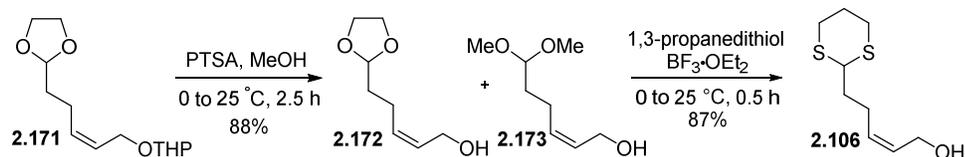
In this chapter, current stereoselective methods for the preparation of α, α' -*cis*- and α, α' -*trans*-oxepanes have been reviewed. The oxa-conjugate addition reaction for the synthesis of oxepanes has been proposed and the handful of reports describing efforts toward this goal have been described. Our lab's own previous studies of this methodology have been summarized and our work in this area has been completed with the aid of ^1H NMR kinetic studies. This work has resulted in a publication describing the importance of the *gem*-disubstituent effect and iminium activation via organocatalysis as key factors affecting the oxa-conjugate addition. Our tandem organocatalytic oxa-conjugate addition/ α -oxidation was also disclosed in the publication.⁸¹ Lastly, efforts to extend the oxa-conjugate addition method to the preparation of 8-membered cyclic ethers have been described.

2.5 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. Unless otherwise stated all reagents were purchased from Sigma–Aldrich, Acros, or Fisher and were used without further purification. All solvents were ACS grade or better and used without further purification except tetrahydrofuran (THF) which was freshly distilled from sodium/benzophenone each time before use. Analytical thin layer chromatography (TLC) was performed with glass backed silica gel (60 Å) plates with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel (particle size 230–400 mesh, 60 Å). All ¹H NMR and ¹³C NMR spectrum were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in CDCl₃ by using the signal of residual CHCl₃, as an internal standard. All NMR δ values are given in ppm, and all *J* values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo–Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102. API/1W) polarimeter.

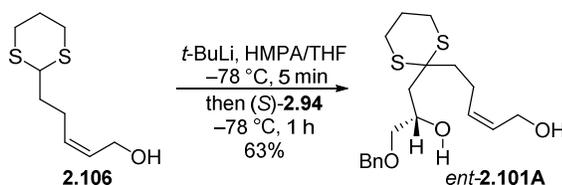
Preparation of Dithiane 2.106



[Deprotection] To a cooled (0 °C) solution of the known tetrahydropyranyl ether (**2.171**)⁸² (2.9 g, 11.8 mmol) in MeOH (17 mL, 0.694 M) was added PTSA (113 mg, 0.6 mmol). The reaction mixture was allowed to warm to 25 °C with stirring over 2.5 h. The reaction mixture was then quenched with Et₃N concentrated *in vacuo*. The resulting residue was dissolved in H₂O and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1 then 1/1) afforded a mixture of (**2.172**) and (**2.173**)⁸² a colorless oil (1.6 g, 88%). **[Conversion to Dithiane]** To a cooled (0 °C) solution of a mixture of **2.172** and **2.173** (518 mg, 3.3 mmol) in CH₂Cl₂ (13 mL, 0.254 M) was added 1,3-propanedithiol (0.7 mL, 6.6 mmol) followed by BF₃·OEt₂ (0.8 mL, 6.5 mmol) dropwise. The reaction mixture was warmed to 25 °C with stirring over 0.5 h. The reaction mixture was then quenched with saturated NaHCO₃ solution and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 9/1 to 7/1) yielded **2.106** as a colorless oil (582 mg, 87%): ¹H NMR (500 MHz, CDCl₃) δ 5.75–5.56 (m, 1H), 5.45 (dt, *J* = 9.5, 7.5 Hz, 1H), 4.15 (d, *J* = 6.5 Hz, 2H), 3.99 (t, *J* = 7.0 Hz, 1H), 2.90–2.69 (m, 4H), 2.28 (dt, *J* = 7.5, 7.0 Hz, 2H), 2.13–2.02 (m, 1H), 1.97 (br s, 1H), 1.88–1.66 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 131.0, 130.1, 58.2,

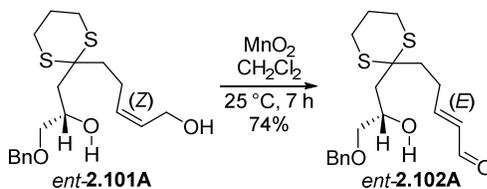
46.4, 34.6, 30.3, 25.9, 24.1; IR (neat) 3380, 2930, 2900, 1423, 1275, 1025 cm^{-1} ; HRMS (ESI) m/z 187.0610 $[(M-H_2O)^+]$, $\text{C}_9\text{H}_{16}\text{OS}_2$ requires 187.0610].

Preparation of Allylic Alcohol *ent*-2.101A



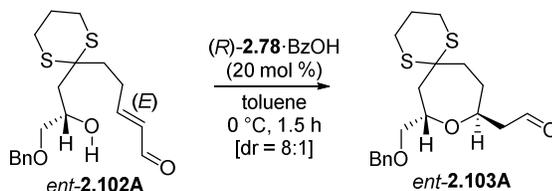
To a cooled ($-78\text{ }^\circ\text{C}$) solution of 1,3-dithiane **2.106** (170 mg, 0.83 mmol) in HMPA/THF (1/10, 10.6 mL, 0.078 M) was added $t\text{-BuLi}$ (1.7 M in pentane, 1.6 mL, 2.72 mmol). After stirring for 5 min, (S) -glycidyl benzyl ether ($(S)\text{-2.94}$) (185 mg, 1.13 mmol) in THF (0.8 mL) was added dropwise and the reaction mixture was stirred for an additional 1 h prior to quenching with NH_4Cl . The aqueous layer was extracted with CH_2Cl_2 , dried with Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1 to 1/1) to provide *ent*-**2.101A** as a colorless oil (192 mg, 63%): $[\alpha]_D^{25} = -11.9$ (c 0.97, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.27 (m, 5H), 5.69–5.58 (m, 1H), 5.58–5.48 (m, 1H), 4.56 (s, 2H), 4.21–4.11 (m, 3H), 3.43 (d, $J = 5.2$ Hz, 2H), 3.18 (br s, 1H), 2.95–2.72 (m, 4H), 2.41–2.31 (m, 1H), 2.30–2.14 (m, 1H), 2.18 (dd, $J = 15.2, 8.4$ Hz, 1H), 2.09–1.85 (m, 5H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.9, 131.8, 129.2, 128.4, 127.7, 74.4, 73.3, 67.5, 58.3, 52.0, 41.3, 39.0, 26.2, 26.0, 25.00, 22.5; IR (neat) 3395, 2908, 1453, 1102, 1027, 739, 699 cm^{-1} ; HRMS (ESI) m/z 391.1373 $[(M+\text{Na})^+]$, $\text{C}_{19}\text{H}_{28}\text{O}_3\text{S}_2$ requires 391.1372].

Preparation of α,β -Unsaturated Aldehyde *ent*-2.102A



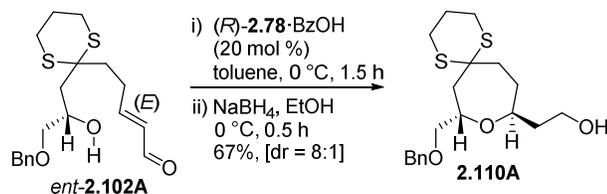
To a solution of allylic alcohol *ent*-2.101A (27 mg, 0.07 mmol) in CH₂Cl₂ (1.3 mL, 0.054 M) was added MnO₂ (30 mg, 0.37 mmol). Additional equivalents of MnO₂ (30 mg, 0.37 mmol) were added every hour for 7 h while stirring. The reaction mixture was then purified by column chromatography (silica gel topped with Celite, hexanes/EtOAc = 3/1) to provide *ent*-2.102A as a colorless oil (20 mg, 74%): $[\alpha]_D^{25} = -11.8$ (*c* 0.94, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.49 (d, *J* = 7.6 Hz, 1H), 7.39–7.25 (m, 5H), 6.85 (dt, *J* = 15.6, 6.4 Hz, 1H), 6.13 (dd, *J* = 15.6, 7.6 Hz, 1H), 4.56 (s, 2H), 4.21–4.13 (m, 1H), 3.48–3.37 (m, 2H), 2.92 (br s, 1H), 2.91–2.74 (m, 4H), 2.69–2.47 (m, 2H), 2.25–2.03 (m, 4H), 2.03–1.87 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 193.8, 157.7, 137.8, 133.0, 128.4, 127.7, 74.4, 73.3, 67.3, 51.8, 41.7, 37.3, 27.8, 26.2, 26.0, 24.8; IR (neat) 3442, 2908, 2857, 1686, 1452, 1422, 1276, 1104, 1027, 973, 740, 699 cm⁻¹; HRMS (ESI) *m/z* 367.1390 [(M+H)⁺, C₁₉H₂₆O₃S₂ requires 367.1394].

Organocatalytic Oxa-Conjugate Addition Reaction of α,β -Unsaturated Aldehyde *ent*-2.102A



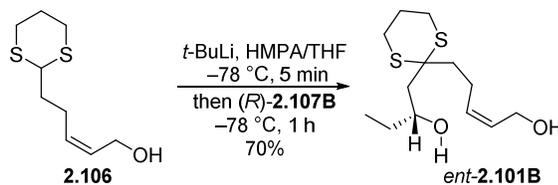
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-2.102A (23 mg, 0.06 mmol) in toluene (0.6 mL, 0.100 M) was added (*R*)-2.78 (4 mg, 0.01 mmol) in toluene (0.5 mL) followed by BzOH (2 mg, 0.01 mmol) in toluene (61 μ L). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with hexanes and filtered through a short column (silica gel, hexanes/EtOAc = 2/1) to afford a mixture of α,α' -*trans*-oxepane aldehyde *ent*-2.103A and its corresponding α,α' -*cis*-isomer as a colorless oil: $[\alpha]_D^{23} = +12.9$ (*c* 0.10, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.75 (s, 1H), 7.38–7.27 (m, 5H), 4.51 (s, 2H), 4.44–4.35 (m, 1H), 3.99 (dt, *J* = 10.0, 5.2 Hz, 1H), 3.41 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.36 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.86 (t, *J* = 5.6 Hz, 2 H), 2.77–2.64 (m, 3H), 2.48–2.32 (m, 3H), 2.11–1.89 (m, 5H), 1.81–1.70 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 201.7, 138.0, 128.4, 127.6, 73.4, 73.2, 71.6, 68.1, 51.0, 48.9, 44.2, 36.6, 29.4, 27.0, 25.6, 25.5, 25.4; IR (neat) 2932, 2859, 1723, 1452, 1112, 740, 699 cm⁻¹; HRMS (ESI) *m/z* 367.1394 [(M+H)⁺, C₁₉H₂₆O₃S₂ requires 367.1394].

One-pot Organocatalytic Oxa-Conjugate Addition/Reduction of α,β -Unsaturated Aldehyde *ent*-2.102A



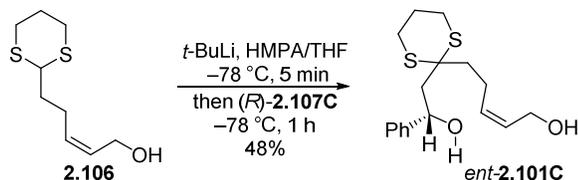
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-2.102A (24 mg, 0.07 mmol) in toluene (0.7 mL, 0.100 M) was added (*R*)-2.78 (4 mg, 0.01 mmol) in toluene (0.5 mL) followed by BzOH (2 mg, 0.01 mmol) in toluene (64 μ L). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with EtOH and treated with NaBH₄ (7 mg, 0.20 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with H₂O and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with H₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 2/1) to provide a mixture of 2.110A and its corresponding α,α' -*cis*-isomer as a colorless oil (16 mg, 67%): ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.23 (m, 5H), 4.55 (s, 2H), 4.10–3.97 (m, 2H), 3.82–3.67 (m, 2H), 3.46–3.33 (m, 2H), 2.97 (br s, 1H), 2.85 (t, *J* = 4.0 Hz, 2H), 2.72 (t, *J* = 4.0 Hz, 2H), 2.40–2.26 (m, 2H), 2.08–1.85 (m, 4H), 1.85–1.62 (m, 2H), 1.62–1.50 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.6, 128.4, 127.9, 127.8, 75.8, 73.4, 73.2, 68.3, 61.2, 51.0, 43.7, 37.5, 30.3, 27.0, 25.6; HRMS (ESI) *m/z* 369.1563 [(M+H)⁺, C₁₉H₂₈O₃S₂ requires 369.1553].

Preparation of Allylic Alcohol *ent*-2.101B



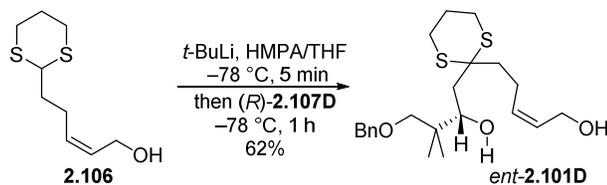
To a cooled ($-78\text{ }^\circ\text{C}$) solution of 1,3-dithiane **2.106** (97 mg, 0.48 mmol) in HMPA/THF (1/10, 6.0 mL, 0.080 M) was added $t\text{-BuLi}$ (1.7 M in pentane, 0.9 mL, 1.52 mmol). After stirring for 5 min, (R) -1,2-epoxybutane ((R) -**2.107B**) (0.1 mL, 0.95 mmol) was added dropwise and the reaction mixture was stirred for an additional 1 h prior to quenching with NH_4Cl . The aqueous layer was extracted with CH_2Cl_2 , dried with Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1 to 1/1) to provide *ent*-**2.101B** as a colorless oil (92 mg, 70%): $[\alpha]_D^{23} = -22.4$ (c 0.65, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.68–5.55 (m, 1H), 5.55–5.45 (m, 1H), 4.22–4.10 (m, 2H), 3.88–3.81 (m, 1H), 3.38 (br s, 1H), 2.99–2.83 (m, 2H), 2.82–2.72 (m, 2H), 2.39–2.27 (m, 1H), 2.27–2.10 (m, 2H), 2.10–1.82 (m, 6H), 1.56–1.37 (m, 2H), 0.93 (t, $J = 7.6$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 131.5, 129.3, 69.7, 58.3, 52.0, 44.3, 39.3, 30.8, 26.3, 26.0, 24.9, 22.5, 9.9; IR (neat) 3378, 2930, 1422, 1028, 991 cm^{-1} ; HRMS (ESI) m/z 299.1109 $[(\text{M}+\text{Na})^+]$, $\text{C}_{13}\text{H}_{24}\text{O}_2\text{S}_2$ requires 299.1110].

Preparation of Allylic Alcohol *ent*-2.101C



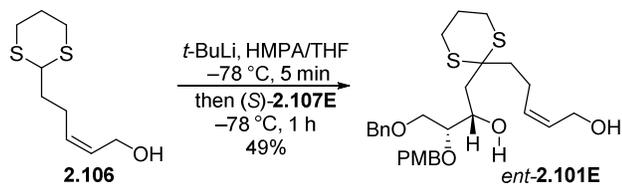
To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of 1,3-dithiane **2.106** (82 mg, 0.40 mmol) in HMPA/THF (1/10, 5.1 mL, 0.078 M) was added *t*-BuLi (1.7 M in pentane, 0.8 mL, 1.36 mmol). After stirring for 5 min, (*R*)-styrene oxide ((*R*)-**2.107C**) (0.1 mL, 0.80 mmol) was added dropwise and the reaction mixture was stirred for an additional 1 h prior to quenching with NH_4Cl . The aqueous layer was extracted with CH_2Cl_2 , dried with Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1 to 1/1) to provide *ent*-**2.101C** as a colorless oil (63 mg, 48%): $[\alpha]_{\text{D}}^{23} = -50.8$ (*c* 0.95, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42–7.24 (m, 5H), 5.69–5.58 (m, 1H), 5.58–5.48 (m, 1H), 5.06 (dd, $J = 9.2, 1.6$ Hz, 1H), 4.25–4.12 (m, 2H), 2.98 (ddd, $J = 14.4, 9.6, 3.2$ Hz, 1H), 2.92–2.73 (m, 3H), 2.51 (dd, $J = 15.2, 9.2$ Hz, 1H), 2.46–2.35 (m, 1H), 2.34–2.21 (m, 1H), 2.21–2.08 (m, 2H), 2.08–1.97 (m, 2H), 1.97–1.85 (m, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 144.6, 131.6, 129.2, 128.5, 127.4, 125.6, 71.2, 58.3, 52.2, 46.9, 39.3, 26.2, 26.0, 24.8, 22.5; IR (neat) 3400, 3017, 2907, 1451, 1423, 1028, 762, 701 cm^{-1} ; HRMS (ESI) m/z 347.1112 [$(\text{M}+\text{Na})^+$, $\text{C}_{17}\text{H}_{24}\text{O}_2\text{S}_2$ requires 347.1110].

Preparation of Allylic Alcohol *ent*-2.101D



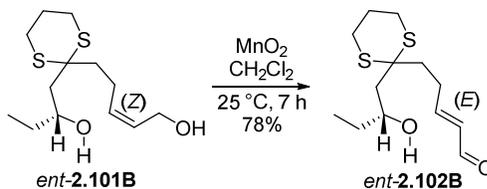
To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of 1,3-dithiane **2.106** (202 mg, 0.99 mmol) in HMPA/THF (1/10, 12.3 mL, 0.080 M) was added *t*-BuLi (1.7 M in pentane, 1.9 mL, 3.17 mmol). After stirring for 5 min, known (*R*)-**2.107D**⁸³ (408 mg, 1.98 mmol) in THF (1.3 mL) was added dropwise and the reaction mixture was stirred for an additional 1 h prior to quenching with NH_4Cl . The aqueous layer was extracted with CH_2Cl_2 , dried with Na_2SO_4 , and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1 to 1/1) to provide *ent*-**2.101D** as a colorless oil (253 mg, 62%): $[\alpha]_D^{23} = -23.2$ (*c* 0.64, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.38–7.27 (m, 5H), 5.70–5.58 (m, 1H), 5.58–5.47 (m, 1H), 4.52 (d, $J = 10.0$ Hz, 1H), 4.49 (d, $J = 9.6$ Hz, 1H), 4.18 (dd, $J = 10.0, 5.0$ Hz, 1H), 4.12 (dd, $J = 10.0, 5.0$ Hz, 1H), 3.85 (d, $J = 5.0$ Hz, 1H), 3.52 (bs, 1H), 3.39 (d, $J = 10.0$ Hz, 1H), 3.30 (d, $J = 10.0$ Hz, 1H), 2.91–2.70 (m, 4H), 2.43–2.29 (m, 1H), 2.29–2.16 (m, 1H), 2.15–1.86 (m, 6H), 1.77 (br s, 1H), 0.96 (s, 3H), 0.93 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 138.0, 132.1, 129.0, 128.4, 127.6, 127.5, 78.6, 74.2, 73.5, 58.3, 52.8, 40.2, 38.9, 38.6, 26.2, 26.1, 25.1, 22.8, 22.6, 20.1; IR (neat) 3425, 2956, 2932, 2906, 2872, 1453, 1095, 1075, 1028, 738, 698 cm^{-1} ; HRMS (ESI) m/z 433.1841 [$(\text{M}+\text{Na})^+$, $\text{C}_{22}\text{H}_{34}\text{O}_3\text{S}_2$ requires 433.1842].

Preparation of Allylic Alcohol *ent*-2.101E



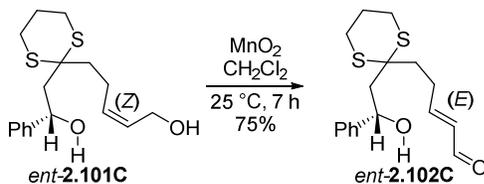
To a cooled (-78 °C) solution of 1,3-dithiane **2.106** (94 mg, 0.46 mmol) in HMPA/THF (1/10, 5.9 mL, 0.078 M) was added *t*-BuLi (1.7 M in pentane, 0.9 mL, 1.47 mmol). After stirring for 5 min, known (*S*)-**2.107E**⁸⁴ (280 mg, 0.89 mmol) in THF (0.6 mL) was added dropwise and the reaction mixture was stirred for an additional 1 h prior to quenching with NH₄Cl. The aqueous layer was extracted with CH₂Cl₂, dried with Na₂SO₄, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1 to 1/1) to provide *ent*-**2.101E** as a colorless oil (117 mg, 49%): $[\alpha]_D^{25} = -24.0$ (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.25 (m, 7H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.60 (dt, *J* = 10.8, 6.4 Hz, 1H), 5.50 (dt, *J* = 10.4, 8.0 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.56 (s, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.10 (d, *J* = 6.8 Hz, 3H), 3.80 (s, 3H), 3.73 (dd, *J* = 8.8, 4.0 Hz, 1H), 3.67 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.50–3.45 (m, 1H), 3.17 (br s, 1H), 2.93–2.68 (m, 4H), 2.34–2.19 (m, 3H), 2.12 (dd, *J* = 15.2, 8.8 Hz, 1H), 2.06–1.84 (m, 4H), 1.73 (br s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 159.2, 138.0, 131.8, 130.3, 129.7, 129.1, 128.4, 127.7, 113.7, 80.4, 73.5, 72.2, 69.6, 69.0, 58.2, 55.2, 52.3, 40.3, 39.1, 26.2, 25.9, 25.0, 22.2; IR (neat) 3428, 2908, 1612, 1513, 1248, 1076, 1032, 822, 738, 699 cm⁻¹; HRMS (ESI) *m/z* 541.2045 [(M+Na)⁺, C₂₈H₃₈O₅S₂ requires 541.2053].

Preparation of α,β -Unsaturated Aldehyde *ent*-2.102B



To a solution of allylic alcohol *ent*-2.101B (105 mg, 0.38 mmol) in CH_2Cl_2 (6.8 mL, 0.056 M) was added MnO_2 (154 mg, 1.90 mmol). Additional equivalents of MnO_2 (154 mg, 1.90 mmol) were added every hour for 7 h while stirring. The reaction mixture was then purified by column chromatography (silica gel topped with Celite, hexanes/EtOAc = 3/1) to provide *ent*-2.101B as a colorless oil (81 mg, 78%): $[\alpha]_D^{24} = -25.7$ (c 1.00, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.45 (d, $J = 8.0$ Hz, 1H), 6.84 (dt, $J = 15.6, 6.4$ Hz, 1H), 6.10 (dd, $J = 15.6, 8.0$ Hz, 1H), 3.88–3.79 (m, 1H), 3.06 (s, 1H), 2.95–2.91 (m, 4H), 2.65–2.53 (m, 1H), 2.53–2.40 (m, 1H), 2.22–2.10 (m, 2H), 2.19–1.82 (m, 4H), 1.54–1.35 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 193.6, 157.4, 133.0, 69.5, 51.7, 44.7, 37.4, 30.9, 27.8, 26.1, 26.00, 24.6, 9.8; IR (neat) 3464, 2934, 2158, 1978, 1687, 1135, 973 cm^{-1} ; HRMS (ESI) m/z 275.1137 $[(\text{M}+\text{H})^+]$, $\text{C}_{13}\text{H}_{22}\text{O}_2\text{S}_2$ requires 275.1134].

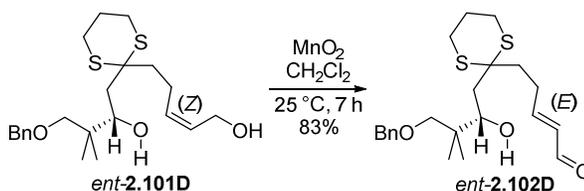
Preparation of α,β -Unsaturated Aldehyde *ent*-2.102C



To a solution of allylic alcohol *ent*-2.101C (63 mg, 0.19 mmol) in CH_2Cl_2 (3.5 mL, 0.054 M) was added MnO_2 (79 mg, 0.97 mmol). Additional equivalents of MnO_2 (79 mg, 0.97

mmol) were added every hour for 7 h while stirring. The reaction mixture was then purified by column chromatography (silica gel topped with Celite, hexanes/EtOAc = 3/1) to provide *ent*-**2.102C** as a colorless oil (47 mg, 75%): $[\alpha]_D^{23} = -45.3$ (*c* 0.71, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.49 (d, *J* = 8.0 Hz, 1H), 7.41–7.22 (m, 5H), 6.86 (dt, *J* = 15.6, 6.8 Hz, 1H), 6.14 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.09 (d, *J* = 9.2 Hz, 1H), 3.19 (s, 1H), 3.03–2.74 (m, 4H), 2.74–2.60 (m, 1H), 2.60–2.41 (m, 2H), 2.34–2.22 (m, 1H), 2.22–2.08 (m, 2H), 2.08–1.85 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 193.8, 157.4, 144.6, 133.1, 128.6, 127.6, 125.6, 71.3, 51.9, 47.3, 37.6, 27.8, 26.2, 26.1, 24.7; IR (neat) 3442, 2157, 1968, 1686, 1138, 1059, 973, 759, 702 cm⁻¹; HRMS (ESI) *m/z* 323.1140 [(M+H)⁺, C₁₇H₂₂O₂S₂ requires 323.1134].

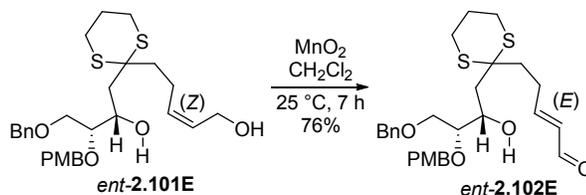
Preparation of α,β -Unsaturated Aldehyde *ent*-**2.102D**



To a solution of allylic alcohol *ent*-**2.101D** (63 mg, 0.15 mmol) in CH₂Cl₂ (2.7 mL, 0.056 M) was added MnO₂ (62 mg, 0.77 mmol). Additional equivalents of MnO₂ (62 mg, 0.77 mmol) were added every hour for 7 h while stirring. The reaction mixture was then purified by column chromatography (silica gel topped with Celite, hexanes/EtOAc = 3/1) to provide *ent*-**2.102D** as a colorless oil (52 mg, 83%): $[\alpha]_D^{27} = -33.2$ (*c* 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.47 (d, *J* = 8.0 Hz, 1H), 7.37–7.27 (m, 5H), 6.83 (dt, *J* = 15.6, 6.4 Hz,

1H), 6.12 (dd, $J = 15.6, 7.6$ Hz, 1H), 4.52 (d, $J = 12.0$ Hz, 1H), 4.48 (d, $J = 12.4$ Hz, 1H), 3.84 (dd, $J = 8.8, 4.4$ Hz, 1H), 3.42 (d, $J = 4.0$ Hz, 1H), 3.38 (d, $J = 9.2$ Hz, 1H), 3.32 (d $J = 9.2$ Hz, 1H), 2.90–2.74 (m, 4H), 2.68–2.57 (m, 1H), 2.56–2.45 (m, 1H), 2.27–2.08 (m, 3H), 2.02–1.90 (m, 3H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 194.0, 158.3, 137.9, 132.9, 128.4, 127.7, 127.5, 78.9, 74.4, 73.5, 52.5, 40.5, 38.8, 36.7, 28.3, 26.2, 26.1, 25.0, 22.6, 20.1; IR (neat) 3484, 2906, 1688, 1076, 739, 699 cm^{-1} ; HRMS (ESI) m/z 408.1872 $[(\text{M}+\text{H})^+]$, $\text{C}_{22}\text{H}_{32}\text{O}_3\text{S}_2$ requires 408.1866].

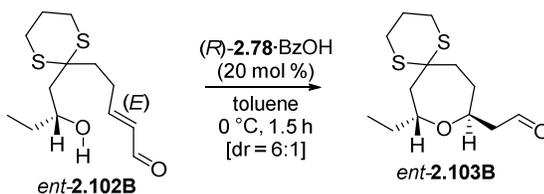
Preparation of α,β -Unsaturated Aldehyde *ent*-2.102E



To a solution of allylic alcohol *ent*-2.101E (41 mg, 0.08 mmol) in CH_2Cl_2 (1.4 mL, 0.057 M) was added MnO_2 (32 mg, 0.40 mmol). Additional equivalents of MnO_2 (32 mg, 0.40 mmol) were added every hour for 7 h while stirring. The reaction mixture was then purified by column chromatography (silica gel topped with Celite, hexanes/EtOAc = 3/1) to provide *ent*-2.102E as a colorless oil (31 mg, 76%): $[\alpha]_D^{25} = -15.3$ (c 1.07, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.46 (d, $J = 7.6$ Hz, 1H) 7.39–7.22 (m, 7H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.79 (dt, $J = 15.6, 6.4$ Hz, 1H), 6.08 (dd, $J = 15.6, 7.6$ Hz, 1H), 4.67 (d, $J = 11.2$ Hz, 1H), 4.55 (d, $J = 3.6$ Hz, 2H), 4.53 (d, $J = 12.8$ Hz, 1H), 4.13–4.06 (m, 1H), 3.79 (s, 3H), 3.76–3.65 (m, 2H), 3.52–3.45 (m, 1H), 2.99 (d, $J = 3.2$ Hz, 1H), 2.93–2.66 (m, 4H), 2.64–2.43 (m,

2H), 2.27 (d, $J = 15.2$ Hz, 1H), 2.21–2.02 (m, 3H), 2.02–1.82 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 193.9, 159.3, 157.8, 137.9, 133.0, 130.3, 129.6, 128.4, 127.7, 113.8, 80.3, 73.6, 72.2, 69.8, 69.3, 55.2, 52.1, 40.8, 37.3, 27.6, 26.2, 25.9, 24.9; IR (neat) 3459, 2907, 1684, 1611, 1512, 1246, 1077, 1030, 972, 821, 739, 699 cm^{-1} ; HRMS (ESI) m/z 534.2336 $[(\text{M}+\text{NH}_4)^+, \text{C}_{28}\text{H}_{36}\text{O}_5\text{S}_2 \text{ requires } 534.2342]$.

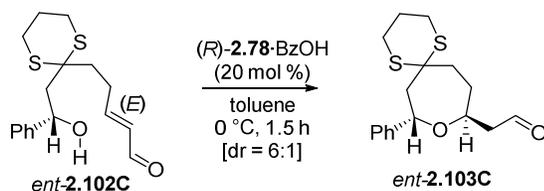
Organocatalytic Oxa-Conjugate Addition Reaction of α,β -Unsaturated Aldehyde *ent*-**2.102B**



To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-**2.102B** (31 mg, 0.11 mmol) in toluene (1.1 mL, 0.100 M) was added (*R*)-**2.78** (7 mg, 0.02 mmol) in toluene (0.9 mL) followed by BzOH (3 mg, 0.02 mmol) in toluene (0.1 mL). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with hexanes and filtered through a short column (silica gel, hexanes/EtOAc = 2/1) to afford a mixture of *ent*-**2.103B** and its corresponding α,α' -*cis*-isomer as a colorless oil: $[\alpha]_D^{23} = -13.8$ (c 0.18, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.83–9.76 (m, 1H), 4.43–4.32 (m, 1H), 3.72–3.60 (m, 1H), 2.95–2.86 (m, 1H), 2.86–2.76 (m, 1H), 2.76–2.62 (m, 3H), 2.45–2.35 (m, 2H), 2.30 (d, $J = 15.6$ Hz, 1H), 2.11–1.93 (m, 4H), 1.85 (dd, $J = 14.8, 10.0$ Hz, 1H), 1.80–1.71 (m, 1H), 1.52–1.33 (m, 2H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.3, 71.0, 70.1, 51.1, 49.4, 48.0, 36.3, 29.4,

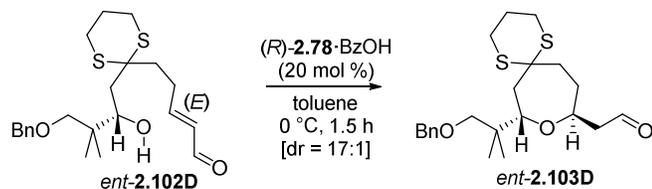
27.0, 25.7, 25.6, 10.6; IR (neat) 2933, 1724, 1136, 1112, 1063 cm^{-1} ; HRMS (ESI) m/z 275.1134 $[(M+H)^+]$, $\text{C}_{13}\text{H}_{22}\text{O}_2\text{S}_2$ requires 275.1134].

Organocatalytic Oxa-Conjugate Addition Reaction of α,β -Unsaturated Aldehyde *ent*-**2.102C**



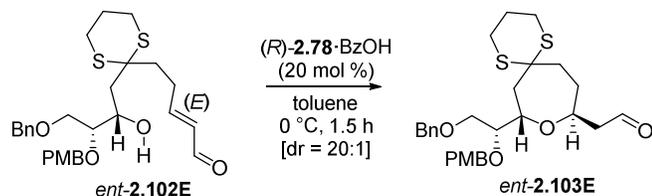
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-**2.102C** (25 mg, 0.08 mmol) in toluene (0.76 mL, 0.105 M) was added *(R)*-**2.78** (5 mg, 0.02 mmol) in toluene (0.6 mL) followed by BzOH (2 mg, 0.02 mmol) in toluene (76 μL). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with hexanes and filtered through a short column (silica gel, hexanes/EtOAc = 2/1) to afford a mixture of *ent*-**2.103C** and its corresponding α,α' -*cis*-isomer as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 9.69–9.64 (m, 1H), 7.36–7.22 (m, 5H), 4.87 (d, $J = 10.4$ Hz, 1H), 4.54–4.44 (m, 1H), 2.90–2.75 (m, 5H), 2.69 (ddd, $J = 16.0, 8.4, 2.4$ Hz, 1H), 2.58 (d, $J = 14.8$ Hz, 1H), 2.48–2.38 (m, 2H), 2.25 (dd, $J = 14.8, 10.0$ Hz, 1H), 2.20–2.09 (m, 1H), 2.08–1.95 (m, 2H), 1.91–1.82 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.2, 143.0, 128.4, 127.3, 125.7, 72.0, 70.6, 51.2, 50.2, 49.1, 36.7, 29.2, 26.9, 25.7, 25.6; IR (neat) 2931, 1722, 1445, 1112, 1065, 758, 700 cm^{-1} ; HRMS (ESI) m/z 345.0954 $[(M+\text{Na})^+]$, $\text{C}_{17}\text{H}_{22}\text{O}_2\text{S}_2$ requires 345.0953].

Organocatalytic Oxa-Conjugate Addition Reaction of α,β -Unsaturated Aldehyde *ent*-2.102D



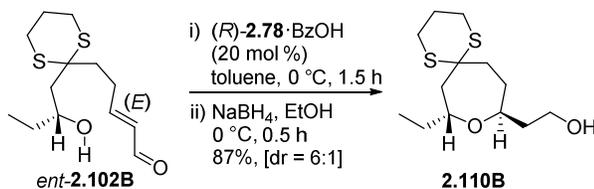
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-2.102D (27 mg, 0.07 mmol) in toluene (0.65 mL, 0.108 M) was added (R)-2.78 (4 mg, 0.01 mmol) in toluene (0.5 mL) followed by BzOH (2 mg, 0.01 mmol) in toluene (65 μ L). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with hexanes and filtered through a short column (silica gel, hexanes/EtOAc = 2/1) to afford a mixture of *ent*-2.103D and its corresponding α,α' -*cis*-isomer as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 9.76 (s, 1H), 7.37–7.26 (m, 5H), 4.51 (d, J = 12.4 Hz, 1H), 4.45 (d, J = 12.4 Hz, 1H), 4.43–4.35 (m, 1H), 3.74 (d, J = 9.6 Hz, 1H), 3.31 (d, J = 8.4 Hz, 1H), 3.05 (d, J = 8.8 Hz, 1H), 2.94–2.78 (m, 2H), 2.78–2.64 (m, 3H), 2.47 (d, J = 15.2 Hz, 1H), 2.35 (dd, J = 14.0, 9.2 Hz, 1H), 2.33 (dd, J = 16.8, 4.4 Hz, 1H), 2.13–1.92 (m, 4H), 1.81 (dd, J = 14.4, 9.6 Hz, 1H), 1.70 (ddd, J = 13.6, 7.6, 4.4 Hz, 1H), 0.93 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.8, 138.8, 128.3, 127.5, 127.4, 73.1, 72.1, 71.5, 51.3, 49.1, 43.5, 39.1, 36.6, 29.0, 27.1, 25.8, 25.5, 22.5, 20.4; IR (neat) 2933, 2906, 2158, 2009, 1973, 1724, 1098, 1076, 737, 698 cm^{-1} ; HRMS (ESI) m/z 431.1685 [(M+Na) $^+$, $\text{C}_{22}\text{H}_{32}\text{O}_3\text{S}_2$ requires 431.1685].

Organocatalytic Oxa-Conjugate Addition Reaction of α,β -Unsaturated Aldehyde *ent*-2.102E



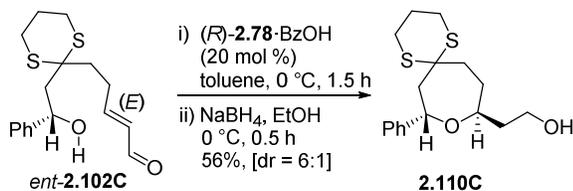
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-2.103E (63 mg, 0.12 mmol) in toluene (1.20 mL, 0.100 M) was added (*R*)-2.78 (8 mg, 0.02 mmol) in toluene (1.0 mL) followed by BzOH (3 mg, 0.02 mmol) in toluene (0.12 mL). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with hexanes and filtered through a short column (silica gel, hexanes/EtOAc = 2/1) to afford a mixture of *ent*-2.103E and its corresponding α,α' -*cis*-isomer as a colorless oil: $[\alpha]_D^{27} = -12.9$ (*c* 0.17, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 9.68 (s, 1H), 7.39–7.21 (m, 7H), 6.86 (dd, *J* = 10.0, 5.0 Hz, 2H), 4.64 (dd, *J* = 10.0, 5.0 Hz, 1H), 4.58–4.46 (m, 3H), 4.40–4.32 (m, 1H), 3.96–3.89 (m, 1H), 3.81 (s, 3H), 3.63–3.57 (m, 1H), 3.57–3.51 (m, 1H), 3.47–3.41 (m, 1H), 2.90–2.56 (m, 6H), 2.37–2.23 (m, 2H), 2.11–1.77 (m, 5H), 1.74–1.65 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 201.4, 159.2, 138.3, 130.6, 129.5, 128.3, 127.7, 127.6, 113.7, 80.4, 73.4, 72.3, 71.9, 69.4, 69.1, 55.3, 51.1, 49.0, 43.4, 37.2, 28.8, 26.9, 25.7, 25.4; IR (neat) 2906, 1723, 1513, 1248, 1093, 1034, 739, 700 cm⁻¹; HRMS (ESI) *m/z* 517.2080 [(M+H)⁺, C₂₈H₃₆O₅S₂ requires 517.2077].

One-pot Organocatalytic Oxa-Conjugate Addition/Reduction of α,β -Unsaturated Aldehyde *ent*-2.102B



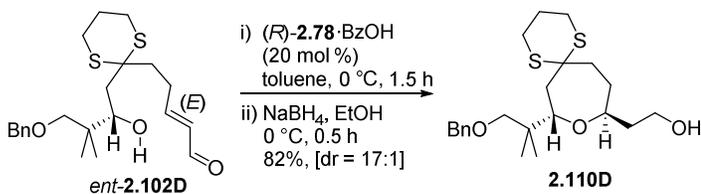
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-**2.102B** (52 mg, 0.19 mmol) in toluene (1.9 mL, 0.100 M) was added (*R*)-**2.78** (12 mg, 0.04 mmol) in toluene (1.5 mL) followed by BzOH (5 mg, 0.04 mmol) in toluene (0.19 mL). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with EtOH and treated with NaBH₄ (22 mg, 0.57 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with H₂O and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with H₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 2/1) to provide a mixture of **2.110B** and its corresponding α,α' -*cis*-isomer as a colorless oil (45 mg, 87%): ¹H NMR (400 MHz, CDCl₃) δ 3.98–3.90 (m, 1H), 3.80–3.68 (m, 3H), 2.92–2.79 (m, 2H), 2.79–2.65 (m, 2H), 2.43–2.27 (m, 3H), 2.05–1.89 (m, 5H), 1.84 (dd, *J* = 14.8, 10.0 Hz, 1H), 1.79–1.71 (m, 1H), 1.71–1.62 (m, 1H), 1.60–1.48 (m, 2H), 1.48–1.37 (m, 2H), 0.91 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 74.7, 70.1, 61.0, 51.2, 47.2, 37.5, 36.9, 30.0, 29.4, 27.0, 25.7, 25.6, 10.4; HRMS (ESI) *m/z* 277.1299 [(M+H)⁺, C₁₃H₂₄O₂S₂ requires 277.1290].

One-pot Organocatalytic Oxa-Conjugate Addition/Reduction of α,β -Unsaturated Aldehyde *ent*-2.102C



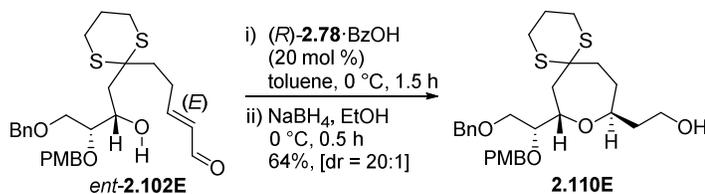
To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-2.102C (16 mg, 0.05 mmol) in toluene (0.5 mL, 0.100 M) was added (*R*)-2.78 (3 mg, 0.01 mmol) in toluene (0.4 mL) followed by BzOH (1 mg, 0.01 mmol) in toluene (48 μ L). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with EtOH and treated with NaBH₄ (6 mg, 0.15 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with H₂O and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with H₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 2/1) to provide a mixture of 2.110C and its corresponding α,α' -*cis*-isomer as a colorless oil (9 mg, 56%): ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.24 (m, 5H), 4.87 (d, *J* = 10.0 Hz, 1H), 4.19–4.11 (m, 1H), 3.72–3.57 (m, 2H), 2.92–2.74 (m, 4H), 2.56 (d, *J* = 15.6 Hz, 1H), 2.41 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.29 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.24–2.08 (m, 2H), 2.08–1.89 (m, 3H), 1.85–1.74 (m, 2H), 1.65–1.55 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 143.3, 128.6, 127.4, 125.7, 76.0, 75.9, 70.6, 61.2, 51.3, 50.2, 36.9, 29.3, 26.9, 25.7, 25.6; HRMS (ESI) *m/z* 347.1117 [(M+Na)⁺, C₁₇H₂₄O₂S₂ requires 347.1110].

One-pot Organocatalytic Oxa-Conjugate Addition/Reduction of α,β -Unsaturated Aldehyde *ent*-2.102D



To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-2.102D (39 mg, 0.10 mmol) in toluene (0.9 mL, 0.111 M) was added (*R*)-2.78 (6 mg, 0.02 mmol) in toluene (0.8 mL) followed by BzOH (2 mg, 0.02 mmol) in toluene (93 μ L). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with EtOH and treated with NaBH₄ (11 mg, 0.29 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with H₂O and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with H₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 2/1) to provide a mixture of 2.110D and its corresponding α,α' -*cis*-isomer as a colorless oil (32 mg, 82%): ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.24 (m, 5H), 4.55–4.43 (m, 2H), 3.98–3.90 (m, 1H), 3.79–3.64 (m, 3H), 3.34 (d, *J* = 8.8 Hz, 1H), 3.15 (d, *J* = 8.8 Hz, 1H), 2.93–2.75 (m, 2H), 2.75–2.65 (m, 2H), 2.49 (d, *J* = 14.8 Hz, 1H), 2.39 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.08–1.90 (m, 4H), 1.90–1.70 (m, 3H), 1.67–1.53 (m, 2H), 0.95 (s, 3H), 0.91 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.8, 128.2, 127.4, 127.3, 74.6, 73.1, 72.5, 60.5, 51.4, 42.7, 39.2, 38.1, 37.5, 29.3, 27.0, 25.8, 25.5, 22.4, 21.0; HRMS (ESI) *m/z* 411.2032 [(M+H)⁺, C₂₂H₃₄O₃S₂ requires 411.2022].

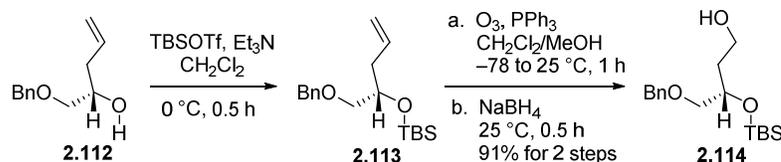
One-pot Organocatalytic Oxa-Conjugate Addition/Reduction of α,β -Unsaturated Aldehyde *ent*-2.102E



To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-**2.102E** (42 mg, 0.08 mmol) in toluene (0.8 mL, 0.100 M) was added (*R*)-**2.78** (5 mg, 0.02 mmol) in toluene (0.7 mL) followed by BzOH (2 mg, 0.02 mmol) in toluene (79 μ L). After stirring for 1.5 h at 0 °C, the reaction mixture was diluted with EtOH and treated with NaBH₄ (9 mg, 0.24 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with H₂O and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with H₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting residue was purified by column chromatography (silica gel, hexanes/EtOAc = 2/1) to provide a mixture of **2.110E** and its corresponding α,α' -*cis*-isomer as a colorless oil (27 mg, 64%): ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.24 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.52 (dd, *J* = 12.0, 6.4 Hz, 2H), 3.98 (dd, *J* = 9.6, 4.4 Hz, 2H), 3.79 (s, 3H), 3.74–3.59 (m, 4H), 3.53 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.88–2.73 (m, 2H), 2.73–2.59 (m, 2H), 2.55 (d, *J* = 14.8 Hz, 1H), 2.29 (dd, *J* = 11.2, 6.8 Hz, 1H), 2.06–1.84 (m, 5H), 1.77–1.50 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 159.2, 138.2, 130.5, 129.6, 128.4, 127.7, 127.6, 113.8, 80.8, 75.6, 73.5, 72.3, 70.5, 69.4, 60.9, 55.3, 51.2, 43.1, 37.7,

29.4, 27.0, 25.7, 25.5; HRMS (ESI) m/z 519.2249 [(M+H)⁺, C₂₈H₃₈O₅S₂ requires 519.2233].

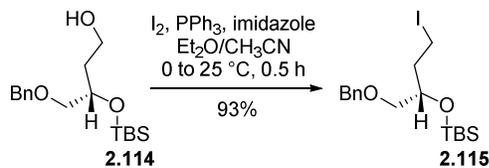
Preparation of Alcohol 2.114



[TBS Protection] To a cooled solution (0 °C) of the known alkene (**2.112**)⁸⁵ (646 mg, 3.36 mmol) in CH₂Cl₂ (11.8 mL, 0.285 M) was added triethylamine (1.9 mL, 13.45 mmol) and TBSOTf (1.5 mL, 6.73 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with saturated aqueous NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc, 40/1) yielded the known silyl ether (**2.113**)⁸⁶ as a colorless oil. **[Ozonolysis]** Ozone was bubbled through a solution of (**2.113**) in CH₂Cl₂/MeOH (1/1, 65 mL) at -78 °C until the solution became light blue. Triphenylphosphine (2.65 g, 10.09 mmol) was added. After stirring for 1 h at 25 °C, NaBH₄ (127 mg, 3.36 mmol) was added. After stirring for 0.5 h at 25 °C, the reaction was quenched with saturated aqueous NH₄Cl and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 5/1) yielded alcohol **2.114** as a colorless oil (950 mg, 91% for two steps): $[\alpha]_D^{27} = -18.9$ (c 1.15, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.39–7.27 (m, 5H), 4.54 (s, 2H), 4.10–4.02 (m, 1H), 3.82–3.69 (m, 2H), 3.49 (dd, $J =$

10.0, 5.0 Hz, 1H), 3.44 (dd, $J = 10.0, 5.0$ Hz, 1H), 2.57 (br s, 1H), 1.94–1.82 (m, 1H), 1.82–1.70 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.0, 128.4, 127.6, 74.1, 73.4, 70.4, 59.7, 36.8, 25.8, 18.0, -4.5, -5.0; IR (neat) 3416, 2953, 2928, 2885, 2856, 1472, 1253, 1097, 1028, 836, 777, 713, 698 cm^{-1} ; HRMS (ESI) m/z 311.2037 [(M+H) $^+$, $\text{C}_{17}\text{H}_{30}\text{O}_3\text{Si}$ requires 311.2037].

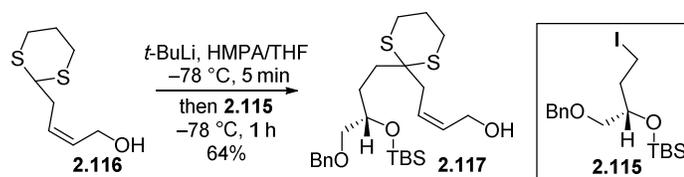
Preparation of Iodide **2.115**



To a cooled (0 °C) solution of alcohol **2.114** (950 mg, 3.06 mmol) in $\text{Et}_2\text{O}/\text{CH}_3\text{CN}$ (3/1, 19 mL, 0.161 M) was added imidazole (417 mg, 6.13 mmol), triphenylphosphine (1.21 g, 4.59 mmol), and iodine (1.17 g, 4.59 mmol). The reaction was warmed to 25 °C over 0.5 h and then diluted with H_2O and Et_2O . The layers were separated and the aqueous layer was washed with Et_2O . The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/ EtOAc = 40/1) yielded **2.115** as a colorless oil (1.198 g, 93%): $[\alpha]_D^{27} = -32.4$ (c 1.00, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.20 (m, 5H), 4.45 (s, 2H), 3.85–3.81 (m, 1H), 3.36 (dd, $J = 9.8, 5.0$ Hz, 1H), 3.29 (dd, $J = 10.0, 5.8$ Hz, 1H), 3.22–3.11 (m, 2H), 2.06–1.88 (m, 2H), 0.81 (s, 9H), 0.03 (s, 3H), 0.0 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.1, 129.6, 128.3, 127.6, 74.00, 73.3, 71.2, 38.7, 25.9, 18.1, 2.9, -4.3, -4.7; IR (neat) 2954, 2928, 2856,

1253, 1118, 835, 778, 697 cm^{-1} ; HRMS (ESI) m/z 421.1056 $[(M+H)^+]$, $\text{C}_{17}\text{H}_{29}\text{IO}_2\text{Si}$ requires 421.1054].

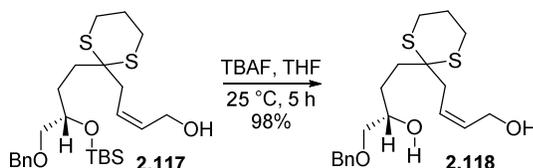
Preparation of Allylic Alcohol **2.117**



To a cooled ($-78\text{ }^\circ\text{C}$) solution of the known dithiane (**2.116**)^{65b} (542 mg, 2.85 mmol) in THF/HMPA (10/1, 38.5 mL, 0.074 M) was added $t\text{-BuLi}$ (1.7 M in pentane, 3.7 mL, 6.29 mmol). After stirring for 5 min at $-78\text{ }^\circ\text{C}$, iodide **2.115** (1.20 g, 2.85 mmol) in THF (2.8 mL, 1.018 M) was added. After stirring at $-78\text{ }^\circ\text{C}$ for 1 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 5/1) yielded **2.117** as a colorless oil (876 mg, 64%): $[\alpha]_D^{23} = -9.0$ (c 0.58, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.27 (m, 5H), 5.79 (dt, $J = 10.8, 7.2$ Hz, 1H), 5.65 (dt, $J = 11.2, 7.4$ Hz, 1H), 4.51 (s, 2H), 4.23–4.11 (m, 2H), 3.84–3.79 (m, 1H), 3.41 (dd, $J = 9.6, 5.2$ Hz, 1H), 3.34 (dd, $J = 9.4, 6.2$ Hz, 1H), 2.87–2.76 (m, 4H), 2.67 (d, $J = 7.6$ Hz, 2H), 2.05 (ddd, $J = 13.6, 13.6, 4.4$ Hz, 1H), 1.98–1.93 (m, 2H), 1.86 (ddd, $J = 13.6, 13.6, 3.6$ Hz, 1H), 1.75 (dddd, $J = 16.5, 16.5, 5.0, 5.0$ Hz, 1H), 1.61–1.55 (m, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.1, 131.7, 128.3, 127.7, 127.6, 126.2, 74.3, 73.3, 71.0, 58.4, 52.6, 35.9, 33.6, 29.1, 26.0, 25.9, 25.2, 18.1, $-4.5, -4.7$; IR (neat) 3472, 2949, 2926, 2887, 2855, 2161, 2012, 1969, 1253,

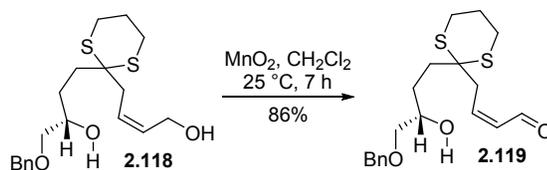
1097, 1004, 835, 776, 697 cm^{-1} ; HRMS (ESI) m/z 500.2686 $[(M+NH_4)^+]$, $C_{25}H_{42}O_3S_2Si$ requires 500.2683].

Preparation of Diol **2.118**



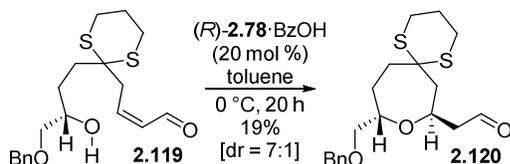
To a solution of **2.117** (876 mg, 1.82 mmol) in THF (10.4 mL, 0.175 M) was added TBAF (1.0 M in THF, 3.6 mL, 3.60 mmol). After stirring for 5 h at 25 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded the diol **2.118** as a colorless oil (656 mg, 98%): $[\alpha]_D^{25} = -4.5$ (c 0.78, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.78 (dt, $J = 10.4, 8.0$ Hz, 1H), 5.64 (dt, $J = 10.0, 8.0$ Hz, 1H), 4.52 (s, 2H), 4.20–4.06 (m, 2H), 3.76 (bs, 1H), 3.46 (dd, $J = 9.2, 3.2$ Hz, 1H), 3.34 (dd, $J = 8.4, 8.4$ Hz, 1H), 2.85 (br s, 1H), 2.80–2.72 (m, 4H), 2.76–2.61 (m, 3H), 2.11 (ddd, $J = 13.6, 13.6, 4.0$ Hz, 1H), 1.95–1.83 (m, 3H), 1.66–1.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 131.7, 128.4, 127.8, 126.1, 74.3, 73.3, 70.2, 58.0, 52.3, 35.4, 33.8, 27.7, 26.00, 25.2; IR (neat) 3392, 2905, 2862, 1453, 1423, 1275, 1094, 1027, 738, 699 cm^{-1} ; HRMS (ESI) m/z 391.1369 $[(M+Na)^+]$, $C_{19}H_{28}O_3S_2$ requires 391.1372].

Preparation of α,β -Unsaturated Aldehyde **2.119**



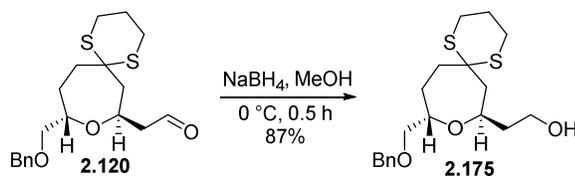
The diol **2.118** (231 mg, 0.63 mmol) was dissolved in CH_2Cl_2 (12.3 mL, 0.864 M) followed by addition of MnO_2 (272 mg, 3.13 mmol) at 25°C . Additional equivalents of MnO_2 (272 mg, 3.13 mmol) were added every hour for 7 h. The reaction mixture was then purified by column chromatography topped with Celite (silica gel, hexanes/EtOAc = 2/1) to provide **2.119** as a colorless oil (198 mg, 86%): $[\alpha]_{\text{D}}^{27} = -5.5$ (c 1.13, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 10.05 (d, $J = 7.6$ Hz, 1H), 7.38–7.28 (m, 5H), 6.76 (dt, $J = 11.6, 7.2$ Hz, 1H), 6.12 (dt, $J = 11.2, 7.6$ Hz, 1H), 4.55 (s, 2H), 3.82–3.79 (m, 1H), 3.50 (dd, $J = 9.2, 2.8$ Hz, 1H), 3.34 (dd, $J = 8.8, 8.8$ Hz, 1H), 3.19 (d, $J = 7.6$, 2H), 2.92–2.78 (m, 4H), 2.36 (d, $J = 4.0$, 1H), 2.24–2.16 (m, 1H), 1.99–1.87 (m, 3H), 1.66–1.60 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 190.6, 146.6, 137.7, 131.6, 128.5, 127.9, 127.8, 74.3, 73.4, 70.2, 52.1, 36.7, 35.0, 27.9, 26.1, 24.7; IR (neat) 3453, 2905, 2859, 1677, 1122, 740, 699 cm^{-1} ; HRMS (ESI) m/z 389.1229 $[(\text{M}+\text{Na})^+]$, $\text{C}_{19}\text{H}_{26}\text{O}_3\text{S}_2$ requires 389.1216].

Preparation of Oxepane **2.120**



To a cooled (0 °C) solution of α,β -unsaturated aldehyde **2.119** (198 mg, 0.54 mmol) in toluene (5.3 mL, 0.102 M) was added (R) -**2.78** (35.2 mg, 0.11 mmol) in toluene (4.4 mL) followed by BzOH (13.3 mg, 0.11 mmol) in toluene (0.53 mL). After stirring for 20 h at 0 °C, the reaction mixture was diluted with hexanes and purified via column chromatography (silica gel, hexanes/EtOAc = 3/1) to afford an inseparable mixture of α,α' -*trans*-oxepane **2.120** and its corresponding α,α' -*cis*-isomer as a colorless oil (38 mg, 19%).

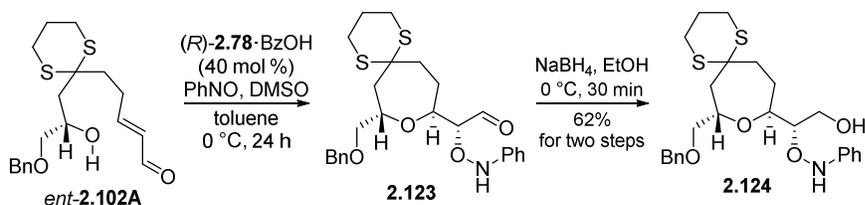
Preparation of Alcohol **2.175** for 2D NMR Analysis



To a cooled (0 °C) solution of a mixture of **2.120** and its corresponding α,α' -*cis*-isomer (38 mg, 0.10 mmol) in MeOH (4.7 mL, 0.021 M) was added NaBH₄ (12 mg, 0.31 mmol). After stirring for 0.5 h at 0 °C, the reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1) yielded α,α' -*trans*-oxepane alcohol **2.175** as a colorless oil (29 mg, 87%): ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.29 (m, 5H), 4.56 (s, 2H), 4.10 (dt, J = 10.0, 2.8 Hz, 1H), 3.99

(dddd, $J = 11.2, 4.8, 4.8, 4.8$ Hz, 1H), 3.85–3.72 (m, 1H), 3.72–3.62 (m, 1H), 3.50–3.39 (m, 2H), 3.29 (br s, 1H), 2.92–2.79 (m, 2H), 2.72 (t, $J = 4.8$ Hz, 1H), 2.71 (t, $J = 4.4$ Hz, 1H), 2.41 (dd, $J = 13.6, 7.2$ Hz, 1H), 2.26 (d, $J = 14.8$ Hz, 1H), 2.13 (ddd, $J = 15.2, 11.6, 11.6$ Hz, 1H), 2.04–1.89 (m, 4H), 1.77–1.56 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.4, 128.4, 128.0, 127.8, 75.0, 73.4, 72.5, 68.3, 60.5, 51.1, 49.1, 38.7, 36.1, 26.9, 25.6, 25.5, 25.2; IR (neat) 3441, 2934, 1079, 738, 699 cm^{-1} ; HRMS (ESI) m/z 391.1372 [(M+Na) $^+$, $\text{C}_{19}\text{H}_{28}\text{O}_3\text{S}_2$ requires 391.1372].

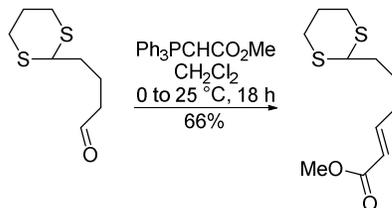
Organocatalytic Tandem Oxa-Conjugate Addition/ α -Oxidation



To a cooled (0 °C) solution of α,β -unsaturated aldehyde *ent*-**2.102A** (70 mg, 0.19 mmol) in toluene (1.9 mL, 0.100 M) was added DMSO (0.2 mL) and nitrosobenzene (25 mg, 0.23 mmol). (*R*)-**2.78** (26 mg, 0.08 mmol) in toluene (1.6 mL, 0.050 M) was added followed by BzOH (9 mg, 0.08 mmol) in toluene (180 μL , 0.500 M). After stirring for 24 h at 0 °C, the reaction was diluted with EtOH and NaBH_4 (22 mg, 0.57 mmol) was added. After stirring for 0.5 h at 0 °C, the reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 2/1) to afford oxepane **2.124** as a light yellow oil (56 mg, 62%): ^1H NMR

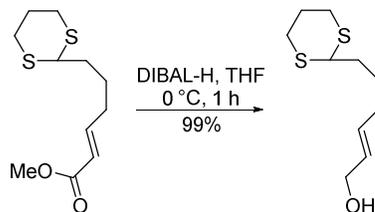
(400 MHz, acetone-D₆) δ 7.80 (s, 1H), 7.39–7.20 (m, 10 H), 6.92 (dt, J = 7.2, 1.2 Hz, 1H), 4.55 (s, 2H), 4.21 (t, J = 10.0 Hz, 1H), 3.89 (t, J = 10.0 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 3.50–3.39 (m, 2H), 3.32 (ddd, J = 9.6, 5.6, 1.2 Hz, 1H), 2.92–2.73 (m, 3H), 2.66–2.52 (m, 2H), 2.30 (ddd, J = 14.4, 9.6, 1.2 Hz, 1H), 2.24–2.08 (m, 3H), 1.96–1.84 (m, 1H), 1.75–1.58 (m, 4H); HRMS (ESI) m/z 475.1925 [(M+H)⁺, C₂₅H₃₃NO₄S₂ requires 476.1924].

Preparation of α,β -unsaturated methyl ester **2.131**



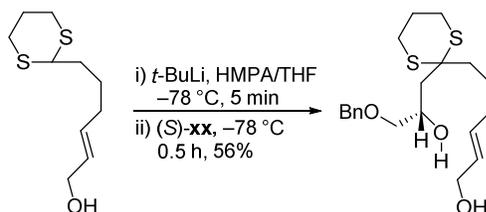
To a cooled (0 °C) solution of aldehyde **2.130** (2.97 g, 15.59 mmol) in CH_2Cl_2 (16.0 mL, 0.974 M) was added methyl (triphenylphosphoranylidene)acetate (5.74 g, 17.15 mmol). The reaction mixture was stirred at 25 °C for 18 h before concentration *in vacuo*. The resulting mixture was washed with pentane and the precipitate was removed by vacuum filtration. Purification by column chromatography (silica gel, hexanes/EtOAc = 7/1) afford α,β -unsaturated methyl ester **2.131** as a colorless oil (2.52 g, 66%): ¹H NMR (400 MHz, CDCl_3) δ 6.90 (dt, J = 15.6, 6.8 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.00 (t, J = 6.8 Hz, 1H), 3.68 (s, 3H), 2.89–2.74 (m, 4H), 2.20 (dt, J = 7.2, 6.8 Hz, 2H), 2.12–2.05 (m, 1H), 1.87–1.61 (m, 3H).

Preparation of allylic alcohol **2.132**



To a cooled (0 °C) solution of α,β -unsaturated methyl ester **2.131** (2.52 g, 10.22 mmol) in THF (34.0 mL, 0.301 M) was added DIBAL-H (1.0 M in toluene, 26.0 mL, 25.54 mmol). The reaction mixture was stirred at 0 °C for 1 h before quenching with 1M NaOH. The reaction mixture was stirred at 25 °C for 1 h and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1) yielded allylic alcohol **2.132** as a colorless oil (2.23 g, 99%): ¹H NMR (400 MHz, CDCl₃) δ 5.68–5.56 (m, 2H), 4.01 (t, *J* = 6.8 Hz, 1H), 2.88–2.76 (m, 4H), 2.12–2.02 (m, 3H), 1.87–1.77 (m, 1H), 1.75–1.69 (m, 1H), 1.65 (br s, 1H), 1.61–1.53 (m, 1H).

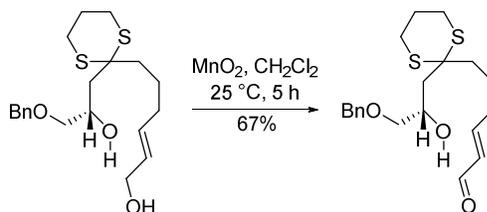
Preparation of Monoallylic Diol **2.133**



To a cooled (-78 °C) solution of dithiane **2.132** (456 mg, 2.09 mmol) in THF/HMPA (10/1, 27.2 mL, 0.077 M) was added *t*-BuLi (1.7 M in pentane, 3.9 mL, 6.68 mmol). After stirring for 5 min at -78 °C, epoxide (*S*)-**2.94** (685 mg, 4.18 mmol) in THF (3.2 mL, 1.306 M) was

added. After stirring at $-78\text{ }^{\circ}\text{C}$ for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1) yielded monoallylic diol **2.133** as a colorless oil (451 mg, 56%): ^1H NMR (400 MHz, CDCl_3) δ 7.45–7.27 (m, 5H), 5.69–5.60 (m, 2H), 4.57 (s, 2H), 4.15–4.10 (m, 1H), 4.06 (d, $J = 4.0$ Hz, 2H), 3.44 (d, $J = 5.2$ Hz, 2H), 3.24 (br s, 2H), 2.95 (ddd, $J = 14.0, 10.0, 3.2$ Hz, 1H), 2.86 (ddd, $J = 14.4, 9.6, 3.2$ Hz, 1H), 2.79–2.72 (m, 2H), 2.24 (dd, $J = 15.2, 8.4$ Hz, 1H), 2.10–2.85 (m, 7H), 1.71–1.50 (m, 2H).

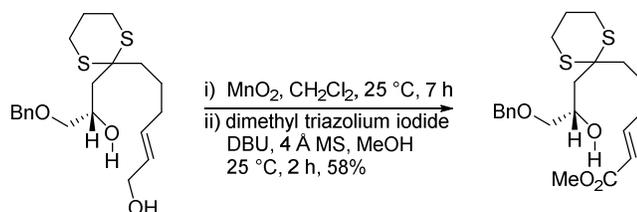
Preparation of α,β -Unsaturated Aldehyde **2.134**



To a solution of monoallylic diol **2.133** (93 mg, 0.24 mmol) in CH_2Cl_2 (4.5 mL, 0.053 M) added MnO_2 (98 mg, 1.22 mmol) at $25\text{ }^{\circ}\text{C}$. Additional equivalents of MnO_2 (98 mg, 1.22 mmol) were added every hour for 5 h. The reaction mixture was then purified by column chromatography topped with celite (silica gel, hexanes/EtOAc = 2/1) to provide α,β -unsaturated aldehyde **2.134** as a colorless oil (62 mg, 67%): ^1H NMR (400 MHz, CDCl_3) δ 9.49 (d, $J = 8.0$ Hz, 1H), 7.39–7.25 (m, 5H), 6.80 (dt, $J = 15.6, 6.8$ Hz, 1H), 6.13 (dd, $J = 15.6, 7.6$ Hz, 1H), 4.56 (s, 2H), 4.16–4.10 (m, 1H), 3.43 (d, $J = 5.2$ Hz, 2H), 3.05 (bs,

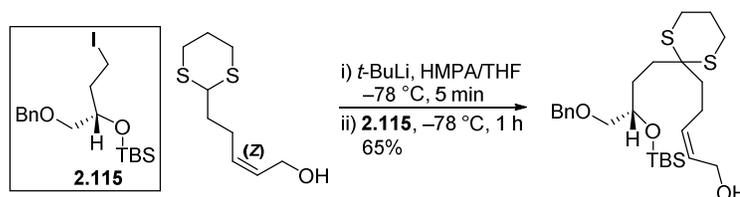
1H), 2.98–2.80 (m, 2H), 2.80–2.71 (m, 2H), 2.34 (q, $J = 7.2$ Hz, 2H), 2.20 (dd, $J = 15.2$, 8.4 Hz, 1H), 2.09 (bs, 1H), 2.07–1.65 (m, 8H).

Preparation of α,β -Unsaturated Methyl Ester **2.137**



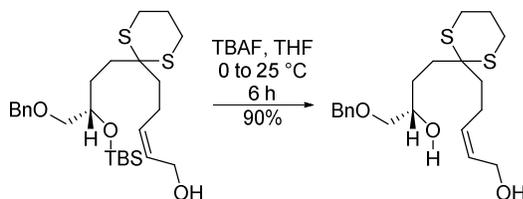
To a solution of monoallylic diol **2.133** (103 mg, 0.27 mmol) in CH_2Cl_2 (5.1 mL, 0.053 M) was added MnO_2 (109 mg, 1.35 mmol) at 25°C . Additional equivalents of MnO_2 (109 mg, 1.35 mmol) were added every hour for 7 h. At this time, dimethyl triazolium iodide (12 mg, 0.05 mmol), DBU (50 μL , 0.32 mmol), MeOH (54 μL , 1.35 mmol) and 4 Å MS (520 mg) were added and stirring continued at 25°C for 2 h. The reaction mixture was then purified by column chromatography topped with celite (silica gel, hexanes/EtOAc = 2/1) to provide α,β -unsaturated methyl ester **2.137** as a colorless oil (64 mg, 58%): ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.27 (m, 5H), 6.95 (dt, $J = 15.6$, 7.2 Hz, 1H), 5.84 (d, $J = 15.6$ Hz, 1H), 4.57 (s, 2H), 4.16–4.10 (m, 1H), 3.72 (s, 3H), 3.43 (d, $J = 6.8$ Hz, 2H), 3.09 (br s, 1H), 2.94 (ddd, $J = 14.4$, 10.0, 3.2 Hz, 1H), 2.85 (ddd, $J = 12.4$, 9.2, 3.2 Hz, 1H), 2.79–2.72 (m, 2H), 2.21 (dt, $J = 8.4$, 6.8 Hz, 2H), 2.07–1.87 (m, 6H), 1.79–1.59 (m, 2H).

Coupling Reaction of Dithiane **2.106** and Iodide **2.115**



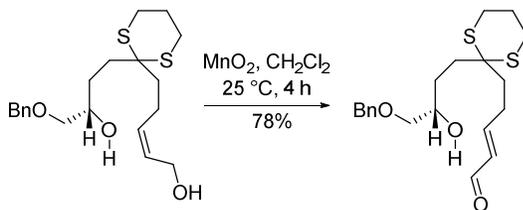
To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of dithiane **2.106** (405 mg, 1.98 mmol) in THF/HMPA (7/1, 23.9 mL, 0.083 M) was added *t*-BuLi (1.7 M in pentane, 3.0 mL, 4.96 mmol). After stirring for 5 min at $-78\text{ }^{\circ}\text{C}$, iodide **2.115** (1.00 mg, 2.38 mmol) in THF (2.5 mL, 0.952 M) was added. After stirring at $-78\text{ }^{\circ}\text{C}$ for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 3/1) yielded **2.139** as a colorless oil (641 mg, 65%): ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.26 (m, 5H), 5.61 (dt, $J = 8.8, 5.2$ Hz, 1H), 5.52 (dt, $J = 8.4, 6.0$ Hz, 1H), 4.52 (s, 2H), 4.17 (bs, 2H), 3.87–3.82 (m, 1H), 3.42 (dd, $J = 7.6, 4.4$ Hz, 1H), 3.37 (dd, $J = 7.6, 4.4$ Hz, 1H), 2.84–2.74 (m, 4H), 2.22 (dt, $J = 6.4, 6.0$ Hz, 2H), 2.06 (ddd, $J = 14.8, 11.2, 3.6$ Hz, 1H), 1.98–1.84 (m, 5H), 1.73 (tt, $J = 10.8, 3.2$ Hz, 1H), 1.64–1.56 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).

Preparation of Monoallylic Diol **2.140**



To a cooled (0 °C) solution of **2.139** (641 mg, 1.29 mmol) in THF (9.2 mL, 0.140 M) was added TBAF (1.0 M in THF, 2.6 mL, 2.58 mmol). After stirring for 6 h at 25 °C, the reaction was quenched with saturated aqueous NH₄Cl and extracted with Et₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1 to 1/1) yielded monoallylic diol **2.140** as a colorless oil (447 mg, 90%): ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.28 (m, 5H), 5.62 (dt, *J* = 10.8, 6.4 Hz, 1H), 5.53 (dt, *J* = 10.8, 7.6 Hz, 1H), 4.55 (s, 2H), 4.18 (d, *J* = 6.4 Hz, 2H), 3.84–3.77 (m, 1H), 3.51 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.35 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.86–2.74 (m, 4H), 2.51 (br s, 2H), 2.28–2.13 (m, 3H), 1.97–1.85 (m, 5H), 1.65–1.54 (m, 2H).

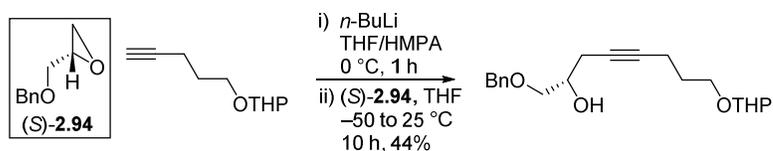
Preparation of α,β -Unsaturated Aldehyde **2.141**



To a solution of monoallylic diol **2.140** (23 mg, 0.06 mmol) in CH₂Cl₂ (1.0 mL, 0.060 M) was added MnO₂ (24 mg, 0.30 mmol) at 25 °C. Additional equivalents of MnO₂ (24 mg,

0.30 mmol) were added every hour for 4 h. The reaction mixture was then purified by column chromatography topped with celite (silica gel, hexanes/EtOAc = 2/1) to provide α,β -unsaturated aldehyde **2.141** as a colorless oil (18 mg, 78%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.50 (d, $J = 8.0$ Hz, 1H), 7.38–7.27 (m, 5H), 6.86 (dt, $J = 15.6, 6.4$ Hz, 1H), 6.14 (dd, $J = 15.6, 8.0$ Hz, 1H), 4.55 (s, 2H), 3.83–3.78 (m, 1H), 3.51 (dd, $J = 9.6, 3.0$ Hz, 1H), 3.35 (dd, $J = 9.6, 7.6$ Hz, 1H), 2.87–2.76 (m, 4H), 2.55–2.49 (m, 2H), 2.42 (bs, 1H), 2.18 (dd, $J = 14.4, 11.2, 5.6$ Hz, 1H), 2.05–2.00 (m, 2H), 1.98–1.86 (m, 3H), 1.66–1.53 (m, 2H).

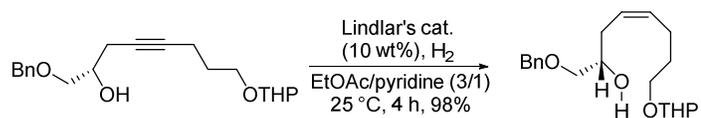
Coupling of Epoxide **2.94** and Alkyne **2.145**



To a cooled (0 °C) solution of the known alkyne (**2.145**) (486 mg, 2.89 mmol) in THF (4.6 mL, 0.628 M) was added *n*-BuLi (2.5 M in hexane, 1.7 mL, 4.33 mmol). After stirring at 0 °C for 1 h, HMPA (0.9 mL, 5.12 mmol) was added. The reaction mixture was cooled to –50 °C and epoxide (*S*)-**2.94** (948 mg, 5.78 mmol) in THF (4.5 mL, 1.284 M) was added. After stirring at –50 °C for 10 min, the reaction was warmed to 0 °C and then gradually warmed to 25 °C over 10 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 3/1) yielded **2.146** as a colorless oil (424 mg, 44%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.38–7.26 (m, 5H), 4.57 (s, 3H), 3.95–3.77 (m, 3H), 3.59 (dd, $J = 9.2, 4.0$ Hz,

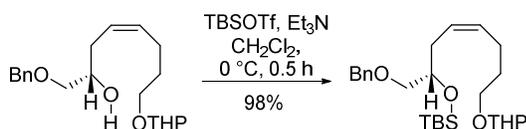
1H), 3.53–3.42 (m, 3H), 2.41 (d, $J = 6.4$ Hz, 2H), 2.27 (t, $J = 6.4$ Hz, 2H), 1.85–1.66 (m, 4H), 1.61–1.46 (m, 4H).

Preparation of (*Z*)-alkene **2.147**



To a solution of alkyne **2.146** (43 mg, 0.13 mmol) in EtOH/pyridine (3/1, 0.53 mL, 0.245 M) was added Lindlar's catalyst (4 mg, 10 wt%). After stirring under an H₂ atmosphere at 25 °C for 4 h, the reaction mixture was filtered through a pad of celite to afford **2.147** as a colorless oil (42 mg, 98%): ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.26 (m, 5H), 5.53 (dt, $J = 10.4, 7.6$ Hz, 1H), 5.43 (dt, $J = 11.2, 7.2$ Hz, 1H), 4.56 (s, 3H), 3.89–3.82 (m, 2H), 3.77–3.70 (m, 1H), 3.54–3.46 (m, 2H), 3.42–3.35 (m, 2H), 2.93 (dd, $J = 12.8, 4.0$ Hz, 1H), 2.34–2.21 (m, 2H), 2.20–2.08 (m, 2H), 1.88–1.76 (m, 1H), 1.76–1.61 (m, 3H), 1.61–1.46 (m, 4H).

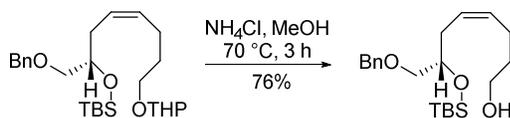
Preparation of TBS ether **2.148**



To a cooled (0 °C) solution of alcohol **2.147** (245 mg, 0.73 mmol) in CH₂Cl₂ (2.6 mL, 0.281 M) was added Et₃N (0.4 mL, 2.93 mmol) followed TBSOTf (0.3 mL, 1.47 mmol). After stirring at 0 °C for 0.5 h, the reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and

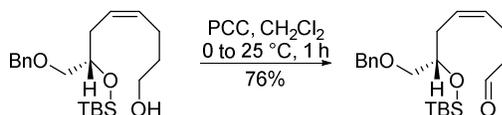
concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 20/1) yielded **2.148** as a colorless oil (321 mg, 98%): ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.26 (m, 5H), 5.50–5.40 (m, 2H), 4.57 (bs, 1H), 4.52 (s, 2H), 3.89–3.83 (m, 2H), 3.73 (ddd, $J = 9.6, 6.8, 6.4$ Hz, 1H), 3.52–3.46 (m, 1H), 3.41–3.43 (m, 1H), 3.39 (d, $J = 4.0$ Hz, 2H), 2.36–2.20 (m, 2H), 2.20–2.05 (m, 2H), 1.87–1.77 (m, 1H), 1.74–1.46 (m, 7H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

Preparation of Alcohol **2.149**



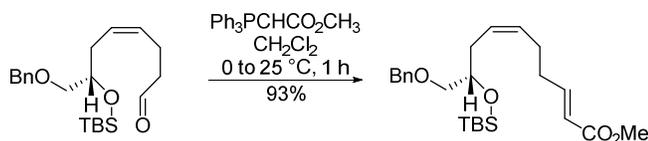
To a solution of THP ether **2.148** (321 mg, 0.72 mmol) in MeOH (11.2 mL, 0.064 M) was added NH_4Cl (191 mg, 3.58 mmol). After stirring at 70 °C for 3 h, the reaction mixture was cooled to room temperature, concentrated *in vacuo*, diluted with H_2O and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 3/1) yielded alcohol **2.149** as a colorless oil (199 mg, 76%): ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.25 (m, 5H), 5.48–5.43 (m, 2H), 4.53 (s, 2H), 3.89–3.83 (m, 1H), 3.62 (t, $J = 6.0$ Hz, 1H), 3.61 (t, $J = 5.6$ Hz, 1H), 3.39 (dd, $J = 5.6, 1.6$ Hz, 2H), 2.30 (dt, $J = 14.8, 5.6$ Hz, 1H), 2.27 (dt, $J = 15.6, 6.2$ Hz, 1H), 2.14 (t, $J = 6.8$ Hz, 1H), 2.12 (t, $J = 6.8$ Hz, 1H), 1.65–1.57 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

Oxidation of Alcohol **2.149**



To a cooled (0 °C) solution of alcohol **2.149** (199 mg, 0.55 mmol) in CH₂Cl₂ (4.9 mL, 0.112 mmol) was added PCC (291 mg, 1.35 mmol). After stirring at 25 °C for 1 h, the reaction was diluted with Et₂O and filtered through celite. Purification by column chromatography (silica gel, hexanes/EtOAc = 3/1) yielded aldehyde **2.150** as a colorless oil (151 mg, 76%): ¹H NMR (400 MHz, CDCl₃) δ 9.74 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.36–7.25 (m, 5H), 5.49 (dt, *J* = 10.8, 7.6 Hz, 1H), 5.42 (dt, *J* = 10.4, 6.4 Hz, 1H), 4.52 (s, 2H), 3.90–3.84 (m, 1H), 3.42–3.34 (m, 2H), 2.49–2.42 (m, 2H), 2.42–2.22 (m, 4H), 0.87 (s, 9H), 0.05 (s, 6H).

Preparation of α,β -Unsaturated Methyl Ester **2.151**



To a cooled solution (0 °C) of aldehyde **2.150** (151 mg, 0.42 mmol) in CH₂Cl₂ (0.6 mL, 0.700 M) was added methyl (triphenylphosphoranylidene)acetate (153 mg, 0.46 mmol). The reaction mixture was stirred at 25 °C for 1 h before concentration *in vacuo*. The resulting mixture was washed with pentane and the precipitate was removed by vacuum filtration. Purification by column chromatography (silica gel, hexanes/EtOAc = 7/1) afford α,β -unsaturated methyl ester **2.151** as a colorless oil (162 mg, 93%): ¹H NMR (400 MHz,

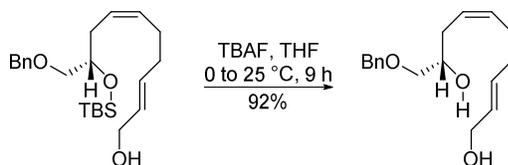
CDCl₃) δ 7.36–7.25 (m, 5H), 6.95 (dt, $J = 15.6, 6.8$ Hz, 1H), 5.82 (d, $J = 15.6$ Hz, 1H), 5.51–5.39 (m, 2H), 4.52 (s, 2H), 3.89–3.83 (m, 1H), 3.72 (s, 3H), 3.38 (d, $J = 8.0$ Hz, 2H), 2.37–2.12 (m, 6H), 0.88 (s, 9H), 0.05 (s, 6H).

Preparation of Allylic Alcohol **2.152**



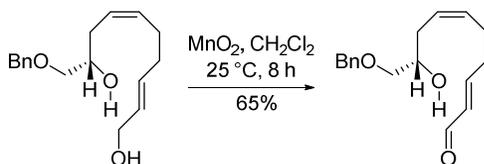
To a cooled (0 °C) solution of α,β -unsaturated methyl ester **2.151** (162 mg, 0.39 mmol) in THF (1.3 mL, 0.300 M) was added DIBAL-H (1.0 M in toluene, 1.0 mL, 0.97 mmol). The reaction mixture was stirred at 0 °C for 1 h before quenching with 1M NaOH. The reaction mixture was stirred at 25 °C for 1 h and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1) yielded allylic alcohol **2.152** as a colorless oil (139 mg, 92%): ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.26 (m, 5H), 5.72–5.59 (m, 2H), 5.45 (t, $J = 4.8$ Hz, 2H), 4.53 (s, 2H), 4.06 (t, $J = 5.2$ Hz, 2H), 3.89–3.83 (m, 1H), 3.39 (d, $J = 5.2$ Hz, 2H), 2.32 (dt, $J = 14.8, 5.2$ Hz, 1H), 2.23 (dt, $J = 14.8, 6.0$ Hz, 1H), 2.17–2.06 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H).

Preparation of Monoallylic Diol **2.153**



To a cooled solution (0 °C) of TBS ether **2.152** (139 mg, 0.36 mmol) in THF (2.6 mL, 0.138 M) was added TBAF (1.0 M in THF, 0.7 mL, 0.71 mmol). After stirring at 25 °C for 9 h, the reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded monoallylic diol **2.153** as a colorless oil (90 mg, 92%): ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.27 (m, 5H), 5.72–5.60 (m, 2H), 5.51 (dt, *J* = 10.4, 6.8 Hz, 1H), 5.43 (dt, *J* = 10.0, 7.6 Hz, 1H), 4.56 (s, 2H), 4.07 (d, *J* = 3.2 Hz, 2H), 3.89–3.82 (m, 1H), 3.52 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.38 (dd, *J* = 9.2, 9.2 Hz, 1H), 2.36 (bs, 2H), 2.35–2.06 (m, 6H).

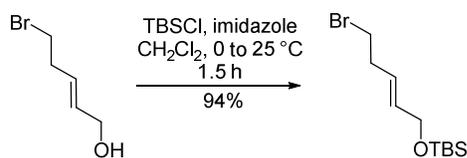
Preparation of α,β -Unsaturated Aldehyde **2.154**



To a solution of monoallylic diol **2.153** (20 mg, 0.07 mmol) in CH₂Cl₂ (1.3 mL, 0.054 M) added MnO₂ (29 mg, 0.36 mmol) at 25 °C. Additional equivalents of MnO₂ (29 mg, 0.36 mmol) were added every hour for 8 h. The reaction mixture was then purified by column chromatography topped with celite (silica gel, hexanes/EtOAc = 2/1) to provide α,β -

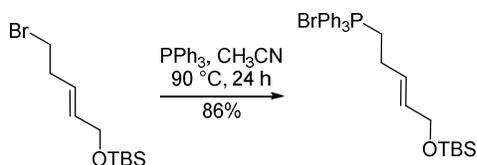
unsaturated aldehyde **2.154** as a colorless oil (13 mg, 65%): ^1H NMR (400 MHz, CDCl_3) δ 9.49 (d, $J = 8.0$ Hz, 1H), 7.38–7.28 (m, 5H), 6.82 (dt, $J = 15.6, 6.8$ Hz, 1H), 6.12 (dd, $J = 15.6, 8.0$ Hz, 1H), 5.54–5.46 (m, 2H), 4.55 (s, 2H), 3.89–3.82 (m, 1H), 3.51 (dd, $J = 9.2, 3.2$ Hz, 1H), 3.37 (dd, $J = 8.4$ Hz, 1H), 2.43–2.34 (m, 2H), 2.34–2.20 (m, 4H).

Preparation of TBS ether **2.157**



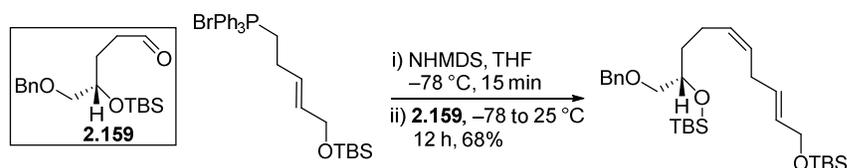
To a cooled (0°C) solution of allylic alcohol (**2.156**) (2.13 g, 12.92 mmol) in CH_2Cl_2 (40.0 mL, 0.323 M) was added imidazole (1.47 g, 21.53 mmol) followed by TBSCl (1.62 g, 10.77 mmol). After stirring at 25°C for 1.5 h, the reaction was quenched with 1 M HCl and diluted with CH_2Cl_2 . After washing with H_2O , the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 40/1) yielded TBS ether **2.157** as a colorless oil (2.83 g, 94%): ^1H NMR (400 MHz, CDCl_3) δ 5.67–5.63 (m, 2H), 4.16–4.13 (m, 2H), 3.39 (t, $J = 6.8$ Hz, 2H), 2.63–2.57 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H).

Preparation of Triphenylphosphine Bromide **2.158**



To a solution of bromide **2.157** (2.83 g, 10.11 mmol) in CH_3CN (44.0 mL, 0.230 M) was added triphenylphosphine (2.65 g, 10.11 mmol). After stirring at $90\text{ }^\circ\text{C}$ for 24 h, the reaction was concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded triphenylphosphine bromide **2.158** as a colorless oil (4.69 g, 86%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.84–7.74 (m, 10 H), 7.70–7.65 (m, 5H), 5.74 (dt, $J = 15.6, 6.4$ Hz, 1H), 5.56 (dt, $J = 15.6, 4.8$ Hz, 1H), 4.00 (d, $J = 4.4$ Hz, 2H), 3.89–3.80 (m, 2H), 3.49–2.38 (m, 2H), 0.83 (s, 9H), -0.01 (s, 6H).

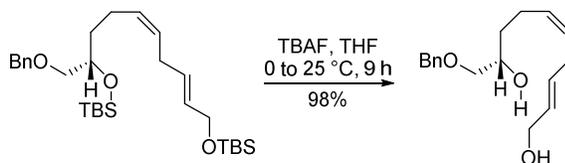
Wittig Reaction of Triphenylphosphine Bromide **2.158** & Aldehyde **2.159**



To a cooled ($-78\text{ }^\circ\text{C}$) solution of triphenylphosphine bromide **2.158** (138 mg, 0.25 mmol) was added NaHMDS (1.0 M in THF, 0.5 mL, 0.51 mmol). After stirring for 15 min, a solution of aldehyde **2.159** (164 mg, 0.51 mmol) in THF (9.9 mL, 0.052 mmol) was added dropwise. After stirring at $25\text{ }^\circ\text{C}$ for 12 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel,

hexanes/EtOAc = 20/1) yielded diene **2.160** as a colorless oil (88 mg, 68%): $[\alpha]_D^{23} = -9.4$ (*c* 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.25 (m, 5H), 5.63 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.55 (dt, *J* = 15.2, 5.2 Hz, 1H), 5.44 (dt, *J* = 10.4, 8.0 Hz, 1H), 5.38 (dt, *J* = 10.8, 6.8 Hz, 1H), 4.53 (s, 2H), 4.12 (d, *J* = 4.8 Hz, 2H), 3.88–3.80 (m, 1H), 3.44–3.34 (m, 2H), 2.77 (t, *J* = 6.2 Hz, 2H), 2.22–2.10 (m, 1H), 2.10–1.95 (m, 1H), 1.68–1.56 (m, 1H), 1.56–1.44 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.67 (d, *J* = 0.8 Hz, 6H), 0.60 (d, *J* = 5.6 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 130.4, 129.5, 129.3, 128.3, 127.6, 127.5, 127.2, 110.0, 74.6, 73.3, 71.2, 63.9, 34.7, 30.0, 26.0, 25.9, 23.0, 18.4, 18.2, -4.4, -4.8, -5.1; IR (neat) 2954, 2928, 2894, 2856, 1254, 1101, 836, 775 cm⁻¹.

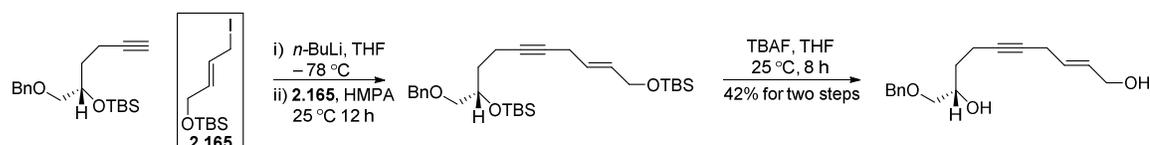
Preparation of Diol **2.161**



To a cooled solution (0 °C) of diene **2.160** (88 mg, 0.17 mmol) in THF (1.3 mL, 0.131 M) was added TBAF (0.7 mL, 1.0 M in THF, 0.7 mmol). The reaction was warmed to 25 °C over 1 h and continued to stir at 25 °C for an additional 8 h. The reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded diol **2.161** as a colorless oil (47 mg, 98%): $[\alpha]_D^{23} = +7.5$ (*c* 0.46, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.27 (m,

5H), 5.71–5.60 (m, 2H), 5.48–5.38 (m, 2H), 4.55 (s, 2H), 4.06 (s, 2H), 3.84–3.77 (m, 1H), 3.49 (dd, $J = 9.2, 3.2$ Hz, 1H), 3.33 (dd, $J = 9.2, 8.0$ Hz, 1H), 2.79 (s, 2H), 2.53 (bs, 1H), 2.23–2.12 (m, 2H), 1.80 (bs, 1H), 1.58–1.42 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.9, 131.2, 130.4, 129.3, 128.4, 127.8, 127.7, 127.3, 74.5, 73.3, 69.7, 63.6, 32.8, 29.9, 23.2; IR (neat) 3401, 2925, 2859, 1090, 972, 738, 698 cm^{-1} .

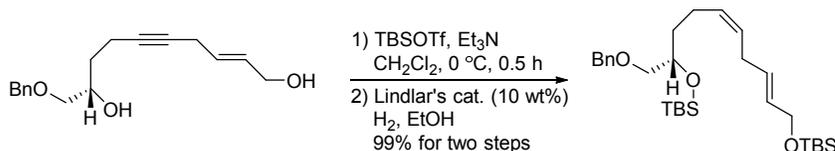
Coupling of Alkyne **2.167** and Allylic Iodide **2.165**



[Coupling] To a cooled (-78 °C) solution of alkyne (**2.167**) (411 mg, 1.29 mmol) in THF (2.1, 0.614 M) was added *n*-BuLi (0.5 mL, 1.29 mmol). After stirring at -78 °C for 0.5 h, HMPA (0.3 mL, 1.72 mmol) was added followed by a solution of allylic iodide (**2.165**) (959 mg, 3.07 mmol) in THF (1.4 mL, 2.193 M). After stirring at 25 °C for 12 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 50/1) yielded an isomeric mixture of **2.168** as a colorless oil. **[Silyl Deprotection]** To a solution of **2.168** in THF (9.8 mL, 0.132 M) was added TBAF (1.0 M in THF, 10.3 mL, 10.3 mmol). After stirring at 25 °C for 9 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded **2.169**

as a colorless oil (147 mg, 42% for two steps): $[\alpha]_D^{23} = -11.6$ (c 1.08, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39–7.26 (m, 5H), 5.81 (dt, $J = 15.2, 4.8$ Hz, 1H), 5.65 (dt, $J = 15.2, 5.2$ Hz, 1H), 4.53 (s, 2H), 4.16 (dd, $J = 5.2, 1.6$ Hz, 2H), 4.00–3.93 (m, 1H), 3.42 (dd, $J = 9.6, 5.2$ Hz, 1H), 3.37 (dd, $J = 9.6, 5.2$ Hz, 1H), 2.92 (s, 2H), 2.27 (t, $J = 7.2$ Hz, 2H), 1.83–1.73 (m, 1H), 1.70–1.60 (m, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 138.4, 130.5, 128.3, 127.6, 127.5, 125.3, 82.1, 74.6, 73.3, 70.2, 63.4, 33.9, 26.0, 25.9, 21.7, 18.4, 18.1, 14.8, –4.4, –4.8, –5.2; IR (neat) 2954, 2928, 2886, 2856, 1472, 1254, 1123, 1087, 971, 836, 776 cm^{-1} .

Preparation of Bis-TBS ether **2.160**



[Bis-TBS Protection] To a cooled ($0\text{ }^\circ\text{C}$) solution of diol **2.169** (105 mg, 0.38 mmol) in CH_2Cl_2 (1.3 mL, 0.292 M) was Et_3N (0.3 mL, 2.30 mmol) followed by TBSOTf (0.3 mL, 1.15 mmol). After stirring at $0\text{ }^\circ\text{C}$ for 0.5 h, the reaction was quenched with saturated aqueous NaHCO_3 and extracted with EtOAc . The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/ $\text{EtOAc} = 20/1$) yielded bis-TBS **2.168** as a colorless oil (173 mg, 90%).

[Hydrogenation] To a solution of alkyne **2.168** (173 mg, 0.34 mmol) in EtOH /pyridine 3/1 (1.8 mL, 0.189 M) was added Lindlar's catalyst (17 mg, 10 wt%). After stirring for 9 h under a hydrogen atmosphere at $25\text{ }^\circ\text{C}$, the reaction was filtered through celite to yield

diene **2.160** as a colorless oil (173 mg, 99%). Spectral data matched that obtained from the Wittig route.

3. Stereoselective Synthesis of α,α' -*cis*-Oxocenes via Gold(I)-Catalyzed Alkoxylation

3.1 Background

As described in Section 2.3, our attempts to extend the oxa-conjugate addition methodology to the preparation of 8-membered cyclic ethers yielded no identifiable oxocane products. Although these results were disappointing, it is common for methodology which is suitable for tetrahydropyrans and even oxepanes to fail in the synthesis of oxocanes.⁸⁷ This is likely due to the increased enthalpic and entropic barriers for cyclization to oxocanes in comparison to oxepanes.³⁵ Only a handful of methods exist for the synthesis of all three oxocycle sizes.⁸⁸ Typically, methods for monocyclic α,α' -disubstituted oxocanes have arisen from the total syntheses of oxocane or oxocene-containing C₁₅ non-terpenoid natural products such as those shown in Figure 15. Despite our failed attempts to apply the organocatalytic oxa-conjugate addition to oxocane synthesis, we were strongly driven by the challenge this moiety poses and sought out alternative methods toward their preparation which could be applied to our substrates.

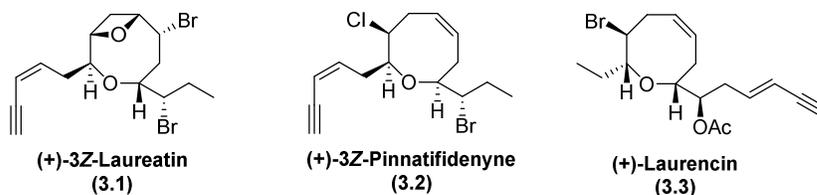


Figure 15: Examples of monocyclic C₁₅ non-terpenoid, marine natural products with an 8-membered cyclic ether skeleton

A particularly eye-catching method was the gold(I)-catalyzed intramolecular amination of allylic alcohols which had been shown to give α -substituted pyrrolidines and piperadines in high yield.⁸⁹ Even more intriguing to us was the application of this catalytic method to the highly stereoselective synthesis of a 1,3-dithiane-containing α,α' -*cis*-piperadine (Figure 16A). It was later realized that an analogous intramolecular alkoxylation for tetrahydropyran synthesis had also been successfully developed (Figure 16B).⁹⁰ Another encouraging finding was the intermolecular variation of the alkoxylation reaction (Figure 16C).⁹¹ These publications were the basis from which we developed the gold(I)-catalyzed alkoxylation (GCA) reaction for stereoselective α,α' -*cis*-oxocene synthesis. Therefore, an introduction to gold(I)-catalysis will be provided in Section 3.1.3 with a detailed discussion of the three key publications represented in Figure 16. Also included in this background section is a discussion of current stereoselective methods for α,α' -*cis*- and α,α' -*trans*-oxocene synthesis.

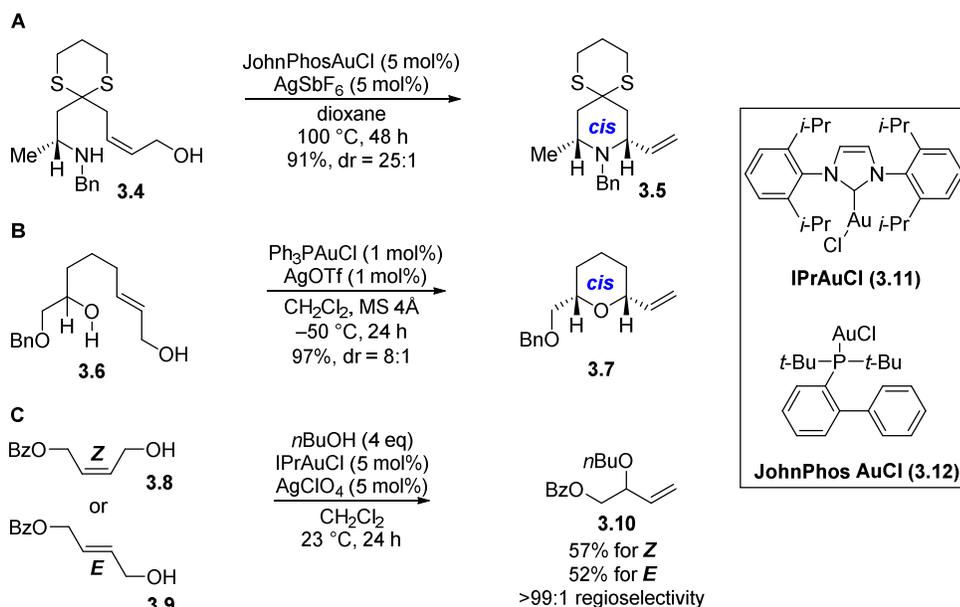


Figure 16: Key inspirational gold(I)-catalyzed functionalization of allylic alcohols

3.1.1 Stereoselective Synthesis of α,α' -Disubstituted Oxocenes

There are a surprising number of methods for oxocene synthesis that allow access to both α,α' -*cis*- and α,α' -*trans*-diastereomers. In fact, the number of methods uncovered for monocyclic α,α' -*trans*-oxocenes during our literature review is higher than the number of methods for monocyclic α,α' -*cis*-oxocenes. Thus, this section comprises stereoselective methods which access either α,α' -*cis*- and/or α,α' -*trans*-oxocenes.

An early example of stereoselective oxocene synthesis came from Kotsuki's studies on the selective reduction of bicyclic ketals (Figure 17).^{88a} The method is similar to Fujiwara's reductive cleavage of bicyclic ketals presented in Figure 5B (Section 2.1)³⁹ and

Murai's Lewis acid directing allylative cleavage of bicyclic ketals presented in Figure 6 (Section 2.1.2).⁴⁶ The main difference between Kotsuki's method and Fujiwara & Murai's methods is the ring size of the bicyclic ketal substrate. Kotsuki prepared dioxabicyclo[4.2.1] nonane **3.15** and dioxabicyclo[5.2.1] decene **3.22** from the corresponding ketones **3.13** and **3.20**, respectively. Unlike Fujiwara and Murai's substrates, **3.15** and **3.22** contain the target 7- or 8-membered cyclic ether as the parent skeleton; thus, the more liable C7–O1 bond is cleaved to give oxepanes or oxocenes, respectively. The alternative C7–O2 bond cleavage in both cases would lead to larger ring sizes; namely the 8- and 9-membered cyclic ethers, respectively.

Initially, Kotsuki and co-workers prepared dioxabicyclo[4.2.1] nonane **2.15** and treated with Et₃Si and TiCl₄ yielding α,α' -*cis*-oxepane **3.16** as a 91:9 mixture of diastereomers. Interestingly, the diastereoselectivity could be switched by employing a chelating hydride donor, DIBAL-H, via the intermediate **3.26** shown in Figure 17D. Treatment of **3.15** with DIBAL-H gave the α,α' -*trans*-oxepane **3.17** in a 98:2 diastereomeric ratio. With the success of this method in oxepane synthesis, Kotsuki and co-workers attempted to extend the methodology to oxocane synthesis. However, all attempts to prepare dioxabicyclo[5.2.1] decane **3.19** from ketone **3.18** were unsuccessful and failed to provide any of the target bicyclic ketal. Therefore, a *cis* alkene was installed into the ketone skeleton as a structural element to facilitate ring closer. Ketone **3.20** did provide dioxabicyclo[5.2.1] decene **3.21** when subjected to acidic conditions, albeit in low yield (32%). As with the analogous bicyclic ketal for oxepane synthesis, either the α,α' -

cis- or α,α' -*trans*-oxocenes **3.23** or **3.24** could be prepared in high yield and diastereoselectivity depending on the nature of the hydride reagent (non-chelating vs chelating).

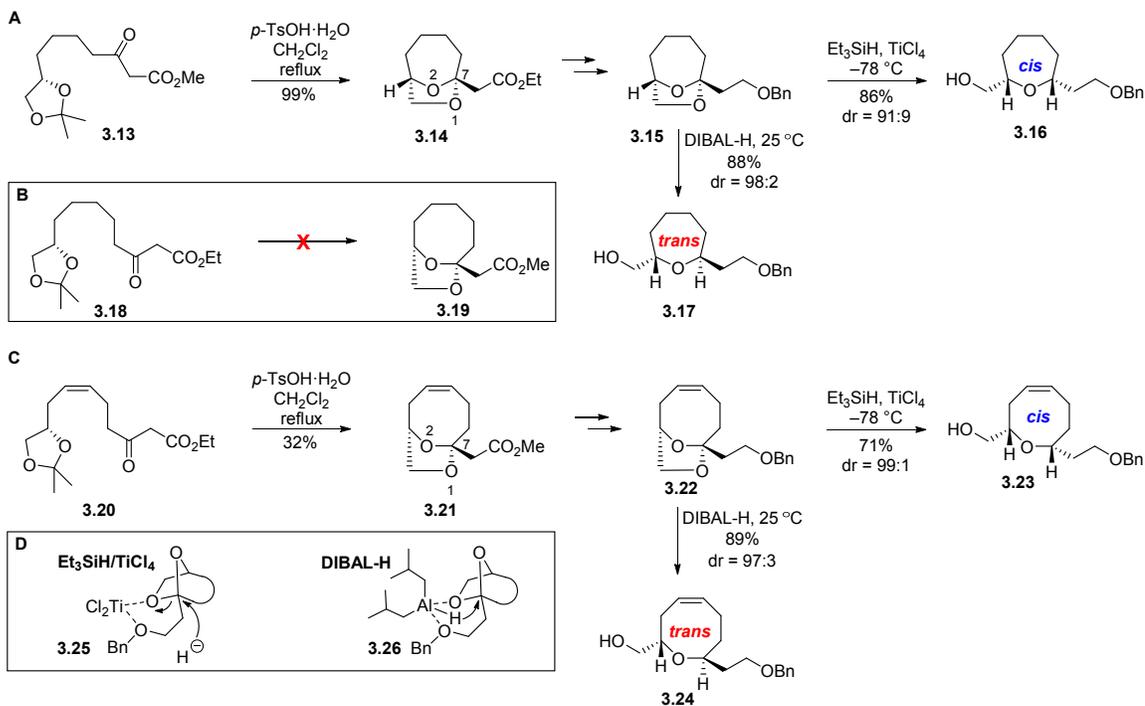
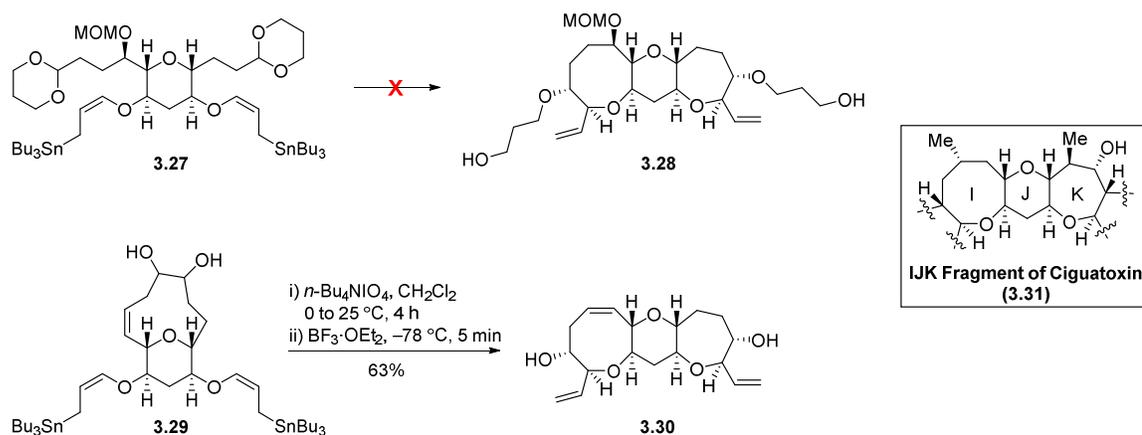


Figure 17: Kotsuki's stereoselective reduction of bicyclic ketals

Although this next example of stereoselective α,α' -*cis*-oxocene is in the context of ladder-shaped polycyclic ether synthesis, it demonstrates a class of methodology that has been used extensively in the preparation of MSCEs. Martín and co-workers employed Yamamoto's intramolecular cyclization of trialkylstannyl ether aldehydes⁹² in a unique

strategy for polycyclic ether synthesis.⁹³ Martín proposed a symmetrical approach to the construction of *trans*-fused oxatricyclic subunits found in many ladder-shaped polycyclic ether natural product. In this symmetrical approach, the tricyclic system would be built up from the center cyclic ether with reactive groups on both sides of the oxocycle being triggered for a simultaneous cyclization to give two new fused oxocycles in a one-pot procedure. Even more interestingly was their ability to apply this approach to the simultaneous construction of different sized oxocycles.

Initially, Martín and co-workers tested their proposed approach on trialkylstannyl ether acetal **3.27** according to Yamamoto's protocol;⁹⁴ however, the target oxocane-oxane-oxepane subunit **3.28** was not obtained. It is possible that only a single cyclization took place under the various Lewis acid conditions tested; unfortunately, information of this type was not disclosed. The authors then turned to the analogous methodology using a more reactive aldehyde as the electrophilic functionality. Bicyclic diol **3.29** was treated with *n*-Bu₄NIO₄ to obtain the dialdehyde intermediate. Subsequent addition of BF₃·OEt₂ in a one-pot procedure resulted in cyclization of both termini to give the 7- and 8-membered cyclic ethers. Although moderate, the yield (63%) is impressive considering two MSCEs were formed in a single transformation. It should be noted that the MOM protected alcohol in **3.27** was replaced with a *cis* alkene in **3.29**, both of which were likely installed as reactive handles for conversion to the methyl substituent in ciguatoxin's I ring. The importance of the *cis* alkene in the successful dual cyclization was not discussed in the publication.

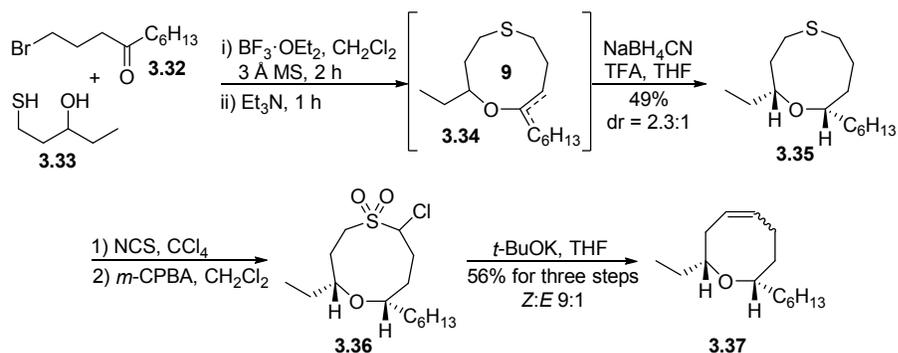


Scheme 25: Martín's strategy for the synthesis of ciguatoxin's IJK ring framework

Ring expansion is a common class of methods used in the preparation of MSCEs; however few protocols within this class utilize a ring expansion with subsequent ring contraction to prepare cyclic ethers. De Voss and co-workers employed a ring expansion/ring contraction method for the preparation of lauthisan, the saturated carbon skeleton of (+)-laurencin.⁹⁵ To prepare sulfur-containing 9-membered cyclic ether **3.35**, condensation of ketone **3.32** with mercapto alcohol **3.33** was induced by treatment with $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 26). The resulting bromooxathiane spontaneously undergoes an intramolecular *S*-alkylation and addition of NaBH_3CN lead to reduction of the sulfonium ion. The resulting α, α' -*cis*-oxathionane **3.35** was obtained as a separable mixture of diastereomers (2.3:1) in 49% combined yield. Each diastereomer underwent the next set of transformations separately. For simplicity, only the α, α' -*cis*-oxathionane **3.35** will be discussed since both diastereomers exhibited the same reactivity. Non-regioselective α -

chlorination of the thioether was accomplished with NCS and CCl₄ and oxidation with *m*-CPBA yielded the sulfone **3.36**. Ramburg–Bäcklund rearrangement occurred upon treatment with *t*-BuOK giving a mixture of (*Z*)- and (*E*)-oxocenes **3.37** (9:1) in 56% yield for three steps.

Although the sequence provided only moderate yield and diastereoselectivity, the feasibility of this concept was demonstrated. Ring expansion was used in a non-traditional manner to circumvent typical barriers to oxocene formation by preparing a larger ring size. Furthermore, the use of a heteroatom for subsequent extrusion with a longer σ Z–C bond likely aided in the initial ring expansion to a 9-membered ring. The use of different heteroatoms could improve the yield for initial ring expansion; however one would need to consider the ease and availability of routes to the pivotal condensation and intramolecular alkylation, as well as the heteroatom extrusion step. The flexibility of 9-membered rings might allow a reagent-induced bidentate chelation with the two ring heteroatoms, which could potentially improve the diastereoselectivity during hydride addition by locking the intermediate into a specific conformation. It would be interesting to determine how these factors might affect the reactivity and stereoselectivity.

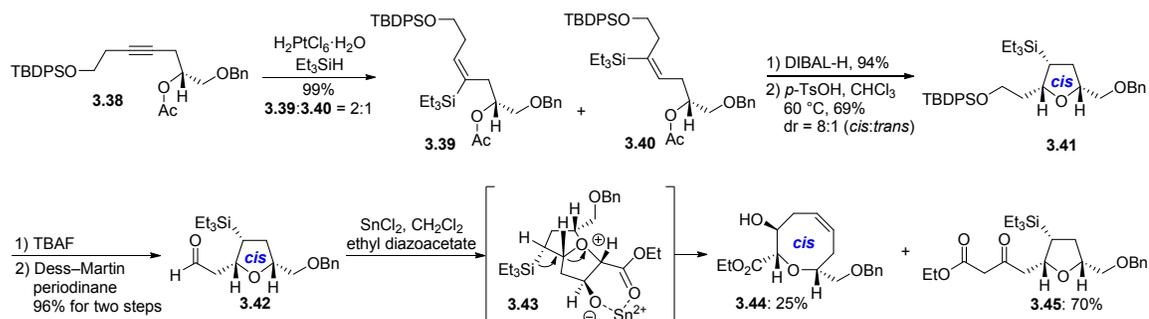


Scheme 26: De Voss's *O,S*-acetal ring expansion/ring contraction method for oxocene formation

Another interesting example of the utility of ring expansion in the stereoselective synthesis of oxocenes was reported by Li and co-workers.⁹⁶ In their approach, diastereomeric tetrahydrofurans were prepared and later expanded to the target oxocenes via aldol reaction with ethyl diazoacetate followed by *in situ* oxonium ion formation and fragmentation. To begin, chiral homopropagyl acetate **3.38** was treated with a catalytic amount of $\text{H}_2\text{PtCl}_6 \cdot \text{H}_2\text{O}$ and Et_3SiH to give a mixture of vinylic silanes **3.39** and **3.40** (2:1) in 99% yield (Scheme 27). Reduction of the mixture with DIBAL-H provided the free secondary alcohol for tetrahydrofuran synthesis. Upon treatment with a catalytic amount of *p*-TsOH, the vinylic silane **3.39** gave a mixture of diastereomeric tetrahydrofurans in a combined 69% yield favoring the α,α' -*cis*-tetrahydrofuran (8:1). Although vinylic silane **3.40** could not directly undergo cyclization to the tetrahydrofuran product, the acidic conditions allowed carbocation formation and a 1,2-silyl migration providing a cyclizable intermediate. The tetrahydrofuran diastereomers were separated at this stage and both were

carried forward in the next set of transformations. Only the *cis* diastereomer is shown in Scheme 27 for simplicity.

Deprotection and oxidation yielded aldehyde **3.42** which was subjected to Holmquist and Roskamp's protocol for aldol reaction with ethyl diazoacetate in the presence of SnCl₂. Initial aldol reaction and subsequent N₂ elimination gave an intermediate which could undergo formation of oxonium ion **3.43**. Ring expansion was then induced by β -Et₃Si *syn* elimination to regioselectively install the *cis* alkene and provide the α,α' -*cis*-oxocene **3.44**. Similarly, the α,α' -*trans*-tetrahydrofuran gave the α,α' -*trans*-oxocene under identical conditions. Although the yield in both cases was low (25% for **3.44**), the reaction was completely stereoselective. In both cases, the major side product was keto ester **3.45** resulting from incomplete oxonium ion formation. Because the α,α' -*trans*-tetrahydrofuran had a similar product distribution (22% α,α' -*trans*-oxocene, 69% keto ester) as **3.41**, one could conclude that the energetic barriers to oxonium ion formation are comparable. Although improvement in the yield would be necessary, α,α' -*cis*-oxocene **3.44** could easily be further transformed into C₁₅ non-terpenoid marine natural products such as those shown in Figure 15.

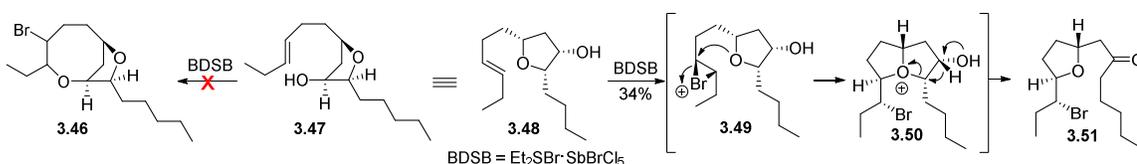


Scheme 27: Li's ring expansion method for stereoselective oxocene synthesis

The structural similarities of the C₁₅ non-terpenoid marine natural products, has prompted studies into the biosynthesis of members on this class. Examination of the natural product class as a whole indicates that many of the members, regardless of ring size, are derived from common intermediates and even other, less functionalized members. Thus, biomimic synthetic approaches to this class of natural products have been attempted. However, the main problem with employing a biomimic strategy for this class of molecules is the poor regio- and stereoselectivity and isolated yields.⁹⁷ These issues can be resolved by employing Synder's ring-expanding bromoetherification protocol.²³

Inspiration for the development of Synder's protocol arose from their attempts to cyclize hydroxy tetrahydrofuran **3.48** to the bicyclic 8-membered cyclic ether **3.46** via a direct bromoetherification (Scheme 28). Instead of the target **3.46**, keto tetrahydrofuran **3.48** was obtained in 34% yield. It was proposed that **3.48** underwent bromoetherification with the ether oxygen resulting in oxonium ion **3.50** formation. Degradation of **3.50** to **3.51** occurred by a carbonyl formation/hydride shift cascade. Synder and co-workers proposed

that this suspected oxonium ion **3.50** could be employed for the synthesis of oxocanes by masking the alcohol with an oxygen containing protecting group, such as acetate, benzoyl or Boc groups. The protecting group oxygen, if correctly positioned, could open the oxonium ion **3.50** via nucleophilic attack at the bridging carbon resulting in formation of an 8-membered cyclic ether.



Scheme 28: Inspiration for Snyder's regio- and stereocontrolled brominium induced ring expansion method

After testing their hypothesis with the protecting groups mentioned earlier, Snyder and co-workers found good yields could be obtained in all cases with high regio- and stereoselective bromoetherification; however, the Boc protecting group was more convenient since it did not produce a mixture of constitutional isomers. The acetate and benzoyl protecting groups underwent migration during the reaction. Thus, tetrahydrofuran **3.52** was treated with BDSB, a brominating reagent, to give brominium ion **3.53** *in situ*. It was proposed that the ether oxygen can attack either facially distinct brominium ions and that an equilibrium is established between all reaction intermediates. However, oxonium ion formation from **3.54** provides a minimal steric interaction in the concave face of the

bicyclic species as shown in Figure 18A. From intermediate **3.54**, α,α' -*trans*-oxocane **3.55** was obtained as a single isomer in 79% yield.

It was demonstrated that the geometry of the tethered alkene in tetrahydrofurans **3.56** and **3.60** determine the stereochemistry of the newly installed bromine (Figure 18B vs 18C). Furthermore, the length of the carbon chain determines whether the bromoetherification occurs via *exo* or *endo* attack (Figure 18C vs 18E). It is noteworthy that either the α,α' -*cis*- or α,α' -*trans*-oxocane can be obtained selectively simply by changing the configuration of the C7 substituent. For example, tetrahydrofurans **3.58** and **3.62** which differ only in the configuration of C7 gave the α,α' -*trans*- and α,α' -*cis*-oxocanes **3.59** and **3.63**, respectively, in approximately the same yield.

The regio- and stereocontrol of this method is exceptional and it is amendable to preparation of members of the C₁₅ non-terpenoid marine natural products. Two key chiral functionalities of this natural product class are installed simultaneously and the skeletal carbonate is strategically positioned to introduce functionalities common to this natural product class. A different C7 substituent would need to be installed in natural product synthesis were to be pursued and caution should be taken with employing a protected alcohol functionality. Alteration of the C7 substituent was not examined and an oxygen functionality in this substituent could potentially interfere with the ring-expanding bromoetherification.

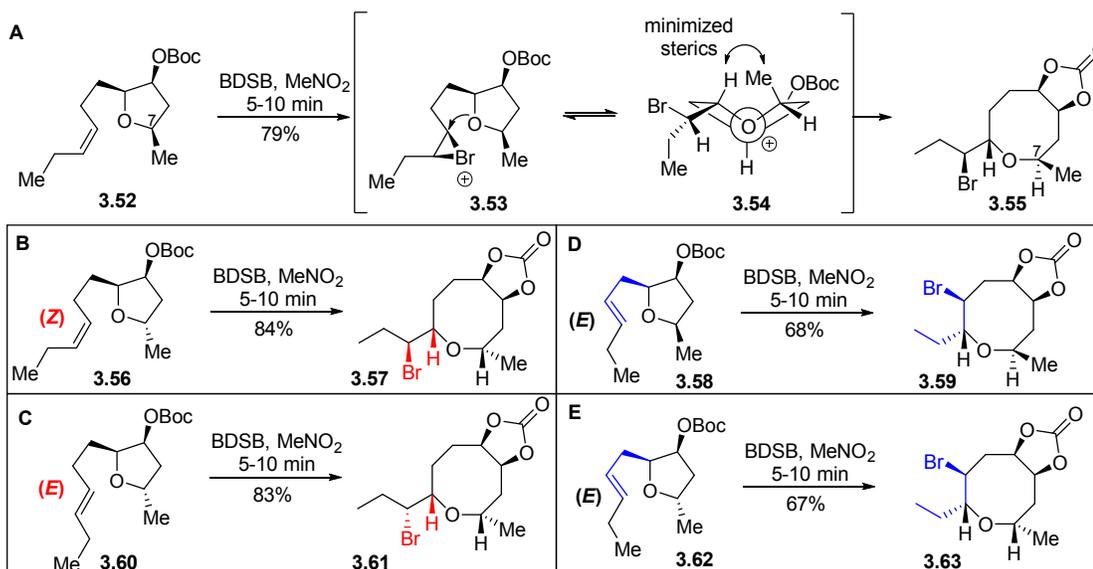


Figure 18: Governing variables in Snyder's ring-expanding bromoetherification

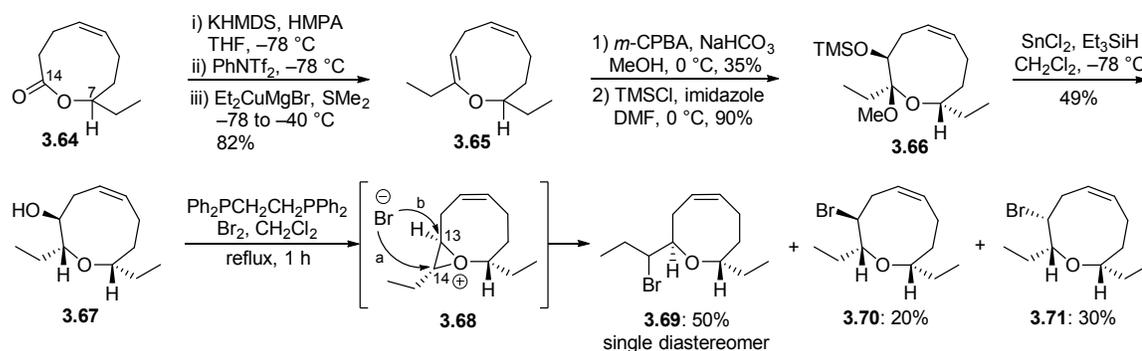
One example of a stereoselective synthesis of α,α' -*trans*-oxocenes was an unexpected outcome of Murai and co-workers' investigations toward the total synthesis of 8- and 9-membered cyclic ethers from the C₁₅ non-terpenoid marine natural product class.⁹⁸ Their goal was to prepare the target natural products by functionalization of known 8- or 9-membered cyclic lactones. The proposed method was successful to some degree for preparation of the unsaturated 9-membered cyclic ether (oxonene). However, the oxocene system was more problematic under the proposed route.

To begin their studies, Murai and co-workers enolized racemic lactone **3.64** and trapped the enolate with PhNTf₂ (Scheme 29). Installation of the C14 ethyl side chain was accomplished via treatment with a Gillman reagent providing the enol ether **3.65** in 82%

yield. The C13 and C14 asymmetric centers were then set by epoxidizing the enol ether with *m*-CPBA in the presence of basic MeOH. The relative stereochemistry between C13 and C14 in **3.66** indicates that the ether oxygen underwent oxonium ion formation prior to attack of the methoxy anion. The conversion for this transformation was low at only 35% yield. Significant side reactions and decomposition were the cause of the poor yield. However, one would expect to obtain a maximum of 50% of the diastereomer **3.66** shown in Scheme xx since the substrate was racemic. Although it is not depicted in the scheme below, the unsaturated 8-membered lactone demonstrated similar reactivity under the same reaction sequence.

The next task was to replace the methoxy substituent at C14 with a hydrogen. Although the reason for TMS protection of the C13 alcohol was not specified, it was accomplished in high yield prior to hydride introduction. Treatment of **3.66** with SnCl₂ and Et₃SiH gave the α,α' -*cis*-oxonene **3.67** in moderate yield (49%) with simultaneous TMS deprotection. This is the point in the sequence where the unsaturated 8-membered lactone failed to give any desired product. According to the original synthetic plan, the α,α' -*cis*-oxonene **3.67** would be treated with a phosphine and Br₂ to accomplish bromination with inversion of stereochemistry at C13. However, a mixture of products was obtained under these conditions. The anticipated product **3.71** was obtained in only 30% yield, along with diastereomeric oxonene **3.70** in 20% yield and α,α' -*trans*-oxocene **3.69** as a single diastereomer in 50% yield. The isolation of **3.69** and **3.70** were surprising and their formation indicated that a reactive oxonium ion intermediate **3.68** was being formed under

the reaction conditions. Oxonene **3.70** which did not exhibit inversion of stereochemistry would arise from bromide ion attack via path b; however, oxocene **3.69** is the expected product from bromide ion attack at C14 (path a). Further investigation into this chemistry as a general method for α,α' -*trans*-oxocene synthesis was not reported. However, Murai and co-workers did study the effects of these reaction conditions on similar oxepine substrates to determine whether high yields of one of the three possible products could be obtained.⁹⁹



Scheme 29: Murai's unanticipated ring contraction method for α,α' -*trans*-oxocene synthesis

The value of oxonium ion formation and ring expansion/contraction in the context of stereoselective oxocene synthesis cannot be underestimated. However, C–O bond cyclization methods have also been developed. The next example utilizes a Lewis acid promoted regioselective epoxide opening method. This approach has been studied in the context of ladder-shaped polycyclic ethers and its application for the synthesis of

monocyclic MSCEs was not disclosed until Suzuki's 2003 report.⁸⁷ Earlier studies found that $\text{Zn}(\text{OTf})_2$ and $(\text{Bu}_3\text{Sn})_2\text{O}$ conditions worked well for oxepine synthesis (Figure 19C).¹⁰⁰ Therefore, a model hydroxyl epoxide **3.72** was treated with $\text{Zn}(\text{OTf})_2$ and $(\text{Bu}_3\text{Sn})_2\text{O}$ with the expectation that oxocene **3.73** would be obtained (Figure 19A). Although the target oxocene was formed, additional equivalents (4.4 eq for **3.72** vs 0.4 eq for **3.74**) were required to drive the reaction to completion and only a moderate yield of **3.73** (51%) was obtained. Therefore, optimization of the Lewis acid was required and $\text{Eu}(\text{fod})_3$ was found to give the best results (Figure 19B).

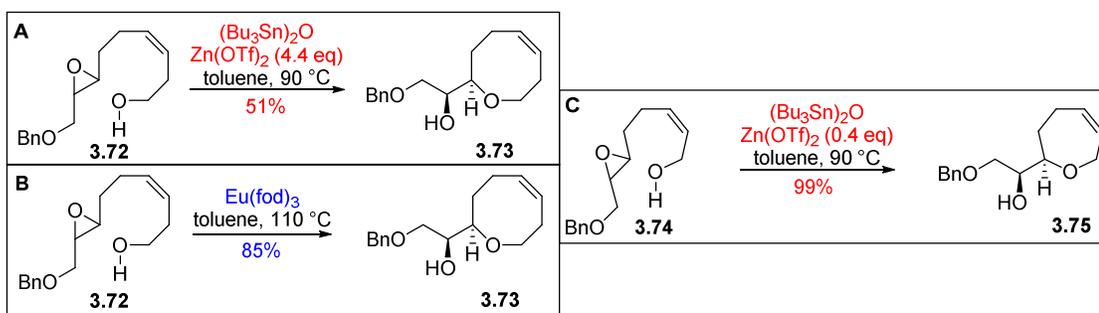


Figure 19: Suzuki's Lewis acid promoted cyclizations of model hydroxyl epoxide **3.72**

The governing factors of the cyclization were then examined. Specifically, the ability to form either the α,α' -*cis*- or α,α' -*trans*-oxocene was determined by preparing hydroxy epoxides **3.76** and **3.79** which differed only in the configuration at C6 (Figure 20). A higher yield for α,α' -*cis*-oxocene **3.80** (97%) was obtained compared to α,α' -*trans*-

oxocene **3.77** (76%). It is uncertain if higher yields would generally be obtained for α,α' -*cis*-oxocenes using this method since a substrate scope was not reported. The geometry of the epoxide had a significant impact on the reactivity. When hydroxy *trans*-epoxides **3.78** and **3.81** were treated with $\text{Eu}(\text{fod})_3$, the yield for both the α,α' -*cis*- and α,α' -*trans*-oxocenes **3.80** and **3.77** decreased compared to the hydroxyl *cis*-epoxides. However, the change was more drastic for α,α' -*trans*-oxocene **3.77** with a 33% decrease. This reaction suffered from competing 9-membered cyclic ether formation via *endo* cyclization. Hydroxy *trans*-epoxide **3.78** was the only non-regioselective substrate.

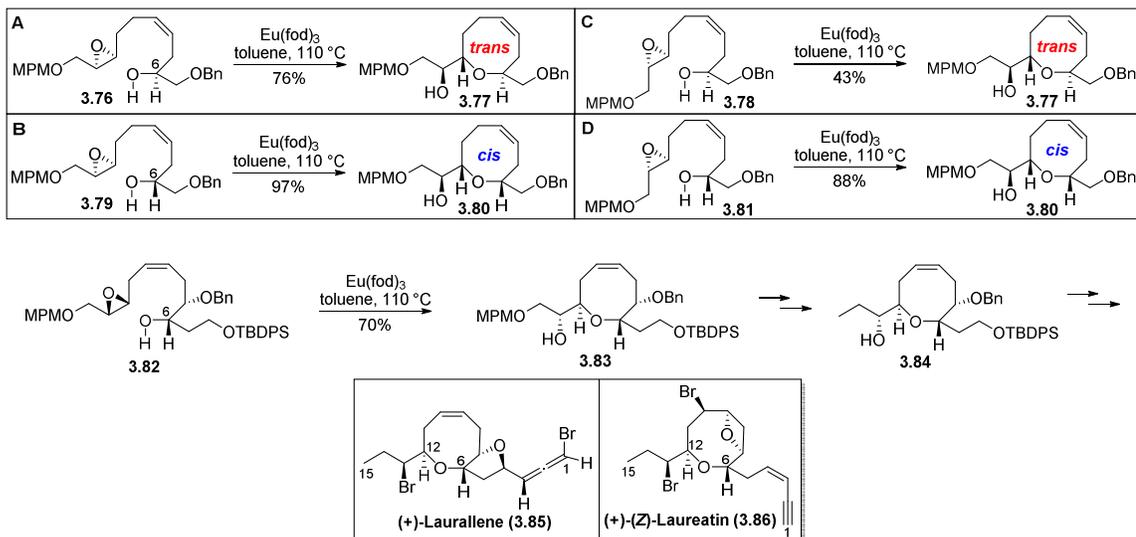


Figure 20: Suzuki's Lewis acid promoted cyclizations of hydroxyl epoxides

Although this method has proven to be highly selective for either the α,α' -*cis*- or α,α' -*trans*-oxocenes, it has been applied to the total synthesis of two α,α' -*trans*-oxocene-containing C₁₅ non-terpenoid marine natural products.¹⁰¹ In the first natural product application, (+)-laureallene (**3.85**) was prepared from hydroxy *cis*-epoxide **3.82**. It is noteworthy that (**3.85**) required alteration of the skeletal *cis* alkene; thus, this total synthesis was not a direct application of the α,α' -*trans*-oxocenes prepared in the method development publication. Furthermore, the total synthesis of (+)-laureallene required substitution at C5 to install the fused tetrahydrofuran. Retrosynthetically, having a C5 functional group prior to oxocene formation would be ideal. With these considerations in mind, Suzuki and co-workers prepared hydroxy *cis*-epoxide **3.82** and subjected it to the previously determined optimized conditions. Despite the structural alterations described above, α,α' -*trans*-oxocene **3.83** was obtained in 70% yield which is comparable to the yield obtained for model oxocene **3.77**. Elaboration of the left hemisphere of (+)-laurallene was completed giving **3.84** as an advanced intermediate in the total synthesis. Suzuki and co-workers later reported the total synthesis of (+)-(*Z*)-laureatin (**3.86**) using advanced intermediate **3.84**. The structural similarities of (**3.85**) and (**3.86**) lead one to assume that they are derived from the same parent metabolite. Thus, preparation of both natural products from the same advanced intermediate is logical and efficient. The high selectivity and yields attained by Suzuki's Lewis acid epoxide opening method and application of the method to two of the more complex C₁₅ non-terpenoid marine natural products makes it a nice example of C–O bond forming cyclization for oxocene synthesis.

3.1.2 Gold(I)-Catalyzed Alkoxylation as a Method for Oxacycle Synthesis

As mentioned in Section 3.1, we thought that gold(I) catalysis could be a potential alternative to our organocatalytic oxa-conjugate addition for the preparation of 8-membered cyclic ethers. Although organometallic catalysis has been well established, the field of homogenous gold catalysis is relatively young. However, the field has received a tremendous amount of attention from the synthetic community since the turn of the century. Unlike the amine catalysts utilized in our organocatalytic oxa-conjugate addition reaction, homogenous gold catalysts typically have stabilizing ligands which permit fine-tuning of the catalytic system.¹⁰² Various ligand types are available including phosphine and *N*-heterocyclic carbenes (NHC) ligands. Through these ligands, the electronic and steric properties can be adjusted accordingly. Gold(I) catalysts have a high π -affinity permitting activation of a number of functionalities including alkenes, alkynes, and allenes. Gold(I) catalysts have also proven to be compatible with many functional groups and demonstrate robust activity allowing low catalyst loadings. Furthermore, gold(I) catalysts are typically commercial, bench stable and safe to handle outside of a fume hood or glove box. Because of these advantages, the field of gold(I) catalysis has grown significantly resulting in its application to various asymmetric transformations,¹⁰³ natural product syntheses¹⁰⁴ and tandem methodologies.¹⁰⁵ Additionally, gold(I) catalysis has been applied to the synthesis of a diverse range of heterocycles.^{103b, 106}

For our purposes, single oxygen-containing α,α' -disubstituted heterocycles were of upmost importance; specifically, 6- through 9-membered heterocycles of this type have been relevant to our studies of 7- and 8-membered cyclic ethers. Although this first inspirational literature example shown in Figure 21A (also presented in Section 3.1) does not contain oxygen, it proved to be a valuable resource in our early studies. Widenhoefer and co-worker reported a gold(I)-catalyzed intramolecular amination of allylic alcohols with alkylamines in which several α substituted pyrrolidines and piperidines were formed in high yield.⁸⁹ The only example of cyclization employing an α,α' -disubstituted amino allylic alcohol was that of **3.4**. When chiral **3.4** was treated with 5 mol% of JohnPhos AuCl and activated with 5 mol% AgSbF₆ at 100 °C for 48 h, α,α' -*cis*-piperidine **3.5** was obtained in high yield (91%) and diastereoselectivity (25:1). Although not tested, the efficient cyclization was likely aided by the skeletal 1,3-dithiane moiety, a feature that reminded us of our conjugate addition substrate collection. Furthermore, the proposed mechanism indicated initial formation of a gold(I) π -alkene complex, subsequent nucleophilic addition of the amine rendering a hydrogen-bonded gold alkyl intermediate **3.87** and proton transfer permitting *anti* elimination of H₂O and gold displacement. Thus, the active gold(I) species served to enhance the electrophilicity of the alkene carbons. Another beneficial feature for our purposes was the use of an allylic alcohol as the electrophilic coupling partner. For our conjugate addition methods, the α,β -unsaturated aldehyde substrates had been prepared from allylic alcohols; hence, we already had fully developed routes to these substrates and even had some on hand for immediate testing.

The analogous intra- and intermolecular gold(I)-catalyzed alkoxylation of allylic alcohols were also served as valued resources. Aponick and co-workers reported the intramolecular version of this reaction and obtained high yields and good diastereoselectivities of several α,α' -*cis*-tetrahydropyrans.⁹⁰ Of the α,α' -*cis*-tetrahydropyrans synthesized, **3.7** was the most similar to our model substrates for preparation of 8-membered cyclic ethers (Figure 21B). When monoallylic diol **3.6** was treated with 1 mol% Ph₃PAuCl and activated with 1 mol% AgOTf at -50 °C for 24 h, α,α' -*cis*-tetrahydropyran **3.7** was obtained in high yield (97%) and good diastereoselectivity (8:1). Within their substrate scope, there appeared to be a temperature effect on the diastereoselectivity. Typically, reactions stirred at lower temperatures (-10 to -78°C) gave higher diastereoselectivities compared to those stirred at room temperature. In select cases, a compromise between high diastereoselectivity and yield was observed; however the isolated yields in these cases could still be categorized as good. In each of Aponick's examples, completely saturated carbon skeletons were utilized; therefore, it was not clear how a structural element such as the dithiane moiety would affect the reactivity and stereoselectivity.

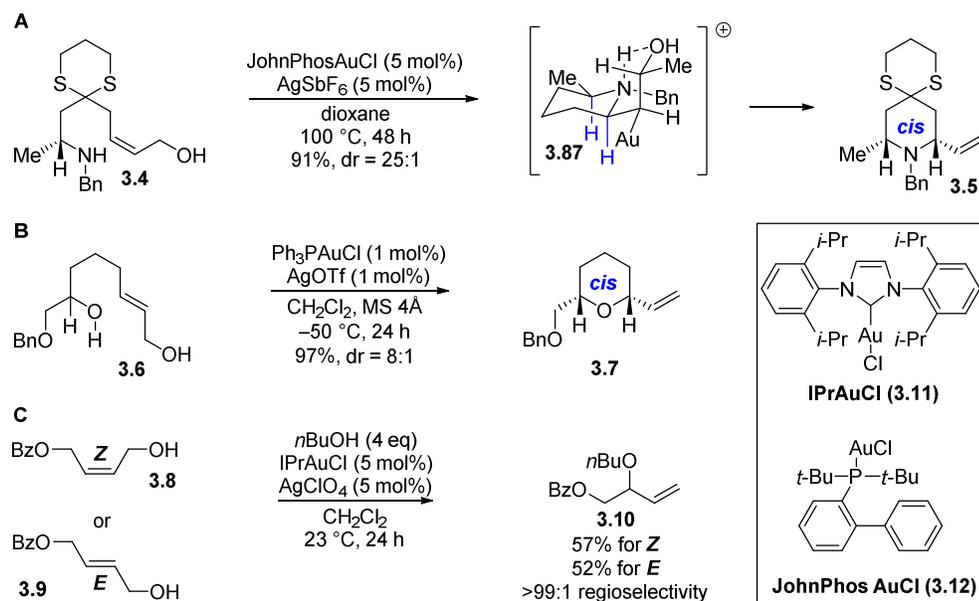


Figure 21: Key inspirational gold(I)-catalyzed functionalization of allylic alcohols

Widenhoefer and co-worker later reported the intermolecular gold(I)-catalyzed alkoxylation of allylic alcohols (Figure 21C).⁹¹ A key observation discussed in this publication was isolation of a mixture of regioisomeric allylic ethers during initial testing. A screening of reaction conditions indicated that this phenomenon was conversion dependent, although improvements could be made by altering the catalyst system and solvent. As the reaction progressed and the target allylic ether (such as **3.10**) formed, a gold(I)-catalyzed alkoxylation was occurring with the initial allylic ether product resulting in a mixture of allylic ethers. This proposed explanation was confirmed through several ¹H NMR studies; therefore, it was essential to quench the reaction upon full conversion to minimize the side reaction. In fact, others have completed reactivity studies of hydroxy

allylic ethers under GCA conditions and demonstrated that these substrates tend to be less reactive than their allylic alcohol counterparts.¹⁰⁷ As an example from Widenhoefer's studies, either the (*Z*)- or (*E*)-allylic alcohols **3.8** or **3.9** were treated with *n*-BuOH in the presence of catalytic IPrAuCl and AgClO₄ for 24 h to give allylic ether **3.10** in high regioselectivity (>99:1). Although the yields for each substrate were moderate, they were comparable, indicating that the geometry of a primary allylic alcohol did not affect the reactivity. This aspect was important to us because we had previously prepared both (*Z*)- or (*E*)-primary allylic alcohols for our oxa-conjugate addition investigations. It should be noted that other substrate combinations gave much higher yields, typically ranging from 76–99%.

At the time our investigation of gold(I)-catalyzed alkoxylation as a potential method for 8-membered cyclic ether synthesis began, there were no publications describing the use of gold(I)-catalysis for oxocane synthesis. However, two reports of oxepane synthesis utilizing gold catalysis were found.¹⁰⁸ Of these two publications, one of them discloses the diastereoselective preparation of a single tetrahydropyran-fused, α,α' -*trans*-oxepane (7:1) albeit in low yield (Figure 20A).^{108a} Since then, an additional publication has been released describing the preparation of oxepanes from hydroxy-tethered propargylic esters under gold-catalyzed conditions.¹⁰⁹ Additionally, a report of 8-membered cyclic ether synthesis via gold catalysis was only recently published.¹¹⁰ Fortunately, the methodology presented in this publication does not yield α,α' -disubstituted 8-membered cyclic ethers and the cyclization occurs via gold(I)-catalyzed 1,2-acyloxy

migration/intramolecular [3+2]cycloaddition from enynyl esters (Figure 22B). Thus, the methodology we've developed and will discuss in the follow sections has not been reported to date.

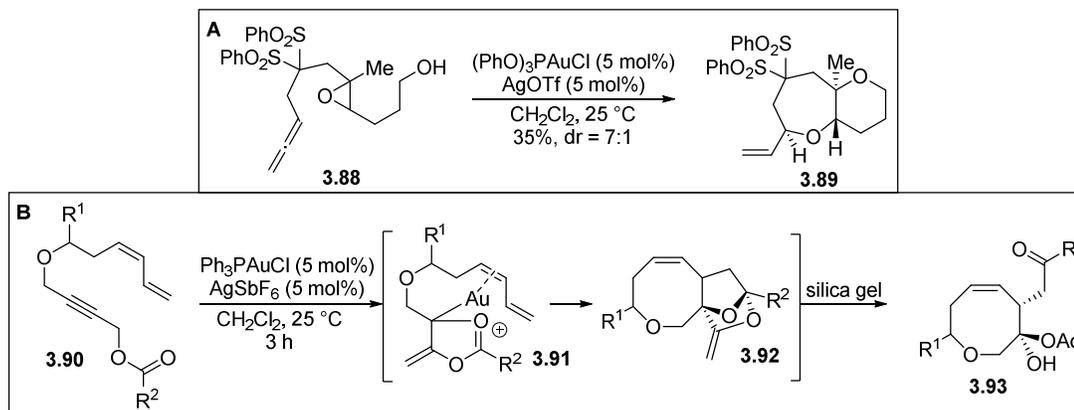


Figure 22: (A) Gagné's gold(I)-catalyzed cascade cyclization of allenyl alcohols (B) She's gold-catalyzed 1,2-acyloxy migration/intramolecular [3+2] 1,3-dipolar cycloaddition cascade reaction

3.1.3 Summary of Background

In this background section, an overview of current methods for stereoselective synthesis of α,α' -*cis*- and α,α' -*trans*-oxocenes has been presented. An introduction to gold(I)-catalysis has been provided and specific examples which aided in our method development have been described. Key features of these foundational literature examples have been summarized with an emphasis on aspects that were particularly important to us.

Additionally, the handful of reports describing gold-catalyzed methods for 7- or 8-membered cyclic ethers have been acknowledged.

3.2 Results and Discussion

3.2.3 Preliminary Studies

Because there was really no method with which to determine how any of the four monoallylic alcohols (**3.94**, **3.96**, **3.98** and **3.100**) would react under the proposed gold(I)-catalyzed alkoxylation conditions, we randomly screened each substrate. For the sake of organization, the preliminary studies for each of these four substrates will be presented in the order with which we tested the organocatalyzed oxa-conjugate addition reaction conditions. We will begin with the two dithiane-containing substrates **3.94** and **3.96** and data obtained from (*Z*)-alkene-containing substrates **3.98** and **3.100** will follow. The preparation of these substrates has been discussed in Section 2.3.

When monoallylic diol **3.94** was treated with 5 mol% IPrAuCl and AgClO₄ at room temperature for 24 h, little to no reaction was observed on TLC (Figure 23). The reaction mixture was then heated to 50 °C for an additional 24 h; however, conversion of **3.94** was not observed. These conditions were initially chosen because they were found to provide optimal yields in the intermolecular GCA reaction. Since little to no reaction occurred even at 50 °C, the gold(I) catalysts was changed and the JohnPhos ligand was employed. Unlike IPrAuCl, the JohnPhos gold complex is stable at temperatures above 50 °C. However, use of 5 mol% JohnPhos AuCl at 100 °C for 24 h resulted in decomposition of the substrate.

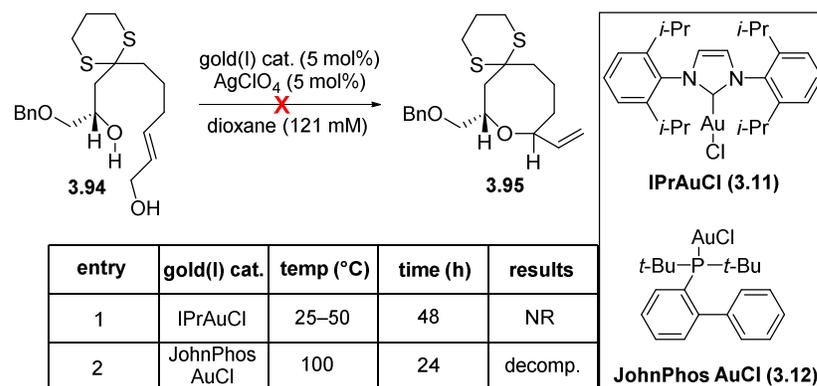


Figure 23: Attempts to cyclize dithiane-containing monoallylic diol 3.94

Similar results were obtained with dithiane-containing monoallylic diol **3.96**. Use of 5 mol% IPrAuCl and AgClO₄ at 25 °C did, however, result in complete consumption of the substrate. Unfortunately, attempts to identify the product spots were futile with none of them corresponding to the target oxocane **3.97** whose terminal olefin would provide distinct peaks in ¹H NMR. Thus, it was determined that these conditions lead to decomposition of **3.96**. Alternating the conditions to 5 mol% JohnPhos AuCl and AgSbF₆ gave similar results with decomposition of the substrate.

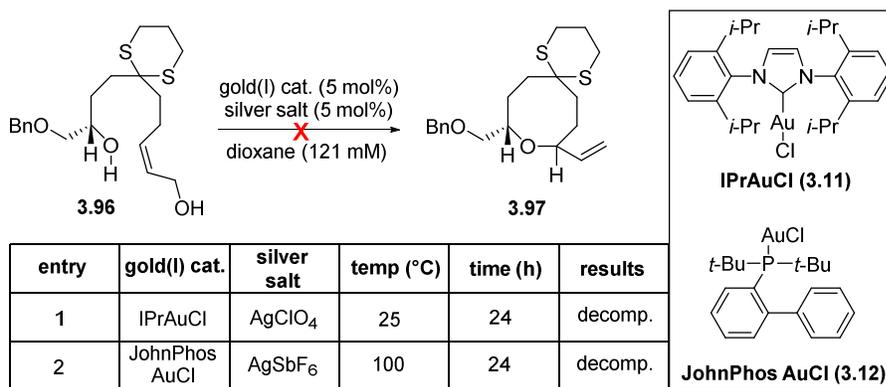


Figure 24: Attempts to cyclize dithiane-containing monoallylic diol 3.96

It should be noted that Paramita Mukherjee, a Ph.D. graduate from the Widenhoefer lab, completed the four experiments with monoallylic diols **3.94** and **3.96** presented in Figures 23 and 24. She was kind enough to train me on how to properly use a glove box for handling the silver salts and complete standard work up procedures for the gold(I)-catalyzed reactions. She was a valuable resource in these preliminary experiments as our practical understanding of this class of reactions was limited at the time.

Next, alkene-containing monoallylic diol **3.98** was treated with 5 mol% IPrAuCl and AgClO₄ at 25 °C for 24 h (Table 4, entry 1). Little to no reaction was observed during this time period. However, heating the reaction mixture to 50 °C resulted in some conversion of the substrate. Although the reaction was allowed to stir at 50 °C for several days, consumption of the starting material was not observed. It was pleasing to find that isolation and characterization of the major product by ¹H NMR revealed that the target oxocene **3.99** had been formed as a single diastereomer. Unfortunately, only trace amounts

of oxocene **3.99** were formed using the JohnPhos AuCl catalyst (entry 2). Use of a different phosphine ligand (Ph_3PAuCl) resulted in a complex mixture of products (entry 3). Thus it was tentatively concluded that gold(I) catalysts with phosphine ligands are not compatible with alkene-containing monoallylic diol **3.98**. It was hypothesized that use of microwave irradiation as the heating source might improve the rate of the reaction and, thus, the isolated yield. Therefore, **3.98** was treated with 5 mol% IPrAuCl and AgClO_4 and was warmed immediately to 50 °C using a microwave reactor. Monitoring of the reaction with TLC revealed that oxocene **3.99** was forming but at a rather slow rate. Continued reacting for ~2 days did not show any improvement in the conversion; hence, oxocene **3.99** was obtained in only 17% yield. Therefore, we concluded that alternative heating sources did not significantly impact the reaction outcome.

Table 4: Gold-catalyzed alkoxylation of Δ^{10} monoallylic diol **3.98**



entry	gold catalyst	silver salt	temp (°C)	time (h)	results
1	IPrAuCl	AgClO_4	25–50	144	18%
2	JohnPhos AuCl	AgOTs	25–100	96	trace amounts
3	Ph_3PAuCl	AgClO_4	25–50	48	complex mixture
4	IPrAuCl	AgClO_4	50 μW	50	17%

With promising results from GCA of monoallylic diol **3.98**, we eagerly tested the conditions on analogous monoallylic diol **3.100**. When treated with 5 mol% IPrAuCl and AgClO₄ at 25 °C for 24 h, monoallylic diol **3.100** underwent little to no conversion. The reaction was then heated to 50 °C and stirred for a total of 144 h in an effort to keep the reaction conditions for **3.100** (Figure 25) consistent with that of **3.98** (Table 4, entry 1). Isolation and characterization of the major product by ¹H NMR revealed that oxocene **3.101** had been synthesized. As with **3.99**, the ¹H NMR spectra of **3.101** indicated that a single diastereomer had been formed. To determine whether phosphine gold(I) ligands are generally incompatible with α,α'-disubstituted oxocene synthesis, the experiment in Figure 25, entry 2 was completed. Unfortunately, treatment of **3.100** with 5 mol% JohnPhos AuCl and AgOTs yielded only trace amounts of oxocene **3.101** even after prolonged reaction at 50 °C. These preliminary results provided motivation to further optimize the conditions for GCA of **3.100**. Our efforts toward this goal will be discussed in detail in Section 3.2.3.

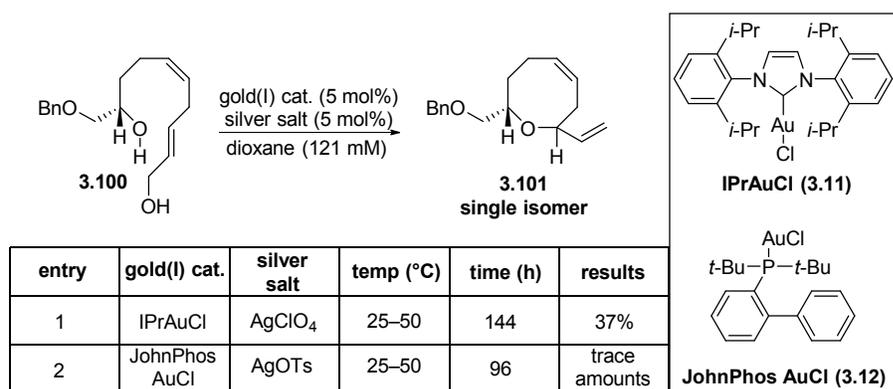
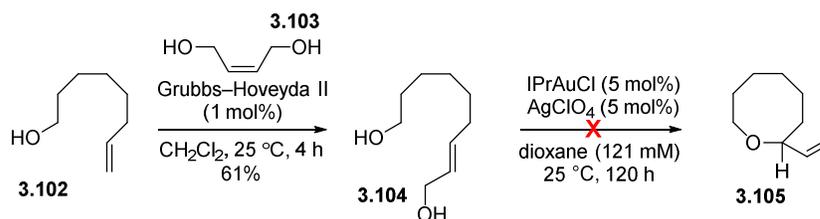


Figure 25: Gold(I)-catalyzed alkoxylation of Δ⁹ monoallylic diol **3.100**

Unlike typical method development approaches, the intramolecular gold(I)-catalyzed alkoxylation for oxocene synthesis was developed via attempts to extend our organocatalyzed oxa-conjugate addition reaction. Thus, preliminary studies for gold(I)-catalyzed alkoxylation began with somewhat structurally complex substrates which were on hand. At this stage, it was helpful to probe simplified substrates to determine the effect of the chiral secondary alcohol, skeletal (*Z*)-alkene and electrophilic functionality. Therefore, monoallylic diol **3.102** was prepared which did not contain the skeletal (*Z*)-alkene or chiral secondary alcohol (Scheme 30). Commercial 7-octen-1-ol (**3.102**) was treated with commercial *cis*-2-butene-1,4-diol (**3.103**) and 1 mol% Grubbs–Hoveyda II catalyst providing monoallylic diol **3.104** in 61% yield. Monoallylic diol **3.104** was then treated with 5 mol% IPrAuCl and AgClO₄ and the reaction progress was monitored over five days. A complex mixture of products formed during this time. It is likely that the mixture included acyclic and cyclic dimers that formed via intermolecular reaction; however, no attempts were made to isolate or characterize any of the products due to the complexity of the product mixture. In retrospect, it is likely that the target oxocene **3.105** would be volatile due to its nonpolar features and low molecular weight.

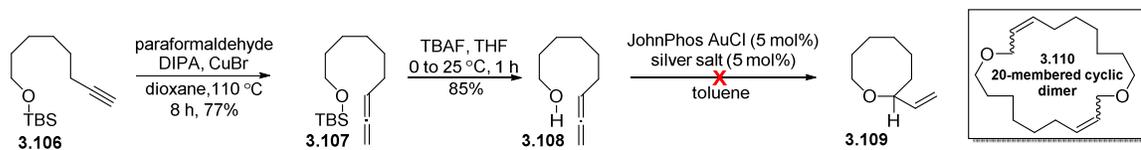


Scheme 30: Preparation of simplified monoallylic diol 3.104 and reaction under gold(I)-catalyzed conditions

As previously mentioned, gold(I)-catalyzed reactions can be completed with a variety of π -bond-containing functionalities. There are examples of gold(I)-catalyzed hydroalkoxylations of allenes.¹¹¹ Thus, a similar simplified substrate **3.108** was also prepared and tested under gold(I)-catalyzed conditions. To synthesize hydroxy allene **3.108**, known TBS protected hydroxy alkyne (**3.106**)¹¹² was subjected to paraformaldehyde, DIPA and a catalytic amount of CuBr to yield allene **3.107**. The silyl ether was then cleaved under TBAF conditions and attempts were made to synthesize oxocane **3.109** (Table 5). The optimal conditions reported for gold(I)-catalyzed hydroalkoxylations of allenes was used in each attempt with slight modifications.^{111b} Thus, hydroxy allene **3.108** was treated with 5 mol% JohnPhos AuCl and AgOTs at room temperature for a 24 hour period followed by heating to 100 °C (entry 1). Analysis of the major product by ¹H NMR revealed that a mixture of two oxacycles was present in the sample. It was hypothesized that one of these oxacycles was potentially the desired oxocane **3.109** due to the presence of terminal alkene peaks and three distinct one proton

multiples in the 3-4 ppm region corresponding to the α and α' protons. The second oxacycle product appeared to correspond with either the 10-membered cyclic ether due to regioisomeric nucleophilic attack or the 20-membered cyclic dimer **3.110** which would be expected to have a similar spectra due to its symmetry. However, the oxacycle mixture was inseparable and it was not until the experiment in entry 2 was completed that we were able to identify one of the two oxacycle products. In this experiment, the silver salt was exchanged for AgOTf and complete consumption of **3.108** was observed after stirring at 25 °C for 20 h. Isolation and characterization of the major product indicated that a single oxacycle had formed and that it was either the 10-membered cyclic ether or 20-membered cyclic dimer. Analysis of the sample by mass spectroscopy indicted that the sample was in fact the 20-membered cyclic dimer **3.110**. Additional attempts were made to shift the product distribution to favor the potential desired product **3.109**. As shown in entry 3, using AgOTs as the silver salt and maintaining the reaction temperature at 0 °C resulted in a 1:1 mixture of the 20-membered cyclic dimer **3.110** and possible oxocane **3.109**. This result indicated that the product distribution was temperature dependent; however, consumption of hydroxy allene **3.108** was not observed even after prolonged reaction time. Because the 20-membered cyclic dimer was an intermolecular side product, we hypothesized that using dilute reaction conditions (13 mM) would reduce the formation of **3.110**. Unfortunately, the conditions shown in entry 4 resulted only in formation of **3.110** with incomplete consumption of **3.108**.

Table 5: Preparation of simple hydroxy allene **3.108 and testing under gold(I)-catalyzed alkoxylation conditions**

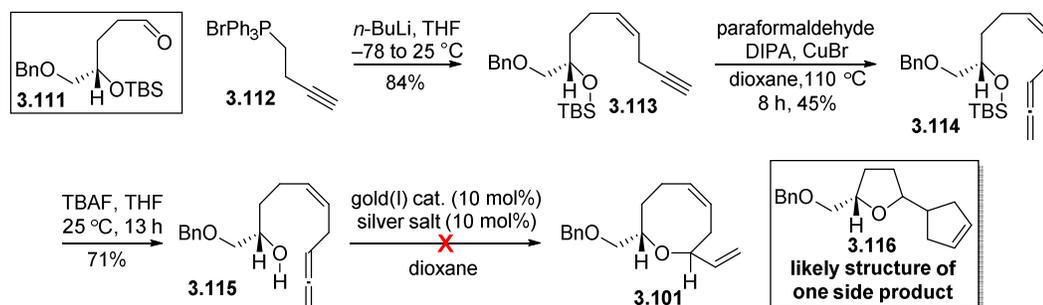


entry	silver salt	rxn conc. (mM)	temp. (°C)	time (h)	results
1	AgOTs	121	25–100	72	3.110:3.109 (3:1)
2	AgOTf	121	25	20	3.110
3	AgOTs	121	0	96	3.110:3.109 (1:1)
4	AgOTs	13	25	120	3.110

At this stage, the preliminary results obtained for hydroxy allene **3.108** prompted us to test the use of the allene functionality in our more complex model system. It was anticipated that side reactions resulting in formation of the 10-membered cyclic ether or dimers via intermolecular reaction would be likely. However, we were hopeful that the chiral secondary alcohol and skeletal *cis*-alkene would restrict the conformational flexibility of hydroxy allene **3.115** and allow preference for oxocene synthesis. Toward this aim, hydroxyl allene **3.115** was prepared via the route shown in Table 6. Known triphenyl phosphine bromide (**3.112**)¹¹³ was treated with *n*-BuLi followed by addition of known aldehyde (**3.111**).⁷⁹ The resulting homoenyne **3.113** was obtained in 84% yield. The alkyne was then treated with paraformaldehyde, DIPA and catalytic CuBr to give the allene **3.114** in moderate yield. Lastly, the silyl ether was cleaved under TBAF conditions to yield the hydroxy allene **3.115** as the substrate for the next set of gold(I)-catalyzed

hydroalkoxylation reactions. Initially, the reaction was tested with 10 mol% IPrAuCl and AgOTf, the optimized conditions for hydroxy allylic alcohol **3.100** (see Section 3.2.3). TLC monitoring revealed that the substrate had been consumed within 4.5 hours and that several side products had formed. Co-spotting with a sample of known oxocene **3.101** revealed that only a trace amount of the target oxocene **3.101** had formed. Attempts were made to isolate and elucidate the structure of each of the three nonpolar side products; however the spectra were not conclusive. Because the reaction occurred within a relatively short time frame, the reaction was repeated and the temperature was maintained at 25 °C (entry 2). Even at this temperature, the hydroxy allene **3.115** was consumed within 0.5 h and produced the same unidentifiable side products without formation any detectable oxocene **3.101**. Use of JohnPhos AuCl (entry 3) as in the simplified model studies with hydroxy allene **3.108** and diluting the reaction concentration (entry 4) did not demonstrate any change in reactivity or product distribution. In a final attempt to obtain the target oxocene **3.101**, the silver salt was changed to AgOTs (entry 5) since it had proven to be less reactive in our studies with monoallylic diol **3.100** (Section 3.2.3). This alteration did in fact reduce the rate of the reaction and prevent formation of the nonpolar side products; however, oxocene **3.101** was not observed by TLC monitoring.

Table 6: Preparation of chiral Δ^9 -hydroxy allene **3.115 and testing under gold(I)-catalyzed alkoxylation conditions**



entry	gold(I) cat.	silver salt	rxn conc. (mM)	temp. (°C)	time (h)	results
1	IPrAuCl	AgOTf	121	50	4.5	Unidentifiable nonpolar side products
2	IPrAuCl	AgOTf	121	25	0.5	“ ”
3	JohnPhos AuCl	AgOTf	121	25	0.25	“ ”
4	JohnPhos AuCl	AgOTf	12	25	2.25	“ ”
5	JohnPhos AuCl	AgOTs	12	25	24	SM not consumed

Although conclusive evidence was not obtained, it was hypothesized that the unidentifiable nonpolar side products were a result of intramolecular attack of the skeletal *cis*-alkene followed by alcohol trapping of the resulting carbocation. Examples of this type of reactivity have been reported.¹¹⁴ Thus, a potential product via this route could be bicyclic tetrahydrofuran **3.116**. In fact, ¹H NMR spectra of one of the side products is consistent with this structure; however, additional 2D NMR spectral analysis would be necessary to confidently assign the structure.

Based on the model studies presented in this section, it was determined that the skeletal *cis*-alkene was better suited for synthesis of 8-membered cyclic ethers than the corresponding 1,3-dithiane containing-substrates **3.94** and **3.96**. Furthermore, the location of the *cis*-alkene likely had an impact on the reactivity of the gold(I)-catalyzed alkoxylation; however reaction condition optimization studies would first need to be completed for **3.100** and the optimized conditions tested on **3.98** prior to making any conclusions. Additionally, removing the skeletal *cis*-alkene and α -substitution has a dramatic impact on the reactivity. Allene substrates are more reactive than allylic alcohols under gold(I)-catalyzed conditions; however regioselectivity is an issue in allene substrates.

From a method development view point, there are several substrates that would be interesting to test under gold(I)-catalyzed conditions. For example, probing the reactivity of chiral secondary alcohols **3.117** and **3.118** without a skeletal *cis*-olefin would demonstrate the importance of the *cis*-olefin as a structural element to promote cyclization (Figure 26). The preliminary studies completed with their primary alcohol counterparts **3.104** and **3.108** suggests that allene **3.118** is most likely to give the target oxocane; however, it is probable that regioselectivity would be an issue. It is anticipated that allylic alcohol **3.117** would not yield the 8-membered cyclic ether if the *cis*-alkene is solely responsible for generating a reactive conformation; however, the importance of the secondary alcohol is unknown at this point. It is possible that some oxocane would be formed from substrate **3.117**. Isomeric hydroxy allene **3.119** could also be examined.

However, it is highly possible that the skeletal *cis*-alkene would participate as a nucleophile in the gold(I)-catalyzed reaction of **3.119** resulting in formation of a fused bicyclic tetrahydrofuran. Additionally, dithiane-containing hydroxy allenes **3.120** and **3.121** were not studied. Use of the dithiane moiety instead of the (*Z*)-olefin as the structural element would obviously prevent the formation of intramolecular side products from participation of the alkene; however it is uncertain if oxocane synthesis could be accomplished.

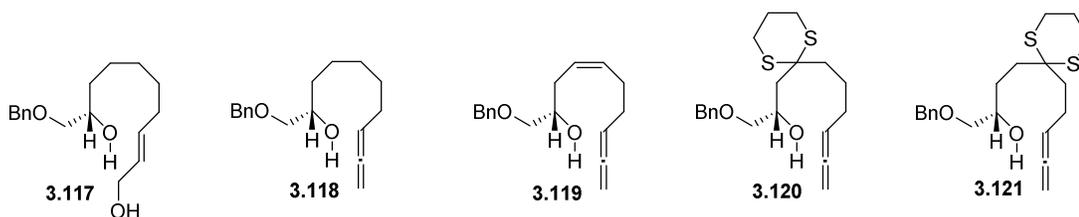


Figure 26: Potential substrates for gold(I)-catalyzed cyclizations

Despite the intriguing results that may have been obtained if the substrates shown in Figure 26 had been studied, the cost of these studies far outweighed the potential benefits. Namely, each of the substrates would require the development of a synthetic route. Typically, 5–10 steps were required to prepare the collection of substrates examined thus far. Furthermore, our aims were not limited to method development. If the method development for 8-membered cyclic ether synthesis was successful, one of our goals was to apply the method to a natural product synthesis. Because many of the naturally occurring monocyclic 8-membered cyclic ethers contain skeletal *cis*-alkenes, we chose to pursue

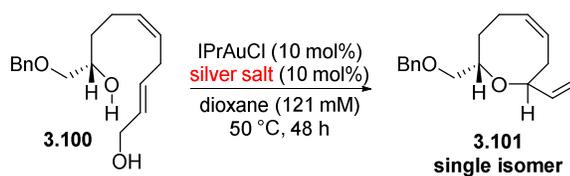
optimization of the GCA conditions for **3.100** whose oxocene product already contained the requisite *cis*-alkene.

3.2.3 Optimization of the Gold(I)-Catalyzed Alkoxylation Reaction for α,α' -Disubstituted-Oxocenes

In the field of gold(I)-catalysis, the active gold species is typically formed *in situ* via metal exchange of the chloride ion, although recent methodologies have begun employing silver free conditions.¹¹⁵ It has been shown that the nature of the silver salt counteranion can significantly affect the reactivity of the gold metal.^{102a, 116} The counteranion chelation to gold has even been used to induce enantioselectivity by employing chiral silver salts.¹¹⁷ Thus, it was essential to examine the effects of various silver salts on our GCA of monoallylic diol **3.100**. During the course of our preliminary studies, it was decided that 10 mol% IPrAuCl should be employed and that the reaction should be stirred at 50 °C for 48 h. Although these particular parameters had not been optimized, they were sufficient to begin our optimization studies. Of the seven silver salts examined, AgOTf provided the highest yield (50%) of oxocene **3.101** (Table 7). AgOAc and AgOTs proved to be ineffective with no reaction being observed. It is likely that these two counteranions chelate too strongly to the gold metal and do not permit π -bond activation. The low yield for AgClO₄ (entry 2) was surprising since an preliminary experiment with AgClO₄ resulted in a 37% yield of oxocene **3.101**. Additional experiments were completed to determine the

cause of this apparent discrepancy and will be discussed later in this section. AgSbF₆ (entry 3) and AgBF₄ (entry 5) gave comparable yields of 35% and 32%, respectively.

Table 7: Screening of silver salts for the gold(I)-catalyzed alkoxylation of Δ^9 monoallylic diol 3.100

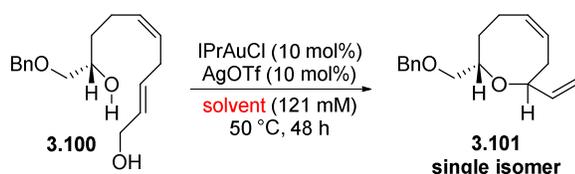


entry	silver salt	yield (%)
1	AgOTf	50
2	AgClO ₄	8
3	AgSbF ₆	35
4	AgOAc	NR
5	AgBF ₄	32
6	AgOTs	NR
7	AgAsF ₆	18

With the optimal silver salt determined we then examined the solvent effect. The catalyst loading, temperature and time were maintained throughout these studies. Thus, entry 1 is a duplicate of Table 7 and is shown here in Table 8 for ease of comparison. Solvents such as CH₂Cl₂ and toluene which had worked well in the inter- and intramolecular gold(I)-catalyzed alkoxylation⁹⁰⁻⁹¹ were tested along with other select

solvents. Unfortunately, no improvement in the isolated yield was obtained with any of the solvents examined. Several solvents only provided trace amounts of oxocene **3.101** (entries 3, 6, & 7) while others significantly decreased the isolated yield (entries 2, 4, & 5).

Table 8: Screening of solvents for the gold(I)-catalyzed alkoxylation of Δ^9 monoallylic diol **3.100**



entry	solvent	yield (%)
1	Dioxane	50
2	Toluene	24
3	acetonitrile	trace amounts
4	THF	14
5	Acetone	17
6	CH ₂ Cl ₂	trace amounts
7	EtOAc	trace amounts

The observed discrepancy with AgClO₄ mentioned previously was addressed next. As shown in Table 9 entry 1, our preliminary experiment with 5 mol% AgClO₄ was completed with stirring at room temperature for the first 24 hours followed by heating at 50 °C. In our silver salt counteranion screening (entry 2), 10 mol% catalyst loading was employed and the reaction was heated to 50 °C initially. Therefore, it was unclear if the

low yield in entry 2 was caused by a temperature and/or catalyst loading effect. To determine the nature of this effect, monoallylic alcohol **3.100** was treated with 10 mol% IPrAuCl and AgClO₄ and stirred at 30 °C for 48 h. Isolation of oxocene **3.101** was accomplished in 22% yield (entry 3). Similarly, monoallylic diol **3.100** was treated with 5 mol% IPrAuCl and AgClO₄ and stirred at 50 °C for 48 h resulting in 28% yield of **3.101**. Based on these two experiments, it could be concluded that both the temperature and catalyst loading have significant effects on the isolated yield.

Table 9: Temperature and catalyst loading effects on the gold(I)-catalyzed alkoxylation of Δ^9 monoallylic diol **3.100 using AgClO₄**

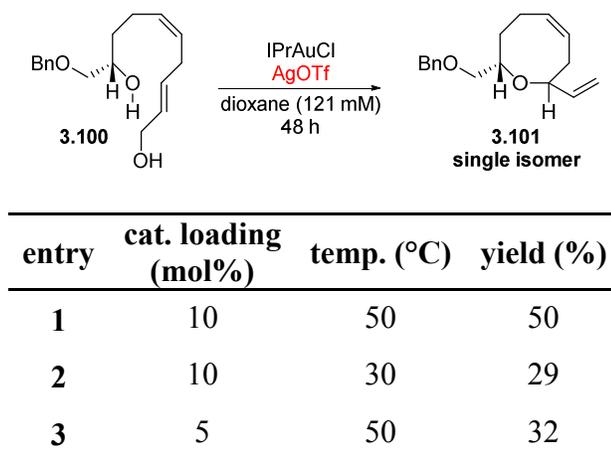


entry	cat. loading (mol%)	temp. (°C)	time (h)	yield (%)
1	5	25–50	144	37
2	10	50	48	8
3	10	30	48	22
4	5	50	48	28

We were then interested in determining if this was a general effect of the gold(I)-catalyzed alkoxylation. Thus, we completed similar experiments using AgOTf, our optimal silver salt. As shown in Table 10 entry 2, use of a lower temperature (30 °C) while

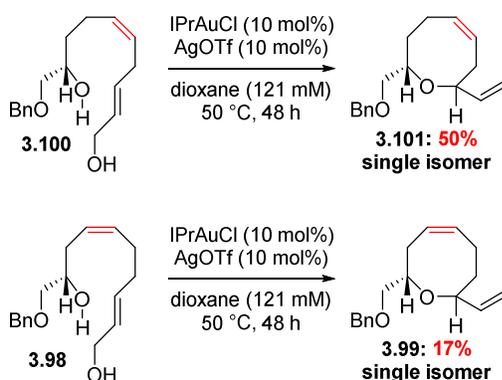
maintaining the catalyst loading resulted in a significant decrease in the isolated yield of **3.101**. Unfortunately, this same trend was observed when the catalyst loading was decreased while maintaining the temperature (entry 3). Hence, it was concluded that the observed catalyst loading/temperature effect was specific to AgClO₄.

Table 10: Temperature and catalyst loading effects on the gold(I)-catalyzed alkoxylation of Δ^9 monoallylic diol **3.100 using AgOTf**



At this point, we had optimized the major parameters of the gold(I)-catalyzed alkoxylation of **3.100**, which served a model substrate for more complex natural product substrates. As mentioned earlier, it was our intent to optimize the conditions for monoallylic alcohol **3.100** since it had provided a higher yield of oxocene **3.101**. Then these conditions would be tested on monoallylic alcohol **3.98** to determine if any improvement could be made in the isolated yield of oxocene **3.99**. Thus, monoallylic alcohol **3.98** was treated with 10 mol% IPrAuCl and AgOTf while stirring in dioxane at 50

°C for 48 h. Isolation of oxocene **3.99** was accomplished in a 17% yield. Compared to our highest yielding (18%) preliminary experiment with monoallylic diol **3.98** (Table 4, entry 1), there was no significant change in the isolated yield. Furthermore, it could be confidently concluded that the location of the *cis*-alkene had a significant effect on the rate of cyclization. In fact, our results are in agreement with Crimmins's calculations for similar regioisomeric oxocenes (Scheme 41).¹¹⁸ Their results indicate that the Δ 9-oxocene is several kcal/mol lower in energy than the Δ 10-oxocene.



Scheme 31: Direct comparison of the reactivity of Δ 9 and Δ 10 monoallylic diols **3.100 and **3.98** under optimized gold(I)-catalyzed alkoxylation conditions**

3.2.4 Determination of the Relative Configuration of α,α' -Disubstituted Oxocene **3.101**

Prior to transitioning into our application of the gold(I)-catalyzed alkoxylation methodology to a natural product synthesis, it was first necessary to determine the relative configuration of the α,α' -disubstituted oxocene **3.101**. It was fortunate that the same single

isomer was obtained in all attempts to cyclize **3.100**. Thus, all that was required was to obtain a ^1H - ^1H COSY NMR spectra to definitively assign the ^1H NMR spectra and ^1H - ^1H NOESY NMR spectra to examine the spatial relationship of the α and α' protons.

The ^1H - ^1H COSY NMR spectra obtained for oxocene **3.101** is shown in Figure 27. Key coupling interactions that aided in the assignment of the ^1H NMR spectra are indicated by red boxes. Namely, the presence of couplings between 12-H and two of the one proton multiplets in the 2-3 ppm region indicated that those peaks corresponded to 11-H protons. Thus, the two remaining one proton multiplets in the 2-3 ppm region must belong to 8-H protons. One of the two 8-H protons possessed a coupling interaction with one of the two one proton multiplets in the 3-4 ppm region indicating that it should be given the assignment of 7-H. Hence, the remaining one proton multiplet in this region was assigned as 13-H. This assignment was confirmed by the observed coupling between 13-H the peak corresponding to 14-H. The last peaks to be assigned were the slightly overlapping alkene peaks corresponding to the skeletal *cis*-alkene. The alkene peak which was downfield shifted had coupling interactions with 8-H peaks while the upfield shifted alkene peak coupled with both 11-H peaks.

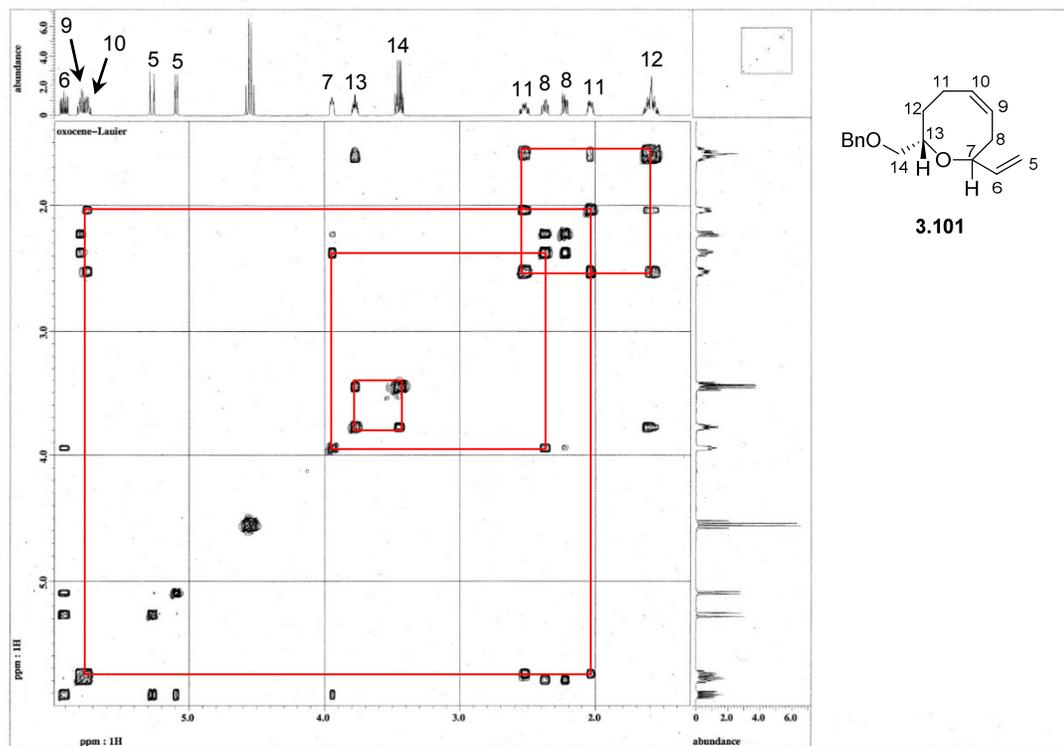


Figure 27: ^1H - ^1H COSY spectra of oxocene 3.101

The ^1H - ^1H NOESY NMR spectra obtained for oxocene **3.101** is shown in Figure 28. Key interactions observed in this spectra are also indicated by red boxes. Initially, the spectra was examined for the presence of an nOe between 7-H and 13-H. If this coupling existed, then the tentative relative assignment of α,α' -*cis* could be made. A coupling between 7-H and 13-H did in fact exist and the spectra was examined for additional coupling interactions which would correspond with the α,α' -*cis*-oxocene. Other key nOe

interactions were observed between 8-H and 11-H which indicates that these two protons are on the same face of the molecule. There were also nOe interactions between 13-H & 10-H and 7-H & 9-H. These interactions could only be explained by a α,α' -*cis*-oxocene in a twist boat conformation and would not be observed in the corresponding α,α' -*trans*-oxocene. Therefore, it was definitively concluded that the α,α' -*cis*-oxocene **3.101** had been stereoselectively synthesized in the gold(I)-catalyzed alkoxylation reactions. With this information we could proceed with selection of a natural product target and determine the feasibility of this methodology in the context of natural product synthesis which will be the topic of chapter 4.

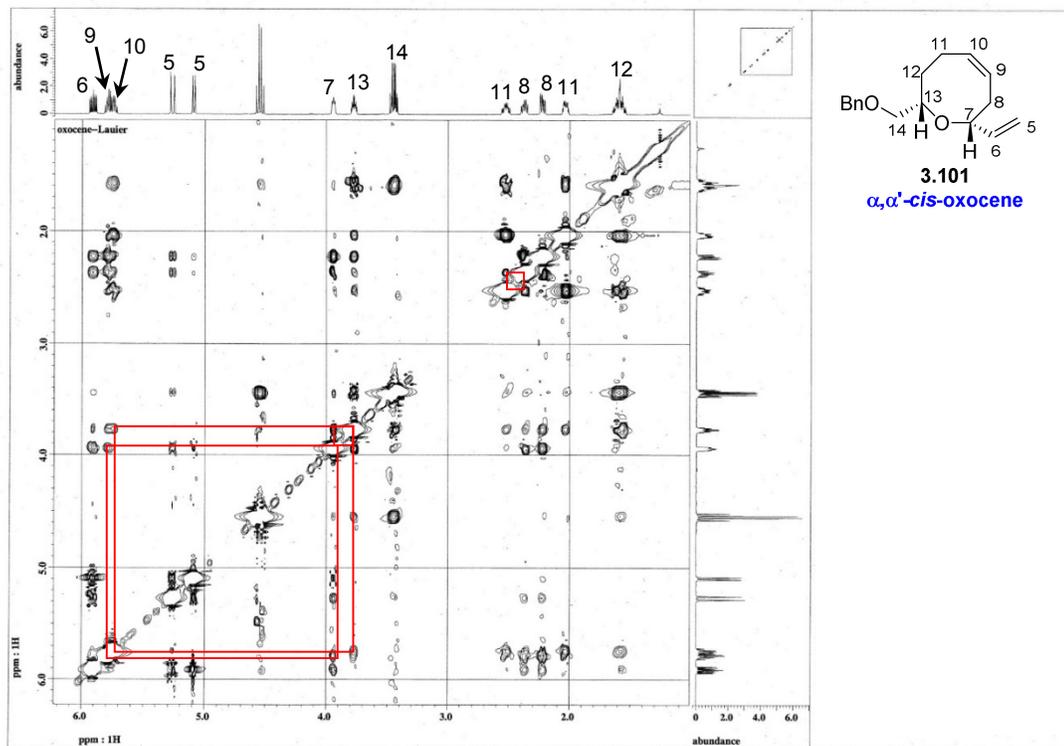


Figure 28: ^1H - ^1H NOESY spectra of oxocene 3.101

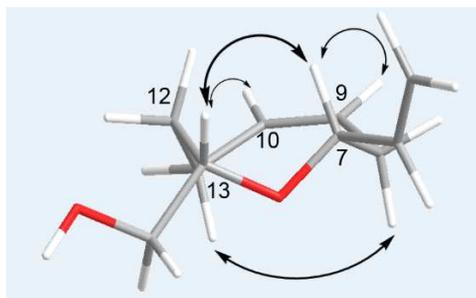


Figure 29: Three dimensional conformation of oxocene 3.101

3.3 Summary

In this chapter, intriguing examples of stereoselective α,α' -disubstituted oxocenes have been discussed with a focus on bond disconnections for the 8-membered cyclic ether and stereoinduction steps. The field of gold(I)-catalysis has been introduced and several key examples which inspired the method development disclosed within have been discussed. Preliminary investigations using a range of substrates and optimization of the gold(I)-catalyzed alkoxylation for Δ^9 monoallylic diol **3.100** has been presented in detail. Lastly, 2D NMR analysis of oxocene **3.101** was described and reasoning for the relative assignment of α,α' -*cis*-oxocene has been provided.

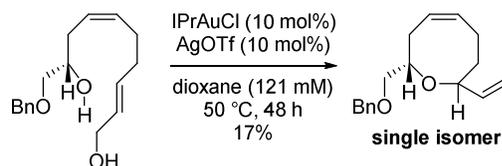
3.4 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. Unless otherwise stated all reagents were purchased from Sigma–Aldrich, Acros, or Fisher and were used without further purification. All solvents were ACS grade or better and used without further purification except tetrahydrofuran (THF) which was freshly distilled from sodium/benzophenone each time before use. Analytical thin layer chromatography (TLC) was performed with glass backed silica gel (60 Å) plates with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel (particle size 230–400 mesh, 60 Å). All ^1H NMR and ^{13}C NMR spectrum

were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in CDCl₃ by using the signal of residual CHCl₃, as an internal standard. All NMR δ values are given in ppm, and all J values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo–Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102. API/1W) polarimeter.

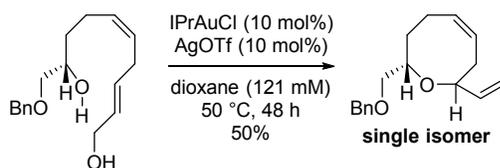
Gold(I)-Catalyzed Alkoxylation of **3.98**



A suspension of IPrAuCl (2.3 mg, 0.004 mmol), AgOTf (0.9 mg, 0.004 mmol), and diol **3.98** (10.1 mg, 0.04 mmol) in dioxane (0.13 mL, 0.121 M) in a sealed tube was stirred at 50 °C for 48 h. The resulting suspension was cooled to room temperature, filtered through a short silica gel plug, and eluted with EtOAc. Purification by column chromatography (silica gel, hexanes/EtOAc = 10/1) yielded α,α' -disubstituted oxocene **3.99** as a colorless oil (1.6 mg, 17%): ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.25 (m, 5H), 5.88–5.69 (m, 3H), 5.30 (dt, J = 17.2, 2.0 Hz, 1H), 5.01 (dt, J = 10.8, 2.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.02–3.95 (m, 1H), 3.59 (dd, J = 9.2, 6.0 Hz, 1H), 3.56–3.50 (m,

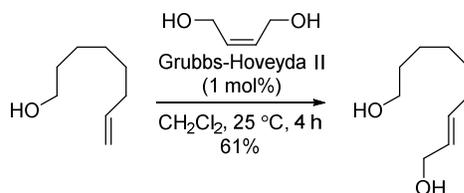
1H), 3.43 (dd, $J = 9.2, 5.2$ Hz, 1H), 2.55 (ddd, $J = 18.0, 12.8, 5.2$ Hz, 1H), 2.40–2.30 (m, 1H), 2.23 (ddd, $J = 10.0, 8.0, 2.0$ Hz, 1H), 2.07–2.00 (m, 1H), 1.73–1.63 (m, 1H), 1.63–1.52 (m, 1H).

Gold(I)-Catalyzed Alkoxylation of **3.100**



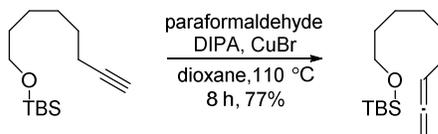
A suspension of IPrAuCl (2.9 mg, 0.005 mmol), AgOTf (1.2 mg, 0.005 mmol), and diol **3.100** (13 mg, 0.05 mmol) in dioxane (0.17 mL, 0.121 M) in a sealed tube was stirred at 50 °C for 48 h. The resulting suspension was cooled to room temperature, filtered through a short silica gel plug, and eluted with EtOAc. Purification by column chromatography (silica gel, hexanes/EtOAc = 10/1) yielded α, α' -*cis*-oxocene **3.101** as a colorless oil (6 mg, 50%): $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.33 (d, $J = 4.6$ Hz, 4H), 7.29–7.25 (m, 1H), 5.91 (ddd, $J = 16.0, 11.0, 5.5$ Hz, 1H), 5.81–5.72 (m, 2H), 5.27 (ddd, $J = 16.9, 3.2, 1.9$ Hz, 1H), 5.09 (ddd, $J = 10.6, 3.2, 1.8$ Hz, 1H), 4.55 (dd, $J = 22.4, 11.9$ Hz, 2H), 3.96–3.92 (m, 1H), 3.80–3.75 (m, 1H), 3.46 (dd, $J = 10.1, 6.9$ Hz, 1H), 3.43 (dd, $J = 10.1, 4.6$ Hz, 1H), 2.53 (dddd, $J = 14.2, 12.8, 9.7, 5.5$ Hz, 1H), 2.40–2.34 (m, 1H), 2.22 (ddd, $J = 14.2, 8.2, 2.3$ Hz, 1H), 2.06–2.01 (m, 1H), 1.65–1.53 (m, 2H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 139.7, 138.6, 131.8, 128.3, 127.6, 127.5, 127.4, 114.2, 81.6, 78.2, 74.5, 73.3, 34.2, 32.0, 23.1.

Preparation of Monoallylic Diol **3.104**



To a solution of 7-octen-1-ol (107 mg, 0.83 mmol) in CH_2Cl_2 (4.2 mL, 0.199 M) was added *cis*-2-butene-1,4-diol (0.14 mL, 1.67 mmol) followed by Grubbs–Hoveyda II catalyst (5 mg, 8.3×10^{-3} mmol). After stirring at 25 °C for 4 h, DMSO (30 μL , 0.42 mmol) was added and the reaction mixture continued to stir for 10 h. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1) yielded (*E*)-non-2-ene-1,9-diol **3.104** as a colorless oil (81 mg, 61%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.72–5.58 (m, 2H), 4.07 (d, $J = 4.4$ Hz, 2H), 3.63 (t, $J = 6.8$ Hz, 2H), 2.04 (dt, $J = 7.2, 6.4$ Hz, 2H), 1.72 (bs, 1H), 1.60–1.27 (m, 9H).

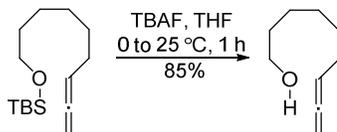
Preparation of Allene **3.107**



To a solution of alkyne **3.106** (360 mg, 1.50 mmol) in dioxane (5.0 mL, 0.300 M) was added paraformaldehyde (90 mg, 2.99 mmol), DIPA (0.4 mL, 2.99 mmol), and CuBr (86 mg, 0.60 mmol). The reaction stirred at 110 °C for 8 h. Purification by column chromatography (silica gel, hexanes/EtOAc = 40/1) yielded allene **3.107** as a colorless oil (294 mg, 77%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.09 (quint, $J = 6.8$ Hz, 1H), 4.65 (dd, $J =$

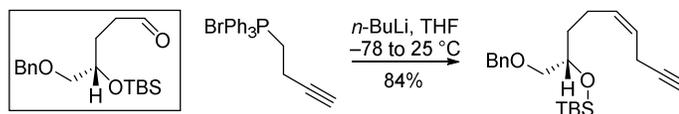
6.4, 3.2 Hz, 1H), 4.64 (dd, $J = 6.4, 3.2$ Hz, 1H), 3.60 (t, $J = 6.8$ Hz, 2H), 2.03–1.95 (m, 2H), 1.56–1.47 (m, 2H), 1.47–1.36 (m, 2H), 1.36–1.28 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H).

Preparation of Hydroxy Allene 3.108



To a solution of **3.107** (294 mg, 1.16 mmol) in THF (8.3 mL, 0.140 M) was added TBAF (1.0 M in THF, 2.3 mL, 2.31 mmol). After stirring for 1 h at 25 °C, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 5/1) yielded nona-7,8-dien-1-ol **3.108** as a colorless oil (138 mg, 85%): ^1H NMR (400 MHz, CDCl_3) δ 5.09 (quint, $J = 6.8$ Hz, 1H), 4.66 (dd, $J = 6.8, 3.2$ Hz, 1H), 4.64 (dd, $J = 6.8, 3.2$ Hz, 1H), 3.64 (t, $J = 6.4$ Hz, 2H), 2.04–1.97 (m, 2 H), 1.61–1.53 (m, 2H), 1.47–1.31 (m, 6H), 1.24 (bs, 1H).

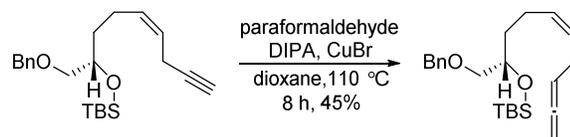
Preparation of Homoenyne 3.113



To a cooled (-78 °C) solution of triphenylphosphonium bromide **3.112** (2.477 g, 6.27 mmol) in THF (26.0 mL, 0.241 M) was added *n*-BuLi (2.3 M in hexanes, 2.7 mL, 6.27 mmol). The reaction was warmed to 0 °C and continued stirring for 1 h. The reaction was

then cooled to $-78\text{ }^{\circ}\text{C}$. After 0.5 h, a solution of aldehyde **3.111** (1.714 g, 5.31 mmol) in THF (14.0 mL, 0.379 M) was added. After stirring at $25\text{ }^{\circ}\text{C}$ for 14 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 50/1) yielded **3.113** as a colorless oil (1.608 g, 84%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39–7.26 (m, 5H), 5.55–4.39 (m, 2H), 4.54 (s, 2H), 3.86 (quint, $J = 5.6\text{ Hz}$, 1H), 3.43 (dd, $J = 9.6, 5.2\text{ Hz}$, 1H), 3.37 (dd, $J = 9.6, 5.6\text{ Hz}$, 1H), 2.93 (d, $J = 7.6\text{ Hz}$, 2H), 2.23–2.12 (m, 1H), 2.11–2.00 (m, 1H), 1.97 (t, $J = 2.8\text{ Hz}$, 1H), 1.71–1.60 (m, 1H), 1.60–1.49 (m, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

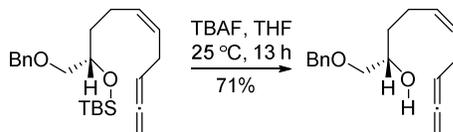
Preparation of Allene **3.114**



To a solution of alkyne **3.113** (1.608 g, 4.48 mmol) in dioxane (6.7 mL, 0.669 M) was added paraformaldehyde (215 mg, 7.17 mmol), DIPA (0.8 mL, 5.38 mmol), and CuBr (331 mg, 1.48 mmol). The reaction stirred at $110\text{ }^{\circ}\text{C}$ for 8 h. Purification by column chromatography (silica gel, hexanes/EtOAc = 40/1) yielded allene **3.114** as a colorless oil (756 mg, 45%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36–7.27 (m, 5H), 5.51–5.38 (m, 2H), 5.10 (quint, $J = 6.8\text{ Hz}$, 1H), 4.70 (dd, $J = 6.4, 3.2\text{ Hz}$, 1H), 4.68 (dd, $J = 6.4, 3.2\text{ Hz}$, 1H), 4.53 (s, 2H), 3.85 (quint, $J = 5.6\text{ Hz}$, 1H), 3.42 (dd, $J = 9.2, 5.6\text{ Hz}$, 1H), 3.37 (dd, $J = 9.6, 5.6$

Hz, 1H), 2.77–2.69 (m, 2H), 2.21–2.10 (m, 1H), 2.10–1.98 (m, 1H), 1.67–1.56 (m, 1H), 1.56–1.46 (m, 1H), 0.89 (s, 9H), 0.08 (s, 6H).

Preparation of Hydroxy Allene **3.115**



To a solution of TBS ether **3.114** (71 mg, 0.19 mmol) in THF (1.5 mL, 0.127 M) was added TBAF (1.0 M in THF, 0.4 mL, 0.38 mmol). After stirring at 25 °C for 13 h, the reaction was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 7/1) yielded **3.115** as a colorless oil (35 mg, 71%): ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.27 (m, 5H), 5.49–5.40 (m, 2H), 5.10 (quint, *J* = 6.4 Hz, 1H), 4.70 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.68 (dd, *J* = 6.8, 3.6 Hz, 1H), 4.56 (s, 2H), 3.86–3.78 (m, 1H), 3.50 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.34 (dd, *J* = 9.2, 8.0 Hz, 1H), 2.79–2.72 (m, 2H), 2.33 (bs, 1H), 2.18 (dt, *J* = 7.6, 7.2 Hz, 2H), 1.61–1.42 (m, 2H).

4. Studies toward a Stereoselective Total Synthesis of (+)-Intricenyne

The promising results in our method development studies for the stereoselective synthesis of α,α' -*cis*-oxocenes via gold(I)-catalyzed alkoxylation (GCA) prompted an investigation into the feasibility of applying this method to a natural product synthesis. Our primary motivation in exploring this method was its potential application to natural product synthesis. As described in section 1.2, oxocenes are found in a variety of marine natural products that can be divided into two primary categories, ladder-shaped polycyclic ethers and monocyclic ethers. The neuro- and cardiotoxic effects⁴⁰ of many ladder-shaped polycyclic ethers, such as brevetoxin B, and their structural complexity has sparked numerous investigations into their laboratory synthesis. The less complex monocyclic ether natural products have mainly been utilized as platforms to test the feasibility of newly developed synthetic methods. The potential biological applications of this class of moderately complex marine natural products, C₁₅ nonterpenoids, have been overlooked thus far with few reports of biological testing.¹¹⁹ Therefore, the aims of this project were twofold: 1) stereoselectively synthesize a naturally occurring monocyclic α,α' -*cis*-oxocene via gold(I)-catalyzed alkoxylation and 2) subject the natural product to a screen for biological activity.

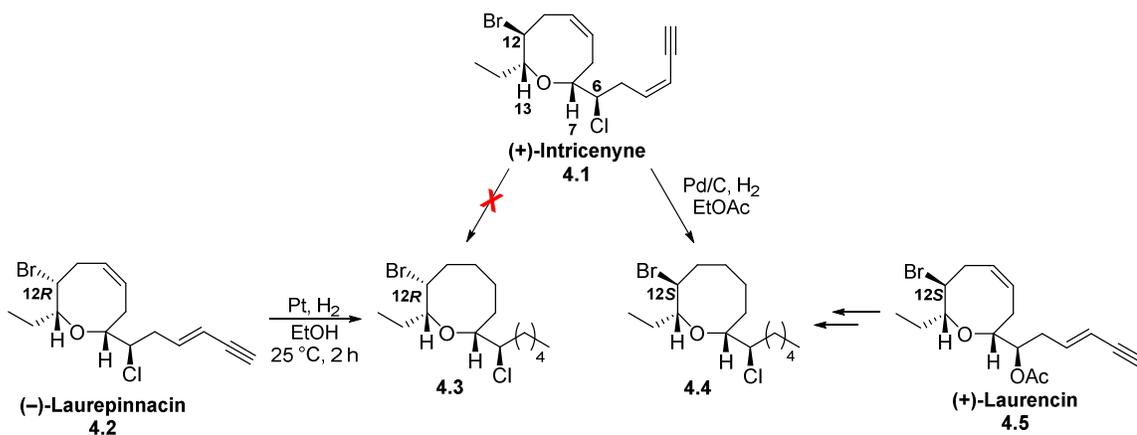
With these aims in mind, it was first necessary to select a natural product target. Several requirements needed to be fulfilled in the structure of the target. Obviously, a *cis* relationship between the two carbons flanking the ether bond (α and α' positions) was

essential. It was unknown how additional substitution in the oxocene backbone would affect the key cyclization; however, this structural feature is common in monocyclic ether natural products and would probe the limits of the GCA. Moderate complexity was desired in the α and α' appendages for several reasons. The ability to functionalize the α,α' -*cis*-oxocene obtained from the GCA had yet to be examined and the main concern was selective differentiation of the internal and terminal double bonds. Complexity in these side chains would also add to the overall value of the natural product synthesis and allow contributions to be made in other areas of this field. Lastly, a natural product target with no or few previous total syntheses would further strengthen our contribution. Therefore, (+)-intricenyne (**4.1**) was chosen as our natural product target. (+)-Intricenyne has an α,α' -*cis*-oxocene core with a moderately complex C7 (*Z*)-enyne appendage, contains substitution in the oxocene backbone and has yet to be synthetically prepared. If a successful total synthesis is to be completed, biological screening would be conducted, potentially leading to the discovery of a new therapeutic or chemical biology tool. The structural similarities of **4.1** to other monocyclic ether natural products (see Section 1.2) would also permit additional investigations into the limits of the GCA method for medium-sized cyclic ether synthesis. Herein, we disclose our stereoselective synthesis of the core structure of (+)-intricenyne (**4.1**) via gold(I)-catalyzed alkoxylation.

4.1 Background

4.1.1 Isolation and Structural Elucidation of (+)-Intricenyne

In 1978 White and Hager reported the initial isolation and partial structural elucidation of **4.1**, collected from the lipid extract of the red alga *Laurencia intricate*.¹⁹ Their fractionation method resulted in the isolation of eleven new isomeric C₁₅ non-terpenoid halogenated compounds with **4.1** being the most nonpolar component. The structural assignment of **4.1**, as shown in Figure xx, was established through HRMS, UV, IR, ¹H NMR, and homonuclear decoupling experiments. The absolute stereochemical assignment of (+)-intricenyne was later determined by Munro and co-workers to be (6*R*,7*R*,12*S*,13*R*).¹²⁰ This assignment was based on spectral data of known compounds **4.3** and **4.4** obtained from structurally similar natural products (–)-laurepinnacin (**4.2**)³³ and (+)-laurencin (**4.5**)¹²¹ (Scheme 32). To determine the stereochemistry, a sample of **4.1** was hydrogenated to give a molecule with spectral data identical to that of **4.4**, thus establishing the configuration of C12. The remaining three stereocenters were determined to be (6*R*, 7*R*, 13*R*) based on the optical rotation of **4.1** which was similar to that of **4.5**.



Scheme 32: Determination of the absolute configuration of (+)-intricenyne

4.1.2 Similar Oxocene Natural Products

(+)-Intricenyne is just one member of a class of monocyclic natural products containing an 8-membered cyclic ether. Should our efforts to stereoselectively prepare **4.1** and probe its potential biological properties be successful, we would have synthetic access to other members of this class of natural products. Although only a handful of C₁₅ nonterpenoids are shown in Figure 30, there are a number of members that have various MSCE skeletons with few to no total syntheses. Application of our proposed GCA to other members of this class would serve two purposes. The limits of our method would be tested by preparing more structurally complex oxocene-containing natural products. Alternatively, we could probe the transferability of our method to MSCEs of different sizes. Thus, a better understanding of the parameters that guide the GCA in the context of MSCE synthesis would be obtained. Furthermore, if promising biological applications do exist for **4.1**, the conserved features within this group of molecules suggests that the biological

properties might also be conserved. Thus, preparation of members of this class shown in Figure 30 could allow for preliminary SAR studies. For these reasons, the purpose of this section is to highlight several other members of this oxocene-containing natural product group and discuss their structural similarities with (+)-intricenyne. Any syntheses or biological studies will also be briefly acknowledged.

Of the natural products shown in Figure 30, (–)-laurepinnacin (**4.2**) has the most structural similarities to (+)-intricenyne and only differs from **4.1** in the stereochemistry of the C12 bromide and configuration of the double bond within the enyne functionality. (–)-laurepinnacin was isolated from *Laurencia pinnata*, a type of marine red alga, by Masamune and Fukuzawa³³. Along with (–)-isolaurepinnacin, a similar $\alpha\alpha'$ -*cis*-oxepine, **4.2** was described as having insecticidal properties; however, data to support that claim was not reported. To date, there are no total syntheses of (–)-laurepinnacin.

Although still very structurally similar to **4.1**, (+)-laurencin (**4.5**) differs in its chemical formula as a result of the C6 acetate functionality in place of the C6 chloride. As with **4.2**, (+)-laurencin contains a terminal (*E*)-enyne as part of the C7 side chain. Laurencin has been the most thoroughly examined member of the group of natural products shown in Figure 30, which could be due to a number of reasons. It was the first to be isolated and structurally elucidated. It is also one of the simpler natural products to synthetically prepare within this natural product group. The (*E*)-enyne functionality is more thermodynamically stable and, thus, easier to access. The inherent C6 acetate eliminates the need to perform a Hooz's chlorination, as in **4.1** or **4.2**, or formation of a tetrahydrofuran, as in **4.6** and **4.7**.

Furthermore, the C6 acetate acts as a natural protecting group, which would likely be required for the preparations of (+)-poiteol (**4.8**) or (+)-bermudenynol (**4.9**). Additionally, a simple methylene unit is present at the C5 position and the Δ^9 -*cis*-olefin remained intact and unfunctionalized during its metabolic synthesis. Hence, there have been a total of 13 syntheses to date. Because of its structural similarities to (+)-intrincenyne and its numerous syntheses, **4.5** will be discussed in more detail in Section 4.1.2.1.

Irie and co-workers isolated (-)-laurefucin (**4.6**) in 1972 from *Laurencia nipponica*.¹²² The first proposed structure, which was determined by chemical and spectral properties, was later revised based on X-ray crystallographic data.¹²³ (-)-Laurefucin possess a unique 2,8-dioxabicyclo[5.2.1]decane skeleton, indicating that is biogenetically derived from deacetylated (+)-laurencin.¹²⁴ (-)-Laurefucin also differs from **4.1** in that it contains an (*E*)-enyne. Thus far, there have been two syntheses of **4.1**.¹²⁵

Interestingly, (-)-laurefucin and (+)-laurencin were both reported to inhibit drug metabolism.¹²⁶ Specifically, **4.5** and **4.6** potentiated the pentobarbitone induced sleep-time in male Swiss mice. Pentobarbitone is a short acting central nervous system (CNS) depressant and is commonly used for dose-dependent sedation or euthanasia. Subjects were injected with DMSO/H₂O solutions of the test molecule (10 mg/kg i.p.) followed by a pentobarbitone sodium administration (60 mg/kg i.p.) 30 minutes later. The duration of the sedative affects were monitored and compared to a control (62 ± 19.1 min.). (-)-Laurefucin (78 ± 13.4 min) and (+)-laurencin (120 ± 18.1 min) both prolonged the sleep-time when compared to the control. Although data was not disclosed, Kaul and co-workers reported

that **4.5** and **4.6** have “little to no pharmacological activity of their own” in preliminary gross behavioral studies. Therefore, the observed biological effects were attributed to a metabolism inhibition mechanism, which was verified by determining the pentobarbitone blood concentrations at 1 hour and upon awakening for the most potent and control test molecules.

The isolation and structural elucidation of (+)-poiteol (**4.8**) and (+)-chlorofucin (**4.7**) were reported simultaneously in 1980 by Fenical, Clardy and co-workers.¹⁸ (+)-Poiteol was isolated from *Laurencia poitei* while **4.7** was isolated from *Laurencia snyderae*. The structural assignments for **4.7** and **4.8** were confirmed by single crystal X-ray diffraction analysis. (+)-Poiteol differs from **4.1** in that the internal olefin is replaced by an epoxide group. Also, **4.8** possesses a C5 chloride and C6 alcohol. (+)-Chlorofucin is structurally very similar to (–)-laurefucin (**4.6**). The major distinguishing feature is its α,α' -*trans* relationship. Although α,α' -*trans*-eight-membered cyclic ethers are less thermodynamically stable than the corresponding *cis* relationship, it is important to note that this type of α,α' relationship is present in natural products and thus poses a challenge for chemists in this field. There are no total synthesis of either **4.7** or **4.8** to date.

Cardellina and co-workers isolated (+)-bermudenynol (**4.9**) in 1982 from *Laurencia intricate*.¹²⁷ The elucidated structure was confirmed by single-crystal X-ray analysis. (+)-bermudenynol differs from **4.1** in its' C5 and C6 substitutions, as well as its unique and synthetically challenging C10 vinyl chloride. Kim and co-workers only recently reported the first total synthesis of **4.9** using their IAEA method.¹²⁸

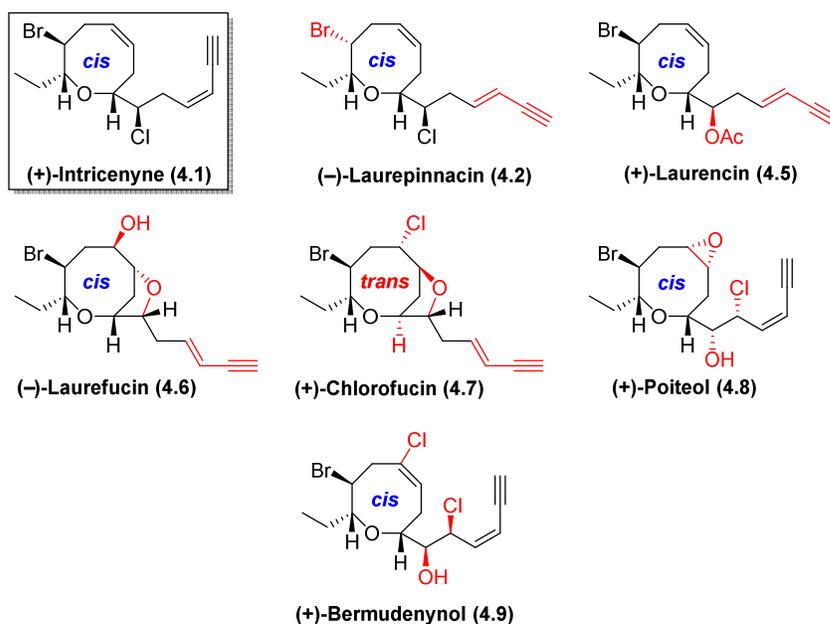


Figure 30: Monocyclic oxocene-containing natural products

4.1.2.1 Total Syntheses of (+)-Laurencin

Since (+)-laurencin so closely resembles (+)-intricenyne and has been chemically synthesized on multiple occasions via diverse routes, it has been chosen as a standard with which to measure our methods for the synthesis of **4.1** presented within. The key challenges associated with construction of both these natural products **4.1** and **4.5** include stereoselective introduction of the α,α' -*cis*-oxocene, regioselective installation of the Δ^9 *cis*-olefin, elaboration of the C7 enyne side chain and stereoselective halogenation. Thus, the following sections will discuss the background of (+)-laurencin and summarize total and formal syntheses of **4.5**. Included in the summary of each synthesis will be a brief description of all transformations required to access the target molecule. Special attention

will be given to steps which install the requisite stereochemistry at the α and α' positions. Furthermore the methods employed for eight-membered ring formation and C7 enyne side chain assembly will be highlighted.

4.1.2.2 Background

In 1965, Irie, Suzuki and Masamune initially reported the isolation of (+)-laurencin (Figure 30) from *Laurencia glandulifera*.¹²¹ Their thorough chemical and spectroscopic studies suggested an eight-membered ring core structure with an internal *cis*-alkene, a bromine substituent, and two hydrocarbon appendages, one of which contained a terminal *trans*-enyne and acetate group. Their proposed structure was initially confirmed through X-ray crystal structure analysis by Robertson and co-workers.¹²⁹ However, decomposition of the crystals by the X-ray beam prevented determination of the absolute stereochemistry. Irie and co-workers used Prelog's atrolactic acid method to determine the absolute stereochemistry of the C6 acetate group.¹³⁰ The (*R*)-configuration for the C6 position was later confirmed by Robertson and co-workers in their full report of the X-ray crystal structure analysis.¹³¹ After disclosure of the absolute stereochemistry of **4.5**, numerous syntheses were reported resulting in one enzymatic synthesis¹³², seven total syntheses¹³³ and five formal syntheses.¹³⁴

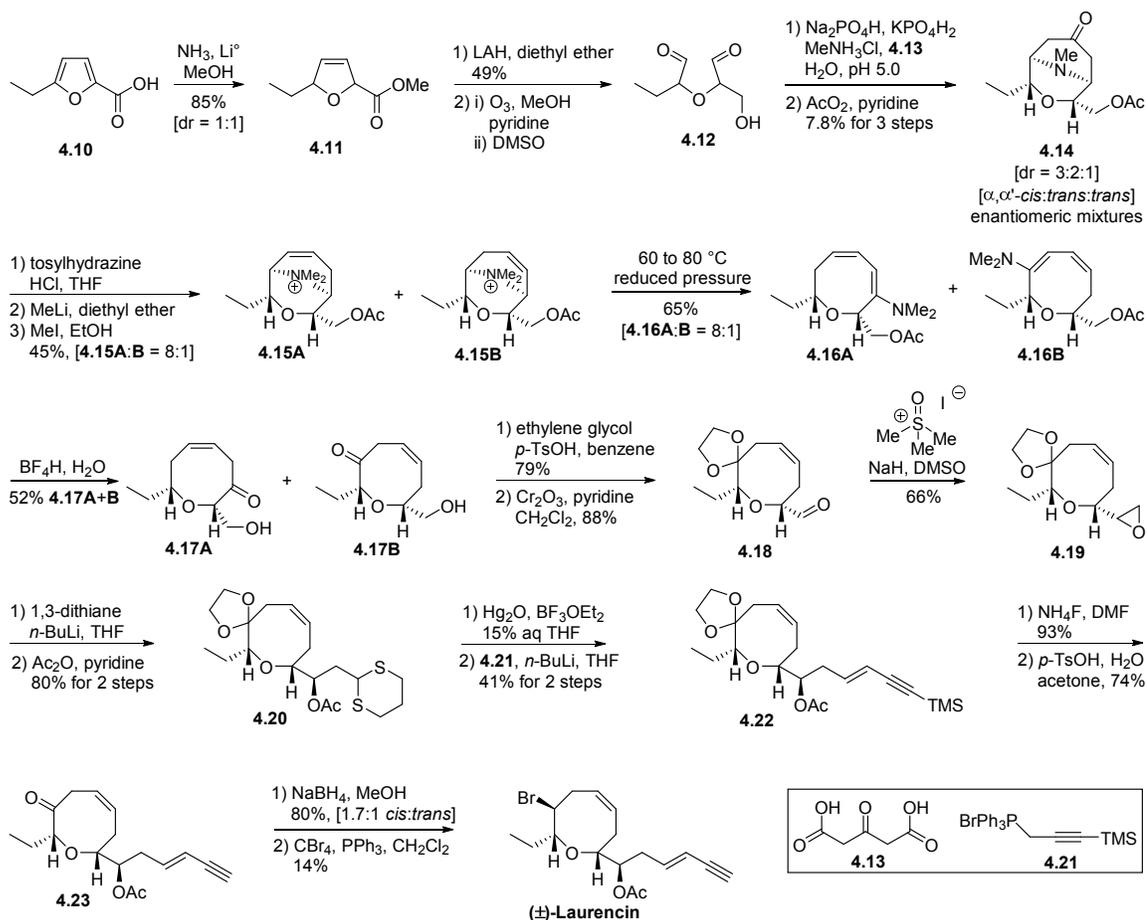
4.1.2.3 Previous Syntheses of Laurencin

4.1.2.3.1 Masamune's synthesis^{133a, 133b, 135}

The first total synthesis of (±)-laurencin was completed by Masamune and co-workers in 21 steps and less than 0.006% overall yield. Key features of the synthesis include a Robinson–Schöpf condensation to prepare the eight-membered cyclic ether core. Furthermore, the enyne side chain was elaborated using Corey's protocol for dimethylsulfoxonium methylide generation and subsequent epoxidation of an aldehyde, 2-lithio-1,3-dithiane epoxide opening, and Wittig reaction of the corresponding aldehyde.

To begin the synthesis, 5-ethyl-2-furoic acid (**4.10**) was subjected to a Birch reduction and esterification to provide a 1:1 mixture of *cis*- and *trans*-2,5-dihydro-2-furoates in 85% yield (Scheme 33). LAH reduction and ozonolysis provided the dialdehyde **4.12**, which was immediately treated with methyl ammonium chloride and acetonedicarboxylic acid under Robinson–Schöpf conditions to yield the [3.3.1]-azabicyclic nonanones **4.14** after an acetylative work-up. It is worth noting that six of sixteen possible isomers were isolated, albeit in 7.8% yield. The major enantiomeric α,α' -*cis* isomers were separated from the remaining four isomers and carried forward in the total synthesis. Treatment of the ketone with tosylhydrazine under acidic conditions followed by addition of methyl lithium gave a mixture of regioisomeric *cis*-alkenes. Formation of the methiodides **4.15** and Hofmann elimination with 1,5-sigmatropic hydride shift gave a dienamine mixture which was hydrolyzed to the homoallylic ketones **4.17**. It was unfortunate that the desired dienamine **4.16B** was formed as the minor product (**4.16A**:**B**

= 8:1). Isolation of ketone **4.17B**, acetalization, and oxidation gave the advanced aldehyde intermediate **4.18**. This aldehyde was converted directly to a mixture of chiral oxiranes using Corey's protocol for dimethylsulfoxonium methylide generation and subsequent epoxidation. Formation of 2-lithio-1,3-dithiane under standard conditions, successive addition of epoxides **4.19** and acetylation provided advanced intermediate **4.20** with the relative configuration of three of the four stereocenters set. At this point, the 1,3-dithiane was converted to the corresponding aldehyde to allow a Wittig reaction with **4.21** and subsequent desilylation to give the desired *trans*-enyne **4.23**. Acetal cleavage and treatment with sodium borohydride installed the final stereocenter favoring the desired C12,C13-*cis* conformation (dr = 1.7:1). Lastly, bromination with inversion of configuration was accomplished with carbon tetrabromide and triphenylphosphine. Poor conversion was obtained for the last step in the total synthesis of (±)-laurencin. The low yield was attributed to the formation of a complex mixture of products, along with incomplete consumption of the alcohol substrate (20% recovered substrate). Despite poor results for a few pivotal transformations in this initial racemic total synthesis, the synthetic strategies employed are quite unique in the realm of syntheses of laurencin. The key cyclization to prepare [3.3.1]-azabicyclic nonanones **4.14** is intriguing and a conformational analysis could be beneficial to the synthetic community should improvements on the yield be made.



Scheme 33: Synthesis of (+)-laurencin by Masamune

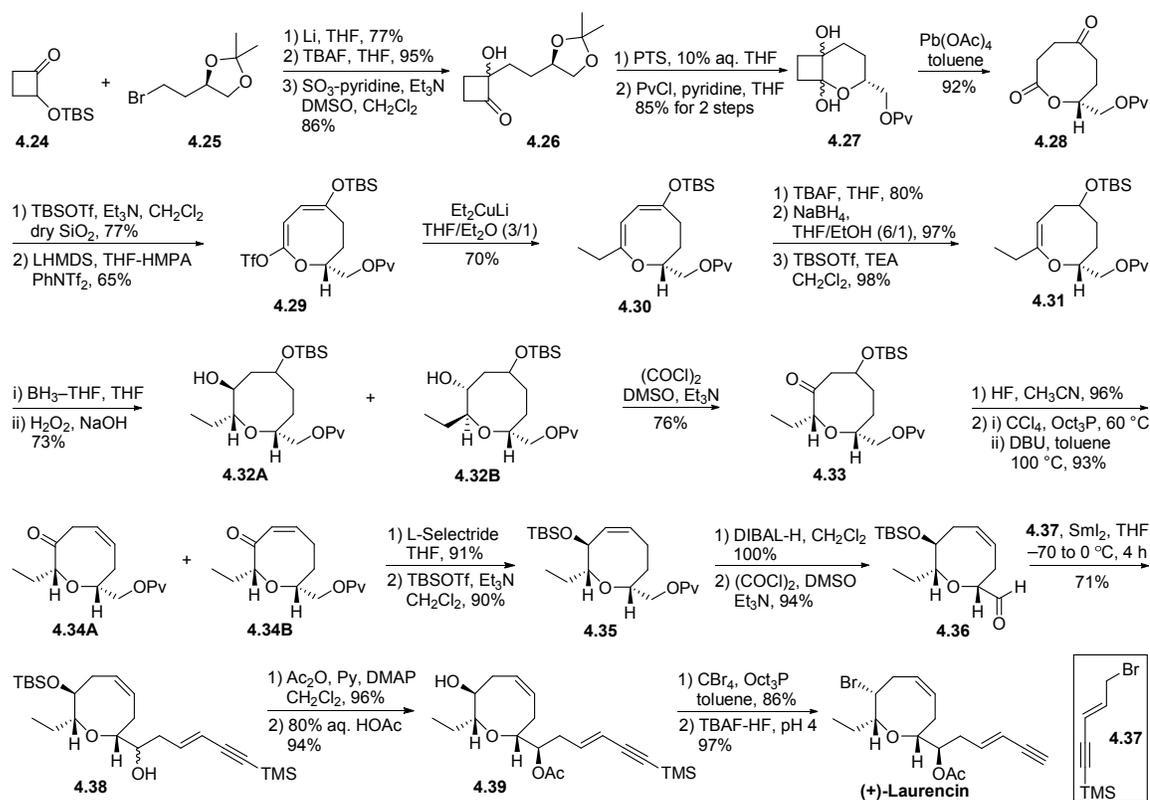
4.1.2.3.2 Murai's synthesis^{133d}

Murai and co-workers were the first to report an enantioselective total synthesis of (+)-laurencin 13 years after Masamune's racemic synthesis had been reported. An overall yield of 4.5 of 2.7% was obtained in 25 linear steps. Murai's strategy for the oxocane core construction can be categorized as a ring expansion method, making it the sole member of

this category for the synthesis of (+)-laurencin. Furthermore, few methods have attempted to install the C7 enyne appendage in a convergent fashion.

To commence the synthesis, the key 4-ketoheptanolide **4.28** was accessed through the following sequence. Organolithium addition to silyloxycyclobutanone **4.24** followed by silyl deprotection and Parikh–Doering oxidation gave **4.26** (Scheme 34). Acid catalyzed 1,2-diol deprotection resulted in spontaneous cyclization to provide the 2-oxabicyclo[4.2.0]octane which was further pivaloylated to give **4.27**. Oxidation with lead (IV) acetate gave 4-ketoheptanolide **4.28** in 92% yield. The ketone in **4.28** was protected as a silyl enol ether while the lactone was converted to an enol triflate for ethylation via a Gilman reagent to provide **4.30**. To prepare for the establishment of stereochemistry at C13, a three-step sequence was completed to selectively reduce the Δ^{10} double bond. Standard hydroboration–oxidation of the remaining alkene gave a mixture of diastereomers in 73% yield. Although the diastereoselectivity was not reported, the following Swern oxidation promoted epimerization at C13 under the basic conditions to give solely the α,α' -*cis*-oxocane. Silyl deprotection, chlorination and E1 β -elimination gave a 7:1 mixture of β,γ - (**4.34A**) and α,β -unsaturated (**4.34B**) ketones in 93% combined yield. Isolation of the minor α,β -unsaturated ketone **4.34B** and treatment with DBU in toluene allowed isomerization to the desired β,γ -unsaturated ketone **4.34A**. Reduction of **4.34A** with L-Selectride gave the desired configuration at C12. Silyl protection, pivaloyl deprotection and Swern oxidation provided aldehyde **4.36** as a key advanced intermediate. Treatment of **4.36** with bromide **4.37** in the presence of samarium (II) iodide gave a 1.2:1 mixture of

secondary alcohols (*R*)- and (*S*)-**4.38** in 71% yield. The minor diastereomer (*S*)-**4.38** was recycled through oxidation and subsequent L-Selectride reduction to give the desired configuration at C6. Although this convergent approach was not stereoselective, it is worth noting that use of an alkylbormide as the coupling partner suppressed the competing Meerwein–Ponndorf–Verley reduction and ring opening from the corresponding γ -attack was not observed. The total synthesis of (+)-laurencin was readily completed by acetylation, selective silyl ether deprotection, bromination and alkyne deprotection.



Scheme 34: Synthesis of (+)-laurencin by Murai

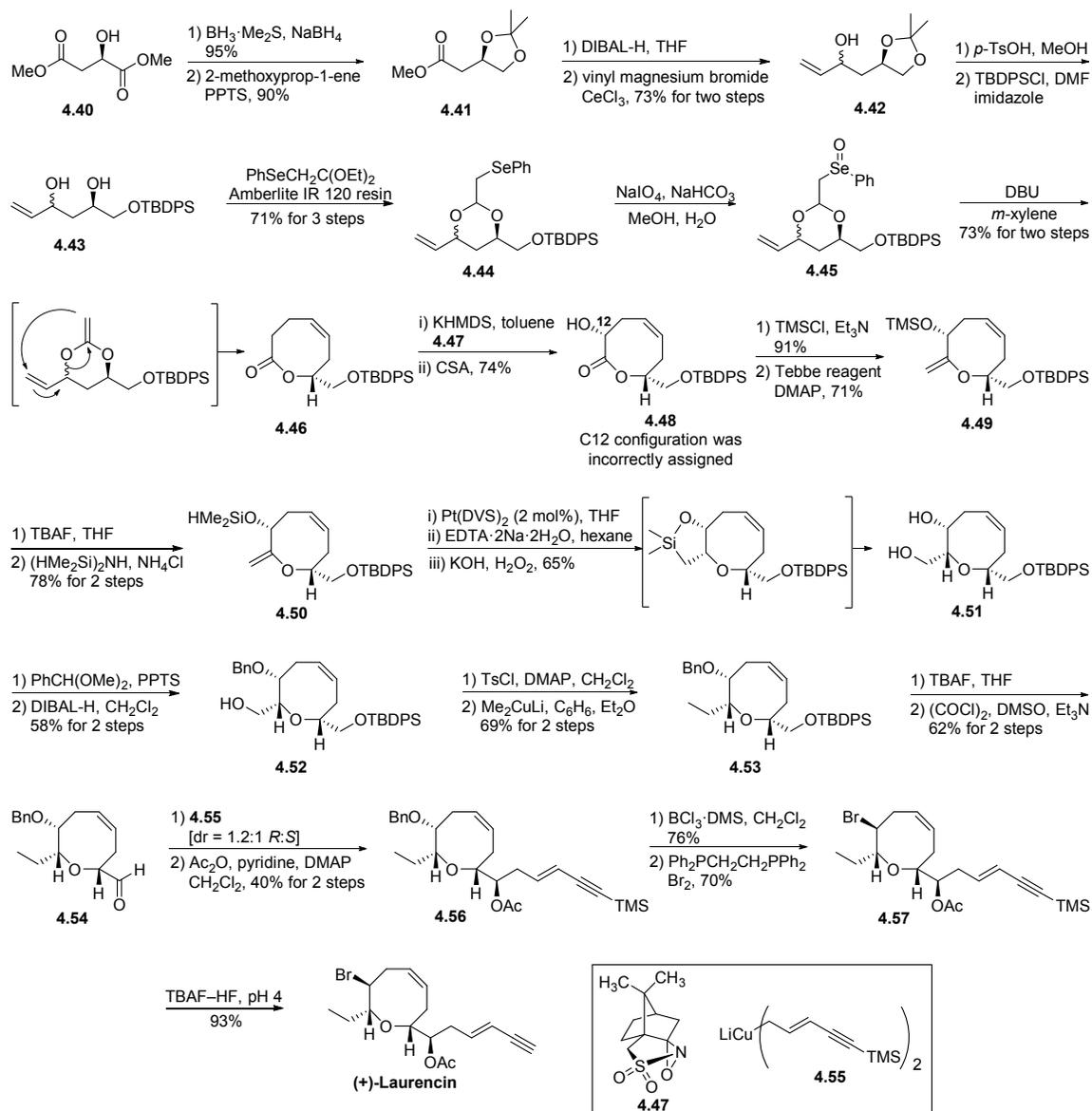
4.1.2.3.3 Holmes's synthesis¹³⁶

Holmes and co-workers reported the second total synthesis of (+)-laurencin. The initial publication in 1993 was later retracted by the authors in 1996 due to an incorrect assignment of the C12 alcohol configuration. In their retraction, Holmes and co-workers briefly reported preparation of the correct isomer with (*R*)-configuration at C12 and successful conversion to (+)-laurencin. They later expanded on this retraction and their synthetic studies in a 1997 publication. In this report, a more efficient alternative route to (+)-laurencin was also described. Schemes 35 and 36 summarize the syntheses of 12*epi*-(+)-laurencin and (+)-laurencin, respectively.

Holmes's synthesis of *epi*-(+)-laurencin was completed in 26 steps and 0.4% overall yield. To commence the synthesis, dimethyl (*R*)-malate was selectively reduced and the resulting 1,2-diol was protected with 2-methoxyprop-1-ene (Scheme 35). The remaining methyl ester was reduced to the aldehyde and a cerium mediated vinyl magnesium bromide addition gave the diastereomeric alcohol mixture **4.42**. Next, the 1,2-diol in **4.42** was deprotected and the primary alcohol was selectively protected with TBDPS allowing the 1,3-diol to react with phenylselenoacetaldehyde diethyl acetal to give dioxane **4.44** in 71% for three steps. Oxidation with sodium periodate under basic conditions yielded the selenoxide **4.45**. Treatment with DBU in refluxing *m*-xylene promoted the key 3,3-sigmatropic rearrangement to give the eight-membered lactone **4.46**. The lactone moiety was then used as a handle to further functionalize the oxocene. Enolate formation and addition of chiral camphorsulfonyloxaziridine **4.47** followed by an acidic

work-up installed the C12 alcohol in 74% yield as a single diastereomer. It was later determined that the (*R*)-configuration at C12 was incorrectly assigned based on Davis's original model for oxidation of ketone enolates using camphorsulfonyl oxaziridines (*vide infra*). Alcohol protection, methylenation with Tebbe conditions and silyl group interchange gave **4.50**, setting the stage for a key hydrosilation. Treatment of **4.50** with a platinum catalyst promoted addition of Si-H across the adjacent double bond via the transition state shown in scheme **xx** to give diol **4.51** in a 3.5:1 ratio with its *2β*-hydroxymethyl epimer after platinum sequestering and oxidative workup. Selective secondary alcohol benzylation, primary alcohol tosylation and methylation completed preparation of the C13 side chain. The C7 side chain could then be elaborated by silyl deprotection and Swern oxidation. Treatment of the resulting aldehyde **4.54** with a lithium cuprate TMS-protected enyne subunit **4.55** followed by acetylation installed the remaining carbon units while simultaneously introducing the final chiral center with a slight preference (1.2:1) for the desired (*R*)-configuration. Isolation of the desired diastereomer (40% for two steps) and debenylation allowed for the final set of key transformations, Hooz's bromination and TMS removal, thus completing the total synthesis of *epi*-(+)-laurencin. In this initial total synthesis by Holmes and co-workers, 2D NMR analysis of the C12 chiral alcohol **4.48** was not performed and the original ¹H NMR spectrum was obtained on a 250 MHz instrument. The authors admittedly relied on Davis's model to assign the C12 configuration despite using a previously untested chiral lactone enolate as the substrate. Holmes and co-workers later noticed discrepancies in their spectral data when

the reaction was repeated and ^1H NMR spectrum was acquired on a 500 MHz instrument, forcing them to retract the original synthesis and perform additional studies.



Scheme 35: Synthesis of 12epi-(+)-laurencin by Holmes

In their 1997 publication, they elaborated on this α -hydroxylation and described a more detailed study of the stereoselectivity, including extensive 2D NMR analysis and NOE studies to confidently establish the configurational assignments. As shown in Figure 31, generation of the potassium lactone enolate in toluene followed by addition of the oxaziridine and an acidic workup gave various ratios of the desired (12*R*)-**4.59** to (12*S*)-**4.59** depending on the oxaziridine employed. Despite using different enantiomers of **4.47**, the desired (12*R*)-**4.59** could not be obtained as the major product. Even use of racemic **4.60** as the oxaziridine (entry 3) resulted in a ratio favoring the (12*S*)-**4.59**, suggesting that the chiral substrate has an inherent conformational bias. It was also shown that a significant solvent effect influenced both the diastereomeric ratio and isolated yield. Generating the potassium lactone enolate in THF gave a 5.3:1 ratio favoring the desired (12*R*)-**4.59**; unfortunately, the yield suffered tremendously (11%). Thus, Holmes and co-workers were forced to pursue an alternative route for the total synthesis of (+)-laurencin.

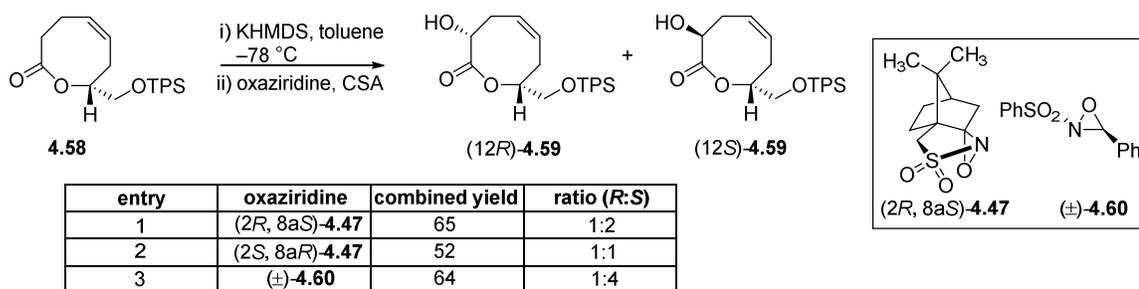
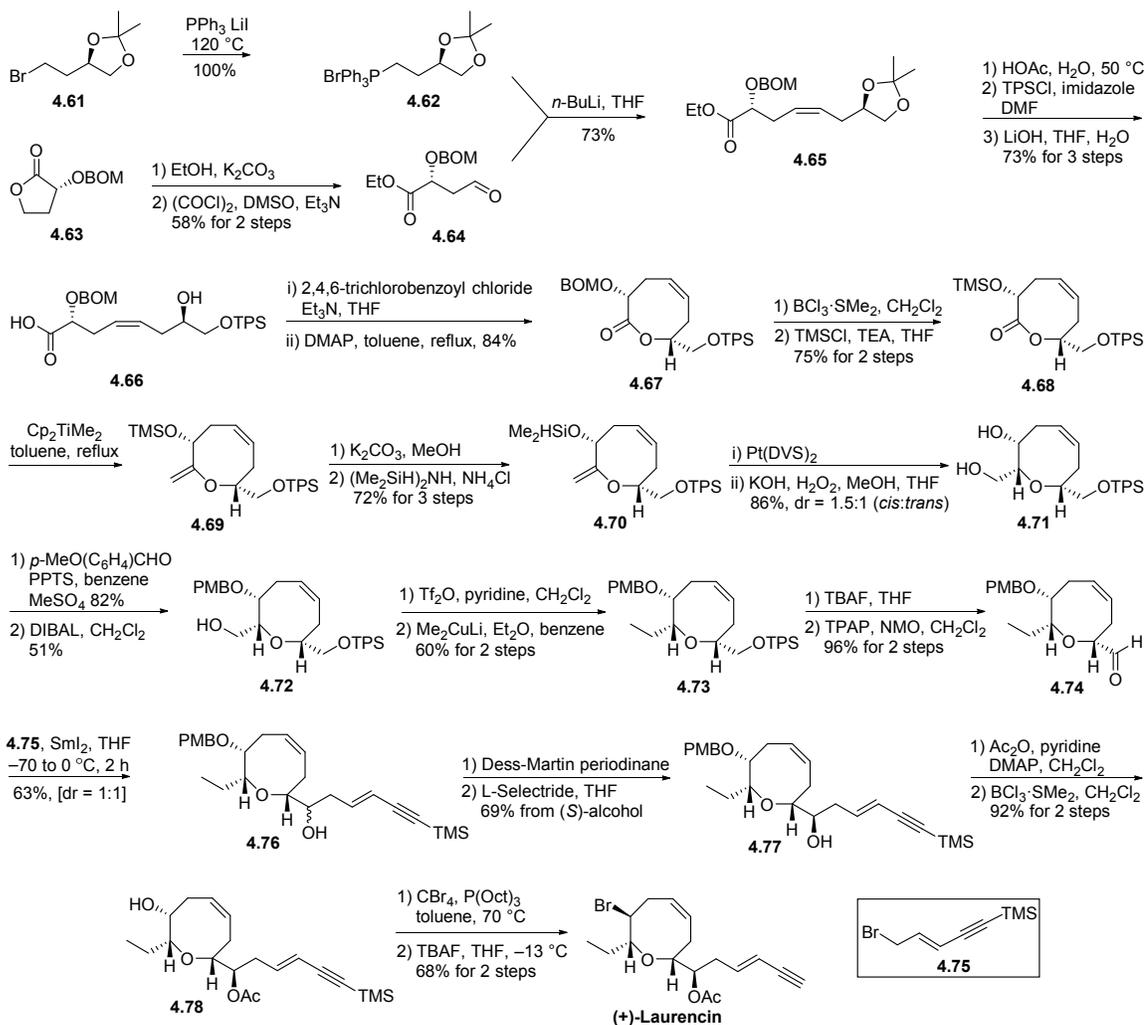


Figure 31: Holmes's attempts to stereoselectively install the C12 alcohol using oxaziridines

The alternative synthesis of (+)-laurencin began with known chiral bromide **4.62** and chiral lactone **4.64**. A triphenyl phosphonium bromide salt was generated from **4.61** while the lactone **4.63** was converted to an aldehyde via basic hydrolysis and Swern oxidation of the resulting primary alcohol. The non-stabilized phosphonium ylide was formed under standard conditions and a typical Wittig reaction occurred after addition of the aldehyde **4.64** to give the (*Z*)-olefin in 73% yield. Diol deprotection, selective primary alcohol protection and ester hydrolysis gave the 7-hydroxylactone **4.66**. Lactonization occurred in a standard two step sequence to give advanced intermediate **4.67**. BOM deprotection allowed an alcohol protection, methylenation with Tebbe conditions and silyl group interchange sequence similar to the original 1993 route gave **4.70**. Platinum mediated hydrosilylation, selective secondary alcohol protection, primary alcohol tosylation, methylation, silyl deprotection and oxidation to aldehyde **4.74** was also completed in a similar fashion to the original route. At this stage the authors decided to employ the samarium(II) iodide Barbier-type reductive coupling that was first reported in the context of a total synthesis of (+)-laurencin by Murai and co-workers. It is unclear why the authors choose to use this samarium mediated coupling to install the enyne side chain instead of their original strategy involving a lithium cuprate. The samarium mediated coupling showed no stereoselectivity, as was originally evidenced by Murai and co-workers and further proved in Holmes's model studies. With the enyne subunit installed, the secondary alcohols (*R*)-**4.76** and (*S*)-**4.76** could be separated and pure (*S*)-**4.76** was oxidized and selectively reduced to the desired (*R*)-**4.76** using L-Selectride. The remainder

of the synthesis was completed by acetylation, alcohol deprotection, bromination and silyl deprotection. Modifications were made to the reaction conditions for the bromination and silyl deprotection in comparison to the original route which only appear to have slightly improved the yield for the two step sequence. Thus, the total synthesis of (+)-laurencin was achieved in 21 steps and 1.4% overall yield.



Scheme 36: Synthesis of (+)-laurencin by Holmes

4.1.2.3.4 Overman's synthesis^{133e}

Overman and co-workers reported a total synthesis of (+)-laurencin in 23 steps and 2.5% overall yield. The key cyclization to prepare the oxocene core was accomplished via a unique Prins cyclization of an acetal–vinyl sulfide. Interestingly, the stepwise approach

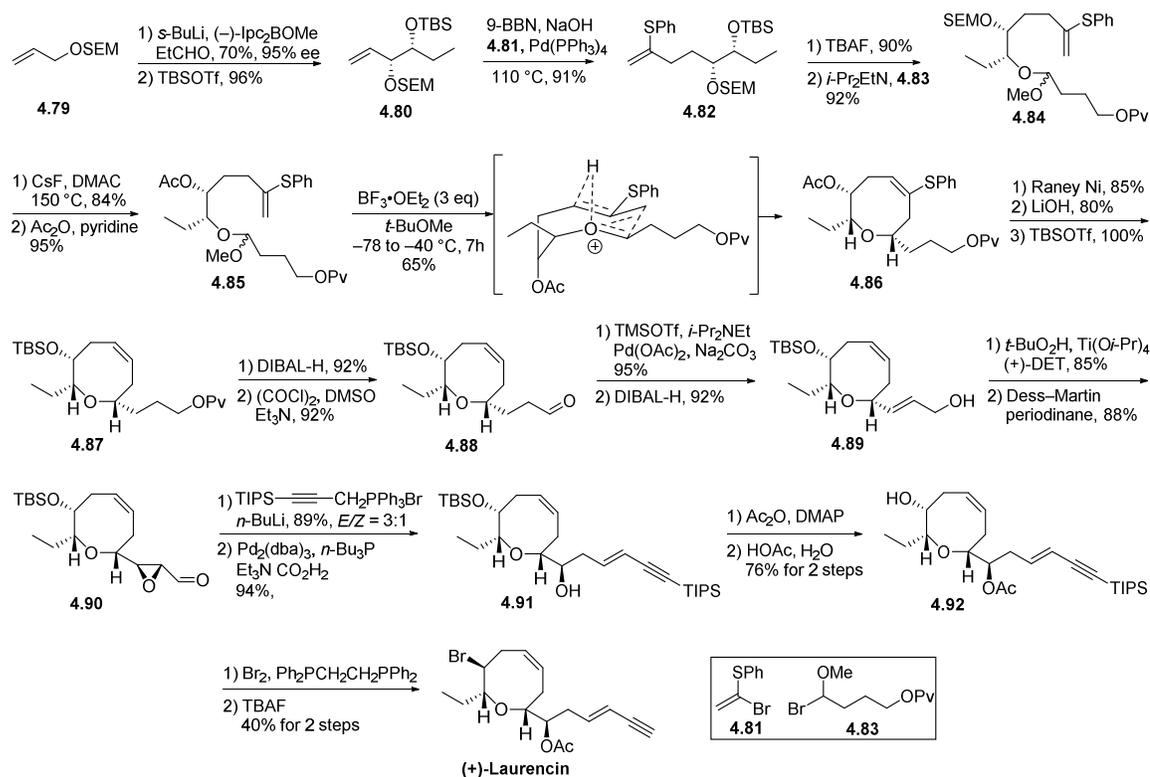
to construct the enyne side chain did not increase the number of overall synthetic steps to complete the total synthesis when compared to previous syntheses, suggesting a more efficient preparation of the core structure with preexisting stereochemistry and functionality.

To begin the synthesis, SEM protected allylic alcohol was treated with modified conditions for a Brown's asymmetric alkylation to produce the 1,2-*syn*-diol in excellent enantiomeric excess (95% ee). Alcohol protection was required prior to completing a Suzuki coupling with vinyl bromide **4.81** (Scheme 37). Silyl removal and reaction with α -bromo ether **4.83** under basic conditions gave the mixed acetal **4.84**. Treatment of this substrate with $\text{BF}_3 \cdot \text{OEt}_2$ in an effort to promote a Prins cyclization resulted in formation of an undesired dioxolane due to the nucleophilicity of the C12 oxygen (reaction not shown). In this case, the target oxocene was not formed in any observable amount. The SEM protecting group had to be exchanged for an acetate protecting group at this stage to moderate the nucleophilicity of the C12 oxygen and allow effective reaction in the key Prins cyclization. Unfortunately, efforts to use an acetate protecting group from the onset of the synthesis were prevented by a low yielding Suzuki coupling with vinyl bromide **4.81**. Treatment of this acetate protected substrate **4.85** with $\text{BF}_3 \cdot \text{OEt}_2$ yielded the desired oxocene as a single stereoisomer via the transition state shown. The moderate yield was attributed to formation of several side products including a tetrahydropyran (7%), two internal vinyl sulfide acetals (18%), and two alcohol products (14%) resulting from oxocarbenium ion formation of the methyl ether. Each of these side products can ultimately

be attributed to a destabilizing effect of the C12 acetate on the desired oxocarbenium ion. Desulfurization proceeded smoothly with Raney nickel.

With the key step completed, all that remained was elaboration of the enyne side chain and bromine installation with inversion of stereochemistry. At this stage, another protecting group switch was required; therefore, the acetate group was cleaved and the C12 alcohol was silylated to give **4.87**. Since the handle for the C7 side chain was a saturated three carbon unit chain, a stepwise approach was used to construct this appendage. Treatment with DIBAL-H revealed the primary alcohol which was further oxidized to aldehyde **4.88**. Saegusa–Ito oxidation exclusively provided the (*E*)-enal. To oxidize C6 and generate a stereocenter, the aldehyde had to be reduced to the primary alcohol and Sharpless asymmetric epoxidation was performed. The primary alcohol then had to be reoxidized to the aldehyde to complete a Wittig reaction providing the TIPS protected (*E*)-enyne in a 3:1 ratio with the (*Z*)-enyne. Palladium-catalyzed hydrogenolysis selectively opened the epoxide at the allylic position yielding the C6 alcohol **4.91**. Desilylation and acetylation of the C12 alcohol allowed a bromination with inversion of stereochemistry to be completed. Finally, TIPS removal upon treatment with TBAF gave (+)-laurencin in 40% yield for the final two steps. The poor conversion was attributed to unsatisfactory bromination in the presence of a TIPS protecting group despite the use of previously reported conditions that gave high yields for similar substrates containing a TMS protected enyne.

Although the chemistry utilized in the stepwise installation of the enyne side chain was unique with regards to previous syntheses, the need for repetitive oxidations and reductions, as well as protecting group manipulations, extended the number of steps required for this overall transformation. Almost half of the total steps to prepare (+)-laurencin can be attributed to the enyne subunit. Thus, it would be intriguing to determine how a mixed acetal similar to **4.85** with one methylene unit between the acetal and protected primary alcohol would react under conditions for the key cyclization. If the reactivity was comparable, then one could envision a deprotection and oxidation sequence that would provide the C6 aldehyde for a convergent side chain installment; thus reducing the total number of steps and improving the overall yield and efficiency.

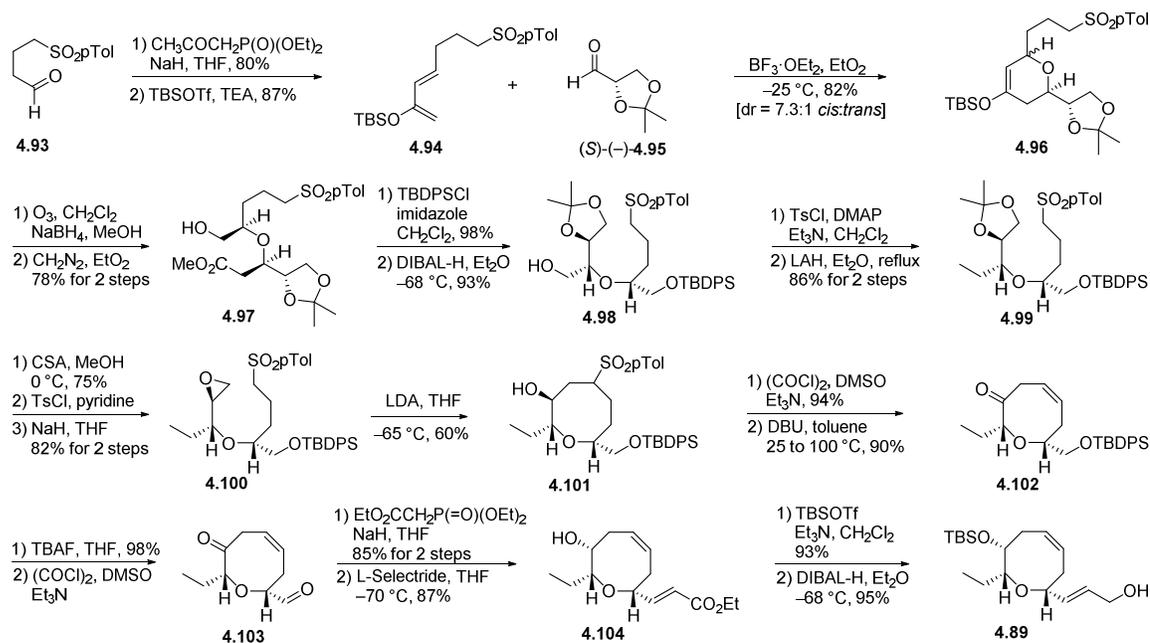


Scheme 37: Synthesis of (+)-laurencin by Overman

4.1.2.3.5 Palenzuela's synthesis¹³⁷

Palenzuela and co-workers reported a formal synthesis of (+)-laurencin by choosing Overman's advanced intermediate **4.89** as their target. Their synthetic strategy involved preparation of a linear ether with all three chiral centers set followed by cyclization to the core oxocene via an epoxide opening reaction. The chiral linear ether was accessed through a hetero Diels–Alder reaction which would stereoselectively set the configurations of the α and α' substituents.

To begin the synthesis, known γ -sulfone aldehyde (**4.93**) was treated with a stabilized ylide to give an allylic methyl ketone which was converted to the silyl protected enolate **4.94** (Scheme 38). This diene was then treated with dienophile (*S*)-(-)-**4.95** under Lewis acidic conditions to induce a stereoselective hetero Diels–Alder. Of the four possible stereoisomers, only two isomers were formed in a 7.3:1 ratio favoring the desired (7*R*,12*R*)-*cis* isomer and in 82% combined yield. Ozonolysis with a reductive-workup followed by methylation of the resulting carboxylic acid yielded **4.97**. Separation of the hetero Diels–Alder diastereomers was accomplished at this stage. Silylation, DIBAL-H reduction, tosylation and hydride addition completed construction of the ethyl side chain. To prepare for the key cyclization, acetal cleavage, tosylation and epoxidation were executed in good yields. Treatment of **4.100** with LDA generated the sulfone carbanion which spontaneously attacked at the less hindered carbon of the tethered epoxide to give **4.101** in 60% yield, along with unreacted substrate. The final challenge was to regioselectively install the internal double bond, which was achieved by first oxidizing the secondary alcohol and treating with DBU to carry out β -elimination of the sulfone. The remainder of the formal synthesis was trivial, requiring desilylation, Swern oxidation and olefination. L-Selectride reduction to give the desired configuration at C12, protection of the resulting C12 alcohol and, lastly, DIBAL-H reduction yielded allylic alcohol **4.89**. Hence, this constituted a formal synthesis of (+)-laurencin in 20 steps and 8% overall yield.



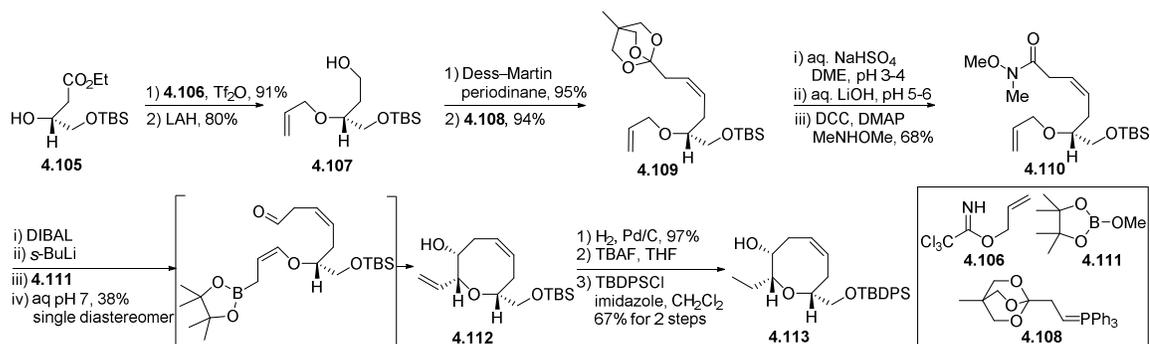
Scheme 38: Formal synthesis of laurencin by Palenzuela

4.1.2.3.6 Hoffmann's synthesis^{134b}

In 1997 Hoffmann and co-workers extended their intramolecular aldehyde–allylboration reaction to include preparation of eight-membered cyclic ethers. Their *syn* selective C–C bond forming methodology had previously been developed in the context of tetrahydropyrans and the authors suspected that the method would be advantageous in a formal synthesis of (+)-laurencin. Since previous syntheses of the natural product utilized a late stage bromination with inversion of stereochemistry, the target oxocene required a *syn*-(12*R*, 13*R*) configuration, the same configuration that was predicted to be selectively induced in their methodology. Furthermore, the intramolecular aldehyde–allylboration reaction, if successful, would result in an oxocene containing a C12 alcohol and C13

ethylene appendage. Both of these functionalities could easily be transformed in the the C12 bromine and C13 ethyl groups found in (+)-laurencin.

The nine step formal synthesis began with allylation of alcohol **4.105**, which was reduced and subsequently oxidized to provide an aldehyde for Wittig reaction with **4.108** (Scheme 39). The OBO ester was converted to the Weinred amide **4.110** in a one-pot sequence including deprotection, hydrolysis and DCC initiated amination. Due to the delicate preparation of an allylboronate moiety in the presence of a reactive aldehyde, the final transformations to access the key step substrate were also accomplished in a one-pot sequence. DIBAL-H treatment generated the aluminum/amide chelate, lithiation followed by addition of borate ester **4.111** provided the masked allylboronate moiety and spontaneous cyclization was achieved upon liberation of the reactive groups using a pH 7 buffer. The resulting oxocene was obtained as a single diastereomer, albeit in moderate yield, suggesting that the preinstalled C7 stereocenter provided sufficient conformational bias. The last challenge was to selectively reduce the terminal olefin in the presence of the internal *cis* double bond. This was achieved after some trial with a surprisingly simple palladium on carbon hydrogenation. Silyl group exchange provided **4.113** in 16% overall yield.



Scheme 39: Formal synthesis of laurencin by Hoffmann

4.1.2.3.7 Crimmins's synthesis^{133h, 134c}

In 1999, Crimmins and co-workers reported a two syntheses, one formal and one total, of (+)-laurencin. They chose a strategy in which a chiral linear ether would be cyclized by ring closing metathesis (RCM). At the onset of their studies, it was uncertain if RCM could be used to access medium sized cyclic ethers without an internal cyclic constraint. Thus, Crimmins set out to prepare simplified substrates to examine the potential of accessing 7-, 8-, and 9-membered cyclic ethers. If successful, their method would be applied to a more complex substrate constituting a formal synthesis of (+)-laurencin by targeting Holmes's advanced intermediate **4.51**. Because of the remarkable efficiency of the RCM method in this challenging application, Crimmins disclosed a second generation total synthesis of (+)-laurencin shortly after the initial report.

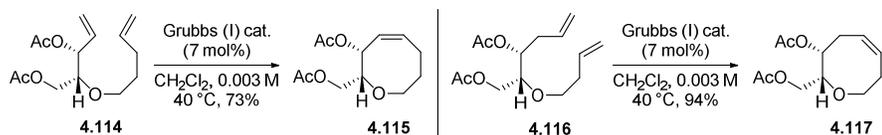
The RCM method development for oxocene synthesis began with preparation of regioisomers **4.114** and **4.116** (Scheme 40). Initially, **4.114** was treated with Grubbs' 1st generation catalyst in dichloromethane (0.003 M) at refluxing temperatures and provided

the desired Δ 10-oxocene in 73% isolatable yield. In this case, 17% of the competing intermolecular product was also obtained. It had already been determined in their studies on oxepene synthesis that a dilute reaction concentration was essential for promoting intramolecular reaction while suppressing the unwanted dimer and oligermization pathways. Use of a 0.003 M reaction concentration resulted in exclusive oxepene formation, suggesting increased enthalpic and entropic energy barriers for the oxocene cyclization. Surprisingly, when regioisomeric **4.116** was treated with identical RCM conditions, the Δ 9-oxocene was formed exclusively in 94% yield. Thus, the authors concluded that the Δ 9-oxocene **4.117** must be lower in energy than Δ 10-oxocene **4.115**.

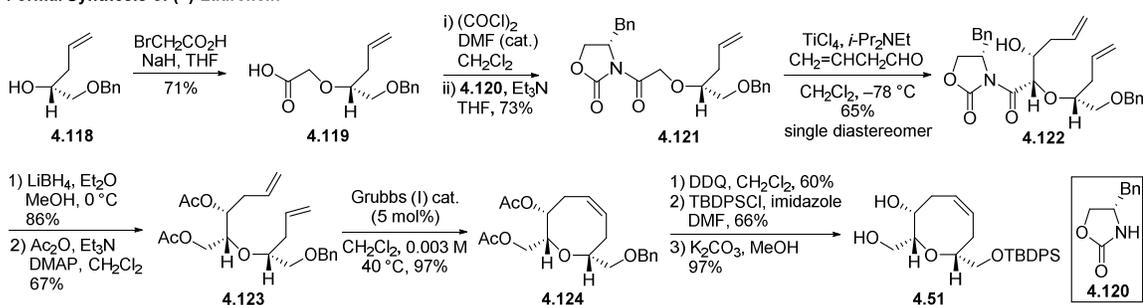
With these promising results, the Crimmins group pursued a formal synthesis of (+)-laurencin which would require a third substitution in the Δ 9-oxocene and demonstrate the potential of RCM as a viable disconnection in naturally occurring oxocenes. To initiate the formal synthesis, known chiral alcohol **4.118** was deprotonated and exposed to bromoacetic acid to yield the alkoxyacetic acid **4.119**. Generation of the acid chloride and subsequent oxazolidine addition gave **4.121**. At this stage, the two remaining stereocenters could be selectively installed per a titanium chelated asymmetric aldol reaction. Exclusive formation of **4.122** was accomplished in 65% yield. Lithium borohydride reduction cleaved the oxazolidine auxiliary and acetylation provided the substrate **4.123** for the key RCM. As their model studies predicted, Δ 9-oxocene **4.124** was obtained in near quantitative yield after treatment with RCM conditions, indicating that the additional C7 appendage did not significantly hinder the cyclization. All that remained to complete the formal synthesis was

a benzyl deprotection, silylation, and deacetylation. Hence, Holmes's advanced intermediate **4.51** was obtained in 9 steps and 7% overall yield.

Development of RCM for Oxocene Synthesis



Formal Synthesis of (+)-Laurencin



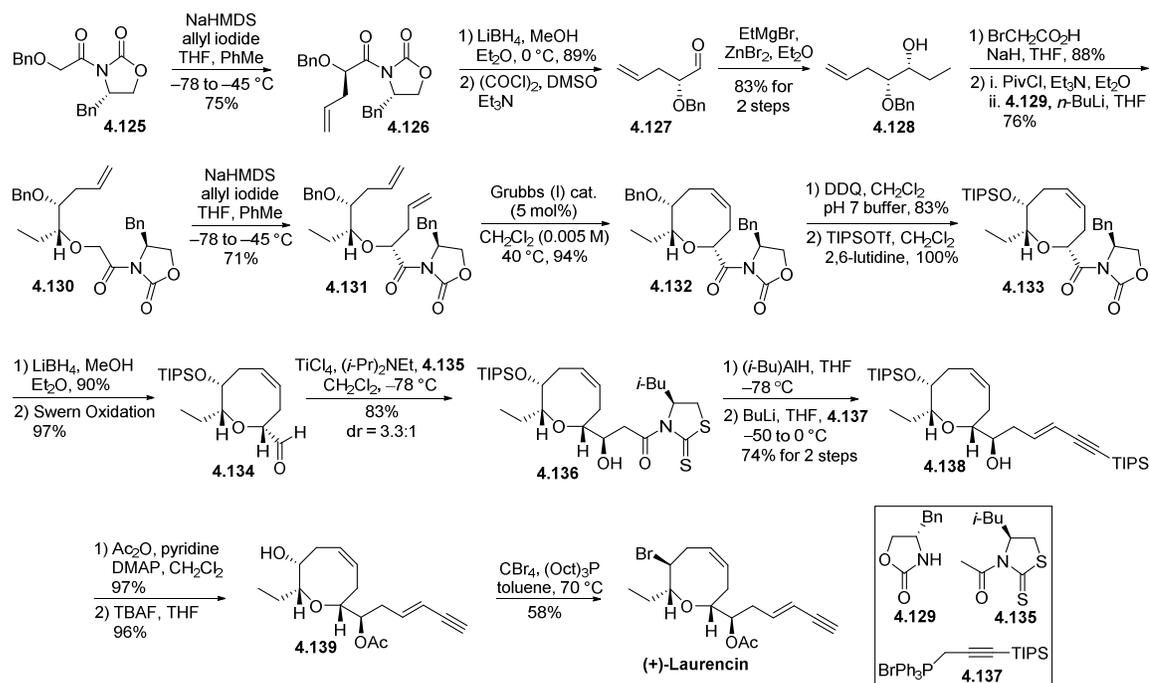
Scheme 40: Formal synthesis of laurencin by Crimmins

With the success of their formal synthesis, the Crimmins group endeavored on a second generation total synthesis of (+)-laurencin. Key changes in the route include using Evan's chiral oxazolidine auxiliaries to asymmetrically introduce both propene units adjacent to the C12 and C7 stereocenters, a chelation-controlled Grignard addition to install the C13 chiral alcohol, RCM prior to reduction of the oxazolidine auxiliary and an asymmetric acetate aldol reaction to incorporate the C6 chiral alcohol and simultaneously extend the side chain.

The synthesis began with preparation of **4.128** by alkylation of the sodium enolate generated from **4.125** with allyl iodide, oxazolidinone reduction with LiBH₄, Swern oxidation and chelation controlled Grignard addition (Scheme 41). Thus, the necessary carbon units, functionality and stereochemistry were prepared for the left hand portion of the natural product. The central ether bond was then formed via coupling with bromoacetic acid and the oxazolidinone auxiliary was introduced. A second asymmetric enolate alkylation was completed giving the requisite diene for RCM. As with their previous RCMs to form oxocenes, **4.132** was obtained in 94% yield after treatment with Grubbs's 1st generation catalyst. Interestingly, the oxazolidinone auxiliary did not need to be cleaved prior to RCM as had been done in their formal synthesis.

Although attempts were made to carry the C12 benzyl protecting group through the entire synthesis, it became necessary to exchange this group for a TIPS protecting group. Removal of the auxiliary and Swern oxidation rendered the aldehyde **4.134**. An asymmetric acetate aldol reaction was chosen to furnish the C6 chiral alcohol and extend the side chain. Best results were actualized when thiazolidinethione **4.135** was enolated and treated with aldehyde **4.134**. The diastereoselectivity (3.3:1) was not as high as had originally been anticipated. This was ascribed to the aldehyde's inherent preference for Felkin addition of nucleophiles (1:2 when treated with achiral 3-acetyl-2-thiazolidinethione). Intriguingly, when the C12 benzyl protecting group was carried forward to this stage, a reversal of selectivity was observed (1:2.5). Despite its apparent remote distance, it was suggested that the oxocene conformation might actually allow titanium chelation of the C12 benzyl ether

and C6 aldehyde and evoke the selectivity switch. To conclude the total synthesis, auxiliary cleavage gave an aldehyde which could be treated with ylide generated from **4.137** to the protected enyne **4.138**. Acetylation, bis-TIPS removal and bromination with inversion of configuration produced (+)-laurencin in 18 steps and 6.6% overall yield.



Scheme 41: Synthesis of (+)-laurencin by Crimmins

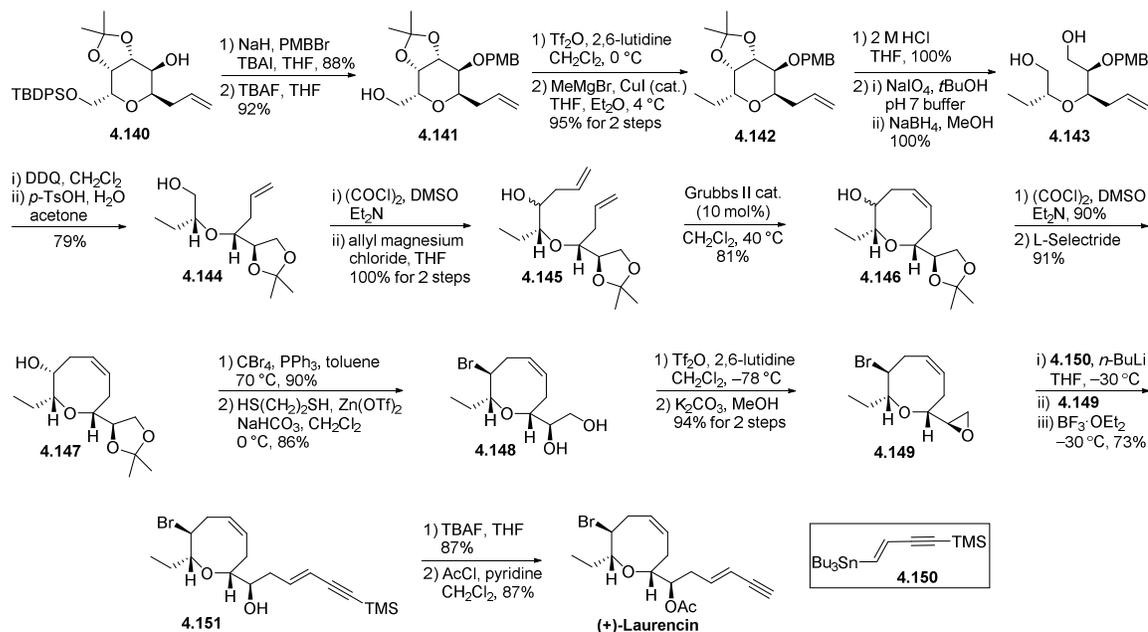
4.1.2.3.8 Fujiwara's synthesis^{133f}

Fujiwara and co-workers reported a total synthesis of (+)-laurencin using a ring closing metathesis strategy for the key cyclization. They choose α,α' -*trans*-C-glycoside **4.140** as their starting point for the total synthesis. It is noteworthy that the authors

previously reported a total synthesis of (+)-prelaureatin, a similar naturally occurring α,α' -*trans*-oxocene, from the same glycoside **4.140**. Their ability to access both an α,α' -*cis*- and α,α' -*trans*-oxocene from the same α,α' -*trans*-C-glycoside was based on how the silyl protected appendage was elaborated prior to cleavage of the 6-membered cyclic ether. In the total synthesis of (+)-prelaureatin, this side chain served as a handle to construct the carbon skeleton of the oxocene core; however, it was utilized as the precursor for the C13 ethane group in the preparation of (+)-laurencin. Once the RCM was complete for (+)-laurencin, the relative configuration of the ether α and α' positions was switched, giving a *cis*-oxocene from an originally *trans*-tetrahydropyran. Another unique feature of this synthesis is the enyne introduction, which employed a lithium exchange with a known organotin enyne subunit followed by addition of epoxide **4.149** then $\text{BF}_3 \cdot \text{OEt}_2$. Fujiwara and co-workers were the first to use this C4-C5 disconnection in their synthetic approach.

The synthesis commenced with conversion of **4.140** to **4.141** via an alcohol protection, silyl deprotection, tosylation and methylation sequence (Scheme 42). Acidic hydrolysis revealed the 1,2-diol for sodium periodate opening of the tetrahydropyran followed by a reductive work up to give linear ether **4.143** in quantitative yield. A one-pot oxidative cleavage of the *p*-methoxyl benzyl ether and acetal formation was completed. Swern oxidation and treatment with allylmagnesium chloride gave the requisite diene **4.145** in a 1:1 mixture of diastereomers and quantitative yield. The key RCM was accomplished with Grubbs's 2nd generation catalyst (10 mol%) resulting in an 81% yield. Crimmins and co-workers obtained near quantitative yields with Grubbs's 1st generation

catalyst using a lower catalyst loading (5 mol%). These results suggest that Grubbs's 1st generation catalyst may be a superior catalyst for oxocene preparation. Alternatively, the free C12 alcohol could be responsible for the decreased reactivity. Swern oxidation and L-Selectride reduction gave (12*R*)-**4.147** in 91% yield. Only 5% of (12*S*)-**4.147** was obtained in the selective reduction. Contrary to previous strategies for the synthesis of (+)-laurencin, Hooz's bromination was performed prior to enyne construction and excellent yield was obtained. Acetal cleavage was carefully achieved under slight basic conditions, the primary alcohol was triflated and treatment with potassium carbonate in methanol gave epoxide **4.149**. To complete the epoxide opening and extend the enyne side chain, organotin **4.150** was first treated with *n*-BuLi. After metal exchange, the epoxide **4.149** could be added followed by BF₃·OEt₂ giving exclusive (*E*)-enyne **4.151**. It was important for the Lewis acid to be added last since pretreatment resulted in only recovered epoxide. All that remained was to deprotect the terminal alkyne and acetylate the C6 alcohol. Hence, the total synthesis of (+)-laurencin was completed in 18 steps and 16% overall yield.



Scheme 42: Synthesis of (+)-laurencin by Fujiwara

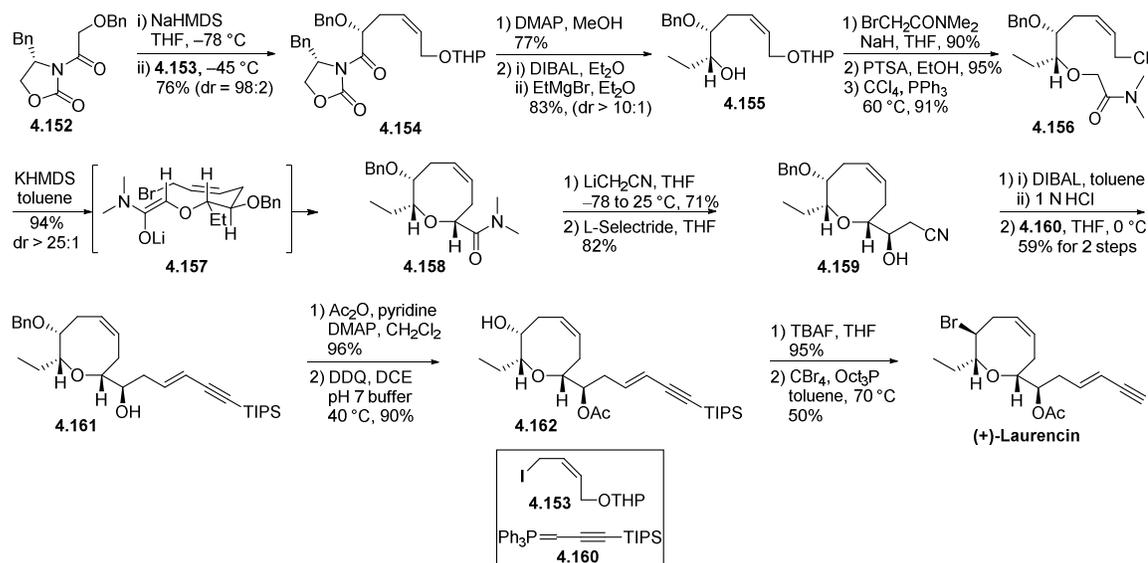
4.1.2.3.9 Kim's synthesis^{133g}

In 2005, Kim and co-workers published a total synthesis of (+)-laurencin and capitalized on their folding strain-controlled intramolecular enolate alkylation method. This method was used extensively in Kim's independent career with S_N2 and S_N2' variations being developed and applied to many cyclic-containing natural products. It was not until their asymmetric total synthesis of (+)-isonitramine that they observed competing olefin geometry-dependent S_N2' and S_N2 pathways providing either n - or $n+2$ -membered cyclic products, respectively. Specifically, (*E*)-allylic halides served to intramolecularly alkylate amide enolates via an S_N2' pathway, while the corresponding (*Z*)-allylic halides reacted through an S_N2 mechanism to give $n+2$ -membered cyclic products. Potential

application of this method was not realized until much later, after Crimmins's set of publications on (+)-laurencin first appeared. With the idea of using this C–C bond forming method for the stereoselective synthesis of medium-sized cyclic ethers, Kim and co-workers pursued a total synthesis of (+)-neoisolaurefucin. In the case of this oxepane synthesis, the target molecule was obtained in a 6:1 ratio with the competing tetrahydrofuran. The success of this total synthesis led the authors to extend the method to a total synthesis of (+)-laurencin and several other naturally occurring 8- and 9-membered cyclic ethers containing either α,α' -*cis*- or *trans*-relationships.

Similarly to Crimmins's total synthesis, Kim and co-workers began with glycolate oxazolidinone **4.152**, which was enolated and treated with allylic iodide **4.153** to give **4.154** in 76% yield and excellent diastereoselectivity (Scheme 43). The oxazolidinone was then cleaved to provide the methyl ester. A one-pot sequence of DIBAL-H reduction & simultaneous chelation followed by Grignard addition (Burke's protocol) resulted in stereoselective reduction and C13 side chain installation to yield alcohol **xx** in good diastereoselectivity (10:1). The alcohol was then alkylated with *N,N*-dimethyl bromoacetamide and the THP protecting group was discarded. Chlorination of the free alcohol set the stage for the pivotal C12–C13 bond forming cyclization. Chloro amide **4.156** was subjected to KHMDS giving rise to oxocene **4.158** in excellent yield (94%) and diastereoselectivity (>25:1). Although an explanation for the α,α' -*cis* selectivity was not apparent at the time, Kim and co-workers later suggested transition state **4.157** as the likely cause in their report on the total syntheses of (+)-3-(*E*)- and (+)-3-(*Z*)-pinnatifidenyne. The

N,N-dimethyl amide functionality served as an advantageous handle for further elaboration of the enyne side chain. As seen in the previously discussed syntheses, introducing the entire enyne fragment via nucleophilic addition to the C6 aldehyde can be cumbersome. Treatment of **4.158** with the lithium anion of acetonitrile allowed a two carbon homologation and direct ketone synthesis. Thus, the (6*R*)-alcohol **4.159** could be accessed selectively by an L-Selectride reduction without the need to separate the diastereomeric mixture, reoxidize, & selectively reduce. The nitrile was then converted to an aldehyde and Wittig reaction with ylide **4.160** was executed. Acetylation, debenzoylation, and TIPS removal provided the substrate for the final step. As with other total syntheses, bromination with inversion of configuration at this stage gave a moderate yield. The synthesis was completed in 15 steps and 5.4% overall yield.

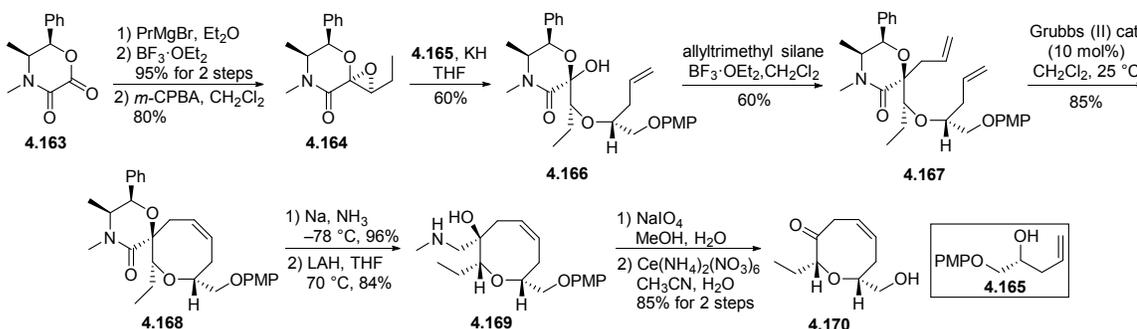


Scheme 43: Synthesis of (+)-laurencin by Kim

4.1.2.3.10 Pansare's synthesis^{134d}

The concise formal synthesis of (+)-laurencin completed by Adsool and Pansare was achieved in 10 steps from known chiral morpholine-dione **4.163**. Key features of the synthesis include a substrate-controlled stereoselective epoxidation and sequential opening, as well as a room temperature ring-closing metathesis to complete the cyclization. To begin the synthesis, morpholine-dione **4.163** was treated with propyl magnesium bromide to reduce the ester moiety followed by Lewis acid dehydration to give the requisite olefin (Scheme 44). Exposure to *m*-CPBA yielded a single epoxide diastereomer whose configuration was determined by analogy to a similar substrate. Alkoxide addition opened the epoxide regioselectively and, thus, the right hand portion of **4.166** was installed. Allylation with BF₃·OEt₂ and allyltrimethyl silane was successfully achieved through anticipated displacement of the free portion of the hemiacetal. With the key diene in hand, the Adsool and Pansare then treated with Grubbs's 2nd generation catalyst at room temperature and obtained oxocene **4.168** in good yield. It is likely that the conformational constraints of the morpholinone moiety are responsible for the relative ease of cyclization at room temperature in comparison to the refluxing conditions reported for similar substrates in laurencin synthesis. A dissolving metal reduction was then carried out to remove the ephedrine portion of the morpholinone and LAH treatment fully reduced the resulting amide. Finally, cleavage of the amide and simultaneous oxidation of the alcohol with NaIO₄ followed by PMP deprotection with Ce(NH₄)₂(NO₃)₆ provided the target oxocene **4.170**. With this approach, Adsool and Pansare were able to drastically reduce the

number of steps to **4.170** in comparison to Palenzuela's 21 steps and significantly improved the overall yield (11.3%).



Scheme 44: Formal synthesis of laurencin by Pansare

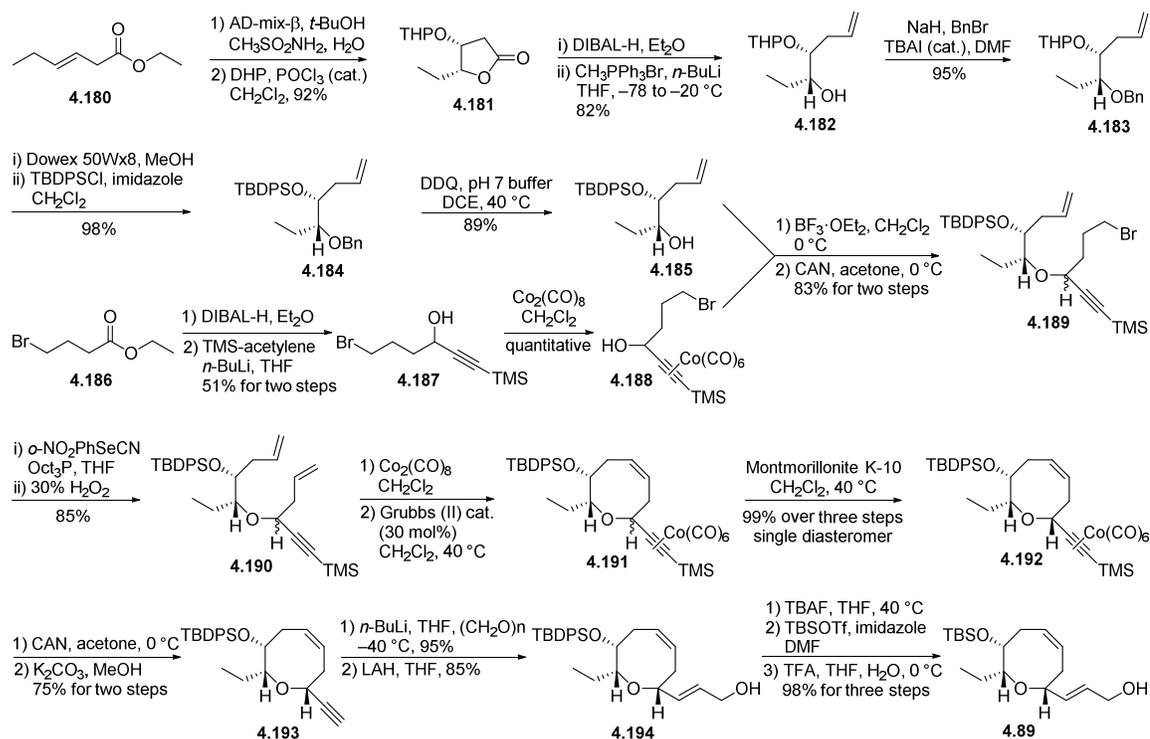
4.1.2.3.11 Martín's synthesis¹³⁸

Martín and co-workers are the most recent group to report a synthesis of (+)-laurencin, with Overman's advanced intermediate **4.89** as their target. Unique features of the formal synthesis include a Nicholas reaction for linear ether preparation, ring closing metathesis, and a montmorillonite K-10 isomerization to give exclusive α,α' -*cis*-oxocene **4.201**. The synthesis began with a Sharpless asymmetric dihydroxylation of ethyl *trans*-3-hexenoate (Scheme 45). The known lactone **4.181** was obtained with the achievement of two goals. First, the requisite stereochemistry of the C12 and C13 positions were installed; secondly, spontaneous regioselective lactonization differentiated the two resulting hydroxyl groups. A great deal of effort was made to determine an optimal protecting group for the C12 alcohol prior to the one-pot DIBAL-H reduction and Wittig reaction. Several

initial attempts to complete this one pot sequence resulted in a mixture of alkenes with a partial protecting group migration. The THP group shown in **4.181** did not succumb to this migration problem. However, a series of deprotection and protection reactions were carried out to exchange the THP group for a TBDPS protecting group to give **4.185**.

The next task was Nicholas reaction with cobalt complexed propargylic alcohol **4.188**, which was prepared from ethyl 4-bromobutyrate by DIBAL-H reduction, nucleophilic addition of lithylated ethynyltrimethylsilane, and treatment with di-cobalt octacarbonyl. Despite testing their Nicholas/RCM method on a simplified substrate, finding this suitable Nicholas coupling partner required a great deal of trial and error. The Nicholas reaction and subsequent decomplexation gave **4.189** was accomplished in 83% for two steps; however no diastereoselectivity was observed. Dienes **4.190** were elaborated from **4.189** using a variant of the Grieco reaction. A second cobalt complex was prepared to protect the alkyne during the RCM reaction, which was realized using 30 mol% of Grubbs's 2nd generation catalyst. At this stage, treatment with montmorillonite K-10 allowed thermodynamic isomerization of the α,α' -*cis*- and *trans*-oxocene mixture was carried out to give exclusively the α,α' -*cis*-isomer **4.201**. Excellent yield was obtained for these three steps. Decomplexation was then performed and the TMS group was cleaved. To extend the C7 side chain, terminal alkyne **4.202** was lithiated and treated with paraformaldehyde. Allylic alcohol **4.203** was obtained in good yield after LAH reduction. Unfortunately, Overman's advanced intermediate **4.89** required that the TBDPS protecting group in **4.203** be exchanged with a TBS group. It is quite disappointing that the authors

were not able to attain satisfactory results in the key Nicholas reaction with the labile TBS group. Thus, the silyl group exchange was completed in excellent yield in three steps via a deprotection, bis-TBS protection and selective deprotection. Martín and co-workers were able to prepare **4.89** in 18 linear steps. In spite of the excessive number of deprotection/protection and cobalt complexation/decomplexation steps, a 26% overall yield was obtained for Overman's advanced intermediate.



Scheme 45: Formal synthesis of laurencin by Hoffmann

4.1.3 Summary of Background

In this background section, the isolation of (+)-intricenyne (**4.1**) has been discussed and several structurally similar natural products have been described. Because (**4.1**) has not been synthesized to date, the numerous synthetic routes to structurally similar (+)-laurencin (**4.5**) have been discussed in detail. These total and formal syntheses serve as a standard for development of our synthetic route to **4.1**.

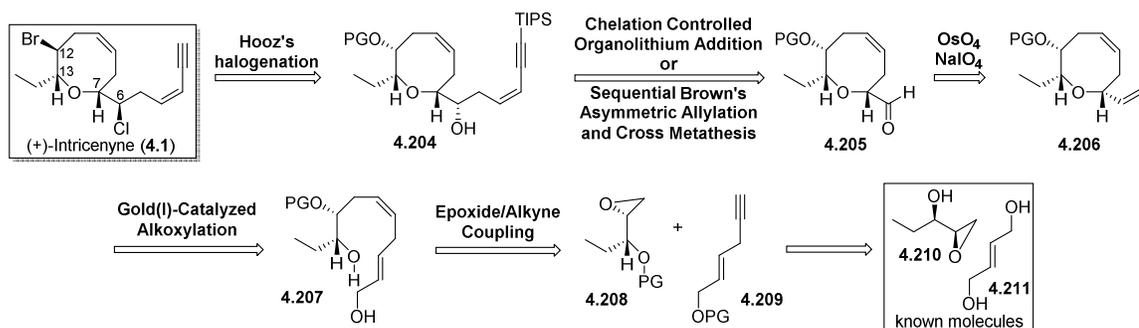
Having fully examined the existing syntheses of laurencin, one of our goals in pursuing a total synthesis of **4.1** was to contribute to the current knowledge of this class of monocyclic marine natural products. Thus, our retrosynthetic analysis would need to contain novel disconnections. Arguably, the most important disconnection is the one which would form the 8-membered ring. As discussed in the above sections, ring expansion, C–C bond forming, ring closing metathesis and lactone formation have been used to prepare the oxocene core. Of these methods, C–C bond forming and RCM are the most common. There is a lack of methods that disconnect the 8-membered cyclic ether at one of the two C–O bonds, likely because this disconnection requires selective installation of one of the four stereocenters in addition to the already challenging cyclization. This is exactly what our gold(I)-catalyzed alkoxylation would accomplish. We also wanted to contribute to the current methods for preparing this class of natural products in other ways. The installation of the C7 enyne side chain was another area in which improvements could be achieved. The previous reports for the synthesis of laurencin provided a foundation for us to explore

methods for a convergent and stereoselective installation. Hence, we developed the retrosynthetic analysis outline in the next section.

4.2 Results and Discussion

4.2.1 Retrosynthetic Analysis of (+)-Intricenyne

As shown in Figure 46, it was initially thought that (+)-intricenyne could be secured from **4.204** through standard Hooz's bromination¹³⁹ seen throughout the (+)-laurencin literature.^{133a, 133d-h, 136b, 136c} Furthermore, there is a precedent⁴⁸ for a similar Hooz's chlorination¹³⁹ at C6 which suppresses competing β -elimination to give a fully conjugated C7 side chain. Based on the approaches for enyne construction discussed in section 4.1.2.3, a convergent approach with nucleophilic addition to aldehyde **4.205** seemed desirable. The main issue with this enyne installation strategy was the lack of stereoselectivity.^{133d, 136b, 136c} Thus, it was hypothesized that a titanium-chelation controlled organolithium addition would selectively provide the desired (6*S*)-alcohol (Figure 32A).¹⁴⁰ Should the testing of this hypothesis give poor results, an alternate strategy could be employed in which well-known Brown's asymmetric allylation¹⁴¹ would selectively reduce aldehyde **4.205** and provide a terminal olefin for late stage cross metathesis¹⁴² (Figure 32B).



Scheme 46: Initial retrosynthetic analysis of (+)-intricenyne

Aldehyde **4.205** could potentially be obtained from terminal alkene **4.206** through a sterically controlled regioselective Lemieux–Johnson oxidation.¹⁴³ Advanced intermediate **4.206** would be obtained through a pivotal stereoselective gold(I)-catalyzed alkoxylation of monoallylic diol **4.207**. This key step would simultaneously cyclize through a C–O bond formation and establish the relative α,α' -*cis* configuration while providing a functional handle for elaboration of the C7 side chain. It was anticipated that **4.207** could be obtained from an epoxide/alkyne coupling reaction of **4.208** and **4.209**, thus allowing the *cis* Δ^9 double bond to be easily accessed by Lindlar hydrogenation. Lastly, chiral epoxide **4.208** and terminal alkyne **4.209** could be prepared from known epoxide **4.210**¹⁴⁴ and (*E*)-2-butene-1,4-diol (**4.211**)¹⁴⁵, respectively.

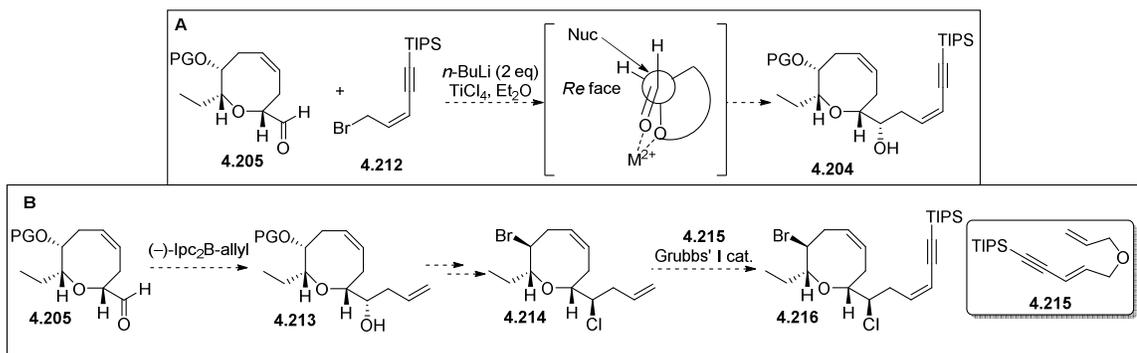


Figure 32: Proposed methods for installation of the C7 enyne side chain

(A) convergent method via a titanium-chelation controlled organolithium addition (B) linear method via Brown's asymmetric allylation and cross metathesis

4.2.2 Preparation and Coupling of the Epoxide and Alkyne Fragments

To begin the proposed synthesis of (+)-intrincenyne, it was necessary to prepare terminal alkyne **4.209**. Initially, TBS was chosen as the alcohol protecting group due to its robust nature and well established and numerous protection/deprotection conditions. Furthermore, it was orthogonal to the PMB protecting group selected for the C12 alcohol. A number of routes were tested for the assembly of **4.220**. As shown in Figure 33A, we anticipated that **4.220** could be obtained by a Dess–Martin oxidation of 3-butyn-1-ol (**4.217**), DIBAL-H reduction, and TBS protection based preparation of the similar, known (*E*)-hept-2-en-6-yn-1-ol.¹⁴⁶ When commercial **4.217** was treated with Dess–Martin periodinane followed by addition of methyl (triphenylphosphoranylidene) acetate desired α,β -unsaturated methyl ester **4.218** was not formed. Instead, the fully conjugated allene **4.221** was obtained. It is possible that maintaining the temperature at $-78\text{ }^{\circ}\text{C}$ would have

prevented formation of allene **4.221**; however, it is likely that this isomerization issue would have arisen again in later steps. Hence, a second route shown in Figure 33C was pursued. In this route, the known bis-TBS protection diol (**4.222**)¹⁴⁷ would be subjected to cross metathesis conditions with commercial 3-buten-1-ol (**4.223**), a Dess–Martin oxidation would provide aldehyde **4.225** and Corey–Fuchs reaction would yield the target alkyne **4.220**. Cross metathesis of **4.223** with three equivalents of **4.222** in the presence of Hoveyda–Grubbs II successfully gave (*E*)-alkene **4.224** in 78% yield. Oxidation of the primary alcohol in **4.224** was also accomplished smoothly; however, one-pot treatment of aldehyde **4.225** with carbon tetrabromide, triphenylphosphine and triethylamine resulted in a mixture of products potentially containing the desired dibromide intermediate. Upon addition of *n*-butyl lithium, a more complex mixture of products was observed. Attempts were made to isolate and identify these product spots without consequence. Additional attempts were made to isolate the suspected dibromide intermediate prior to treatment with *n*-butyl lithium which also failed. Thus, it had become apparent that phosphonium ylides were not compatible building blocks for either termini of the target alkyne **4.220**.

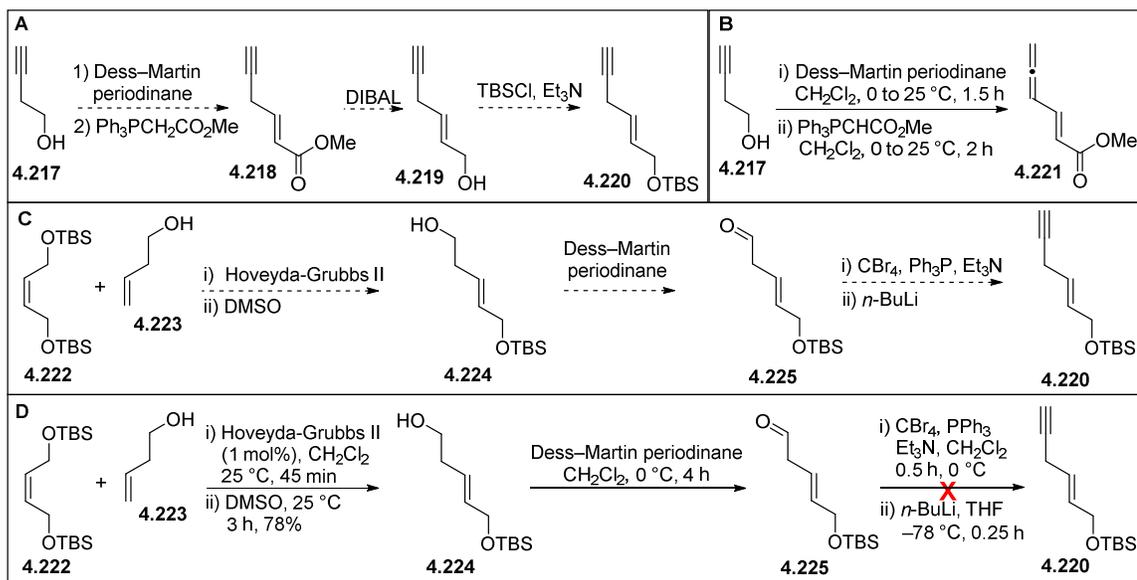
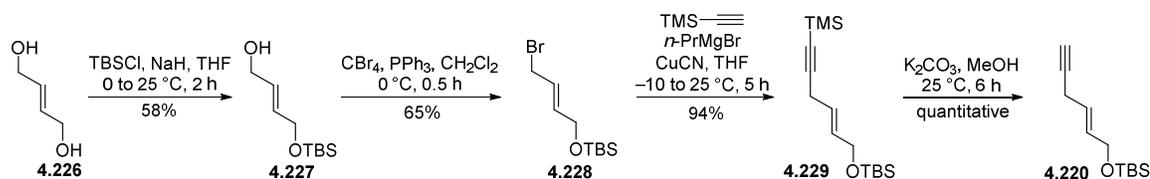


Figure 33: Attempts to prepare terminal alkyne 4.220

(A) First proposed route to the terminal alkyne (B) Experimental results for the first proposed route to the terminal alkyne (C) Second proposed route to terminal alkyne (D) Experimental results for the second proposed route to the terminal alkyne

The only successful preparation of alkyne **4.220** was the four step sequence shown in Scheme 47 based on the literature preparation of the known TMS protected alkyne (**4.229**).^{80a} Mono-TBS protection of (*E*)-2-butene-1,4-diol (**4.226**)¹⁴⁵ gave silyl ether **4.227** in 58% yield.^{80a} Hooz's bromination protocol¹³⁹ was employed to give the known bromide (**4.228**)¹⁴⁸ in a moderate 65% yield. The alkyne functionality was introduced by copper-mediated addition of ethynyltrimethylsilane, which was generated *in situ* prior to exposure with bromide **4.228**. Excellent yields were typically obtained for this transformation without observation of the S_N2' or double bond isomerization side products. The terminal alkyne was quantitatively revealed upon treatment with basic conditions.



Scheme 47: Optimized route to terminal alkyne 4.220

Since it was anticipated that terminal alkyne **4.220** would be a volatile substance, our first attempt at the epoxide/alkyne coupling reaction was completed with TMS-protected alkyne (**4.229**) and racemic benzyl glycidol ether (**4.230**) as a model epoxide using Smith's procedure for a similar coupling reaction (Figure 43A).¹⁴⁹ TMS-protected alkyne (**4.229**) was treated with methyl lithium at room temperature. After 30 minutes of stirring, a solution of the epoxide (**4.230**) was added dropwise followed by $\text{BF}_3 \cdot \text{OEt}_2$. Unfortunately, the limiting substrate (**4.230**) was unreacted and the TMS-protected alkyne (**4.229**) was consumed. Although the major product was isolated and a ^1H NMR spectrum was obtained, a structure could not be assigned. It is likely that **4.229** degraded upon exposure to the harsh basic conditions at room temperature prior to epoxide addition. Therefore, our next attempts at epoxide/alkyne coupling were conducted with terminal epoxide **4.220**. Treatment of **4.220** with *n*-BuLi at 0 °C followed by addition of HMPA and epoxide **4.231** at -40 °C with gradual warming to room temperature was also completed without avail. It was suspected that these conditions were also too harsh. A more mild

procedure⁷⁸ was then employed, in which alkyne **4.220** was treated with butyl lithium followed by $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C prior to dropwise addition of epoxide **4.231** (Figure 43C). The desired homopropagylc alcohol **4.232** was isolated as a mixture with an unidentified side product in 50% yield (2.2:1). Further purification gave a small sample of **4.232** to confirm the spectral assignment.

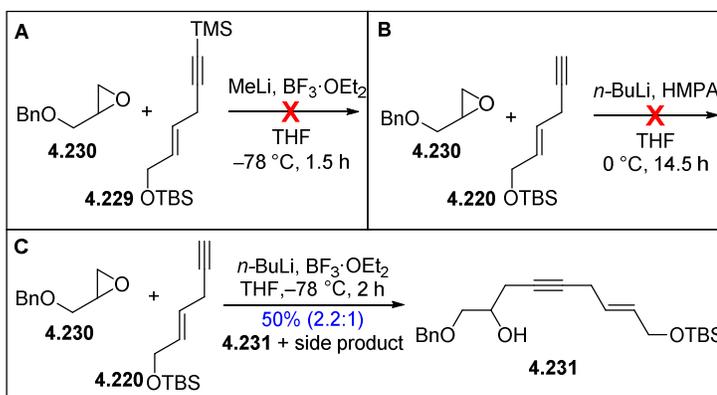
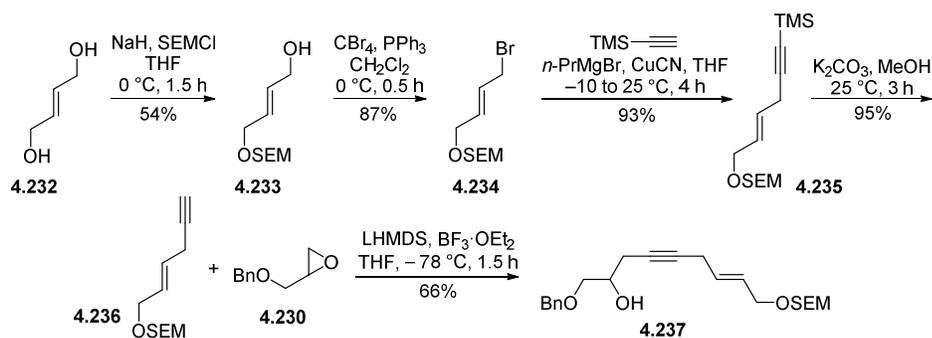


Figure 34: Model studies for epoxide/alkyne coupling reaction

At this stage, we thought that the now known volatility of alkyne **4.220** was partially responsible for the poor epoxide/alkyne coupling results. This physical property made handling the molecule difficult and hindered our ability to obtain completely anhydrous conditions required for the coupling reaction. Therefore, we abandon the TBS protecting group and selected the SEM protecting group as a replacement due to its similar nature and known ability to increase the boiling point of analogous silyl ethers. Luckily,

the optimized route developed for terminal alkyne **4.220** also proved successful for preparation of alkyne **4.236**. Mono-SEM protection of commercial (*E*)-2-butene-1,4-diol, bromination of the free alcohol and a copper-mediated nucleophilic addition of TMS-acetylene gave **4.235**, which was deprotected under basic conditions, revealed the terminal alkyne **4.236** in 42% overall yield. Use of this SEM-protected alkyne **4.236** in the model epoxide/alkyne coupling reaction under *n*-BuLi/BF₃·OEt₂ conditions gave a 50% isolated yield of homopropaglyc alcohol **4.237**. When *n*-BuLi was replaced with LHMDS under otherwise identical conditions to give the homopropaglyc alcohol **4.237** in 66% yield. With a promising epoxide/alkyne coupling procedure in hand, we turned our attention to the preparation of epoxide **4.240**, the epoxide subunit required for our retrosynthetic analysis of (+)-intricenylene.



Scheme 48: Preparation of terminal alkyne **4.236 and coupling with model epoxide **4.230****

Although (*R,R*)-**4.240** is known¹⁴⁴, no procedural or spectral data had been reported in the literature likely because its enantiomer (*S,S*)-(**4.240**)¹⁵⁰ had been reported previously. Unfortunately, the handful of publications reporting the preparation or use of (*S,S*)-**4.240** also had little to no procedural or spectral data. The most useful information was obtained from Suzuki's publication on their formal synthesis of (+)-isolaurepinnacin, a naturally occurring α,α' -*cis*-oxepane, in which a seven step preparation of (*S,S*)-**4.240** from (+)-2,3-*O*-isopropylidenthreitol was disclosed.^{150c} Full procedural and spectral data was not published. Instead, only partial reaction conditions were depicted in the schemes. The length of Suzuki's route to (*S,S*)-**4.240** was a major drawback; therefore, it was initially proposed to prepare epoxide (*R,R*)-**4.240** from commercial (*R*)-(+)-1,2-epoxybutane (**4.238**) in a two step sequencing using a one-carbon atom homologation via reaction with dimethylsulfonium methylide followed by a *m*-CPBA epoxidation which would give a diastereomeric mixture of **4.240** (Figure 35A). Based on literature examples¹⁵¹, we knew that the small ethyl group would not provide enough conformational bias during the *m*-CPBA epoxidation of allylic alcohol **4.239**. Therefore, it would be necessary to separate the diastereomers. Conversion of epoxide (**4.238**) to allylic alcohol **4.239** was successfully accomplished as confirmed by a crude ¹H NMR of the volatile sample (Figure 35B). The *m*-CPBA epoxidation was also achieved and gave a 1:1 mixture of epoxides **4.240** as determined by ¹H NMR comparison with literature spectra.^{144, 150b, 150c, 152} The volatile nature of epoxides **4.240** dictated that alcohol protection be accomplished prior to chromatographic separation. Thus, two attempts to protect with either the PMB¹⁴⁴ or Bn¹⁵³

functional groups were made since the (*R,R*)-configurations of each are known. Protection with PMBCl under standard basic conditions was achieved and spectral data was consistent with the literature data; however, chromatographic separation was problematic. Similar results were also obtained with the benzyl protected epoxide mixture **4.242**.

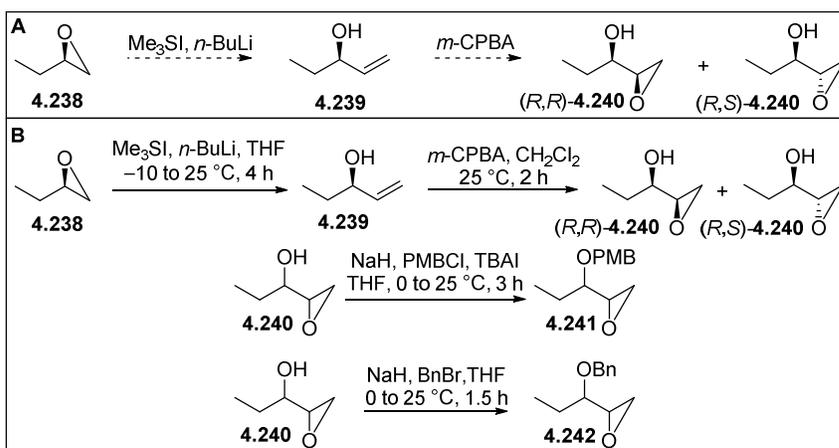


Figure 35: Attempts to prepare hydroxy epoxide (*R,R*)-4.240

Because chromatographic separation of the *p*-methoxy benzyl epoxides **4.241** and benzyl epoxides **4.242** was not attainable, we decided to use Suzuki's seven step sequence for the preparation of epoxide (*R,R*)-**4.240**. As depicted in Figure 36A, commercial threitol (–)-(**4.249**)¹⁵⁴ was monobenzylated and tosylated in good yield to give **4.243**. Methylation via a Gilman reagent was completed to provide the ethyl group required for the C13 side chain of (+)-intrincenyne. As shown in Scheme 36A, slight excess of the Gilman reagent was employed which resulted in an inseparable mixture of desired **4.244** and iodide side

product **4.245** in 46% yield (9:1 **4.244**:**4.245**). When this mixture was carried forward to the debenzoylation step, no reaction was observed upon prolonged treatment with Pearlman's catalyst despite testing various solvent, temperatures, catalyst loadings and commercial catalyst sources. Therefore, the methylation was repeated using a large excess (5 eq) of the Gilman reagent which resulted in complete conversion to **4.244** without any observed iodide side product **4.245**. When pure **4.244** was treated with Pearlman's catalyst under Suzuki's originally reported conditions, alcohol **4.246** was obtained in high yield; thus, it is likely that the iodide side product was poisoning the palladium catalyst. Tosylation and acetal cleavage were completed without complication. Lastly, it was necessary to complete an epoxidation under basic conditions and protect the free alcohol. Suzuki and co-workers had reported epoxidation using K_2CO_3 and MeOH in CH_2Cl_2 . When these conditions were tested, a crude 1H NMR spectrum confirmed the formation of an epoxide (Figure 36B). However, the volatility of (**2.240**) made it essential to protect the free alcohol to obtain a satisfactory 1H NMR confirming its identity. Protection of the crude epoxide with PMBCl under standard conditions gave known (**4.241**)¹⁴⁴ whose experimental and literature spectra were in good agreement.

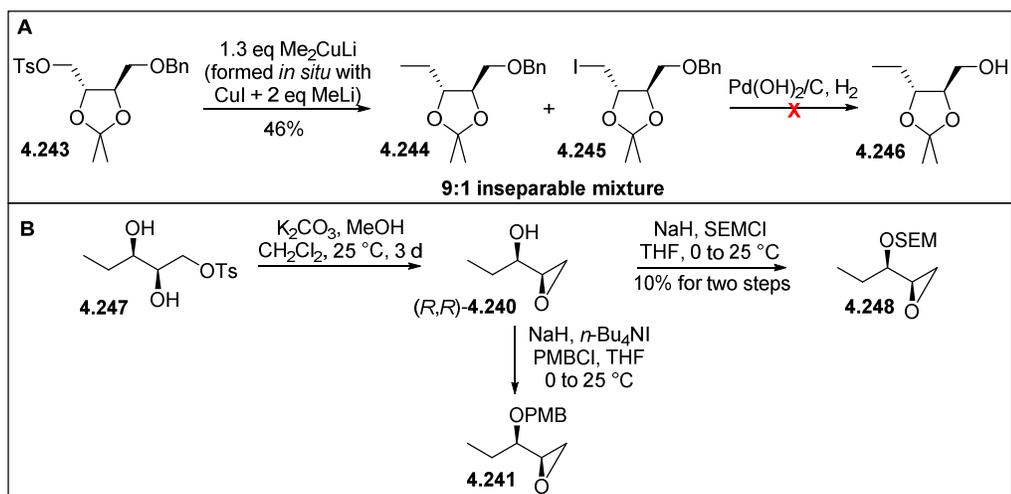
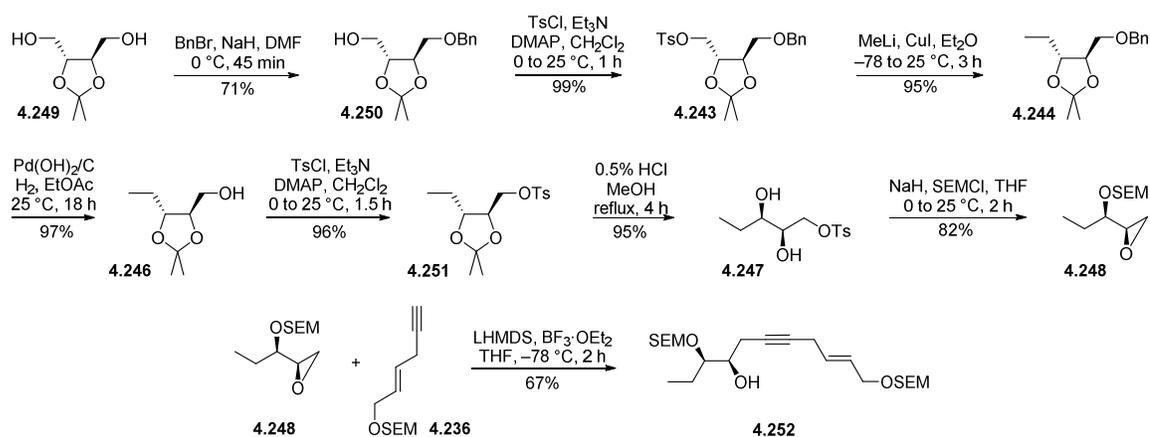


Figure 36: Attempts to prepare epoxide (R,R)-4.240 via Suzuki's route

(A) Initial attempts to methylate and debenzylate **4.243** (B) initial epoxidation attempts with diol **4.247**

Our retrosynthetic analysis dictated that the alcohol of epoxide **4.208** be protected with the same protecting group as the terminal alkyne **4.209**, allowing simultaneous cleavage to reveal key diol **xx** just prior to the pivotal gold(I)-catalyzed cyclization. Thus, unknown **4.248** (PG = SEM) was our target epoxide, requiring the development of a protection procedure using SEMCl. An initial two step sequence in which epoxidation was achieved using K_2CO_3 and MeOH in CH_2Cl_2 followed by treatment of the crude epoxide with NaH and SEMCl was somewhat successful, giving desired **4.248** in 10% yield. However, there were several drawbacks to this procedure including prolonged reaction time for the epoxidation and the potential loss of volatile epoxide **4.240** during aqueous workup. It was hypothesized that the epoxidation and SEM protection could be achieved

in a single step using NaH as the base for both purposes, hence eliminating the long reaction time for epoxidation and aqueous workup prior to protection. As depicted in Scheme 49, treatment of **4.247** with excess NaH and SEMCl gave epoxide **4.248** directly in 82% isolated yield and 43% overall yield from commercial (**4.249**). Suzuki and co-workers achieved a similar overall yield (44%) for epoxide (**4.240**)^{150c} The optimized route to epoxide **4.248** is shown in Scheme 49.



Scheme 49: Optimized route to epoxide **4.248 and coupling with alkyne **4.236****

Now that access to epoxide **4.248** was achieved, we attempted the epoxide/alkyne coupling using conditions that had been optimized with alkyne **4.236** and epoxide **4.248**. Satisfyingly, treatment of alkyne **4.236** with LHMDS followed by addition of $\text{BF}_3 \cdot \text{OEt}_2$ prior to dropwise addition of SEM-protected epoxide **4.248** gave homopropargylic alcohol **4.252** in 67% yield. The moderate yield could be attributed to incomplete consumption of

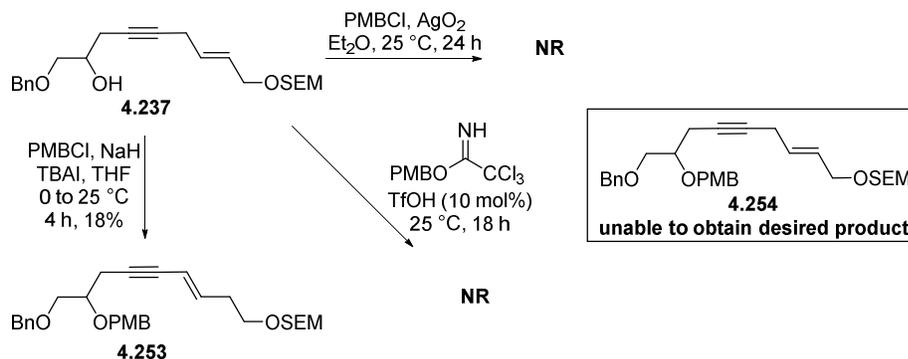
the limiting epoxide **4.248** and side reaction due to the acidic homoene protons. Fortunately, the incomplete consumption of substrate and amount of side product formed appeared to be consistent with the results obtained in the model system; thus, these issues are not a result of the identity of the epoxide used.

4.2.3 Selection of a suitable protecting group for the C12 alcohol

The next phase of the total synthesis required protection of the C12 alcohol, selective hydrogenation of the alkyne to the Δ^9 *cis* alkene, and bis-deprotection of the SEM groups. Surprisingly, this task was complicated by several seemingly trivial obstacles. For example, the choice of a suitable protecting group was pivotal in later steps. Protecting group migration due to the 1,2-diol relationship of alcohols C12 and C13 was observed in certain cases during either bis-SEM deprotection or gold(I)-catalyzed alkoxylation. Furthermore, the selective Lindlar hydrogenation was sensitive and optimization of conditions was required for each protecting group examined. Thus, this section is dedicated to the discussion of three ostensibly effortless steps.

For our original retrosynthetic analysis, a PMB protecting group was chosen to mask the C12 alcohol prior to the key GCA. Since homopropagyl alcohol **4.237** was on hand, it was employed as a model system for the C12 alcohol protection step. When **4.237** was treated with standard basic conditions (NaH/PMBCl), double bond isomerization occurred to give the C12 PMB protected enyne **4.253** (Scheme 50). Attempts to protect

under traditional acidic conditions with 4-methoxybenzyl-2,2,2-trichloroacetimidate were not profitable. These conditions did not provide any desired product **4.254**; instead, the unreacted starting material was recovered. Use of $\text{AgO}_2/\text{PMBCl}$ conditions gave similar disappointing results. It was suspected that the secondary alcohol was either sterically hindered or not nucleophilic enough for attack of the methylene unit in the PMB protecting group. Therefore, two changes were made to the system. First, the homopropagyl alcohol **4.237** was no longer used as the substrate since it contained more steric bulk near the C12 alcohol than the chiral homopropagyl alcohol **4.252**. The second change was to use a different protecting group that had more electrophilic character at the site of attack.



Scheme 50: Attempts to protect model homoallylic alcohol 4.237 with PMB group

Thus, a standard acetylation under weakly basic conditions using chiral homopropagyl alcohol **4.252** was tested and promptly gave the C12 acetate in high yield (93%). After optimizing the Lindlar hydrogenation to suppress overreduction, we eagerly

began the bis-SEM deprotection which would provide us with substrate for our key gold(I)-catalyzed alkoxylation (Figure 37A). Unfortunately, a screening of several methods gave disappointing results. The most concerning outcome of this screening was a suspected protecting group migration observed under acidic conditions (entries 4-6) to give an inseparable ~1:1 mixture of diols **4.257** and proposed **4.258**. In hindsight, the MgBr₂/MeNO₂ conditions (entry 3) gave the desired diol **4.257** without the appearance of the inseparable side product albeit in low yield. This result can be attributed to the short reaction time since additional spots were observed by TLC analysis. One would expect to observe two intermediates from unselective mono-SEM deprotection. The inseparable side product would likely have formed if the reaction had been allowed to progress since the three additional unexpected intermediates were potentially a result of acetyl migration occurring simultaneously with the mono-SEM deprotection. Hence, the short reaction time can actually be viewed as a fortunate mistake, allowing a pure sample of the desired diol **4.257** to be obtained for ¹H NMR comparison with the mixed samples.

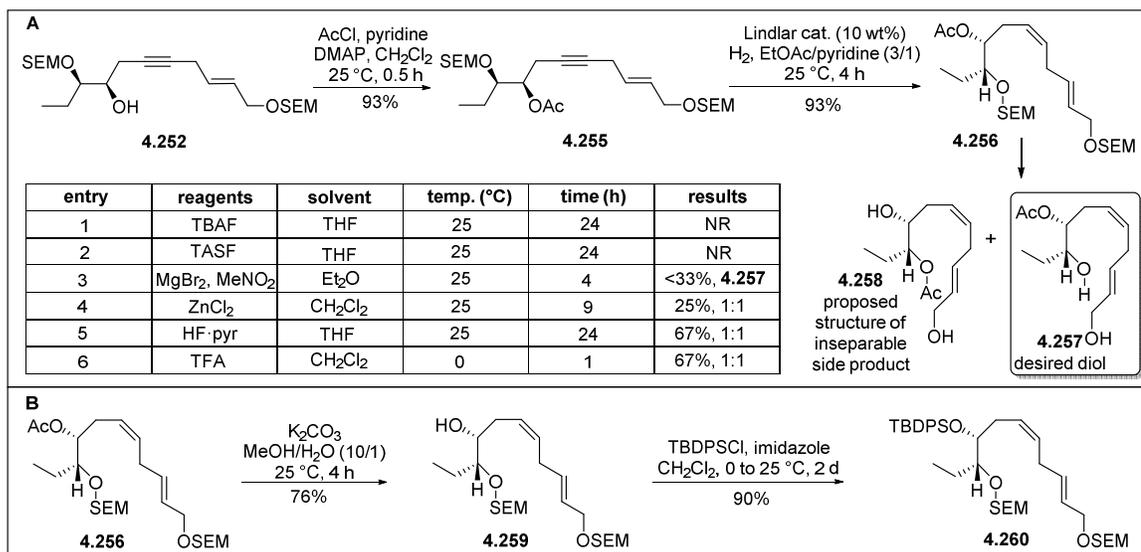


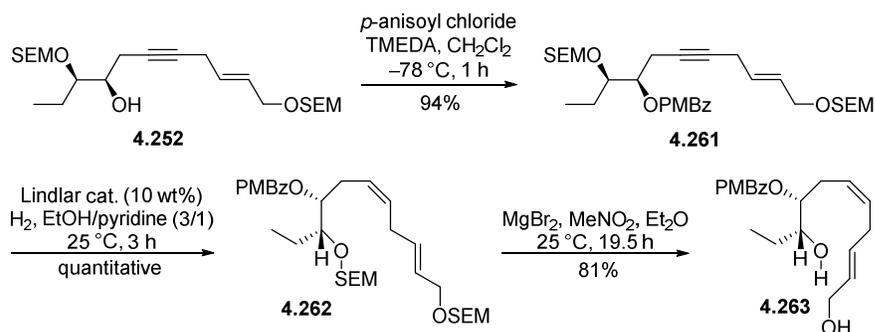
Figure 37: Acetate and TBDPS protecting groups for C12 alcohol

(A) Preparation and attempts to deprotect bis-SEM ether 4.256 (B) Preparation of TBDPS protected C12 alcohol 4.260

With the protecting group migration concern in mind, we tested the bis-SEM deprotection in the presence of the bulky TBDPS protecting group (Figure 37B). Deacetylation of **4.256** and TBDPS protection were accomplished under standard conditions. Regrettably, complex mixtures were obtained in each effort to complete the bis-SEM deprotection using **4.260** despite using various reaction conditions (TFA or MgBr₂/MeNO₂). These preliminary results, in combination with the prolonged reaction time required to achieve high yields for the protection step, discouraged any further

attempts to examine the bis-SEM deprotection in the presence of a C12 TBDPS-protected alcohol.

Next, we decided to use the *p*-methoxy benzoyl (PMBz) protecting group because the acid chloride appeared to react more readily with the C12 secondary alcohol and the benzoyl derivative had been reported to be less susceptible to migration. Protection of the C12 alcohol with standard *p*-methoxy benzoylation conditions (Et₃N/DMAP/PMBzCl) were also found to be sluggish; thus, TMEDA was used as the amine base due to its known ability to promote benzoylations¹⁵⁵. The Lindlar hydrogenation of alkyne **4.261** was optimized. In the case of **4.255** (PG = Ac), the hydrogenation was accomplished in EtOAc/pyridine (3/1) using 10 wt% catalyst loading. Use of these conditions for **4.261** (PG = PMBz) gave diene **4.262** after 4 days and a total catalyst loading of 30 wt%. Thus, the solvent was altered to EtOH/pyridine (3/1) which gave diene **4.262** quantitatively in just 3 hours. As with the acetyl protecting group, use of the PMBz protecting group gave a ~1:1 mixture of diols upon bis-SEM deprotection with TFA or HF·pyridine conditions. Treatment of **4.262** with TBAF resulted in very little conversion of substrate, as was observed with **4.255** (PG = Ac). Upon exposure to MgBr₂/MeNO₂ conditions, **4.262** cleanly yielded diol **4.263** in 81% yield. Thus, we finally had access to pure diol **4.263** for the subsequent key gold(I)-catalyzed cyclization. The optimized route to diol **4.263** is shown in Scheme 51.

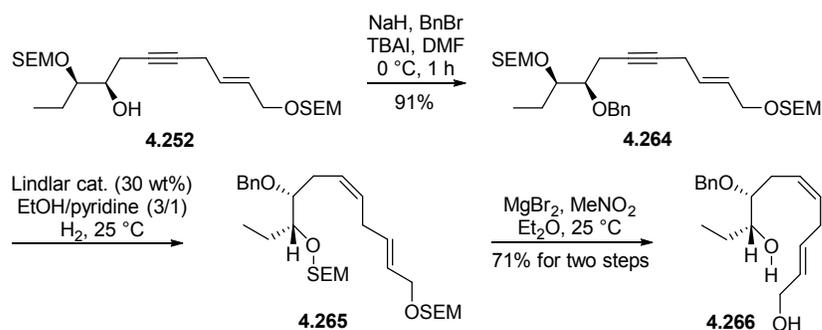


Scheme 51: Optimized route to C12 PMBz protected alcohol 4.263

As will be discussed in Section 4.2.4, cyclization of diol **4.263** was moderately successful. Unexpected protecting group migration occurred during initial tests of the key step. Furthermore, our original proposal to further construct the natural product by subjecting the key oxocene intermediate **4.206** to a Lemieux–Johnson oxidation resulted in oxidation of the internal Δ^9 *cis* olefin instead of the anticipated C7 terminal alkene. Due to these complications, it became necessary to revise our retrosynthetic analysis and, consequently, change the C12 protecting group. The last and optimal protecting group examined was the benzyl (Bn) group.

It's similarities to the PMB protecting group and our previous efforts to mask the C12 alcohol with PMB suggested that standard NaH conditions could be problematic. Initially, treatment of alcohol **4.252** with Bundle's trichloroacetimidate reagent and TfOH as an acid catalyst showed no reaction even after two days of stirring at room temperature. Thinking back to our initial studies with PMB protection of the C12 alcohol, protection of

the alcohol with NaH/PMBCl conditions was successful but double bond isomerization to the enyne made it unattractive. Use of highly solvating DMF and a reaction temperature of 0 °C during benzylation with NaH gave high yields of benzyl-protected alcohol **4.264** (Scheme 52). It is noteworthy that increasing the reaction temperature to 25 °C caused significant amounts of double bond isomerization even when DMF is employed as the solvent. Despite having previously optimized the Lindlar hydrogenation for **4.261**, adjustments to the catalyst loading were necessary to achieve reasonable reactivity. In the case of alkyne **4.264** (PG = Bn), it was essential to treat with 30 wt% Lindlar catalyst initially, as batchwise additions over time were not effective. Furthermore, the chance of overreduction occurring rapidly regardless of careful monitoring is much more probable. Bis-SEM deprotection was accomplished upon treatment with MgBr₂ and MeNO₂ giving diol **4.266** in 71% for two steps. Optimization of the bis-SEM deprotection step was not needed as initial testing was successful.



Scheme 52: Optimized route to C12 Bn protected alcohol 4.266

To summarize, five different protecting groups were examined for compatibility with the route to diol **4.207**, the proposed substrate for the key GCA (Figure 38). The first to be tested was the *p*-methoxy benzyl protecting group, was not successfully installed. The acetyl protecting protecting group was carried forward to the diene **4.256**, but gave a diol mixture under acidic bis-SEM deprotection conditions. TBDPS was also tested as the C12 protecting group but gave complex product mixtures upon bis-SEM deprotection. The *p*-methoxy benzoyl and benzyl protecting groups gave clean conversion to diols **4.263** and **4.266**, respectively, when treated with MgBr₂ and MeNO₂. Thus, the pivotal GCA was probed with diols **4.263** and **4.266**. So far, the benzyl protecting group has provided the best results in the gold(I)-catalyzed cyclization and later transformations.

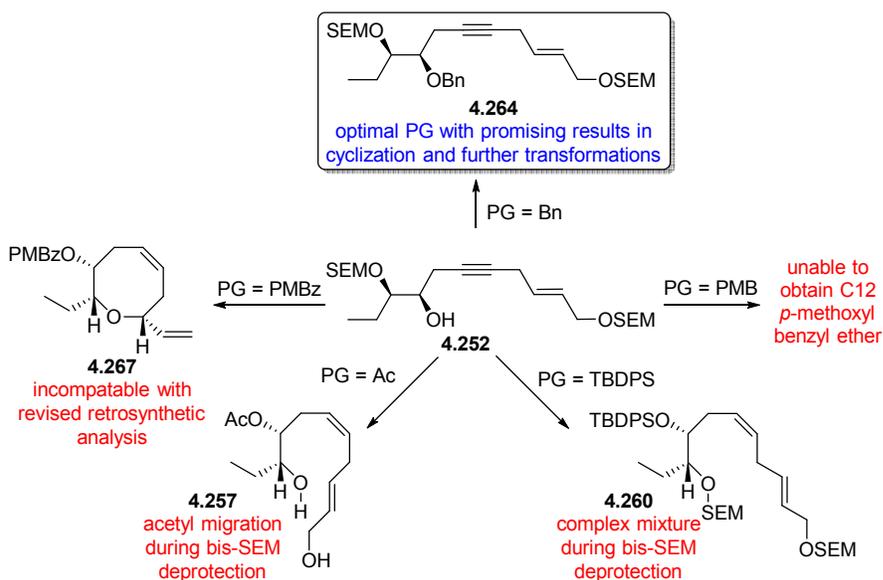


Figure 38: Summary of protecting group compatibility with synthetic route to (+)-intrincenyne

4.2.4 The Gold(I)-Catalyzed Alkoxylation for α,α' -*cis*- Δ 9-Oxocene Formation

With diol **4.263** in hand, we initially tested the GCA with the optimized conditions (Table 11, entry 1) established by our model system (Section 3.2.3). Isolation of the suspected product was completed in 21% yield; however, the ^1H NMR spectrum of the sample revealed a mixture of products. Although identifying the components of this mixture was challenging due to difficult separation and low yield, it was eventually determined that the mixture was comprised of the desired α,α' -*cis*- Δ 9-oxocene **4.267**, with tentatively assigned α,α' -*trans*- Δ 9-oxepine **4.268**, and α,α' -*cis*- Δ 9-oxepine **4.269**.

Furthermore, the mixture was predominately made up of the suspected oxepines **4.268** and **4.269** (9:1 **4.268**+**4.269**:**4.267**).

It was not until diol **4.263** was treated with buffered gold(I)-catalyzed conditions in 1,2-dichloroethane (DCE) as shown in Figure 39A that a sufficient yield was obtained on a large scale to permit identification of the components within the mixture. To chromatographically separate the mixture, PMBz deprotection was accomplished by treatment with 5% NaOH in MeOH. Separation of the three resulting alcohols provided sufficient sample to tentatively assign structures based on comparison of ^1H NMR spectra with those of structurally similar, known oxacycles (Figure 39B). The known α,α' -*cis*-oxocene **4.273**¹⁵⁶ differs from **4.270** in that the C7 side chain is an ethyl group and the relative stereochemistry of the C7, C12 and C13 positions are enantiomerically related to that of **4.270**. Distinctive features of the ^1H NMR of **4.273** acquired on a 100 MHz instrument included a three proton multiplet at δ 2.30 assigned to C8 and C11 positions, a one proton doublet of doublet at δ 2.63 ($J = 8, 12$ Hz) assigned to C11 and a one proton multiplet at δ 3.68 assigned to C12. The ^1H NMR (400 MHz instrument) of the major product from cyclization and deprotection had similar features. A three proton multiplet at δ 2.38–2.27, a one proton doublet of doublet of doublet at δ 2.56 ($J = 12.5, 9.5, 9.0$ Hz) and a one proton doublet of doublet of doublet at δ 3.69 ($J = 9.5, 4.5, 2.0$ Hz) were all present in the spectrum. Unfortunately, additional NMR analysis of known **4.273** was not reported.

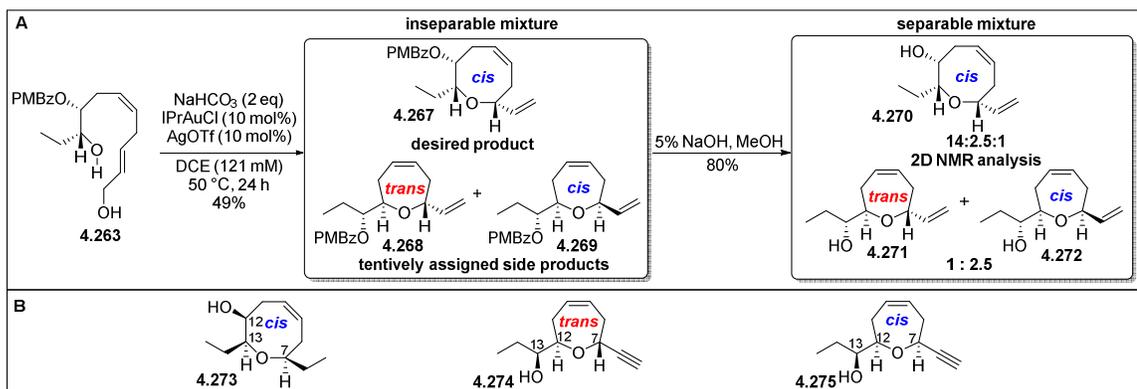


Figure 39: Isolation and determination of target α,α' -*cis*-oxocene

- (A) Experimental conditions which lead to the isolation and spectral characterization of α,α' -*cis*-oxocene
 (B) Similar oxacycles reported in the literature

Due to the protecting group migration issues encountered in the previous bis-SEM deprotection of **4.256**, it was hypothesized that the inseparable mixture contained oxepines α,α' -*trans*-**4.272** and α,α' -*cis*-**4.271** which would form after protecting group migration and nucleophilic attack of the C12 alcohol on the gold-coordinated, electron poor carbon at position seven. Thus, the ^1H NMR spectra of known oxepines α,α' -*trans*-**4.274** and α,α' -*cis*-**4.275**¹⁵⁷ were examined and compared to the spectra of the two minor products **4.271** and **4.272** from cyclization and deprotection. These known oxepines differ from the proposed side product structures in their C7 side chain which is a simple acetylene unit and configuration of the C13 alcohol. Unlike the ^1H NMR spectrum of oxocene **4.273**, the spectra of α,α' -*trans*-**4.274** and α,α' -*cis*-**4.275** each contained four one proton peaks corresponding to the C8 and C11 positions. The ^1H NMR spectra of the minor products **4.271** and **4.272** did not contain a single peak for each of the four C8 and C11 positions;

instead, two multiplets corresponding to two protons each were present. It is possible that this difference between the literature and experimental spectra is due to different conformations of the molecules caused by their slight structural differences. Another interesting feature was the drastic difference in chemical shift of the C12 proton in the spectrum for α,α' -*cis*-**4.275** (δ 3.36) when compared to that of α,α' -*trans*-**4.274** (δ 4.03). The assignment for the literature spectra had been established by 2D NMR studies that included NOESY spectrum for each isomer, allowing assignment of the spectrum with high confidence. Comparison of the literature spectra and those obtained for the minor products **4.271** and **4.272** revealed the same change in chemical shift for a one proton multiplet (δ 3.39–3.33 vs. δ 3.94–3.88). Based on these comparisons, the structures were tentatively assigned as shown in Figure 39.

Two-dimensional NMR analysis, including ^1H - ^1H COSY and ^1H - ^1H NOESY, was completed for the major product from cyclization and deprotection, which had been tentatively assigned the structure of α,α' -*cis*- Δ 9-oxocene **4.270**. The ^1H NMR of **4.270** contained three, one proton multiplets in the 3-4 ppm region which corresponded to the C7, C12 and C13 positions. However, the precise assignment could not be determined from simple calculation and comparison of coupling constants. The ^1H - ^1H COSY spectrum permitted a spectral assignment to be given to the ^1H NMR with a high level of confidence. Important interactions that aided in this assignment are indicated by blue boxes in Figure 40 and include coupling of 7-H & 8-H, 11-H & 12-H and 13-H & 14-H. A ^1H - ^1H NOESY spectrum was then collected for the major product **4.270** and three important interactions

were observed that permitted a tentative structural assignment. As might be expected for the α,α' -*cis*-oxocene **4.270**, nOe interactions were observed for 12-H & 13-H and 13-H & 7-H. Interestingly, a strong nOe coupling was also observed for 12-H & 7-H. This nOe interaction was not observed in the ^1H - ^1H NOESY spectrum obtained for our model oxocene **3.100** (Section 3.2.4). Therefore, we closely examined the literature NOESY spectra for oxepines **4.274** and **4.275** to determine if both 13-H & 7-H and 12-H & 7-H couplings were present. The literature spectra revealed that a coupling for 13-H & 7-H could not possibly be present in either the α,α' -*cis*- or α,α' -*trans*-oxepines **4.271** or **4.272**, due to the spatial distance. For α,α' -*trans*-oxocene (not shown), one would not expect to see either the 13-H & 7-H nor 12-H & 7-H nOe interactions; thus, that potential structure could also be eliminated. We suspected that the 12-H & 7-H nOe coupling is observed in **4.270** and not **3.100** because the C12 substituent forces the molecule to adapt a different conformation than **3.100** which lacks this C12 substitution; thus, placing 12-H and 7-H in close spatial proximity.

A possible three dimensional conformation which would account for the observed nOe interactions is shown in Figure 42. The twist boat conformation orients 12-H and 7-H in close proximity to each other through space despite their seemingly large distance from each other in a two-dimensional drawing. From this conformation, one would also expect to observe other key nOe interactions including 12-H & 8-H_a. Unfortunately, these nOe couplings were not observed in the experimental spectrum. Despite this seeming

discrepancy, we felt confident enough in our structural assignment to move forward with the total synthesis.

The free C12 alcohol **4.270** was protected with the PMBz functionality, permitting a clean ^1H NMR spectrum of the target oxocene to be obtained. This ^1H NMR spectrum of pure **4.267** was compared to previous spectrum which showed mixtures of oxocycles and ratios were calculated based on integration values of peaks characteristic of either the target oxocene **4.267** or competitively formed oxepines **4.268** and **4.269**. Hence, we gained a better understanding of the effects of specific components of the reaction conditions, such as solvent, gold catalyst or silver salt counteranion. Many of these reaction condition changes had been somewhat randomly selected up to this point, but a hypothesis-based approach could now be used in further studies with a method for conclusive result analysis. A discussion of the reaction conditions tested is provided below.

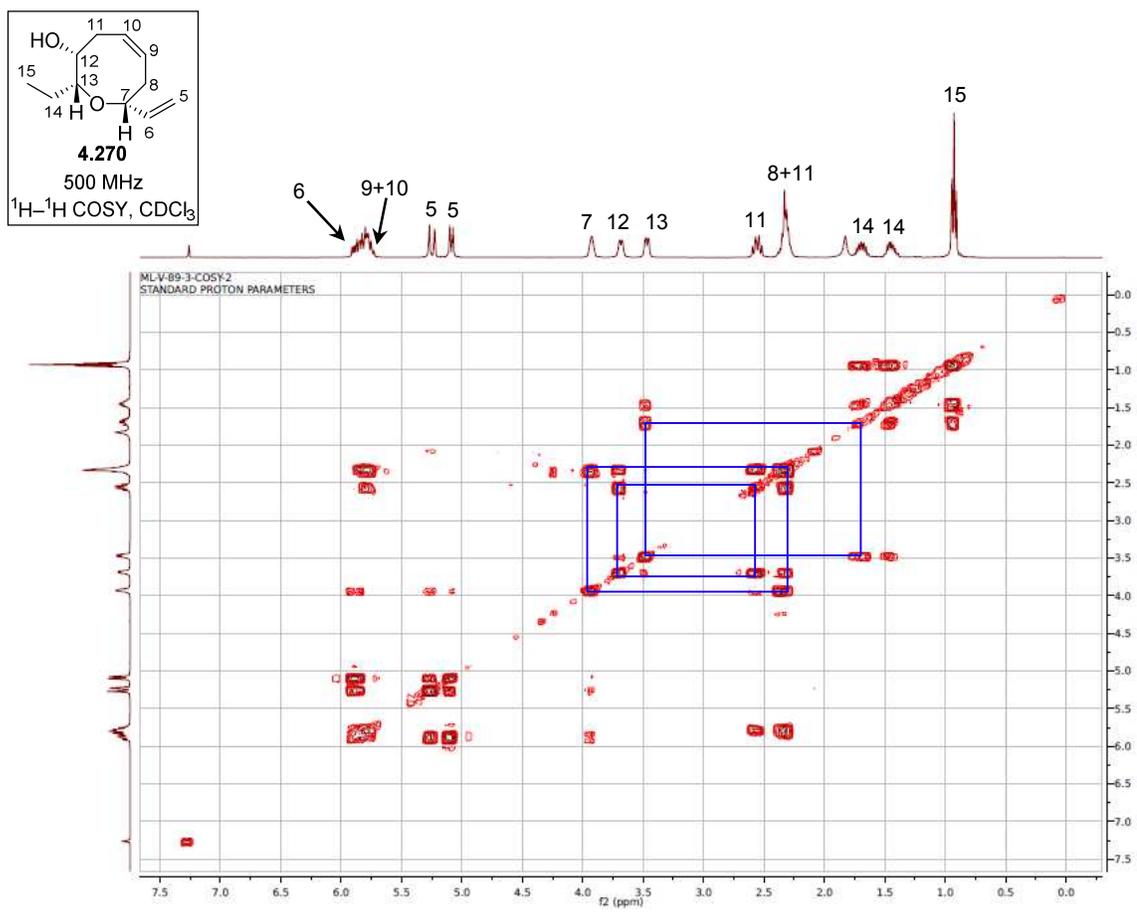


Figure 40: ^1H - ^1H COSY NMR spectra of α,α' -*cis*-oxocene 4.270

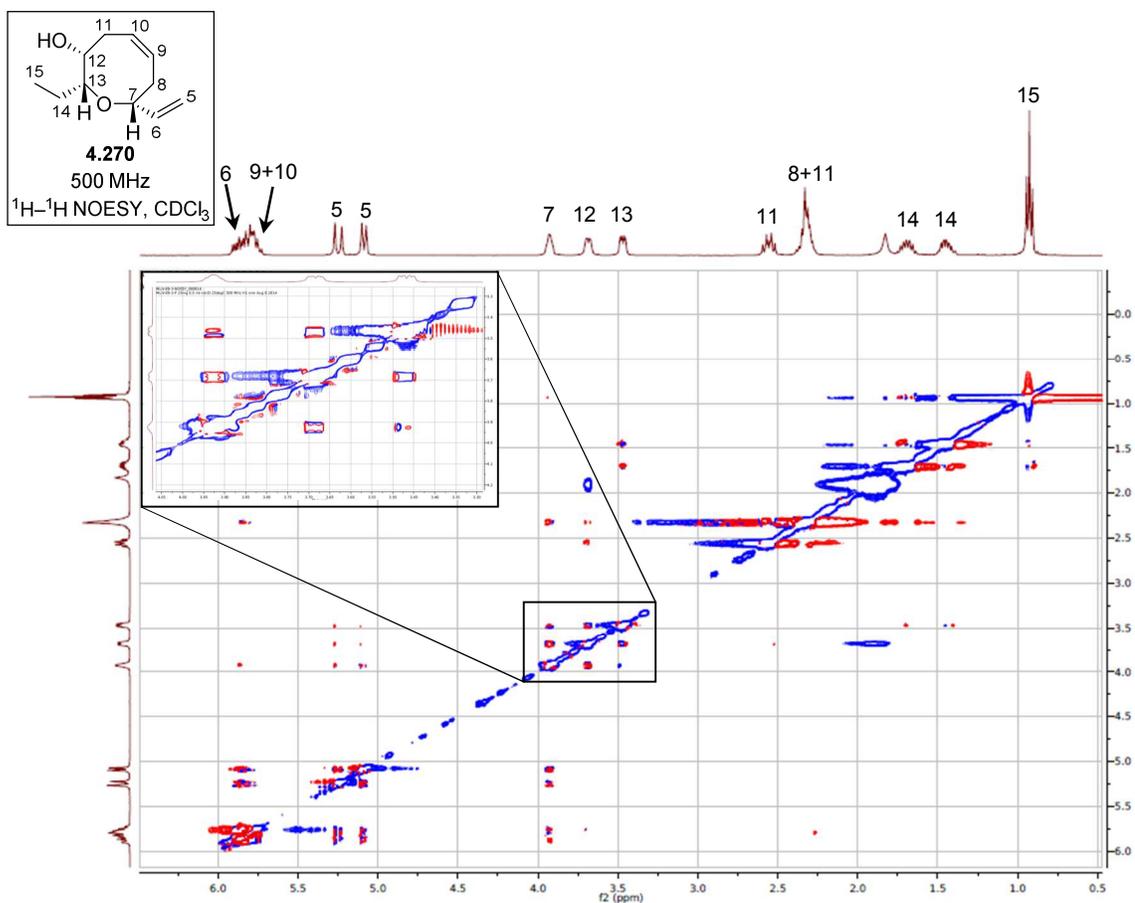


Figure 41: ^1H - ^1H NOESY NMR spectra of α,α' -*cis*-oxocene 4.270

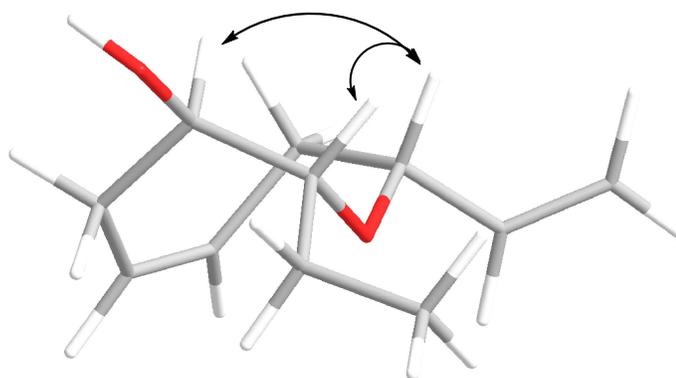
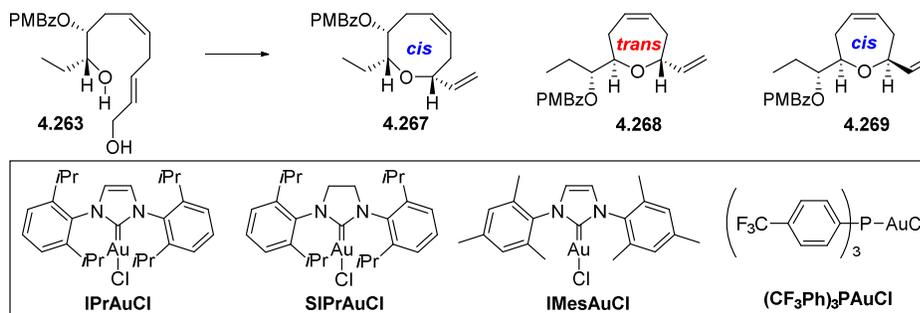


Figure 42: Possible three dimensional configuration of α,α' -*cis*-oxocene 4.270

Use of AgSbF_6 as an alternative silver salt showed a dramatic shift in the product distribution (Table 11 entry 2), suggesting that the counteranion involved in the active catalytic species had a role in determining the reaction pathway. From an inorganic perspective, the Pearson acid base properties of the silver salt counteranions could either promote or suppress the migration pathways. It was also suspected that the migration pathway could be temperature dependent, which was proven correct when the reaction was maintained at room temperature (entry 3). The product distribution slightly favored oxocene **4.267** in this case; however, the isolated yield suffered due to the high enthalpic and entropic barriers to forming medium-sized cyclic ethers. Based on reports of gold(I)-catalyzed reactions “buffered” by bases such as NaHCO_3 and CaCO_3 , it was hypothesized that use of NaHCO_3 to maintain the pH might also suppress protecting group migration and thus oxepine synthesis. Again a small improvement was achieved with addition of NaHCO_3 to the reaction mixture (entry 4), resulting in a 1:3 ratio favoring **4.267**; unfortunately, the yield remained poor. Carbonates are known to be strong chelators for gold metals, thus the poor yield was attributed to partial quenching of the gold(I) catalyst by NaHCO_3 . Thus, changing the solvent to 1,2-dichloroethane (DCE) as in entry 5 resulted in a significant increase in yield (45%) while maintaining the product distribution. Full suppression of protecting group migration and oxepine formation was realized when a combination of silver salt counteranion, pH, and solvent effects were combined as in entry 6. Adjusting the reaction concentration suppressed side product formation but also resulted

in an isolatable amount of unreacted diol **4.263** (entry 7). Other gold(I) catalysts were also examined (entries 8-10) without improvement. Catalyst loading was also screened (entries 11-13) providing the optimal yield to date (50%) of oxocene **4.267** when using a 20 mol% catalyst loading. The comparable yields for entries 12 and 13, which differ in the catalyst loading, indicate that an equilibrium might be established between **4.267** and **4.263**.¹⁵⁸ Polar side products were observed and attempts were made to isolate and characterize them. ¹H NMR spectra of these side products were complex and indicated the presence of multiple molecules within each sample. At this stage, the moderate yield of oxocene **4.267** provided sufficient quantities to attempt the proposed Lemieux–Johnson oxidation.

Table 11: Optimization of conditions for the gold(I)-catalyzed alkoxylation of monoallylic diol 4.263



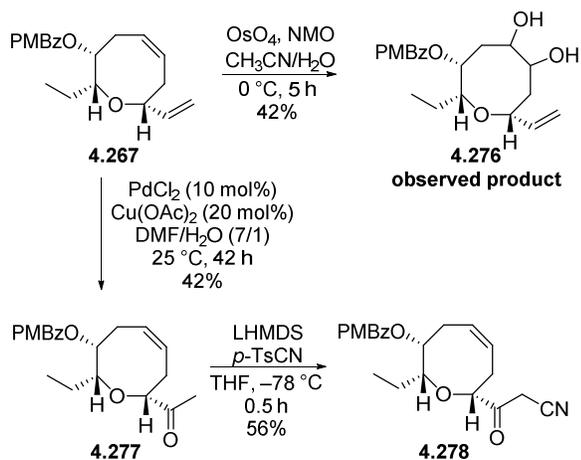
entry	gold catalyst (mol%)	silver salt (mol%)	temp (°C)	base	solvent (mM)	isolated yield (:4.267:4.268+4.269)
1	IPrAuCl (10)	AgOTf (10)	50	N/A	dioxane (121)	21 (1:9)
2	IPrAuCl (10)	AgSbF ₆ (10)	50	N/A	dioxane (121)	25 (1:2)
3	IPrAuCl (10)	AgOTf (10)	25	N/A	dioxane (121)	6 (1.2:1)
4	IPrAuCl (10)	AgOTf (10)	50	NaHCO ₃	dioxane (121)	16 (3:1)
5	IPrAuCl (10)	AgOTf (10)	50	NaHCO ₃	DCE (121)	45 (4:1)
6	IPrAuCl (10)	AgSbF ₆ (10)	50	NaHCO ₃	DCE (121)	35 (4.267 only)
7	IPrAuCl (10)	AgSbF ₆ (10)	50	NaHCO ₃	DCE (60)	29 (42% BRSM) ^a
8	(CF ₃ Ph) ₃ PAuCl (10)	AgSbF ₆ (10)	50	NaHCO ₃	DCE (121)	16 (3:1)
9	SIPrAuCl (10)	AgSbF ₆ (10)	50	NaHCO ₃	DCE (60)	NR
10	IMesAuCl (10)	AgSbF ₆ (10)	50	NaHCO ₃	DCE (60)	NR
11	IPrAuCl (5)	AgSbF ₆ (5)	50	NaHCO ₃	DCE (60)	35 (40% BRSM) ^a
12	IPrAuCl (20)	AgSbF ₆ (20)	50	NaHCO ₃	DCE (60)	50 (4.267 only)
13	IPrAuCl (30)	AgSbF ₆ (30)	50	NaHCO ₃	DCE (60)	48 (4.267 only)

^aBRSM = based on recovered starting material

Treatment of oxocene **4.267** with catalytic OsO₄ and stoichiometric NMO at 0 °C gave a single product which was identified as diol **4.276** resulting from reaction at the internal alkene (Scheme 53). Although we were hopeful for a sterically biased reaction at the terminal olefin, the outcome is not surprising due to the potential for a release in ring strain upon oxidation. At this stage, it seemed necessary to revise our retrosynthetic analysis for three main reasons: 1) only limited success in the key cyclization was achieved in the presence of a PMBz protecting group, 2) the desired oxidation regioselectivity was not observed and 3) two-dimensional NMR analysis of the major cyclization product was not completed with 100% confidence. In addition to altering the protecting group, it was essential to regioselectively functionalize the C7 terminal olefin for construction of the enyne side chain. Furthermore, we wished to oxidize the C6 position in such a way that stereoselective reduction could be accomplished later to give the 6*R* alcohol. The Tsuji–Wacker oxidation is known to selectively react at less substituted alkenes yielding methyl ketones.¹⁵⁹ This transformation seemed to satisfy our requirements, allowing regioselective oxidation of C6. Simple enolation of the methyl ketone and electrophilic addition could further functionalize the C7 side chain for elaboration. Two approaches could be taken to address the third issue. In the first approach, the major product from gold(I)-catalyzed alkoxylation would require 2D NMR analysis to establish the structural assignment with 100% certainty. Since we had problems with this approach while using the free C12 alcohol **4.270**, the alternative method of preparing a well characterized, known advanced oxocene intermediate in one of the many laurencin syntheses was preferred. A review of the

laurencin literature for potential candidates revealed Kim's cyanoketone **4.158** as a target molecule. Using the newly proposed two step route for functionalization of oxocene **4.267** described above, we thought that we could easily prepare Kim's cyanoketone **4.158** and compare our experimental spectral data to that reported by Kim and co-workers. Hence, we could firmly establish the structure of oxocene **4.206**. Because of this structural conformation aim, we were forced to choose the benzyl protecting group for the C12 alcohol.

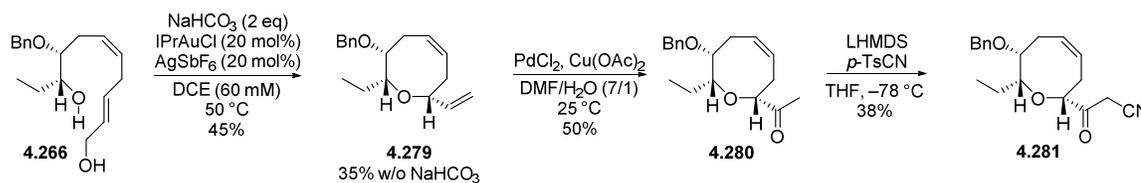
Moving forward, we first needed to test the feasibility of the Wacker oxidation/cyanation via enolation route, which could be accomplished using oxocene **4.267**. Treatment with catalytic PdCl₂ and Cu(OAc)₂ under aqueous conditions provided methyl ketone **4.277** in 42% yield (Scheme 53). The moderate yield was a result of competitive formation of the aldehyde. Allylic ethers are known to have regioselectivity issues under traditional Tsuji–Wacker conditions resulting from coordination of the oxygen atom to the Lewis acidic palladium.¹⁶⁰ Fortunately, this limitation has prompted others to determine alternative Wacker-type oxidation conditions that could potentially give much higher yields of **4.277**.¹⁶¹ Enolation of **4.277** with mild LHMDS followed by TsCN addition smoothly gave methyl ketone in 56% yield. These promising results motivated us to revisit the C12 protection and apply this new route to benzyl ether **4.266** (see Section x for preparation).



Scheme 53: Functionalization of α, α' -*cis*-oxocene **4.267**

After optimization of the route to diol **4.266** (PG = Bn), the optimized conditions from studies using **4.263** (PG = PMBz) were applied to the key cyclization of **4.266**. These conditions (Table 11, entry 12) provided oxocene **4.279** as a single isomer in 45% yield (Scheme 54). Because protecting group migration was not an issue in this case, **4.266** was also subjected to GCA conditions in the absence of NaHCO_3 which gave a 35% yield. This result is perplexing since our hypothesis was that NaHCO_3 served to buffer the cyclization and prevent protecting group migration but that the carbonate also partially quenched the catalyst through strong chelation of the gold metal. If our hypothesis had been correct, an increase in yield would have been observed instead of the 10% decrease. This suggests that the role of NaHCO_3 is more complex than originally thought. Similar to the oxidation of **4.267** (PG = PMBz), treatment of oxocene **4.279** with standard Tsuji–Wacker oxidation conditions gave the methyl ketone **4.280** in 50% yield. Formation of the aldehyde was also

responsible for the moderate yield in this case. Treatment of methyl ketone **4.280** with LHMDS followed by *p*-TsCN successfully gave cyano ketone **4.281** in 38% yield (not optimized). All spectral data (¹H NMR and HRMS) was in agreement with that reported by Kim and co-workers, thus constituting a formal synthesis of (+)-laurencin. Kim's ¹H NMR of cyanoketone **4.281** and Lanier's ¹H NMR of cyanoketone **4.281** are shown in Figures 43 and 44, respectively. Efforts to optimize the formation of methyl ketone with alternative Wacker conditions¹⁶¹ and scale up of the cyanation are ongoing. Once sufficient quantities of methyl ketone **4.280** are obtained, the cyanation will be completed again to obtain enough cyanoketone **4.281** for full spectral characterization including ¹³C NMR, specific rotation and IR. It is also suspected that the isolated yield will increase on the larger reaction scale.



Scheme 54: Gold(I)-catalyzed alkoxylation of monoallylic alcohol 4.266 and further functionalization of α,α' -cis-oxocene 4.279

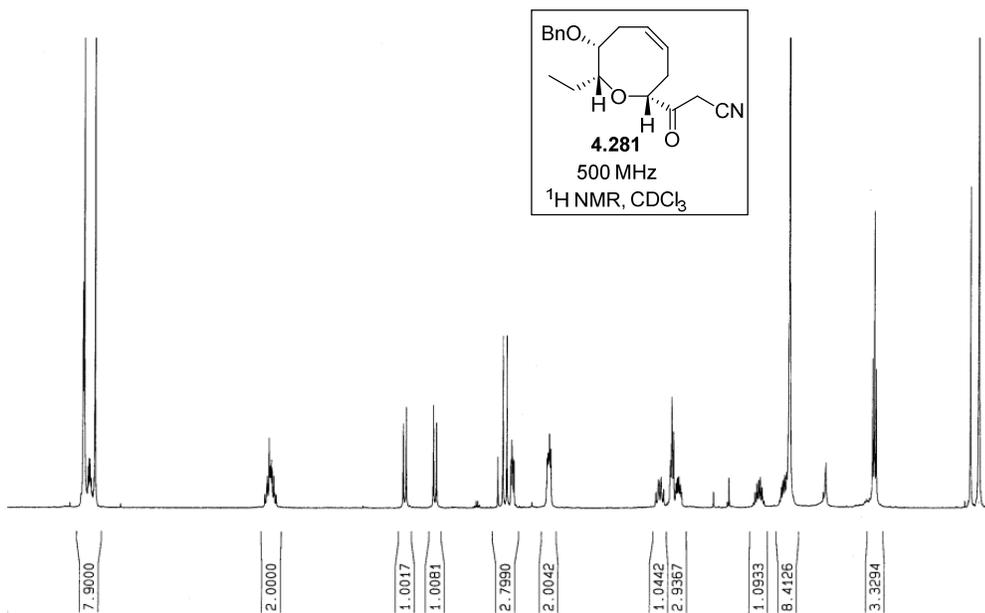


Figure 43: Kim's ¹H NMR of cyanoketone 4.281

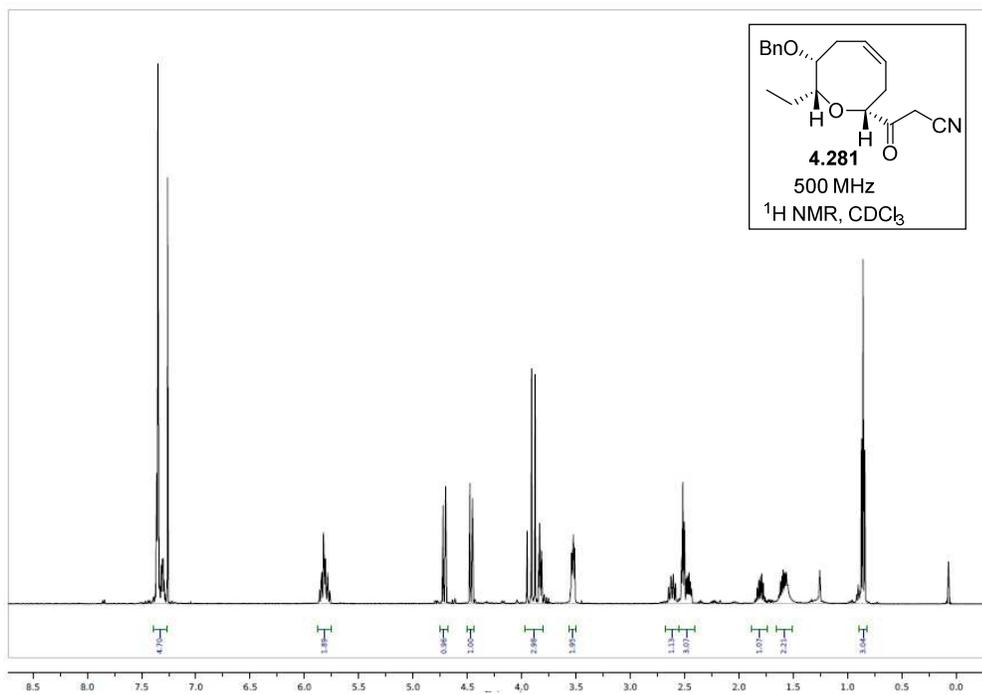
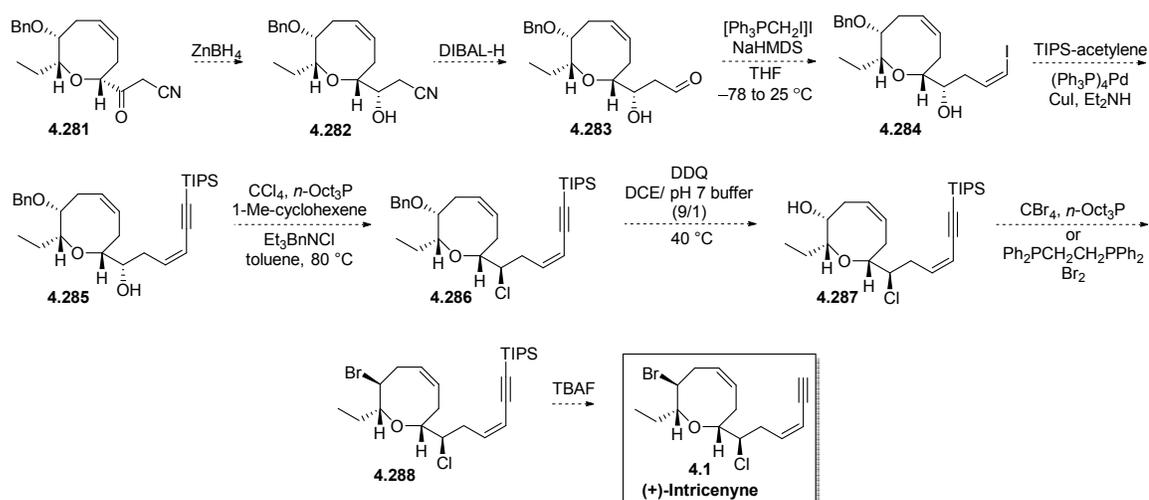


Figure 44: Lanier's ¹H NMR of cyanoketone 4.281

4.2.5 Proposed Plan to Complete the Total Synthesis of (+)-Intricenyne

Our ability to prepare cyanoketone **4.281** and the consistency of its experimental spectral data with literature reports affirm the feasibility of a total synthesis of (+)-intricenyne via gold(I)-catalyzed alkoxylation. Although the total synthesis has yet to be completed, the large volume of reports on similar naturally occurring 7-, 8-, and 9-membered cyclic ethers will allow a well guided pursuit of our target natural product. To complete the synthesis, exposure of cyanoketone **4.281** to ZnBH_4 is expected to selectively provide 6*R* alcohol **4.282** via a chelation induced Felkin–Anh model similar to our originally proposed titanium chelation controlled organolithium addition to aldehyde **4.283** (Section 4.2.1). DIBAL-H reduction^{133g} would provide aldehyde **4.283** for Wittig reaction with Stork’s iodophosphorane and subsequent Sonogashira coupling with TIPS-acetylene to selectively construct the (*Z*)-enyne.^{48, 162} Although other methods are available for the preparation of the (*Z*)-enyne, number of steps¹⁶³ or moderate yield and (*Z*)-olefin selectivity^{162a, 164} are drawbacks. Although the Wittig/Sonogashira approach requires two steps and is a less novel approach, the yields and (*Z*)-olefin selectivity are often high. Should this approach be unsuccessful or a novel approach be desired for publication purposes, other literature methods could be pursued. Crimmins’ protocol for a modified Hooz’s chlorination of homoallylic alcohol **4.285** would give chloride **4.286**.⁴⁸ Crimmins used this protocol to reduce the amount of elimination side product formed during chlorination, which we suspect will also be a potential problem in our chlorination step.

Debenzylation using Kim's conditions in their (+)-laurencin total synthesis^{133g} would then be tested. The isolated yields reported for Hooz's bromination in the context of laurencin synthesis have varied greatly; therefore, testing of several conditions will likely be required and we propose use of either $\text{CBr}_4/\text{Oct}_3\text{P}$ ^{133d, 133g, 133h, 136b} or $\text{Br}_2/\text{Ph}_2\text{CH}_2\text{CH}_2\text{PPh}_2$ ^{133e} since good yields have been reported with those conditions. TIPS deprotection following Kim's report^{133g} would furnish (+)-intricenyne in 19 steps from known (*E*)-2-butene-1,4-diol.



Scheme 55: Proposed route for final steps in the synthesis of (+)-intricenyne

4.3 Summary

In this chapter, current knowledge of (+)-intricenyne (4.1), its sibling natural product, (+)-laurencin (4.5), and other members of the C_{15} non-terpenoid, 8-membered cyclic ether-containing natural products have been discussed. Since 4.1 has no total

syntheses to date, the extensive synthetic studies on preparation of **4.5** have been described and have served as a standard by which to evaluate our synthetic approach to **4.1**.

Experimentally, we have established routes to alkyne **4.236** and epoxide **4.248**. Based on our original retrosynthetic analysis, coupling of these molecules through an alkyne boronate/epoxide opening method has been achieved. Various protecting groups for the homopropagyl alcohol **4.252** have been examined for compatibility with the pivotal gold(I)-catalyzed alkoxylation and subsequent elaboration of the advanced oxocene intermediate **4.206**. Thus far, the benzyl protecting group has given optimal results. Lindlar hydrogenation was employed to install the internal *cis*- Δ^9 olefin and bis-SEM deprotection was accomplished under $\text{MgBr}_2/\text{MeNO}_2$ conditions to provide the diol substrates **4.263** and **4.266** used in the key gold(I)-catalyzed alkoxylation. Interestingly, protecting group migration of **4.263** and thus, suspected oxepine formation was observed under certain cyclization conditions. Adjustment of the GCA conditions allowed suppression of the protecting group migration and yielded target α,α' -*cis*- Δ^9 -oxocene **4.267** as the only intramolecular cyclization product. Although this migration issue hindered progress toward the total synthesis of (+)-intericenyne, the tunability of GCAs has been demonstrated. Furthermore, we now have preliminary evidence that both α,α' -*cis*- and α,α' -*trans*-oxepines can be formed via GCAs. Based on a revised retrosynthetic analysis, the advanced oxocene intermediate **4.266** has been transformed to known cyanoketone (**4.281**), constituting a formal synthesis of (+)-laurencin. The completion of the total synthesis of

4.1 will be accomplished in the near future via an eight step sequence from cyanoketone (4.281) as outlined in section 4.2.5.

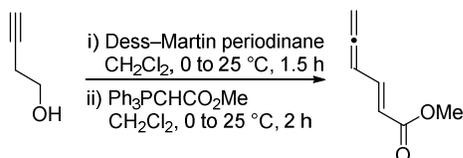
4.4 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. Unless otherwise stated all reagents were purchased from Sigma–Aldrich, Acros, or Fisher and were used without further purification. All solvents were ACS grade or better and used without further purification except tetrahydrofuran (THF) which was freshly distilled from sodium/benzophenone each time before use. Analytical thin layer chromatography (TLC) was performed with glass backed silica gel (60 Å) plates with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel (particle size 230–400 mesh, 60 Å). All ¹H NMR and ¹³C NMR spectrum were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in CDCl₃ by using the signal of residual CHCl₃, as an internal standard. All NMR δ values are given in ppm, and all *J* values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo–Fisher (Nicolet 6700) spectrometer. Optical

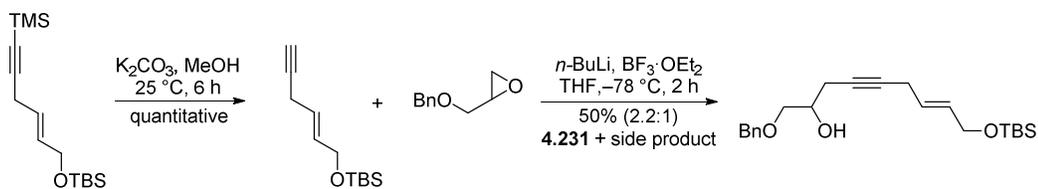
rotation values were measured with a Rudolph Research Analytical (A21102. API/1W) polarimeter.

Attempt to Prepare Methyl Ester 4.218



To a cooled (0 °C) solution of 3-butyn-1-ol (76 mg, 1.08 mmol) in CH₂Cl₂ (10.8 mL, 0.100 M) was added Dess–Martin periodinane (506 mg, 1.19 mmol). After stirring at 25 °C for 1.5 h, the reaction mixture was diluted with pentane and filtered through celite. The resulting solution was cooled (0 °C) and treated with methyl (triphenylphosphoranylidene) acetate (399 mg, 1.19 mmol). After stirring at 25 °C for 2 h, the reaction mixture was concentrated, diluted with a small amount of pentane and filtered through celite. Purification by column chromatography (silica gel, hexanes/EtOAc, 20/1) yielded allene **4.221** as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.18 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.92 (dt, *J* = 10.8, 6.8 Hz, 1H), 5.87 (d, *J* = 15.2 Hz, 1H), 5.03 (d, *J* = 6.4 Hz, 2H), 3.73 (s, 3H).

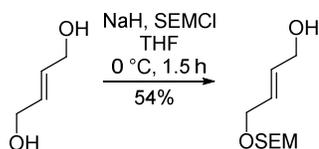
Preparation of Terminal Alkyne **4.220** and Epoxide Coupling



To a solution of TMS-acetylene **4.229** (95 mg, 0.34 mmol) in MeOH (1.6 mL, 0.213 M) was added K_2CO_3 (46 mg, 0.34 mmol). After stirring at 25 °C for 6 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O . The combined organic layers were dried with Na_2SO_4 and carefully concentrated *in vacuo*. The crude terminal alkyne **4.220** was carried forward without further purification: 1H NMR (400 MHz, $CDCl_3$) δ 5.84 (dt, $J = 15.2, 5.2$ Hz, 1H), 5.65 (dt, $J = 15.2, 5.6$ Hz, 1H), 4.16 (d, $J = 5.2$ Hz, 2H), 2.97–2.93 (m, 2H), 2.09 (t, $J = 2.8$ Hz, 1H), 0.90 (s, 9H), 0.06 (s, 6H). To a cooled (-78 °C) solution of terminal alkyne **4.220** in THF (0.5 mL, 0.680 M) was added $n-BuLi$ (2.3 M in hexanes, 0.2 mL, 0.40 mmol). After stirring at -78 °C for 10 min, $BF_3 \cdot OEt_2$ (42 μ L, 0.34 mmol) was added dropwise. After stirring at -78 °C for 10 min, racemic benzyl glycidol ether **4.230** (51 μ L, 0.34 mmol) was added dropwise. After stirring at -78 °C for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracting with $EtOAc$. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/ $EtOAc = 4/1$) yielded a mixture of homopropagyl alcohol **4.231** and unidentified side product as a colorless oil (63 mg, 50%). Further purification by column chromatography (silica gel, hexanes/ $EtOAc = 8/1$) yielded a pure sample of homopropagyl alcohol **4.231**: 1H NMR (400 MHz, $CDCl_3$)

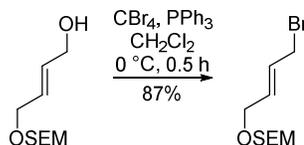
δ 7.37–7.28 (m, 5H), 5.78 (dt, $J = 15.2, 5.2$ Hz, 1H), 5.63 (dt, $J = 15.2, 5.2$ Hz, 1H), 4.57 (s, 2H), 4.15 (d, $J = 4.8$ Hz, 2H), 3.98–3.91 (m, 1H), 3.61 (dd, $J = 9.2, 3.6$ Hz, 1H), 3.50 (dd, $J = 9.6, 6.8$ Hz, 1H), 2.95–2.90 (m, 2H), 2.48–2.44 (m, 2H), 2.41 (br s, 1H), 0.91 (s, 9H), 0.07 (s, 6H).

Preparation of Mono-SEM protected Alcohol **4.233**



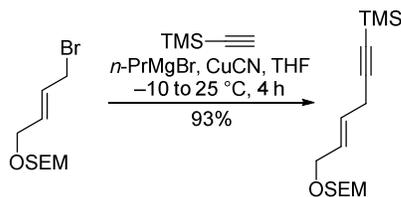
To a cooled solution (0 °C) of *trans*-2-butene-1,4-diol **4.232** (490 mg, 5.56 mmol) in THF (7.2 mL, 0.772 M) was added NaH (267 mg, 6.67 mmol). After stirring at 0 °C for 0.5 h, SEMCl (1.0 mL, 5.56 mmol) was added dropwise. After stirring at 0 °C for 1 h, the reaction was quenched with H₂O and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc, 3/1) yielded the SEM ether **4.233** as a colorless oil (652 mg, 54%): ¹H NMR (400 MHz, CDCl₃) δ 5.92 (dt, $J = 15.6, 5.2$ Hz, 1H), 5.83 (dt, $J = 15.2, 5.6$ Hz, 1H), 4.69 (s, 2H), 4.17 (t, $J = 6.0$ Hz, 2H), 4.09 (d, $J = 5.6$ Hz, 2H), 3.63 (dd, $J = 9.6, 8.8$ Hz, 2H), 1.37 (t, $J = 5.6$ Hz, 1H), 0.95 (dd, $J = 9.6, 8.4$ Hz, 2H), 0.02 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 132.2, 127.4, 94.0, 67.2, 65.2, 62.8, 18.1, -1.5; IR (neat) 3412, 2951, 2879, 1248, 1056, 1027, 835 cm⁻¹; HRMS (ESI) m/z 241.1230 [(M+Na)⁺, C₁₀H₂₂O₃Si requires 241.1230].

Preparation of Bromide 4.234



To a cooled solution ($0\text{ }^\circ\text{C}$) of alcohol **4.233** (674 mg, 3.09 mmol) in CH_2Cl_2 (31.5 mL, 0.098 M) was added CBr_4 (2.047 g, 6.17 mmol) then PPh_3 (1.214 g, 4.63 mmol). The reaction stirred at $25\text{ }^\circ\text{C}$ for 0.5 h before diluting with hexanes. Purification by column chromatography (silica gel, hexanes/EtOAc, 40/1) yielded the bromide **4.234** as a colorless oil (751 mg, 87%): ^1H NMR (400 MHz, CDCl_3) δ 5.97 (dt, $J = 15.2, 7.6$ Hz, 1H), 5.86 (dt, $J = 15.2, 5.2$ Hz, 1H), 4.69 (s, 2H), 4.09 (d, $J = 5.6$ Hz, 2H), 3.97 (d, $J = 7.2$ Hz, 2H), 3.62 (t, $J = 8.4$ Hz, 2H), 0.94 (t, $J = 8.4$ Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 131.4, 128.6, 94.2, 66.6, 65.2, 31.8, 18.1, -1.4 ; IR (neat) 2951, 2881, 1247, 1025, 831, 692, 591 cm^{-1} .

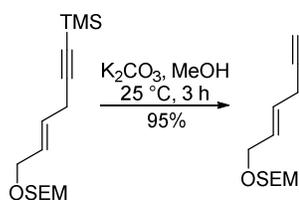
Preparation of TMS-acetylene 4.235



To a cooled solution ($0\text{ }^\circ\text{C}$) of ethynyltrimethylsilane (0.37 mL, 2.58 mmol) in THF (2.1 mL, 1.229 M) was added *n*-propyl magnesium bromide (2.7 mL, 1.087 M in THF). The solution was stirred at $25\text{ }^\circ\text{C}$ for 2h before transferring via cannula to a cooled solution (–

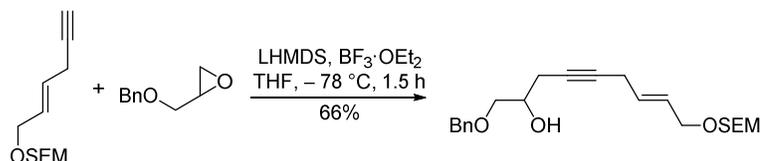
10 °C) of bromide **4.234** (484 mg, 1.72 mmol) and copper cyanide (8 mg, 0.09 mmol) in THF (2.7 mL, 0.637 M). The reaction stirred at 25 °C for 2h before quenching with saturated aqueous NH₄Cl and extracting with ether. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded the TMS-acetylene **4.235** as a colorless oil (477 mg, 93%): ¹H NMR (400 MHz, CDCl₃) δ 5.85 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.70 (dt, *J* = 15.2, 5.2 Hz, 1H), 4.69 (s, 2H), 4.07 (dd, *J* = 5.6, 0.8 Hz, 2H), 3.63 (dd, *J* = 8.8, 8.0 Hz, 2H), 3.02 (dd, *J* = 5.2, 1.6 Hz, 2H), 0.95 (dd, *J* = 8.8, 8.0 Hz, 2H), 0.16 (s, 9H), 0.02 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 127.9, 127.5, 103.4, 94.0, 86.9, 67.3, 65.1, 22.9, 18.1, 0.1, – 1.4; IR (neat) 2954, 2895, 2177, 1248, 1032, 831, 758, 693 cm⁻¹; HRMS (ESI) *m/z* 321.1677 [(M+Na)⁺, C₁₅H₃₀O₂Si₂ requires 321.1677].

Preparation of Alkyne **4.236**



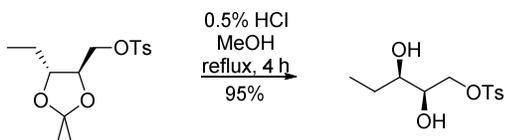
To a solution of TMS-acetylene **4.235** (416 mg, 1.39 mmol) in methanol (6.9 mL, 0.202 M) was added potassium carbonate (193 mg, 1.39 mmol). After stirring at 25 °C for 3 h, the reaction was quenched with saturated aqueous NH₄Cl and extracted diethyl ether. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*.

Coupling of Epoxide 4.230 and Alkyne 4.236



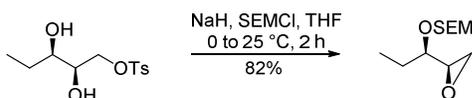
To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of terminal alkyne **4.236** (103 mg, 0.46 mmol) in THF (0.6 mL, 0.767 M) was added LHMDS (1.0 M in THF, 0.5 mL, 0.46 mmol). After stirring at $-78\text{ }^{\circ}\text{C}$ for 10 min, $\text{BF}_3\cdot\text{OEt}_2$ (56 μL , 0.46 mmol) was added dropwise. After stirring at $-78\text{ }^{\circ}\text{C}$ for 10 min, racemic benzyl glycidol ether **4.230** (50 μL , 0.30 mmol) was added dropwise. After stirring at $-78\text{ }^{\circ}\text{C}$ for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracting with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 8/1) yielded homopropargylic alcohol **4.237** as a colorless oil (78 mg, 66%): ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.27 (m, 5H), 5.82 (dt, $J = 15.2, 6.0$ Hz, 1H), 5.70 (dt, $J = 15.2, 5.2$ Hz, 1H), 4.68 (s, 2H), 4.57 (s, 2H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.97–3.91 (m, 1H), 3.65–3.56 (m, 3H), 2.33 (dd, $J = 9.2, 6.4$ Hz, 1H), 2.97–2.92 (m, 2H), 2.48–2.43 (m, 2H), 0.94 (dd, $J = 8.0, 8.0$ Hz, 2H), 0.02 (s, 9H).

Preparation of Diol 4.247



To a solution of tosylate **4.251** (725 mg, 2.31 mmol) in MeOH (6.7 mL, 0.345 M) was added 0.5% aqueous HCl (0.74 mL). The reaction mixture stirred at reflux for 4 h and was then concentrated *in vacuo*. The crude material was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ followed by a brine solution. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. The resulting solid was washed with pentane several times to yield diol **4.247** as a white solid (599 mg, 95%): ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.13 (dd, *J* = 10.4, 5.2 Hz, 1H), 4.05 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.78–3.71 (m, 1H), 3.55–3.48 (m, 1H), 2.46 (s, 3H), 2.43–2.39 (m, 1H), 1.99–1.95 (m, 1H), 1.59–1.50 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H).

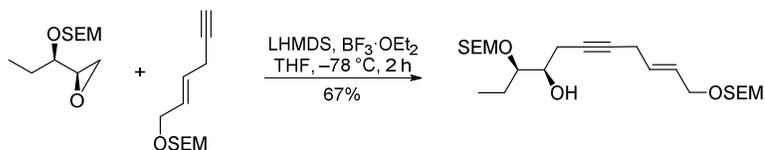
Preparation of α-epoxy SEM Ether 4.248



To a cooled (0 °C) solution of diol **4.247** (103 mg, 0.38 mmol) in THF (3.4 mL, 0.118 M) was added NaH (45 mg, 1.13 mmol) followed by SEMCl (0.1 mL, 0.75 mmol). The reaction was warmed to 25 °C and stirred for 2 h before quenching with saturated aqueous NH₄Cl. The reaction mixture was diluted with H₂O and extracted with diethyl ether. The

combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 20/1) yielded α -epoxy SEM ether **4.248** as a yellow oil (71 mg, 82%): ¹H NMR (400 MHz, CDCl₃) δ 4.89 (d, *J* = 6.8 Hz, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 3.71 (ddd, *J* = 9.6, 9.6, 6.4 Hz, 1H), 3.61 (ddd, *J* = 9.6, 9.6, 6.4 Hz, 1H), 3.24 (dt, *J* = 6.8, 6.4 Hz, 1H), 2.98 (ddd, *J* = 6.8, 4.0, 2.8 Hz, 1H), 2.78 (dd, *J* = 4.8, 4.0 Hz, 1H), 2.54 (dd, *J* = 4.8, 2.8 Hz, 1H), 1.68–1.56 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.99–0.88 (m, 2H), 0.01 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 93.7, 79.0, 65.2, 54.4, 43.7, 25.3, 18.0, 9.9, –1.5; IR (neat) 2951, 2877, 1249, 1107, 1055, 1026, 860, 836 cm⁻¹; HRMS (ESI) *m/z* 255.1383 [(M+Na)⁺, C₁₁H₂₄O₃Si requires 255.1387].

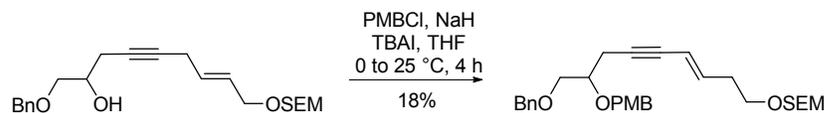
Preparation of Homopropargylic Alcohol **4.252**



To a cooled (–78 °C) of alkyne **2.36** (172 mg, 0.76 mmol) in THF (1.0 mL, 0.760 M) was added LHMDS (1.0 M in THF, 0.8 mL, 0.76 mmol). After stirring for 10 min, BF₃·OEt₂ (94 μ L, 0.76 mmol) was added. After stirring for 10 min, α -epoxy SEM ether **4.248** (118 mg, 0.51 mmol) in THF (0.8 mL, 0.638 M) was added. The reaction mixture stirred for 1.5 h before quenching with saturated aqueous NH₄Cl. The reaction mixture was extracted with EtOAc, the combined organic layers were dried with Na₂SO₄, and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 8/1) yielded

alcohol **4.252** as a colorless oil (157 mg, 67%): $[\alpha]_D^{24} = -29.5$ (c 0.70, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.83 (dt, $J = 15.2, 6.4$ Hz, 1H), 5.70 (dt, $J = 15.2, 5.2$ Hz, 1H), 4.78 (d, $J = 6.8$ Hz, 1H), 4.72 (d, $J = 7.2$ Hz, 1H), 4.67 (s, 2H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.73–3.65 (m, 2H), 3.61 (dd, $J = 8.4, 8.4$ Hz, 3H), 3.51 (dt, $J = 6.8, 5.2$ Hz, 1H), 3.02 (d, $J = 4.4$ Hz, 1H), 2.94–2.89 (m, 2H), 2.47–2.32 (m, 2H), 1.73–1.61 (m, 1H), 1.59–1.48 (m, 1H), 0.99–0.90 (m, 7H), 0.01 (s, 18H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 128.4, 127.5, 95.3, 93.9, 82.7, 78.8, 78.6, 71.2, 67.3, 65.8, 65.1, 24.0, 23.8, 21.9, 18.1, 9.7, $-1.4, -1.5$; IR (neat) 3470, 2953, 2882, 1249, 1057, 1029, 860, 835 cm^{-1} ; HRMS (ESI) m/z 471.2776 [(M+Na) $^+$, $\text{C}_{23}\text{H}_{46}\text{O}_5\text{Si}_2$ requires 471.2776].

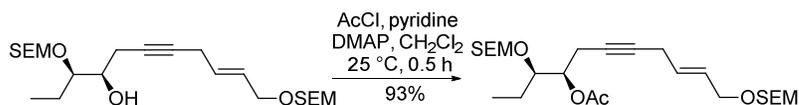
Attempt to Protect Homopropargylic Alcohol **4.237** with PMB



To a cooled (0 °C) solution of homopropargylic alcohol **4.237** (60 mg, 0.15 mmol) in THF (0.7 mL, 0.214 M) was added NaH (9 mg, 0.23 mmol). After stirring for 15 min at 0 °C, TBAI (3 mg, 0.01 mmol) and PMBCl (31 μL , 0.23 mmol) were added. After stirring at 25 °C for 4 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 40/1 to 20/1) yielded **4.253** as a colorless oil (14 mg, 18%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.36–7.30 (m, 5H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 5.90 (dt, $J = 10.8, 6.8$ Hz, 1H), 5.52 (d, $J = 11.2$ Hz,

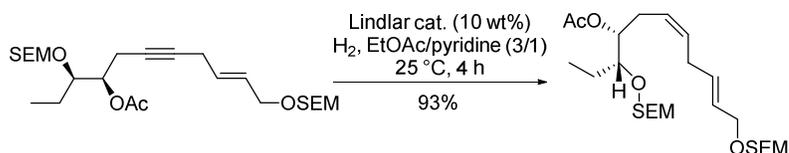
1H), 4.66 (s, 2H), 4.61 (d, $J = 3.6$ Hz, 2H), 4.56 (s, 2H), 3.80 (s, 3H), 3.79–3.72 (m, 1H), 3.67–3.55 (m, 6H), 2.66 (dt, $J = 6.8, 2.0$ Hz, 2H), 2.56 (q, $J = 6.8$ Hz, 2H), 0.94 (dd, $J = 8.0, 8.0$ Hz, 2H), 0.02 (s, 9H).

Preparation of Acetate **4.255**



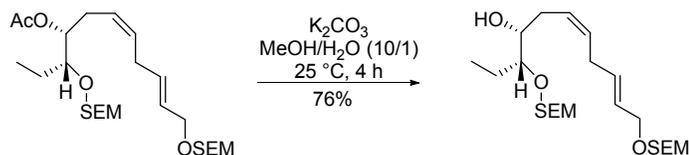
To a solution of alcohol **4.252** (17 mg, 0.04 mmol) in CH₂Cl₂ (0.8 mL, 0.050 M) was added pyridine (4 μL, 0.06 mmol), DMAP (0.5 mg, 0.004 mmol), and acetyl chloride (4 μL, 0.06 mmol) at 25 °C. After stirring for 0.5 h, the reaction mixture was quenched with H₂O and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 8/1) to afford acetate **4.255** a colorless oil (15 mg, 79%): ¹H NMR (400 MHz, CDCl₃) δ 5.81 (dt, $J = 15.2, 6.0$ Hz, 1H), 5.69 (dt, $J = 15.2, 5.2$ Hz, 1H), 5.06 (dt, $J = 6.4, 3.6$ Hz, 1H), 4.78 (d, $J = 6.8$ Hz, 1H), 4.75 (d, $J = 7.2$ Hz, 1H), 4.68 (s, 2H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.76–3.59 (m, 5H), 2.93 (bs, 2H), 2.62–2.45 (m, 2H), 2.09 (s, 3H), 1.66–1.51 (m, 2H), 0.99–0.89 (m, 7H), 0.02 (s, 18H).

Preparation of Diene 4.256



To a solution of acetate **4.255** (15 mg, 0.03 mmol) in EtOAc/pyridine 3/1 (0.1 mL, 0.300 M) was added Lindlar catalyst (2 mg, 10 wt%) at 25 °C. After stirring under a hydrogen atmosphere for 4 h, the reaction was filtered through celite to yield diene **4.256** as a colorless oil (14 mg, 93%): ¹H NMR (400 MHz, CDCl₃) δ 5.70 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.58 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.51 (dt, *J* = 10.8, 6.4 Hz, 1H), 5.42 (dt, *J* = 10.8, 8.0 Hz, 1H), 5.01 (dt, *J* = 8.4, 4.0 Hz, 1H), 4.73 (s, 2H), 4.66 (s, 2H), 4.01 (d, *J* = 6.0 Hz, 2H), 3.71–3.60 (m, 2H), 3.61 (dd, *J* = 8.4, 8.4 Hz, 2H), 3.57–3.49 (m, 1H), 2.82 (dd, *J* = 6.8, 6.0 Hz, 2H), 2.48–2.38 (m, 1H), 2.38–2.29 (m, 1H), 2.06 (s, 3H), 1.62–1.50 (m, 2H), 0.98–0.88 (m, 7H), 0.02 (s, 9H), 0.01 (s, 9H).

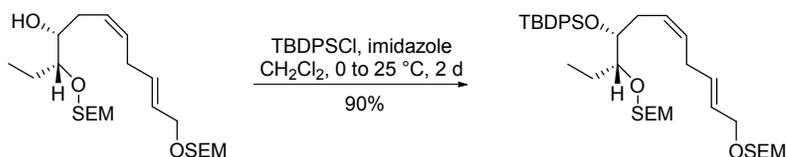
Deacetylation of 4.256



To a solution of acetate **4.256** (108 mg, 0.21 mmol) in MeOH/H₂O (10/1, 2.3 mL, 0.091 M) was added K₂CO₃ (297 mg, 2.15 mmol). After stirring at 25 °C for 4 h, the reaction mixture was concentrated, diluted with H₂O and extracted with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column

chromatography (silica gel, hexanes/EtOAc = 6/1) to afford secondary alcohol **4.259** a colorless oil (75 mg, 76%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.70 (dt, $J = 15.2, 6.0$ Hz, 1H), 5.62–5.50 (m, 3H), 4.81 (d, $J = 6.8$ Hz, 1H), 4.64 (d, $J = 6.8$ Hz, 1H), 4.66 (s, 2H), 4.00 (d, $J = 6.0$ Hz, 2H), 3.74–3.50 (m, 7H), 3.32 (q, $J = 6.0$ Hz, 1H), 2.82 (t, $J = 6.4$ Hz, 2H), 2.27–2.22 (m, 2H), 1.70–1.56 (m, 1H), 1.56–1.40 (m, 1H), 0.98–0.89 (m, 5H), 0.01 (s, 18H).

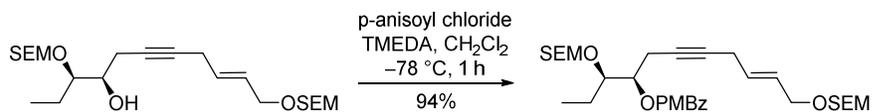
TBDPS Protection of Secondary Alcohol **4.259**



To a cooled (0 °C) solution of secondary alcohol **4.259** (38 mg, 0.08 mmol) in CH_2Cl_2 (0.2 mL, 0.400 M) was added imidazole (11 mg, 0.16 mmol) followed by TBDPSCl (32 μL , 0.12 mmol). After stirring at 25 °C for 2 d, the reaction mixture was quenched with saturated aqueous NaHCO_3 and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 20/1) yielded silyl ether **4.260** as a colorless oil (52 mg, 90%): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.75–7.65 (m, 5H), 7.45–7.33 (m, 5H), 5.61 (dt, $J = 15.2, 6.0$ Hz, 1H), 5.49 (dt, $J = 15.6, 6.0$ Hz, 1H), 5.40 (dt, $J = 10.8, 6.8$ Hz, 1H), 5.31 (dt, $J = 10.0, 7.2$ Hz, 1H), 4.66 (s, 2H), 4.39 (s, 2H), 3.98 (d, $J = 6.0$ Hz, 2H), 3.86–3.80 (m, 1H), 3.62 (t, $J = 8.4$ Hz, 2H), 3.56–3.40 (m, 2H), 3.28–3.22 (m, 2H), 2.64 (t, $J = 6.4$ Hz, 2H),

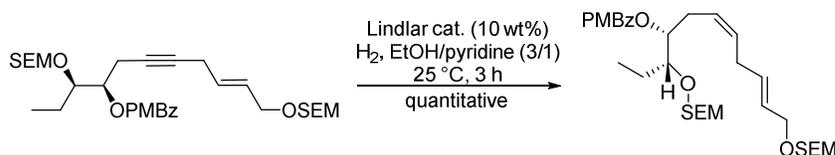
2.30–2.15 (m, 2H), 1.85–1.74 (m, 1H), 1.47–1.35 (m, 1H), 1.06 (s, 9H), 0.94 (t, $J = 8.0$ Hz, 2H), 0.86 (t, $J = 7.2$ Hz, 3H), 0.02 (s, 9H), –0.03 (s, 9H).

Preparation of *p*-Methoxybenzoyl Ether **4.261**



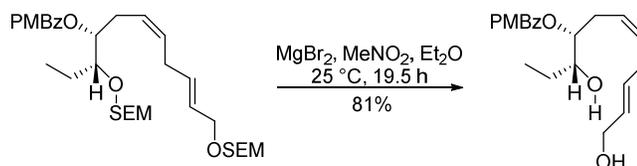
To a cooled (–78 °C) solution of alcohol **4.252** (676 mg, 1.47 mmol) in anhydrous CH₂Cl₂ (13.2 mL, 0.111 M) was added TMEDA (0.24 mL, 1.62 mmol) followed by *p*-methoxybenzoyl chloride (0.24 mL, 1.77 mmol). The reaction mixture was stirred at –78 °C for 1 h before quenching with saturated aqueous NH₄Cl. The reaction mixture was extracted with CH₂Cl₂, the combined organic layers were dried with Na₂SO₄, and concentrated in vacuo. Purification by column chromatography (silica gel, hexanes/EtOAc = 10/1) yielded *p*-methoxybenzoyl ether **4.261** as a colorless oil (824 mg, 94%): ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, $J = 8.4$ Hz, 2H), 6.92 (d, $J = 8.4$ Hz, 2H), 5.79 (dt, $J = 15.2$, 6.0 Hz, 1H), 5.65 (dt, $J = 15.6$, 5.2 Hz, 1H), 5.26 (dt, $J = 6.4$, 4.4 Hz, 1H), 4.82 (d, $J = 7.2$ Hz, 1H), 4.76 (d, $J = 6.8$ Hz, 1H), 4.65 (s, 2H), 3.99 (d, $J = 5.6$ Hz, 2H), 3.86 (s, 3H), 3.87–3.80 (m, 2H), 3.73–3.65 (m, 1H), 3.65–3.58 (m, 3H), 2.90 (br s, 2H), 2.69 (dd, $J = 16.4$, 6.0 Hz, 1H), 2.60 (dd, $J = 16.8$, 6.4 Hz, 1H), 1.68–1.59 (m, 2H), 1.00–0.90 (m, 7H), 0.02 (s, 9H), 0.00 (s, 9H).

Preparation of Diene 4.262



To a solution of *p*-methoxybenzoyl ether **4.261** (824 mg, 1.39 mmol) in EtOH/pyridine 3/1 (6.7 mL, 0.207 M) was added Lindlar catalyst (82 mg, 10 wt%) at 25 °C. After stirring under a hydrogen atmosphere for 3 h, the reaction was filtered through celite to yield diene **4.262** as a colorless oil (826 mg, 100%): ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.65 (dt, *J* = 6.0, 15.2 Hz, 1H), 5.59–5.42 (m, 3H), 5.24 (dt, *J* = 4.6, 8.0 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.64 (s, 2H), 3.95 (d, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 3.71–3.56 (m, 5H), 2.89–2.74 (m, 2H), 2.58–2.40 (m, 2H), 1.70–1.52 (m, 2H), 1.02–0.85 (m, 7H), 0.02 (s, 9H), 0.01 (s, 9H).

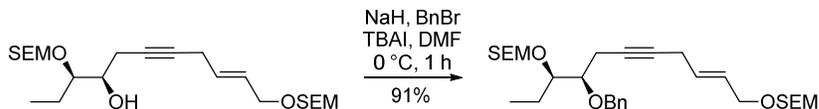
Preparation of Diol 4.263



To a solution of diene **4.262** (826 mg, 1.39 mmol) in diethyl ether (12.9 mL, 0.108 M) was added a solution of magnesium bromide (5.112 g, 27.77 mmol) and nitromethane (3.0 mL, 55.54 mmol) in diethyl ether (12.9 mL). The reaction mixture stirred for 19.5 h at 25 °C before quenching with saturated aqueous H₂O. The reaction mixture was extracted with

CH₂Cl₂, the combined organic layers were dried with Na₂SO₄, and concentrated in vacuo. Purification by column chromatography (silica gel, hexanes/EtOAc = 1/1) yielded diol **4.263** as a colorless oil (374 mg, 81%): $[\alpha]_D^{24} = +9.7$ (*c* 0.64, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.65–5.61 (m, 2H), 5.55–5.47 (m, 2H), 5.08 (ddd, *J* = 7.0, 7.0, 3.5 Hz, 1H), 4.03 (d, *J* = 2.0 Hz, 2H), 3.85 (s, 3H), 3.64 (ddd, *J* = 8.5, 5.0, 3.5 Hz, 1H), 2.88–2.76 (m, 2H), 2.60–2.47 (m, 2H), 2.03 (bs, 2H), 1.60–1.46 (m, 2H), 0.98 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.9, 163.5, 131.7, 130.6, 129.8, 129.5, 125.5, 122.4, 113.6, 75.8, 73.5, 63.5, 55.4, 30.0, 28.7, 26.7, 10.1; IR (neat) 3400, 2936, 1707, 1606, 1512, 1257, 1169, 1103, 1029, 770 cm⁻¹.

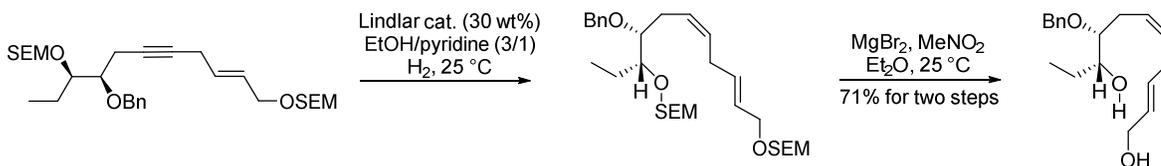
Benylation of Alcohol **4.252**



To a cooled (0 °C) solution of alcohol **4.252** (162 mg, 0.35 mmol) and TBAI (13 mg, 0.04 mmol) in DMF (7.5 mL, 0.047 M) was added NaH (28 mg, 0.71 mmol) followed by BnBr (0.13 mL, 1.06 mmol). After stirring for 1 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 15/1) yielded benzyl ether **4.264** as a colorless oil (177 mg, 91%): $[\alpha]_D^{23} = -15.0$ (*c* 0.97, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.24 (m, 5H), 5.83 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.70 (dt, *J* = 15.2, 5.2 Hz, 1H), 4.77

(d, $J = 7.2$ Hz, 1H), 4.72 (d, $J = 7.2$ Hz, 1H), 4.81 (d, $J = 12.0$ Hz, 1H), 4.67 (s, 2H), 4.50 (d, $J = 12.0$ Hz, 1H), 4.04 (d, $J = 6.0$ Hz, 2H), 3.71–3.57 (m, 6H), 2.97–2.91 (m, 2H), 2.59–2.42 (m, 2H), 1.74–1.60 (m, 1H), 1.60–1.45 (m, 1H), 0.94 (t, $J = 7.2$ Hz, 2H), 0.92 (t, $J = 8.0$ Hz, 2H), 0.85 (t, $J = 7.4$ Hz, 3H), 0.02 (s, 9H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 128.3, 128.2, 127.9, 127.5, 127.4, 94.9, 93.9, 79.6, 79.6, 78.5, 78.1, 72.5, 67.2, 65.2, 65.0, 23.0, 21.8, 20.2, 18.0, 17.9, 10.1, -1.47 , -1.53 .; IR (neat) 2952, 2879, 1249, 1030, 835, 696 cm^{-1} ; HRMS (ESI) m/z 566.3689 $[(\text{M}+\text{NH}_4)^+]$, $\text{C}_{30}\text{H}_{52}\text{O}_5\text{Si}_2$ requires 566.3692].

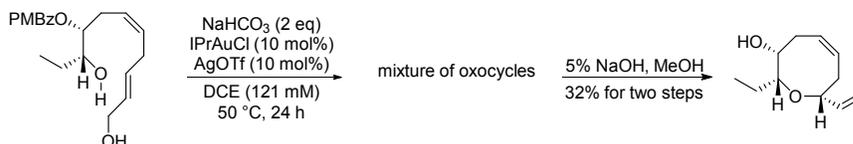
Preparation of Diol 4.266



To a solution of alkyne **4.264** (105 mg, 0.19 mmol) in EtOH/pyridine (3/1, 0.9 mL, 0.211 M) was added Lindlar's catalyst (32 mg, 30 wt%). After stirring under an H₂ atmosphere at 25 °C for 3 h, the reaction mixture was filtered through a pad of celite to afford crude **4.265** as a light yellow oil (105 mg): ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.24 (m, 5H), 5.69 (dt, $J = 15.2, 6.8$ Hz, 1H), 5.61–5.42 (m, 3H), 4.75 (d, $J = 7.2$ Hz, 1H), 4.70 (d, $J = 7.2$ Hz, 1H), 4.67 (s, 2H), 4.61 (d, $J = 11.6$ Hz, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.00 (d, $J = 6.4$ Hz, 2H), 3.71–3.58 (m, 4H), 3.58–3.50 (m, 1H), 3.50–3.45 (m, 1H), 2.81 (t, $J = 6.4$ Hz,

2H), 2.40–2.25 (m, 2H), 1.75–1.64 (m, 1H), 1.55–1.40 (m, 1H), 0.98–0.87 (m, 7H), 0.02 (s, 9H), 0.00 (s, 9H). ^{13}C NMR (125 MHz, CDCl_3) δ 138.7, 132.4, 128.4, 128.2, 127.8, 127.4, 127.3, 126.4, 95.0, 93.8, 80.1, 80.0, 72.4, 67.8, 65.2, 65.0, 30.2, 27.8, 23.0, 18.1, 10.3, –1.4, –1.5; HRMS (ESI) m/z 568.3848 [(M+NH $_4$) $^+$, C $_{30}$ H $_{54}$ O $_5$ Si $_2$ requires 568.3848]. To a solution of crude bis–SEM ether **4.265** (105, 0.19 mg) in Et $_2$ O (1.8 mL, 0.106 M) was added a solution of MgBr $_2$ (702 mg, 3.81 mmol) in Et $_2$ O/MeNO $_2$ (4.4/1, 2.2 mL, 1.732 M). After stirring at 25 °C for 22 h, the reaction mixture was diluted with H $_2$ O and DCM. The layers were separated and the aqueous layer was washed with DCM. The combined organic layers were dried with Na $_2$ SO $_4$ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1) yielded a mixture of diol **4.266** and an overreduction product. Further purification by column chromatography (silica gel, CHCl $_3$ /MeOH = 100/1) yielded diol **4.266** as a colorless oil (40 mg, 71% for two steps): $[\alpha]_D^{24} = -42.2$ (c 0.88, CHCl $_3$); ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.27 (m, 5H), 5.70–5.64 (m, 2H), 5.56–5.49 (m, 2H), 4.80 (d, $J = 11.0$ Hz, 1H), 4.39 (d, $J = 11.0$ Hz, 1H), 4.05 (d, $J = 4.5$ Hz, 2H), 3.44 (ddd, $J = 8.0, 4.4, 4.4$ Hz, 1H), 3.34 (dt, $J = 5.6, 5.2$ Hz, 1H), 2.87–2.78 (m, 2H), 2.47 (ddd, $J = 14.8, 6.0, 6.0$ Hz, 1H), 2.36 (ddd, $J = 14.8, 5.2, 5.2$ Hz, 1H), 2.16 (bs, 2H), 1.60–1.45 (m, 2H), 0.95 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.2, 130.6, 129.5, 129.1, 128.4, 127.8, 127.7, 126.2, 81.1, 73.7, 72.3, 63.5, 30.1, 28.2, 26.5, 10.1; IR (neat) 3389, 2933, 1455, 1070, 972, 737, 698 cm^{-1} ; HRMS (ESI) m/z 313.1776 [(M+Na) $^+$, C $_{18}$ H $_{26}$ O $_3$ requires 313.1774].

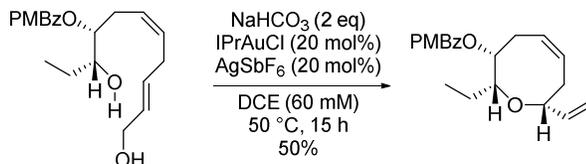
Experiments for Identification of Oxocene 4.270



A suspension of IPrAuCl (29.9 mg, 0.05 mmol), AgOTf (12.4 mg, 0.05 mmol), NaHCO₃ (81 mg, 0.96 mmol), and diol **4.263** (161 mg, 0.48 mmol) in 1,2-dichloroethane (4.0 mL, 0.120 M) in a sealed tube was stirred at 50 °C for 24 h. The resulting suspension was cooled to room temperature, filtered through a short silica gel plug, and eluted with EtOAc. Purification by column chromatography (silica gel, hexanes/EtOAc = 10/1) yielded a mixture of oxocycles as a colorless oil (74 mg). To the mixture of oxocycles (74 mg, 0.23 mmol) was added a solution of 5% NaOH in MeOH (8.2 mL, 0.028 M). After stirring at 25 °C for 19 h, the reaction mixture was concentrated, diluted with EtOAc and washed with H₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 8/1) yielded alcohol **4.270** as a colorless oil (28 mg, 32% for two steps): $[\alpha]_D^{24} = -51.8$ (*c* 0.38, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 5.87 (ddd, *J* = 17.5, 10.5, 5.5 Hz, 1H), 5.84–5.73 (m, 2H), 5.25 (d, *J* = 17.5 Hz, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 3.94–3.91 (m, 1H), 3.69 (ddd, *J* = 9.5, 4.5, 2.0 Hz, 1H), 3.47 (ddd, *J* = 9.5, 4.5, 1.5 Hz, 1H), 2.56 (ddd, *J* = 12.5, 9.5, 9.0 Hz, 1H), 2.38–2.27 (m, 3H), 1.89 (bs, 1H), 1.70 (dq, *J* = 9.5, 7.5 Hz, 1H), 1.45 (dq, *J* = 7.5, 4.5 Hz, 1H), 0.93 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.0, 129.3, 129.1, 114.5,

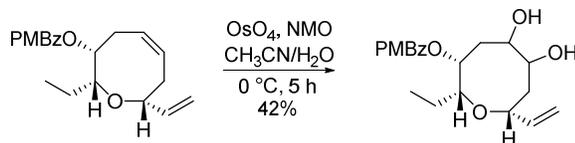
82.3, 81.1, 74.4, 33.9, 33.6, 25.9, 10.5; IR (neat) 3438, 3017, 2963, 2932, 1069, 911, 730 cm^{-1} ; HRMS (ESI) m/z 205.1202 $[(M+Na)^+]$, $\text{C}_{11}\text{H}_{18}\text{O}_2$ requires 205.1199].

Gold(I)-Catalyzed Alkoxylation to Prepare *cis*-Oxocene **4.267**



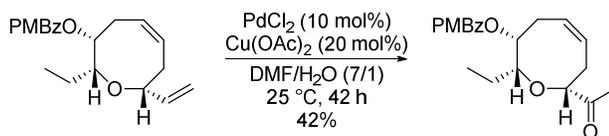
A suspension of IPrAuCl (6.3 mg, 0.01 mmol), AgSbF₆ (3.5 mg, 0.01 mmol), NaHCO₃ (8.5 mg, 0.10 mmol), and diol **4.263** (17 mg, 0.05 mmol) in 1,2-dichloroethane (0.9 mL, 0.056 M) in a sealed tube was stirred at 50 °C for 15 h. The resulting suspension was cooled to room temperature, filtered through a short silica gel plug, and eluted with EtOAc. Purification by column chromatography (silica gel, hexanes/EtOAc = 10/1) yielded α,α' -*cis*-oxocene **4.267** as a colorless oil (8 mg, 50%): $[\alpha]_{\text{D}}^{24} = -88.2$ (c 0.40, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, $J = 9.2$ Hz, 2H), 6.91 (d, $J = 9.2$ Hz, 2H), 5.97 (ddd, $J = 5.4, 10.8, 16.0$ Hz, 1H), 5.95–5.86 (m, 1H), 5.85–5.75 (m, 1H), 5.31 (d, $J = 17.6$ Hz, 1H), 5.18–5.10 (m, 2H), 3.86 (s, 3H), 3.81 (dd, $J = 5.4, 10.2$ Hz, 1H), 3.68 (dt, $J = 3.2, 9.6$ Hz, 1H), 2.87 (ddd, $J = 11.0, 11.0, 11.0$ Hz, 1H), 2.59–2.49 (m, 1H), 2.38 (ddd, $J = 5.8, 11.6, 17.6$ Hz, 1H), 2.19 (dd, $J = 8.2, 14.2$ Hz, 1H), 1.66–1.54 (m, 1H), 1.44–1.32 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.0, 163.3, 139.6, 131.8, 130.3, 128.5, 122.8, 114.3, 113.5, 83.3, 82.3, 77.1, 55.4, 34.9, 29.5, 25.6, 10.6; IR (neat) 3018, 2963, 2936, 1708, 1606, 1511, 1255, 1167, 1102, 770 cm^{-1} .

Oxidation of Diene 4.267



To a cooled ($0\text{ }^\circ\text{C}$) of diene **4.267** (17 mg, 0.05 mmol) in CH_3CN (0.1 mL, 0.500 M) was added a solution of OsO_4 in H_2O (0.5 wt% in H_2O , 0.17 mL, 0.005 mmol) followed by NMO (19 mg, 0.16 mmol). After stirring at $0\text{ }^\circ\text{C}$ for 5 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 . The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 2/1 to 1/1) yielded diol **4.276** as a colorless oil (8 mg, 42%): ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 5.89 (ddd, $J = 16.4$, 10.4, 4.8 Hz, 1H), 5.47 (dd, $J = 4.0$, 4.0 Hz, 1H), 5.44 (dd, $J = 4.4$, 4.0 Hz, 1H), 5.34 (d, $J = 17.6$ Hz, 1H), 5.13 (d, $J = 10.4$ Hz, 1H), 4.23–4.15 (m, 1H), 4.15–4.04 (m, 2H), 3.86 (s, 3H), 3.62–3.56 (m, 1H), 2.32 (ddd, $J = 15.2$, 10.8, 4.8 Hz, 1H), 2.13–1.94 (m, 3H), 1.71–1.63 (m, 2H), 1.00 (t, $J = 7.6$ Hz, 3H).

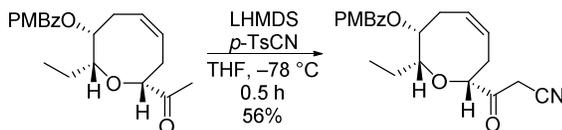
Preparation of Methyl Ketone 4.277



To a solution of oxocene **4.267** (18 mg, 0.06 mmol) in $\text{DMF}/\text{H}_2\text{O}$ (7/1, 0.6 mL, 0.100 M) was added PdCl_2 (1.0 mg, 0.006 mmol) and $\text{Cu}(\text{OAc})_2$ (2.1 mg, 0.01 mmol). After stirring

under aerobic conditions for 2 d at 25 °C, the reaction mixture was diluted with H₂O and extracted with Et₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 5/1) yielded methylketone **4.278** as a colorless oil (8 mg, 42%): ¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.95–5.80 (m, 2H), 5.18 (ddd, *J* = 7.6, 5.2, 2.8 Hz, 1H), 3.87 (s, 3H), 3.73 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.70–3.65 (m, 1H), 2.81 (q, *J* = 10.8 Hz, 1H), 2.58–2.39 (m, 3H), 2.36 (s, 3H), 1.72–1.60 (m, 1H), 1.57–1.44 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H).

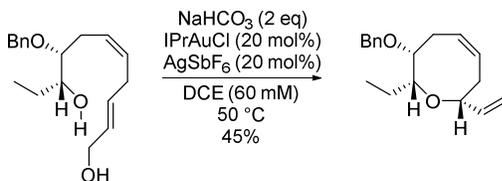
Preparation of Cyanoketone **4.278**



To a cooled (–78 °C) solution of methyl ketone **4.277** (8 mg, 0.02) in THF (0.2 mL, 0.100 M) was added LHMDS (1.0 M in THF, 29 μL, 0.03 mmol). After stirring at –78 °C for 0.5 h, a solution of *p*-TsCN (9 mg, 0.05 mmol) in THF (0.5 mL, 0.100 M) was added. After stirring for 30 min, the reaction mixture was quenched with NH₄OH, acidified with 1 M HCl and extracted with EtOAc. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 4/1) yielded cyanoketone **4.278** as a colorless oil (5 mg, 56%): ¹H NMR (500 MHz, CDCl₃) δ 8.01 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 5.93–5.83 (m, 2H), 5.18 (ddd, *J* = 7.2, 5.2, 2.4 Hz, 1H), 3.97 (d, *J* = 20.0 Hz, 1H), 3.92–3.89 (m, 2H), 3.86 (s, 3H), 3.83

(d, $J = 20.0$ Hz, 1H), 3.73–3.67 (m, 1H), 2.72 (q, $J = 10.4$ Hz, 1H), 2.60–2.49 (m, 2H), 2.49–2.40 (m, 1H), 1.72–1.58 (m, 1H), 1.58–1.47 (m, 1H), 0.87 (t, $J = 7.6$ Hz, 3H).

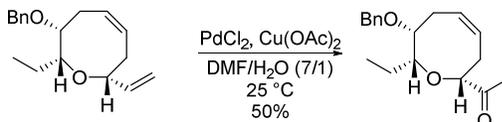
Gold(I)-Catalyzed Alkoxylation to Prepare *cis*-Oxocene **4.279**



A suspension of IPrAuCl (24 mg, 0.04 mmol), AgSbF₆ (13 mg, 0.04 mmol), NaHCO₃ (33 mg, 0.39 mmol), and diol **4.266** (57 mg, 0.20 mmol) in 1,2-dichloroethane (3.3 mL, 0.061 M) in a sealed tube was stirred at 50 °C for 20 h. The resulting suspension was cooled to room temperature, filtered through a short silica gel plug, and eluted with EtOAc. Purification by column chromatography (silica gel, hexanes/EtOAc = 10/1) yielded α,α' -*cis*-oxocene **4.279** as a colorless oil (24 mg, 45%): $[\alpha]_{\text{D}}^{24} = -45.7$ (c 0.41, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.24 (m, 5H), 5.98 (ddd, $J = 17.2, 10.4, 5.6$ Hz, 1H), 5.84 (dt, $J = 10.4, 7.6$ Hz, 1H), 5.69 (dt, $J = 10.4, 8.8$ Hz, 1H), 5.22 (d, $J = 17.2$ Hz, 1H), 5.04 (d, $J = 10.8$ Hz, 1H), 4.82 (d, $J = 12.0$ Hz, 1H), 4.36 (d, $J = 12.0$ Hz, 1H), 3.74 (dd, $J = 10.0, 5.6$ Hz, 1H), 3.50 (dt, $J = 9.6, 3.2$ Hz, 1H), 3.44 (ddd, $J = 10.8, 5.2, 2.8$ Hz, 1H), 2.73 (ddd, $J = 11.2, 10.8, 10.8$ Hz, 1H), 2.55–2.46 (m, 1H), 2.39 (ddd, $J = 12.4, 5.6, 5.6$ Hz, 1H), 2.12 (dd, $J = 14.0, 8.4$ Hz, 1H), 1.83–1.70 (m, 1H), 1.41–1.30 (m, 1H), 0.88 (t, $J = 7.6$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.9, 138.8, 129.8, 129.3, 128.2, 127.9, 127.4, 113.9, 83.3,

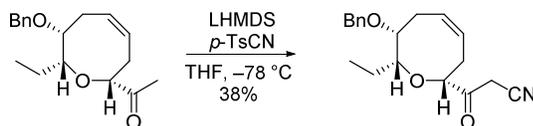
83.0, 81.3, 71.2, 35.0, 29.2, 25.8, 10.7; IR (neat) 2930, 2873, 1454, 1072, 729, 698 cm^{-1} ;
HRMS (ESI) m/z 273.1849 [(MH)⁺, C₁₈H₂₄O₂ requires 273.1849].

Preparation of Methyl Ketone 4.280



To a solution of oxocene **4.279** (13 mg, 0.05 mmol) in DMF/H₂O (7/1, 0.5 mL, 0.100 M) was added PdCl₂ (0.9 mg, 0.005 mmol) and Cu(OAc)₂ (1.7 mg, 0.01 mmol). After stirring under aerobic conditions for 2 d at 25 °C, the reaction mixture was diluted with H₂O and extracted with Et₂O. The combined organic layers were dried with Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 6/1) yielded methylketone **4.280** as a colorless oil (7 mg, 50%): $[\alpha]_D^{24} = +58.1$ (*c* 0.18, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.38–7.27 (m, 5H), 5.84 (dt, *J* = 10.4, 8.0 Hz, 1H), 5.74 (ddd, *J* = 10.4, 6.4, 1.6 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 3.63 (dd, *J* = 10.0, 2.4 Hz, 1H), 3.54–3.47 (m, 2H), 2.69 (ddd, *J* = 11.6, 10.4, 10.4 Hz, 1H), 2.54–2.37 (m, 3H), 2.32 (s, 3H), 1.88–1.77 (m, 1H), 1.58–1.48 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 210.2, 138.4, 129.7, 129.0, 128.3, 127.9, 127.6, 87.8, 84.7, 81.0, 71.5, 31.2, 29.0, 26.8, 25.6, 10.8; IR (neat) 2965, 1717, 1455, 1352, 1087, 726, 698 cm^{-1} ; HRMS (ESI) m/z 311.1618 [(M+Na)⁺, C₁₈H₂₄O₃ requires 311.1618].

Preparation of Cyanoketone 4.281



To a cooled ($-78\text{ }^{\circ}\text{C}$) solution of methyl ketone **4.280** (7 mg, 0.02) in THF (0.2 mL, 0.100 M) was added LHMDS (1.0 M in THF, 29 μL , 0.03 mmol). After stirring at $-78\text{ }^{\circ}\text{C}$ for 0.5 h, a solution of *p*-TsCN (9 mg, 0.05 mmol) in THF (0.5 mL, 0.100 M) was added. After stirring for 15 min, the reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc = 6/1) yielded cyanoketone **4.281** as a colorless oil (3 mg, 38%): $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.37–7.28 (m, 5H), 5.86–5.77 (m, 2H), 4.71 (d, $J = 12.0\text{ Hz}$, 1H), 4.47 (d, $J = 11.5\text{ Hz}$, 1H), 3.92 (d, $J = 20.0\text{ Hz}$, 1H), 3.86 (d, $J = 20.5\text{ Hz}$, 1H), 3.83 (dd, $J = 7.5, 5.0\text{ Hz}$, 1H), 3.55–3.51 (m, 2H), 2.61 (ddd, $J = 11.5, 10.0, 10.0\text{ Hz}$, 1H), 2.54–2.49 (m, 2H), 2.49–2.43 (m, 1H), 1.85–1.74 (m, 1H), 1.63–1.53 (m, 1H), 0.86 (t, $J = 7.5\text{ Hz}$, 3H); HRMS (ESI) m/z 336.1571 [$(\text{M}+\text{Na})^+$, $\text{C}_{19}\text{H}_{23}\text{NO}_3$ requires 336.1570].

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Biography

Megan L. Lanier was born on May 3, 1988 in Hammond, Louisiana. She earned her Bachelor Science degree in Chemistry in May of 2010 from the department of chemistry and physics at Southeastern Louisiana University. In the fall of 2010, she began her graduate career at Duke University and received her Doctor of Philosophy in organic chemistry in April of 2015.

Honors and Awards

- C. R. Hauser Memorial Fellowship for outstanding fourth year student in organic chemistry, Duke University, Department of Chemistry, 2014
- Pharmacological Science Training Program Fellowship for interdisciplinary training, Duke University, Department of Pharmacology and Cancer Biology, 2011–2013
- Walter H. Corkern Scholarship & Award for academic excellence in organic chemistry, Southeastern Louisiana University, Department of Chemistry and Physics, 2009–2010
- Gladys Anderson Emerson Scholarship for excellence in chemistry, Iota Sigma Pi – National Honor Society for Women in Chemistry, 2009

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