I. Catalytic Redox-Initiated Glycolate Aldol Additions of Silyl Glyoxylates

II. Diastereoselective De Novo Synthesis of Pentasubstituted γ-Butyrolactones From Silyl Glyoxylates and Ketones Via Double Reformatsky Reactions

III. Progress Toward the Total Synthesis of Leustroducsin B

Stephen Nathaniel Greszler

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

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ABSTRACT

STEPHEN NATHANIEL GRESZLER

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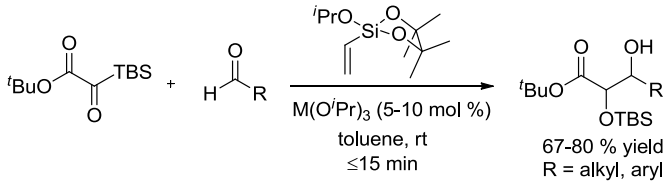
II. Diastereoselective De Novo Synthesis of Pentasubstituted γ-Butyrolactones From Silyl Glyoxylates and Ketones Via Double Reformatsky Reactions

III. Progress Toward the Total Synthesis of Leustroducsin B

(under the direction of Professor Jeffrey S. Johnson)

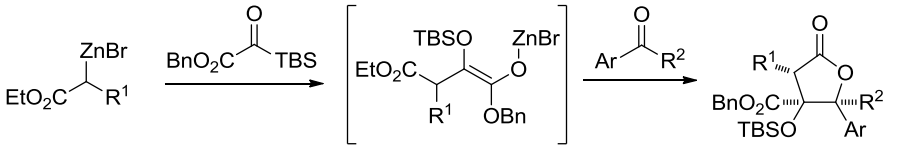
I. Catalytic Redox-Initiated Glycolate Aldol Additions of Silyl Glyoxylates

An investigation of the reaction parameters necessary for achieving a catalytic redox-initiated glycolate aldol addition of silyl glyoxylates and metal alkoxides was performed. The reaction achieved catalytic turnover through the use of strain-release Lewis acidic silacycles, which effectively mediated the necessary alkoxide metathesis in the turnover step. Lanthanide (III) isopropoxides were found to be effective catalysts in this reaction, and praseodymium (III) isopropoxide in particular resulted in full conversion of the silyl glyoxylates in under five minutes. Preliminary efforts toward imparting asymmetry in the title reaction were also performed.



II. Diastereoselective De Novo Synthesis of Pentasubstituted γ-Butyrolactones From Silyl Glyoxylates and Ketones Via Double Reformatsky Reactions

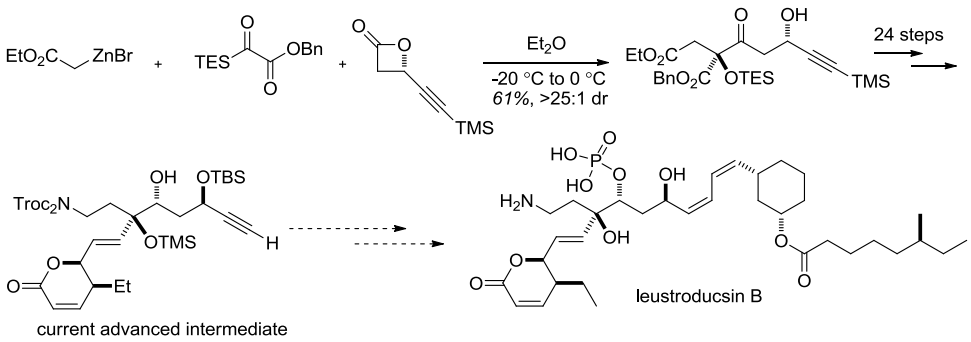
The development of a double Reformatsky reaction cascade from Reformatsky reagents, silyl glyoxylates, and aldehydes/ketones is discussed. The reaction affords highly substituted γ-butyrolactones with an unexpectedly high level of diastereoselectivity when alkyl-aryl ketones are used as the terminating electrophiles. The use of monosubstituted Reformatsky reagents was determined to be necessary to achieve a high degree of diastereoselectivity, and a boat-like transition state model was proposed to account for the production of the major diastereomers. Several secondary transformations added to the synthetic utility of the lactone products.



up to 73% yield
up to ≥ 25:1 dr

III. Progress Toward the Total Synthesis of Leustroducsin B

Progress toward the total synthesis of leustroducsin B is presented. The synthesis commenced with an unprecedented three-component coupling reaction of silyl glyoxylates, Reformatsky reagents, and enantioenriched β-lactones. The resulting Reformatsky/Claisen reaction cascade affords β-hydroxyketone products with greater than 25:1 diastereomeric ratio. Strategies for the introduction of the dihydropyrone are discussed, along with the challenges faced in the functionalization of advanced intermediates. The optimized synthetic route to the advanced intermediate shown is presented as well as a discussion of projected endgame strategies.


EtO2C
ZnBr
TES
OBn
TMS
Et2O
-20 °C to 0 °C
61%, >25:1 dr
EtO2C
BnO2C
OTES
OH
TMS
24 steps
Troc2N
OH
OTBS
OTMS
H
Et
current advanced intermediate
HO
P
HO
H2N
OH
OH
leustroducsin B

ACKNOWLEDGEMENTS

Throughout my graduate career, I have been extremely grateful for all of the direct and indirect support I have received from my family, friends, and coworkers. I must first acknowledge my advisor, Professor Jeff Johnson. Jeff has been an excellent boss and mentor, and I'm still amazed after five years at the level of knowledge and creativity he possesses and at the fact that he's been able to remain so humble and engaged as his profile has grown. I've always appreciated Jeff's open-door policy, and I can't think of an occasion where he seemed unwilling or unable to offer assistance when I've come to him with a questions or problems, no matter how foolish they may have been. The value of an advisor as reassuring and enthusiastic as Jeff cannot be overstated, and I know that I absolutely made the right choice in joining the Johnson group.

I would like to thank Professors Marcey Waters, Maurice Brookhart, Dave Nicewicz, and Erik Alexanian for serving on my final defense committee, as well as Professors Michel Gagné and Joe Templeton for serving on my preliminary defense committee.

I have had the privilege of working with extremely talented and ambitious people over the years, and we've always had a close-knit group regardless of roster. It has been easy to come to work knowing that there will never be a dull moment and that even if you have a bad day, everyone will be there to remind you that they're "in your corner."

For always maintaining a work environment that was both scientifically engaging and entertaining, I thank former and current group members: Becca Duenes, Matthew Campbell, Shanina Sanders, Andy Satterfield, Chris Tarr, Andrew Parsons, Austin Smith, Mike Slade, Dan Schmitt, Greg Boyce, Kim Steward, Justin Malinowski, Michael Corbett, and Do Dung. Positioned in the middle lab, I have appreciated the hightened level of traffic and have gotten to know most of the current and former group members well. In particular, I would like to acknowledge former middle labmates Matthew Campbell and Becca Duenes, who have been great friends and who always made sure the middle lab was filled with "good times and great oldies." I'd also like to thank the current members of Clown Town: Greg Boyce, Justin Malinowski, Adam Gray, and Kimberly Steward for helping the room live up to its nickname and for always providing a source of entertainment. Additional gratitude goes out to the "leustroduction" crew, Justin Malinowski and Adam Gray, without whose help the synthesis certainly wouldn't have progressed as much as it did.

Enough cannot be said about the support I have received from my family. I have been lucky to have my grandmother, Geraldine Tobias, within a short distance of here, and I thank her for providing Sunday dinners, for her company, and for always showing an interest in my work. I also want to acknowledge my siblings, Cristina Greszler, Craig Greszler, and Melanie Stock, to whom I have surprisingly grown closer even as we have all become busier and moved further apart. Finally, I really can't say enough about the love and support I have received from my parents. This is likely the last of my formal education, and I owe a sincere

debt of gratitude to my mother and father, Martha Stock and Alan Greszler, who have for as long as I can remember been incredibly supportive of me and my schooling. At every point throughout the long journey I have taken to get here, they have instilled in me the value of education and helped to make sure I've stayed the same person. Even though they don't always understand what I am working on, I can always feel how genuinely proud they are of me. I am not often good at expressing my appreciation for them, but it's something words really cannot explain. This work is dedicated more to them than anyone else.

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2D-NMR	two-dimensional nuclear magnetic resonance
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetate
Alloc	allyloxycarbonyl
AOM	*p*-anisyloxymethyl
Ar	aryl
aq	aqueous
atm	atmospheres
BAIB	[bis(acetoxy)iodo]benzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BPO	benzoylperoxide
BOC	benzyloxycarbonyl
br	broad
br s	broad singlet
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
C–C	carbon-carbon bond

cat	catalytic amount or catalyst
COD	cyclooctadiene
conv	conversion
COSY	correlated spectroscopy
Cp	cyclopentadienyl
*m*CPBA	*meta*-chloroperoxybenzoic acid
CSF	colony stimulating factor
d	doublet or days
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
dd	doublet of doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
ddt	doublet of doublet of triplets
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DIBAL–H	diisobutylaluminum hydride
DIEA	ethyldiisopropylamine
dq	doublet of quartet
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio

dt	doublet of triplet
E	*entgegen*
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
E^+ or El	electrophile
endo	endocyclic
eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
exo	exocyclic
FID	flame ionization detector
GI	Grubbs' first generation catalyst
GII	Grubbs' second generation catalyst
H-GI	Hoveyda-Grubbs' first generation catalyst
H-GII	Hoveyda-Grubbs' second generation catalyst
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
n-hexanal	*normal*-hexanal
HOAc	acetic acid

HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
Ipc	isopinocampheyl
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
L or Ln	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
Menth	menthyl
MeOH	methanol
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz

MIB	3-*exo*-morpholinoisoborneol
min	minutes
mL	milliliter
mmol	millimole
mp	melting point
MPM	*para*-methoxybenzyl
MPV	Meerwein-Ponndorf-Verley
n	number of atoms or counterions
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NBSH	*o*-nitrobenzenesulfonylhydrazide
nd	not determined
NHK	Nozaki-Hiyama-Kishi
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
nr	no reaction
Nu	nucleophile
OO	Oppenauer Oxidation
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl

pin	pinacolato
ppm	parts per million
PPTS	pyrdinium *p*-toluenesulfonate
^{i}Pr	*iso*-propyl
q	quartet
R	substituent
R_f	retention factor
rac	racemic
RCHO	aldehyde
RCM	ring-closing metathesis
rt	room temperature
s	singlet
^{29}Si NMR	proton nuclear magnetic resonance spectroscopy
SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
T	temperature
t	triplet
$t_{1/2}$	half-life
t_r	retention time
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate

TC	thiophenecarboxylate
TEA	triethylamine
Teoc	(2-trimethylsilyl)ethyloxycarbonyl
TEMPO	tetramethylpiperidine-*N*-oxide
TES	triethylsilyl
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	trityl or triphenylmethyl
triflate	trifluoromethanesulfonate
Troc	Trichloroethyloxycarbonyl
Ts	*para*-toluenesulfonyl
UV	ultraviolet
X	anionic ligand, halide, substituent, or number
X_c^*	chiral auxiliary
Z	*zusammen*
Å	Ångstrom
[α]	optical rotation
δ	chemical shift or partial charge
μL	microliter

CHAPTER ONE

CATALYTIC REDOX-INITIATED GLYCOLATE ALDOL ADDITIONS OF SILYL GLYOXYLATES*

1.1 Introduction

Reaction efficiency and atom economy have increasingly moved toward the forefront of organic synthesis, and monetary and ecological costs have spurred the development of unique strategies to address the waste associated with complex synthetic transformations. Among the recent developments in this area are bimolecular reactions that achieve dual symbiotic activation of both reaction partners. Examples of this unusual reactivity mode include carbonyl allylations initiated by formal H_2 redistribution[1-3] and aldol reactions[4] initiated by redox reactions between silyl glyoxylates[5] and magnesium alkoxides.[6] In the latter studies, a limitation that emerged was the absence of a turnover mechanism, which resulted in the need for a stoichiometric metal species. This initial chapter delineates reaction parameters that were determined to be essential for enabling catalysis of that process. We specifically discuss the use of strain-release Lewis acidic siloxanes in facilitating alkoxide metathesis in the turnover step and present preliminary results on the potential for inducing asymmetry.

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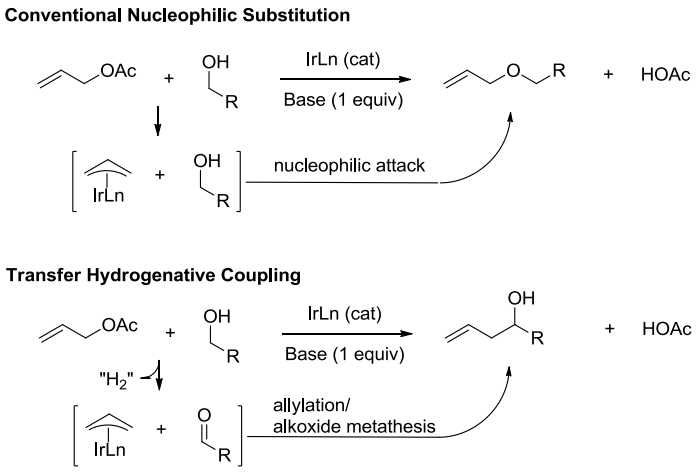
1.2 Background

1.2.1 Symbiotic Activation in Carbonyl Allylation

Symbiotic reagent activation offers new opportunities for intermolecular coupling reactions that overcome the conventional limitations imposed by oxidation state. Recent developments in this area now permit the synthesis of carbonyl allylation[1-2] and alkylation[3] products from the alcohol level, transformations that were previously restricted to the parent aldehyde or ketone. In 2008 Krische reported an enantioselective iridium-catalyzed carbonyl allylation from the alcohol oxidation state using allyl acetate as an allyl metal surrogate.[1]

Figure 1-1. Variable Modes of Alcohol Reactivity with Iridium Complexes

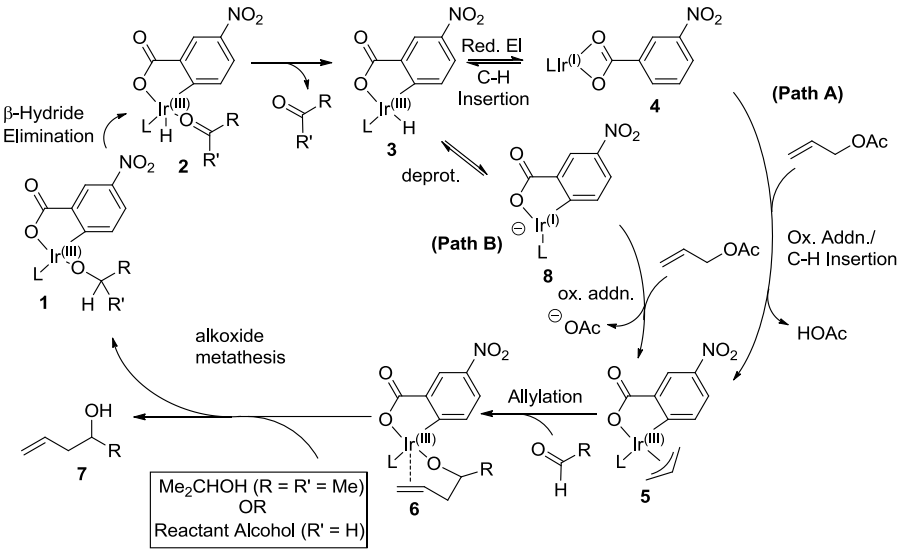


Krische's work defied the traditional mode of reactivity for allyl metal species with alcohols, where nucleophilic attack by the alcohol to give the allyl ether is most common.[7] The concept of *C*-allylation via transfer hydrogenative couplings follows a distinct pathway, however, consisting of *in situ* oxidation to the carbonyl with formal H_2 redistribution to the metal center and an external base.[1-2] Allylation ensues, and alkoxide metathesis with a

second equivalent of the aldehyde regenerates the catalyst with expulsion of the allylated product (Figure 1-1).

Two plausible mechanistic pathways for this transformation were provided and are shown in Figure 1-2.[2] From the alcohol oxidation state, β-hydride elimination generates an iridium hydride species **2** with subsequent dissociation of the carbonyl from the metal center.

Figure 1-2. Plausible Mechanistic Pathways for the Iridium-Catalyzed Hydrogenative Coupling



Either a reductive elimination/C–H insertion pathway or deprotonation of the iridium hydride likely delivers an iridium (I) species that is stabilized by coordination to the carboxylate and BINAP ligands (**4** or **8;** Ln = BINAP**)**. Oxidative addition to allyl acetate and loss of HOAc or ⁻OAc with either C-H insertion (path A) or dissociation (path B), respectively, generates the active allylating agent **5**. Coordination of the aldehyde is followed by the allylation step, and alkoxide metathesis with another equivalent of the primary alcohol starting material achieves catalytic turnover (**6** to **1)**.

In order to provide a reaction amenable to the use of reagents in the aldehyde oxidation state, a secondary hydride source was necessary to achieve catalytic turnover and regenerate the iridium hydride species. Isopropanol was found to be a suitable choice in these systems due the noncompetitive rate of allylation of the acetone byproduct with the allyl metal species **5** relative to allylation of the desired aldehyde electrophile. Notably, the use of enantioenriched BINAP ligands permitted a catalytic, enantioselective allylation, which afforded homoallylic alcohols in good to moderate yields and with enantiomeric excesses largely over 90%.[2]

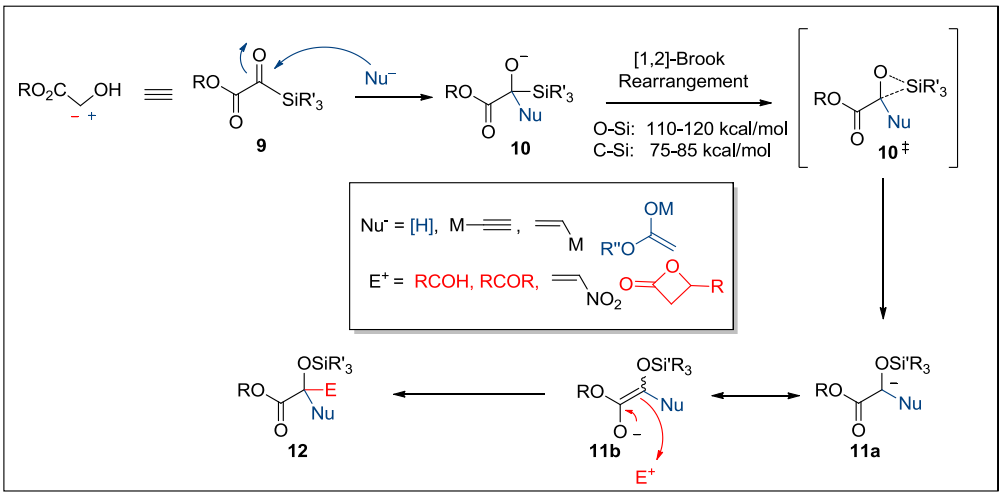
1.2.2 Symbiotic Aldol Reactions Between Silyl Glyoxylates and Magnesium Alkoxides

A symbiotic activation protocol for the coupling of alcohols and silyl glyoxylates was developed in our laboratory by Xin Linghu and Andrew Satterfield.[6] Silyl glyoxylates (**9**) offer unique reactivity patterns due to their propensity to function initially as electrophilic species and secondarily as nucleophilic species, a feature facilitated by an intermediate [1,2]-Brook rearrangement[8] (C to O silyl migration) that generates a glycolate enolate (**11b**) *in situ* after nucleophilic attack (Figure 3). This Brook rearrangement is favored by the strength of the Si-O bond (~ 40 kcal/mol higher than a typical C–Si bond) as well as the presence of the electron-withdrawing ester functionality, which helps to stabilize the developing carbanion in the transition state (**10**‡ to **11a**).

Consequently, silyl glyoxylates function effectively as conjunctive reagents and allow access to a variety of substituted glycolic acid derivatives (**12**). Extant coupling reactions with silyl glyoxylates include initiation of reactions by nonstabilized organometallic species[9-11] (metal acetylides and vinyl nucleophiles), hydride donors,[6] and stabilized organometallics

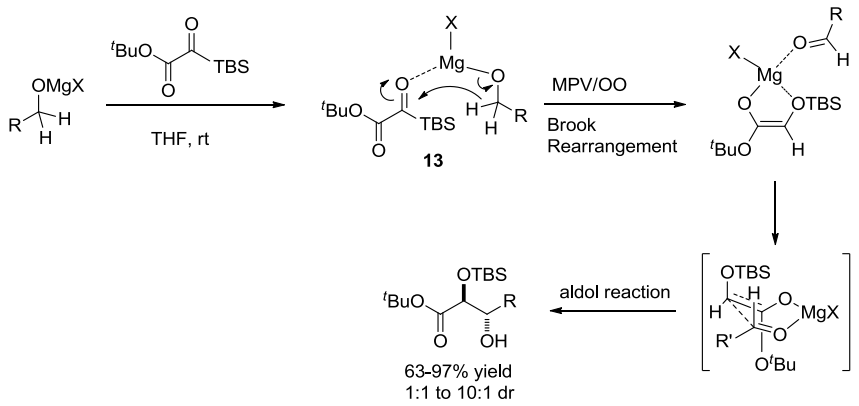
(enolates, Reformatsky reagents),[12] and termination of cascades through glycolate aldol reactions with aldehydes and ketones,[6, 9, 10, 12] Michael reactions with nitroalkenes,[13] and Claisen reactions with β-lactones (Figure 1-3).[14]

Figure 1-3. Silyl Glyoxylate Reactivity



Linghu and Satterfield found magnesium alkoxides to be competent hydride donors that initiated a cascade reaction with silyl glyoxylates involving Meerwein-Ponndorf-Verley (MPV) reduction[15-17] of the silyl glyoxylate, [1,2]-Brook rearrangement of the resulting alkoxides to the glycolate enolates, and aldol reaction to give dihydroxyesters that featured orthogonally protected hydroxyl groups (Figure 1-4).[6] An attractive feature of this cascade is the atom economy provided by the symbiotic redox chemistry that occurs to simultaneously generate the glycolate enolate and electrophile during the Meerwein-Ponndorf-Verley reduction/Oppenauer oxidation (MPV/OO) step (**13**). The alkoxide performs a dual role in the reaction, acting initially as a hydride donor and subsequently as an electrophile after its oxidation. A limitation that was encountered in this system, however, was that the absence of a turnover mechanism necessitated the use of a stoichiometric metal alkoxide.

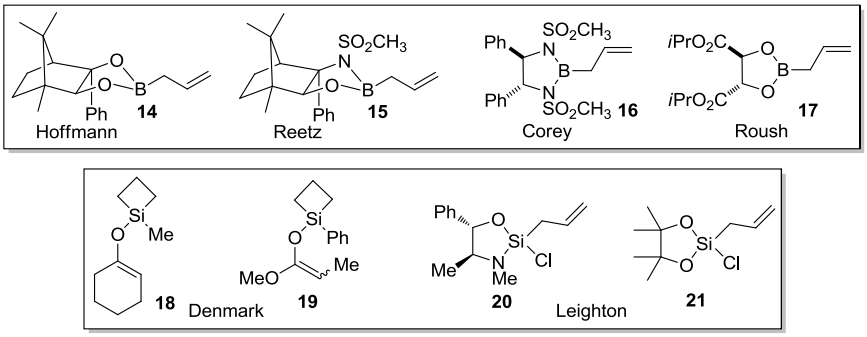
Figure 1-4. MPV/Brook Rearrangement/Aldol Cascade



1.2.3 Stoichiometric Silicon-Based Transfer Agents for Allylation and Aldol Reactions of Aldehydes

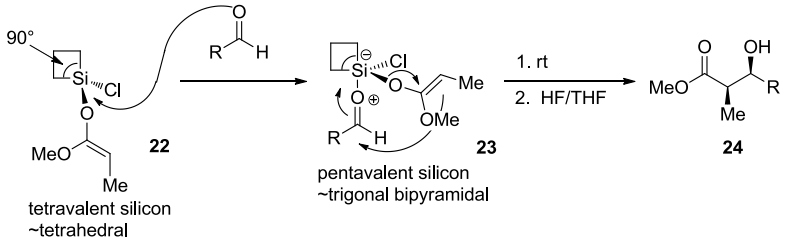
Several different classes of stoichiometric transfer reagents have been developed for the enantioselective allylation and aldol reaction of carbonyl compounds. Summarized in Figure 1-5, the majority of these are boron derivatives. Reetz[18] and Hoffmann[19] demonstrated the utility of isoborneol ligands (**14**, **15**), and Corey[20] and Roush[21] have reported similar allylations with diamino and tartrate ligands (**16, 17**). Of particular interest to our work here are the strain-release silacycles developed by Leighton,[22-23] Denmark,[24] and Myers[25] for use in the enantioselective allylation[22-23] and aldol[23-25] reactions of aldehydes (**18-21**).

Figure 1-5. Stoichiometric Allyl and Enolate Transfer Agents



The enhanced Lewis acidity of these reagents is due to the geometric contraints involved with restraining silicon in a 4-or 5-membered ring, which produces distorted bond angles that are exacerbated by the increased length of the C-Si bond.[24] An illustration of this concept is provided by Figure 1-6. Silacyclobutanes derived from silyl ketene acetals have been shown by Denmark to react with aldehydes to give the corresponding aldol products.[24] The typical reactivity pattern exhibited by these reagents involves initial reaction of the silacycle (**22)** with the Lewis basic carbonyl to give the pentavalent intermediate **23**.

Figure 1-6. Reactivity Profile of Strained Silacycles



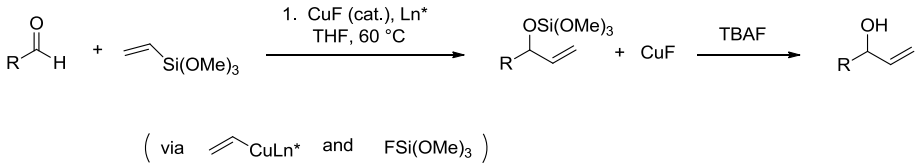
The approximately 90° angle for the C–Si–C bonds indicated in the silacyclobutane is considerably smaller than the 109.5° angle typically preferred between substituents on tetrahedral atoms, and the Lewis acidity of the silicon atom is consequently enhanced. The intermediate pentavalent species after reaction with the aldehyde, however, possesses a 90°

angle between the apical and equatorial substituents, which is appropriate for a trigonal bipyramidal complex. The pentavalent species then undergoes a rapid aldol reaction with the aldehyde, affording the aldol product **24** after a fluoride workup that effectively cleaves the silacycle from the aldolate. Strain-release Lewis acidic silacycles have been exploited in several other related systems,[22-26] yet to our knowledge they have not been used in alkoxide metathesis reactions prior to this work.

1.2.4 Origin of the Title Reaction

The genesis of the current work was a byproduct obtained by Andrew Satterfield during his studies on vinyl transfer from silanes to silyl glyoxylates, experiments inspired by Shibasaki's work on asymmetric vinyl additions to aldehydes catalyzed by chiral copper complexes (Scheme 1-1).[27] In the Shibasaki system, the combination of a copper fluoride catalyst and chiral phosphine ligand afforded *in situ* generation of the vinyl cuprate and trimethoxysilyl fluoride from vinyltrimethoxysilane. This cuprate performed asymmetric vinylation of aldehydes, and catalytic turnover occurred through silylation of the transient copper alkoxide by the silyl fluoride, with concomitant release of copper fluoride.

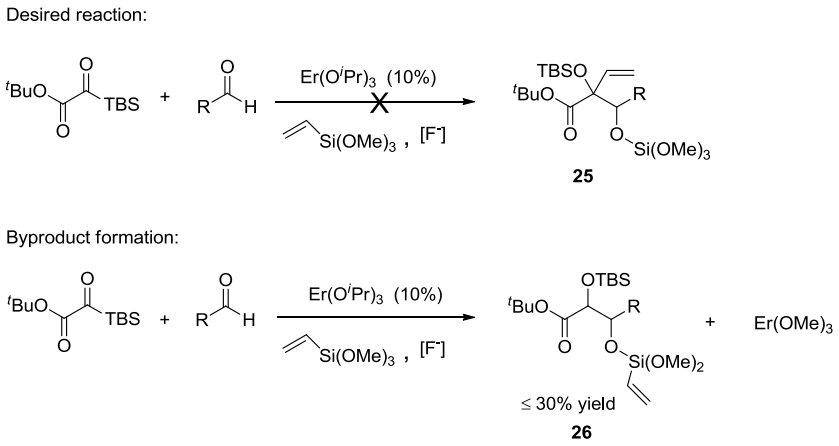
Scheme 1-1. Catalytic, Enantioselective Vinylation of Aldehydes[27]



When attempting to apply this catalytic system toward silyl glyoxylate cascade reactions, Andrew observed the production of an interesting bissilylated byproduct with certain metal isopropoxide catalysts (Figure 1-7). Rather than obtaining the product from silylation with

$(MeO)_3SiF$ (**25**), product **26** was isolated, which likely arose from alkoxide metathesis with vinyltrimethoxysilane and with concurrent generation of $Er(OMe)_3$.[28] We conjectured that this unique reactivity might allow for catalysis of the cascade reaction depicted in Figure 1-4. Presented in this chapter are the results we obtained from our investigation of the necessary parameters for catalysis of the title reaction as well as preliminary efforts toward the development of an asymmetric variant.

Figure 1-7. Relevant Byproduct Formation in Preliminary Vinylation Attempts[28]



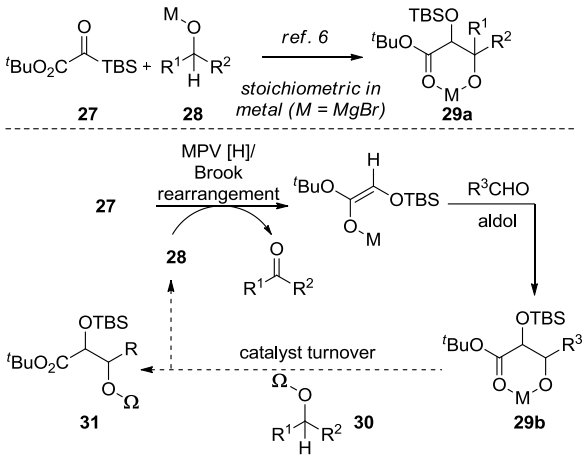
1.3 Results and Discussion

1.3.1 Investigation of Mechanistic Parameters

Key mechanistic features of the projected catalytic reaction are summarized in Figure 8. Following the established silyl glyoxylate reactivity pattern of Meerwein-Ponndorf-Verley (MPV) reduction, Brook rearrangement, and aldol reaction,[6] our point of departure from the stoichiometric reaction would be the transfer of some undefined moiety Ω from **30** to the terminal metal aldolate **29b**. This proposed alkoxide metathesis would concurrently release the aldolate product and regenerate the MPV reductant **28**.

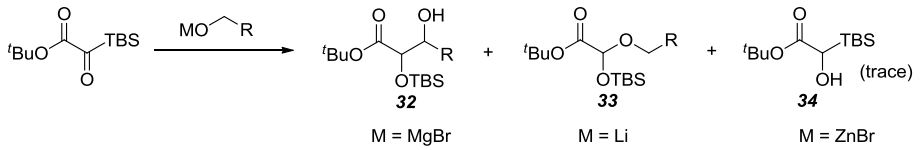
Preliminary experiments focused on defining two key reaction components. First, the identity of the metal cation would likely prove a determining factor, as previous reactions employing silyl glyoxylates have required the careful selection of a metal that not only promotes MPV reduction of the silyl glyoxylate but also Brook rearrangement of the intermediate *C*-silyl alkoxides.[6,9,29]

Figure 1-8. Proposed Catalytic Reaction



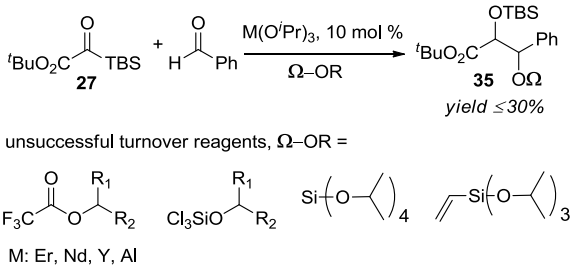
A clear illustration of this is the variable product distribution that was found in Linghu's work with magnesium alkoxides: a screen of various metal alkoxides provided the desired product with magnesium (**32**), but the corresponding lithium alkoxides reacted primarily through nucleophilic attack and Brook rearrangement to give **33**, while zinc alkoxides afforded MPV reduction of the silyl glyoxylate without subsequent Brook rearrangement (**34,** Figure 1-9).[6,9]

Figure 1-9. Screens of Metal Alkoxides[6]



Second, alkoxide donor **30** must be sufficiently labile in order to facilitate effective catalytic turnover. We initially screened several common metal triisopropoxides with acylating agents such as trifluoroacetates and silylating agents such as alkoxytrichlorosilanes, tetraalkoxysilanes, and vinyltriisopropoxysilane. We achieved no greater than 30% conversion to the desired aldol product **35** in these reactions, suggesting that alkoxide transfer from the putative turnover reagents was not occurring and that the origin of the observed products was simply complete consumption of the metal triisopropoxides (Figure 1-10).

Figure 1-10. Unsuccessful Turnover Reagents

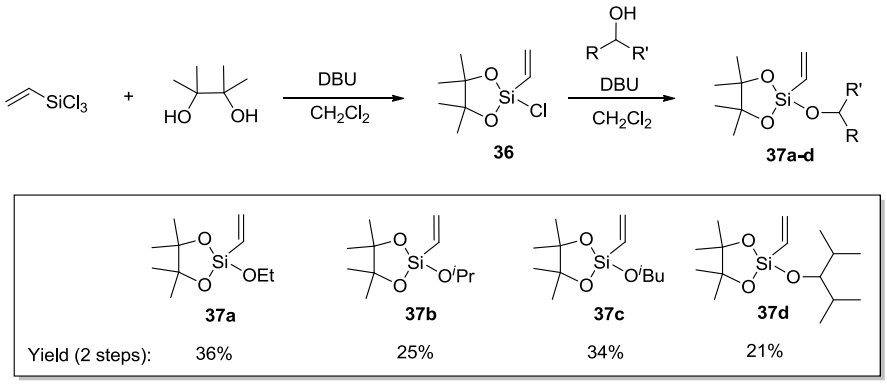


1.3.2 Synthesis and Utility of Strain-Release Silacycles

Realizing that a more reactive turnover agent may be necessary, we turned to strain-release silacycles. As discussed previously, the enhanced Lewis acidity of these silacycles is due to their ring constraints and contributes to their ability to function as potent allylating

agents and enolate equivalents.[22-25] We wondered if they might exhibit accelerated substitution chemistry relative to unconstrained variants.

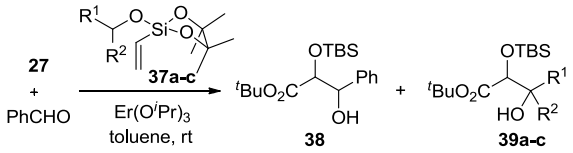
Scheme 1-2. Synthesis of Silacycle Derivatives



We initially synthesized ethoxysilacycle **37a** in two steps from vinyltrichlorosilane following modified procedures from Leighton for chloride displacement by pinacol and a secondary alcohol.[22] Several substituted derivatives were prepared in the yields shown for the two-step sequence. Gratifyingly, in the presence of **37a** and 5 mol % of erbium(III) isopropoxide, silyl glyoxylate **27** and benzaldehyde reacted completely in under five minutes to provide **38** in a 50% yield; however, product analysis of this preliminary trial revealed an important pitfall: aldol reaction with the sacrificial equivalent of acetaldehyde generated from the ethoxide transfer and MPV/OO redox sequence proved to be competitive with the desired reaction with benzaldehyde, yielding 32% of byproduct **39a** (Table 1-1, entry 1).

Isobutoxysilacycle **37b** afforded a similar product ratio (Table 1-1, entry 2), but isopropoxysilacycle **37c** provided the desired coupling product in a 62% yield and with only 3% of the byproduct **39c** present (entry 3), resulting from reaction with the equivalent of acetone generated.

Table 1-1. Preliminary Trials Using Strain-Release Silacycles[a]



entry	R^1	R^2 (silacycle)	mol % Er(O^{i}Pr)$_3$	% yield **38** (**39**)[b]	time (min)
1	Me	H(**37a**)	5	50 (32)	5
2	^{i}Pr	H(**37b**)	5	50 (28)	40
3	Me	Me(**37c**)	5	62 (3)	60
4	Me	Me(**37c**)	10	84 (6)	30
5	Me	Me(**37c**)	1	trace	120

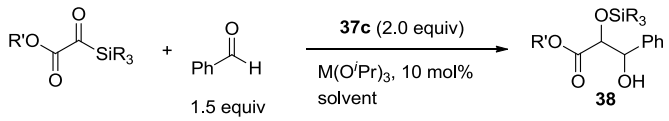
[a] Conditions: 1.5 equiv of PhCHO, 2.0 equiv of **37**, $[\mathbf{27}]_0 = 0.2$ M. [b] Yields determined by ^{1}H NMR versus an internal standard.

Increased yields could be attained with the use of 10% of the metal catalyst, while catalyst loadings less than 5% provided only trace product formation (entries 4 and 5). Our success with isopropoxy-substituted silacycles parallels the selectivities observed by Krische that were discussed previously insofar as isopropanol could also be utilized as a hydride source in the iridium-catalyzed allylations of aldehydes because the acetone byproduct was less reactive toward the allylating agent than the aldehydes also present in solution.[1-2]

1.3.3 Screens of Additional Reaction Parameters

Having determined a successful means for catalytic turnover, we screened additional silyl glyoxylates and evaluated possible solvent effects. Toluene proved to be a fortuitous solvent choice, providing the desired product in moderate yields and in shorter reaction times than in ether, while incomplete reactions were observed in dichloromethane, THF, and 2-methyl-THF (Table 1-2, entries 4-8).

Table 1-2. Solvent and Silyl Glyoxylate Screens[a]



entry	M	R′	SiR_3	solvent	time	yield[b]	d.r.
1	Pr	Bn	TBS	toluene	1 min	53	1:1
2	Pr	^{t}Bu	TES	toluene	3 min	67	1.6:1
3	Pr	^{t}Bu	TBS	toluene	1 min	80	1.5:1
4	Er	^{t}Bu	TBS	toluene	1 h	62	
5	Er	^{t}Bu	TBS	CH_2Cl_2	3 h	18	
6	Er	^{t}Bu	TBS	THF	3 h	15	
7	Er	^{t}Bu	TBS	Et_2O	3 h	68	
8	Er	^{t}Bu	TBS	2-Me-THF	5 h	trace	

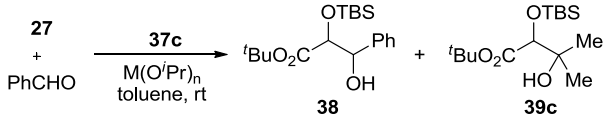
[a] Conditions: 1.5 equiv of PhCHO, 2 equiv of **37c**, $[\text{silyl glyoxylate}]_0$ = 0.2 M. [b] Yields determined by ^{1}H NMR spectroscopy versus an internal standard.

These initial screens were completed with erbium triisopropoxide at 10 mol% catalyst loading. We could potentially attribute the poor reactivity of the metal species in THF and 2-methyl-THF to the coordinating abilities of these solvents, although the equally poor result observed in methylene chloride may suggest that additional factors are contributing to these effects. Likewise, few trends could be discerned from our short silyl glyoxylate screen. The *tert*-butyl (*tert*-butyldimethylsilyl) glyoxylate clearly offered the optimal results among these compounds (Table 1-2, entry 3); the triethylsilyl-substituted derivative afforded lower yields of the desired product (entry 2), and the benzyl (*tert*-butyldimethylsilyl) glyoxylate resulted in both lower diastereoselectivity and yield than in our initial screens with silyl glyoxylate **27** (entry 1).

Interesting results were obtained upon screening a variety of metal isopropoxide catalysts. Among the cations investigated, aluminum[15] and magnesium[6] provided only trace

product in this catalytic system; their failure here contrasts their widespread use in MPV reductions and likely reflects an inability to undergo alkoxide metathesis under these conditions rather than an inability to function as hydride donors. $Y(O^iPr)_3$ and a variety of lanthanides exhibited an inverse relationship between ionic radius[30] and reaction time (Table 1-3, entries 5-11). Reactions employing 10 mol % $Er(O^iPr)_3$ required 30 minutes to reach completion, while an equimolar quantity of $Pr(O^iPr)_3$ catalyzed the addition to >98% conversion in approximately 1 minute with benzaldehyde (entries 7, 11).

Table 1-3. Screen of Metal Catalysts[a]



entry	$M(O^iPr)_n$ (mol %)	% yield **38** (**39c**)[b]	reaction time (min)	radius (Å)[c]
1	$Al(O^iPr)_3$ (5)	trace	300	
2	$Dy(O^iPr)_3$ (5)	trace	300	
3	$Zr(O^iPr)_4$ (5)	trace	300	
4	$Mg(O^iPr)_2$ (5)	trace	300	
5	$Y(O^iPr)_3$ (5)	52 (1)	120	0.900
6	$Er(O^iPr)_3$ (5)	62 (5)	120	0.890
7	$Er(O^iPr)_3$ (10)	84 (6)	30	0.890
8	$Gd(O^iPr)_3$ (10)	67 (12)	25	0.938
9	$Yb(O^iPr)_3$ (10)	72 (8)	15	0.868
10	$Sm(O^iPr)_3$ (10)	60 (11)	10	0.958
11	$Pr(O^iPr)_3$ (10)	91 (8)	1	0.997

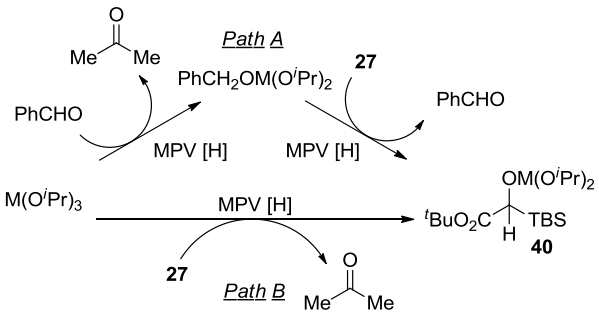
[a] Conditions: 1.5 equiv of PhCHO, 2 equiv of **37c**, $[\mathbf{27}]_0$ = 0.2 M. [b] Yields determined by ^{1}H NMR spectroscopy versus an internal standard. [c] Reference 30, for coordination number = 6.

1.3.4 Isotopic Labeling Studies

Two reasonable reduction mechanisms could be formulated to account for the observed reductive aldol products (Figure 1-11). Initial MPV reduction of benzaldehyde to a

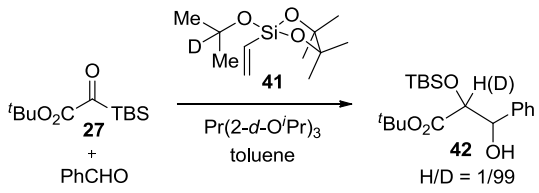
benzyl alkoxide could be followed by an MPVH/OO redox sequence between the benzyl alkoxide and silyl glyoxylate **27** to arrive at **40** and benzaldehyde (Path A); alternatively, *C*-silyl alkoxide intermediate **40** could be intercepted through a direct MPV reduction of the silyl glyoxylate by the metal isopropoxide (Path B).

Figure 1-11. Possible Hydride Transfer Pathways



We attempted to distinguish the two mechanisms through an application of the deuterium-labeled isopropylsiloxane **41**, which was prepared from 2-*d*-O^{i}Pr.[31] If reduction of the silyl glyoxylate were occurring faster than reduction of benzaldehyde, we would expect to see incorporation of deuterium α-to the ester. If, however, reduction of benzaldehyde were competitive with reduction of the silyl glyoxylate, we would expect to see deuterium incorporation at the β-position.

Figure 1-12. Isotopic Labeling Study[a]



[a] Conditions: 1.5 equiv of PhCHO, 2 equiv of **41**, $[\mathbf{27}]_0 = 0.2$ M.

In order to eliminate potential complications arising from the use of 30 mol% of 2-H-isopropoxide from the catalyst, we performed an alkoxide exchange with 2-*d*-^{i}PrOH to generate Pr(2-*d*-O^{i}Pr)$_3$ as the active catalyst.[32] Using 10 mol % of this catalyst, we observed 99% incorporation of deuterium at C_α (Figure 1-12). This result indicates that hydride scrambling via aldehyde reduction does not contribute appreciably to product formation and that Path B is active in this system. This is consistent with the increased electrophilicity of **27** relative to aldehydes that is generally observed.[6,9,10]

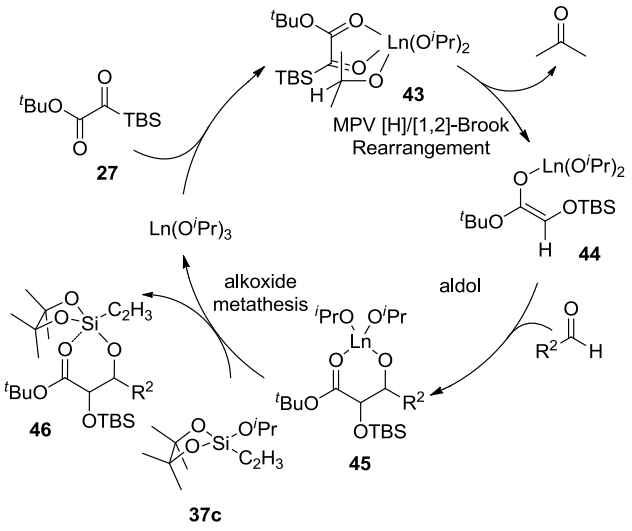
1.3.5 Proposed Mechanism and Catalytic Cycle

Based on previous studies of related reactions from our laboratory and the results of the deuterium labeling experiment, we proposed the catalytic cycle depicted in Figure 1-13. MPV reduction of silyl glyoxylate **27** results in generation of a transient alkoxide intermediate that undergoes Brook rearrangement to afford glycolate enolate **44**. Aldol reaction with the aldehyde provides terminal alkoxide **45,** which then attacks the strained silacycle **37c** and expels another isopropoxide equivalent to regenerate the lanthanide triisopropoxide catalyst, possibly facilitated by participation of the ester carbonyl.[24] A sacrificial equivalent of acetone is generated in the initial step of this cycle; dissociation of acetone from the metal catalyst therefore must proceed more rapidly than its aldol reaction occurs to avoid predominant production of byproduct **39c**.

This selectivity concurs with competition experiments previously conducted in related systems by Linghu and Satterfield.[6] When the MPV reduction produces a sacrificial aldehyde, however, competitive aldol reactions afford the product ratios observed in Table 1-1 (entries 1 and 2). The inverse relationship between ionic radius and reaction time shown in

Table 1-3 potentially reflects steric limitations in the alkoxide transfer step; the larger coordination sphere of praseodymium likely facilitates the necessary complex formation as well as dissociation of the final product from the metal center.

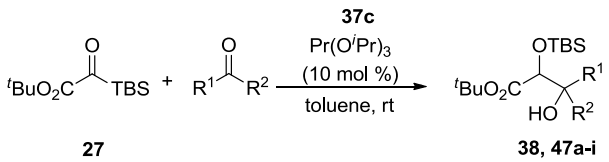
Figure 1-13. Proposed Catalytic Cycle Employing Silacycle 37c



1.3.6 Reaction Scope

An investigation of the scope of the reaction showed that the aryl, linear and branched alkyl, and heteroaromatic aldehydes shown in Table 1-4 were all viable substrates. In spite of the modest diastereoselectivities observed, reactions were generally quite rapid and gave good yields of the glycolate aldol products. Reaction with acetophenone and propiophenone provided only 17% of the desired addition product (Table 1-4, entries 5-6), with the remaining silyl glyoxylate consumed by addition to acetone. The background reaction proceeded over 15 minutes to give the coupling product **47i** in 67% yield (Table 1-4, entry 10).

Table 1-4. Electrophiles for the Reductive Aldol[a]

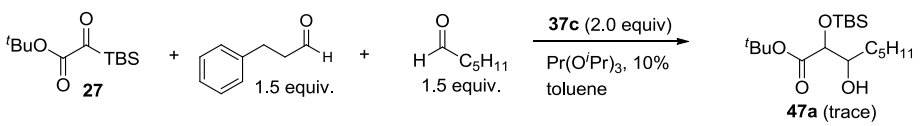


entry	product	R^1	R^2	yield (%)[b]	time (min)	d.r.
1	**38**	Ph	H	80[c]	1	1.5:1
2	**47a**	$CH_3(CH_2)_4$	H	69	2	1.5:1
3	**47b**	2-furyl	H	73[c]	3	1.3:1
4	**47c**	^{i}Pr	H	71	1	1.5:1
5	**47d**	Ph	Me	17	7	1.3:1
6	**47e**	Ph	Et	18	5	1.2:1
7	**47f**	PhC≡C	H	trace	120	n.d.
8	**47g**	(*E*)-PhCH=CH	H	trace	120	n.d.
9	**47h**	$PhCH_2CH_2$	H	trace	120	n.d.
10[d]	**47i**	Me	Me	67[c]	15	n/a

[a] Reaction conditions: 1.5 equiv of aldehyde or ketone, 10% Pr(O^{i}Pr)$_3$, 2 equiv of **37c**, [**27**]$_0$ = 0.08 M. [b] Unless otherwise noted, yields were determined by ^{1}H NMR spectroscopy versus an internal standard. [c] Isolated yield. [d] No aldehyde or ketone was added.

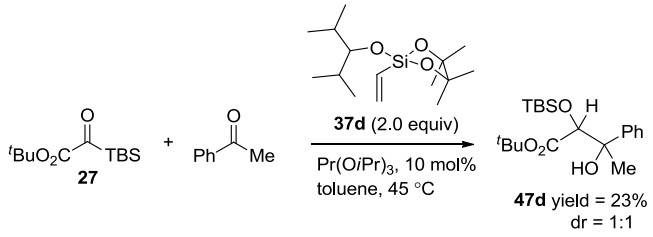
Notably poor substrates were α,β-unsaturated aldehydes and dihydrocinnamaldehyde (Table 1-4, entries 7 to 9); no greater than trace quantities of desired product were observed. Although we cannot provide a detailed rationale for the failure of such substrates, they possibly impede reaction through either complexation with or degradation of the metal catalysts. A control experiment was run in which equimolar quantities of hydrocinnamaldehyde and hexanal were subjected to the standard reaction conditions. We again observed only trace product, supporting this hypothesis (Scheme 1-3).

Scheme 1-3. Control Experiment with Hydrocinnamaldehyde



We attempted to expand the substrate scope to include ketones. We recognized that in order to accomplish that goal we would need to generate a ketone byproduct that would react slower in the aldol stage than would the desired ketone electrophile. Silacycle **37d** was synthesized accordingly. Nevertheless, this silacycle proved to be too hindered for effective turnover, and we observed no conversion at room temperature. Slightly elevated temperatures resulted in decomposition and low yields of the desired product (Scheme 1-4).

Scheme 1-4. Attempted Inclusion of Ketone Substrates



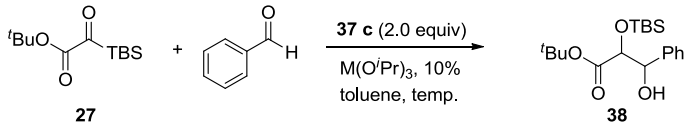
1.3.7 Efforts Toward the Development of an Asymmetric Variant

We next investigated the feasibility of inducing asymmetry into the catalytic system, specifically through the use of chiral ligands bound to the metal center. Several key mechanistic features were identified that might hamper the successful incorporation of chiral metal complexes. Initially it was unclear whether the diastereoselectivities observed in the substrate scope were a reflection of kinetic or thermodynamic control. We recognized that a rapid, reversible aldol reaction prior to alkoxide metathesis could lead to deterioration of any inherent kinetic preference; however, if the rate of alkoxide metathesis could be lowered such that selective reaction with either the *syn*- or *anti*-aldolate occurred, high diastereoselectivities could still be achieved. The identity of the ligands bound to the lanthanide metal center would likely affect the steric and electronic properties of the

complex, which might translate into drastically altered reaction rates and selectivities. Unfortunately, *de novo* design of catalyst systems based on lanthanides is particularly challenging due the unpredictability of coordination numbers and aggregation states.[33]

Additional studies were aimed at elucidating the potential reversibility of the aldol reaction. Table 1-5 illustrates the effects of temperature and conversion on the diastereoselectivity of the reaction. Erbium allowed for more flexibility in terms of controlling conversion because of the longer reaction times that were observed; due to the extremely rapid reactions with praseodymium (< 1 min at rt), accuracy in prematurely halting

Table 1-5. Temperature Effect on Diastereoselectivity[a,b]



entry	M	conversion (%)	temperature (°C)	dr
1	Er	54	0	1.8:1
2	Er	80	0	1.5:1
3	Er	100	rt	1.2:1
4	Er	29	-10	1.6:1
5	Pr	100	-10	1.9:1
6	Pr	100	0	1.8:1
7	Pr	100	rt	1.5:1

[a] Reaction conditions: 1.5 equiv of aldehyde or ketone, 10% $M(O^iPr)_3$, 2 equiv of **37c**, $[\mathbf{27}]_0$ = 0.08 M. [b] Unless otherwise noted, conversions and diastereomeric ratios were determined by ^{1}H NMR spectroscopy versus an internal standard.

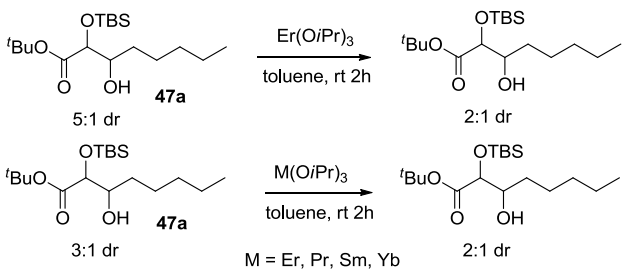
reactions was difficult to achieve. As a general trend, increasing conversion with erbium led to a decrease in diastereoselectivity (Table 1-5, entries 1-3). The reaction was found to proceed to nearly complete conversion at temperatures greater than or equal to 0 °C but did not progress sufficiently at lower temperatures (entry 4). At 54% conversion at 0 °C, a 1.8:1

dr was observed. At 80% conversion, the highest that was able to be achieved at this temperature, the diastereoselectivity had decreased moderately to 1.5:1, and at room temperature complete conversion and a 1.2:1 dr resulted. At -10 °C low conversions and diastereoselectivities were observed (29% conversion after 2 h, 1.6:1 dr).

Not surprisingly, higher reactivity was observed with praseodymium, and complete conversion could be achieved a -10 °C. Diastereoselectivities ranged from 1.9:1 at this temperature to 1.5:1 at rt (entries 5-7). These results suggest that temperature does not play a major role in determining the diastereoselectivity of the reaction, and based on sluggish reactivity at reduced temperature, we were not optimistic about our ability to thermally alter the diastereoselectivity.

Further evidence that the aldol reaction was a reversible reaction was shown by resubjecting a diastereomerically enriched sample of the addition product to hexanal (**47a**) to reaction with the metal isopropoxide, which led to a deterioration of the diastereomeric ratio from 3:1 to 2:1 (Scheme 1-5). This deterioration occurred with M = Pr, Er, Yb, and Sm, and suggests that either a retro-aldol/aldol equilibrium may be occurring or that the major diastereomer is simply degraded faster under these conditions.[34]

Scheme 1-5. Reversibility Studies

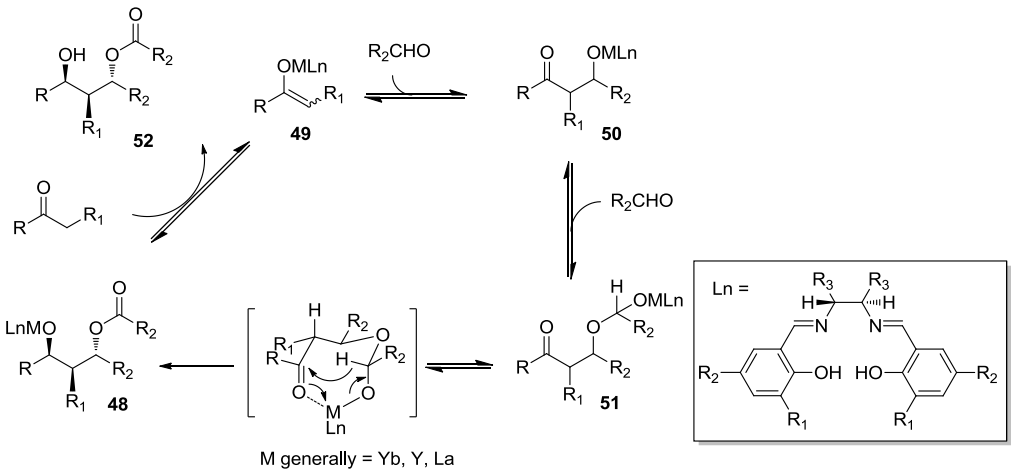


We initially screened several common chiral ligands such as *N*-methylephedrine and (-)-sparteine as well as achiral ligands like TMEDA. These preliminary trials demonstrated an increased rate of reactivity for the metal complexes, but we observed no enantioselectivity or enhanced diastereoselectivity in our system. After searching the literature for analogous reactivity, we identified the enantioselective aldol-Tishchenko cascade that was developed by Morken.[35]

1.3.8 Asymmetric Aldol-Tishchenko Reactions[35]

In 2001 Morken and coworkers reported an asymmetric variant of the catalytic aldol-Tishchenko reaction of ketone enolates and aldehydes. The proposed mechanism for this transformation involves a rapid and reversible aldolization step (**49** to **50**), which precedes a rate-determining and irreversible Tishchenko reduction[36] of the aldolate to alkoxide **48**. The catalytic cycle achieves turnover through a deprotonation of another equivalent of ketone by the terminal metal alkoxide, which regenerates the ketone enolate **49**. The reaction was rendered enantioselective by the use of enantioenriched salen ligands bound to the lanthanide metal centers, with the absolute stereocontrol occurring in the irreversible Tishchenko reduction step (**51** to **48,** Figure 1-14). Similarities to the work discussed in this current chapter include the use of lanthanide complexes (bound to salen ligands) and a rapid, reversible aldol step that precedes the Tishchenko reaction and allows for the observed selectivities. Based on the data presented above, we believed that our aldol step was reversible, and therefore the work by Morken offered a reasonable starting point toward imparting asymmetry here.

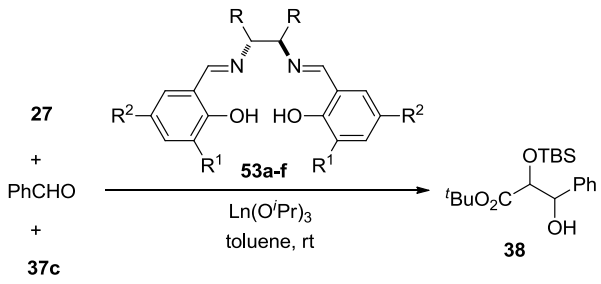
Figure 1-14. Catalytic Cycle for Asymmetric Aldol-Tishchenko Reaction



1.3.9 Ligand Screens

Based on the precedent set by Morken,[35] several salen ligands were screened with moderate success. Table 1-6 illustrates these results, and although we were not able to achieve high enantiomeric ratios, we verified that ligand to product chirality transfer was feasible, with **53c**·Pr(O^iPr)$_3$ providing the desired product with no decrease in yield (80%) and with a 63:37 e.r. Ongoing studies in our group aim to build upon these preliminary results.

Table 1-6. Results Using Salen Ligands[a]



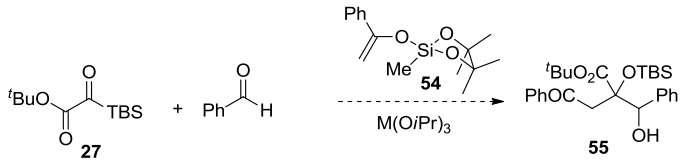
entry (ligand)	Ln	R	R^1	R^2	% yield	e.r.[b]	d.r.
1 (**53a**)	Er	-$(CH_2)_4$-	Me	H	18	50:50	1.5:1
2 (**53b**)	Er	-$(CH_2)_4$-	^{t}Bu	^{t}Bu	trace	n.d.	-
3 (**53a**)	Sm	-$(CH_2)_4$-	Me	H	63	61:39	1.4:1
4 (**53c**)	Sm	Ph	^{t}Bu	^{t}Bu	41	55:45	2.1:1
5 (**53d**)	Sm	-$(CH_2)_4$-	H	H	0	n.a.	-
6 (**53e**)	Sm	-$(CH_2)_4$-	^{t}Bu	OMe	45	57:43	2.1:1
7 (**53a**)	Pr	-$(CH_2)_4$-	Me	H	33	58:42	1.9:1
8 (**53c**)	Pr	Ph	^{t}Bu	^{t}Bu	80	63:37	2:1
9 (**53f**)	Pr	naphthyl	^{t}Bu	^{t}Bu	58	53:47	1.7:1

[a] Reaction conditions: 1.5 equiv of PhCHO, 10 mol % of Ln(O^{i}Pr)$_3$, 2 equiv of **37c**, 10 mol % of **53a-f**, [**27**]0 = 0.08 M. [b] For major diastereomer.

1.3.10 Additional Studies on the Incorporation of Enol Nucleophiles

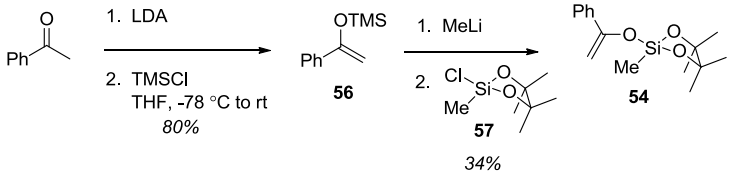
Based on the propensity of strain-release enol silacycles to effect aldolization of aldehydes,[22-24] we briefly investigated their ability to participate in an enol transfer analogous to the previously described alkoxide transfer observed with silacycles **37a-c**. By incorporating an enol nucleophile and an aldehyde electrophile, we had hoped to arrive at 4-hydroxycarbonyl compounds (**55**, Figure 1-15).

Figure 1-15. Proposed Reactivity with Strain-Release Silyl Enol Ethers



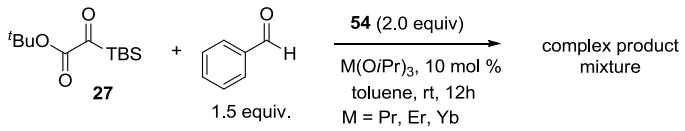
Toward this goal, strain-release silyl enol silacycle **54** was prepared in two steps from acetophenone. After preparation of the trimethylsilyl enol ether **56** according to literature procedure,[37] treatment with methyllithium generated the lithium enolate *in situ*,[38] which was reacted with chlorosilane **57** (prepared from trichloromethylsilane and pinacol) to give the desired product in a 34% yield.

Scheme 1-6. Preparation of Strain-Release Enol Silacycles



This strain-release silacycle exhibited low reactivity with silyl glyoxylate **27** at room temperature in the presence of 10 mol % praseodymium, erbium, or ytterbium isopropoxides; after stirring at room temperature overnight in toluene, complex product mixtures were observed. Although the results here are not promising, Chapter Two details an alternative strategy for the incorporation of enolate nucleophiles.

Scheme 1-7. Attempted Reactions with Strain-Release Enol Silacycles



1.4 Conclusion

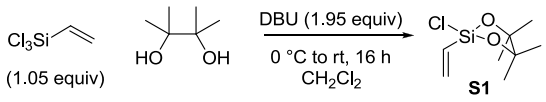
We have developed a new catalytic method for the MPV reduction/Brook rearrangement/aldol cascade reaction of silyl glyoxylates that rapidly assembles glycolate aldol products. The reaction features catalysis by lanthanide triisopropoxides and achieves turnover through alkoxide transfer from strain-release Lewis acidic silacycles. To our knowledge this is the first use of strain release for this type of functionality transfer. Reactions catalyzed by praseodymium isopropoxide with aldehydes were exceedingly fast, achieving completion in 1-5 min at room temperature, and yields were generally good within the subset of aldehyde electrophiles. Initial screens of salen-metal complexes also suggest the potential for the introduction of asymmetry into these reactions, as moderate enantioselectivities have verified that ligand to product chirality transfer is feasible.

1.5 Experimental Details

Materials and Methods: General. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton, carbon, and silicon magnetic resonance spectra (^{1}H NMR, ^{13}C NMR, ^{29}Si NMR) were recorded on a Bruker model Avance 400 or a Bruker 300 MHz (^{1}H NMR at 400 MHz or 300 MHz, ^{13}C NMR at 100 MHz, and ^{29}Si NMR at 79.5 MHz) spectrometer with tetramethylsilane or solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm; ^{29}Si NMR: TMS at 0.00 ppm,). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s =

singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. The identities of compounds **16a, 16b, 8b,** and **16d** were determined by comparison with data reported in the literature.[1] Enantiomeric excesses were obtained using a Supercritical Fluid Chromatograph equipped with a UV-Vis detector using a Chiralcel Chiralpak OD HPLC column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH.

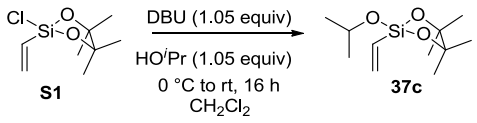
Preparation of Silacycles:



2-chloro-4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxasilolane (S1):

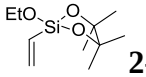
General procedures from Leighton[23] were followed with slight modifications. Azeotropic removal of water from commercially available pinacol with benzene or toluene was performed prior to use. DBU (30.7 mL, 204 mmol, 1.95 equiv) was dissolved in dry

dichloromethane (250 mL). The solution was cooled to 0 °C, and trichlorovinyl silane (13.9 mL, 109 mmol, 1.05 equiv) was added dropwise. Dried pinacol (12.36 g, 104 mmol, 1.0 equiv) was dissolved in dichloromethane (150 mL), and this solution was added to the reaction via cannula over 30 min. The solution was allowed to warm to room temperature and was stirred for 16 h. Dichloromethane was removed in vacuo, and dry diethyl ether (150 mL) was added. After stirring for 1 h to precipitate all salts, the solids were removed by filtration through an oven-dried fritted funnel into a dry round-bottomed flask, using short vacuum pulses to achieve rapid filtration. The filter cake was washed with dry diethyl ether and the filtrate was concentrated in vacuo. The residue was distilled under vacuum (0.05 mm Hg) to give the desired product as a clear, colorless oil. Yield = 40%. bp = 42 °C (0.05 mm Hg); Analytical data: **IR** (thin film, cm^{-1}): 2983, 2246, 1602, 1405, 1393, 1142, 1109, 1009; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 14.1, 3.6 Hz, 1H), 6.22 (dd, *J* = 20.4, 3.6 Hz, 1H), 5.98 (dd, *J* = 14.1, 20.4 Hz, 1H), 1.35 (s, 6H), 1.29 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.8, 129.5, 83.5, 25.5, 25.2; **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -48.4.

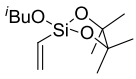


2-isopropoxy-4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxasilolane (37c): A flame-dried round-bottomed flask was charged with DBU (2.23 mL, 14.78 mmol, 1.05 equiv). Dry dichloromethane (50 mL) was added, the solution was cooled to 0 °C, and chlorosilane **S1** (2.90 g, 14.1 mmol, 1.0 equiv) was added dropwise. Dry isopropanol (1.13 mL, 14.78 mmol, 1.05 equiv) in dichloromethane (15 mL) was added dropwise via syringe pump over 1 h. The reaction was stirred at room temperature for 16 h and then concentrated in vacuo. To the

resulting light pink slurry was added dry diethyl ether (35 mL), and the suspension was stirred for 1 h. Filtration as described for the preparation of chlorosilane **S1** was performed, and after removal of the solvent in vacuo, the residue was distilled under vacuum (0.05 mm Hg) to give the desired product as a clear, colorless oil (2.38 g, 74%, bp = 50 °C). Analytical data: **IR** (thin film, cm^{-1}): 2979, 2246, 1711, 1600, 1370, 1225, 1144, 1009; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.14 (dd, *J* =14.4, 4.4 Hz, 1H), 6.09 (dd, *J* = 20.4, 4.4 Hz, 1H), 5.93 (dd, *J* = 20.4, 14.0 Hz, 1H), 4.29 (h, *J* = 5.6 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.20 (d, *J* = 5.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ137.7, 129.7, 81.4, 65.9, 25.8, 25.6, 25.4; **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ –41.9.



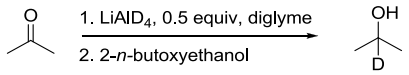
2-ethoxy-4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxasilolane (37a): Prepared from chlorosilane **S1** and dry ethanol according to the procedure for **37c**. Yield = 55%. bp = 42 °C (0.05 mm Hg); Analytical data: **IR** (thin film, cm^{-1}): 2956, 1600, 1463, 1389, 1368, 1162, 1113, 976. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 14.4, 4 Hz, 1H), 6.10 (dd, *J* = 20.8, 4 Hz, 1H), 5.93 (dd, *J* = 14.4, 20.8 Hz, 1H), 3.88 (q, *J* = 6.8 Hz, 2 H), 1.30 (s, 6H), 1.25 (s, 6H) 1.23 (t, *J* = 6.8, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.1, 129.1, 81.4, 59.1, 25.7, 25.6, 18.1; **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -40.9.



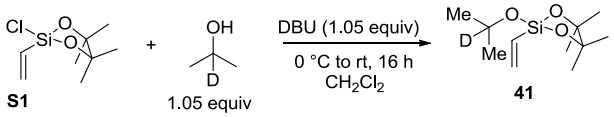
2-isobutoxy-4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxasilolane (**37b)**: Prepared from chlorosilane **S1** and dry isobutyl alcohol according to the procedure for **37c**. Yield = 64%. bp = 52 °C (0.05 mm Hg); Analytical data: **IR** (thin film, cm^{-1}): 3526, 2957, 2244, 1469, 1368, 1162, 908, 730; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.06 (dd, *J* = 14.4, 3.6 Hz, 1H), 6.02 (dd, *J* = 20.4, 3.6 Hz, 1H), 5.83 (dd, *J* = 14.4, 20.4 Hz, 1H), 3.48 (d, *J* = 4.4 Hz, 2 H), 1.72 (th, *J* = 4.4, 6.8 Hz,1H), 1.21 (s, 6H) 1.16 (s, 6H), 0.81 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR**

(100 MHz, $CDCl_3$) δ 137.9, 128.9, 81.1, 69.7, 30.3, 25.6, 25.4, 18.6; **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ – 41.3.

Preparation of *tert*-butyl 2-(*tert*-butyldimethylsilyloxy),2-*d*-3-hydroxy-3-phenylpropanoate (11):



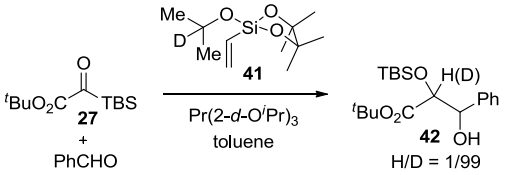
2-*d*-isopropanol was prepared according to Friedman's procedure: [31] a flame-dried 25-mL round-bottomed flask with attached reflux condenser was charged with lithium aluminum deuteride (1.39 g, 33.1 mmol, 0.5 equiv). Dry diglyme (13 mL) was added, and the solution was cooled to 0 °C. Dry acetone (4.85 mL, 3.84 g, 66.1 mmol, 1.0 equiv) was added dropwise, and the reaction was warmed slowly to room temperature for 1 hour and then heated to 100 °C for 45 min. The flask was cooled to 0 °C and the reaction was quenched by the addition of 2-*n*-butoxyethanol (13 mL). The resulting suspension was stirred at room temperature for 1 h, and the desired product was distilled from the product mixture. Spectral data for the distilled product matched the reported data;[39] 5% diglyme was present, but the product was used without further purification in the next reaction.



2-(2-d-isopropoxy)-4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxasilolane (41). The title compound was prepared from chlorosilane **S1** and 2-*d*–isopropanol according to the general procedure. Yield = 63%. bp = 46 °C (0.05 mm Hg); Analytical data: **IR** (thin film, cm^{-1}): 2975, 2246, 1713, 1600, 1407, 1368, 1223, 1183, 1148 . **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.13 (dd, *J* = 14.4, 4.4 Hz, 1H), 6.09 (dd, *J* = 20.8, 4.4 Hz, 1H), 5.92 (dd, *J* = 14.4, 20.8 Hz, 1H),

1.29 (s, 6H), 1.23 (s, 6H), 1.20 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.7, 129.7, 81.4, 65.3 (R_3C-D), 25.7, 25.6, 25.3; **^{29}Si NMR** (79.5 MHz, $CDCl_3$) δ -42.0.

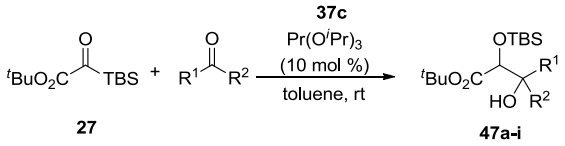
Labeling Studies Using Siloxane 10



***tert*-butyl 2-(*tert*-butyldimethylsilyloxy),2-*d*-3-hydroxy-3-phenylpropanoate (42):** In a nitrogen-filled glove box, a 20-mL scintillation vial was charged with praseodymium (III) isopropoxide (6.4 mg, 0.02 mmol, 0.1 equiv). The vial was sealed and transferred to a fume hood with an attached nitrogen inlet, wherethe praseodymium catalyst was stirred with 2-*d*-isopropanol (0.3 mL) for 1 h at room temperature. The excess alcohol was removed under high vacuum (0.05 mm Hg). A separate oven-dried 20-mL scintillation vial was charged with *tert*-butyl *tert*-butyldimethylsilyl glyoxylate (50 mg, 0.204 mmol, 1.0 equiv) and benzaldehyde (32 mg, 0.302 mmol, 1.5 equiv). The vial was flushed with nitrogen, and toluene (1.0 mL) was added. A solution of siloxane **41** (94 mg, 0.41 mmol, 2.0 equiv) in toluene (1 mL) was added to the praseodymium salt, and the solution of silyl glyoxylate and aldehyde were added via syringe in one portion at room temperature to the solution of praseodymium (III) isopropoxide and siloxane **41**. Additional toluene (1 mL) was used to effect complete transfer of reagents. After complete consumption of the starting material as indicated by TLC (1 min), the reaction was quenched by the addition of saturated ammonium chloride and extracted with ether (3x5 mL). The combined organic fractions were washed

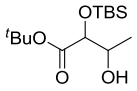
with brine, dried with magnesium sulfate, and concentrated in vacuo. The crude material was purified via flash chromatography using 92.5:7.5 hexanes:ethyl acetate to give the deuterium-labeled product as a clear, colorless oil (40 mg , 54%, 1.5:1 dr). See reference 4 for the analytical data for the unlabeled compound. Analytical data: **IR** (thin film, cm^{-1}): *mixture of diastereomers:* 2930, 2851, 2345, 1735, 1460, 1362, 1214, 1151, 997, 850, 773; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer:* δ 7.37- 7.28 (m, 5H), 4.95 (d, *J* = 7.2 Hz, 1H), 3.05 (d, *J* = 7.2 Hz, 1H), 1.42 (s, 9H), 0.84 (s, 9H), -0.02 (s, 3H), -0.18 (s, 3H); *minor diastereomer:* 7.40- 7.28 (m, 5H), 4.85 (d, *J* = 4.4 Hz, 1H), 3.02 (d, *J* = 4.4 Hz, 1H), 1.39 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), -0.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) *mixture of diastereomers*: δ 170.8, 170.6, 140.5, 140.0, 128.1, 128.0, 127.9, 127.7, 127.2, 126.4, 81.8, 75.5, 75.3, 27.9, 25.6, 18.2, 18.1, -5.0, -5.2, -5.7, -5.8 (three coincident resonances in the 75-82 ppm range, two coincident resonances in the 18-28 ppm range); **LRMS**: *mixture of diastereomers:* [m+Na^+] expected: 376.2, observed: 376.3.

General Procedure for Lanthanide-Catalyzed Cascade Reactions:

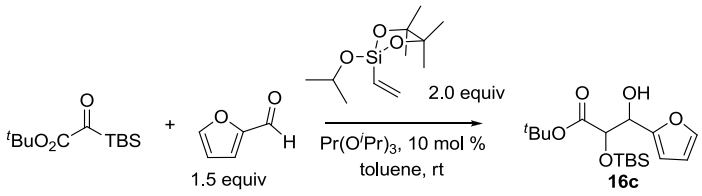


***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-phenylpropanoate (47a)**: In a nitrogen-filled glove box, a 20-mL scintillation vial was charged with praseodymium (III) isopropoxide (6.4 mg, 0.02 mmol, 0.1 equiv). The vial was sealed and transferred to a fume hood and a nitrogen inlet was attached. A separate oven-dried 20-mL scintillation vial was charged with *tert*-butyl *tert*-butyldimethylsilyl glyoxylate (50 mg, 0.204 mmol, 1.0 equiv) and benzaldehyde (32 mg, 0.301 mmol, 1.5 equiv). The vial was flushed with nitrogen, and

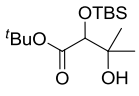
toluene (1.0 mL) was added. A solution of siloxane **6c** (94 mg, 0.41 mmol, 2.0 equiv) in toluene (1.0 mL) was added to the praseodymium salt, and then the solution of silyl glyoxylate and aldehyde were added via syringe in one portion at room temperature. Additional toluene (1 mL) was used to effect complete transfer of reagents. After complete consumption of the starting material as indicated by TLC (95:5 hexanes:ethyl acetate, R_f = 0.44, 1 min), the reaction was quenched by the addition of saturated ammonium chloride and extracted with ether (3x5 mL). The combined organic fractions were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The crude material was purified via column chromatography using 92.5:7.5 hexanes:ethyl acetate to give the desired product as a clear, colorless oil (94 mg , 83%, 1.5:1 dr). Spectral data matched those reported in the literature.[6]



***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-hydroxybutanoate (47a).** The title compound was isolated as a byproduct in reactions employing silacycle **37a (**ca. 1:1 d.r.). Analytical data: **IR** (thin film, cm^{-1}): 2977, 2958, 2933, 2898, 2887, 2858, 1750, 1727, 1474, 1368, 1254, 1146, 878, 837, 775, 673; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer:* δ 4.01 (d, *J* = 4.8 Hz, 1H), 3.976 to 3.901 (m, 1H), 2.34 (d, *J* = 6.4 Hz, 1H), 1.46 (s, 9H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); *minor diastereomer:* δ 3.976 to 3.901 (m, 1H), 3.88 (d, *J* = 4 Hz, 1H), 3.88 (d, *J* = 4 Hz, 1H), 2.40 (d, *J* = 7.6, 1H), 1.45 (s, 9H), 1.19 (d, *J* = 6 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) *mixture of diastereomers*: δ 171.2, 170.9, 81.6, 76.6, 76.2, 69.5, 28.0, 25.7, 19.3, 18.2, 17.8, -4.8, -5.4, -5.5; **LRMS**. expected: 290.2, observed: 290.2. **TLC** (90:10 hexanes:EtOAc): R_f = 0.18.



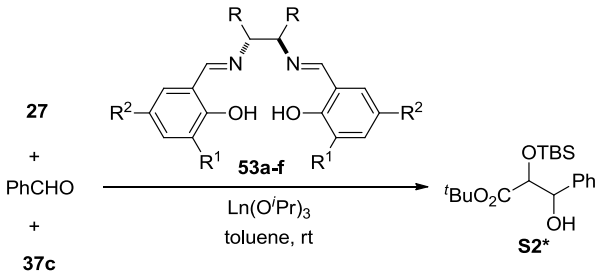
***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-(furan-2-yl)-3-hydroxypropanoate (47c)**. The title compound was prepared according to the general procedure and was isolated as a clear, light yellow oil (71%, 1.3:1 d.r.). Analytical data: **IR** (thin film, cm^{-1}): *mixture of diastereomers:* 2925, 2858, 2363, 1742, 1474, 1368, 1252, 1150, 1005, 876, 780; *major diastereomer* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.6 Hz, 1H), 6.33 (dd, *J* = 1.6, 3.2 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 4.94 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.40 (d, *J* = 3.6 Hz, 1H), 2.98 (d, *J* = 8.8 Hz, 1H), 1.44 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), -0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.2, 153.5, 141.7, 110.3, 107.3, 81.9, 74.4, 70.4, 27.9, 25.5, 18.1, -5.1, -5.8; **LRMS**: (*m*+Na^+/*z*) expected: 365.18, observed: 365.2. *minor diastereomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 0.8 Hz, 1H), 6.34 (d, *J* = 1.6 Hz, 1H), 6.31 (dd, *J* = 1.6, 0.8 Hz, 1H), 4.87 (dd, *J* = 5.6, 6.8 Hz, 1H), 4.37 (d, *J* = 5.6 Hz, 1H), 2.79 (d, *J* = 6.8 Hz, 1H), 1.40 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), -0.05 (s, 3H); **^{13}C NMR:** δ 170.3, 152.9, 141.9, 110.3, 108.2, 81.9, 74.7, 69.7, 27.9, 25.6, 18.1, -5.0, -5.6**; LRMS**: (*m*+Na^+/*z*) expected: 365.18, observed: 365.2. **TLC** (90:10 hexanes: EtOAc): major diastereomer: R_f = 0.27; minor diastereomer: R_f = 0.18.



***tert*-butyl-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-methylbutanoate (47c)**. Isolated as a byproduct in reactions employing silacycle **6c**. Analytical data: **IR** (thin film, cm^{-1})*:* 3464, 2974, 2936, 2858, 1722, 1698, 1473, 1128, 838, 782; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.85 (s, 1H), 2.91 (s, 1H), 1.48 (s, 9H), 1.22 (s, 3H), 1.20 (s, 3H), 0.92 (s, 9H), 0.08

(s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.3, 81.8, 79.0, 72.3, 28.0, 25.7, 25.4, 18.1, -4.8, -5.4**; LRMS**: (*m+Na$^+$/z)* expected: 304.21, observed: 304.2. **TLC** (90:10 hexanes:EtOAc): R_f = 0.2.

Ligand Screens: General Procedure:

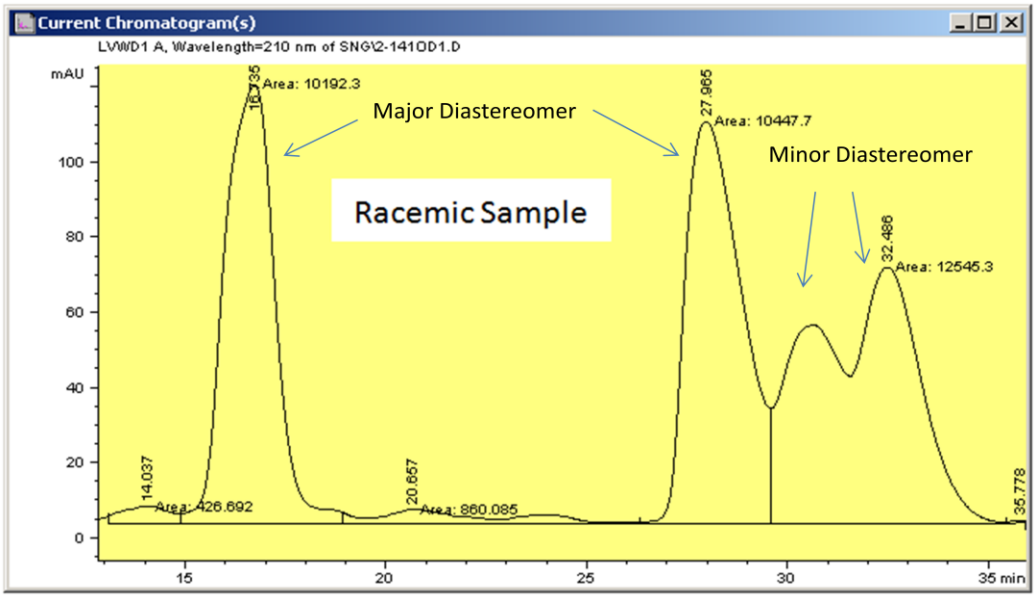


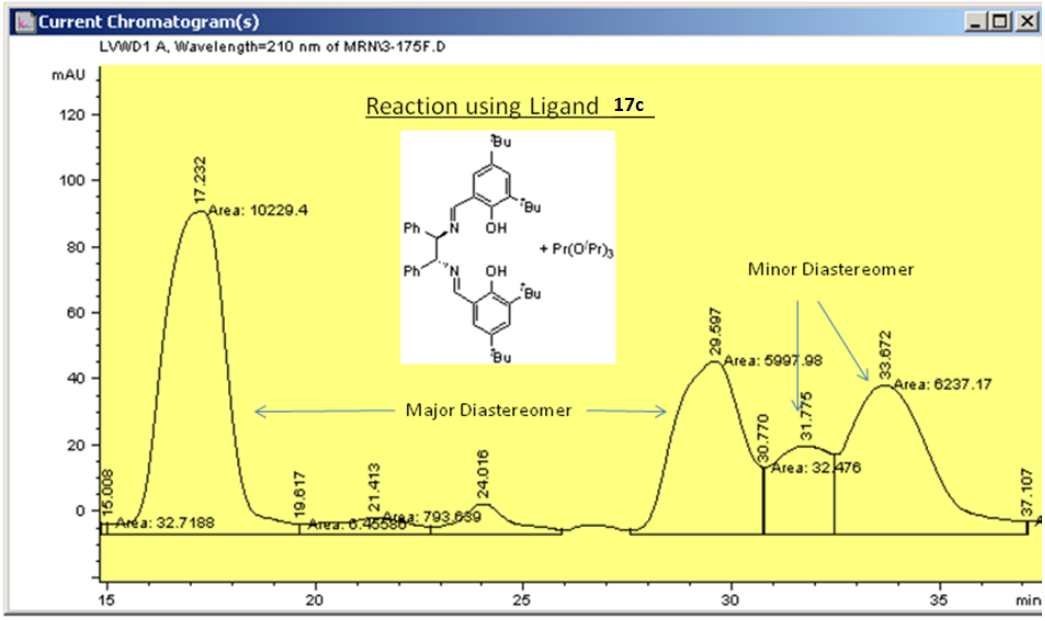
In a nitrogen-filled glove box, a 20-mL scintillation vial was charged with ligand **53b** (9.4 mg, 0.015 mmol, 0.1 equiv) and $Pr(O^iPr)_3$ (4.8 mg, 0.015 mmol, 0.1 equiv). The vial was sealed and removed to a fume hood and flushed with nitrogen. Dry toluene (1.0 mL) was added, and the reaction was stirred for 30 min. The solvent was removed using high vacuum to afford the ligand-metal complex. Toluene (1.0 mL) was again added and removed after 30 min. A separate oven-dried 20-mL scintillation vial was charged with *tert*-butyl *tert*-butyldimethylsilyl glyoxylate **1** (38 mg, 0.157 mmol, 1.0 equiv) and benzaldehyde (23.9 mg, 0.225 mmol, 1.5 equiv). The vial was flushed with nitrogen, and the reagents were dissolved in toluene (1.0 mL). Siloxane **6c** (72 mg, 0.314 mmol, 2.0 equiv) in toluene (0.5 mL) was added to the praseodymium complex, and the solution of silyl glyoxylate and aldehyde were added via syringe all at once at room temperature to the suspension of the ligand-metal complex. Additional toluene (0.5 mL) was used to effect complete transfer of reagents. After complete consumption of the starting material as indicated by TLC (20 min), the reaction was quenched by the addition of saturated ammonium chloride and extracted with

ether (3x5 mL). The combined organic fractions were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography using 90:10 hexanes: ethyl acetate to give the desired product in 80% yield. SFC analysis showed a 63:37 e. r. for the major diastereomer.

SFC Analytical Data:

CSP-SFC analysis of **S2*** showed that the major diastereomer was formed in a 63:37 e.r. as determined by CSP-SFC analysis (Chiralpak OD column, 0.5% MeOH, 1.0 mL/min, 150 psi, 24 °C, 210 nm, t_r-major diastereomer, major enantiomer: 16.1 min, t_r- major diastereomer, minor enantiomer: 28.0 min, t_r-minor diastereomer, minor enantiomer: 30.7 min, t_r- minor diastereomer, major enantiomer: 32.5 min; CSP-SFC traces for the racemic and enantioenriched products are attached in the following pages).


Current Chromatogram(s)
LVWD1 A, Wavelength=210 nm of SNG\2-141OD1.D
mAU
Area: 10192.3
16.735
Major Diastereomer
27.965
Area: 10447.7
Minor Diastereomer
Racemic Sample
32.486
Area: 12545.3
14.037
Area: 426.692
20.657
Area: 860.085
35.778
min


Current Chromatogram(s)
LVWD1 A, Wavelength=210 nm of MRN\3-175F.D
mAU
Reaction using Ligand 17c
17.232
Area: 10229.4
+ Pr(OiPr)3
Minor Diastereomer
29.597
Area: 5997.98
33.672
Area: 6237.17
Major Diastereomer
30.770
31.775
Area: 32.476
16.008
Area: 32.7188
19.617
21.413
24.016
Area: 793.659
37.107
min

1.6 References

[1] Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am Chem. Soc.* **2008**, *130*, 6340-6341.

[2] Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891-14899.

[3] Catalytic functionalization of carbinol C-H bonds have also been achieved: Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W. J. *J. Am. Chem. Soc.* **2005**, *127*, 10836-10837.

[4] For a monograph on the aldol reaction, see: *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

[5] Nicewicz, D. A.; Breteche, G.; Johnson, J. S.; Bryan, C.; Lautens, M. *Org. Synth.* **2008**, *85*, 278-286.

[6] Linghu, X.; Satterfield, A. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 9302-9303.

[7] Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426-3427.

[8] Brook, A. G. *Acc. Chem. Res*. **1974**, *7*, 77-84.

[9] Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc*. **2005**, *127*, 6170-6171.

[10] Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008,** *130*, 17281-17283.

[11] Schmitt, D. C.; Johnson, J. S. *Org. Lett.*, **2010**, *12*, 944-947.

[12] Greszler, S. N.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3689-3691.

[13] Boyce, G. R. Unpublished results.

[14] See chapter three for additional details.

[15] (a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, 1007- 1017. (b) Campbell, E. J.; Hongying, Z.; Nguyen, S. T. *Org. Lett.* **2001,** *3*, 2391-2393. (c) Yin, J.; Huffman, M. A.; Conrad, K. A.; Armstrong, J. D. *J. Org. Chem.* **2006**, *71*, 840- 843.

[16] Adkins, H.; Franklin, R. C. *J. Am. Chem. Soc.* **1941**, *63*, 2381-2383.

[17] Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429-1433.

[18] Reetz, M. T. *Pure Appl. Chem.* **1988**, *60*, 1607-1614.

[19] Herold, T.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 768-769.

[20] Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.

[21] Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.

[22] Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X., Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920-7921.

[23] Wang, X.; Meng, Q; Perl, N.; Yue, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12806-12807.

[24] Denmark, S. E.; Griedel, B. D.; Coe, D. M. *J. Org. Chem.* **1993**, *58*, 988-990.

[25] Myers, A. G.; Widdowson, K. L.; Kukkola, P. J. *J. Am. Chem. Soc.* **1992**, *114*, 2765 2767.

[26] Sunderhaus, J. D.; Lam, H.; Dudley, G. B. *Org. Lett*. **2003,** *5*, 4571-4573.

[27] Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138-4139.

[28] Satterfield, A. D. I. *[1,2]-Brook rearrangement: application of silyl glyoxylates in a novel glycolate aldol reaction and in a controlled oligomerization to complete the total synthesis of zaragozic acid C. II. Progress toward the total synthesis of pactamycin*, Diss. The University of North Carolina at Chapel Hill, **2009**. Chapel Hill, NC: University of North Carolina at Chapel Hill, **2009**.

[29] For reduction of acyl silanes, see: (a) Bolm, C.; Kasyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Guenther, K.; Wagner, C. *Org. Lett.* **2002**, *4*, 2265-2267. (b) Brook, A. G.; Quigley, M. A.; Peddle, G. J. D.; Schwartz, N. V.; Warner, C. M. *J. Am. Chem. Soc.* **1960**, *82*, 5102-5106. (c) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609-5617.

[30] For coordination number of 6, M^{3+}: Shannon, R. D.; Prewitt, C. T. *Acta Cryst. A* **1976**, *32*, 751-767.

[31] Friedman, L.; Jurewicz, A. T. *J. Org. Chem.* **1968**, *33*, 1254-1255.

[32] Mehrotra, R. C.; Singh, A.; Tripathi, U. M. *Chem. Rev.* **1991**, *91*, 1287-1303.

[33] Aspinall, H. C. *Chem. Rev.* **2002,** *102*, 1807-1850.

[34] Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453-463.

[35] Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 601-603.

[36] Tishchenko, J. *Russ. Phys. Chem. Soc.* **1906**, *38*, 482.

[37] Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. Eur. J.* **2003**, *9*, 2419-2438.

[38] Eames, J.; Coumbarides, G. S.; Suggate, M. J.; Weerasoriya, N. *Eur. J. Org. Chem.* **2003**, *4*, 634-641.

[39] Klomp, D.; Maschmeyer, T.; Hanefeld, U.; Peters, J. A. *Chem. Eur. J.* **2004**, *10*, 2088-2093.

CHAPTER TWO

DIASTEREOSELECTIVE DE NOVO SYNTHESIS OF PENTASUBSTITUTED γ-BUTYROLACTONES FROM SILYL GLYOXYLATES AND KETONES VIA DOUBLE REFORMATSKY REACTIONS*

2.1 Introduction

The prevalence of γ-butyrolactone substructures in natural products continues to stimulate interest in the development of concise and selective methods for their preparation. Assembly of γ-butyrolactones possessing multiple stereocenters typically requires the synthesis of complex precursors via specialized routes,[1-3] and consequently, modular assembly strategies that circumvent this limitation are welcome additions to the synthetic toolbox. In this chapter, we report diastereoselective reactions of Reformatsky reagents, silyl glyoxylates, and ketones that provide densely functionalized pentasubstituted γ-butyrolactones containing three contiguous stereocenters. The reactions collectively constitute a rare example of the diastereoselective generation of vicinal stereogenic tertiary alcohols via aldolization.[4-6]

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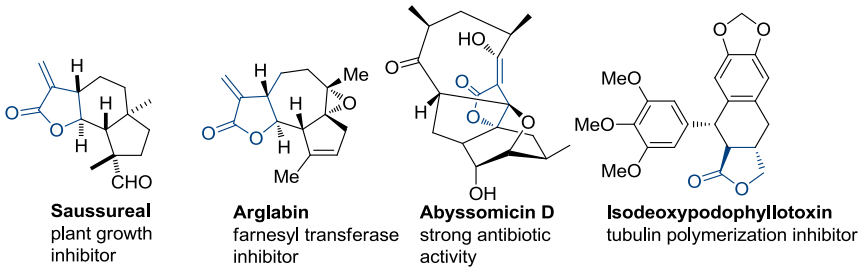
2.2 Background

2.2.1 Prevalence of γ-Butyrolactones in Nature

The γ-butyrolactone moiety is an exceedingly common structural element found in nearly 10% of all natural products.[1,7] In addition to mono-, di-, and trisubstituted monocyclic examples, countless natural products also contain γ-butyrolactones embedded in a complex molecular framework. Because many of these compounds exhibit biological properties of medicinal relevance, the development of routes that allow access to complex γ-butyrolactone products remains an important synthetic goal. Few general methods exist for the synthesis of functionalized lactones; most approaches are target-driven, allowing access to very specialized substructures.[2] Figure 2-1 illustrates several examples of natural products containing γ-butyrolactone subunits as well as their reported biological activities.

Figure 2-1. Representative Natural Products Bearing γ-Butyrolactone Subunits[2]

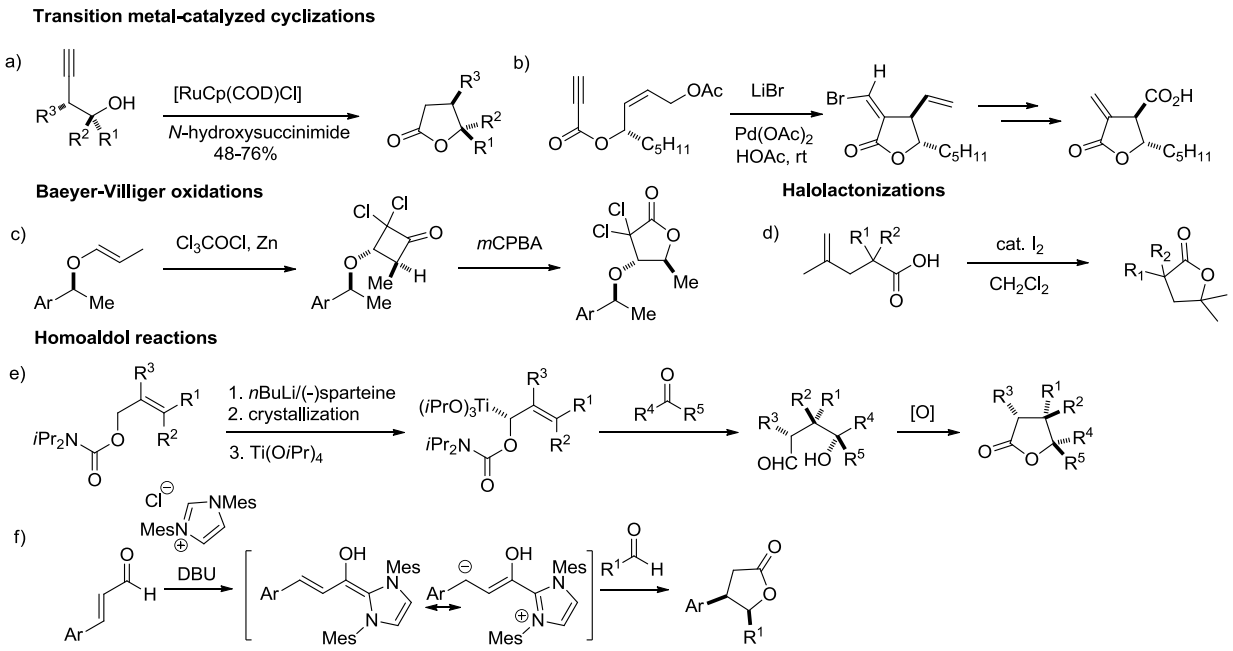


2.2.2 Synthetic Approaches to γ-Butyrolactones

Apart from the obvious lactonization of γ-hydroxybutyric acid derivatives, a variety of unique approaches have been devised for the synthesis of highly functionalized γ-butyrolactones (Figure 2-2). Among these are the transition metal-catalyzed cyclizations of either homopropargylic alcohols[8] or enynes,[9] Baeyer-Villiger oxidations of cyclobutanone derivatives,[10] iodolactonizations of γ,δ–unsaturated acids,[11] and homoaldol reactions.[12,13] The latter have received considerable interest from Hoppe, who has developed several

asymmetric syntheses of γ-butyrolactones from chiral homoenolates;[12] the necessary stereocontrol is afforded by the propensity of the allylic carbamate precursors to undergo stereoselective deprotonation by butyllithium in the presence of (–)-sparteine. A major challenge that emerges from an examination of these routes, however, is the requisite synthesis of often complex precursors prior to the lactone-forming transformations. Consequently, methods that allow for the *de novo* synthesis of densely functionalized γ-butyrolactones from simple starting materials are particularly enticing.

Figure 2-2. Common Synthetic Routes to γ-Butyrolactones



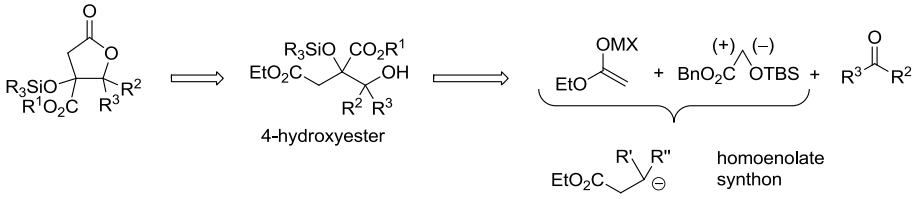
A general retrosynthetic analysis leads to a 4-hydroxycarbonyl compound as an appropriate precursor; however, while the aldol reaction is the preeminent method for the introduction of the 3-hydroxycarbonyl moiety,[14] the 4-hydroxy analogue suggests the use of the less established homoaldol approach. In addition to the aforementioned homoenolate approach developed by Hoppe,[15] nucleophilic carbene catalysis has emerged as a general

method for the synthesis of γ-butyrolactones from enal precursors via an intermediate 4-hydroxyaldehyde equivalent.[13]

2.2.3 Silyl Glyoxylate Utility in Three-Component Coupling Reactions

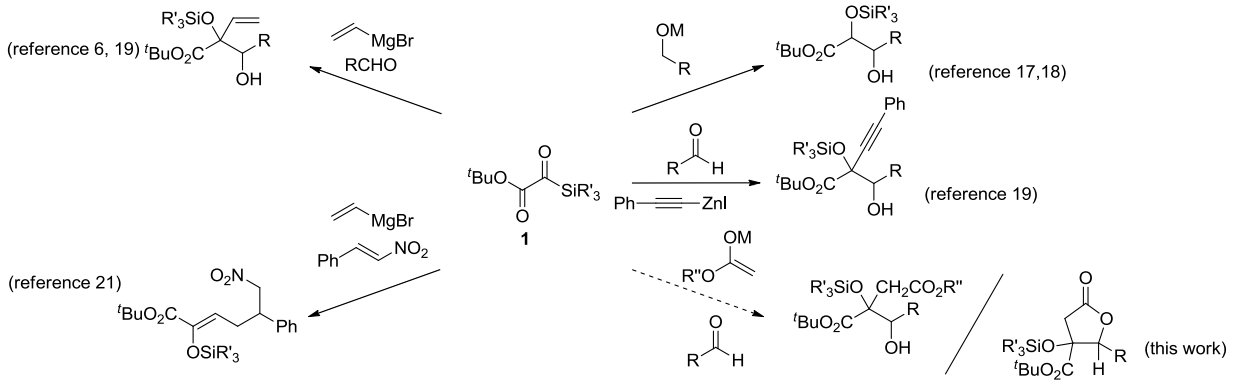
In this chapter, we discuss our work on the development of a highly diastereoselective synthesis of pentasubstituted γ-butyrolactones from Reformatsky reagents, silyl glyoxylates, and ketones. The origin of the title reaction was our speculation that the secondary glycolate enolate, generated through nucleophilic attack on the silyl glyoxylate by a metal enolate, could function effectively as a formal homoenolate and allow access to the 4-hydroxy ester subunit through a terminal reaction with an aldehyde or ketone (Figure 2-3).

Figure 2-3. Plausible Route to γ-Butyrolactones from Silyl Glyloxylates



As discussed in chapter one, silyl glyoxylates[16] (**1,** Figure 2-4) frequently participate in coupling reactions that are initiated by hydridic[17,18] and nonstabilized carbon nucleophiles[6,19-21] and are generally terminated by reactions with electrophiles such as aldehydes and ketones[6,17-19] or Michael acceptors.[21] Prior to this work, the initiation of silyl glyoxylate cascades by enolate nucleophiles had not been thoroughly investigated,[22] and we recognized that their successful incorporation into the silyl glyoxylate reaction manifold would allow access to new classes of functionalized products.

Figure 2-4. Nucleophilic Promoters and Electrophiles in Silyl Glyoxylate Cascades



2.2.4 Reformatsky Reagents: Background and Experimental Protocols

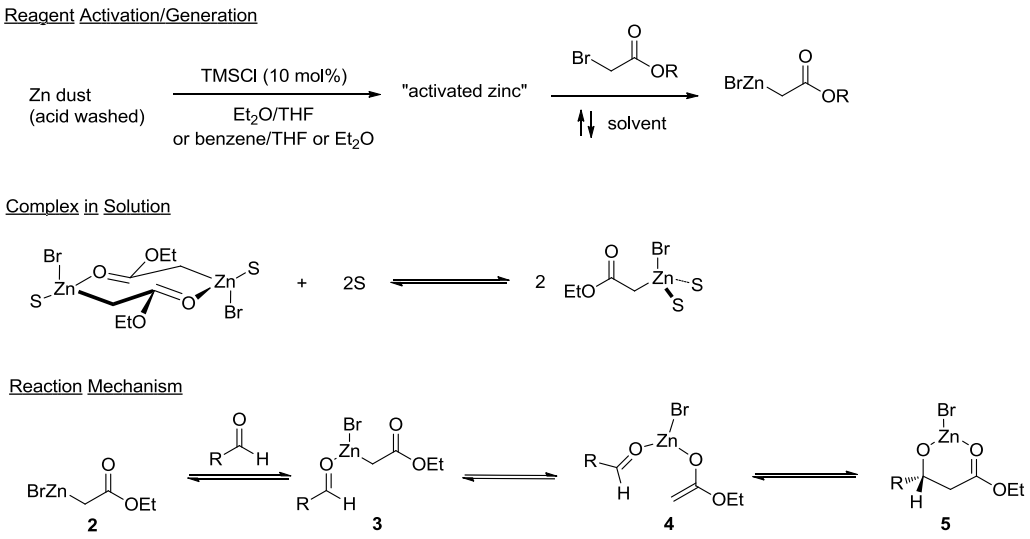
For over a century the Reformatsky reaction has found widespread use as a mild method for generating β-hydroxyalkanoates. The reaction is formally an oxidative addition of zinc into the carbon-halogen bond of an α-haloester or ketone followed by an aldol reaction with an aldehyde or ketone electrophile. Advantages typically cited in the use of Reformatsky reagents are good chemoselectivities, the ability to run the reactions under neutral conditions, the use of nontoxic and cheap metals, and their frequent success in intramolecular reactions of highly functionalized derivatives. Nevertheless, the classical Reformatsky reaction has acquired a reputation for poor reproducibility and low enantio- and diastereoselectivities, which has to some degree hindered developments in its use. [23,24,25]

Paramount to achieving reproducibility in Reformatsky reactions is the generation of a highly activated zinc suspension. As an alternative to the generation of Rieke zinc,[26] commercial zinc dust has been subject to several different activation protocols, including dibromoethane,[27] trimethylsilyl chloride,[28] and bromine,[29] all of which act to remove the oxide coating from the surface of the metal. Suspensions of activated zinc powder readily

undergo oxidative addition into the C–Br bond of α-bromoesters and ketones to give a solution of the Reformatsky reagent **2**, which then reacts with aldehydes and ketones to give aldol products. The reactions may also be performed under Barbier conditions, where a solution of the bromoester and electrophile are added slowly to a refluxing suspension of zinc.[25]

Reformatsky reagents have been shown to exist as dimers in solution that are in equilibrium with the solvated monomers, with the position of equilibrium determined by the polarity and coordinating ability of the solvent.[30] NMR studies suggest that the C-metalated form of the enolate predominates, and the commonly accepted mechanism for conversion to the O-metalated isomer involves initial coordination of the electrophile to the C–metalated reagent **2** to induce a reversible C-to-O zinc migration that arrives at a more standard zinc enolate (**3** to **4**). Aldol reaction may then proceed through a standard six-membered transition state (Figure 2-5).[30]

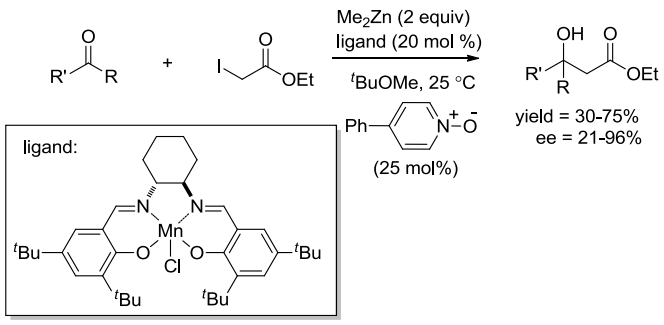
Figure 2-5. Reformatsky Reagent Generation and Reaction Mechanism



2.2.5 Reformatsky Reagents: Recent Advances and Asymmetric Applications

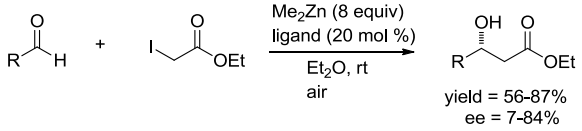
Progress has recently been made in the development of an asymmetric version of the Reformatsky reaction through the introduction of chiral ligands or the use of chiral auxiliaries.[25c] Although these stoichiometric means have been met with some success, few examples of a truly catalytic, enantioselective Reformatsky reaction have been reported. In 2006 Cozzi achieved the first practical catalytic enantioselective addition of iodoacetate-derived Reformatsky reagents to ketones through a dimethylzinc-mediated process.[31] Manganese salen complexes were found to be effective asymmetric catalysts, and the β-hydroxyalkanoate products were obtained in low to moderate yields and with enantioselectivities up to 96% for several ketone substrates (Scheme 2-1). Although a mechanistic proposal was not included, the authors were able to rule out a radical mechanism through the succesful use of allyl iodoacetate as the parent bromoester.

Scheme 2-1. Catalytic Enantioselective Addition of Reformatsky Reagents to Ketones[31]



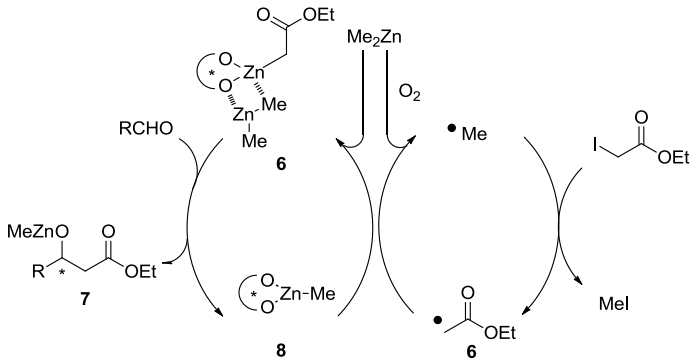
Feringa has reported catalytic enantioselective Reformatsky reactions with aldehydes which likely proceeded through a radical pathway initiated by reaction of dimethylzinc with O_2.[32] The reaction afforded moderate to good yields of the desired products with enantioselectivities up to 84% (Scheme 2-2).

Scheme 2-2. Catalytic, Enantioselective Reformatsky Reactions with Aldehydes[32]



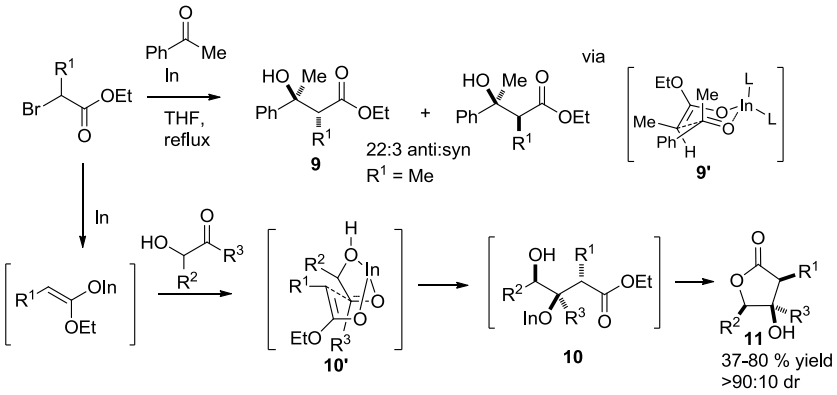
The proposed catalytic cycle involves homolysis of the Zn–Me bond to give a reactive methyl radical, which undergoes propagation with the iodoacetate to generate the stabilized radical species **6**. Reformatsky reaction with the aldehyde is believed to occur by simultaneous metathesis with dimethylzinc to release the zinc aldolate **7** and regenerate the methylzinc species **8** (Figure 2-6). The reaction was rendered enantioselective through the use of chiral binol derivatives.

Figure 2-6. Proposed Catalytic Cycle[32]



Baba and coworkers recently reported an increase in the diastereoselectivity in Reformatsky reactions of ketones mediated by indium, which they explained with a cyclic transition state model.[33] With nonchelating ketones, chair-like transition state **9′** was proposed to explain the predominant production of the *anti* diastereomer **9**. The addition of indium enolates to chelating ketones was also shown to afford good diastereoselectivities for the *syn* products, which undergo spontaneous lactonization under the reaction conditions. (Figure 2-7).

Figure 2-7. Diastereoselective Indium-Mediated Reactions[33]

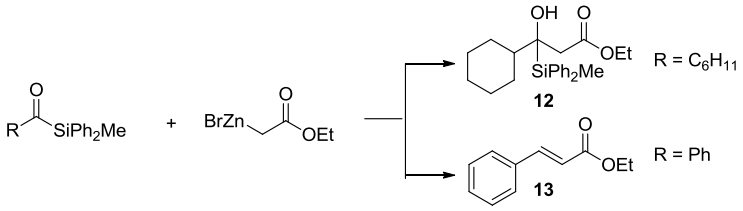


In order to explain the formation of the *syn* product **11** with chelating ketones, a boat-like transition state was invoked (**10′**). Worth noting is the variety of transition states that are proposed for Reformatsky reactions; depending on the structure of the electrophile and the identity of the metal, chair, boat, and twist-boat transition states have all been proposed to account for observed diastereoselectivities.[25]

2.2.6 Reformatsky Reactions with Acyl Silanes

No precedent existed for the reaction of Reformatsky reagents with silyl glyoxylates prior to this work, but reactions with acyl silanes have been reported by Fürstner et al.[34] Reformatsky reactions with aryl and alkyl acyl silanes occured through divergent pathways. Brook rearrangement was disfavored with alkyl acyl silanes, affording hydroxysilane **12** as the major product (Figure 2-8). With aryl acyl silanes, Brook rearrangement occurred, but elimination of the silanoate was favorable, giving ethyl cinnamate as the major product. Although we could not predict the propensity for these byproducts to form in reactions with silyl glyoxylates, we were cognizant of their potential production as we approached the studies detailed in the current chapter.

Figure 2-8. Reformatsky Reactions of Acyl Silanes[34]

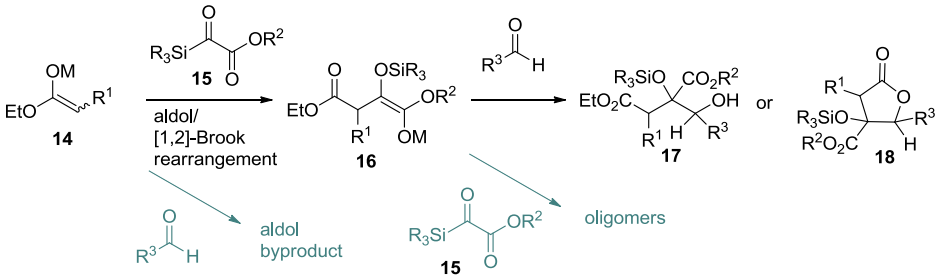


2.3 Results

2.3.1 Anticipated Mechanistic Challenges

We intially undertook an investigation of enolates and their equivalents in an effort to expand the range of nucleophilic promoters in silyl glyoxylate-based transformations.[22] The proposed reaction pathway illustrated by Figure 2-9 involves initial reaction of the silyl glyoxylate with an ester enolate, which, after [1,2]-Brook rearrangement, exposes a secondary glycolate enolate **16** capable of reacting with an aldehyde or ketone electrophile to afford the linear alkanoate **17**. If lactonization were facile, expulsion of ethoxide should result in the formation of γ-lactones of the type **18**.

Figure 2-9. Proposed Reactivity and Chemoselectivity Issues



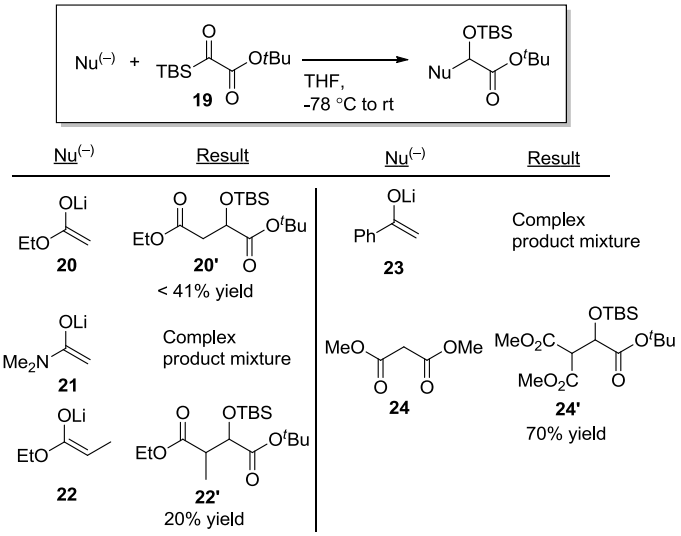
We recognized two key reaction parameters that would determine the ultimate success of the proposed coupling. The presence of multiple enolates in solution presented a chemoselectivity issue. The initial Reformatsky reagent would need to react selectively with the silyl glyoxylate, and the secondary glycolate enolate would need to react selectively with the aldehyde or ketone. Aldol byproducts and silyl glyoxylate oligomers would be expected

if these chemoselectivity mandates were not met. Additionally, the identity of the cation has been shown to be crucial in mediating Brook rearrangement of silyl glyoxylates, and while magnesium,[6,17] lithium,[17] and lanthanide[18] cations have previously been shown to be effective, mixed results have been reported with zinc.[17,19,20,35]

2.3.2 Identification of Competent Enolate Nucleophiles

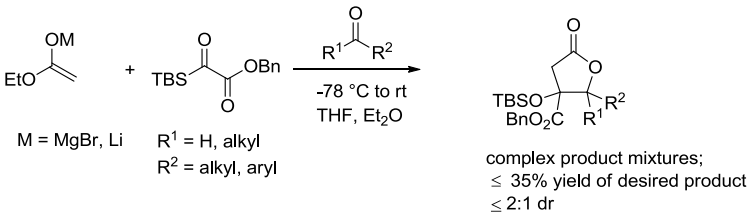
Several stabilized carbanion additions to silyl glyoxylate **19** were initially investigated (Figure 2-10). Lithium ester enolates afforded the desired adducts **20′** and **22′**, albeit in low yields, while amide enolates and ketone enolates (**21** and **23**) gave complex product mixtures. Yields of the products from addition of malonate nucleophiles were generally good, although subsequent attempts to utilize these additions in three-component couplings with aldehyde or ketone electrophiles failed. This is presumably due to the higher acidity of substituted malonates than the intermediate glycolate enolates;[36] proton transfer likely returned **24′** under these conditions through a glycolate enolate quench, and therefore incorporation of aldehyde or ketone electrophiles was not successful.

Figure 2-10. Stabilized Carbanion Nucleophile Reactivity



The moderate yields with ester enolates led us to further investigate their viability in cascade reactions with silyl glyoxylates. Preliminary results with lithium and magnesium enolates did in fact result in production of the desired lactone products, but complex product mixtures were observed in all cases and with no greater than 35% yield and 2:1 dr (Scheme 2-3).

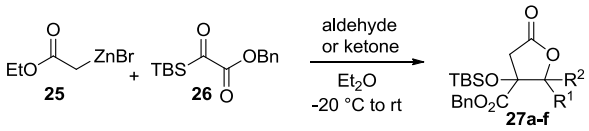
Scheme 2-3. Preliminary Enolate Screens

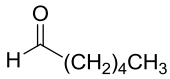
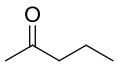


Much of the failure of these initial attempts can be attributed to poor chemoselectivity: silyl glyoxylate oligomer production and aldol reactions with the aldehyde or ketone electrophiles also present in solution were the largest sources of byproduct formation. Because desired product was obtained in these reactions, however, further experimentation was warranted. We hypothesized that modulation of the enolate reactivity might improve chemoselectivities as well as the yields of the desired products. A logical means for accomplishing this goal was the use of Reformatsky reagents.

Our initial experimental protocol consisted of addition of a solution of the silyl glyoxylate and carbonyl to a cooled solution of the Reformatsky reagent (-20 °C), followed by warming the reactions to room temperature. We were pleased to observe complete consumption of the silyl glyoxylate and production of the desired lactones with all electrophiles screened, but poor to moderate yields and diastereoselectivities were achieved. Aldehydes were particularly poor substrates, (Table 1, entries **27a-c**), as they were found to

Table 2-1. Initial Electrophile Screens with Reformatsky Reagents[a]



entry	electrophile	yield[b]	dr
27a		27%	1.7:1
27b		33%	1.5:1
27c		53%	2:1
27d		61%	n/a
27e		59%	2:1
27f		57%	1.3:1

[a.] All reactions: 2.0 equiv aldehyde or ketone, 1.5 equiv Reformatsky reagent, [**26**]$_0$ = 0.05 M in Et_2O, reactions started at -20 °C and warmed to rt over 30 min. [b.] Isolated yields. See section 2.5 for additional experimental details.

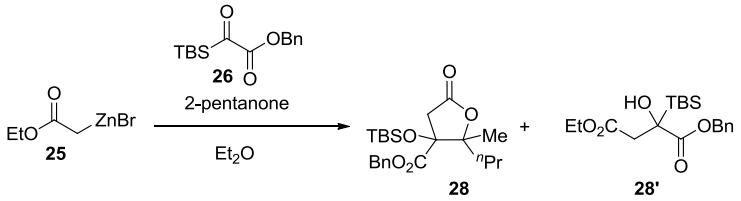
be much more competitive electrophiles with the Reformatsky reagents than were ketones. Moderate yields were realized with acetone, acetophenone, and 2-pentanone (**27d-f**); isobutyraldehyde gave much higher yields than did linear and aryl aldehydes. The intermediate results with 2-pentanone prompted an investigation of the temperature effects on the diastereoselection. These studies led to a greater understanding of the mechanism of the reaction and ultimately yielded an improved experimental protocol.

2.3.3 Optimization of Reaction Conditions

Because of the attenuated reactivity of Reformatsky reagents,[25] we could perform the reactions at temperatures no lower than -20 °C in order to achieve reaction with the silyl glyoxylate. Complete consumption of the starting material was observed at this temperature, although we also observed only trace product formation. Curiously, the major product formed under these conditions was the hydroxysilane **28′**, which resulted from reaction with

the Reformatsky reagent but without subsequent Brook rearrangement of the intermediate zinc alkoxides. We conjectured that we might exploit this apparent suppression of Brook rearrangement via careful control of the reaction temperature, which might circumvent the initial chemoselectivity issues with the carbonyl electrophile.

Table 2-2. Effects of Temperature on Product Distribution[a]

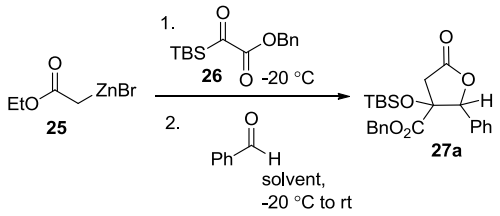


entry	T (°C)	yield **28**[b]	yield **28′**[b]
1	-20	trace	81%
2	-20 to -10[c]	33%	41%
3	-20 to rt[c]	73%	trace

[a.] All reactions: 2.0 equiv ketone, 1.5 equiv Reformatsky reagent, [**26**]$_0$ = 0.05 M in Et_2O, 30 min reaction time. [b.] Yield determined by ^{1}H NMR spectroscopy with internal standard. [c.] Ketone added after complete consumption of **26** was observed at -20 °C. See section 2.5 for additional experimental details.

Warming the reaction to -10 °C resulted in comparable yields of the desired lactone products and the hydroxysilane byproduct, suggesting that Brook rearrangement proceeded at this temperature. Optimal conditions involved reacting the silyl glyoxylate with the Reformatsky reagent at -20 °C in the absence of the electrophile. Once the silyl glyoxylate was consumed, addition of the aldehyde or ketone was performed, followed by gradually warming the reaction to room temperature. Using these conditions, a 73% yield of **28** was obtained. Gratifyingly, this protocol resulted in higher yields with benzaldehyde as well, affording the desired lactone **27a** in a 62% yield compared to the 27% yield observed previously.

Table 2-3 Solvent Effects[a]



entry	solvent[b]	yield[c]	dr
1	Et_2O	62%	1.5:1
2	CH_2Cl_2	53%	3:1
3	toluene	60%	1:1
4	THF	trace	n/d

[a.] All reactions: 1.5 equiv Reformatsky reagent, 2.0 equiv benzaldehyde, [**26**]$_0$ = 0.05 M. [b.] 5:1 solvent:Et_2O. [c.] Yields determined by internal standard using ^{1}H NMR spectroscopy. See section 2.5 for additional experimental details.

A solvent screen was equally instructive, further exposing the conditions necessary to control Brook rearrangement. Diethyl ether provided the optimal results with in terms of both yield and diastereoselectivity (Table 2-3, entry 1). Reactions in 5:1 CH_2Cl_2:Et_2O gave improved diastereoselectivities but at the expense of yield and 5:1 toluene:Et_2O provided worse diastereoselectivities than in diethyl ether alone (entries 2 and 3). Tetrahydrofuran failed to afford greater than trace product under these conditions, instead providing complex product mixtures due to silyl glyoxylate oligomerization. We attribute this solvent effect to the coordinating ability of THF, which likely increases the ionic character of the O–Zn bond and lowers the energy barrier for Brook rearrangement.[37] We also observed this effect when coordinating ligands were present in solution, as the addition of TMEDA or chiral diamine/diol ligands resulted in premature rearrangement of the initial adduct and led to oligomer formation. The impact of the countercation on the facility of the Brook rearrangement is a continuing point of interest and development.[35] The present example appears to involve an equilibrating mixture of C–Si and O–Si isomers: warming a solution of the unrearranged zinc aldolate to room temperature in the absence of a ketone electrophile

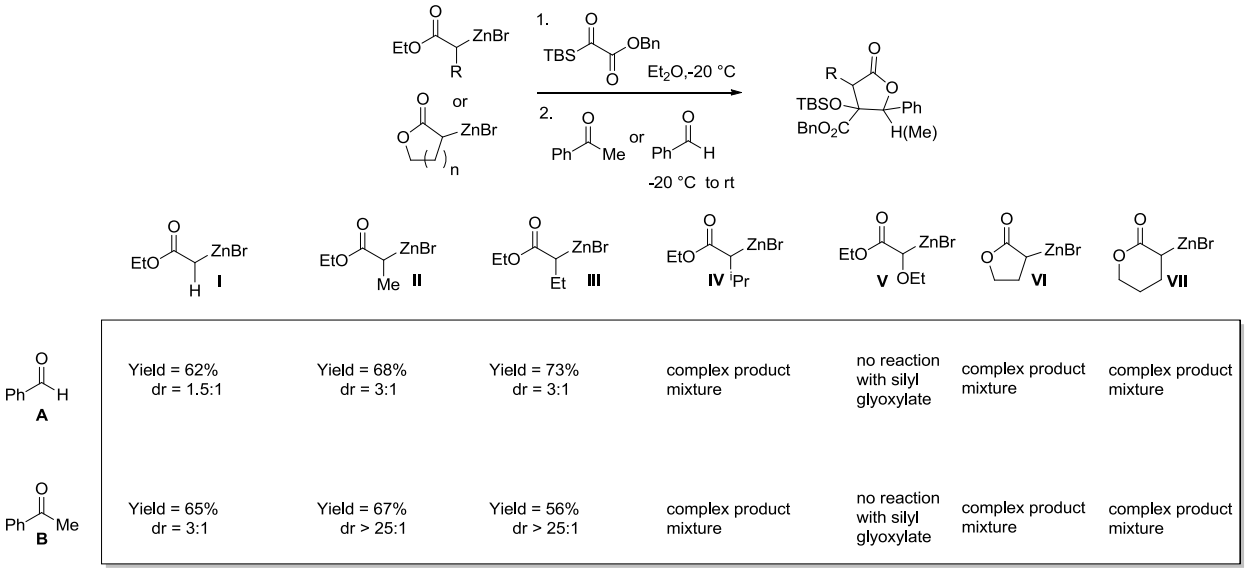
resulted in a complex mixture that contained both the hydroxysilane 2**8′** and the product derived from protonation of the glycolate enolate (*cf.* **16)** in a comparable ratio.

2.3.4 Optimization of Reaction Diastereocontrol

Having elucidated conditions for control of the Brook rearrangement of the intermediate zinc aldolate, subsequent experiments were directed at improving the reaction diastereoselection. We felt that the ability of ligands to induce Brook rearrangment at lower temperatures precluded their use as stereocontrol elements in this reaction, a suspicion that was supported by initial experiments where the addition of common ligands ((–)MIB,[38] *N*-methylephedrine, cinchonidine, cyclohexyldiamine) largely resulted in low yields (20-30%) and enantioselectivities (<10%) for the lactone products.

We next probed the effects of substitution on the Reformatsky reagent (Figure 2-11). Using benzaldehyde and acetophenone as representative electrophiles, we analyzed their three-component coupling reactions with silyl glyoxylates and the Reformatsky reagents derived from from ethyl bromoacetate (**I**), -propionate (**II**), -butyrate (**III**), and –isovalerate (**IV**). For benzaldehyde a modest increase in diastereoselection occurred with the propionate and the butyrate (3:1 vs 1.5:1 dr with the acetate). With acetophenone and ethyl bromopropionate, however, we were pleased to observe lactone production with a greater than 25:1 diastereomeric ratio and yields comparable to reactions with the acetate (Figure 2-11, **IIB**). The analogous butyrate **IIIB** afforded equal diastereoselection and a slight decrease in yield.

Figure 2-11. Use of Substituted Reformatsky Reagents

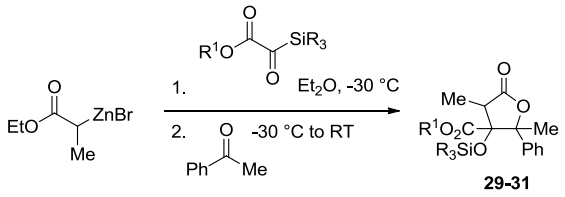


	I	II	III	IV	V	VI	VII
A	Yield = 62% dr = 1.5:1	Yield = 68% dr = 3:1	Yield = 73% dr = 3:1	complex product mixture	no reaction with silyl glyoxylate	complex product mixture	complex product mixture
B	Yield = 65% dr = 3:1	Yield = 67% dr > 25:1	Yield = 56% dr > 25:1	complex product mixture	no reaction with silyl glyoxylate	complex product mixture	complex product mixture

The isovalerate reagent **IV** resulted in mixtures of lactonized and linear products as well as reduced diastereoselectivities and was therefore not employed in additional screens (**IVA, IVB)**. We attempted to use an ethoxy-substituted Reformatsky reagent, although in diethyl ether no reaction with the silyl glyoxylate was observed. The use of cyclic Reformatsky reagents in the form of the butyro- and valerolactones **VI** and **VII** was also attempted but again resulted in complex product mixtures.

A short screen of silyl glyoxylate structures revealed the fortuitous choice of the benzyl *tert*-butyldimethylsilyl glyoxylate in initial experiments. Use of the *tert*-butyl ester functionality still afforded the desired product with high diastereoselectivities but with a significant decrease in yield (**30**). The *tert*-butyl triethylsilyl glyoxylate furnished the desired products with a similar yield but with a lower dr (**31,** Table 2-4).

Table 2-4. Effect of Silyl Glyoxylate Structure[a]



entry	R_3Si	R^1	yield[b]	dr
29	TBS	Bn	67%	>25:1
30	TBS	^{t}Bu	50%	>25:1
31	TES	^{t}Bu	55%	10:1

[a.] All reactions: 1.5 equiv Reformatsky reagent, 2.0 equiv acetophenone, [silyl glyoxylate]$_0$ = 0.05 M in Et_2O. [b.] Yields determined by internal standard using ^{1}H NMR spectroscopy. See section 2.5 for additional experimental details.

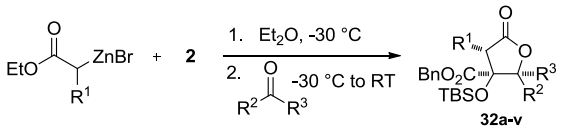
2.3.5 Reaction Scope

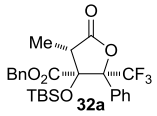
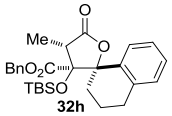
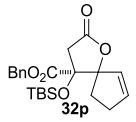
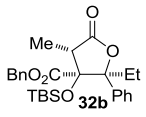
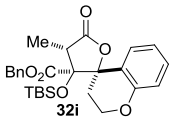
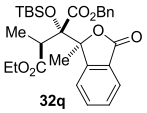
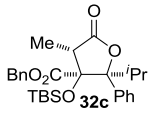
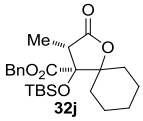
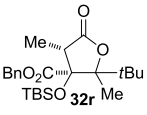
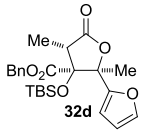
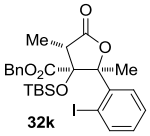
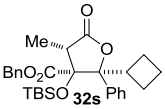
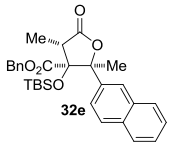
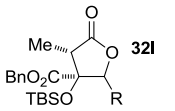
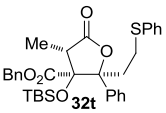
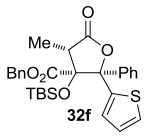
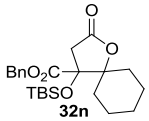
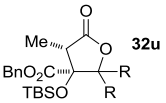
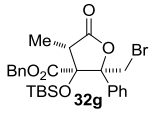
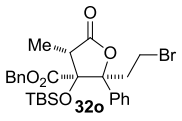
With a means for generating highly diastereomerically enriched lactones from substituted Reformatsky reagents, we next investigated the scope of electrophiles amenable to the reaction. Alkyl-aryl ketones were successfully incorporated and provided the desired lactones with a 7.5 to >25:1 dr and with yields ranging from 21 to 71%. The reaction was also tolerant of heteroaromatic ketones (entries **32d** and **32f**) and cyclic substrates (entries **32h-j** and **32n**). The use of cyclopentenone resulted exclusively in [1,2]-addition (**32p**). Aldehydes afforded the desired products in comparable yields (entries **32l,m**), but diastereoselectivities were far lower than those observed with the aryl ketones. These results are particularly interesting because additions of enolates to ketones are generally poorly diastereoselective, due largely to their lower reactivities and binding affinities to metals.[25c,39]

Problematic substrates included hindered ketones such as isopropyl phenyl ketone, pivalone, and cyclobutyl phenyl ketone (products **32c, 32r,** and **32s**). A likely unproductive pathway with these substrates is proton transfer from the ketone to the glycolate enolate:

large quantities of the quenched enolate **34** were isolated from these reactions (Figure 2-12). This type of proton transfer has been observed in other Reformatsky reactions.[40]

Table 2-5. Substrate Scope[a,b]



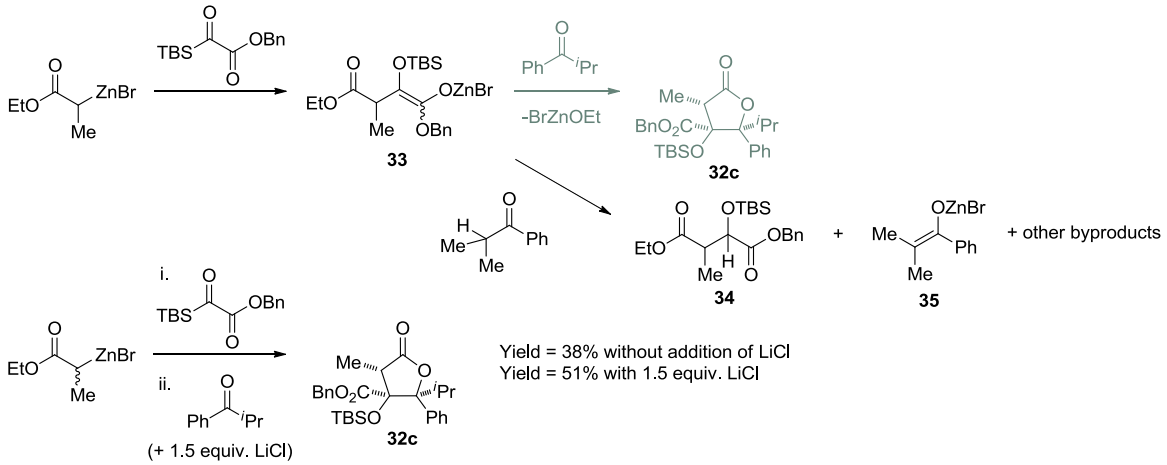
product	yield (%)	dr	product	yield (%)	dr	product	yield (%)	dr
 **32a**	52	11:1	 **32h**	67	>25:1	 **32p**	68	1.2:1
 **32b**	67	>25:1	 **32i**	57	30:1	 **32q**	51	20:1
 **32c**	46	>25:1	 **32j**	53	>25:1	 **32r**	41[c]	n.d.[d]
 **32d**	73	7.5:1	 **32k**	40	>25:1	 **32s**	39[c]	n.d.[d]
 **32e**	70	18:1	 **32l** R = Ph **32m** R = Et	68 63	3:1 1.6:1	 **32t**	21	>25:1
 **32f**	41	9.5:1	 **32n**	71	n/a	 **32u** R = Ph **32v** R = Me	31[c] 62	>25:1 >25:1
 **32g**	48	>25:1	 **32o**	44	>25:1			

[a.] All reactions: 1.5 equiv enolate, 3.0 equiv ketone, 1.0 equiv **2**, $[\mathbf{26}]_0$ = 0.05 M in Et_2O, -20 °C to rt. [b.] See the Supporting Information for detailed procedures. Stereostructures were determined via NOESY experiments. We attempted to determine the relative stereochemistry of product **32q** through derivatization studies but could not arrive at an unambiguous assignment, and thus the stereochemistry depicted in Table 2-5 was assigned by analogy. [c.] Yield determined by ^{1}H NMR with internal standard. [d.] Diastereomeric ratios were not determined.

Knochel has reported an increase in the reactivity of organozinc reagents in the presence of lithium chloride, a phenomenon generally attributed to the formation of a zincate

complex.[41] With isopropyl phenyl ketone, we did observe slightly improved yields with the addition of 1.5 equivalents of lithium chloride: a 51% yield of the desired product was observed, while the yield was 38% in its absence (Figure 2-12). No benefit was observed with additional equivalents of lithium chloride, nor was this effect observed with all substrates.[42]

Figure 2-12. Ketone Deprotonation Pathway and Addition of Lithium Chloride

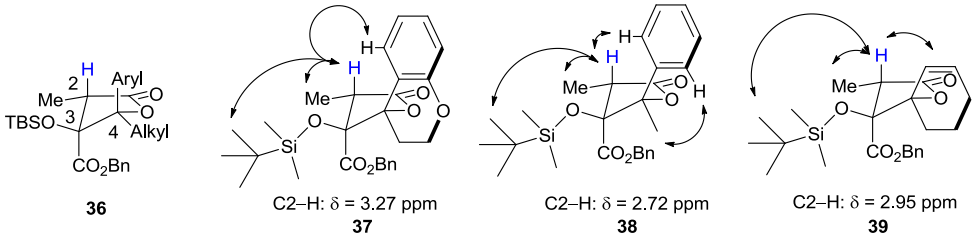


2.3.6 Determination of Relative Stereochemistry

The identity of the major diastereomer in most cases was determined by NOESY NMR experiments. The identities of the major diastereomers were generally assigned based on an observed nOe between the axial methine proton at C2 on the butyrolactone and the silyl group at C3 (generally the ^{t}Bu substituent), which establishes the two substituents as *cis* (Figure 2-13). Additionally, a C4–aryl↔C2 methine nOe was generally observed, which in many cases could be identified as the ketone aryl group to establish the ketone aryl substituent as *cis* to the C2 methine proton. In cases where insufficient resolution of C3-CO_2CH_2**Ar** and C4-**Ar** protons was observed in the ^{1}H NMR spectrum, the aryl↔C2 methine nOe could generally be established as distinct from the nOe observed between the

C3-CO_2**CH_2**Ph protons and their neighboring C3-CO_2CH_2**Ph** protons. The absence of an nOe between the protons in the C2 methyl group of the lactone and either the aryl or alkyl substituents of the ketone supports this analysis and the equatorial assignment of the C2 methyl group of the lactone. In general, an nOe between the silyl group and this methyl group supports their assigned gauche orientation. The chemical shifts of the C2-methine proton in each spectrum are consistent with the expected aryl anisotropy: a deshielding effect is observed in substrates where rotation of the ketone aryl group is restricted (compounds **32h**, **32i**) or when a heteroaromatic group is coaxial (compounds **32d**, **32f**) with the C2 methine proton, resulting in typical chemical shifts of δ 3.2-3.4 for the C2 methine proton. In other substrates where free aryl rotation is possible (compounds **32a, 32b, 32c, 32e, 32g, 32k, 32o, 32s,** and **32u**), an upfield shift for the C2 methine proton to δ 2.7-2.8 is observed. This can be compared to the intermediate shift of approximately δ 3.0 that is observed for the C2 methine proton when an axial interaction is with the alkyl portion of the cyclohexanone-derived product **32j (**Figure 2-13, **37-39**).

Figure 2-13. Representative NOE Interactions

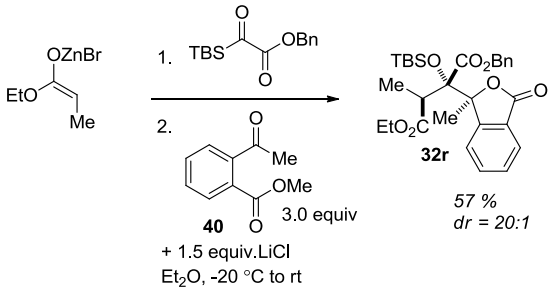


2.3.7 Origin of Diastereoselectivity

We sought an explanation for the unusually high diastereoselectivities we observed. A potential rationale that we could not initially exclude involved an epimerization of the C2 stereocenter of the lactone product that placed the methyl group in an equatorial position. In an effort to determine the origin of the diastereoselection, ketoester **40** was synthesized in

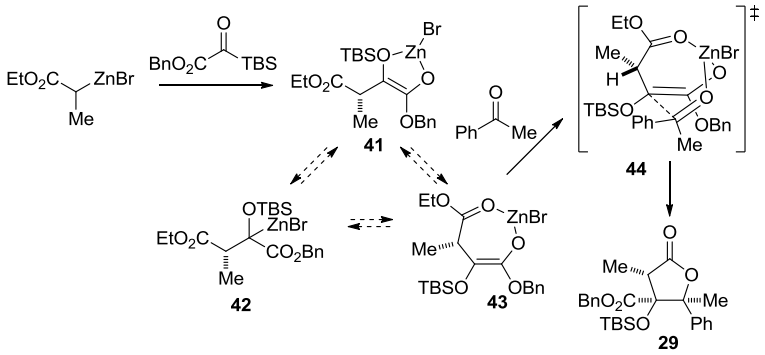
two steps from isobenzofuran-1,3-dione.[43] This substrate was designed to provide an alternative site for lactonization. If equilibration were responsible for the high diastereoselectivities in compounds **32**, we would expect to see lower selectivities in the isobenzofuranone product **32r**, as epimerization of the α-methyl stereocenter should be less favorable in the linear product lacking diaxial interactions.

Scheme 2-4. Stereochemical Probe



The high diastereoselectivity observed in the formation of isobenzofuranone **32r**, which must lactonize via a topographically distinct transition state, suggests that selective lactonization by one of a mixture of equilibrating stereoisomeric aldolates is probably not responsible for the remarkable diastereocontrol. The alkyl group R^1 (R^1 = Me in Figure 2-9) in the substituted Reformatsky reagents is thus a likely determinant of the facial selectivity in the second Reformatsky reaction. In the present case, the ethyl ester could conceivably enforce the illustrated boat/twist boat transition state[33a,b] via chelation.

Figure 2-14. Transition State Model



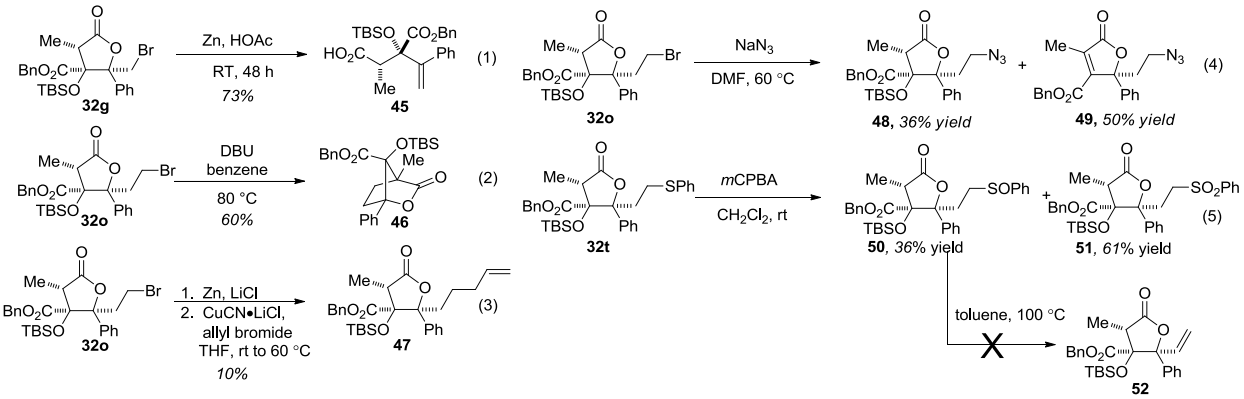
This type of organized structure (**44**) provides a plausible rationalization for the high enolate facial selectivity insofar as approach of the ketone *syn* to the methine proton should be preferred.[44] The propensity of zinc enolates to undergo O–C zinc migration[30] potentially allows for interconvertion of the various plausible enolates and chelated species depicted in Figure 14. The model shown in Figure 2-14 further supposes a pseudo-equatorial placement of the aryl group and an (*E*)-enolate geometry (**41**), but discounting alternative models (including those involving other structures of the intermediate organometallic) in the absence of more complete experimental data would be premature.

2.3.8 Subsequent Transformations of Lactone Products

The transformations shown in Figure 2-15 further highlight the synthetic utility of this methodology. The zinc insertion/elimination reaction of bromolactone **32g** provided γ,δ-unsaturated acid **45**, a compound that can be viewed formally as a product of glycolate enolate alkenylation (eq 1). Alkylation occurred faster than dehydrohalogenation when **32o** was heated with DBU, resulting in the formation of bicyclic lactone **46** bearing three contiguous fully substituted asymmetric centers (eq 2). Generation of the organozinc reagent under conditions described by Knochel (Zn, LiCl, TMSCl)[41a,b] followed by transmetalation to copper and alkylation with allyl bromide afforded low yields of alkene **47** (eq 3).

Displacement of the primary bromide occurred with sodium azide in DMF at elevated temperatures (**48**), but we observed significant byproduct formation due to elimination of silyloxide to give butenolide **49** (eq 4). Product **32t**, derived from reaction with 1-(4-methoxyphenyl)-3-(phenylthio)propan-1-one, was oxidized to sulfoxide **50** with *m*CPBA,[45] although overoxidation to sulfone **51** proved competitive (eq 5). Attemped extrusion of phenylsulfenic acid to give alkene **52**[46] resulted in decomposition.

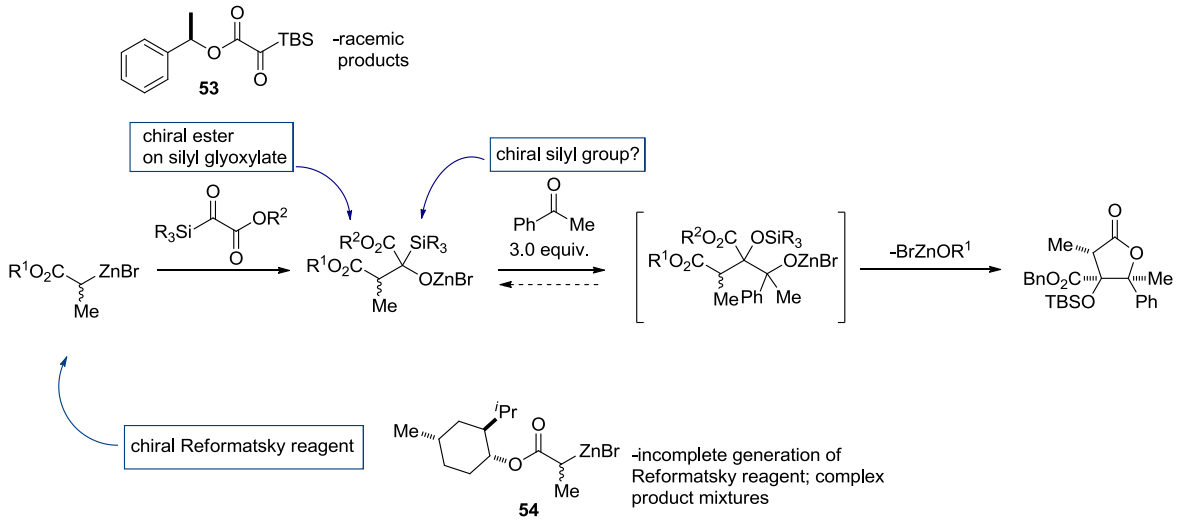
Figure 2-15. Subsequent Transformations of Functionalized Products



2.3.9 Efforts Toward Asymmetric Reaction Development

Final experiments were directed toward the development of an asymmetric variant of our double Reformatsky cascade. Several potential points of asymmetric induction were identified based on the mechanistic constraints discussed previously in the chapter (Scheme 2-5). Because the absolute stereochemistry of the initial addition of Reformatsky reagent to the silyl glyoxylate likely dictates the facial selectivity of the glycolate aldol (*vide supra*), a successful stereocontrol element must be active in the initial phase of the reaction.

Scheme 2-5. Potential Points of Asymmetric Induction

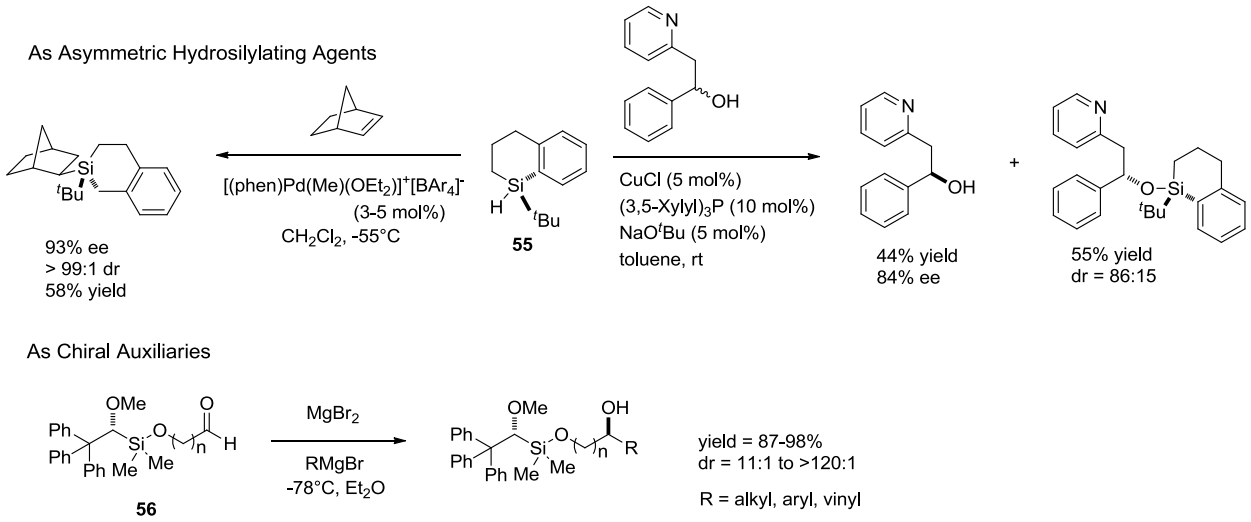


The propensity of ligands to induce premature Brook rearrangement[37] likely precludes their use in directing the stereoselection of this reaction; as described in section 2.3.3, preliminary trials afforded low yields and stereoselectivities for formation of the lactone products. Consequently, substrate control appeared to be the most viable option. Reformatsky precursor **54** was synthesized from a condensation of bromopropionic acid and (–)-menthol, although generation of the Reformatsky reagent from this substrate did not go to complete conversion, and reactions with the silyl glyoxylate and ketones resulted in intractable mixtures. Silyl glyoxylate **53** was synthesized from (*R*)-*sec*-phenethyl alcohol according to standard procedures[42] but gave no enolate facial selectivity.

Another potential option for asymmetric induction was the use of a chiral silyl group on the silyl glyoxylate. Ideally, this functionality could effect facial control in the initial addition of Reformatsky reagent and control the facial selectivity of the secondary glycolate aldol reaction after Brook rearrangement. Successful examples of chiral silanes as stereoinductors are rare in the literature;[47] a complicating factor is the increased length of the C–Si bond relative to C–C bonds (1.87 vs 1.53 Å),[48] which allows for increased rotational freedom than in all-carbon stereocenters. The few examples that do exist either employ

cyclic silanes or silanes with chelating elements. Oestreich has developed cyclic silanes of the type **55**, which have been used succesfully in asymmetric hydrosilylations of alkenes and ketones.[47] Bienz has also demonstrated the potential of methoxy-substituted silane **56** to function as a chiral auxiliary, which was effective in the asymmetric addition of Grignard reagents to aldehydes (Figure 2-16).[49]

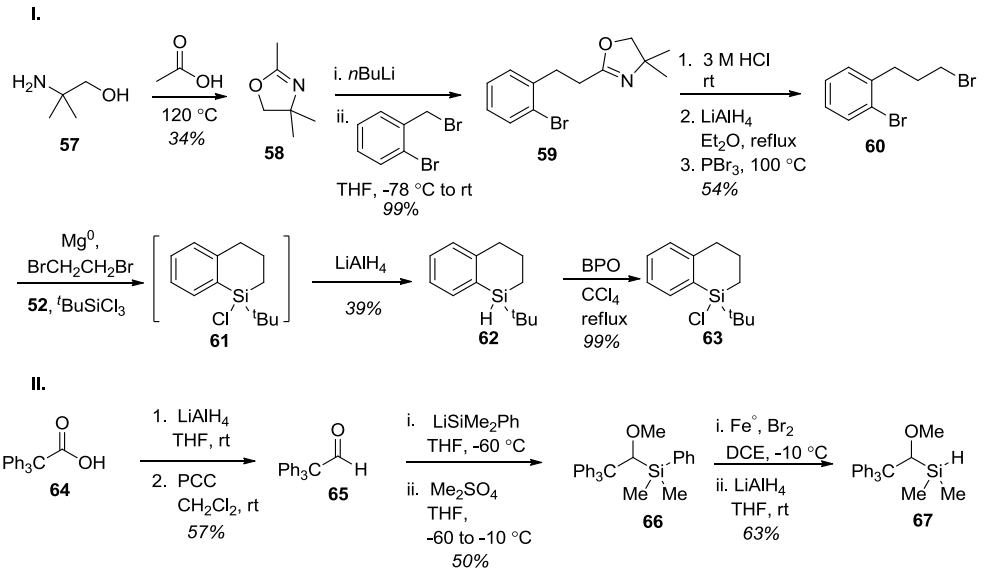
Figure 2-16. Successful Applications of Chiral Silanes[47,49]



These examples prompted us to synthesize silyl glyoxylates bearing similar functionalities. Racemic silane **62** was synthesized uneventfully via Oestreich's protocol (Scheme 2-6). Condensation of aminoalcohol **57** with acetic acid gave the oxazoline, which was benzylated by reaction of its lithium anion with α-bromo-2-bromotoluene. Treatment with HCl deprotected the oxazoline and afforded the carboxylic acid.[50] Reduction to the alcohol with lithium aluminum hydride gave the primary alcohol, which was converted to the primary bromide **60** with PBr_3 in 54% yield over three steps. *In situ* generation of the dialkyl

magnesium complex and its subsequent silylation were accomplished by slow addition of a solution of the aryl bromide and *tert*-butyltrichlorosilane to a refluxing magnesium suspension in accordance with the procedure from Oestreich.[47] The resulting silyl chloride intermediate **61** was reduced to the hydrosilane **62** with lithium aluminum hydride.[51] After purification, the silane could also be chlorinated in nearly quantitative yield in carbon tetrachloride after radical initiation with benzoyl peroxide (BPO).[52]

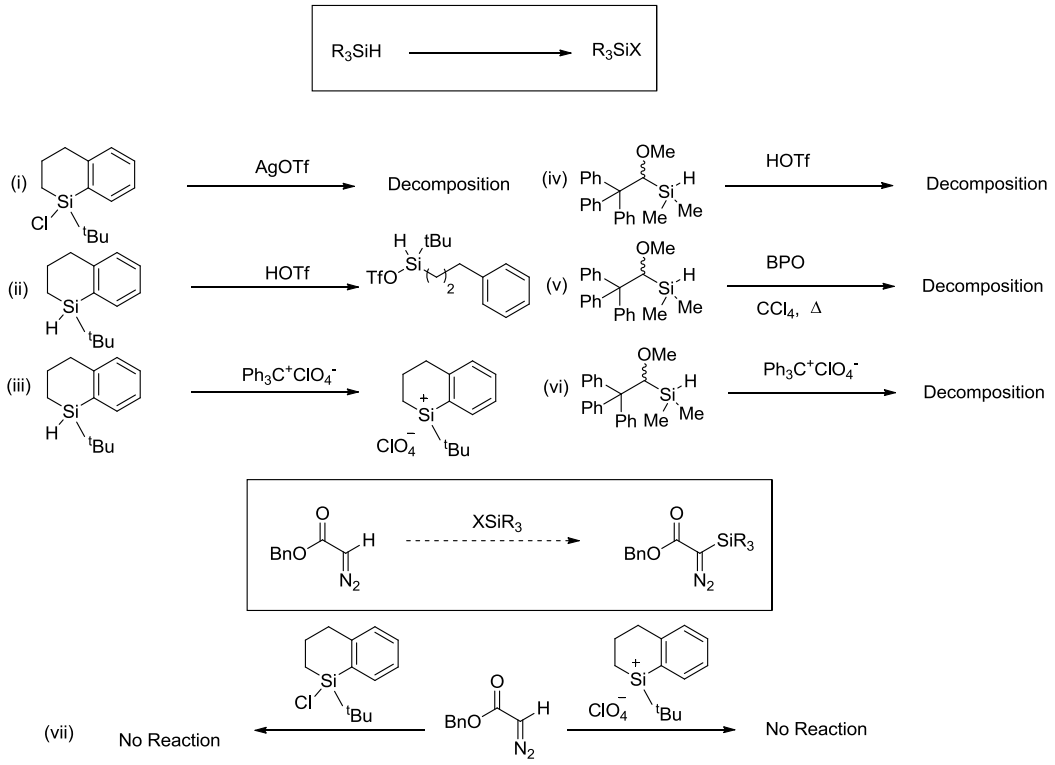
Scheme 2-6. Preparation of Chiral Silane and Chlorosilane Silylating Agents



Synthesis of the Bienz silyl auxiliary was also according to the established procedure.[49] Triphenylacetaldehyde was prepared in two steps and a 57% yield from triphenylacetic acid via lithium aluminum hydride reduction and subsequent oxidation with PCC. Silyl anion addition to this aldehyde and methylation with dimethylsulfate afforded the α–methoxysilane **66** in a 50% yield over two steps. Bromodesilylation was accomplished by treatment with Fe^0 and Br_2, and *in situ* reduction with lithium aluminum hydride gave silane **67** in a 63% yield.

The introduction of the trialkylsilyl functionalities in the established synthesis of silyl glyoxylates involves silylation of a diazoacetate intermediate.[16] Silyl triflates are generally employed for this transformation due to their enhanced reactivity relative to silyl chlorides. Attempts to generate the silyl triflate of **63** through anion metathesis with AgOTf[53] gave decomposition, while treatment of the silane with triflic acid[54] led to protodesilylation (Figure 2-17, eq i, ii). No silylation of the diazoacetate was observed with either the silyl chloride or the silyl perchlorate (generated from treatment with trityl perchlorate,[55] eq iii, vii).

Figure 2-17. Attempted Syntheses of Silylating Agents and Silylation of Diazoacetates



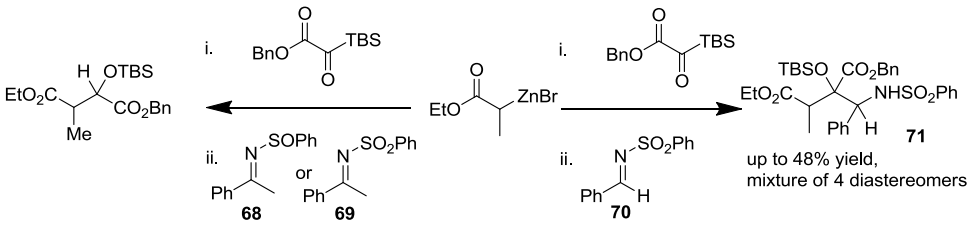
Unfortunately, attempts to convert silane **67** to the silyl triflate, perchlorate, or chloride led to decomposition as well, presumably due to the instability of the trityl group and methoxy groups adjacent to the putative silyl cation or radical under these conditions (Figure 2-17, eq iv to vi). At this point, we abandoned attempts to synthesize silyl

glyoxylates bearing silicon-based chirality and instead chose to investigate additional electrophiles in these cascades and to research its potential application to natural product synthesis.

2.3.10 Imine Electrophiles in Reformatsky Cascades

In an effort to expand the range of product classes available from a double Reformatsky cascade, additional electrophilic components were evaluated. We attempted to extend the reaction to imine electrophiles, and sulfonylaldimine **70** and sulfinyl- and sulfonyl ketimines **68** and **69** were synthesized accordingly.[56] Using the procedure optimized for the double Reformatsky reactions of ketones, aldimine **70** proved to be a competent electrophile, although the resulting products were the straight chain sulfonyl imines **71** rather than the corresponding lactams. This can be possibly be attributed to coordination of the products with Zn^{2+} or the steric bulk of the sulfonyl group.

Scheme 2-7. Imine-Terminated Cascades



Moderate yields of the linear products were obtained- albeit in a mixture of four inseparable diastereomers- with no greater than 6:1 dr between any two stereoisomeric pairs. Sulfonyl ketimines resulted primarily in production of the quenched enolate **34**, presumably through the proton transfer pathway described in Figure 2-12. The decreased acidity of sulfinyl ketimines has been used to minimize proton transfer in other cases,[57] although here we observed the quenched enolate product in their presence as well (Scheme 2-7). Future efforts may seek to improve upon these preliminary results.

2.4 Conclusion

We have developed a means for employing enolates in the form of Reformatsky reagents as nucleophilic initiators of silyl glyoxylate cascades. Secondary Reformatsky reactions of the intermediate glycolate enolates with aldehydes or ketones led to spontaneous lactonization of the terminal zinc aldolates and furnished the corresponding γ-butyrolactone products. Critical to our success in the development of these reactions was the discovery that with zinc enolates, Brook rearrangement could be suppressed at -20 °C while still permitting reaction of the Reformatsky reagents with the silyl glyoxylates. Consequently, many of the chemoselectivity issues that plagued preliminary reactions with lithium and magnesium enolates could be alleviated. Yields for the title reaction are generally moderate, but they are significantly offset by the complexity engendered: two carbon-carbon bonds and three contiguous stereocenters are generated with remarkable diastereoselection. Secondary transformations of many of the products add to the synthetic utility of this methodology and suggest that it may be amenable to incorporation into the syntheses of more complex products. Preliminary efforts toward the development of an asymmetric variant with silicon-based chirality on the silyl glyoxylate met an impasse due to difficulties in the synthesis of the desired starting materials, but ongoing efforts seek to overcome these limitations.

2.5 Experimental Details

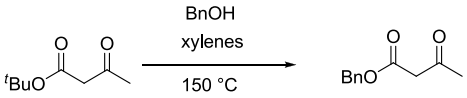
Materials and Methods: General. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 or a Bruker 300 MHz (^{1}H NMR at 400 MHz or 300 MHz and ^{13}C NMR at 100 MHz) spectrometer with

solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium nitrate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica gel (40-63μm) purchased from Silicycle and/or crystallization from pentanes. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. Zinc metal was washed with 1 M HCl, water, acetone, and diethyl ether and then dried under vacuum at 60 °C for 16 h prior to storage in a nitrogen-filled glove box. Bromo esters were purified by washing with 50% calcium chloride, saturated sodium carbonate, and brine, and distilling from calcium chloride. Ketones were purchased from Sigma-Aldrich Chemical and were used as received unless otherwise noted. Purification via HPLC was performed on a Varian Prepstar SD-1 Solvent Delivery System equipped with a Cyano 60 Å 6u column from Berger Instruments. Specific parameters used in the separation of compounds are detailed under applicable entries.

Preparation of Reactants and Reagents

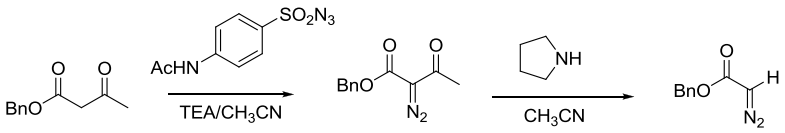
Synthesis of Benzyl *tert*-butyldimethylsilyl glyoxylate (26):[58]

(a) Benzyl acetoacetate[59]



Tert-butylacetoacetate (10 g, 63.2 mmol, 1.0 equiv) and benzyl alcohol (6.8 g, 67.3 mmol, 1.06 equiv) were dissolved in xylenes (18 mL) in a 50-mL round bottomed flask. A distillation apparatus was attached, and the solution was heated to 120-130 °C, at which point *tert*-butyl alcohol began to distill out of the mixture. When *tert*-butyl alcohol production had ceased, xylenes was removed via distillation. The remaining liquid was cooled, and the product was distilled under vacuum (0.05 mm Hg, bp 120 °C). Spectral data for the resulting clear, colorless oil matched those reported for the title compound[59] (10.8 g, 90%).

(b) Benzyl-2-diazoacetate:

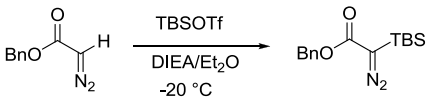


Benzyl acetoacetate (3.0 g, 15.6 mmol, 1.0 equiv) and *p*-acetamidobenzene sulfonyl azide (*p*ABSA)[60] (3.8 g, 15.9 mmol, 1.02 equiv) were dissolved in acetonitrile (37 mL). The solution was cooled to 0 °C, and triethylamine (6.5 mL, 46.9 mmol, 3.0 equiv) was added dropwise via syringe. When the benzyl acetoacetate had disappeared by TLC (R_f = 0.28, 70:30 hexanes: ethyl acetate, 20 min), all solids were removed by filtration through a fritted funnel, and the filtrate was concentrated in vacuo. The residue was dissolved in diethyl ether (50 mL) and was washed with water (2x20 mL) and brine, dried with magnesium sulfate, and concentrated in vacuo to give the desired product as a light yellow solid. The ^{1}H NMR

spectrum of this compound matched the reported spectral data[61] and the product was used without further purification (3.0 g).

The benzyl diazoacetoacetate was dissolved in acetonitrile (30 mL), and pyrrolidine (3.0 mL, 30.4 mmol, 2.2 equiv) was added. The reaction was stirred for 16 h at room temperature or until it was determined to be complete by ^{1}H NMR analysis of an aliquot. The solvent was removed in vacuo, and the residual oil was dissolved in diethyl ether (50 mL), washed with 1 M NaOH (3x20 mL), water (20 mL), brine, dried with magnesium sulfate, and concentrated in vacuo. The resulting orange oil was purified through a short plug of silica, eluting with 7:3 hexanes:ethyl acetate to give the product as a yellow oil (1.8 g, 65% over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 to 7.26 (m, 5H), 5.21 (s, 2H), 4.81 (br s, 1H).

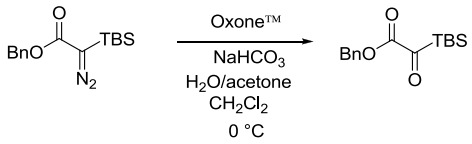
(c) Benzyl 2-*tert*-butyldimethylsilyl-2-diazoacetate



A flame-dried 50-mL round bottomed flask was charged with benzyl-2-diazoacetate (1.80 g, 10.3 mmol, 1.0 equiv) and dry diethyl ether (15 mL). The solution was cooled to -30 °C and diisopropylethylamine (2.3 mL, 13.2 mmol, 1.3 equiv) was added. *Tert*-butyldimethylsilyltrifluoromethanesulfonate (10.3 mL, 1.3 equiv) was added dropwise via syringe pump over 30 min. When the addition of TBSOTf was complete, the resulting suspension was allowed to warm to -20 °C and was stirred at -20 °C for 24 h. When the reaction was complete as judged by TLC analysis (R_f = 0.26, 90:10 hexanes:ethyl acetate for the diazoacetate), the suspension was allowed to warm to room temperature, hexanes was added to fully precipitate the ammonium triflate salt, and solids were removed by filtration

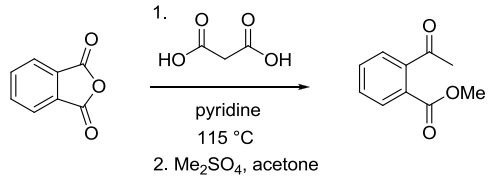
through a fritted funnel. The filtrate was concentrated in vacuo to give a yellow oil that was used without further purification. ^{1}H NMR spectral data matched those reported for the title compound.[58]

(d) Benzyl *tert*-butyldimethylsilyl glyoxylate (26)



The material from the previous step was dissolved in methylene chloride (25 mL). A 250-mL round bottomed flask was charged with sodium bicarbonate (6.94 g, 82.6 mmol, 8 equiv). Water (30 mL) and acetone (20 mL) were added, and the resulting suspension was cooled to 0 °C. Oxone® (12.7 g, 20.7 mL, 2.0 equiv) was added in small portions. When the addition of Oxone® was complete, the solution of the diazoacetate was added all at once. When the reaction was judged to be complete by TLC analysis (R_f = 0.51, 95:5 hexanes: ethyl acetate for the silyl diazoacetate, typically 3-4 hours), all solids were removed by filtration through a fritted funnel. Water was added to the filtrate, and the layers were separated. The organic layer was washed with water (3x 20 mL) and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified via flash chromatography (19:1 hexanes: ethyl acetate, R_f = 0.37) to give the desired product as a bright yellow oil (2.2 g, 78% over two steps). Spectral data matched those reported for the title compound.[58]

Preparation of Methyl-2´-acetyl-benzoate:

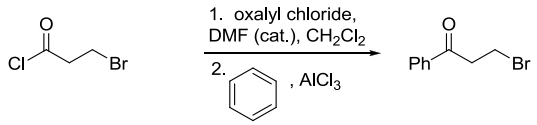


The general procedure from Li, et. al. was followed.[62] Phthalic anhydride (7.93 g, 53.6 mmol, 1.0 equiv) and malonic acid (6.68 g, 64.3 mmol, 1.2 equiv) were dissolved in pyridine (7.5 mL) and were heated to reflux for 3 h. The solution was cooled to 30 °C, water was added (50 mL), and the suspension was stirred for 30 min. Insoluble material was removed by filtration through a fritted funnel and the filtrate was brought to pH = 3-4 and was then stored at 10 °C for 16 hours to precipitate the product. The resulting solid was recrystallized from $CHCl_3$/MeOH to give 3.5 g of 2´-acetyl benzoic acid (40%). Spectral data matched those reported in the literature.

A 25-mL flame-dried and N_2-purged round bottomed flask was charged with 2´-acetylbenzoic acid (1.7 g, 10.4 mmol, 1.0 equiv) and potassium carbonate (0.862 g, 6.24 mmol, 0.6 equiv). Dry acetone (10 mL) was added, followed by dimethylsulfate (1.18 mL, 12.48 mmol, 1.2 equiv). The mixture was heated at reflux for 4 h, at which point TLC analysis (R_f = 0.32, 70:30 hexanes: ethyl acetate) indicated the reaction was complete. The resulting suspension was cooled to room temperature, and triethylamine (2 mL) was added to quench the excess dimethylsulfate. After stirring for 30 min, all solids were removed by filtration through a fritted funnel, and the reaction was concentrated to 1/3 the initial volume. The residue was dissolved in ethyl acetate, washed with water and brine, dried with magnesium sulfate, and concentrated in vacuo to give a red oil. The oil was purified by filtration through a short silica plug, eluting with 70:30 hexanes: ethyl acetate, to give the

desired product as a clear colorless oil whose spectral data matched those reported for the title compound (1.44 g, 78%).[62]

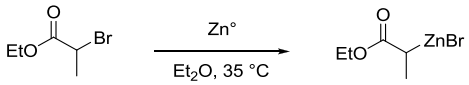
Preparation of β-bromo-propiophenone:



A 100-mL round bottomed flask was charged with 3-bromopropionic acid (7 g, 45.8 mmol, 1.0 equiv). Dry dichloromethane (55 mL) was added, followed by oxalyl chloride (6.39 g, 50.34 mmol, 1.1 equiv). Dimethylformamide (0.2 mL) was added to catalyze the reaction. When HCl production had ceased, the solvent was removed in vacuo, and the product was distilled under vacuum to give 3-bromo-propionyl chloride as a clear, colorless oil (2.6 g, 27%). Spectral data matched those reported for the title compound.[63]

The general procedure from Sonda[64] was followed. A flame-dried, N_2-purged 50-mL round bottomed flask was charged with 3-bromopropionyl chloride (2.1 g, 12.25 mmol, 1.0 equiv), benzene (5.4 mL, 61.25 mmol, 5.0 equiv) and dry dichloromethane (15 mL). The solution was cooled to 0 °C and aluminum chloride (1.8 g) was added in one portion. The resulting suspension was stirred for 3 h at 25 °C. The reaction was quenched by pouring the orange-colored solution into an ice/water mixture. Dichloromethane (3x20 mL) was used to extract the desired product, and the combined organic were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The desired product was purified via column chromatography using 95:5 to 80:20 hexanes:ethyl acetate. Yield = 1.76 g (67%). Spectral data matched those reported for the title compound.[65]

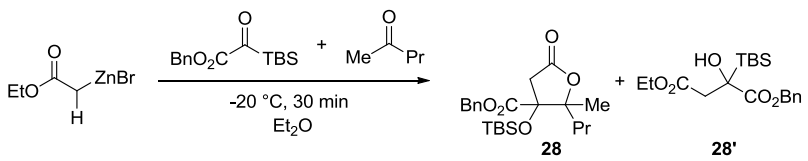
General Procedure for Preparation of Reformatsky Reagents.[28]



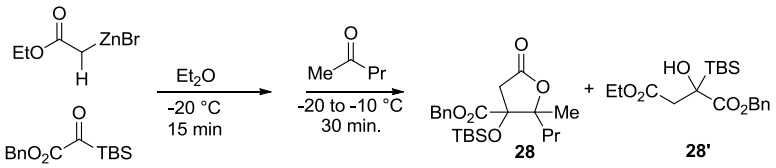
In a nitrogen-filled glove box, a flame-dried 25-mL round bottomed flask was charged with zinc (400 mg, 6.2 mmol, 1.34 equiv) and sealed with a septum. The flask was removed to a fume hood and placed under nitrogen, and dry diethyl ether (10 mL) was added. Trimethylsilyl chloride[28] (0.060 mL, 0.47 mmol, 0.1 equiv) was added, and the resulting suspension was stirred for 30 min at room temperature. An oven-dried reflux condenser was attached to the flask, and the suspension was brought to reflux under nitrogen. Ethyl 2-bromopropionate (0.6 mL, 4.59 mmol, 1.0 equiv) was added over 15 min, and the mixture was heated at reflux for 2-3 hours. The reaction can be monitored by ^{1}H NMR spectroscopy for disappearance of ethyl 2-bromopropionate. Upon disappearance of the starting material (generally 1.5-2 h), the resulting grey suspension was stirred at room temperature until all solids were dissolved to give a light green solution. The resulting Reformatsky reagent solution can be titrated with iodine[66] (0.36 to 0.40 M); however, performing reactions with an excess of Reformatsky reagent as indicated in subsequent procedures was generally performed without such a titration and gave consistent results in terms of yield and reaction cleanliness.

Optimization Studies

Temperature Screen (Table 2-2):

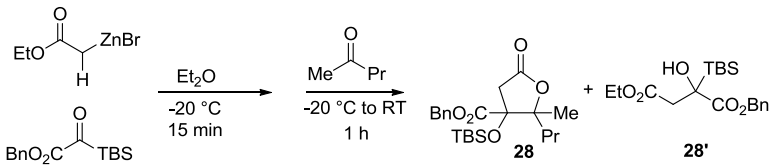


Entry 1: A solution of the Reformatsky reagent was prepared according to the described procedure. An excess of this solution (0.90 mL, 0.36 mmol) was diluted with dry diethyl ether (3 mL) and cooled to -20 °C in an acetone/dry ice bath. A solution of benzyl *tert*-butyldimethylsilyl glyoxylate (56 mg, 0.2 mmol, 1.0 equiv) and 2-pentanone (34 mg, 0.4 mmol, 2.0 equiv) in dry diethyl ether (1 mL) was added dropwise. Additional diethyl ether (0.5 mL) was used to effect complete reagent transfer. After stirring the reaction for 30 min at -20 °C, the reaction was quenched by the addition of saturated ammonium chloride and was warmed to room temperature. Diethyl ether and water were added, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated. The yield of hydroxysilane (81%) was determined by ^{1}H NMR analysis using mesitylene as internal standard.



Entry 2: A solution of Reformatsky reagent was prepared according to the described procedure. An excess of this solution (0.90 mL, 0.36 mmol) was diluted with dry diethyl ether (3 mL) and cooled to -20 °C in an acetone/dry ice bath. A solution of benzyl *tert*-butyldimethylsilyl glyoxylate (56 mg, 0.2 mmol, 1.0 equiv) in dry diethyl ether (1 mL) was added dropwise. Additional diethyl ether (0.5 mL) was used to effect complete reagent transfer. After stirring the reaction for 15 min at -20 °C, 2-pentanone (34 mg, 0.4 mmol, 2.0 equiv) in diethyl ether (1 mL) was added dropwise, and the reaction mixture was allowed to warm to -10 °C for 30 min. The reaction was quenched by the addition of saturated ammonium chloride and was warmed to room temperature. Diethyl ether and water were added, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined

organic extracts were dried with magnesium sulfate and concentrated. The yields of hydroxysilane **28′** and the desired lactone **28** were determined by ^{1}H NMR analysis using mesitylene as the internal standard.

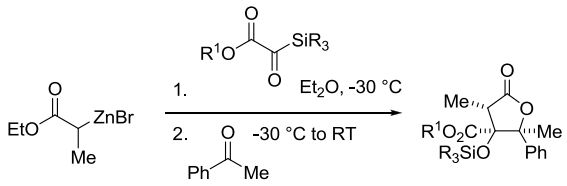


Entry 3:

The Reformatsky reagent solution (1.5 mL, 0.6 mmol, 1.5 equiv) was diluted with diethyl ether (4 mL), and the solution was cooled to -30 °C in an acetone/dry ice bath (bath temperature, monitored with a thermocouple probe). An oven-dried vial was charged with benzyl *tert*-butyldimethylsilyl glyoxylate (112 mg, 0.4 mmol, 1.0 equiv) and diethyl ether (1 mL). The vial was purged with N_2 and the solution was added dropwise over 2 min with a syringe to the Reformatsky reagent solution. Additional diethyl ether (0.5 mL) was used to rinse the vial. After consumption of the silyl glyoxylate was complete (generally 10-15 min at -30 °C, monitored by TLC, 19:1 hexanes: ethyl acetate, R_f = 0.37), acetophenone (0.140 mL 1.2 mmol, 3.0 equiv) was added, and the reaction was allowed to warm to 0 °C in the acetone bath over 45 min and was then warmed to room temperature for 1 h. The reaction was diluted with diethyl ether (5 mL), and the reaction was quenched with saturated ammonium chloride (1 mL), stirring until a clear solution was observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined organic were washed with brine, dried with magnesium sulfate, and concentrated in vacuo.

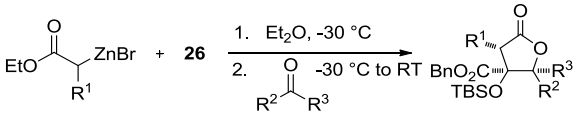
Silyl Glyoxylate Screen

General procedure 1 (see below) was followed using the corresponding silyl glyoxylate and acetophenone as the terminal electrophile. Yields are for the isolated products, available as oils in the case of entries 2 and 3, and for the solid product after crystallization in the case of entry 1. Diastereomeric ratios were determined from the proton NMR spectra of the unpurified products.



entry	R_3Si	R^1	Yield	dr
1	TBS	Bn	67	>25:1
2	TBS	^{t}Bu	50	>25:1
3	TES	^{t}Bu	55	10:1

Procedures for the Synthesis of Compounds 32a-v



(a) Synthesis of Pentasubstituted Lactones: General Procedure I

The Reformatsky reagent solution (1.5 mL, 0.6 mmol, 1.5 equiv) was diluted with diethyl ether (4 mL), and the solution was cooled to -30 °C in an acetone/dry ice bath (bath temperature, monitored with a thermocouple probe). An oven-dried vial was charged with benzyl *tert*-butyldimethylsilyl glyoxylate **26** (112 mg, 0.4 mmol, 1.0 equiv). The vial was purged with N_2, and a solution of the silyl glyoxylate in diethyl ether (1 mL) was added dropwise to the Reformatsky reagent solution over 2 min with a syringe. Additional diethyl

ether (0.5 mL) was used to rinse the vial. After consumption of the silyl glyoxylate was complete (generally 10-15 min at -30 °C, monitored by TLC), acetophenone (0.140 mL, 1.2 mmol, 3.0 equiv) was added, and the reaction was allowed to warm to 0 °C in the acetone bath over 45 min. The reaction was then warmed to room temperature for 30 min. The reaction was diluted with diethyl ether (5 mL) and quenched with saturated ammonium chloride (1 mL), stirring until a clear solution was observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined organic extracts were washed with brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was purified via flash chromatography with 9:1 hexanes: ethyl acetate and the product was crystallized from pentanes to give the desired product as clear, colorless crystals (121 mg, 69%).

(b) Synthesis of Pentasubstituted Lactones: General Procedure II

The Reformatsky reagent solution (1.5 mL, 0.6 mmol, 1.5 equiv) was diluted with diethyl ether (4 mL), and the solution was cooled to -30 °C in an acetone/dry ice bath (bath temperature, monitored with a thermocouple probe). An oven-dried vial was charged with benzyl *tert*-butyldimethylsilyl glyoxylate (112 mg, 0.4 mmol, 1.0 equiv). The vial was purged with N_2, and a solution of the silyl glyoxylate in diethyl ether (1 mL) was added dropwise to the Reformatsky reagent solution over 2 min with a syringe. Additional diethyl ether (0.5 mL) was used to rinse the vial. After consumption of the silyl glyoxylate was complete (generally 10-15 min at -30 °C, monitored by TLC), benzoylthiophene (226 mg, 1.2 mmol, 3.0 equiv) was added as a solution in diethyl ether (1 mL), and the reaction was allowed to warm to 0 °C in the acetone bath over 45 min. The reaction was then warmed to

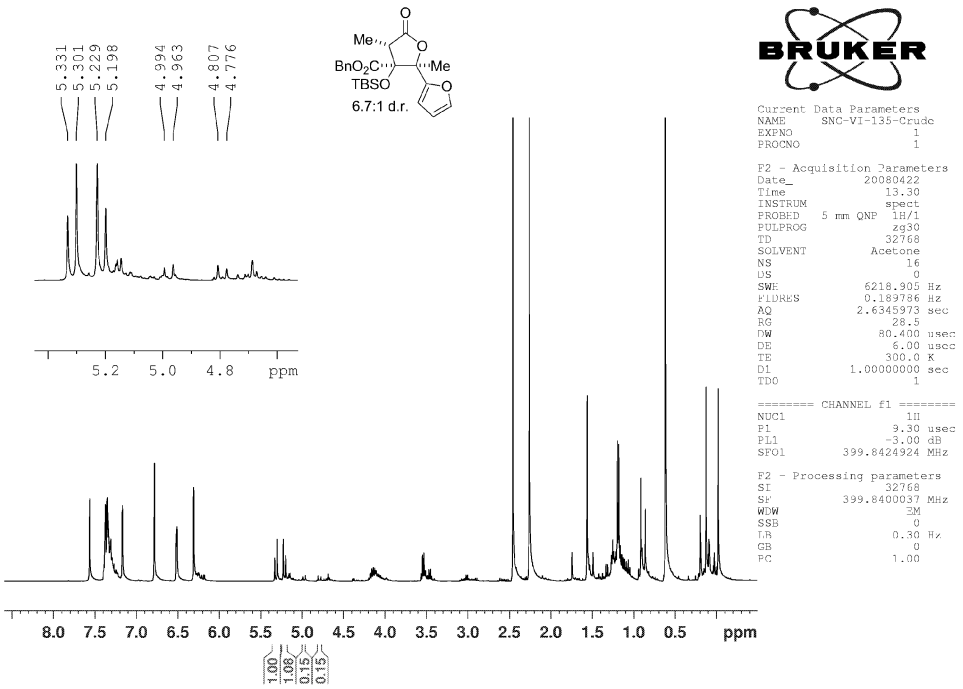
room temperature for 30 min. The reaction was diluted with diethyl ether (5 mL) and was quenched with saturated ammonium chloride (1 mL), stirring until a clear solution was observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was dissolved in methanol (5 mL), and sodium borohydride (91 mg, 2.4 mmol, 6 equiv) was added in small portions. The resulting suspension was stirred at room temperature until the excess ketone was consumed (10 min). Ethyl acetate (10 mL) was added, and the reaction was quenched with saturated ammonium chloride. The aqueous layer was extracted with EtOAc (3x5 mL), and the combined organic were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (80:20 hexanes:EtOAc) and triturated from pentanes to give the desired product as a white solid with > 25:1 diastereomeric ratio (86 mg, 41%).

(c) Synthesis of Pentasubstituted Lactones: General Procedure III

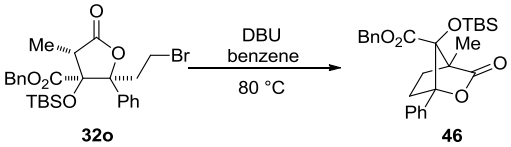
The Reformatsky reagent solution (1.5 mL, 0.6 mmol, 1.5 equiv) was diluted with diethyl ether (4 mL), and was cooled to -30 °C in an acetone/dry ice bath (bath temperature, monitored with a thermocouple probe). An oven-dried vial was charged with benzyl (*tert*-butyldimethylsilyl) glyoxylate (112 mg, 0.4 mmol, 1.0 equiv). The vial was purged with N_2, and a solution of the silyl glyoxylate in diethyl ether (1 mL) was added dropwise to the solution of the Reformatsky reagent over 2 min with a syringe. Additional diethyl ether (0.5 mL) was used to rinse the vial. After consumption of the silyl glyoxylate was complete (generally 10-15 min at -30 °C, monitored by TLC), 2-methyl-1-phenylpropan-1-one (0.180

mL, 1.2 mmol, 3.0 equiv) and lithium chloride[41] (34 mg, 0.8 mmol, 2.0 equiv) were added. The reaction was allowed to warm to 0 °C in the acetone bath over 45 min and was then warmed to room temperature for 30 min. After dilution with diethyl ether (5 mL), the reaction was quenched with saturated ammonium chloride (1 mL), stirring until a clear solution was observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined organic were washed with brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was dissolved in methanol (5 mL), and sodium borohydride (91 mg, 2.4 mmol, 6 equiv) was added in small portions. The resulting suspension was stirred at room temperature until the excess ketone was consumed (10 min). Ethyl acetate (10 mL) was added, and the reaction was quenched with saturated ammonium chloride. The aqueous layer was extracted with EtOAc (3x5 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (19:1 hexanes:ethyl acetate) and then crystallized from pentanes to give the desired product as a white solid of one diastereomer (90 mg, 47%).

Calculation of Diastereomeric Ratios: Diastereomeric ratios were generally calculated using the ratio of the benzyl methylene protons for each diastereomer. In the following example, the d.r. for the unpurified material obtained from the reaction employing 2-acetylfuran shows compound **32d** in a 6.7:1 d.r.:

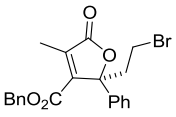


Preparation of (±)-(1*S*,4*S*,7*S*)-benzyl 7-(*tert*-butyldimethylsilyloxy)-4-methyl-3-oxo-1-phenyl-2-oxabicyclo[2.2.1]heptane-7-carboxylate (13)

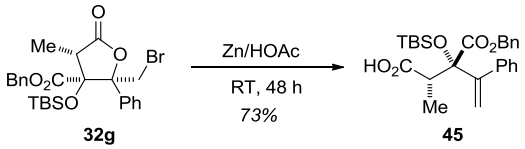


A 20-mL scintillation vial was charged with **32o** (54 mg, 0.1 mmol, 1.0 equiv) and the solid was dissolved in benzene (3 mL). DBU (0.060 mL, 4 mmol, 4.0 equiv) was added, and the solution was heated to 80 °C in a sealed vial. The reaction was monitored by TLC until the

starting material was completely consumed. The precipitated ammonium salt was removed via filtration, and the filtrate was concentrated in vacuo. The product was purified via flash chromatography (9:1 hexanes: ethyl acetate) to give the desired product in a 2:1 ratio with byproduct **S1** (benzyl 2-(2-bromoethyl)-4-methyl-5-oxo-2-phenyl-2,5-dihydrofuran-3-carboxylate--see below). The desired product could be isolated via HPLC (9:1 hexanes: ethyl acetate, 15mL/min, 254 nm UV absorbance) as a clear, colorless oil (28 mg, 61%). Analytical data: **^{1}H NMR** *major diastereomer* (400 MHz, $CDCl_3$): δ 7.52-7.19 (m, 10H), 5.23 (d, *J* = 11.6 Hz, 1H), 5.11 (d, *J* = 11.6 Hz, 1H), 2.53 (ddd, *J* =13.8, 10.8, 4.8 Hz, 1H), 2.26 (ddd, *J* =13.4, 10.8, 4.4 Hz, 1H), 2.06 (ddd, *J* =13.8, 10.4, 4.4 Hz, 1H), 1.75 (ddd, *J* =13.4, 10.4, 4.8 Hz, 1H), 1.32 (s, 3H), 0.80 (s, 9H), -0.15 (s, 3H), -0.56 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 177.4, 167.9, 134.1, 133.7, 129.6, 129.1, 128.7, 128.4, 127.8, 127.1, 93.1, 91.4, 67.6, 57.6, 31.0, 27.7, 25.8, 18.9, 10.7, -3.6, -3.9; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 489.21, observed: 489.2; **IR** (thin film, cm^{-1}): 3434, 3031, 2954, 2928, 2856, 1746, 1706, 1639, 1172, 837. **TLC** (80:20 hexanes: ethyl acetate): R_f = 0.43.

Byproduct **S1**: 

Preparation of (±)-(2*S*,3*S*)-3-(benzyloxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-4-phenylpent-4-enoic acid (14):



A 20-mL scintillation vial was charged with **10g** (75 mg, 0.14 mmol, 1 equiv), and glacial acetic acid (1.5 mL). Acid-washed, dried zinc metal (91 mg, 1.4 mmol, 10 equiv) was added, and the suspension was stirred for 48 h at room temperature. Ethyl acetate and water were

added (5 mL each). The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (3x5 mL). The combined organic were washed with water (5 mL), brine, (3 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was purified via flash chromatography (80:20 hexanes:ethyl acetate) to give the desired product as a white solid (46 mg, 73%). Analytical data: **^{1}H NMR** *major diastereomer* (400 MHz, $CDCl_3$): δ 7.26-7.17 (m, 6H), 7.01-6.94 (m, 4H), 5.74 (s, 1H), 5.22 (s, 1H), 5.00 (d, *J* = 12 Hz, 1H), 4.65 (d, *J* = 12 Hz, 1H), 3.29 (q, *J* = 7.2 Hz, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.09 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 178.5, 171.8, 148.7, 139.9, 134.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.4, 119.0, 83.8, 67.2, 44.5, 26.4, 19.6, 11.6, -2.6, -3.1; **LRMS (ESI^{+})** expected[M+ Na^{+}]$^{+}$: 477.21, observed: 477.2; **IR** (thin film, cm^{-1})**:** 3433, 3033, 2959, 2089, 1793, 1334, 837; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.47.

Analytical Data for Pentasubstituted Lactones in Table 2-5

General Method for Structural Assignment Based on NOESY Analysis:

See section 2.3.6 for full details on the assignment of diastereomer identities. As an example, the NOESY spectrum with labeled key interactions for compound **32i** is presented:

An nOe between the C2 methine proton and the silyl group is observed (A), along with a strong nOe between the ketone aryl proton indicated and the C2 methine proton (C). The expected nOe between the C2 methine proton and its coupled methyl group (B) accompanies a weaker nOe between the silyl group and the C2 methyl group (E). The nOe between the aryl and methylene protons of the benzyl ester is indicated by D. No nOe is observed between the C2 methyl group and any of the chromanone protons. Deshielding of the C2 methine proton is also observed, as indicated by the chemical shift (δ 3.27).

Key nOe Interactions Observed:

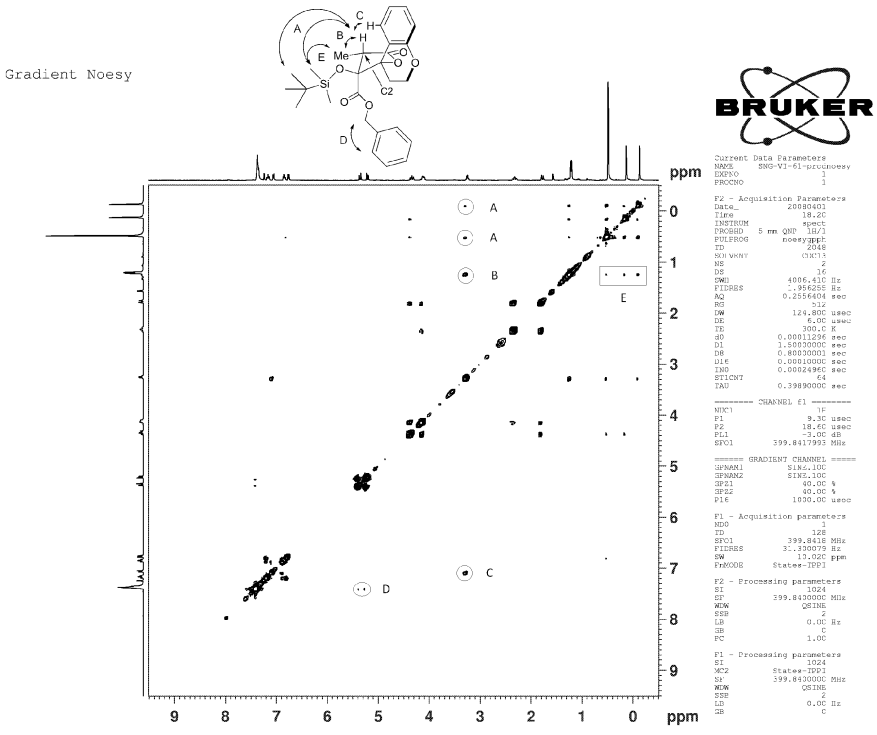
A: silyl (^{t}Bu and methyl) ↔ C2 methine.

B: C2 methine ↔ lactone C2 methyl

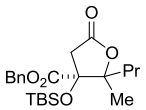
C: C2 methine ↔ aryl (ketone)

D: benzyl methylene ↔ β-aryl (ester)

E: silyl (^{t}Bu and methyl) ↔ lactone C2 methyl

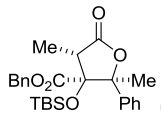


Characterization Data for Lactone Products



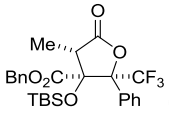
(+)(3S)-benzyl-3-(tert-butyldimethylsilyloxy)

-2-methyl-5-oxo-2-propyltetrahydrofuran-3-carboxylate (28). Synthesized according to procedure I to give the desired product as a mixture of inseparable diastereomers (1.6 : 1 dr). Purified by column chromatography (92.5:7.5 hexanes: ethyl acetate). Analytical data (: **^{1}H NMR** (400 MHz, $CDCl_3$): mixture of diastereomers; major diastereomer δ 7.40-7.29 (br s, 5H), 5.26 (d, *J* = 12 Hz, 1H), 5.14 (d, *J* = 12 Hz, 1H), 3.26 (d, *J* = 17.2 Hz, 1H), 2.66 (d, *J* = 17.2 Hz, 1H), 1.38 (s, 3H), 1.50-1.26 (m, 4H), 0.86 (s, 9H), 0.74 (t, *J* = 6.4 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 3H); minor diastereomer δ 7.40-7.29 (br s, 5H), 5.25 (d, *J* = 12 Hz, 1H), 5.12 (d, *J* = 12 Hz, 1H), 3.40 (d, *J* = 17.6 Hz, 1H), 2.62 (d, *J* = 17.6 Hz, 1H), 1.87-1.69 (m, 2H), 1.26-1.14 (m, 2H), 1.11 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** mixture of diastereomers: δ 172.6, 172.5, 170.4, 170.2, 134.4, 129.1, 129.0, 128.8, 128.6, 90.8, 90.5, 83.7, 83.3, 77.3, 77.0, 76.7, 67.8, 67.6, 41.0, 40.1, 38.2, 36.6, 25.5, 20.5, 18.7, 18.2, 16.8, 14.4, 14.2, -3.7, -4.0, -4.1; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 429.2, observed: 429.3; **IR** (thin film, cm^{-1}): 3431, 2940, 2886, 1790, 1745, 1468, 1293, 1211, 1135, 967, 910, 842; **TLC (**95:5 hexanes:ethyl acetate**):** R_f 0.28.

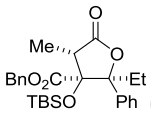


(±)-(2*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (29). Synthesized according to general procedure I to give the desired product as colorless crystals of 1 diastereomer. Purified via column chromatography (9:1 hexanes:ethyl acetate). Analytical data: mp 113-115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.24 (m, 10H), 5.35 (d, *J* = 12 Hz, 1H), 5.21 (d, *J* = 12 Hz, 1H), 2.72 (q, *J* = 7.2 Hz, 1H), 1.54 (s, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.54 (s, 9H), 0.20 (s, 3H), -0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 175.1, 170.3, 139.6, 134.2, 129.0, 128.8, 128.7, 128.4, 127.9, 127.8, 126.5, 87.0, 86.9, 67.7, 44.1, 25.8, 23.3, 18.4, 9.3, -2.7, -2.9; **LRMS (ESI$^+$)**

expected: 454.22, observed: 454.2; **IR** (thin film, cm^{-1}): 3432, 2935, 1792, 1753, 1498, 1383, 1298, 1220, 1143, 1058, 942.3; **TLC (**95:5 hexanes:ethyl acetate**):** R_f 0.27.

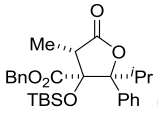


(±)-(2*S*,3S,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxo-2-phenyl-2-(trifluoromethyl)tetrahydrofuran-3-carboxylate (32a): Synthesized according to general procedure I to give the desired product as a white solid, which was one diastereomer. Analytical data: mp: 108-109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 9.2 Hz, 2H) 7.46-7.35 (m, 8H), 5.42 (d, *J* = 12 Hz, 1H), 5.13 (d, *J* = 12 Hz, 1H), 2.61 (q, *J* =6.8 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.67 (s, 9H), 0.27 (s, 3H), -0.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.2, 168.7, 133.7, 130.3, 129.6, 129.1, 128.9, 128.7, 128.3, 127.6, 84.9, 69.1, 44.2, 25.9, 18.7, 8.6, -2.7, -3.0; **LRMS (ESI$^+$)** expected: 508.19, observed: 508.2; **IR** (thin film, cm^{-1}): 3432, 2952, 2931, 2857, 2360, 2341, 1817, 1757, 1644, 1472, 1302, 1175, 1067, 830, 783, 727; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.32.

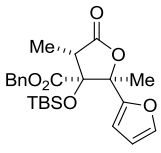


(±)-(2*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-ethyl-4-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (32b): Synthesized according to general procedure 1 to give the desired product as colorless crystals of 1 diastereomer. Analytical data: mp: 115-117 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.23(m, 10H), 5.37 (d, *J* = 12 Hz, 1H), 5.23 (d, *J* = 12 Hz, 1H), 2.69 (q, *J* =6.8 Hz, 1H), 2.08 (m, 1H), 1.50 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.60 (s, 9H), 0.58 (t, *J* = 7.2 Hz, 3H), 0.22 (s, 3H), -0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 175.4, 170.4, 136.3, 134.3, 129.0, 128.8, 128.7, 127.9, 127.7, 127.5, 90.4, 87.5, 67.7, 44.2, 28.4, 25.9, 18.5, 9.2, 8.4, -2.7, -2.8; **LRMS (ESI$^+$)** expected: 468.23,

observed: 468.2; **IR** (thin film, cm^{-1}): 3430, 2935, 2858, 2363, 1792, 1753, 1460, 1298, 1213, 1151, 981, 834; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.5.

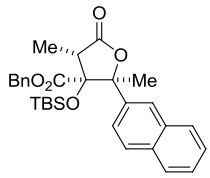


(±)-(2*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-isopropyl-4-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (32c): Synthesized according to general procedure III to give the desired product as a white solid, which was one diastereomer. Analytical data: mp: 106-108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (m, 2H), 7.45-7.28 (m, 8H), 5.37 (d, *J* = 12 Hz, 1H), 5.26 (d, *J* = 12 Hz, 1H), 2.51 (q, *J* =6.8 Hz, 1H), 1.9 (heptet, *J* = 6.8 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.79 (s, 9H), 0.55 (d, *J* = 6.8 Hz, 3H), 0.28 (s, 3H), -0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 174.7, 170.7, 134.9, 134.3, 129.3, 128.8, 128.6, 128.4, 127.9, 127.3, 90.7, 88.9, 67.9, 45.3, 35.3, 26.2, 18.9, 18.5, 17.4, 9.6, -2.4, -2.5; **LRMS (ESI$^+$)** expected $(M+H)^+$: 483.26, observed: 483.3; **IR** (thin film, cm^{-1}): 3472, 3063, 3034, 2952, 2886, 2858, 1791, 1747, 1472, 1292, 1210, 1139, 1004, 830; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.36.

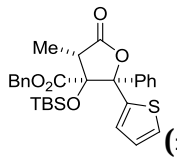


(±)-(2*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-(furan-2-yl)-2,4-dimethyl-5-oxotetrahydrofuran-3-carboxylate (32d): Synthesized according to general procedure I to give the desired product as a light yellow oil, which was a 7.5:1 mixture of diastereomers. Analytical data (major diastereomer): **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5H), 6.31 (s, 2H), 5.32 (d, *J* = 12 Hz, 1H), 5.22 (d, *J* = 12 Hz, 1H), 3.54 (q, *J* = 6.8 Hz, 1H), 1.57 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.62 (s, 9H), 0.13 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 174.9, 170.0, 152.9, 142.7, 134.2, 128.9, 128.7, 128.5, 110.3,

109.5, 87.5, 83.2, 67.6, 44.0, 25.4, 19.2, 18.2, 9.5, -2.9, -3.0; **LRMS (ESI$^+$)** expected: 467.23, observed: 467.2; **IR** (thin film, cm^{-1}): 3434, 2951, 2930, 2857, 1794, 1752, 1636, 1463, 1300, 1216, 1143, 1053, 838, 781; *Minor diastereomer:* **^{1}H NMR** (400 MHz, $CDCl_3$): 7.40 -7.24 (m, 4H), 6.25 (d, *J* = 1.6 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.00 (d, *J* = 12.4 Hz, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 3.02 (q, *J* =6.8 Hz, 1H), 1.75 (s, 3H), 0.92 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.19 (s, 3H), 0.09 (s, 3H); **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.33.

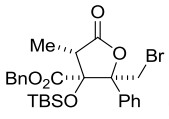


(±)-(2*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-2-(naphthalen-2-yl)-5-oxotetrahydrofuran-3-carboxylate (32e): Synthesized according to general procedure I to give the desired product as a colorless oil, which was an 18:1 mixture of diastereomers. Analytical data (*major diastereomer)*: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86-7.78 (m, 4H), 7.51-7.37 (m, 8H), 5.42 (d, *J* = 12 Hz, 1H), 5.28 (d, *J* = 12 Hz, 1H), 2.85 (q, *J* =7.2 Hz, 1H), 1.66 (s, 3H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.52 (s, 9H), 0.29 (s, 3H), -0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 175.2, 170.3, 137.2, 134.2, 132.7, 129.0, 128.9, 128.7, 128.3, 127.4, 127.3, 126.3, 126.2, 125.2, 124.8, 87.4, 87.0, 67.8, 44.2, 25.7, 23.6, 18.4, 9.3, -2.7, -2.9; **LRMS (ESI$^+$)** expected (M+ Na^+): 527.22, observed: 527.2; **IR** (thin film, cm^{-1}): 3434, 3061, 2952, 2930, 2857, 1790, 1768, 1471, 1379, 1297, 1057, 938, 857, 737; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.39.

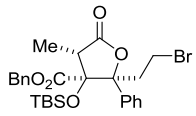


(±)-(2*R*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxo-2-phenyl-2-(thiophen-2-yl)tetrahydrofuran-3-carboxylate (32f): Synthesized according to

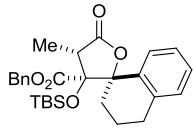
general procedure II to give the desired product as a white solid that was a >25:1 mixture of diastereomers. Analytical data (major diastereomer): mp: 128-130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.54 (m, 2H), 7.34-7.21 (m, 7H), 7.10-7.02 (m, 2H), 6.95-6.89 (m, 2H), 4.77 (d, *J* = 12 Hz, 1H), 4.44 (d, *J* = 12 Hz, 1H), 3.42 (q, *J* =7.2 Hz, 1H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.74 (s, 9H), 0.32 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 173.9, 169.8, 143.6, 139.8, 134.0, 128.6, 128.5, 128.2, 128.0, 127.9, 126.5, 126.3, 125.0, 89.2, 88.8, 67.6, 44.3, 25.8, 18.5, 10.0, -2.4, -2.5; **LRMS (ESI$^+$)** expected $(M+Cs)^+$: 655.09, observed: 655.1; **IR** (thin film, cm^{-1}): 3433, 2951, 2929, 2856, 1790, 1752, 1635, 1471, 1201, 1136, 1015, 838; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.41.



(±)-(2*S*,3*S*,4*S*)-benzyl-2-(bromomethyl)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (32g): Synthesized according to general procedure II to give the desired product as clear colorless crystals of one diastereomer. Analytical data: melting point: 131-132 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 -7.36 (m, 8H), 7.28-7.26 (m, 2H), 5.39 (d, *J* = 12 Hz, 1H), 5.30 (d, *J* = 12 Hz, 1H), 3.79 (d, *J* = 11.2 Hz, 1H), 3.34 (d, *J* = 11.2 Hz, 1H), 2.77 (q, *J* = 7.2 Hz, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 0.61 (s, 9H), 0.24 (s, 3H), -0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 173.8, 169.6, 135.3, 133.7, 129.2, 129.2, 128.9, 128.4, 128.0, 127.1, 88.2, 86.6, 68.3, 44.8, 34.5, 25.8, 18.4, 9.2, -2.7, -2.9; **LRMS (ESI$^+$)** expected $(M+Na)^+$: 555.12, observed: 555.1; **IR** (thin film, cm^{-1}): 3434, 2953, 2930, 2858, 1797, 1748, 1644, 1471, 1137, 1009, 838; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.48.

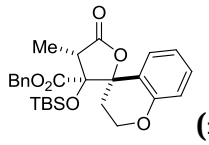


(±)-(2*S*,3*S*,4*S*)-benzyl-2-(2-bromoethyl)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate(32o): Synthesized according to general procedure II to give the desired product as colorless crystals of one diastereomer. Analytical data: melting point: 129-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46-7.31 (m, 8H), 7.27-7.25 (m, 2H), 5.41 (d, *J* = 12 Hz, 1H), 5.27 (d, *J* = 12 Hz, 1H), 3.12 (ddd, *J* = 4.4, 9.6, 12.8 Hz, 1H), 2.74 (ddd, *J* = 4.8, 12.0, 14.8, 1H), 2.70-2.60 (m, 2H), 2.04 (d, *J* = 4.4, 10.0, 13.6 Hz, 1H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.60 (s, 9H), 0.24 (s, 3H), -0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 174.6, 169.9, 134.9, 133.9, 129.3, 129.1, 128.9, 128.4, 128.3, 127.1, 89.0, 87.0, 68.1, 43.6, 39.4, 26.3, 25.8, 18.5, 9.1, -2.7, -2.9; **LRMS (ESI^{+})** expected $(M+Na)^{+}$: 569.13, observed: 569.2; **IR** (thin film, cm^{-1}): 3433, 2952, 2857, 1797, 1636, 1446, 1142, 827; **TLC:** (80:20 hexanes:ethyl acetate): R_f = 0.54..

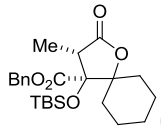


(±)-(1'*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxo-3',4,4',5-tetrahydro-2'H,3H-spiro[furan-2,1'-naphthalene]-3-carboxylate (32h): Synthesized according to general procedure II to give the desired product as a white solid of one diastereomer. Analytical data: melting point: 115-118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.24 (m, 5H), 7.19- 7.08 (m, 4H), 5.36 (d, *J* = 12 Hz, 1H), 5.24 (d, *J* = 12 Hz, 1H), 3.24 (q, *J* = 6.8 Hz, 1H), 2.83-2.79 (m, 1H), 2.15-1.87 (m, 3H), 1.74-1.68 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.41 (s, 9H), 0.11 (s, 3H), -0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 175.7, 170.7, 138.7, 135.6, 134.2, 129.6, 129.0, 128.8, 128.7, 128.2, 125.4, 124.5, 88.5, 86.5, 67.6, 44.7, 31.8, 27.9, 25.2, 18.0, 17.5, 9.8, -2.9, -3.2; **LRMS (ESI^{+})** expected

$(M+Cs)^+$: 613.14, observed: 613.1; **IR** (thin film, cm^{-1}): 3434, 2951, 2884, 2856, 1791, 1749, 1635, 1458, 1214, 1148, 977, 834; **TLC**(80:20 hexanes:ethyl acetate):R_f = 0.44.

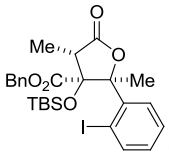


(±)-(2'*S*,3'*S*,4'*S*)-benzyl-3'-(*tert*-butyldimethylsilyloxy)-4'-methyl-5'-oxo-4',5'-dihydro-3'H-spiro[chroman-4,2'-furan]-3'-carboxylate (32i): Synthesized according to general procedure II to give the desired product as clear, colorless crystals. Analytical data: melting point: 120-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39- 7.26 (m, 5H), 7.19 (t, *J* = 8 Hz, 1H), 7.08 (d, *J* = 8 Hz Hz, 1H), 6.87 (t, *J* = 8 Hz, 1H), 6.79 (d, *J* = 8 Hz, 1H), 5.38 (d, *J* = 12 Hz, 1H), 5.23 (d, *J* = 12 Hz, 1H), 4.36 (dt, *J* = 2, 12 Hz, 1H), 4.15- 4.11 (m, 1H), 3.27 (q, *J* = 7.2 Hz, 1H), 2.33 (dt, *J* = 14, 4.8 Hz, 1H), 1.79 (dd, *J* = 2, 14 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.50 (s, 9H), 0.14 (s, 3H), -0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 175.0, 170.1, 155.2, 134.0, 130.1, 129.1, 129.0, 128.7, 124.7, 121.1, 119.7, 117.2, 88.2, 82.5, 67.8, 62.2, 44.2, 30.4, 25.1, 18.0, 9.8, -3.1, -3.2; **LRMS (ESI$^+$)** expected $(M+K)^+$: 521.18, observed: 521.2; **IR** (thin film, cm^{-1}) 3434, 2935, 2858, 1792, 1753, 1614, 1491, 1298, 1213, 1151, 1058, 981, 834; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.55.

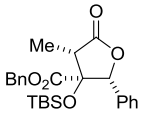


(±)-(3*S*,4*S*)-benzyl-4-(*tert*-butyldimethylsilyloxy)-3-methyl-2-oxo-1-oxaspiro[4.5]decane-4-carboxylate (32j): Synthesized according to general procedure I to give the desired product as a clear, colorless oil. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.28 (d, *J* = 12 Hz, 1H), 5.16 (d, *J* = 12 Hz, 1H), 2.95 (q, *J* = 6.8 Hz, 1H), 1.80-1.50 (m, 7H), 1.42-1.18 (m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.19 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 174.6, 170.3, 134.4, 128.7, 128.6,

128.6, 87.6, 86.5, 67.3, 43.9, 31.8, 31.0, 25.9, 25.2, 22.3, 21.6,.18.8, 9.2, -2.7, -2.8; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 455.22, observed: 455.3; **IR** (thin film, cm^{-1}) 3434, 2935, 2889, 1792, 1753, 1468, 1375, 1298, 1213, 1135, 1058, 966, 911, 842; **TLC**(85:15 hexanes:ethyl acetate): R_f = 0.30.



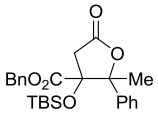
(±)-(2*S*,3*S*,4*S*)-benzyl-3-(*tert*-butyldimethylsilyloxy)-2-(2-iodophenyl)-2,4-dimethyl-5-oxotetrahydrofuran-3-carboxylate (32k): Analytical Data: melting point: 110-111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.44-7.29 (m, 7H), 6.92-6.88 (m, 1H), 5.36 (d, *J* = 12 Hz, 1H), 5.25 (d, *J* = 12 Hz, 1H), 2.81 (q, *J* = 7.2 Hz, 1H), 1.95 (br. s, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.50 (s, 9H), 0.29 (br. s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 174.7, 170.1, 143.6, 134.2, 129.3, 129.2, 129.0, 128.8, 127.5, 89.4, 88.0, 67.7, 46.6, 26.3, 25.6, 18.3, 10.6, -2.0, -2.3; **LRMS (ESI$^+$)** expected $(M+Na)^+$: 580.11, observed: 580.1; **IR** (thin film, cm^{-1}): 3445, 2950, 2928, 2856, 2360, 1788, 1750, 1462, 1297, 1142, 837; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.5.



(±)-Benzyl-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (32l): Synthesized according to general procedure I to give the desired product as a colorless oil, which was a 3:1 mixture of diastereomers. Analytical data (*major diastereomer*): **^{1}H NMR** 400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 8H), 7.13-7.11 (m, 2H), 5.29 (s, 1H), 4.85 (d, *J* = 12 Hz, 1H), 4.71 (d, *J* = 12 Hz, 1H), 3.01 (q, *J* = 7.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 174.3, 168.6, 134.1,133.6, 128.7, 128.6, 128.1, 125.6, 87.6, 85.5, 67.4,

47.5, 25.7, 18.5, 9.4, -2.7, -2.9 (*minor diastereomer):* **^{1}H NMR** 400 MHz, $CDCl_3$): δ 7.40 (br. s, 5H), 7.29- 7.20 (m, 5H), 5.86 (s, 1H), 5.35 (d, *J* = 12.0 Hz, 1H), 5.23 (d, *J* = 12.0 Hz, 1H), 2.88 (q, *J* = 7.6, 1H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.55 (s, 9H), 0.03 (s, 3H), -0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 176.3, 169.8, 134.4, 133.8, 129.2, 129.0, 128.8, 128.3, 128.0, 126.6, 84.7, 84.5, 68.0, 47.8, 25.5, 18.2, 12.0, -2.9, -3.3; **IR** (thin film, cm^{-1}): 3434, 2952, 2929, 2857, 1788, 1749, 1645, 1198, 1015, 838; **LRMS (ESI^{+})** expected $[M+Na]^{+}$: 463.19, observed: 463.2; **TLC** (95:5 hexanes:ethyl acetate): R_f = 0.27, major diastereomer;, R_f = 0.19, minor diastereomer.

Note: NOESY analysis was inconclusive, but through comparison with alternative substrates, the absence of an anisotropic effect of the aldehyde-derived benzene ring likely contributes to the downfield chemical shift of the α-methine proton of the lactone (3.00 vs 2.88) as well as the upfield shift of the methylene protons of the benzyl group (4.85 and 4.71 vs 5.35 and 5.23) to suggest the major diastereomer shown.

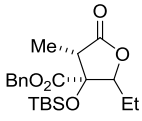


(±)-Benzyl-3-(*tert*-butyldimethylsilyloxy)-2-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (27e): Synthesized according to general procedure I to give the desired product as a colorless oil, which was a 3:1 mixture of diastereomers Analytical data (*major diastereomer*): **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.38 (m, 5H), 7.26 (br. s, 5H), 5.39 (d, *J* = 12 Hz, 1H), 5.17 (d, *J* = 12 Hz, 1H), 3.46 (d, *J* = 17.6, 1H), 2.67 (d, *J* = 17.6, 1H), 1.55 (s, 3H), 0.57 (s, 9H), -0.20 (s, 3H), -0.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.7, 170.5, 138.9, 134.3, 129.3, 129.1, 128.8, 127.7, 127.5, 126.3, 91.2, 83.6, 68.1, 41.4, 25.7, 25.4, 24.1, 17.9, -3.9, -4.3; **LRMS (ESI^{+})** expected $[M+Na]^{+}$: 463.19, observed: 463.2; **IR** (thin film, cm^{-1}) 3430, 2935, 2858, 1800, 1753, 1290, 1182, 1089, 942,

842; **IR** (thin film, cm^{-1}) 3432, 2935, 2858, 1800, 1753, 1290, 1182, 1089, 942, 842; **TLC:** R_f = 0.25, 92.5:7.5 hexanes:ethyl acetate.

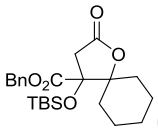
Minor Diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33- 7.26 (m, 8H), 7.08- 7.06 (m, 2H), 4.67 (d, *J* = 12 Hz, 1H), 4.54 (d, *J* = 12 Hz, 1H), 3.14 (d, *J* = 16.8 Hz, 1H), 2.84 (d, *J* = 16.8 Hz, 1H), 1.78 (s, 3H), 0.94 (s, 9H), 0.12 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.0, 170.6, 139.8, 134.2, 128.5, 128.1, 128.0, 124.7, 90.8, 84.0, 67.6, 40.9, 25.7, 25.0, 18.4, -3.7, -3.8; **IR** (thin film, cm^{-1}) 3431, 2958, 1823, 1762, 1460, 1220, 1174, 1066, 923, 834; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 440.20, observed: 440.2; **TLC** (92.5:7.5 hexanes:ethyl acetate): R_f = 0.32.

Note: NOESY Analysis was inconclusive for this substrate.

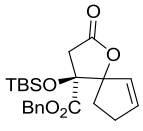


(3S,4S)-benzyl 3-(tert-butyldimethylsilyloxy)-2-ethyl-4-methyl-5-oxotetrahydrofuran-3-carboxylate (**32m**): Synthesized accordine to procedure I to give the desired product as a mixture of inseparable diastereomers (1.6 : 1 dr). Purified by column chromatography (92.5:7.5 hexanes: ethyl acetate). Analytical data (: **^{1}H NMR** (400 MHz, $CDCl_3$): mixture of diastereomers; major diastereomer δ 7.40-7.26 (br s, 5H), 5.24 (d, *J* = 12 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 4.04 (dd, *J* = 3.6, 9.6 Hz, 1H), 2.82 (q, *J* = 7.2 Hz, 1H), 1.84-1.50 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.87 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H); minor diastereomer δ 7.40-7.26 (br s, 5H), 5.23 (d, *J* = 12 Hz, 1H), 5.16 (d, *J* = 12 Hz, 1H), 4.66 (dd, *J* = 5.2, 8 Hz, 1H), 2.72 (q, *J* = 8 Hz, 1H), 1.49-1.39 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.84 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** mixture of diastereomers: δ 176.1, 174.7, 169.7, 169.5, 134.4, 128.9, 128.6, 128.6, 86.6, 85.4, 85.3, 83.5, 77.3, 77.0, 76.7, 67.7, 67.3, 47.8, 47.3, 25.7, 25.6,

22.2, 22.1, 18.6, 18.3, 11.9, 10.8, 9.9, 8.8, -2.8, -3.0, -3.0, -3.2; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 415.2, observed: 415.2; **IR** (thin film, cm^{-1}): 3430, 2940, 2890, 1787, 1753, 1465, 1291, 1210, 1136, 973, 842; **TLC (**95:5 hexanes:ethyl acetate**):** R_f 0.27.

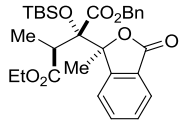


(±)-(*S*)-Benzyl-4-(*tert*-butyldimethylsilyloxy)-2-oxo-1-oxaspiro[4.5]decane-4-carboxylate (32n): Synthesized according to general procedure I. The desired product was obtained as a colorless oil. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37- 7.26 (m, 5H), 5.26 (d, *J* = 12 Hz, 1H), 5.08 (d, *J* = 12 Hz, 1H), 3.32 (d, *J* = 17.6 Hz, 1H), 2.61 (d, *J* = 17.6 Hz, 1H), 1.99 (d, *J* = 10.8 Hz, 1H), 1.72-1.41 (m, 7H), 1.11–0.96 (m, 2H), 0.84 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.7, 170.3, 134.5, 129.0, 128.9, 128.7, 89.8, 83.5, 67.7, 40.8, 32.2, 29.7, 25.6, 24.9, 21.9, 21.8, 18.3, -3.6, -4.0; **LRMS (ESI$^+$)** expected $[M+Na]^+$:441.21, observed: 441.2; **IR** (thin film, cm^{-1}) 3430, 2935, 1858, 1792, 1753, 1614, 1491, 1298, 1213, 1151, 1058, 980, 834; **TLC** (85:15 hexanes:ethyl acetate): R_f = 0.28.



(±)-(4*S*)-benzyl-4-(*tert*-butyldimethylsilyloxy)-2-oxo-1-oxaspiro[4.4]non-6-ene-4-carboxylate (32p): Synthesized according to general procedure I to give the desired product as a colorless oil, which was a 1.1:1 mixture of diastereomers. Analytical data (*mixture of diastereomers*): **^{1}H NMR** *major diastereomer* (400 MHz, $CDCl_3$): δ 7.35- 7.26 (m, 5H), 6.11 (m, 1H), 5.86 (m, 1H), 5.25 (d, *J* = 12 Hz, 1H), 5.13 (d, *J* = 12 Hz, 1H), 3.22 (d, *J* = 17.2 Hz, 1H), 2.73 (d, *J* = 17.2 Hz, 1H), 2.74 to 2.67 (m, 1H), 2.51 to 2.40 (m, 1H), 1.98 to 1.81 (m, 2H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H) *minor diastereomer:* δ 7.35-7.26 (m, 5H), 5.98 (m, 1H), 5.44 (m, 1H), 5.20 (d, *J* = 12 Hz, 1H), 5.03 (d, *J* = 12 Hz, 1H),

3.46 (d, *J* = 17.2 Hz, 1H), 2.69 (d, *J* = 17.2 Hz, 1H), 2.51- 2.40 (m, 1H), 2.23- 2.13 (m, 1H) 2.10-2.01 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) **(***mixture of diastereomers)***:** δ 172.9, 172.4, 170.8, 169.7, 140.4, 138.4, 134.5, 129.1, 128.8, 127.4, 103.2, 102.2, 83.6, 82.9, 67.7, 41.5, 31.4, 31.1, 29.6, 25.6, 18.3, -3.6, -3.9, -4.1; **LRMS (ESI$^+$) (***mixture of diastereomers)*expected $[M+Na]^+$: 425.18, observed: 425.2; **IR** (thin film, cm^{-1}) **(***mixture of diastereomers)* 3432, 2958, 2858, 1792, 1738, 1460, 1298, 1197, 935, 834, 780; **TLC** (85:15 hexanes:ethyl acetate): R_f = 0.22.



(±)-(2*S*,3*S*)-1-benzyl 4-ethyl 2-(tert-butyldimethylsilyloxy)-3-methyl-2-((*S*)-1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)succinate (32q): Synthesized according to general procedure II to give the desired product as a colorless oil, which was a 20:1 mixture of diastereomers. Analytical data (*mixture of diastereomers*): *major diastereomer:* **^{1}H NMR** *major diastereomer* (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 6.4 Hz, 1H), 7.44-7.39 (m, 7H), 6.87 (d, *J* = 7.2 Hz, 1H), 5.31 (d, *J* = 12 Hz, 1H), 5.21 (d, *J* = 12 Hz, 1H), 4.09-3.98 (m, 2H), 3.54 (q, *J* = 6.8 Hz, 1H), 1.76 (s, 3H), 1.52 (d, *J* = 6.8 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.77 (s, 9H), -0.02 (s, 3H), -0.81 (s, 3H) ; **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.8, 171.3, 169.4, 150.7, 134.4, 133.6, 129.5, 129.3, 128.9, 128.7, 125.4, 122.8, 89.8, 84.8, 68.2, 61.0, 46.7, 26.4, 24.0, 19.5, 14.1, 12.7, -2.5, -4.2; **LRMS (ESI$^+$) (***mixture of diastereomers)* expected $[M+ Cs^+]^+$: 659.14, observed: 659.2; **IR** (thin film, cm^{-1})**:** 3433, 2958, 2855, 2074, 1772, 1644, 1465, 1249, 1162, 1034, 835; **TLC** (80:20 hexanes:ethyl acetate): R_f = 0.27.

Note: Stereochemistry for the title compound was assigned based on analogy with other substrates.

2.6 References

[1] Hoffmann, H. M. R.; Rabe, J. *Angew. Chem.* **1985,** *97*, 96-112.

[2] Reiser, O.; Seitz, M. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285-292.

[3] Collins, I. *J. Chem. Soc., Perkin Trans. 1*. **1998**, 1869-1888.

[4] Evans, D. A.; Trotter, B. W.; Barrow, J. C. *Tetrahedron* **1997**, *53*, 8779-8794.

[5] Nakamura, S.; Sato, H.; Hirata, Y.; Watanabe, N.; Hashimoto, S. *Tetrahedron* **2005**, *61*, 11078-11106.

[6] Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281-17283.

[7] Koch, S. S. C.; Chamberlin, A. R.: *Enantiomerically pure gammabutyrolactones in natural products synthesis. In Studies in Natural Products Chemistry*, Vol. 16. **1995**, 687-725, Atta-ur-Rahman, Ed. Elsevier Science.

[8] Trost, B. M.; Rhee Y. H. J Am Chem Soc **1999**, *121*, 11680-11683.

[9] Lu, X.; Zhu, G.; Wang, Z.; Shengming, M.; Jianguo, J.; Zhang, Z. *Pure Appl. Chem.* **1997**, *69*, 553-558.

[10] Lee, J.; Barchi, J.J.; Marquez, V.E. *Chem. Lett.* **1995**, *24*, 299-300.

[11] Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.*, **1979**, *8*, 171-197.

[12] Ozlugedik, M.; Kristensen, J.; Reuber, J.; Frohlich, R.; Hoppe, D. *Synthesis* **2004**, 2303- 2316.

[13] Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370-14371.

[14] For a monograph on the aldol reaction, see: *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

[15] Hoppe, D. *Angew. Chem. Int. Ed. Engl.* **1984,** *23*, 932-948.

[16] Nicewicz, D. A.; Breteche, G.; Johnson, J. S.; Bryan, C.; Lautens, M. *Org. Synth.* **2008**, *85*, 278-286.

[17] Linghu, X.; Satterfield, A. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 9302-9303.

[18] Greszler, S. N.; Johnson, J. S. *Org. Lett.* **2009**, *11*, 827-830.

[19] Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc*. **2005**, *127*, 6170-6171.

[20] Schmitt, D. C.; Johnson, J. S. *Org. Lett.*, **2010**, *12*, 944-947.

[21] Boyce, G. R. Unpublished results.

[22] For addition of enolates to acyl silanes: a) Takeda, K.; Yamawaki, K.; Hatakeyama, N. *J. Org. Chem*. **2002**, *67*, 1786-1794; b) Lettan, R. B.; Reynolds, T. E.; Galliford, C. V.; Scheidt, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 15566-15567; c) Lettan, R. B.; Woodward, C. C.; Scheidt, K. A. *Angew. Chem.* **2008,** *120*, 2326-2329; *Angew. Chem. Int. Ed.* **2008**, *47*, 2294-2297.

[23] Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*, Oxford, New York, **1999**.

[24] Erdik, E. *Organozinc Reagents in Organic Synthesis*, CRC, New York, **1996** and references therein.

[25] Reviews of Reformatsky reagents: a) Ocampo, R.; Dolbier, W. R. *Tetrahedron* **2004**, *60*, 9325-9374; b) Fürstner, A. *Synthesis* **1989**, 571-590; c) Cozzi, P. G. *Angew. Chem. Int. Ed*. **2007**, *46*, 2568-2571.

[26] Rieke, R. D. *Science*, **1989,** *246*, 1260–1264.

[27] Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron*, **1988**, *44*, 4495-4508.

[28] Picotin, G.; Miginiac, P.; *J. Org. Chem.* **1987**, *52*, 4796-4798.

[29] Kimura, M.; Seki, M. *Tetrahedron Lett.* **2004**, *45*, 1635-1637.

[30] Dewar, M.; Merz, K. *J. Am. Chem. Soc.* **1987**. *109*, 6553-6554.

[31] Cozzi, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2951-2954.

[32] Fernández-Ibáñez, M. A.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1317-1319.

[33] a) Babu, S. A.; Yasuda, M.; Okabe, Y.; Shibata, I.; Baba, A. *Org. Lett.* **2006**, *8*, 3029–3032; b) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **2005**, *70*, 10408–10419.

[34] a) Fürstner, A.; Kollegger, G.; Weidmann, H. *J. Organomet. Chem*. **1991**, *414*, 295-305; b) Narasaka, K.; Saito, N.; Hayashi, Y.; Ichida, H. *Chem. Lett*. **1990**, *19*, 1411-1414.

[35] Unger, R.; Cohen, T.; Marek, I. *Org. Lett*. **2005**, *7*, 5313-5316 and reference 19.

[36] Arnett, E. M.; Maroldo, S. G.; Schillig, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759-6767.

[37] Moser, W. H. *Tetrahedron*, **2001**, *57*, 2065-2084.

[38] Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A.; Kendall, C.; Wipf, P. *Org. Synth.* **2009**, *11*, 702-707.

[39] Selected recent exceptions that successfully employ ketone substrates in diastereo- or enantioselective Reformatsky reactions: a) Cozzi, P. G.; Mignogna, A.; Vicennati, P.; *Adv. Synth. Catal*. **2008**, *350*, 975-978; b) Fernáñdez-Ibánez, M. Á.; Maciá, B. Minnaard, A. J.; Feringa, B. L. *Chem. Commun*. **2008**, 2571-2573; c) Fernández-Ibáñez, M. Á.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Org. Lett*. **2008**, *10*, 4041-4044.; also, ref. 33a,b and ref. 31.

[40] Intermolecular proton transfer is detrimental in other hindered cases: a) Newman, M. S. *J. Am. Chem. Soc*. **1942**, *64*, 2131-2133; b) Evans, F. J.; Newman, M. S. *J. Am. Chem. Soc*. **1955**, *77*, 946-947.

[41] (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem.* **2006,** *118*, 6186-6190; *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 6040-6044. (b) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107-1110. In this work, with certain hindered substrates a higher yield was observed in the presence of excess lithium chloride.

[42] See section 2.5 for more details.

[43] Li, J.; Zhao, Y.-F.; Yuan, X.-Y.; Xu, J.-X.; Gong, P. *Molecules* **2006**, *11*, 574-582.

[44] Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467-2472.

[45] Rao, A. S.; Mohan, H. R.; Charette, A. "*m*-Chloro-Peroxybenzoic Acid" in *Encyclopedia of Reagents for Organic Synthesis*, Vol. 2; Paquette, L. A., Ed.; Wiley: Chichester, **1995**, 1192.

[46] Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810-1819.

[47] Oestreich, M.; *Synlett*. **2007**, *11*, 1629-1643.

[48] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc. Perkins Trans. II***, 1987**, S1-S19.

[49] Campagna, M.; Trzoss, M.; Bienz, S. *Org. Lett.* **2007**, *7*, 3793-3795.

[50] Oestreich, M.; Schmid, U. K.; Auer, G.; Keller, M. *Synthesis* **2003**, 2725-2739.

[51] Oestreich, M.; Auer, G.; Keller, M. *Eur. J. Org. Chem.* **2005**, 184-195.

[52] Terunuma, D.; Senda, K.; Sanazawa, M.; Nohira, H. *Bull. Chem. Soc. Jap.* **1982**, *55*, 924-927.

[53] Asadi, A.; Avent, A. G.; Eaborn, C.; Hill, M. S.; Hitchcock, P. B.; Meehan, M. M.; Smith, J. D. *Organometallics* **2002**, *21*, 2183-2188.

[54] Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1985,** *26*, 6113-6114.

[55] (a) Dauben, H. H.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442-1445. (b) Wilcox, C. S.; Babston, R. E. *Synthesis*, **1985**, 941-943.

[56] (a) Ruano, J. L. G.; Aleman, J.; Perra, A.; Cid, M. B. *Org. Synth.* **2007**, *84*, 129-138. (b) Murphy, J. A.; Mahesh, M.; McPheators, G.; Anand, R. V.; McGuire, T. M.; Carling, R.; Kennedy, A. R. *Org. Lett.* **2007**, *9*, 3233-3236.

[57] Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron*, **2004**, *60*, 8003-8030.

[58] **Bolm**, C.; Kasyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Günther, K.; Wagner, C. *Org. Lett.* **2002**, *4*, 2265-2267.

[59] Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713-1718.

[60] Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Comm.* **1987**, *17*, 1709-1716.

[61] Meyer, M. E.; Ferreira, E. M.; Stoltz, B. M. *Chem. Commun.* **2006**, 1316-1318.

[62] Li, J.; Zhao, Y.-F.; Yuan, X.-Y.; Xu, J.-X.; Gong, P. *Molecules* **2006**, *11*, 574-582.

[63] Hoffmann, H. M. R. *Synthesis* **1981**, *9*, 715-719.

[64] Sonda, S.; Katayama, K.; Kawahara, T.; Sato, N.; Asano, K. *Bioorg. Med. Chem.* **2004**, *12*, 2737-2747.

[65] Jiao, J.; Nguyen, L. X.; Patterson, D. R.; Flowers, R. A. *Org. Lett.* **2007**, *9*, 1323-1326.

[66] Kloetzing, R. J.; Thaler, T.; Knochel, P. *Org. Lett.* **2006**, *8*, 1125-1128.

CHAPTER THREE

PROGRESS TOWARD THE TOTAL SYNTHESIS OF LEUSTRODUCSIN B

3.1.1 Introduction

Multicomponent reactions offer unique opportunities in natural product synthesis. Through the selection of appropriately functionalized coupling partners, a rapid buildup of complexity can be achieved when several transformations are combined in a tandem fashion. In an effort to expand upon the double Reformatsky reactions of silyl glyoxylates and ketones, we envisioned the application of a new cascade toward the synthesis of leustroduscin B, a potent colony stimulating factor produced by *Streptomyces platensis*. In this third and final chapter, we discuss the development of a tandem Reformatsky/Claisen cascade and our progress toward the synthesis of leustroducsin B from the β-hydroxyketone products it affords. Highlighted are the results from the myriad synthetic routes we investigated and our observations on the behavior of key intermediates.

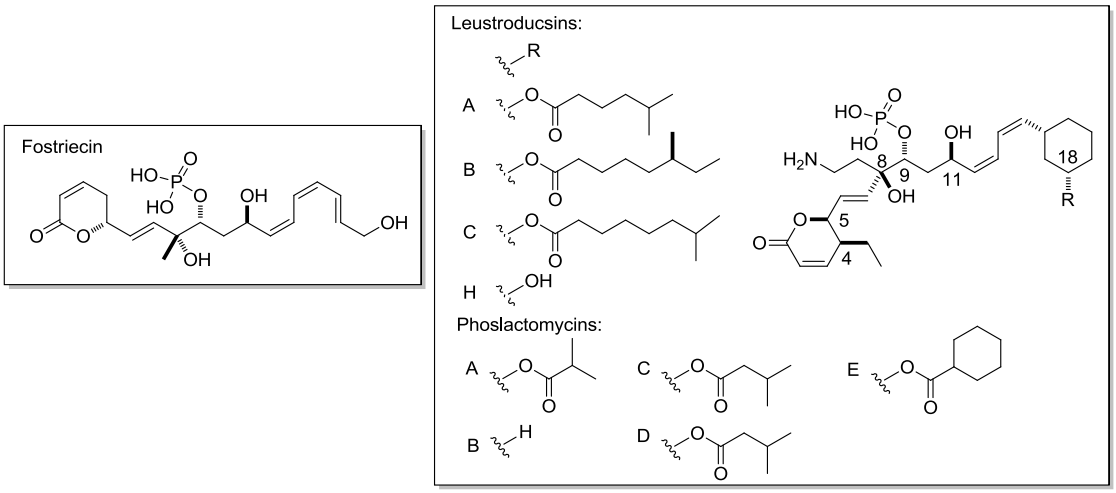
3.1.2 Biological Activity and Biosynthetic Proposals of Leustroducsins and Related Natural Products

With over 500 species currently identified, the *Streptomyces* genus represents the largest group of Actinobacteria.[1] The genus is characterized by a complex secondary metabolism, which produces numerous structurally intriguing and biologically active compounds. While the *Streptomyces* are rarely pathogenic in humans, they produce nearly

two-thirds of the clinically useful antibiotics of natural origin,[1] a testament to the value of research into the bioactive components of their cultures.

The leustroducsin[2] and phoslactomycin[3] families of natural products were isolated in 1993 by Kohama et al. from the culture broth of *Streptomyces platensis* and were later found to exhibit interesting antifungal, antibacterial, and antitumor activities.[2b,3b,4] In addition to their attractive biological properties, these groups of natural products boast intriguing molecular architectures.

Figure 3-1. Leustroducsins and Related Natural Products



In each, a highly congested and functionalized core is flanked by dihydropyrone and cyclohexyl moieties and bears a central tertiary alcohol with vicinal phosphate and aminoethyl substituents. The individual members in each group and the groups themselves are largely distinguished by the identity of the substituent on the cyclohexyl ring: the (*Z*,*Z*)-diene portion is terminated by an unsubstituted cyclohexyl side chain in phoslactomycin B, whereas the leustroducsin family and other members of the phoslactomycins have an additional site of oxygenation at C18. These groups of natural products are more distantly

related to fostriecin,[5] which has a less functionalized core and side chains (Figure 3-1) but has received considerably more attention from the synthetic community due to its potent *in vitro* activity against leukemia, lung, breast, and ovarian cancer cell lines.

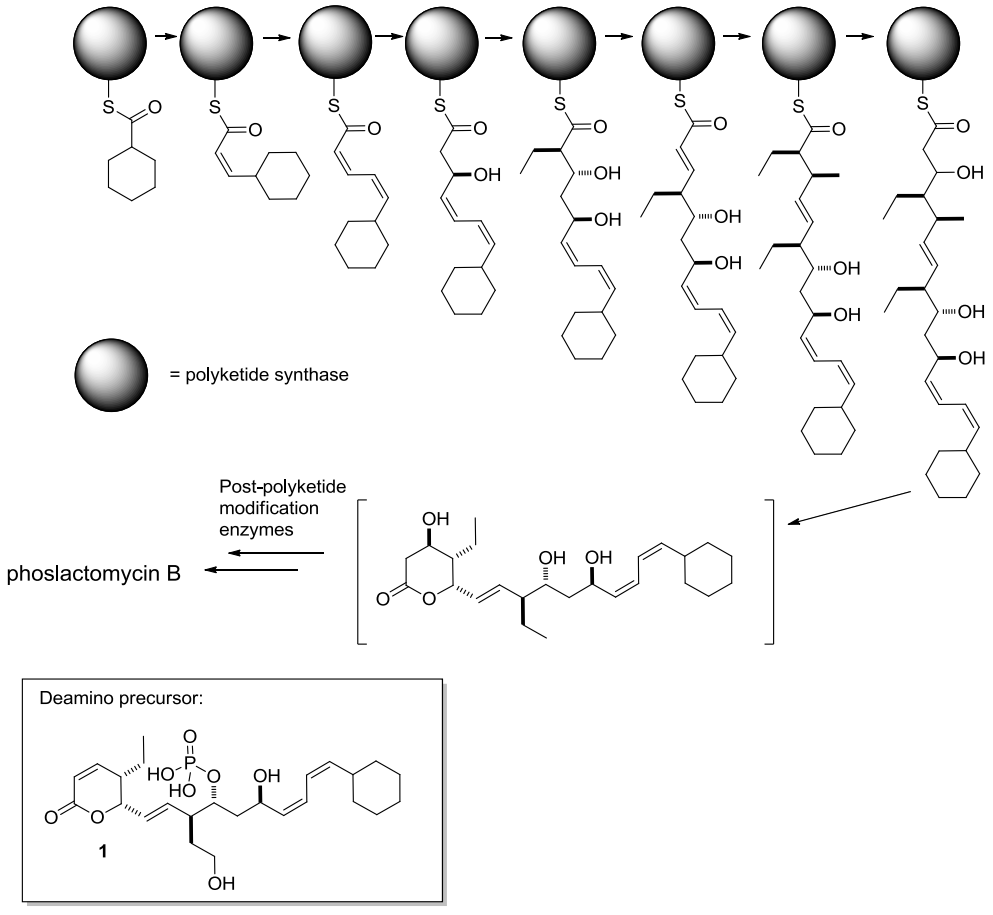
Our primary interest was in the synthesis of leustroducsin B,[2a,b] which possesses a 6-methyloctanoate substituent at C18. The selection of this target was due in part to its exhibited biological activity. Isolated alongside leustroducsins A and C, leustroducsin B was originally purified as a potent colony stimulating factor (CSF) inducer.[2a] In humans, the CSF induction has specifically been associated with cytokine production via NF-κB activation at the transcriptional and posttranscriptional levels.[6] A wide variety of other biological activities have been attributed to this compound: *in vitro*, leustroducsin B induces granulocyte-CSF and granulocyte-macrophage-CSF production by KM-102 cells;[2a,7a,7b] *in vivo*, the molecule has been shown to augment host resistance in lethal *E. coli* infections[7a] and to induce thrombocytosis when administered to mice.[8] Coupled with the unique structure of leustroducsin B, these important biological properties warrant increased interest in its total synthesis.

Adding to the attraction to leustroducsin B are several challenges associated with the isolation of large quantities of the molecule from natural sources. Although *Streptomyces* strains are easily cultured in the laboratory, the individual leustroducsin and phoslactomycin members are generally isolated as complex mixtures from these strains and require strenuous purification to obtain the pure compounds; consequently, only 9.83 mg of leustroducsin B was obtained from a 60-L culture broth in the initial isolation paper.[2a] Since no microbial strain has yet been found to produce leustroducsin B selectively, chemical synthesis appears

to be the most viable route for the production of larger quantities for additional biological testing.

Detailed biosynthetic proposals for the leustroducsins are nonexistent, yet analogies can be drawn from phoslactomycin B. In 2003 Reynolds and Palaniappan reported that the phoslactomycin polyketide synthase[9a] produced several unusual linear unsaturated polyketide chains containing both (*E*)- and (*Z*)- alkenes from a cyclohexanecarboxylic acid primer (Figure 3-2).[9b]

Figure 3-2. Polyketide Synthase-Based Biosynthetic Proposal for Phoslactomycin B



The authors reported a plausible role for several of the polypeptides associated with the biosynthesis of phoslactomycin B, which were proposed to effect largely linear homologations throughout the course of the biosynthetic pathway. Additionally, a deamino-precursor has been identified which has been shown to produce phoslactomycin B when fed to *Streptomyces* cultures (**1**, Figure 3-2).[9b]

3.2 Prior Syntheses of Leustroducsin B

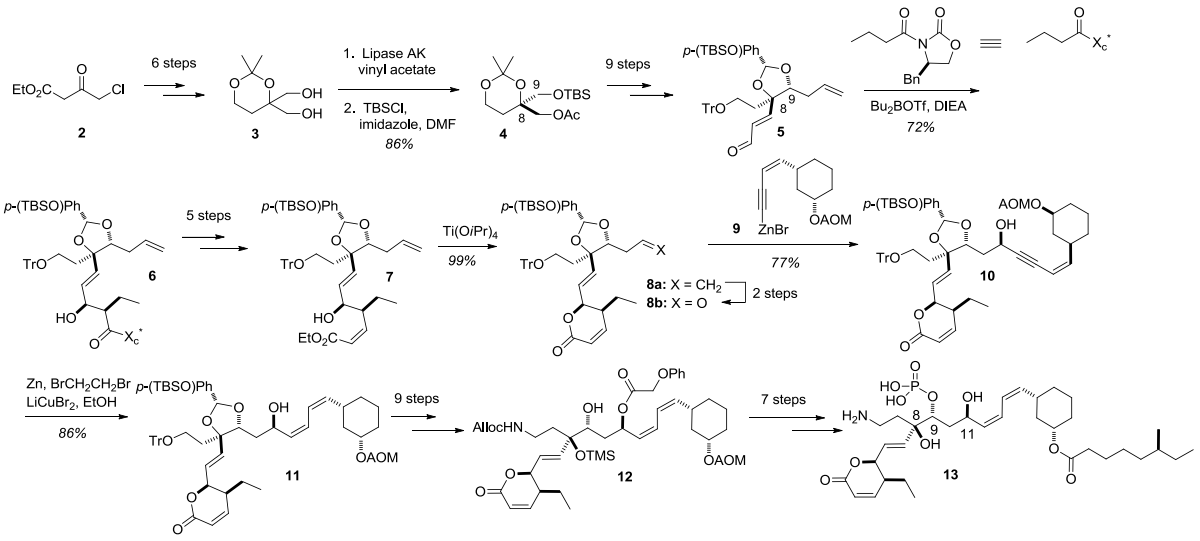
3.2.1 Overview of Fukuyama's Synthesis

A handful of total and partial syntheses have been completed for both phoslactomycin B[10] and leustroducsin B.[11-14] Total and partial syntheses of leustroducsin B will be summarized here; distinguishing features of phoslactomycin B syntheses will be discussed throughout the results section as they apply to specific steps related to our synthetic route. A retrosynthetic analysis that unites the existing synthetic routes to these molecules is the initial establishment of the highly functionalized core, specifically the stereochemistry of the quaternary center and the adjacent secondary alcohol (C8 and C9, Figure 3-1). Prior syntheses have often employed asymmetric dihydroxylation strategies for this purpose; they subsequently diverge in terms of the installation of the dihydropyrone portion and in the incorporation of the amine and diene functionalities.

Leustroducsin B has yielded two total syntheses and one formal synthesis since its intial isolation in 1993. Fukuyama reported the first total synthesis in 2003,[11] a significant contribution that nevertheless required 47 linear steps (Scheme 3-1). The synthesis commenced with the six-step preparation of meso-diol **3**, which underwent desymmetrization/acetylation with lipase AK[15] and subsequent silylation to give

orthogonally protected tetraol **4.** After a nine-step sequence of transformations including a directed allylation that set the stereochemistry at C9, the dihydropyrone was installed using an Evans aldol approach. Conversion of the Evans aldol product **6** to the corresponding aldehyde and a *cis*-selective Ando phosphonate Wittig reaction[16] provided (*Z*)-enoate **7**, which underwent condensation to the lactone by treatment with titanium tetraisopropoxide. Oxidative cleavage of the allyl group provided aldehyde **8b**, a viable substrate for chelation-controlled addition of alkynylzinc **9** that gave enyne **10**. Reduction of the enyne to the diene was achieved through a zinc-based reduction method developed by Brandsma[17] after several other reduction methods resulted in overreduction products. A series of protecting group manipulations, including amine installation and protection, provided intermediate **12** after nine steps. The remaining seven steps in the route involved DCC coupling to install the correct side chain on the cyclohexyl ring and phosphorylation using an activated phosphoramidite.[18] Deprotection of the Alloc groups in the final step gave leustroducsin B.

Scheme 3-1. Summary of Fukuyama's Synthesis



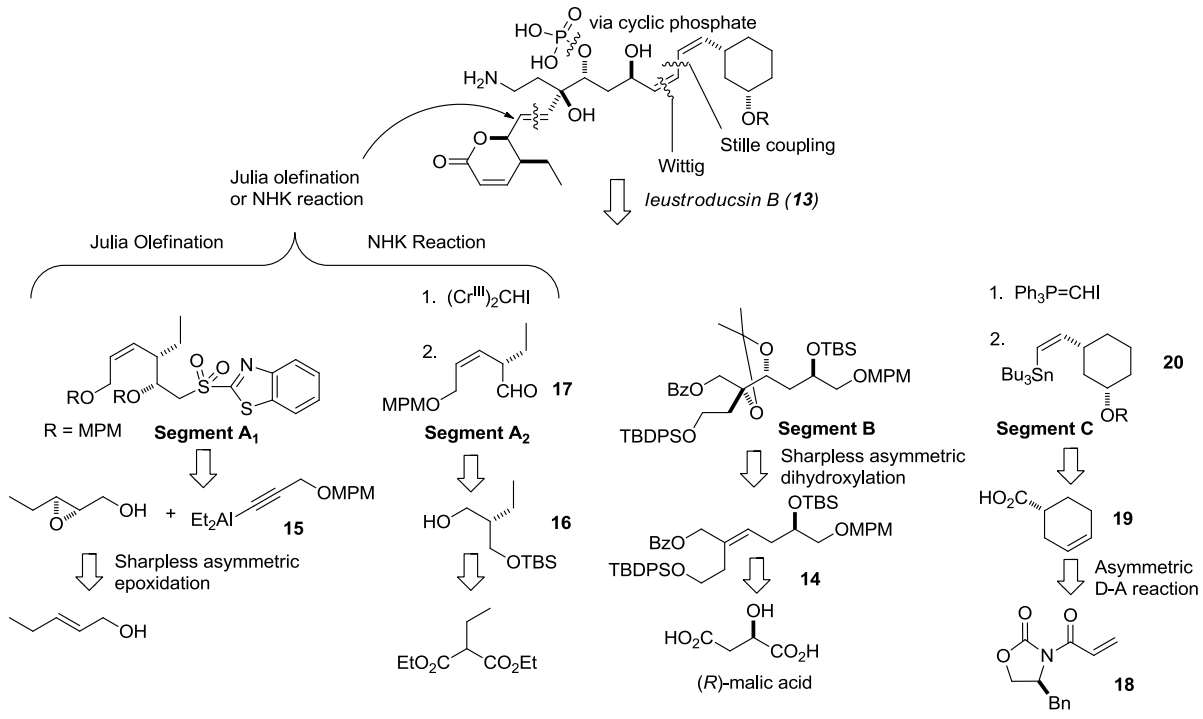
Although a lengthy endeavor, the Fukuyama route offered significant insight into the stability of advanced intermediates and an effective protecting group strategy that permitted mild

deprotection conditions. The Fukuyama route also revealed the primary challenge in the synthesis of leustroducsin B: selective functionalization of intermediates containing several hydroxyl groups and other nucleophilic functionalities.

3.2.2 Overview of Imanishi's Total Synthesis

The second total synthesis of leustroducsin B was reported by Imanishi and coworkers in 2006.[12a,b] Imanishi's route involved 32 steps in the longest linear sequence and featured an exploration of additional strategies for the installation of the pyrone and the (*Z*,*Z*)-diene.

Figure 3-3. Summary of Imanishi's Synthesis



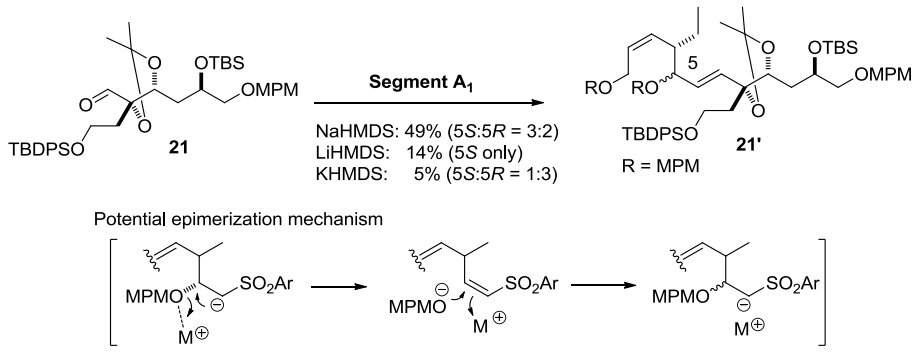
Shown in Figure 3-3 is Imanishi's retrosynthetic analysis, which deconstructs the molecule into the three main components: congested core (Segment B), cyclohexyl side

chain (Segment C), and dihydropyrone (installed either through homologation of Segment B with Segment A_1 or A_2).

The synthesis of segment B utilized the chiral pool in starting from (*R*)-malic acid, which allowed the authors to set the remaining two stereocenters of the core through a Sharpless asymmetric dihydroxylation[19] of intermediate **14**. After orthogonal protection of all six hydroxyl groups, selective deprotection and oxidation steps converted this intermediate into several viable coupling partners prior to the introduction of the additional segments.

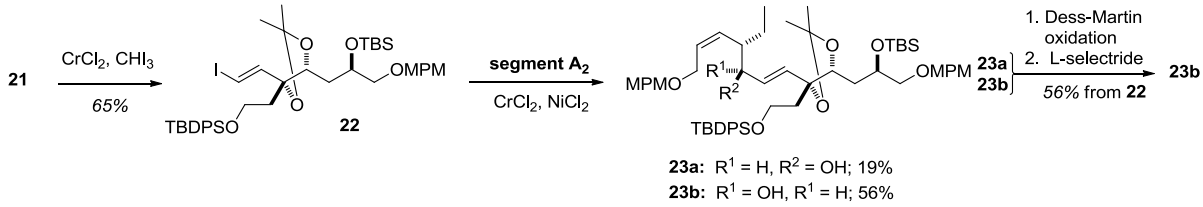
The dihydropyrone installation was initially envisioned to occur through a Julia olefination[20] process using segment A_1. The necessary Julia reagent was prepared over six steps from *trans*-2-penten-1-ol, wherein the two stereocenters of the pyrone were set through a Sharpless asymmetric epoxidation[19] and regioselective epoxide opening with aluminum acetylide **15**. Although the preparation of segment A_1 proceeded uneventfully, its use in the proposed Julia coupling resulted in low yields of the desired olefin and an epimerization of the C5 stereocenter, which was proposed to occur through the rapid β-elimination/addition equilibrium shown in Figure 3-4.[21] These poor results caused Imanishi to explore additional strategies for the introduction of the pyrone, specifically a Nozaki-Hiyama-Kishi (NHK) reaction.[22]

Figure 3-4. Julia Coupling with Segment A_1



To investigate the feasibility of the proposed NHK reaction, aldehyde **21** was converted into *E*-vinyl iodide **22** through a Takai olefination.[23] Unfortunately, the NHK reaction with segment A_2 resulted in a mixture of diastereomers in favor of the undesired stereoisomer. After a stereochemical correction consisting of Dess-Martin oxidation[24] and diastereoselective reduction with *L*-selectride,[25] the desired diastereomer was obtained in greater than 20:1 dr (Scheme 3-2).

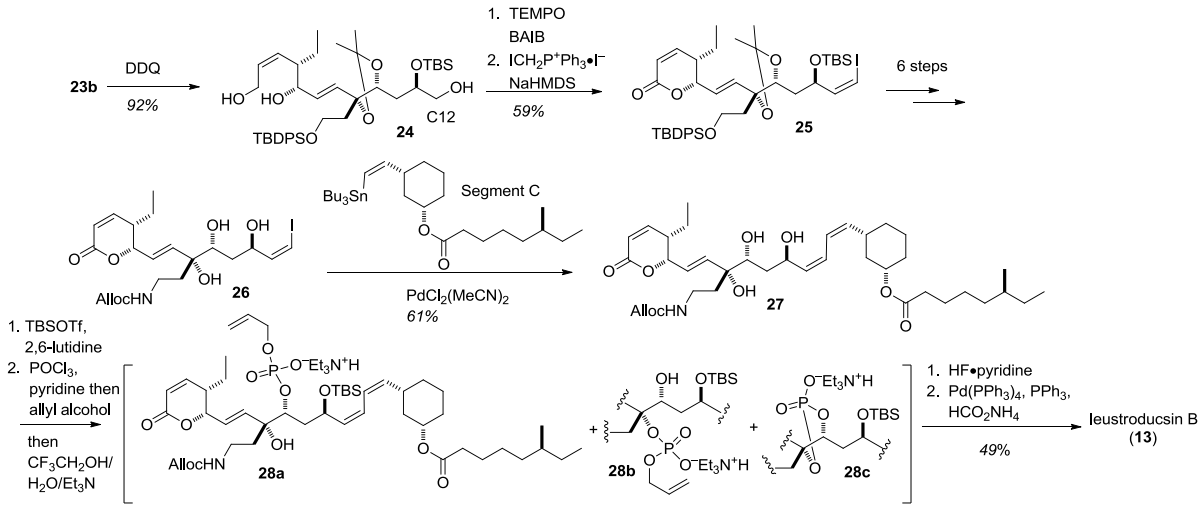
Scheme 3-2. NHK Coupling Strategy



The authors determined that the NHK coupling strategy was the most attractive for the completion of the synthesis of leustroducsin B, and the synthesis proceeded according the route depicted in Scheme 3-3. Removal of the MPM (*p*-methoxybenzyl) protecting groups and TEMPO oxidation[26] of the resulting triol afforded the lactone and provided the aldehyde at C12. The latter underwent a Stork-Zhao olefination[27] to afford the *Z*-vinyl iodide. An

additional six steps converted vinyl iodide **25** to triol **26**, where amine installation was achieved through an azide displacement of the corresponding primary mesylate and Staudinger reduction[28]/Alloc protection. Stille coupling of this triol with Segment C (prepared in nine steps starting with the asymmetric Diels-Alder reaction of **18**) afforded the *Z,Z*-diene **27**. Selective silylation of the less hindered secondary alcohol with TBSOTf and treatment of the resulting diol with phosphorus oxychloride in pyridine afforded the mixture of phosphates **28a-c**. The combined phosphates were subjected to the final deprotection steps: first, removal of the silyl group with HF•pyridine; and second, deallylation with $Pd(PPh_3)_4$, PPh_3, and ammonium formate. After purification by preparative-scale thin-layer chromatography (PTLC), leustroducsin B was isolated as a single stereoisomer. Although the Imanishi synthesis was 15 linear steps shorter than the Fukuyama route, its reliance on several stereochemical correction steps and the poor selectivities observed in the key coupling strategies explored for the dihydropyrone introduction and in the phosphorylation left ample opportunities for improvement.

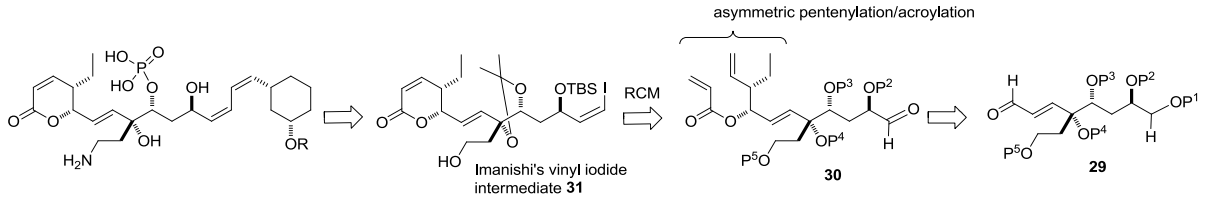
Scheme 3-3. Completion of Leustroducsin B Synthesis



3.2.3 Overview of Cossy's Formal Synthesis

The most recent synthesis of leustroducsin B was a 2008 formal synthesis by Cossy.[13] Cossy's strategy sought to overcome some of the difficulties Imanishi and Fukuyama encountered in the dihydropyrone installation. Fukuyama's Evans aldol strategy offered excellent selectivity in the formation of the C4 and C5 stereocenters, yet several steps were necessary to install the requisite dihydropyrone from the enal. Imanishi's NHK coupling and Julia olefination strategies were more efficient from a total step count, yet the poor diastereoselectivities observed rendered them far less useful synthetically. Cossy's formal synthesis provided a novel approach to the formation of the lactone through an asymmetric pentenylation[29]/acroylation/ring-closing metathesis (RCM) strategy. Retrosynthetically, this required access to enal **29** (Figure 3-5).

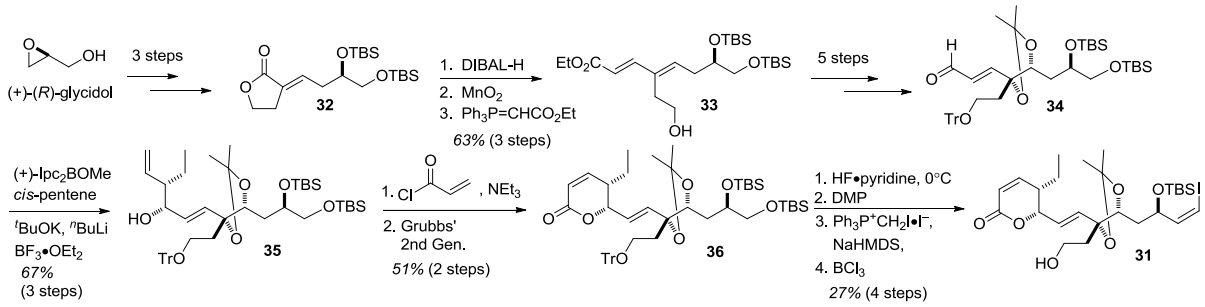
Figure 3-5. Cossy's Retrosynthetic Analysis



Cossy's synthesis began with commercially available (+)-(*R*)-glycidol, which provided the correct stereochemistry for C11. Regioselective epoxide allylation with subsequent protection of the resulting alcohol and cross metathesis with α-methylidine-γ-butyrolactone gave intermediate **32**. Reduction with DIBAL to the diol was followed by allylic oxidation and a Wittig reaction to give dienoate **33** in 63% yield over three steps. Selective asymmetric dihydroxylation of the dienoate using Sharpless conditions[19] was used to set the stereochemistry of the alcohols at C8 and C9. An additional four steps converted

the resulting polyol to enal **34**. An asymmetric pentenylation strategy[30] was successfully employed to set the stereocenters of the lactone with greater than 95:5 diastereoselectivity.

Scheme 3-4. Summary of Cossy's Formal Synthesis



Acroylation of the resulting allylic alcohol and ring-closing metathesis with Grubbs' second generation catalyst afforded the desired dihydropyrone (**36**) in 51% yield over two steps. Finally, a four-step sequence consisting of selective deprotection of the primary TBS ether, oxidation to the aldehyde, Stork-Zhao olefination, and trityl ether deprotection allowed the authors to intercept Imanishi's intermediate **31** in 18 total steps from their glycidol starting material, an compound that Imanishi obtained in 23 linear steps. No additional partial or total syntheses of leustroducsin B have been completed since Cossy's 2008 communication, and we approached our synthetic plan with a desire to streamline the installation of the sterically congested core. Described in the remainer of this chapter is our development of an unprecedented three-component coupling that we used toward that goal. We have also explored additional strategies for the installation of the pyrone and the cyclohexyl side chain, and the results of those studies as well as our current synthetic route to an advanced intermediate are presented.

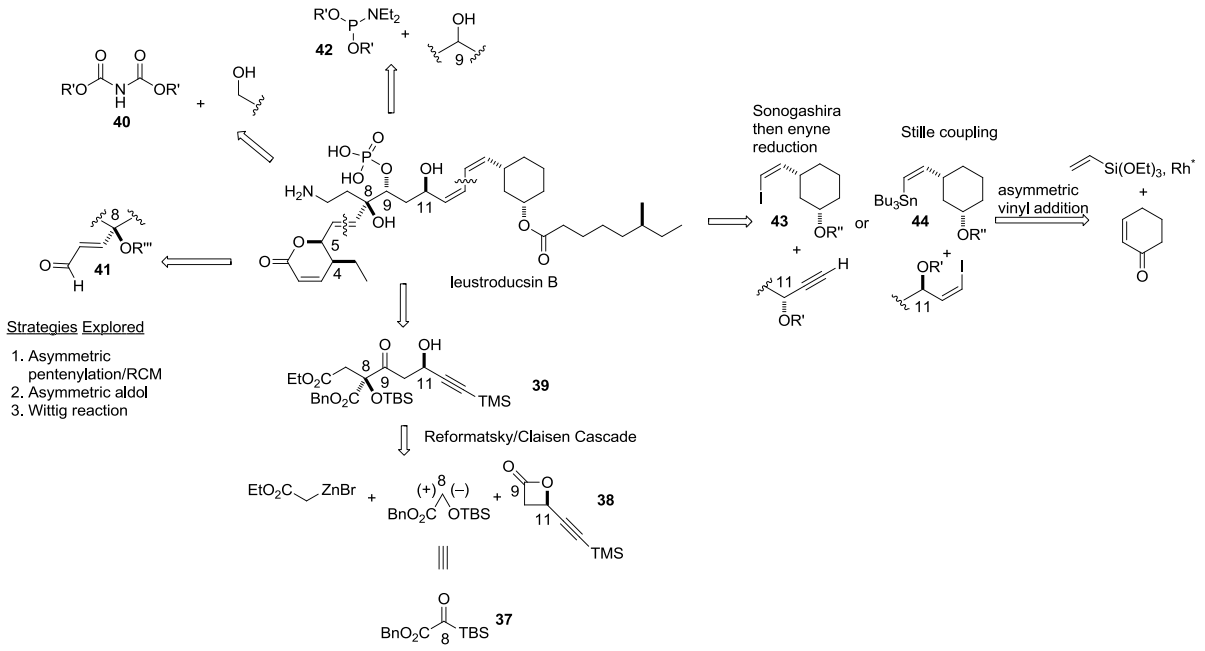
3.3 Results and Discussion

3.3.1 Preliminary Retrosynthetic Analysis

Our retrosynthetic analysis of leustroducsin B relied on the incorporation of a variant of our three-component coupling of silyl glyoxylates, Reformatsky reagents, and ketones that was discussed in chapter two.[31] Although our double Reformatsky cascade allowed for the synthesis of highly functionalized γ-butyrolactone products derived from alkyl-aryl ketone substrates, we were interested in expanding the scope of this chemistry to electrophiles that were more amenable to the synthesis of leustroducsin B and other types of natural products; specifically, we were interested in determining the feasibility of terminating the Reformatsky cascade with a chiral β-lactone (**38**),[32,33] which would accomplish the incorporation of both α-carbonyl and γ-hydroxyl functionalities relative to the developing quaternary stereocenter. The desired three-component coupling depicted in Figure 3-7 (*vide infra*) could then allow rapid access to the core of leustroducsin B through intermediate **39** while providing sufficient flexibility in the installation of the remaining components of the carbon skeleton.

Several routes to the dihydropyrone were envisioned from enal **41**, including the aforementioned pentenylation/RCM strategy, reaction with a functionalized Wittig reagent, and an asymmetric aldol reaction. Synthesis of the (*Z*,*Z*)-diene could be accomplished through a Sonogashira reaction of the deprotected alkyne followed by enyne reduction or a Stille coupling with the corresponding vinyl iodide (**43** or **44**). The necessary coupling partners could be prepared over several steps starting from an asymmetric vinyl addition to cyclohexen-2-one.

Figure 3-6. Retrosynthetic Analysis Based on Proposed Three-Component Coupling



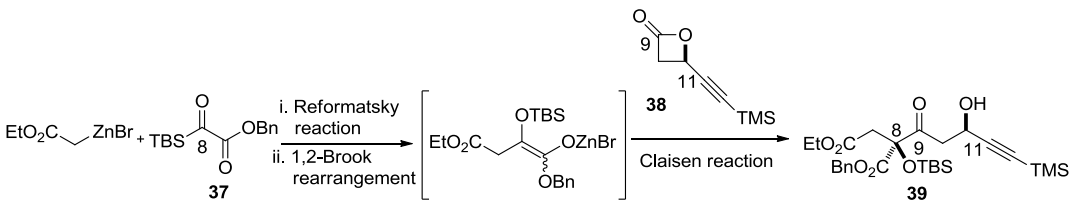
Conversion of the ethyl ester of the Reformatsky reagent to the aminoethyl side chain was envisioned to occur through a Mitsunobu reaction of the primary alcohol with a *bis*-carbamate[34] (**40**). Phosphorylation of the C9 hydroxyl would be accomplished by oxidation of the appropriately protected phosphite precursor, itself a product of the reaction of the free hydroxyl with a phosphoramidite[18] (**42**).

3.3.2 Proposed Reformatsky/Claisen Cascade and Preparation of Coupling Partners

In Chapter Two we discussed the ability of Reformatsky reagents to undergo addition reactions with silyl glyoxylates that expose, after [1,2]-Brook rearrangement, glycolate enolates poised to undergo a second Reformatsky reaction with aldehyde and ketone electrophiles. In order to more easily incorporate this methodology into natural product synthesis, we recognized that we would need to expand the range of viable electrophiles past the alkyl-aryl ketone subset that provided the impressive diastereoselectivities in our double

Reformatsky cascade. The proposed reaction depicted in Figure 3-7 involves termination of the Reformatsky-initiated cascade with a β-lactone electrophile, which we envisioned undergoing a Claisen reaction to give β-hydroxyketone products (**39**).[35] Preliminary efforts toward the synthesis of leustroducsin B focused on the preparation of the requisite coupling partners for this three-component coupling and an investigation of the potential chemo- and diastereoselectivity issues inherent in this approach.

Figure 3-7. Proposed Three-Component Coupling with β-Lactones

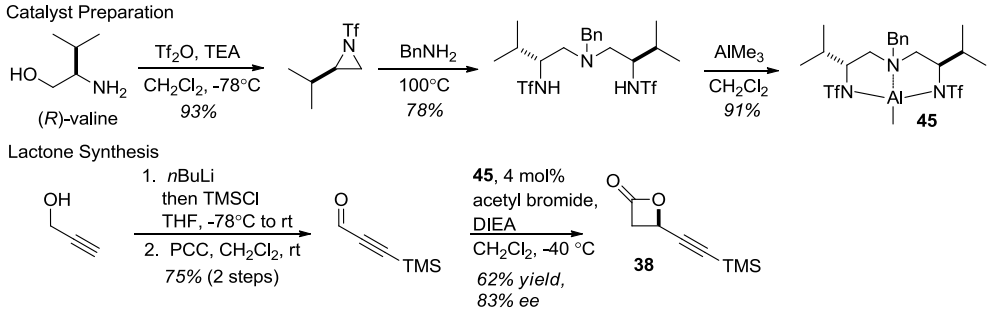


Nelson and coworkers recently reported a general procedure[32] for the asymmetric synthesis of β-lactones that used an aluminum bis(triflamide) catalyst to impart stereoselection in the formal [2+2] cycloaddition of ketenes with a variety of aldehydes. With their high reported selectivities (ee's ≥ 89%) and scalability (multigram scale) for this cycloaddition, we felt this was an appropriate means for the synthesis of a large quantity of enantioenriched lactone for our three-coupling coupling reaction.

Preparation of the bistriflamide catalyst **45** for the ketene cycloaddition proceeded uneventfully from (*R*)-valine according to the Organic Syntheses procedure described by Nelson,[32b] and 3-trimethylsilyl-propynal was prepared in two steps from the *C*-silylation and oxidation of propargyl alcohol[36] in an overall 75% yield. The desired β-lactone **38** could be prepared on multigram scale in an average 62% yield and 83% ee[37] using Nelson's

cycloaddition conditions (Scheme 3-5).[32a] Silyl glyoxylate **37** was prepared as discussed in chapter two.

Scheme 3-5. Synthesis of β-lactone Coupling Partner



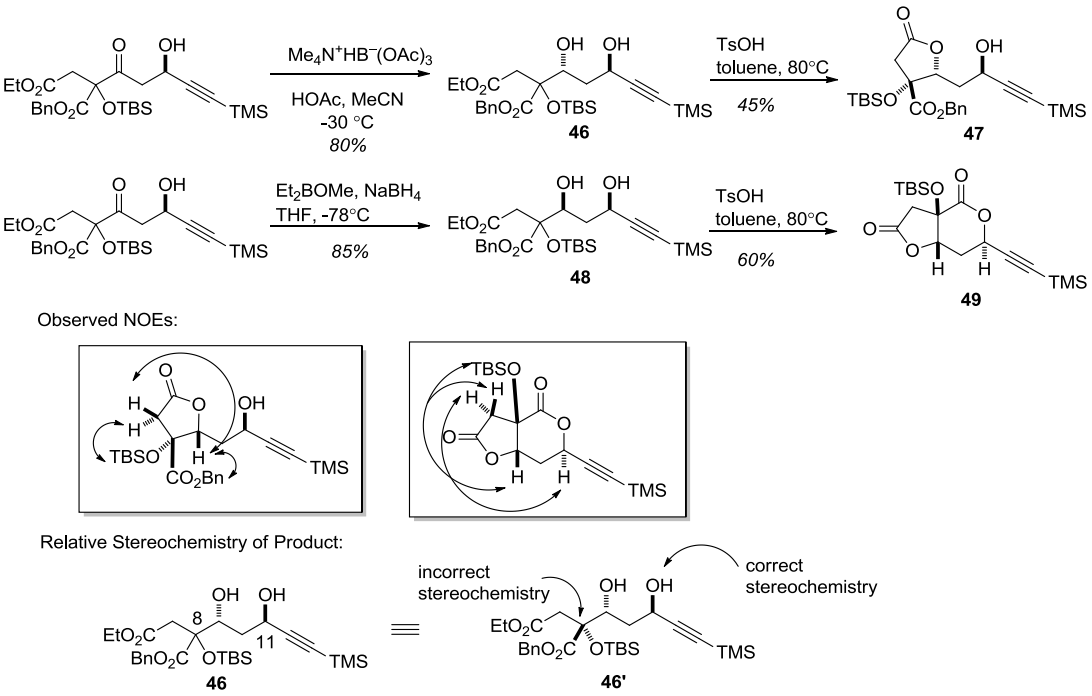
3.3.3 Three-Component Coupling Reactions and Determination of Diastereomer Identity

Initial trials of the three-component coupling of the silyl glyoxylate, β-lactone, and Reformatsky reagent proceeded to give the desired β-hydroxyketone product **39**.[37] Our preliminary conditions consisted of sequential addition of the silyl glyoxylate and β-lactone to a solution of the Reformatsky reagent in accordance with our work on the double Reformatsky cascade, where such a stepwise addition method afforded improved yields of the desired products. Prior to advancing toward additional optimization studies, we elected to determine the relative stereochemistry at C8 and C11. Those efforts are depicted in Figure 3-8.

The β-hydroxyketone product underwent diastereoselective *anti*-reduction using the Evans reduction protocol[38] as well as *syn*-reduction using Prasad conditions[39] to give diols **46** and **48**, respectively. Lactonization was achieved via treatment with TsOH in toluene at

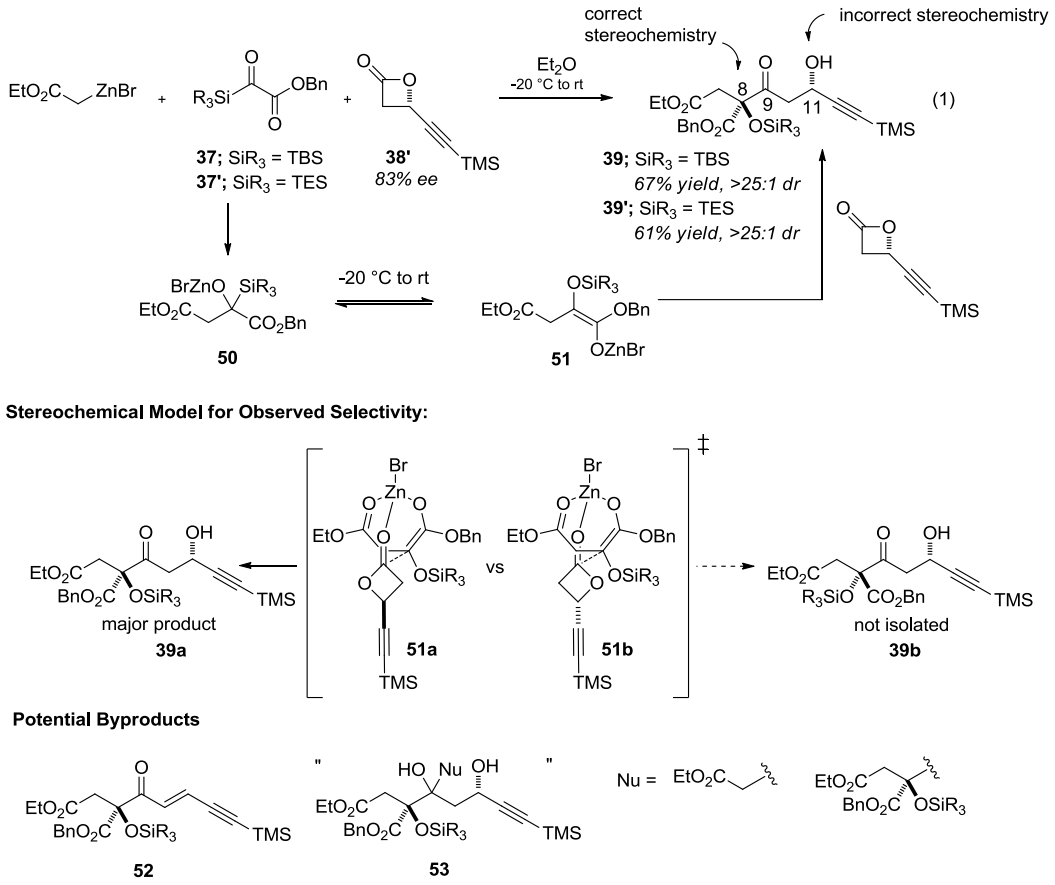
elevated temperatures, which resulted in the formation of monolactone **47** in the case of the *anti*-diol and *bis*-lactone **49** in the case of the *syn*-diol.

Figure 3-8. Stereochemical Determination



Observed NOE interactions in the NOESY spectra of these compounds supported the stereochemical assignment shown in Figure 3-8 for the quaternary center (**46′**), which unfortunately was of the incorrect stereochemistry for C8 of leustroducsin B. Based on this assignment, we could also rationalize the formation of the two different products obtained under the lactonization conditions: formation of a *bis*-lactone from the *anti*-diol would require cyclization of product **46′** to give a *trans*-substituted [5,6]-bicycle, which should have a higher activation energy than the formation of the analogous *cis*-fused [5,6]-bicycle **49**,[40] which results from acid-catalyzed lactonization of the *syn*-diol.

Figure 3-9. Three-Component Coupling



Although the relative stereochemistry of the two stereocenters is incorrect for leustroducsin B, we recognized that this should be easily corrected by the use of the opposite lactone enantiomer (**38′**) in the initial coupling. This would provide the correct stereochemistry for the tertiary alcohol, and the stereochemistry of the C11-secondary hydroxyl group could be corrected at a later stage through a Mitsunobu reaction.[34] After preparation of the (*S*)-β-lactone, we proceeded to optimization of the three-component coupling (Table 3-1).

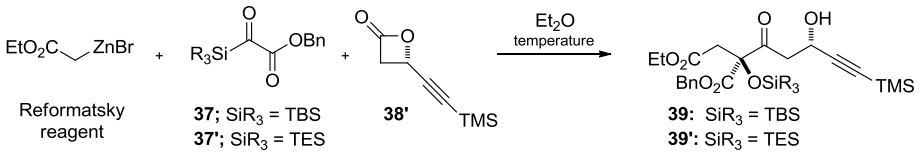
We found that addition of a solution of silyl glyoxylate and lactone to a cooled solution of the Reformatsky reagent provided identical results to the stepwise addition

previously employed with ketones. The chemoselectivity issues that necessitated the latter method appeared to be significantly attenuated here, as we did not observe reaction of the Reformatsky reagent with the β-lactone, even up to room temperature; the rapid reaction we observed between the lactone and the fully substituted glycolate enolate in the presence of an excess of the less hindered Reformatsky reagent was certainly a fortuitous result. Additionally, we were pleased to observe a greater than 25:1 diastereomeric ratio, an unexpected selectivity that we cannot yet explain. Mechanistically, the reaction likely proceeds through the alkoxysilane **50**, which Brook rearranges to reveal glycolate enolate **51** prior to undergoing Claisen reaction with the β-lactone. Nelson has shown that *tert*-butyl acetate nucleophiles will undergo a Claisen reaction with β-lactones,[33,35] yet to the best of our knowledge this is the first example of a glycolate enolate undergoing a similar transformation. A plausible stereochemical model for the observed selectivity in this cascade is provided in Figure 3-9. Chelation of the (*E*)-zinc enolate with the pendant ester carbonyl provides a cyclic transition state, where additional coordination of the β-lactone carbonyl to zinc allows the lactone stereocenter to dictate the facial selectivity for the glycolate enolate. Although both **51a** and **51b** minimize steric interactions with the TMS-protected alkyne functionality, only **51a** leads to the relative stereochemistry of the isolated products (**39a**). In the absence of additional experimentation, we cannot at this time expand on the apparent preference for transition state **51a**.

Table 3-1 shows the optimization studies on the three-component coupling. The following general conclusions can be made: first, the benzyl *tert*-butyldimethylsilyl glyoxylate largely afforded higher yields of the desired product than did the benzyl triethylsilyl glyoxylate. This is likely due to the lability of the triethylsilyl group, which is

discussed in greater detail throughout this chapter; second, optimal conditions for the TBS derivative involved warming to room temperature, while greater yields were realized with the TES derivative when reactions were maintained at 0 °C (entries 4-6, 10-11).

Table 3-1. Optimization of Reformatsky/Claisen Cascade[a,b]



Entry	SiR_3	activation method	equiv Reformatsky reagent	equiv lactone	temp. (°C)	yield (%)
1	TBS	5 mol % TMSCl	1.5	2.0	-20 to 0	43
2	TBS	5 mol % TMSCl	1.5	3.0	-20 to 0	51
3	TBS	5 mol % TMSCl + 2.0 equiv LiCl	1.5	3.0	-20 to rt	54
4	TBS	5 mol % TMSCl	1.5	2.5	-20 to rt	68
5	TBS	5 mol % TMSCl	1.5	1.5	-20 to rt	63
6	TBS	5 mol % TMSCl	2.3	1.5	-20 to rt	56
7	TES	5 mol % TMSCl	1.5	1.4	-30 to rt	50
8	TES	5 mol % TMSCl	1.8	1.6	-30 to rt	66
9	TES	5 mol % TMSCl	2.3	1.6	-30 to rt	62
10	TES	25 mol % Br_2	2.3	1.6	-30 to rt	48
11	TES	25 mol % Br_2	2.3	1.6	-30 to 0	61
12	TBS	25 mol % Br_2	2.3	1.6	-30 to 0	57
13	TBS	25 mol % Br_2	1.6	1.6	-30 to 0	56
14	TBS	25 mol % Br_2	1.1	1.6	-30 to 0	23

[a] All reactions: yields determined by ^{1}H NMR analysis using an internal standard.[b] Diastereomeric ratios were all >25:1. See section 3.5 for additional information.

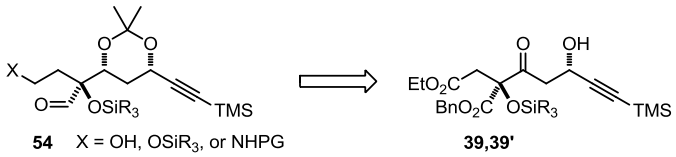
This can be attributed to increased generation of byproducts in the reaction of the latter, which we believe arise through nucleophilic attack on the product ketone (**53**, Figure 3-9). With the bulkier TBS-protected tertiary alcohol, both the desired Claisen reaction and undesired reactions with the resulting ketone should be disfavored, which might explain the higher reaction temperatures required as well as the suppression of byproduct formation.

In most of the initial screens, the use of TMSCl as an activating agent for zinc dust was sufficient,[41] but its use in the generation of larger quantities of the Reformatsky reagent gave inconsistent results. The use of bromine as an activator[42] afforded reproducible concentrations for the Reformatsky solution and yields of the desired product (entries 10-14) upon scaleup. Although the yields were slightly lower with the use of bromine (the presence of larger quantities of zinc bromide may activate the ketone of the product for nucleophilic attack, leading to production of **53**), they were sufficient for the purpose of running the reaction on multigram scale (up to 6.0 g of silyl glyoxylate). We also found that significant quantities of enyne **52** were produced in large-scale reactions, which is likely the result of elimination of the zinc alkoxide, a common degradation pathway in Reformatsky reactions.[43] Cooling the reaction to 0 °C prior to aqueous workup appeared to suppress the production of this enyne.

3.3.4 Retrosynthetic Analysis Toward the Leustroducsin B Core

Having optimized our desired three-component coupling reaction, we next focused on conversion of β–hydroxyketone **39** or **39′** into aldehyde **54**, which would allow us to investigate several options for the introduction of the dihydropyrone moiety.

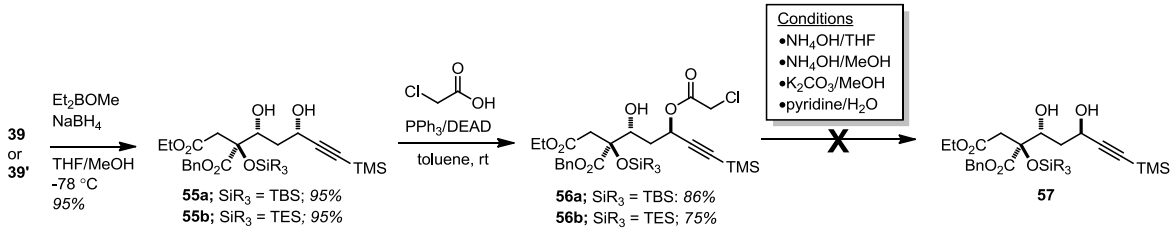
Figure 3-10. Plausible Core Target



Prasad reduction[39] of the ketone proceeded uneventfully to give the *syn*-diol (**55a,b**) in greater than 90% yield. We were pleased to discover that a Mitsunobu reaction of this diol

with chloroacetic acid[44] gave excellent selectivity at the propargylic site with both **55a** and **55b**, which allowed us to perform the necessary stereochemical correction of C11 at an early stage. Unfortunately, attempts to cleave chloroacetate **56a** or **56b** led to decomposition or low yields of the desired diol amid significant byproduct formation; potential unproductive pathways include a retroaldol reaction induced by desilylation of the tertiary silyl ether, elimination of the chloroacetate to the enyne, and lactonization with one or both of the pendant esters. We ultimately decided that we would attempt to exploit this selectivity at a later stage in the synthesis, where we would use the Mitsunobu reaction to orthogonally protect the hydroxyl groups at C9 and C11 prior to phosphorylation.

Scheme 3-6. Early Attempts at Stereochemical Correction



After protection of the diol as the acetonide (**58a**) in an average 82% yield (over two steps from **39**), we performed a short screen of reducing agents for the reduction of the TBS-protected diester. Lithium aluminum hydride resulted in complete reduction and desilylation to triol **60**, a common result obtained in the reduction of α-silyloxy esters with this reagent (Table 3-2, entry 1).[45] DIBAL-H gave complete reduction of the ethyl ester to the monoalcohol (**59a**), while the benzyl ester proved far more difficult to reduce, likely due to its proximity to the fully substituted stereocenter (entries 2 and 3).

Scheme 3-7. Conversion to Acetonide and Reduction of Diester

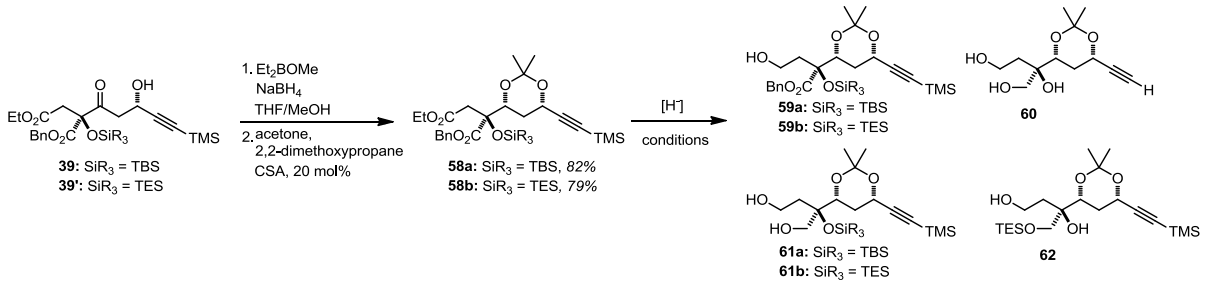


Table 3-2. Screen of Hydride Sources for Reduction of **58a** and **58b**

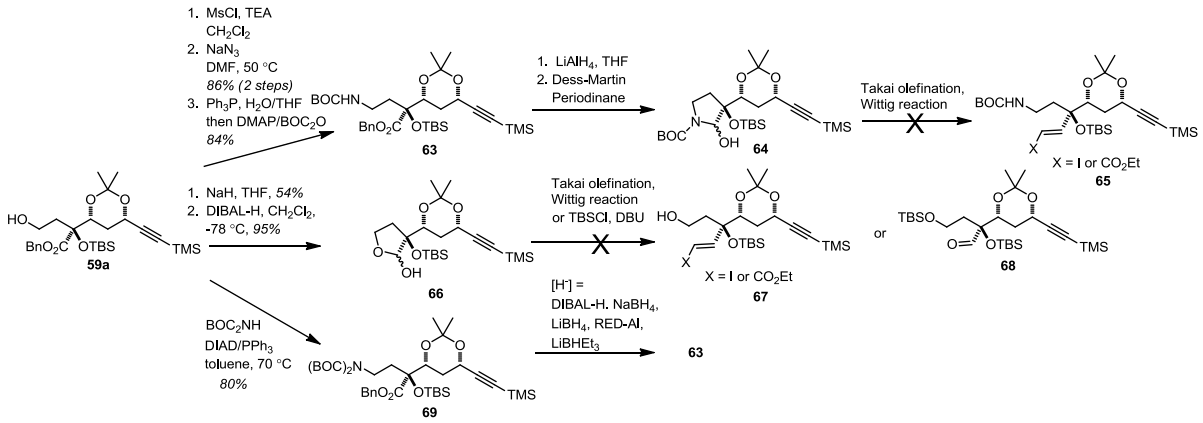
entry	acetonide	reducing agent	solvent	temp. (°C)	result
1	**58a**	$LiAlH_4$ (4.0 equiv)	Et_2O	35	**60**, 73% yield
2	**58a**	DIBAL-H (5.0 equiv)	THF	-78 to rt	**59a**, 89% yield
3	**58a**	DIBAL-H (5.0 equiv)	CH_2Cl_2	-10 to rt	**59a**
4	**58a**	$LiBHEt_3$ (7.0 equiv)	THF	rt	mess
5	**58a**	$LiBHEt_3$ (7.0 equiv)	THF	-10	**59a**
6	**58a**	$LiBHEt_3$ (7.0 equiv)	9:1 Et_2O:THF	-10	1:1 **59a:61a**
7	**58a**	$LiBHEt_3$ (7.0 equiv)	15:1 Et_2O: THF	-10 to 0	**61a**, 58% yield
8	**58a**	$LiBHEt_3$ (7.0 equiv)	12:1 CH_2Cl_2: THF	-50 to rt	**61a**, 75% yield
9	**58b**	DIBAL-H (5.0 equiv)	CH_2Cl_2	-10 to rt	**59b**
10	**58b**	$LiBHEt_3$ (7.0 equiv)	THF	-30 to 0	**59b**
11	**58b**	$LiBHEt_3$ (7.0 equiv)	10:1 toluene:THF	-30 to rt	1:1 **61b:62**
12	**58b**	$LiBHEt_3$ (7.0 equiv)	10:1 Et_2O:THF	-50 to rt	1:1 **61b:62**
13	**58b**	$LiBHEt_3$ (5.0 equiv)	10:1 Et_2O:THF	-30 to rt	1:1 **61b:62**
14	**58b**	$LiBHEt_3$ (7.0 equiv)	10:1 CH_2Cl_2:THF	-30 to 0	**61b,** 73% (40 mg scale)
15	**58b**	$LiBHEt_3$ (7.0 equiv)	10:1 CH_2Cl_2:THF	-30 to -10	1:1 **61b**:**62**
16	**58b**	$LiBHEt_3$ (7.0 equiv)	10:1 CH_2Cl_2:THF	-30 to -20	**61b**, 60%; **59b**, 12%(1g scale)
17	**58b**	$LiBHEt_3$ (7.0 equiv)	12:1 CH_2Cl_2: THF	-20	**61b**, 52% yield

Lithium triethylborohydride (Superhydride®) proved to be reactive enough that reduction of the benzyl ester could also be achieved, but the product ratio was highly dependent on solvent[46]: the reduction of **58a** with Superhydride® in THF gave primarily the monoalcohol **59a** (entry 5), while running the reduction in 9:1 Et_2O:THF gave mixtures of the monoalcohol and the desired diol **61a** (entries 6 and 7), and 12:1 CH_2Cl_2: THF from -50 °C to rt gave the diol as the major product (entry 8).

3.3.5 Preliminary Attempts at Amine Installation

With effective reduction methods for obtaining the monoalcohol and diol products, we investigated several routes to introduce the amine functionality and convert the benzyl ester to the aldehyde. Conversion of the monoalcohol **59a** to the mesylate and displacement with sodium azide afforded the primary azide as a latent amine source in 86% yield over two steps. Staudinger reduction of the azide[28] with *in situ* BOC protection gave carbamate **63**. Reduction of the benzyl ester could be achieved with lithium aluminum hydride at this stage, and oxidation with Dess-Martin periodinane[24] gave the aldehyde, which existed exclusively as the hemiaminal **64**. Lactol **66** could be accessed by treatment of **59a** with sodium hydride, followed by DIBAL-H reduction of the resulting lactone. We attempted to use the lactol and hemiaminal in subsequent steps, but we found no desired product in Wittig reactions or under Takai olefination conditions, and attempts to silylate the primary alcohol also failed (**64** → **65**; **66** → **67** or **68**). We were able to perform a Mitsunobu reaction on the primary alcohol with BOC_2NH at elevated temperatures. Unfortunately, reductive cleavage of the BOC group from the *bis*-carbamate occurred faster than reduction of the benzyl ester and resulted in the production of monoprotected amine **63**.

Scheme 3-8. Introduction of Amine and Failed Olefination Attempts



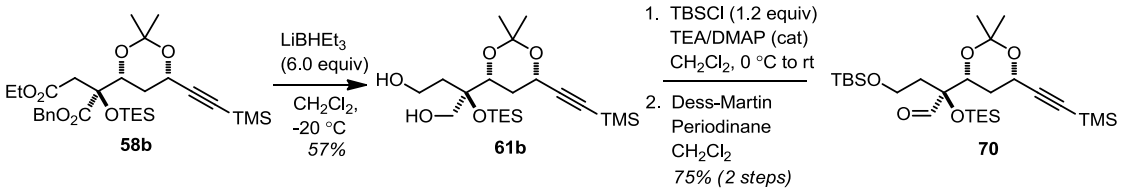
3.3.6 Revised Synthetic Route to Aldehyde Core from Benzyl Triethylsilyl Glyoxylate

Based on the failure of the routes shown in Scheme 3-8, a modified route to the aldehyde was followed, which involved delayed incorporation of the amine functionality and reduction of the diester to the diol. Additionally, the protecting group strategy was adjusted, due to what we felt was a tenuous removal of the hindered tertiary *tert*-butyldimethylsilyl ether at a late stage in the synthesis. The use of the more labile triethylsilyl ether would likely allow greater flexibility in modifying our synthetic route, should problems arise in the later stages of the synthesis. Throughout the remainder of the chapter, discussions will focus mainly on the use of the TES derivatives, although many screens were performed on TBS-protected advanced intermediates, and these will be clearly indicated in the text and figures.

The synthesis of the TES-protected diester **58b** was accomplished through a route identical to that used for the TBS derivative. Yields were comparable in general, although the lability of the TES group likely resulted in the loss of some material and diminished yields in some cases (Scheme 3-7). Once the desired diester intermediate was obtained, reducing agents were again screened for conversion to the diol (Table 3-2, entries 9-17).

This transformation proved challenging, but we eventually achieved adequate conversion to the desired product with lithium triethylborohydride in CH_2Cl_2 at -20 °C. DIBAL-H again failed to fully reduce the diester, providing primarily the monoalcohol **59b**. Lithium triethylborohydride provided some diol in initial attempts, but the product ratio was highly dependent on the solvent and temperature employed. The higher coordinating ability of THF rendered the reagent far less reactive in that solvent[46] and only conversion to the monoalcohol occurred (entry 10). Reductions run up to rt in 10:1 toluene: THF gave a mixture of the desired diol **61b** and regioisomeric **62**, where the tertiary silyl group had migrated to the less hindered vicinal primary hydroxyl (entry 11).

Scheme 3-9. Diester Reduction and Selective Alcohol Protection



This problem was exacerbated at elevated temperatures or when employing basic workup conditions ($NaOH/H_2O_2$) and was also solvent-dependent (entries 11-13), occurring more readily in diethyl ether and toluene. A similar product ratio was initially observed in CH_2Cl_2 at 0 °C, but the silyl migration could be minimized by lowering the reaction temperature to -20 °C. On small scale reactions, this procedure resulted in good yields of the desired diol (entry 14), but gram scale reactions resulted in either production of the migration product **62** or afforded incomplete reactions (entries 15-17). Optimal conditions for the reduction of **58b** were found to be premature quenching at -20 °C with HOAc followed by acidic workup conditions to cleave the boronate (HOAc/MeOH). After reduction to the diol in an average

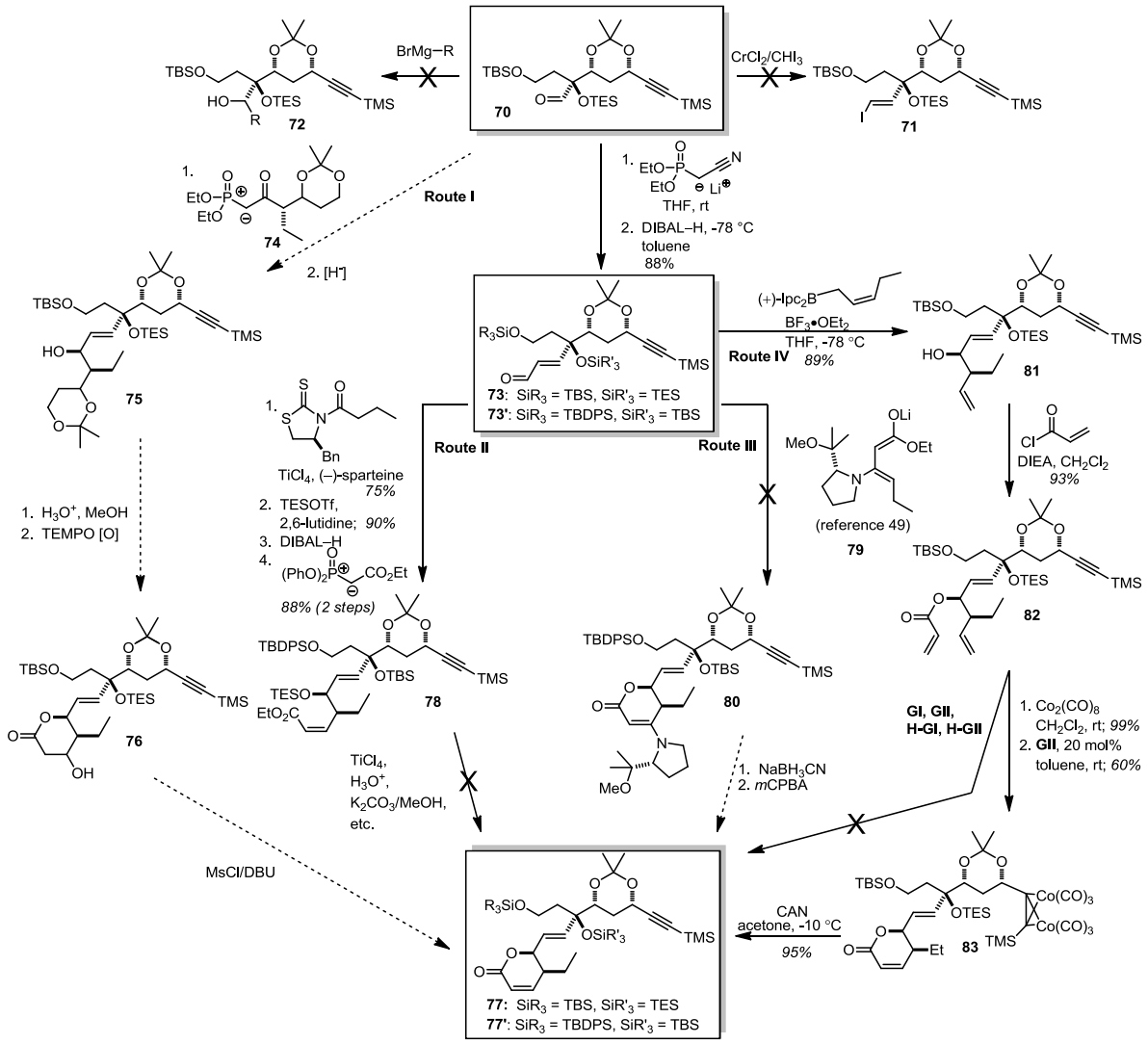
57% yield on gram-scale reactions, the less hindered primary hydroxyl group could be selectively protected with TBSCl/TEA in CH_2Cl_2 using DMAP as a catalyst. Oxidation of the crude reaction mixture gave the desired aldehyde **70** in an average 75% yield over two steps (Scheme 3-9).

3.3.7 Dihydropyrone Introduction

Figure 3-11 outlines several routes we investigated for the installation of the dihydropyrone. Based on the precedent set by the Imanishi synthesis,[12] we were skeptical of our ability to perform a highly selective NHK reaction[22] from aldehyde **70**; our inability to perform a Takai olefination[23] on this aldehyde precluded such an approach (**70** to **71**). Curiously, the aldehyde was also unreactive toward Grignard reagents (**70** to **72**). Two-carbon homologation to the enal **73** proceeded uneventfully in 88% yield over two steps using the Horner-Wadsworth-Emmons nitrile Wittig reaction[47]and DIBAL-H reduction.

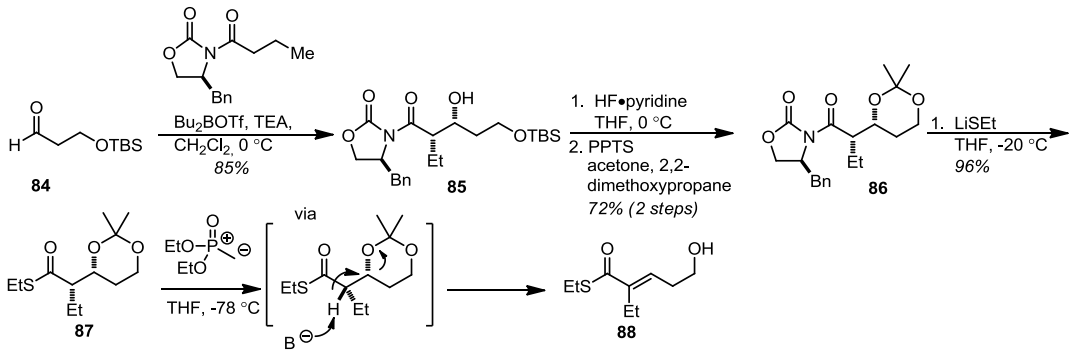
Related to the Imanishi approach were attempts to employ a functionalized Wittig reagent (Figure 3-11, Route **I**). We envisioned the use of Wittig reagent **74**, the enone product of which could undergo diastereoselective reduction to give the proper *syn*-relationship with the ethyl group (**75**).[12] Deprotection of the acetonide would give the triol, which we anticipated undergoing oxidation to lactone **76** via the lactol with the use of a mild oxidant such as TEMPO or Dess-Martin periodinane.[24] Ideally the secondary hydroxyl β- to the lactone carbonyl would remain intact, and an elimination of the corresponding mesylate would install the necessary unsaturation to give **77**. An attempted synthesis of the desired Wadsworth-Emmons Wittig reagent is shown in Scheme 3-10.

Figure 3-11. Attempted Dihydropyrone Installation Strategies



After employing an Evans aldol reaction to set the stereochemistry of the ethyl group through reaction with aldehyde **84** to give **85**, we arrived at acetonide **86** over two steps. Auxiliary removal with lithium ethanethiolate gave the corresponding thioester **87**. Unfortunately, this route proved problematic after attempts to generate the desired Wittig reagent from the thioester resulted in exclusive formation of thioenoate **88**, which presumably occurs via a β-elimination of the alkoxide.

Scheme 3-10. Attempted Synthesis of Wadsworth-Emmons Wittig Reagent **74**.



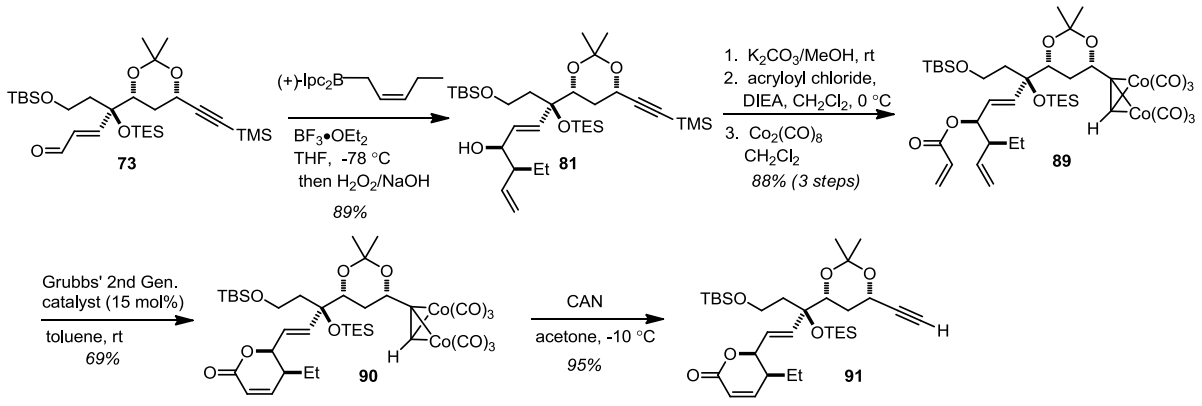
Similar to Fukuyama's approach, a thiazolidine thione-based aldol strategy[48] was also explored to install the dihydropyrone (Route **II** from **73′**).[48c] This method provided excellent selectivities in the generation of the vicinal stereocenters (>20:1 dr). Triethylsilyl protection of the alcohol and auxiliary cleavage with DIBAL-H afforded the aldehyde. A (*Z*)-selective Wittig reaction using Ando's protocol[16] gave the desired enoate **78** in 79% yield over three steps, but attempts to deprotect the secondary triethylsilyl ether with tandem lactonization failed to produce the desired dihydropyrone.

We briefly entertained a dienolate strategy, which has been utilized by Schlessinger et al. in the synthesis of methyl-substituted dihydropyrone analogues (Route **III** from **73′**).[49] The authors achieved asymmetric induction in those reactions through the incorporation of an enantioenriched proline-derived auxiliary in what is formally a hetero Diels-Alder reaction. Cleavage of the amine is accomplished in these systems via reduction of the iminium tautomer of the products with sodium cyanoborohydride followed by elimination of the amine oxide after oxidation with *m*CPBA.[49b] After synthesis of the requisite hexanoate **79**, we were discouraged by the lack of reactivity of this dienolate with the enal, and the strategy was subsequently abandoned.

Based on this series of failed attempts at pyrone installation, we ultimately adopted the use of Cossy's asymmetric pentenylation/RCM strategy.[13] Pentenylation and acroylation gave intermediate **82** in an 89% and 93% yield, respectively, but we were distressed to discover that this intermediate was unreactive toward all ring-closing-metathesis conditions screened. We conjectured that the presence of the alkyne might be impeding reactivity, as coordination of ruthenium to free alkynes has been blamed in other unsuccessful RCM reactions.[50] This roadblock was overcome by protection of the alkyne with dicobaltoctacarbonyl.[51] This protection occurred in nearly quantitative yield, and we were pleased to discover that ring closing metathesis then proceeded at room temperature to afford the desired dihydropyrone.

The optimized route to the dihydropyrone from aldehyde **73** is summarized in Scheme 3-11. Pentenylation consistently gave the desired product in an average 89% yield. Although the acroylation could be performed at this stage, it was preferable to deprotect the alkyne first with potassium carbonate and methanol, as deprotection after acroylation and ring-closing metathesis appeared to provide some saponification of the lactone.

Scheme 3-11. Dihydropyrone Installation

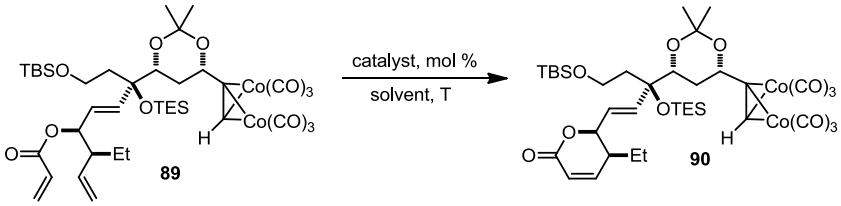


Desilylation of the alkyne, acroylation, and alkyne protection with dicobaltoctacarbonyl could be performed with only a single purification, and this sequence cleanly afforded **89** in an average 88% over three steps.

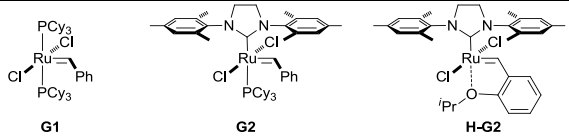
A brief screen of ring-closing metathesis conditions was performed and is shown in Table 3-3. Optimized conditions involved the addition of 15 mol % of Grubbs' second generation catalyst to a toluene solution of the acrylate at room temperature. After stirring for 16 h, the desired product was obtained, typically with the recovery of unreacted starting material. Among the catalysts screened (entries 1-3), only Grubbs' second generation catalyst afforded the desired product. Poor conversion was observed with this catalyst in dichloromethane and dichloroethane, even at elevated temperatures (entries 3, 8, 11), but conversions were markedly improved in toluene (entry 4). Catalyst loadings of 15 mol % were sufficient to obtain good conversion to the desired product, with no significant increase in yield at 20 mol % loading (entries 13-16). Full conversion was never obtained in this reaction; sparging the reaction with nitrogen[53] and employing higher temperatures or longer reaction times offered no noticeable improvement. We also attempted portionwise addition

of the catalyst (5 mol % every two hours for six hours, entry 15) but results were largely identical to those obtained by single additions. Yields were 69% on average for this transformation; they rose to 80% based on recovered starting material.

Table 3-3. Screen of RCM Conditions (**89** to **90**) [a]



entry	catalyst	mol % cat.	T (°C)	solvent	time (h)	conversion/yield[b]
1	**GI**	10-20	rt-100	CH_2Cl_2/ toluene	4	NR
2	**H-GII**	10-20	rt-45	CH_2Cl_2	4	NR
3	**GII**	10	rt-45	CH_2Cl_2	4	poor
4	**GII**	10	rt-45	toluene	4	moderate
5	**GII**	10	rt	toluene	16	moderate-good
6	**GII**	20	rt	toluene	16	good
7	**GII**	20	45	toluene	16	moderate
8	**GII**	20	rt	CH_2Cl_2	6	moderate
9	**GII**	20	rt	toluene	6	good
10	**GII**	20	80	toluene	6	moderate
11	**GII**	20	0-80	DCE	6	NDP
12	**GII**	15	rt	toluene	16	good
13	**GII**	15	rt	toluene	6	52%
14	**GII**	20	rt	toluene	16	60%
15[c]	**GII**	3x5	rt	toluene	16	50%
16	**GII**	15	rt	toluene	16	69%



[a] All reactions: $[\mathbf{89}]_0$ = 0.0039 M in sealed vial. [b] Conversions determined by qualitative assessment through TLC analysis. [c] 5 mol % **GII** added every 2h for 6h.

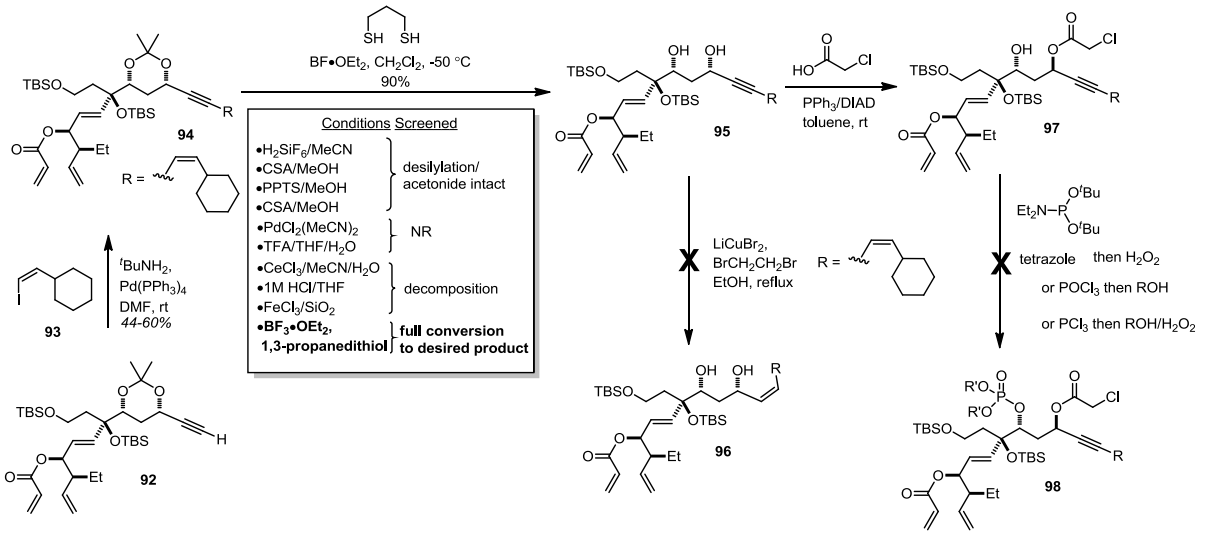
Deprotection of the alkyne could be most cleanly accomplished by treatment with 5.0 equivalents of ceric ammonium nitrate (CAN)[53a] in acetone at -10 °C (Scheme 3-11). We

found that small quantities of **90** could be deprotected cleanly by heating on SiO_2 in the presence of air, but this deprotection method provided significant byproduct formation on larger scale. Reactions with NMO[53b] or CAN at higher temperatures gave the desired product **91**, albeit in diminished yields. After optimizing the dihydropyrone synthesis, we proceeded toward introduction of the cyclohexyldiene moiety and introduction of the amine and phosphate.

3.3.8 Diene Installation Attempts and Acetonide Deprotection Screens

Our original retrosynthetic plan introduced the cyclohexyl moiety via a Sonogashira reaction of the free alkyne and the corresponding vinyl iodide (*vide supra*, Figure 3-6). As a model system, alkyne **92** was used here due to its availability from previously terminated synthetic routes. Cyclohexyl vinyl iodide **93**, available in one step from cyclohexanecarboxaldehyde via a Stork-Zhao olefination,[27] was used as a model cross-coupling partner. Sonogashira reactions of this (*Z*)-vinyl iodide and alkyne **92** afforded the desired enyne **94**, but yields were quite variable in this step and significant byproduct formation was often observed. A potential complicating factor is a base- or phosphine-catalyzed isomerization of the product.[54] Although attempts were made to improve these yields and avoid degradation of the unstable enyne products, these were largely met with failure.

Scheme 3-12. Acetonide Deprotection and Enyne Reduction Screens



With a plausible route to the enyne in hand, we investigated the incorporation of the primary amine and the necessary stereochemical correction at C11. Additionally, reduction of the enyne to the diene was necessary, although we were concerned about the stability of the diene functionality over several steps. We hoped that the orthogonal protecting group strategy that existed at this stage would allow us to deprotect the acetonide and perform selective Mitsunobu inversion of the C11-hydroxyl group as we had done previously (Scheme 3-6, **55a,b).** Using acetonide **94** as a model system (Scheme 3-12), several Lewis and Brønsted acidic conditions were screened toward this end. Most Brønsted acidic conditions led to deprotection of the primary alcohol, while Lewis acidic conditions generally gave decomposition. Success with this transformation was finally achieved through transketalization with boron trifluoride diethyl etherate and 1,3-propanedithiol at reduced temperature,[55] which consistently afforded the desired diol **95** in a 90% yield.

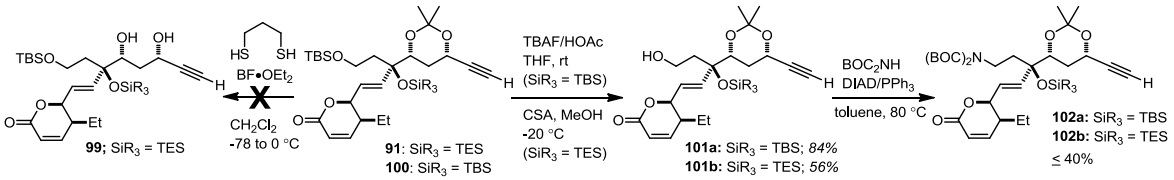
With the free propargylic alcohol, we attempted to employ the Brandsma method of enyne reduction (Zn, dibromoethane, $LiCuBr_2$, EtOH),[17] which was used in Fukuyama's

synthesis.[11] After repeated failed attempts, we briefly investigated other routes with this diol. Mitsunobu reaction of **95** proceeded with excellent selectivity for the propargylic site as predicted, but the remaining secondary alcohol was found to be unreactive toward common phosphorylating agents (**97→98**). We attributed this lack of reactivity to the steric bulk of the TBS group, and the TES derivative was subsequently prepared. Alternative routes to the (*Z*,*Z*)-diene are discussed later in the chapter along with a detailed synthetic scheme that affords the substituted side chain.

3.3.9 Additional Core Modification Strategies

We modified our synthetic route at this point to permit installation of the amine at an earlier stage in anticipation of the projected instability of the diene and phosphate functionalities. Selective desilylation of the primary TBS ether in the presence of the tertiary TBS ether was trivial, but TBAF buffered with acetic acid[56] was necessary to avoid decomposition (**100→101a**). When the tertiary alcohol was protected as the TES ether **91**, however, selective deprotection of the primary TBS group was a challenging transformation, and only moderate to poor yields of the desired monoalcohol **101b** could be obtained using 20 mol % of CSA in methanol at -20 °C. We also found that the TES-protected **91** decomposed under the conditions previously successful for acetonide deprotection (propanedithiol and BF_3•OEt_2). After several unsuccessful attempts to suppress the degradation of **91** under these conditions, we recognized the need to investigate alternative strategies.

Figure 3-12. Attempted Core Modification Strategies

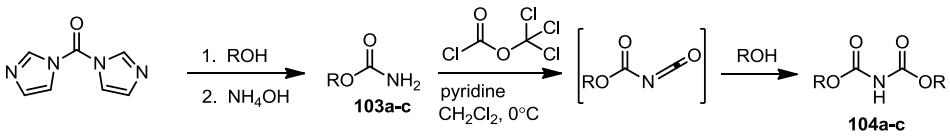


We subsequently discovered that a Mitsunobu reaction between BOC_2NH and either primary alcohol **101a** or **101b** no longer proceeded at room temperature. Elevated temperatures gave moderate yields of the desired products **102a** and **102b**, but significant byproduct formation and decomposition occurred as well. Additionally, an analysis of the existing literature related to leustroducsin B suggested that advanced intermediates might not withstand the acidic conditions necessary for BOC group deprotection,[11-14] and thus similar *bis*-protected amine alternatives that might require milder deprotection conditions were synthesized.

3.3.10 Synthesis of Amine Nucleophiles for Mitsunobu Reactions

A general method for the synthesis of these *bis*-carbamates is shown in Scheme 3-13. Carbonyl diimidazole was treated first with one equivalent of the appropriate alcohol of the protecting group and then excess ammonium hydroxide, which afforded the monoprotected amines **103a-c** in moderate to good yields.[57] Treatment of these carbamates with diphosgene and pyridine in methylene chloride generated the isocyanates *in situ*, which were reacted with a second equivalent of the desired alcohol to afford the *bis*-carbamates **104a-c**.[58] Of these, $Alloc_2NH$ has been employed in Mitsunobu reactions; to our knowledge, $Teoc_2NH$ and $Troc_2NH$ have not been previously prepared.

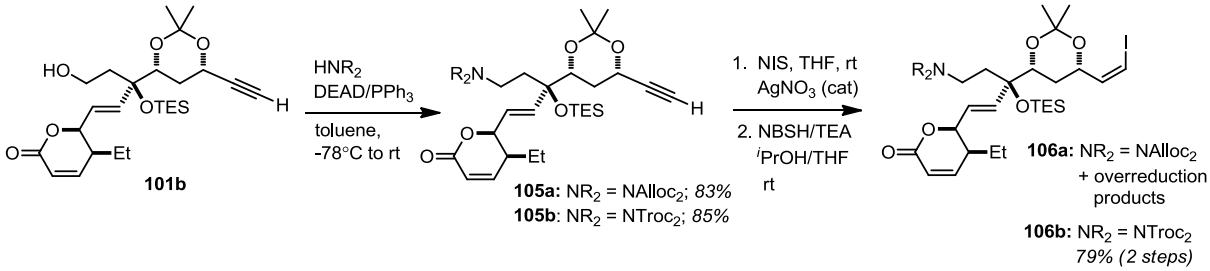
Scheme 3-13. Preparation of Protected Amine Reagents for Mitsunobu Reactions



entry	HOR		yield (2 steps)
104a	HO	Alloc	24%
104b	HO–TMS	Teoc	44%
104c	HO–CCl_3	Troc	29%

Test reactions with hydrocinnamyl alcohol revealed that these amine derivatives were viable substrates in Mitsunobu reactions, and we were pleased to find that $Alloc_2NH$ and $Troc_2NH$ reacted with primary alcohol **101b** at room temperature to give the desired protected amines **105a** and **105b** in 80-85% yield.

Scheme 3-14. Alternative Amine Introduction



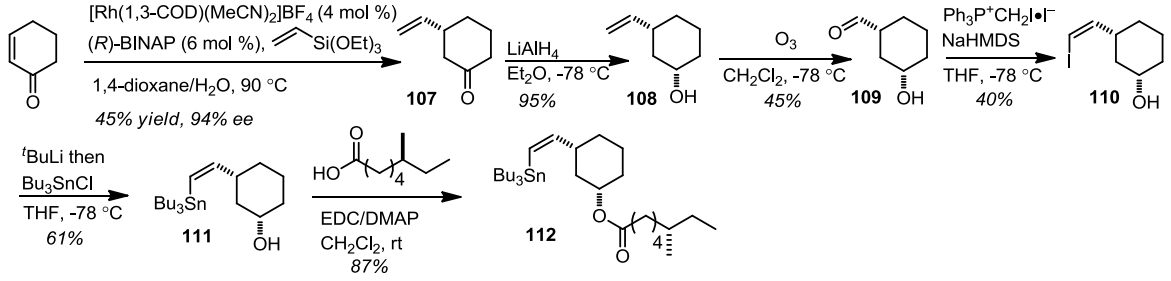
Alkyne **105a** underwent conversion to the alkynyl iodide using *N*-iodosuccinimide and silver nitrate as a catalyst in THF,[59] and reduction to the vinyl iodide was attempted with diimide, generated *in situ* from triethylamine-promoted decomposition of *o*-nitrobenzenesulfonylhydrazide (NBSH).[60] Although we did observe production of the vinyl iodide **106a** in these reactions, reduction of the allyl groups or overreduction to the alkyl iodide were competitive pathways. Consequently, the Troc derivative was prepared from

Mitsunobu reaction of **105b** with $Troc_2NH$. Conversion to the vinyl iodide proceeded uneventfully with this compound, affording **106b** in a 79% yield over two steps.

3.3.11 Diene Synthesis via Stille Coupling and Side Chain Synthesis

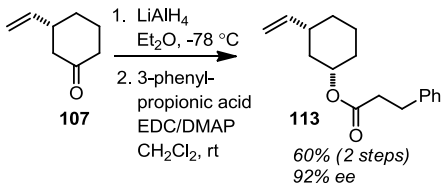
Because of the low yields observed in the Sonogashira reactions attempted for the side chain introduction (Scheme 3-12), Stille coupling[61] was investigated as an alternative. A synthesis of the requisite vinyl stannane coupling partner **112** for cross-coupling with vinyl iodide **106b** is shown in Scheme 3-15.

Scheme 3-15. Side Chain Synthesis



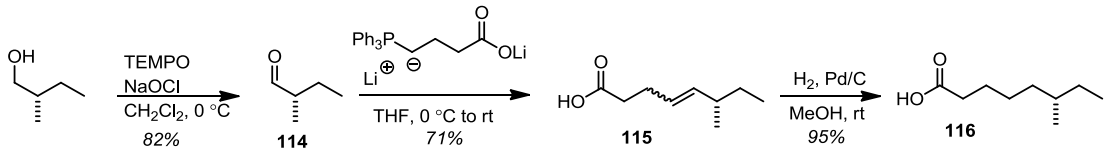
The side chain synthesis commenced with an asymmetric rhodium-catalyzed conjugate vinyl addition from vinyl triethoxysilane as reported by Oi and Inoue.[62] Using (*R*)-BINAP as a chiral ligand, the reaction afforded the desired cyclohexanone **107** in 45% yield and 92% ee. The enantiomeric excess of this sample was determined by conversion of the ketone to phenylpropionate **113** and SFC analysis of the final product (Figure 3-13).[63]

Figure 3-13. Assessment of Enantiomeric Excess of **107**.



Reduction of ketone **107** with lithium aluminum hydride occurred with greater than 25:1 diastereoselectivity to give *syn*-alcohol **108** in 95% yield. Ozonolysis of this alcohol provided aldehyde **109**, albeit in moderate yield. A Stork-Zhao olefination of the crude aldehyde gave vinyl iodide **110**. Conversion of the vinyl iodide to the corresponding stannane was accomplished without protection of the free hydroxyl group by lithium halogen exchange and addition of tributyltin chloride. EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) coupling of the vinyl stannane with (*S*)-6-methyloctanoic acid[14] afforded the desired side chain **112**. (*S*)-6-methyloctanoic acid (**116**) was prepared in three steps from commercially available (*S*)-2-methylbutan-1-ol as shown in Scheme 3-16. TEMPO oxidation[64] and Wittig reaction of the resulting aldehyde gave alkene **115** in 82% and 71% yield, respectively. This alkene existed as a mixture of diastereomers that converged to the desired acid **116** after hydrogenation.

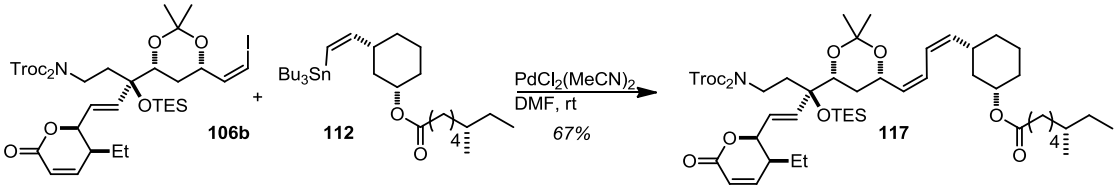
Scheme 3-16. Synthesis of (S)-6-Methyloctanoic Acid



Gratifyingly, Stille coupling of **106b** and **112** finally allowed access to diene **117** in an unoptimized 67% yield. Remaining steps at this stage prior to the final deprotections were

removal of the acetonide, inversion of the alcohol stereocenter at C11, and phosphorylation of the C9 hydroxyl group. Unfortunately, diene **117** was found to be unstable to Lewis and Brønsted acidic conditions for acetonide deprotection, which suggested that its stability over the several remaining steps would be poor. Consequently, a modified and fully functionalized coupling partner was selected as a target. Current and future efforts toward the synthesis of this coupling partner are presented in the final section.

Scheme 3-17. Stille Coupling to Afford *Z,Z*-Diene

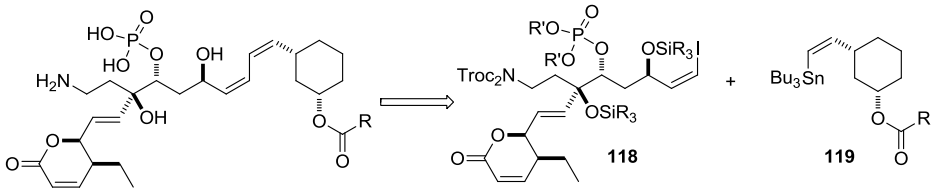


3.3.12 Revised Vinyl Iodide Target Synthesis

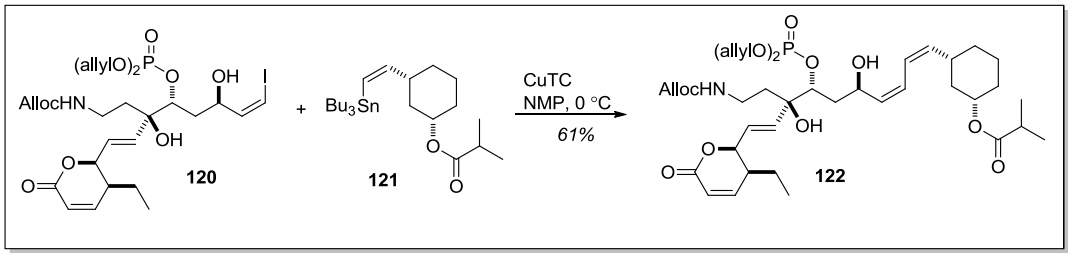
Our revised retrosynthetic plan involved the Stille coupling of the functionalized vinyl iodide **118** and vinyl stannane **119** as shown in Figure 3-14. A Stille-Liebeskind coupling[65] of similar partners was recently used in a synthesis of phoslactomycin A in 2009 as reported by Koert (Figure 3-14),[10e] and we felt that our proposed vinyl iodide could likewise be utilized with success. To this end, synthesis of the Troc protected amine **105b** was accomplished as previously described from primary alcohol **101b** (Scheme 3-18**),** and treatment of this product with 40 mol % camphorsulfonic acid in MeOH afforded the corresponding triol **120**. This compound and others in which the tertiary alcohol at C8 was unprotected were found to be somewhat unstable to silica gel chromatography, likely due to their propensity to form tertiary allylic cations. Treatment of the crude triols with a large

excess of TMSCl and imidazole (50 equiv) was necessary to effect silylation of the tertiary alcohol, as the C8 hydroxyl was found to be resistant to silylation by bulkier silylating agents

Figure 3-14. Revised Retrosynthetic Analysis

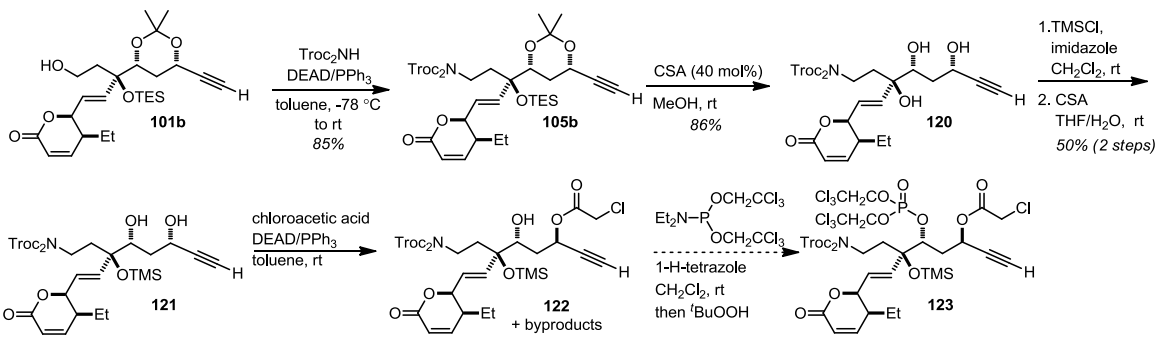


Koert Phoslactomycin A Synthesis, **2009:**



(TESCl, TESOTf), even up to room temperature. After complete silylation of the triol, treatment with 1.0 equiv of CSA in a 10:1 THF:H_2O mixture[10e] was found to be effective in cleaving the secondary TMS groups selectively, affording **121** in 43% yield over three steps. To our dismay, difficulties were encountered when this diol was subjected to the previously optimized Mitsunobu conditions for stereochemical correction of the propargylic hydroxyl group.

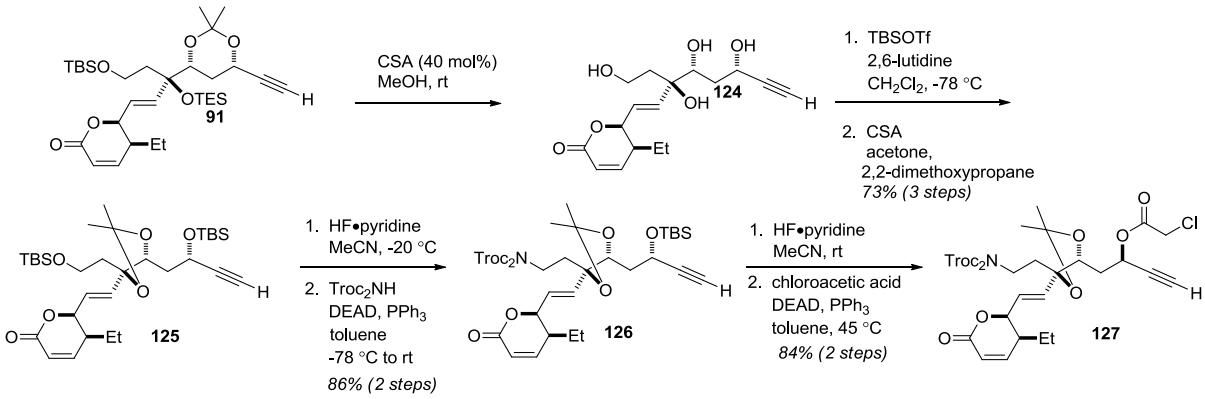
Scheme 3-18. Alternative Core Functionalization Strategy A



Although the desired product **122** was obtained, several other byproducts were observed. Likely pathways include an elimination of the chloroacetate to the alkene and migration of the chloroacetate to the C9 secondary alcohol. This type of migration has been observed on silica gel in other cases.[66] This migration should be less favored as the steric bulk of the silyl group on the adjacent tertiary alcohol increases, which may explain the cleanliness of earlier selective Mitsunobu reactions in which triethylsilyl and *tert*-butyldimethylsilyl protecting groups were employed (see Figure 3-6).

We postulated that a monoalcohol would be a more suitable advanced intermediate for the stereochemical correction, and a conversion of acetonide **91** into acetonide **125** was accomplished in three steps and 73% yield by conversion to the tetraol **124**, selective silylation of the primary and propargylic alcohols, and protection of the remaining diol as the acetonide (Scheme 3-19).

Scheme 3-19. Alternative Core Functionalization Strategy B

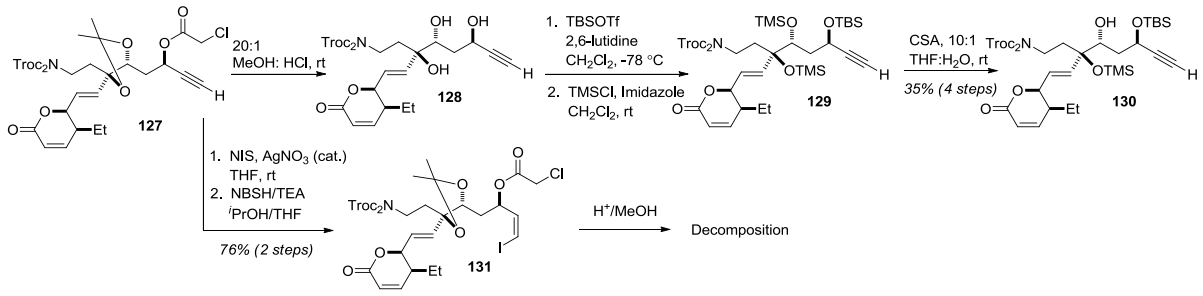


Selective deprotection of the primary TBS group in the presence of the secondary TBS group was possible with HF•pyridine in acetonitrile at -20 °C, affording the monoalcohol cleanly with less than 5% of the diol present. Installation of the *bis*-protected

amine provided **125** in 86% yield over two steps. Desilylation of the remaining secondary TBS ether with HF•pyridine in acetonitrile at room temperature was followed by Mitsunobu reaction with chloroacetic acid, which required mild heating but gave the desired chloroacetate **127** in 84% yield over two steps.

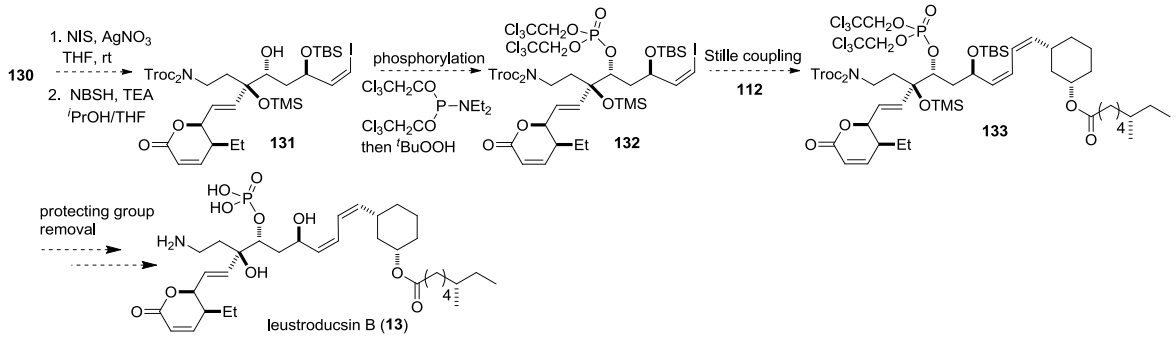
Remaining modifications to the core at this stage were phosphorylation of the C9 hydroxyl group and conversion of the alkyne to the vinyl iodide. Chloroacetate **127** could be converted to the vinyl iodide using the previously described conditions (*N*-iodosuccinimide and diimide reduction; *cf.* Figure 3-14), but these reactions were found to be sluggish, likely due to the electron-withdrawing properties of the chloroacetate. Additionally, standard acetonide deprotection conditions (CSA/MeOH, MeOH/HCl, BF_3•OEt_2/propanedithiol, etc.) generally led to decomposition or poor yields when the vinyl iodide was present. After screening several other deprotection conditions, we discovered that treatment of chloroacetate **127** with 20:1 MeOH:HCl[12] led to both hydrolysis of the chloroacetate and deprotection of the acetonide, affording triol **128**. Selective TBS protection of the propargylic hydroxyl group was again straightforward using TBSOTf at -78 °C, and the remaining hydroxyl groups were then protected as the TMS ethers with TMSCl and imidazole.

Scheme 3-20. Synthesis of Phosphate Precursor



Deprotection of the secondary trimethylsilyl ether with CSA in THF/H_2O gave monoalcohol **130**, which we obtained in an unoptimized 35% yield over four steps. Studies are currently underway to phosphorylate this intermediate with phorphoramidite reagents, after which conversion of the alkyne to the vinyl iodide should allow us to arrive at the desired coupling partner **132** (Scheme 3-21).

Scheme 3-21. Proposed Completion of Synthesis from Vinyl Iodide



3.4 Conclusion

Toward our goal of completing a total synthesis of leustroducsin B, we have developed a new three-component coupling reaction of Reformatsky reagents, silyl glyoxylates, and β-lactones. The Reformatsky/Claisen cascade affords highly functionalized β-hydroxyketone products in good yields and, remarkably, with greater than 25:1

diastereoselectivities. After advancing this initial intermediate through five additional steps, we were able to arrive at a suitably functionalized core to which the remaining carbon skeleton could be appended. Several strategies for introduction of the dihydropyrone were discussed, although Cossy's pentenylation strategy was ultimately the most successful. Clearly highlighted by this work are the challenges we encountered in functionalizing advanced intermediates, which required several iterations of protecting group manipulations and reorganization of the order of effective transformations to maximize material throughput. We have arrived at a late-stage intermediate with phosphorylation of the C9 stereocenter and deprotection of the amine and alcohol functionalities remaining as the primary challenges, and we are optimistic that the synthesis of leustroducsin B will be completed in the near future.

3.5 Experimental Details

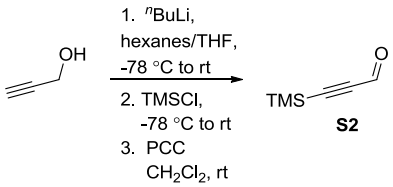
Materials and Methods: General. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 or a Bruker 300 MHz (^{1}H NMR at 400 MHz or 300 MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and/or aqueous ceric ammonium nitrate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Siliaflash-P60 silica

gel (40-63μm) purchased from Silicycle and/or crystallization. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables or figures, which are averages of at least two experiments. Tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. Hexanes were dried by distillation from sodium metal immediately prior to use. Acetone was dried by stirring with calcium sulfate followed by distillation from calcium sulfate. Zinc metal was washed with 1 M HCl, water, acetone, and diethyl ether and then dried under vacuum at 60 °C for 16 h prior to storage in a nitrogen-filled glove box. Bromo esters were purified by washing with 50% calcium chloride, saturated sodium carbonate, and brine, and distilling from calcium chloride. Unless otherwise noted, all reagents were purchased from Sigma-Aldrich or Acros and used as received without further preparation. Enantiomeric excesses were obtained using a Supercritical Fluid Chromatograph equipped with a UV-Vis detector using a Chiralcel Chiralpak OD HPLC column. Samples were eluted with SFC grade CO_2 at the indicated percentage of MeOH. Specific parameters used in the separation of compounds are detailed under applicable entries.

I. Preparation of Starting Materials for Three-Component Coupling

Preparation of β-Lactone 38′:

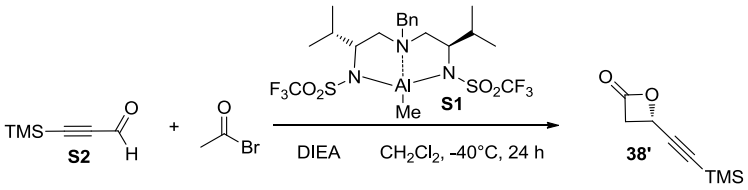
Catalyst **S1** (see below) was prepared according to Nelson's procedure.[32] Silyl glyoxylates **37** and **37′** were prepared as described in chapter two (section 2.4). 2-(trimethylsilyl)-propiolaldehyde (**S2**) was prepared according to the following:



3-(trimethylsilyl)propiolaldehyde (S2): A flame-dried and N_2-purged 500-mL round-bottomed flask equipped with a magnetic stir bar was charged with THF (125 mL) and propargyl alcohol (5.8 mL, 5.6 g, 100 mmol, 1.0 equiv). The resulting solution was cooled to -78 °C in an acetone-dry ice bath, and a solution of ^{n}BuLi (1.54 M in hexanes, 150 mL, 230 mmol, 2.3 equiv) was added dropwise over 20 min. Once the addition of ^{n}BuLi was complete, the flask was allowed to warm to rt for 1 h. The flask was returned to -78 °C, and TMSCl (29 mL, 25.2 g, 230 mmol, 2.3 equiv) was added dropwise. The resulting cloudy white suspension was allowed to warm slowly to rt overnight. After stirring for 12 h at rt, the solution was cooled to 0 °C, and 1M HCl (130 mL) was added dropwise over 5 min. The resulting clear biphasic mixture was stirred for 1 h at rt, at which point the layers were separated, and the aqueous layer was extracted with Et_2O (3x50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and dried with $MgSO_4$ then concentrated *in vacuo* to give 3-(trimethylsilyl)prop-2-yn-1-ol (12.8 g, ~quantitative) as a yellow oil, which was used without additional purification.

A 500-mL flame-dried and N_2-purged round-bottomed flask equipped with a magnetic stir bar was charged with the crude 3-(trimethylsilyl)prop-2-yn-1-ol (12.8 g, 100 mmol, 1.0 equiv) and CH_2Cl_2 (150 mL). PCC (33.0 g, 150 mmol, 1.5 equiv) was added in small portions, and the resulting suspension was stirred at rt for 4 h. Stirring was ceased, and the resulting solution was decanted onto a column of SiO_2 once all solids had settled. The desired product was eluted with CH_2Cl_2 to give the title compound as a bright yellow oil (9.5

g, 75% over two steps), whose spectral properties matched those reported in the literature.[67] The enantiomeric excess of **38′** was determined to be 83% through SFC analysis of compound **39′**.



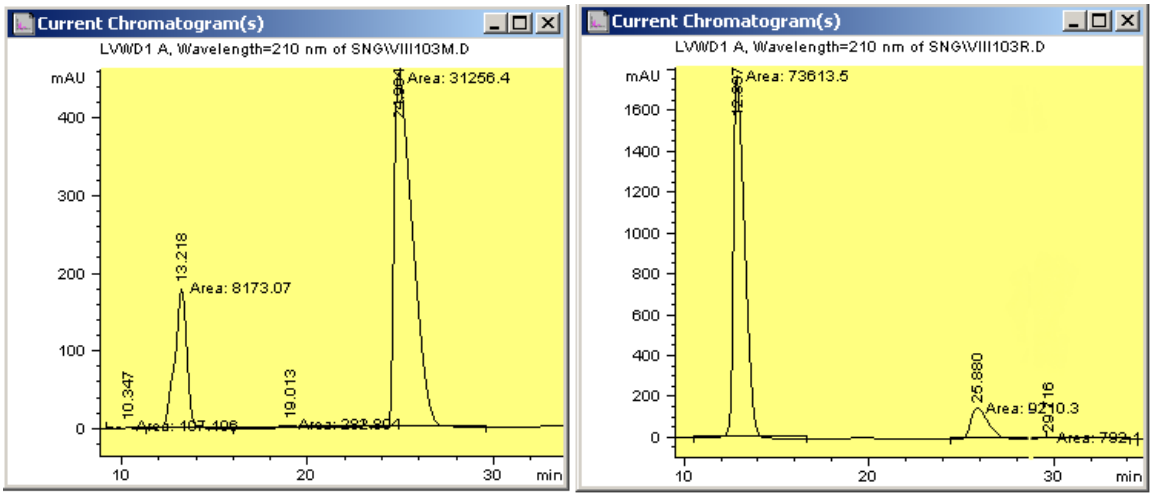
(S)-4-((trimethylsilyl)ethynyl)oxetan-2-one (38′):

The title compound was prepared according to the procedure described by Nelson[32a] with the following modifications:

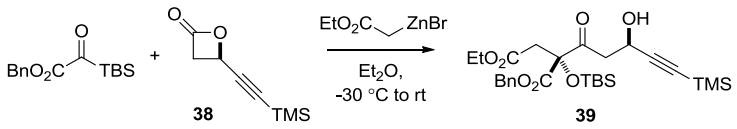
1. Instead of purification via Kugelrohr distillation, the crude β-lactone was purified via flash chromatography (92.5:7.5 to 85:15 hexanes:ethyl acetate), affording the title compound (67% yield) as a light yellow oil whose spectral properties matched those reported in the literature.[3]

2. The enantiomeric excess of the prepared lactone was assayed via Supercritical Fluid Chromatographic (SFC) analysis of the corresponding β-hydroxyketone **39′** (*vide infra*). Enantiomeric excesses ranged from 78-83% using this method. CSP-SFC analysis of a sample of **39′** showed that the product was enriched to 78% ee as determined by CSP-SFC analysis (Chiralpak OD column, 3.0% MeOH, 1.0 mL/min, 150 psi, 24 °C, 210 nm, t_r-major enantiomer: 12.9 min, t_r-minor enantiomer: 25.9 min; CSP-SFC traces for a mixture of enantiomers and of the enantioenriched product are attached below:

Enantiomeric Mixture: Enantioenriched Sample:

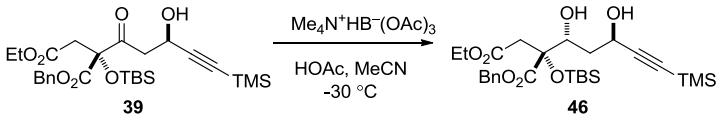


II. Stereochemical Assignment of Three-Component Coupling Products:



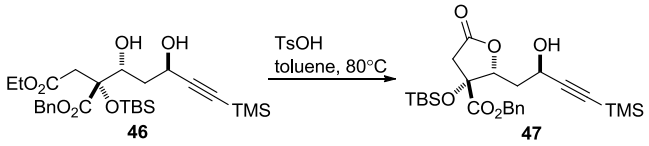
(*R*)-1-benzyl 4-ethyl 2-((tert-butyldimethylsilyl)oxy)-2-((*R*)-3-hydroxy-5- (trimethylsilyl) pent-4-ynoyl)succinate (39): A solution of Reformatsky reagent (0.43 M, 50 mL) was prepared according to the standard procedure (chapter two, section 2.4). The Reformatsky reagent solution (18.6 mL, 8.0 mmol, 1.5 equiv) was diluted with diethyl ether (60 mL), and the solution was cooled to -30 °C in an acetone/dry ice bath (bath temperature, monitored with a thermocouple probe). An oven-dried vial was charged with benzyl *tert*-butyldimethylsilyl glyoxylate (1.48 g, 5.33 mmol, 1.0 equiv) and (*R*)-4-((trimethylsilyl)ethynyl)oxetan-2-one (2.24 g, 13.3 mmol, 2.5 equiv) **38**. The vial was purged with N_2, and a solution of the silyl glyoxylate and β-lactone in diethyl ether (10 mL)

was added dropwise to the Reformatsky reagent solution over 5 min via cannula transfer. Additional diethyl ether (5 mL) was used to rinse the vial. The flask was allowed to warm slowly in the acetone bath (generally over 30 min from -30 °C to 0 °C). Consumption of the silyl glyoxylate was observed by TLC analysis between -15 °C and -10 °C. Once the reaction had reached 0 °C, it was then warmed to room temperature for 30 min, at which point it was recooled to 0 °C, quenched with saturated ammonium chloride (30 mL), and stirred until two clear layers were observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x30 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (93.5:7.5 to 70:30 petroleum ether: diethyl ether) to give the desired product as a light yellow oil with > 25:1 diastereomeric ratio (2.16 g, 76%). Analytical data: $[\alpha]_D^{25.2}$ = + 7.8 (*c* = 0.43, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12 Hz, 1H), 4.86 (dd, *J* = 9.2, 4.8 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.46 (d, J = 16.8 Hz, 1H), 3.37 (dd, *J* = 18.8, 2.4 Hz, 1H), 3.13 (dd, *J* = 18.4, 8.8 Hz, 1H), 2.95 (d, *J* = 17.2, 1H), 2.91 (d, *J* = 4.4, 1H), 1.22 (t, *J* = 7.2, 3H), 0.86 (s, 9H), 0.15 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 208.8, 169.3, 168.3, 134.3, 128.7, 128.6, 128.5, 104.9, 89.3, 83.6, 68.1, 61.1, 58.7, 46.3, 42.2, 25.5, 18.2, 14.0, -0.3, -3.6, -4.2; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 557.3, observed: 557.2; **IR** (thin film, cm^{-1}) 3433, 2844, 2386, 2100, 1646, 1558, 1541, 1456, 1250, 1013, 494; **TLC**(80:20 Hexanes:EtOAc): R_f = 0.42.



(R)-1-benzyl 4-ethyl 2-((tert-butyldimethylsilyl)oxy)-2-((1R,3R)-1,3-dihydroxy-5-(trimethylsilyl) pent-4-yn-1-yl)succinate (46): An oven-dried and cooled vial equipped with a magnetic stir bar was charged with MeCN (1 mL), $Me_4NHB(OAc)_3$ (147 mg, 0.56 mmol, 5.0 equiv), and dry HOAc (0.45 mL). The resulting solution was cooled to -35 °C in a Cryocool apparatus. A solution of ketone **39** (46 mg, 0.112 mmol, 1.0 equiv) in MeCN (1 mL) was added to the reaction dropwise, and additional MeCN (0.5 mL) was used to rinse the vial. The reaction was allowed to warm to -25 °C and was maintained at the same temperature for 60 h. The reaction was quenched by the addition of a 25% saturated aqueous solution of sodium potassium tartrate (0.3 mL) and was allowed to warm slowly to room temperature. A saturated aqueous solution of $NaHCO_3$ was added until the pH of the reaction was neutral. The resulting suspension was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated *in vacuo* to afford a crude colorless oil. The crude material was purified via column chromatography, eluting with 80:20 hexanes:EtOAc, to give the title compound as a viscous light yellow oil with > 25:1 diastereomeric ratio. Analytical data: $[\alpha]_D^{24.3}$ = + 19.1 (*c* = 0.67, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43-7.26 (m, 5H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 4.61 (br. s, 1H), 4.32 (dd, *J* = 9.2, 8.4 Hz, 1H), 4.06 (q, *J* = 7.2 Hz, 2H), 3.13 (d, *J* = 7.2 Hz, 1H), 3.01 (d *J* = 7.2 Hz, 1H), 2.93 (d, *J* = 15.2 Hz, 1H), 2.86 (d, *J* = 15.2 Hz, 1H), 1.88 (ddd, *J* = 17.6, 14.4, 3.2 Hz, 1H), 1.67 (dd, *J* = 14.4, 6.4 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H) 0.85 (s, 9H), 0.16 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.0, 170.3, 135.3, 128.7, 128.6, 128.5, 106.2, 89.9, 80.7, 73.6, 67.6, 61.0, 60.9, 41.7, 37.8, 25.9, 18.7, 14.0, -0.1, -2.9, -3.1; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 559.2,

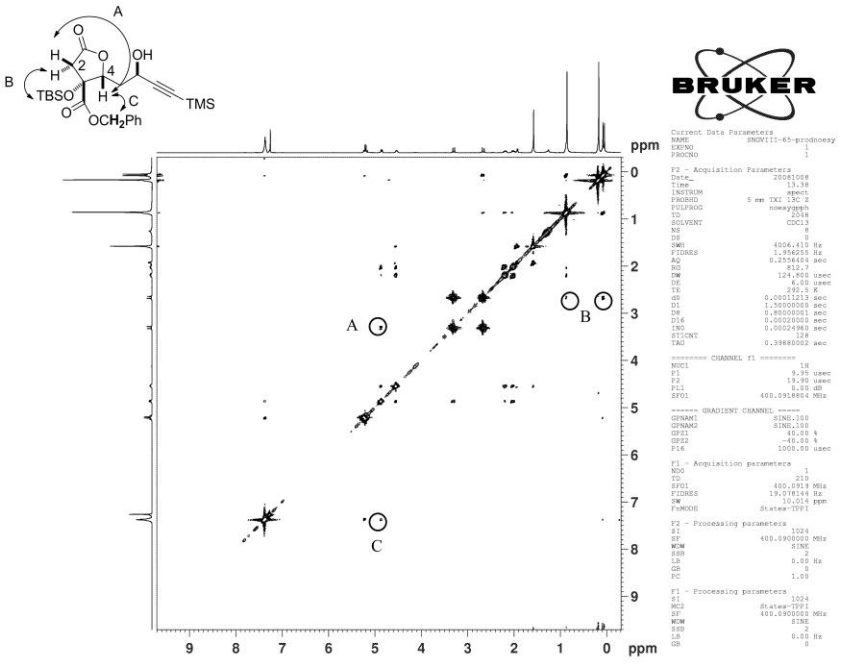
observed: 559.2; **IR** (thin film, cm^{-1}): 3853, 2089, 1647, 1541, 1457, 1250, 1175, 1031, 521, 509, 496; **TLC**(80:20 Hexanes:EtOAc): R_f = 0.38.

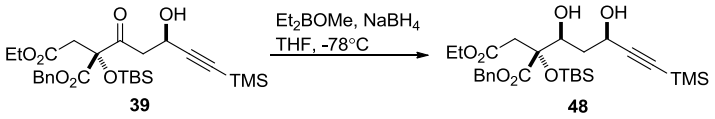


(2R,3R)-benzyl 3-((tert-butyldimethylsilyl)oxy)-2-((R)-2-hydroxy-4-(trimethylsilyl)but-3-yn-1-yl)-5-oxotetrahydrofuran-3-carboxylate (47): An oven-dried and cooled vial equipped with a magnetic stir bar was charged with diol **46** (12 mg, 0.022 mmol) and toluene (0.75 mL). TsOH (cat.) was added, and the vial was sealed with a Teflon cap. The solution was heated to 80 °C in a sand bath for 1 h. After cooling to rt, the solvent was removed *in vacuo*, and the crude residue was purified via column chromatography, eluting with 80:20 hexanes:EtOAc. The title compound was obtained as a colorless oil (5 mg, 45%). Analytical data: $[\alpha]_D^{25.4}$ = +17.3 (*c* = 0.23, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37 (br. s., 5H), 5.23 (d, *J* = 12.0 Hz, 1H), 5.18 (d, *J* = 12.0 Hz, 1H), 4.86 (dd, *J* = 9.5, 3.0 Hz, 1H), 4.53 (br. s., 1H), 3.30 (d, J = 17.5 Hz, 1H), 2.66 (d, *J* = 17.0 Hz, 1H), 2.187 (ddd, *J* = 14.5, 9.5, 3.5 Hz, 1H), 2.00 (ddd, *J* = 12.5, 9.0, 3.0 Hz, 1H), 1.92 (d, *J* = 5.5, 1H) 0.85 (s, 9H), 0.17 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.7, 170.1, 128.8, 90.4, 83.3, 81.0, 68.3, 59.4, 42.6, 36.8, 25.6, -0.2, -3.5, -3.7; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 513.2, observed: 513.2; **IR** (thin film, cm^{-1}) 3433, 3021, 2961, 2330, 2089, 1646, 1361, 1215, 775, 668; **TLC**(80:20 Hexanes:EtOAc): R_f = 0.40.

Spectral analysis (NOESY) supported the structural assignment shown for **47**: A strong nOe was observed between the C4 methine C–**H** and the *syn*-methylene C–**H** at C2 as well as between the C4 methine C–**H** and the CO_2**CH_2**Ph benzyl protons (interactions A and C,

respectively). Additionally, an nOe was observed between the *anti*-methylene C–**H** at C2 and the methyl and *tert*-butyl substituents of the TBS ether, which suggested their relative *syn* orientation (interaction B).

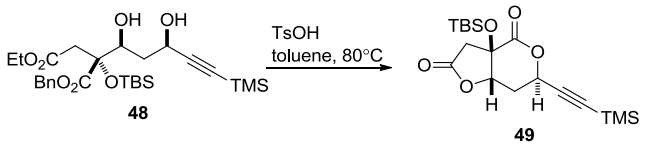




39 48

(R)-1-benzyl 4-ethyl 2-((tert-butyldimethylsilyl)oxy)-2-((1S,3R)-1,3-dihydroxy-5-(trimethylsilyl)pent-4-yn-1-yl)succinate (48): The title compound was prepared analogously to **55b** (*vide infra*). Yield = 95%, > 25:1 dr. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (br. s, 5H), 5.19 (s, 2H), 4.58 (br. s, 1H), 4.09-3.95 (m, 1H), 4.07 (t, *J* = 7.6 Hz, 2H), 2.96 (br. s, 1H), 2.72 (d *J* = 15.2 Hz, 1H), 1.95 (dd, *J* = 13.6, 6.4 Hz, 1H), 1.77 (dd, *J* = 17.6, 10 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.17 (s, 3H), 0.14 (s, 9H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.0, 169.8, 135.0, 128.5, 128.5, 128.4,

105.7, 89.7, 80.8, 75.2, 67.5, 61.7, 60.8, 41.3, 38.7, 25.9, 18.7, 13.9, -0.3, -2.9, -3.2; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 559.3, observed: 559.2; **IR** (thin film, cm^{-1}): 3436, 2957, 2856, 2360, 1739, 1637, 1457, 1372, 1251, 1188, 1112, 840; **TLC**(80:20 Hexanes:EtOAc): R_f = 0.38.



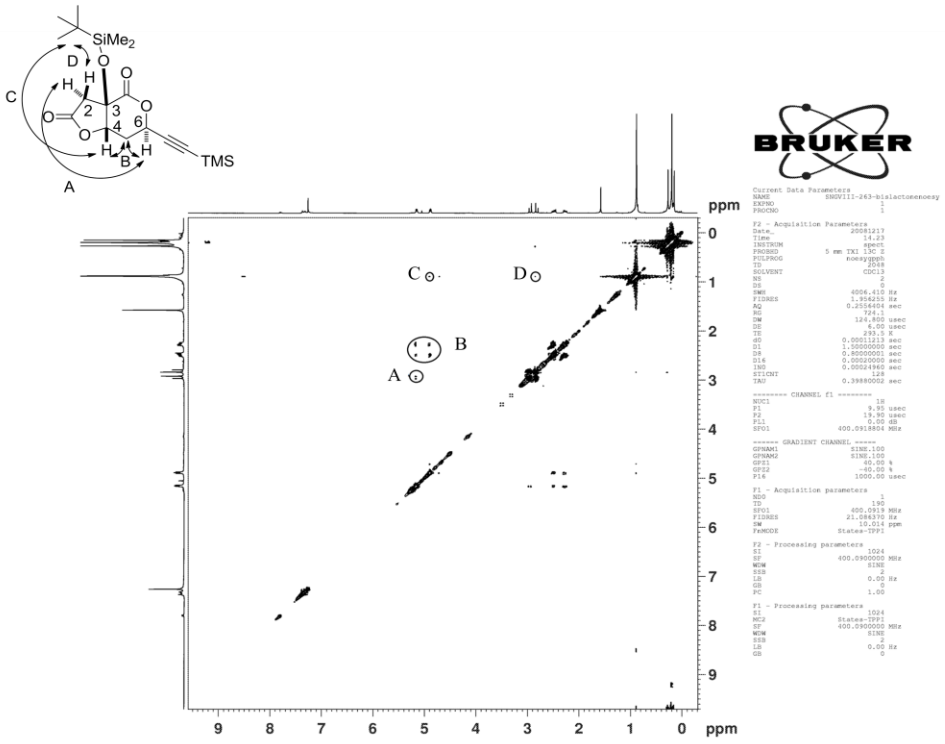
(3a*R*,6*R*,7a*S*)-3a-((*tert*-butyldimethylsilyl)oxy)-6-((trimethylsilyl)ethynyl)tetrahydro-2H-furo[3,2-c]pyran-2,4(6H)-dione (49): An oven-dried and cooled vial equipped with a magnetic stir bar was charged with diol **48** (15 mg, 0.0275 mmol) and toluene (1 mL). TsOH (cat.) was added, and the vial was sealed with a Teflon cap. The solution was heated to 80 °C in a sand bath for 1 h. After cooling to rt, the solvent was removed *in vacuo*, and the crude residue was purified via column chromatography, eluting with 10:90 to 20:80 EtOAc: hexanes. The title compound was obtained as a colorless oil (6.4 mg, 60%). Analytical data: $[\alpha]_D^{25.1}$ = +13.1 (*c* = 0.15, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.15 (dd, *J* = 7.2, 3.6 Hz, 1H), 4.89 (dd, *J* = 6.8, 4.8 Hz, 1H), 2.94 (d, *J* = 18.4 Hz, 1H), 2.81 (d, *J* = 18.0 Hz, 1H), 2.48 (ddd, *J* = 12.4, 7.6, 4.8 Hz, 1H), 2.26 (ddd, *J* = 10.4, 7.2, 3.6 Hz, 1H), 0.88 (s, 9H), 0.26 (s, 3H), 0.19 (s, 9H), 0.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 171.6, 169.1, 98.5, 95.1, 82.6, 76.3, 65.8, 42.0, 34.0, 25.5, 18.1, -0.5, -3.5, -3.7; **IR** (thin film, cm^{-1}) 3433, 3019, 1645, 1215, 771, 669; **TLC**(80:20 Hexanes:EtOAc): R_f = 0.50.

Spectral analysis (HMBC, NOESY) supported the stereochemical assignment shown for compound **49**: The NOESY spectrum shows a distinct nOe between the methine C-H at C6 and the *syn* methylene proton at C2 (interaction A), which suggests their orientation on the

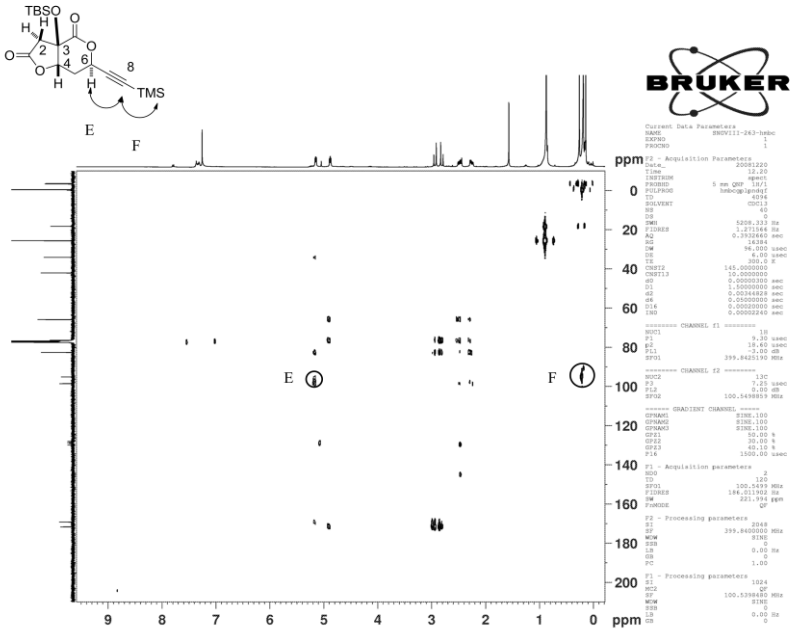
concave face of the bicycle. Additionally, both the C2 C–**H** proton on the convex face of the bicycle and the C4 methine C–**H** show an nOe with the *tert*-butyl group of the TBS ether, which suggests their mutual orientation on the convex face of the molecule (interactions C and D). The assignment of the C4 and C6 methine C–**H** protons was a result of the observation of a mutual correlation between the latter and the TMS methyl groups with the alkyne carbon indicated (interactions E and F).

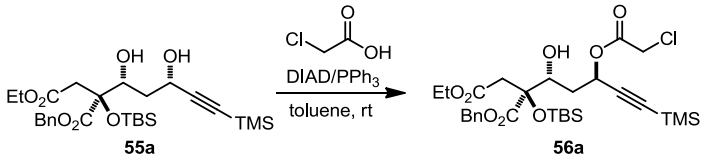
NOESY and HMBC SPECTRA:

NOESY:



HMBC:

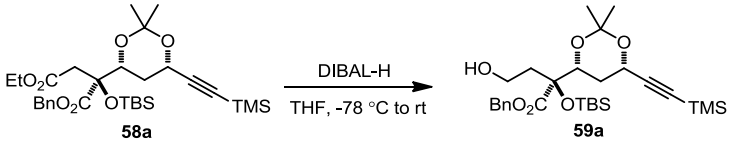




(S)-1-benzyl 4-ethyl 2-((tert-butyldimethylsilyl)oxy)-2-((1R,3R)-3-(2-chloroacetoxy)-1-hydroxy-5-(trimethylsilyl)pent-4-yn-1-yl)succinate (56a): An oven-dried and cooled 20-mL scintillation vial equipped with magnetic stir bar was charged with diol **55a** (37 mg, 0.068 mmol, 1.0 equiv), PPh_3 (55 mg, 0.211 mmol, 3.1 equiv), and chloroacetic acid (12 mg, 0.127 mmol, 1.9 equiv). The vial was purged with N_2, and toluene (2 mL) was added. DIAD (0.031 mL, 36 mg, 0.204 mmol, 3.0 equiv) was added dropwise, and the resulting solution was stirred at rt for 30 min, at which point TLC analysis indicated complete consumption of the starting material (R_f = 0.24, 80:20 hexanes:EtOAc). The reaction was loaded directly onto an SiO_2 plug and eluted with 90:10 hexanes:EtOAc to afford the desired chloroacetate (**56a**) as a colorless oil (27 mg, 65%). Analytical data**: ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35

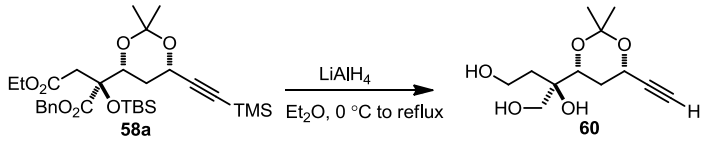
(br. s., 5H), 5.62 (d, *J* = 7.6 Hz, 1H), 5.21 (br. s., 2H), 4.05 (br. s., 4H), 3.84 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.92 (d, *J* = 15.6 Hz, 1H), 2.73 (d, *J* = 15.6 Hz, 1H), 2.44 (d, *J* = 7.2 Hz, 1H), 2.15 (dd, 23.6, 13.6 Hz, 1H), 1.82 (dd, *J* = 23.6, 11.6 Hz, 1H), 1.20 (t, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.16 (s, 9H), 0.16 (s, 3H; 2 coincident resonances), 0.10 (s, 3H); **TLC** (80:20 hexanes:EtOAc): R_f = 0.4.

III. Representative Reduction Reactions from Table 3-1



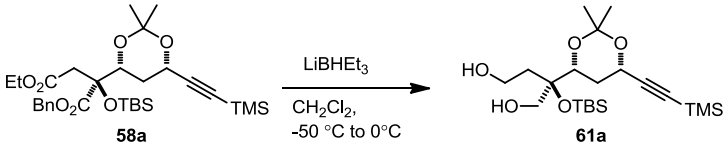
(S)-benzyl-2-((tert-butyldimethylsilyl)oxy)-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl) ethynyl)-1,3-dioxan-4-yl)-4-hydroxybutanoate (59a): An oven-dried and cooled 20-mL scintillation vial was charged with diester **58a** (95 mg, 0.164 mmol, 1.0 equiv) and THF (4 mL). The vial was cooled to -78 °C, and a solution of DIBAL-H (1.46 mL, 0.562 M in THF, 0.820 mmol, 5.0 equiv) was added dropwise. When the addition of DIBAL-H was complete, the reaction was maintained at -78 °C for 20 min then was allowed to warm to rt for 10 min. The reaction was quenched by the addition of saturated aqueous sodium potassium tartrate (3 mL) and was diluted with Et_2O (5 mL). The resulting biphasic mixture was stirred vigorously until clear layers were observed. Additional diethyl ether was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3x 5 mL), and combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a light yellow oil, which was purified via column chromatography, eluting with 70:30 hexanes: EtOAc , to afford the title compound as a colorless oil (74 mg, 84%). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.26 (br. s, 5H), 5.32 (d, *J* = 12.0 Hz,

1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 8.0 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.71 (t, *J* = 4.0 Hz, 2H), 2.11-1.45 (m, 4H), 1.34 (s, 3H), 1.18 (s, 3H), 0.92 (s, 9H), 0.22 (s, 3H), 0.19 (s, 3H), 0.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.5, 152.4, 135.6, 128.9, 128.4, 128.3, 104.0, 99.4, 89.3, 82.2, 81.3, 72.7, 67.0, 60.4, 42.3, 35.2, 29.5, 26.4, 19.2, 18.8, -0.2, -2.1, -2.5; **TLC**(80:20 hexanes:EtOAc): R_f = 0.12.



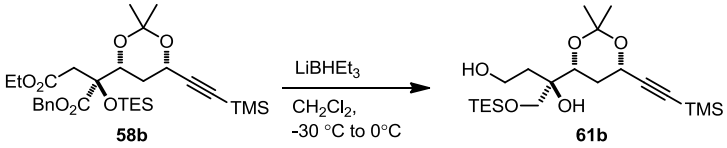
(R)-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)butane-1,2,4-triol (60): An oven-dried and cooled 20-mL scintillation vial was charged with diester **58a** (130 mg, 0.225 mmol, 1.0 equiv). The vial was purged with N_2, and diethyl ether (5 mL) was added. The resulting solution was cooled to 0 °C, and a solution of $LiAlH_4$ (1.0 M in Et_2O, 0.901 mL, 0.901 mmol, 4.0 equiv) was added dropwise. Once the addition of $LiAlH_4$ was complete, the vial was sealed with a Teflon cap, and the contents were heated to 35 °C. After 2 h at the same temperature, TLC analysis indicated complete consumption of the starting material (R_f = 0.30, 80:20 hexanes:EtOAc), and the reaction was quenched by the addition of 1 M HCl (3 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3x 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, and brine and dried with $MgSO_4$. Concentration *in vacuo* gave a crude oil, which was purified via column chromatography, eluting with 70:30 to 60:40 hexanes:EtOAc, to afford the triol as a colorless oil (52 mg, 73%). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.68 (d, *J* = 12.0 Hz, 1H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.87 (t, *J* = 4.0, 2H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.06 (s, 1H), 2.69-2.49 (br. s, 1H),

2.49 (s, 1H), 1.89-1.60 (m, 4H), 1.48 (s, 3H), 1.45 (s, 3H); **TLC**(70:30 hexanes:EtOAc): R_f = 0.09.



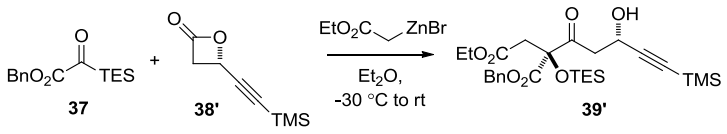
(R)-2-((tert-butyldimethylsilyl)oxy)-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)butane-1,4-diol (61a): A flame-dried and cooled 100-mL round-bottomed flask equipped with a magnetic stir bar was charged with diester **58a** (0.98 g, 1.7 mmol, 1.0 equiv). The flask was purged with N_2, and CH_2Cl_2 (40 mL) was added. The resulting solution was cooled to -50 °C in an acetone-dry ice bath. Lithium triethylborohydride (10. 2 mL, 1 M in THF, 10.2 mmol, 6.0 equiv) was added dropwise, and the reaction was allowed to warm slowly to rt over 1.5 h. Once TLC analysis indicated complete consumption of the starting material and monoalcohol **59a** (R_f = 0.53 and 0.20, 60:40 hexanes:EtOAc, respectively), the reaction was quenched by the addition of glacial HOAc (3 mL). MeOH (20 mL) was added, and the solvent was removed *in vacuo*. Additional MeOH (4x20 mL) was added, and the solvent was again removed *in vacuo*. The resulting crude semisolid was partitioned between EtOAc and saturated aqueous $NaHCO_3$, and the organic extracts were washed with $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a light yellow oil, which was purified via column chromatography, eluting with 80:20 to 70:30 petroleum ether:diethyl ether. The title compound was obtained as a colorless oil (506 mg, 70%). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.66 (d, *J* = 11.6 Hz, 1H), 3.93 (d, *J* = 11.6 Hz, 1H), 3.86-3.74 (m, 3H), 3.50 (d, *J* = 11.2 Hz, 1H), 3.25-2.75 (br. s, 1H), 1.87-1.68 (m, 4H), 1.45 (s, 6H), 0.86 (s, 9H), 0.16 (s, 3H), 0.16 (s, 9H, 2 coincident

resonances), 0.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 103.8, 99.6, 89.4, 78.2, 72.4, 64.9, 60.8, 57.9, 37.7, 31.1, 29.8, 26.0, 19.3, 18.7, -0.21, -1.99, -2.13; **TLC**(75:25 hexanes:EtOAc): R_f = 0.09.



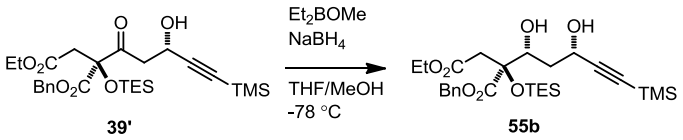
(R)-3-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-4-((triethylsilyl) oxy)butane-1,3-diol (61b): The title compound was obtained as a byproduct in reductions of diester **58b** (*vide supra*, Scheme 3-7, Table 3-2). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.67 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.99 (d, *J* = 8.0 Hz, 1H), 3.97-3.89 (m, 2H), 3.60 (d, *J* = 4.0 Hz, 2H), 3.20-2.92 (br. s, 1H), 2.92-2.60 (br. s, 1H), 2.00-1.52 (m, 4H), 1.44 (s, 6H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.61 (q, *J* = 8.0 Hz, 6H), 0.17 (s, 9H); **TLC**(80:20 hexanes:EtOAc): R_f = 0.14.

III. Steps in Longest Linear Sequence (Compound 39′ to Compound 130)



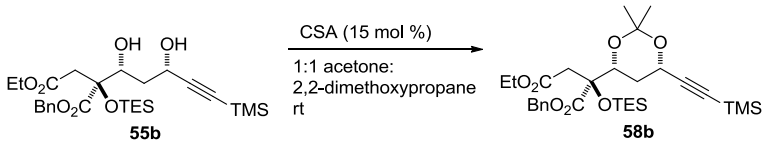
(S)-1-benzyl-4-ethyl-2-((S)-3-hydroxy-5-(trimethylsilyl)pent-4-ynoyl)-2-((triethylsilyl) oxy)succinate (39′): A solution of Reformatsky reagent (0.34 M, 150 mL) was prepared according to the standard procedure. The Reformatsky reagent solution (120 mL, 40.9 mmol, 2.3 equiv) was diluted with diethyl ether (150 mL), and the solution was cooled to -30 °C in an acetone/dry ice bath (bath temperature, monitored with a thermocouple probe). An oven-dried vial was charged with benzyl triethylsilyl glyoxylate **37** (4.95 g, 17.8 mmol, 1.0

equiv) and (S)-4-((trimethylsilyl)ethynyl)oxetan-2-one (4.8 g, 28.5 mmol, 1.6 equiv) **38′**. The vial was purged with N_2, and a solution of the silyl glyoxylate and β-lactone in diethyl ether (20 mL) was added dropwise to the Reformatsky reagent solution over 5 min via cannula transfer. Additional diethyl ether (5 mL) was used to rinse the vial. The flask was allowed to warm slowly in the acetone bath (generally over 30 min from -30 °C to 0 °C). Consumption of the silyl glyoxylate was generally observed by TLC analysis between -15 °C and -10 °C. Once the reaction had reached 0 °C, it was then warmed to room temperature for 30 min. Once the reaction was complete as indicated by TLC analysis, it was quenched with saturated ammonium chloride (75 mL) and was stirred until clear layers were observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x30 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (93.5:7.5 to 70:30 petroleum ether: diethyl ether) to give the desired product as a light yellow oil with > 25:1 diastereomeric ratio (6.57 g, 69%). Analytical data**:** $[\alpha]_D^{25.3}$ = -5.30 (*c* = 1.25, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.17 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.87 (dd, *J* = 6.5, 4.5 Hz, 1H), 4.09 (q, *J* = 7.5 Hz, 2H), 3.47 (d, *J* = 17 Hz, 1H), 3.36 (dd, *J* = 18.5, 2.5 Hz, 1H), 3.12 (dd, *J* = 18.5, 9.0 Hz, 1H), 2.91 (d, *J* = 17.0 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.56 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 208.8, 169.3, 168.5, 134.4, 128.7, 128.6, 128.5, 104.8, 89.3, 83.7, 68.1, 61.1, 58.8, 46.0, 42.5, 14.0, 6.7, 5.7, -0.2; **LRMS (ESI$^+$)** expected $[M+H]^+$: 535.3, observed: 535.3; **IR** (thin film, cm^{-1}) 3515, 2958, 2911, 2878, 2176, 1738, 1456, 1373, 1343, 1250, 1181, 844, 699; **TLC**(80:20 Hex:EtOAc): R_f = 0.42.

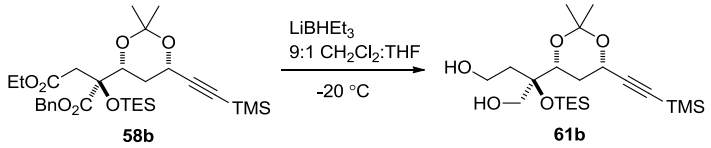


(S)-1-benzyl 4-ethyl 2-((1R,3S)-1,3-dihydroxy-5-(trimethylsilyl)pent-4-yn-1-yl)-2-((triethylsilyl)oxy)succinate (55b): A flame-dried and N_2-purged 500-mL round-bottomed flask was charged with ketone ***39′*** (6.0 g, 11.2 mmol, 1.0 equiv). Tetrahydrofuran (200 mL) and methanol (50 mL) were added. The solution was cooled to -78 °C (acetone/dry ice), and diethylmethoxyborane (1 M in tetrahydrofuran, 14.6 mL, 14.6 mmol) was added dropwise. After stirring for 45 minutes at -78 °C, sodium borohydride (1.27 g, 33.7 mmol, 3.0 equiv) was added in one portion and the reaction was maintained at the same temperature. Once TLC indicated complete consumption of the starting material (3.5 h), the reaction was quenched with acetic acid (9.0 mL). After warming to room temperature, the reaction was stirred for 1.5 h and was then concentrated *in vacuo*. Methanol (30 mL) was added, and the solution was again concentrated *in vacuo*; this procedure was repeated with four additional portions of methanol (30 mL). The residue was dissolved in ethyl acetate and saturated sodium bicarbonate, and the organic layer was washed with saturated sodium bicarbonate, water, and brine. The organic extracts were dried with magnesium sulfate and concentrated *in vacuo* to give a light yellow viscuous oil (5.7 g, 95%) that was used without additional purification. Analytical data**:** $[\alpha]_D^{25.2}$ = -1.74 (*c* = 1.25, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.33 (m, 5H), 5.20 (s, 2H), 4.60 (br. s., 1H), 4.10-3.99 (m, 3H), 3.05 (d, *J* = 6.0 Hz, 1H), 2.87 (d, *J* = 4.0 Hz, 1H), 2.83 (d, *J* = 9.0 Hz, 2H), 1.98 (dd, *J* = 13.5, 5.5 Hz, 1H), (dd, *J* = 10.5, 2.5 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.67-0.62 (m, 6H), 0.15 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.1, 169.9, 135.0, 128.6, 128.5, 128.4, 105.6, 89.7, 80.6, 75.3, 67.6, 62.1, 60.9, 41.2, 38.7, 14.0, 7.1, 6.4, -0.2; **LRMS (ESI$^+$)**

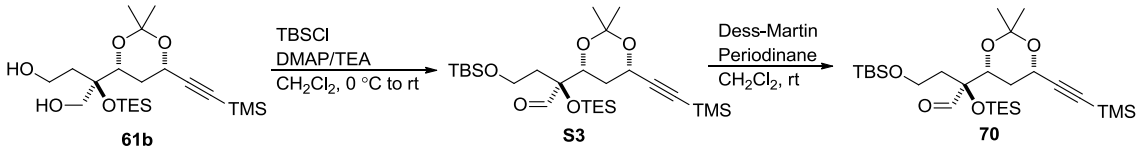
expected $[M+Na]^+$: 559.3, observed: 559.3; **IR** (thin film, cm^{-1}) 3470, 2957, 2876, 2172, 1740, 1185, 1022, 844, 734; **TLC**(80:20 Hex:EtOAc): R_f = 0.21.



(S)-1-benzyl-4-ethyl-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-2-((triethylsilyl)oxy) succinate (58b) A 500-mL round-bottomed flask was charged with diol **55b** (11.0 g, 20.6 mmol, 1.0 equiv), acetone (250 mL) and 2,2-dimethoxypropane (250 mL). CSA (0.716 g, 3.09 mmol, 0.15 equiv) was added, and the reaction was allowed to stir at room temperature for 16 h. The reaction was quenched by the addition of 0.5 mL of triethylamine and was concentrated *in vacuo*. The residue was purified via column chromatography (90:10 hexanes: ethyl acetate) to give the product as a white solid (8.6 g, 73%). Analytical data: $[\alpha]_D^{25.4}$ = -13.96 (*c* = 1.5, $CHCl_3$); melting point: 75-79 °C**; ^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35-7.33 (m, 5H), 5.30 (d, *J* = 12.5 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.62 (dd, *J* = 12.0, 2.5 Hz, 1H), 4.12-4.06 (m, 3H), 2.74 (d, *J* = 14.5 Hz, 1H), 2.65 (d, *J* = 14.0 Hz, 1H), 1.88-1.60 (m, 2H), 1.33 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.19 (s, 3H), 0.95 (t, *J* = 16.0 Hz, 9H), 0.74-0.65 (m, 6H), 0.17 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.6, 169.4, 135.6, 128.7, 128.4, 128.3, 103.7, 99.6, 89.4, 80.2, 72.9, 67.0, 60.7, 60.5, 41.9, 30.8, 29.5, 18.8, 14.0, 7.3, 6.7, -0.21; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 599.3, observed: 599.3; **IR** (thin film, cm^{-1}) 2956, 2875, 2181, 1739, 1457, 1379, 1251, 1163, 844, 734; **TLC**(80:20 Hex:EtOAc): R_f = 0.30.



(R)-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-2-((triethylsilyl) oxy)butane-1,4-diol (61b): A flame-dried and cooled 1L round-bottomed flask was charged with acetonide **58b** (5.0 g, 8.7 mmol, 1.0 equiv). The flask was purged with N_2, and CH_2Cl_2 (500 mL) was added. The solution was cooled to -30 °C, and lithium triethylborohydride (1M in THF, 57 mmol, 57 mL) was added dropwise over 15 min via syringe pump. The reaction temperature was maintained for 2 h, at which point the temperature was increased to -20 °C for 1 h. The reaction was quenched by the dropwise addition of HOAc (8 mL) and MeOH (30 mL). The resulting suspension was warmed to room temperature and concentrated *in vacuo*, keeping the bath temperature at or below 30 °C to avoid migration of the triethylsilyl group. The residue was redissolved in MeOH (30 mL) and concentrated *in vacuo* an additional four times. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate, and the organic extracts were washed successively with saturated sodium bicarbonate (x2), water, and brine. The combined organic extracts were dried with sodium sulfate and concentrated *in vacuo*. The resulting crude oil was purified via column chromatography, eluting with a gradient of 80:20 to 70:30 hexanes: ethyl acetate to give the desired diol as a white solid (2.1 g, 56%). Analytical data: $[\alpha]_D^{25.2}$ = -2.82 (*c* = 1.8, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.67 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.93 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.86-3.73 (m, 3H), 3.50 (dd, *J* = 11.0, 3.0 Hz, 1H), 2.83 (s, 1H), 2.65 (s, 1H), 1.98-1.70 (m, 4H), 1.46 (s, 6H), 0.95 (t, *J* = 3.5 Hz, 9H), 0.74-0.65 (dq, *J* = 16.0, 3.0 Hz 6H), 0.17 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 103.7, 99.6, 89.6, 78.0, 73.2, 65.6, 60.9, 58.3, 37.7, 31.3, 29.9, 19.2, 7.1, 6.8, -0.2; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 453.3, observed: 453.4; **IR** (thin film, cm^{-1}) 3389, 2956, 2876, 2183, 1739, 1460, 1380, 1250, 1161, 1055, 844, 733; **TLC**(75:25 Hex:EtOAc): R_f = 0.09.



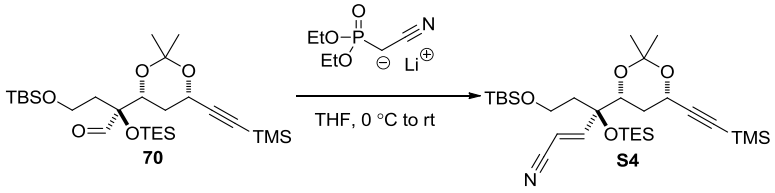
(S)-4-((tert-butyldimethylsilyl)oxy)-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-2-((triethylsilyl)oxy)butanal (**70):** A 100-mL oven dried and cooled round bottomed flask was charged with diol **61b** (0.840 g, 1.95 mmol, 1.0 equiv), which was dissolved in CH_2Cl_2 (60 mL). The solution was cooled to 0 °C, and triethylamine (0.540 mL, 3.9 mmol, 2.0 equiv), *tert*-butyldimethylsilyl chloride (0.339 g, 2.25 mmol, 1.15 equiv), and DMAP (0.071 g, 0.585 mmol, 0.3 equiv) were added successively. The reaction was allowed to warm slowly to room temperature over 1 h. Once TLC analysis indicated complete consumption of the starting material (5 h), the reaction was quenched by the addition of 5 mL of saturated aqueous sodium bicarbonate. The organic layer was washed with saturated $NaHCO_3$, water, and brine and was then dried with sodium sulfate. After concentration *in vacuo*, the resulting crude oil was used without further purification:

The crude oil was dissolved in dry CH_2Cl_2 (30 mL) in an oven-dried 250-mL round-bottomed flask, and Dess-Martin Periodinane (1.32 g, 3.12 mmol, 1.6 equiv) was added in one portion at room temperature. The reaction was stirred at the same temperature under an N_2 atmosphere. Once TLC analysis indicated complete consumption of the monoalcohol (1.5 h), the reaction was diluted with diethyl ether (30 mL). Saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium thiosulfate (20 mL) were added, and biphasic mixture was stirred vigorously for 15 minutes. After partitioning the layers, the aqueous layer was extracted with diethyl ether (3x10 mL), and the combined organic extracts were washed with water and brine and dried with sodium sulfate. The combined extracts

were concentrated *in vacuo* to give a crude oil, which was purified via column chromatography (95:5 hexanes: ethyl acetate) to give the desired product **70** as a colorless oil (0.880 g, 83% over two steps).

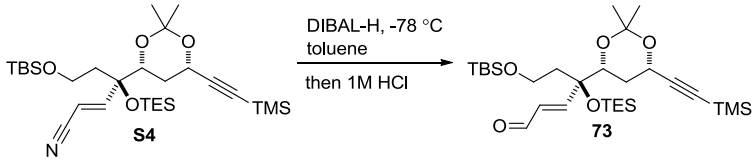
Mono alcohol S3: Analytical data: $[\alpha]_D^{25.6}$ = -7.09 (*c* = 2.15, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.66 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.90 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.88-3.80 (m, 1H), 3.75-3.65 (m, 2H), 3.48-3.39 (m, 2H), 1.87-1.64 (m, 4H), 1.45 (s, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.71-0.56 (m, 6H), 0.17 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 104.1, 99.4, 89.1, 78.3, 72.1, 64.7, 60.9, 58.7, 37.4, 31.0, 29.9, 25.8, 19.3, 18.1, 7.2, 6.8, -0.2, -5.6; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 567.3, observed: 567.5; **IR** (thin film, cm^{-1}) 3492, 2955, 2877, 2360, 2183, 1463, 1414, 1251, 1107, 841, 736; **TLC**(85:15 Hex:EtOAc): R_f = 0.54.

Aldehyde 70: Analytical data**:** $[\alpha]_D^{25.2}$ = -15.01 (*c* = 1.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 4.68 (dd, *J* = 12.0, 2.8 Hz, 1H), 4.13 (dd, *J* = 12.0, 2.8 Hz, 1H), 3.74 (ddd, *J* = 12.0, 4.0, 2.8 Hz, 1H), 3.62 (ddd, *J* = 12.0, 4.0, 2.8 Hz, 1H), 1.90-1.65 (m, 4H), 1.40 (s, 3H), 1.39 (s, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.86 (s, 9H), 0.81-0.66 (m, 6H), 0.17 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.2, 103.9, 99.5, 89.4, 83.7, 72.3, 60.7, 57.8, 38.7, 30.9, 29.6, 25.8, 19.1, 18.1, 7.2, 6.9, -0.2, -5.5, -5.6; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 565.3, observed: 565.3; **IR** (thin film, cm^{-1}) 2955, 2876, 2360, 2342, 1736, 1462, 1415, 1380, 1251, 1110, 842, 738; **TLC**(85:15 Hex:EtOAc): R_f = 0.67.



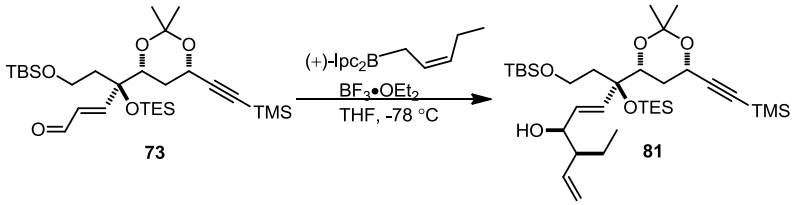
(R,E)-6-((tert-butyldimethylsilyl)oxy)-4-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-4-((triethylsilyl)oxy)hex-2-enenitrile (S4): A flame-dried and cooled 25-mL round-bottomed flask was charged with the Horner-Wadsworth-Emmons Wittig reagent (0.320 g, 1.81 mmol, 1.05 equiv). THF (11.0 mL) was added, and the solution was cooled to 0 °C. *n*-Butyllithium (1.2 mL, 1.5 M in hexanes, 1.05 equiv) was added dropwise, and the resulting orange solution was stirred for 1h at the same temperature. A second flame-dried and cooled 100-mL round-bottomed flask was charged with the aldehyde (0.917 g, 1.69 mmol, 1.0 equiv), and THF (25 mL) was added. The aldehyde solution was cooled to 0 °C, and the Wittig solution was added via cannula. After the addition was complete, the reaction was warmed to room temperature for 30 minutes, at which point the starting material had been completely consumed as indicated by TLC analysis. The reaction was quenched by the addition of saturated ammonium chloride (0.3 mL), and the resulting suspension was concentrated to approximately 3 mL *in vacuo*. The remaining suspension was loaded directly onto a short silica plug and eluted with 95:5 hexanes: ethyl acetate to give the desired nitrile (0.920 g, 96%) with greater than 25:1 diastereoselectivity for the (*E*)-isomer. Analytical data**:** $[\alpha]_D^{25.7}$ = +2.87 (*c* = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.81 (d, *J* = 16.0 Hz, 1H), 5.61 (d, *J* = 16.0 Hz, 1H), 4.60 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.70 (dd, *J* = 10.8, 2 Hz, 1H), 2.14 (ddd, *J* = 21.2, 14.4, 7.2 Hz, 1H), 1.81 (ddd, *J* = 19.6, 13.6, 6.8 Hz, 1H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.55-1.46 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 0.98 (t, *J* = 7.6 Hz, 9H), 0.89 (s, 9H), 0.65 (q, *J* = 8.0 Hz, 6H), 0.18 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.8, 117.6, 103.2, 99.5, 99.2, 89.8, 79.1, 74.2, 60.6, 58.3, 40.3, 32.0, 29.8, 25.9, 19.1, 18.2, 7.1, 6.7, -0.2, -5.3, -5.4; **LRMS**

(ESI$^+$) expected $[M+Na]^+$: 588.3, observed: 588.5; **IR** (thin film, cm^{-1}) 2956, 2878, 2224, 1461, 1379, 1251, 1106, 840, 740; **TLC**(90:10 Hex:EtOAc): R_f = 0.46.



(R,E)-6-((tert-butyldimethylsilyl)oxy)-4-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-4-((triethylsilyl)oxy)hex-2-enal (73): A 50-mL oven dried and cooled round-bottomed flask was charged with the nitrile **S4** (0.920 g, 1.63 mmol, 1.0 equiv), and the flask was purged with N_2. Dry toluene (20 mL) was added, and the resulting solution was cooled to -78 °C in an acetone/dry ice bath. A solution of DIBAL-H (0.56 M in toluene, 4.9 mL, 1.7 equiv) was added dropwise, and the reaction was stirred at the same temperature for 1.5 h. Methanol (2.5 mL) was added at -78 °C, and the solution was warmed to 0 °C. Ice cold 1M HCl (20 mL) was added, and the biphasic mixture was stirred vigorously for 10 min at room temperature. Diethyl ether (20 mL) was added and the layers were separated. The aqueous layer was extracted with additional ether (3x5 mL), and the combined organic extracts were washed with saturated sodium bicarbonate, water, and brine and dried with magnesium sulfate. The dried extracts were concentrated *in vacuo* to give a light yellow oil, which was purified via column chromatography (93.5:7.5 hexanes: ethyl acetate) to give enal **73** as a colorless oil (0.745 g, 81%). Analytical data**:** $[\alpha]_D^{25.4}$ = +6.19 (*c* = 0.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.60 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 15.6 Hz, 1H), 6.30 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.62 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.77 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.76-3.52 (m, 2H), 2.20-2.13 (m, 1H), 1.92-1.85 (m, 1H), 1.76 (d, *J* = 13.2 Hz, 1H), 1.53 (dd, *J* = 24.4, 12.0 Hz, 1H), 1.44 (s, 6H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.86 (s, 9H),

0.65 (q, *J* = 8.0 Hz, 6H), 0.16 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.6, 159.5, 131.7, 103.5, 99.5, 89.7, 79.0, 60.8, 58.6, 40.7, 32.1, 29.9, 25.9, 19.2, 18.2, 7.1, 6.9, -0.2, -5.3, -5.4; **LRMS (ESI$^+$)** expected $[M+Cs]^+$: 701.2, observed: 701.3; **IR** (thin film, cm^{-1}) 2956, 2878, 1694, 1462, 1379, 1251,1105, 842; **TLC**(90:10 Hex:EtOAc): R_f = 0.33.



(3S,4S,7R,E)-9-((tert-butyldimethylsilyl)oxy)-7-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)-3-ethyl-7-((triethylsilyl)oxy)nona-1,5-dien-4-ol (81):

Preparation of (+)-Ipc_2BH:

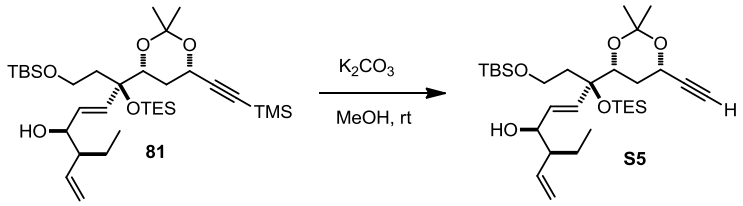
A flame-dried and cooled 200-mL round-bottomed flask equipped with a magnetic stir bar was charged with (–)-α-pinene (5 mL, 4.28 g, 31.4 mmol, 2.4 equiv) and THF (4 mL). The flask was purged with N_2 and was placed into a room temperature water bath. Borane•DMS (2M in THF, 6.5 mL, 0.981 g, 13.08 mmol, 1.0 equiv) was added dropwise with vigorous stirring over 2 min. Stirring of the reaction was ceased, and the stir bar was removed. The flask was again purged with N_2, and the resulting solution was allowed to sit at room temperature for 16 h. Crystals were observed on the side of the flask after 1 h at room temperature. The solvent was removed from the flask via cannula, and the remaining solid was washed with dry hexanes (2x20 mL), which was removed via cannula transfer. The flask was evacuated to remove residual solvent, and the resulting white solid was

removed to a dry box freezer. The reagent was able to be stored without degradation for months when prepared and stored in this manner (2.7 g, 73%).

(+)-Ipc_2BOMe was prepared *in situ* according to the following:

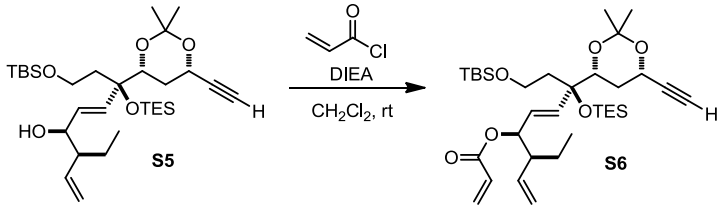
An oven-dried and cooled 50-mL round-bottomed flask was charged with Ipc_2BH (2.95 g, 10.32 mmol, 2.5 equiv) under a nitrogen atmosphere and dry THF (30 mL). Dry MeOH (0.417 mL, 10.32 mmol, 2.5 equiv) was added dropwise, and the resulting solution was stirred at room temperature for 4 h. A second 250-mL oven-dried round-bottomed flask was charged with potassium *tert*-butoxide (0.926 g, 8.26 mmol, 2.0 equiv) under a nitrogen atmosphere. Dry THF (45 mL) and *cis*-2-pentene (2.68 mL, 24.8 mmol, 6.0 equiv) were added, and the solution was cooled to -50 °C in an acetone/dry ice bath. ^{n}Butyllithium (1.5 M, 5.5 mL, 2.0 equiv) was added dropwise, and the resulting orange solution was stirred at the same temperature for 5 minutes before cooling to -78 °C. The solution of (+)-Ipc_2BOMe was added dropwise via cannula transfer, and the resulting colorless solution was stirred at -78°C for 20 minutes. BF_3•OEt_2 (1.02 mL, 8.26 mmol, 2.0 equiv) was added, followed by a solution of the aldehyde (2.35 g, 4.13 mmol, 1.0 equiv) in dry THF (10 mL + 5 mL rinse). The bath temperature was maintained at -78 °C until complete consumption of the starting material was indicated by TLC analysis (2 h). The reaction was quenched by the dropwise addition of 3M NaOH (6.0 mL) and 30% H_2O_2 (3.2 mL). After warming to room temperature, the suspension was refluxed for 1 h. The cooled biphasic mixture was partitioned between ether and water, and the combined ethereal extracts were washed with water and brine and dried with magnesium sulfate. The organic extracts were concentrated *in vacuo* to give a crude oil, which was purified via flash chromatography (93.5:7.5 to 90:10 petroleum ether: ether) to give the desired product as a viscous colorless oil (2.23 g, 85%).

Analytical data**:** $[\alpha]_D^{25.2}$ = +1.79 (*c* = 0.50, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.73 (dd, *J* = 16.0, 5.5 Hz, 1H), 5.66 (dd, *J* = 15.5, 10.5 Hz, 1H), 5.55 (ddd, *J* = 17.5, 9.5, 6.0 Hz, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.13 (t, *J* = 6.0 Hz, 1H), 3.66-3.61 (m, 3H), 1.94-1.91 (m, 2H), 1.59-1.42 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 9H), 0.89 (s, 9H), 0.63 (q, *J* = 7.5 Hz, 6H), 0.17 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 132.8, 130.6, 118.0, 104.1, 99.1, 89.1, 78.2, 74.1, 74.0, 60.9, 59.4, 52.7, 40.0, 31.9, 29.9, 26.0, 23.3, 19.2, 18.3, 11.9, 7.2, 6.9, -0.2, -5.2, -5.3; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 661.4, observed:661.4; **IR** (thin film, cm^{-1}) 3465, 2956, 2877, 2183, 1461, 1378, 1251, 1090, 842; **TLC**(90:10 Hex:EtOAc): R_f = 0.30.



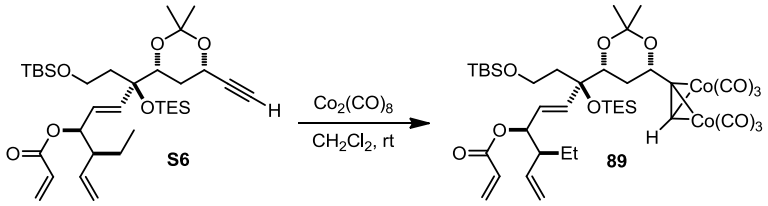
(3S,4S,7R,E)-9-((tert-butyldimethylsilyl)oxy)-3-ethyl-7-((4R,6S)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)-7-((triethylsilyl)oxy)nona-1,5-dien-4-ol (S5): Allylic alcohol **81** (2.2 g, 3.46 mmol, 1.0 equiv) was dissolved in methanol (20 mL), and potassium carbonate (0.2 g, 1.45 mmol, 0.42 equiv) was added at room temperature. Once the starting material was completely consumed as indicated by TLC analysis (R_f = 0.30, 90:10 Hex:EtOAc; 1 h), the suspension was loaded directly onto a short silica plug and eluted with 80:20 hexanes:ethyl acetate to give the crude alkyne. Analytical data**:** $[\alpha]_D^{25.3}$ = +6.16 (*c* = 1.70, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.72 (dd, *J* = 16.0, 5.5 Hz, 1H), 5.65 (d, *J* = 14.0 Hz, 1H), 5.55 (dd, *J* = 9.5, 7.5 Hz, 1H), 5.17 (d, *J* = 15.0 Hz, 1H), 5.11 (d, *J* = 17.0 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.13 (br. s., 1H), 3.68-3.63 (m, 3H), 2.46 (s, 1H), 2.14-2.12 (m, 1H), 1.94-1.91

(m, 6H), 1.43 (s, 3H), 1.41 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 9H), 0.89 (s, 9H), 0.63 (q, *J* = 7.5 Hz, 6H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 132.7, 130.7, 118.1, 99.2, 82.7, 78.1, 73.9, 73.8, 72.7, 60.3, 59.4, 52.7, 40.1, 31.6, 29.9, 26.0, 23.3, 19.2, 18.3, 11.9, 7.2, 6.8, -5.2, -5.3; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 589.4, observed: 589.4; **IR** (thin film, cm^{-1}) 3433, 3032, 2958, 2359, 2253, 1637, 908, 725, 650, 452; **TLC**(75:25 Hex:EtOAc): R_f = 0.39.



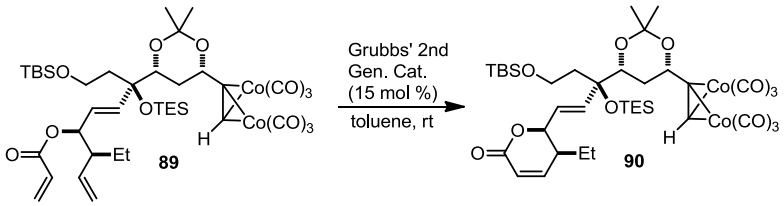
(3S,4S,7R,E)-9-((tert-butyldimethylsilyl)oxy)-3-ethyl-7-((4R,6S)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)-7-((triethylsilyl)oxy)nona-1,5-dien-4-yl acrylate (S6): A flame-dried and cooled 100-mL round-bottomed flask equipped with a magnetic stir bar was charged with the crude alkyne (1.95 g, 3.46 mmol, 1.0 equiv) and dry CH_2Cl_2 (40 mL), and the solution was cooled to 0 °C. Hünig's base (1.82 mL, 10.73 mmol, 3.1 equiv) and acryloyl chloride (0.846 mL, 10.37 mmol, 3.0 equiv) were added dropwise. After maintaining the solution at 0 °C for 1.5, TLC analysis indicated complete consumption of the starting material (R_f = 0.39, 75:25 Hex:EtOAc). The reaction was quenched by the addition of saturated sodium bicarbonate (10.0 mL), and the organic layer was washed with additional saturated sodium bicarbonate (3x 10.0 mL), water, and brine and was dried with magnesium sulfate. Concentration *in vacuo* yielded a colorless oil (2.14 g), which was used without additional purification. Analytical data: $[\alpha]_D^{25.0}$ = +24.87 (*c* = 0.21, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.40 (d, *J* = 17.6 Hz, 1H), 6.12 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.81 (d, *J* = 13.0, Hz, 1H), 5.70-5.52

(m, 3H), 5.32 (t, *J* = 7.5 Hz, 1H), 5.14 (d, *J* = 12.5 Hz, 1H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 3.66-3.59 (m, 3H), 2.45 (s, 1H), 2.32-2.19 (m, 1H), 1.99-1.80 (m, 2H), 1.77-1.61 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H), 1.35-1.15 (m, 2H), 0.94 (t, *J* = 9.5 Hz, 9H), 0.88 (s, 9H), 0.60 (q, *J* = 7.6 Hz, 6H), 0.03 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2, 137.4, 135.2, 130.5, 128.7, 126.7, 117.6, 99.2, 82.7, 778.0, 76.2, 73.8, 72.6, 60.3, 59.3, 49.8, 40.0, 31.2, 29.9, 26.0, 23.2, 19.2, 18.3, 11.5, 7.2, 6., -5.2, -5.3; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 643.4, observed: 643.3; **IR** (thin film, cm^{-1}) 3426, 2956, 2877, 2359, 1798, 1725, 1634, 1402, 1097, 981, 836, 630; **TLC**(80:20 Hex:EtOAc): R_f = 0.63.



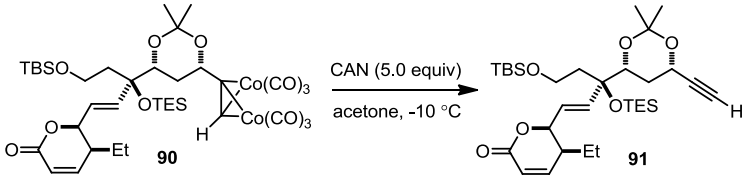
Protected Alkyne 89: The crude acrylate **S6** (2.14 g, 3.46 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (40 mL) under an atmosphere of nitrogen, and dicobalt octacarbonyl (1.18 g, 3.46 mmol, 1.0 equiv) was added. The reaction was stirred at room temperature for 1.5 h, at which point TLC analysis indicated complete consumption of the starting material (R_f = 0.63, 80:20 Hex:EtOAc). The reaction was concentrated *in vacuo*, and the crude material was purified via flash chromatography (95:5 petroleum ether: ether) to give the desired product as a dark red oil (2.7 g, 89% over 3 steps). Analytical data**:** $[\alpha]_D^{24.2}$ = -153.87 (*c* = 0.46, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.38 (d, *J* = 17.2 Hz, 1H), 6.10 (dd, *J* = 28.0, 10.4 Hz, 1H), 5.96 (s, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 5.74-5.54 (m, 3H), 5.36 (t, *J* = 5.2 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 5.04 (d, *J* = 17.2 Hz, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 3.78 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.68-3.63 (m, 2H), 2.27-2.20 (m, 1H), 1.95-1.90 (m, 2H), 1.82 (d, *J* = 12.4 Hz, 1H),

1.49-1.32 (m, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.63-0.56 (m, 6H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 199.7, 165.1, 137.5, 134.6, 130.5, 128.7, 126.3, 117.3, 99.2, 77.9, 75.9, 74.0, 70.4, 69.6, 59.4, 49.8, 40.1, 34.0, 29.5, 26.0, 22.9, 19.8, 18.4, 11.6 7.2, 6.8, 6.7, -5.2, -5.3; **LRMS (ESI$^+$)** expected $[M+Cs]^+$: 1039.1, observed:1039.0; **IR** (thin film, cm^{-1}) 2956, 2929, 2877, 2857, 2095, 2054, 2030, 1726, 1462, 1404, 1190, 1098, 836; **TLC**(80:20 Hex:EtOAc): R_f = 0.71.



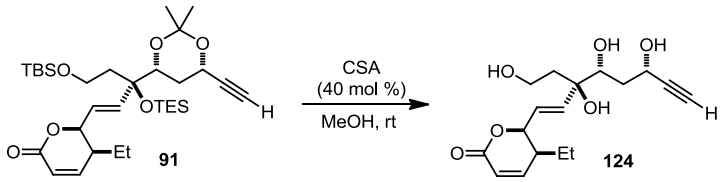
Dihydropyrone 89: A 250-mL flame-dried and cooled round-bottomed flask was charged with acrylate **89** (0.530 g, 0.543 mmol, 1.0 equiv). Under a nitrogen atmosphere, dry toluene (125 mL) and Grubbs' Second Generation catalyst (0.092 g, 0.122 mmol, 0.15 equiv) were added, and the reaction was stirred under nitrogen for 16 h at room temperature. The solvent was removed *in vacuo*, and the resulting crude oil was purified via column chromatography (90:10 to 80:20 hexanes:ethyl acetate) to give the dihydropyrone as a dark red oil (0.340 g, 66%). Analytical data: $[\alpha]_D^{24.7}$ = -29.53 (*c* = 2.55, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.93 (dd, *J* = 9.5, 5.0 Hz, 1H), 6.04 (d, *J* = 9.5 Hz, 1H), 5.98 (s, 1H), 5.93 (d, *J* = 16.0 Hz, 1H), 5.74 (dd, *J* = 15.5, 5.5 Hz, 1H), 4.99 (t, *J* = 4.5 Hz, 1H), 4.87 (d, *J* = 11.5 Hz, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.66 (t, *J* = 8.0 Hz, 2H), 2.43-2.34 (m, 1H), 2.07-1.82 (m, 3H), 1.68-1.56 (m, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.95 (t, *J* = 7.0 Hz, 9H), 0.89 (s, 9H), 0.63 (q, *J* = 7.5 Hz 6H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 199, 6, 164.0, 149.8, 135.7, 124.6, 120.9, 99.4, 97.0, 80.1, 78.1, 74.4, 40.6, 69.6, 59.3, 40.5, 39.4,

34.0, 29.5, 25.9, 21.6, 19.7, 18.3, 11.0, 7.2, 6.8, -5.2, -5.3; **LRMS (ESI$^+$)** expected $[M+Cs]^+$: 1011.0, observed:1011.0; **IR** (thin film, cm^{-1}) 2928, 2856, 2360, 2095, 2054, 2029, 1732, 1462, 1379, 1254, 1099, 835, 776; **TLC**(80:20 Hex:EtOAc): R_f = 0.48.

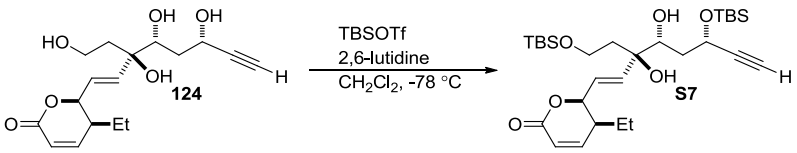


(5S,6S)-6-((R,E)-5-((tert-butyldimethylsilyl)oxy)-3-((4R,6S)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)-3-((triethylsilyl)oxy)pent-1-en-1-yl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (91): A 50-mL round-bottomed flask was charged with **90** (0.340 g, 0.400 mmol, 1.0 equiv) and acetone (20 mL). The flask was cooled to -10 °C (acetone-ice), and ceric ammonium nitrate (0.988 g, 1.8 mmol, 4.5 equiv) was added in small portions. The reaction was stirred at -10 °C for 45 minutes, at which time TLC analysis indicated complete consumption of the starting material. The reaction was poured into saturated aqueous sodium bicarbonate (20 mL) and was extracted with diethyl ether (3x 20 mL). The combined organic extracts were washed with saturated bicarbonate, water, and brine and were dried with magnesium sulfate. Removal of the solvent *in vacuo* afforded a light yellow oil (220 mg, 93%), which was used without further purification. Analytical data: $[\alpha]_D^{25.3}$ = -57.60 (*c* = 0.49, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 10.0, 5.5 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 5.76 (dd, *J* = 15.5, 5.5 Hz, 1H), 5.03 (t, *J* = 5.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.63 (t, *J* = 8.0 Hz, 2H), 2.46 (s, 1H), 2.42-2.41 (m, 1H), 1.76 (d, *J* = 13.0 Hz, 1H), 1.60-1.41 (m, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.96 (t, *J* = 8.0 Hz, 3H); 2 coincident resonances, 0.95 (t, *J* = 7.0 Hz, 9H), 0.88 (s, 9H), 0.64 (dq, *J* = 8.0, 4.0 Hz, 6H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.0, 149.9, 135.2, 124.8, 120.8, 103.8, 99.2,

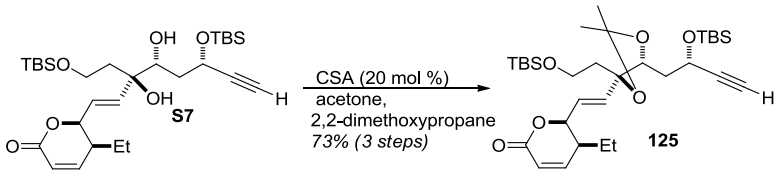
89.2, 80.0, 78.2, 74.2, 60.7, 59.2, 39.7, 39.6, 32.0, 29.9, 25.9, 21.5, 19.2, 18.2, 11.0, 7.2, 6.8, -0.2, -5.3, -5.4; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 615.4, observed: 615.4; **IR** (thin film, cm^{-1}) 3420, 3029, 2874, 2359, 1645, 1384, 1112, 821, 581; **TLC**(75:25 Hex:EtOAc): R_f = 0.32.



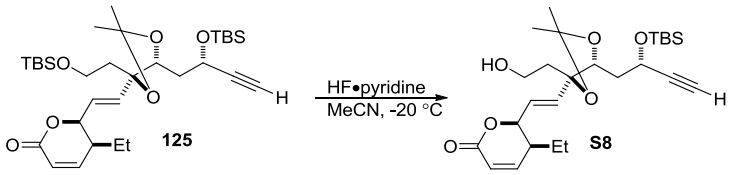
(5S,6S)-5-ethyl-6-((3R,4R,6S,E)-3,4,6-trihydroxy-3-(2-hydroxyethyl)oct-1-en-7-yn-1-yl)-5,6-dihydro-2H-pyran-2-one (124): A 20-mL scintillation vial was charged with alkyne **91** (150 mg, 0.253 mmol, 1.0 equiv) and methanol (5 mL). CSA (24 mg, 0.101 mmol, 0.4 equiv) was added, and the reaction was allowed to stir at room temperature for 1 h. The reaction was quenched with triethylamine (0.050 mL) and was concentrated in vacuo. The crude material was pushed through a short silica plug (95:5 to 92.5:7.5 CH_2Cl_2: MeOH, SiO_2 deactivated with TEA) to give the crude tetraol as a yellow oil, which was used without further purification. Analytical data: $[\alpha]_D^{25.4}$ = +78.3 (*c* = 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.99 (dd, *J*= 5.5, 10.0 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 6.00 (dd, *J* = 5.0, 15.5 Hz, 1H), 5.95 (d, *J* = 16.0 Hz, 1H), 5.09 (t, *J* = 4.5 Hz, 1H), 4.62 (br. s., 1H), 4.34 (br. s., 1H), 3.87 (br. s., 2H), 3.75 (d, *J* = 9.5 Hz, 1H), 3.65 (br. s., 1H), 3.00 (br. s., 1H), 2.50 (d, *J* = 1.5 Hz, 1H), 2.50-2.46 (m, 1H), 2.12-1.42 (m, 6H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 164.4, 150.4, 135.4, 126.0, 120.6, 84.1, 80.3, 77.9, 76.3, 73.2, 61.8, 59.7, 39.2, 38.2, 35.9, 29.7, 21.5, 11.0; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 347.2, observed: 347.2; **IR** (thin film, cm^{-1}) 3433, 3019, 2400, 1645, 1521, 1215, 928, 768, 669; **TLC**(90:10 CH_2Cl_2:MeOH): R_f = 0.37.



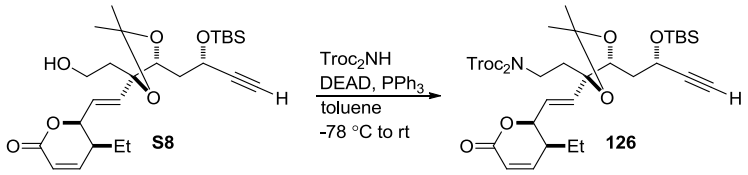
(5S,6S)-6-((3R,4R,6S,E)-6-((tert-butyldimethylsilyl)oxy)-3-(2-((tert-butyldimethylsilyl) oxy)ethyl)-3,4-dihydroxyoct-1-en-7-yn-1-yl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (S7): An oven-dried 20-mL scintillation vial was charged with crude tetraol **124** (82 mg, 0.218 mmol, 1.0 equiv) and CH_2Cl_2 (6.0 mL). The solution was cooled to -78 °C in an acetone-dry ice bath, and 2,6-lutidine (0.060 mL, 54mg, 0.501 mmol, 2.3 equiv) and TBSOTf (0.105 mL, 121 mg, 0.458 mmol, 2.1 equiv) were added successively. The reaction was maintained at -78 °C for 10 min, at which point TLC indicated complete consumption of the starting material and clean formation of the desired diol. The reaction was quenched by the addition of MeOH (0.100 mL) and was warmed to room temperature. After diluting with diethyl ether (20 mL), the solution was washed with 1 M HCl (3x5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL) and was dried with sodium sulfate. Concentration *in vacuo* gave a light yellow oil (110 mg), which was used without additional purification. Analytical data: $[\alpha]_D^{25.6}$ = +41.2 (*c* = 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.89 (dd, *J*= 10.0, 4.8 Hz, 1H), 6.04-5.88 (m, 3H), 5.03 (t, *J* = 4.4 Hz, 1H), 4.55 (dd, *J* = 13.6, 1.6 Hz, 1H), 4.53 (br. s. 1H), 3.83 (t, *J* = 3.6 Hz, 2H), 3.66 (d, *J* = 9.2 Hz, 1H), 2.48-2.42 (m, 1H), 2.40 (d, *J* = 2.0 Hz, 1H), 2.01-1.36 (m, 6H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.8, 149.5, 136.3, 125.4, 120.9, 84.6, 80.6, 80.0, 77.4, 75.8, 73.0, 62.9, 60.8, 39.4, 36.5, 25.7, 25.7 (2 coincident resonances), 21.6, 18.0, 17.9, 11.0, -4.5, -5.2, -5.7, -5.8; **LRMS (ESI$^+$)** expected $[M+\underline{Na}]^+$: 575.3, observed: 575.3; **IR** (thin film, cm^{-1}): 3433, 3019, 2930, 2359, 1646, 1472, 1212, 983, 769, 668; **TLC**(90:10 CH_2Cl_2:MeOH): R_f = 0.79.



(5S,6S)-6-((E)-2-((4R,5S)-5-((S)-2-((tert-butyldimethylsilyl)oxy)but-3-yn-1-yl)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (125): A 20-mL scintillation vial was charged with crude diol **S7** (110 mg, 0.200 mmol, 1.0 equiv). Dry acetone (6.0 mL) and 2,2-dimethoxypropane (6.0 mL) were added, followed by CSA (10.0 mg, 0.040 mmol, 0.22 equiv). The reaction was allowed to stir at room temperature for 1.5 h, at which point TLC analysis indicated complete consumption of the diol (R_f = 0.45, 60:40 hexanes:EtOAc). The reaction was quenched with TEA (4 drops) and was concentrated *in vacuo*. The resulting crude oil was purified via flash chromatography, eluting with 80:20 hexanes: ethyl acetate to give the desired product in 73% yield over 3 steps (109 mg) as a colorless oil. Analytical data: $[\alpha]_D^{24.3}$ = +43.9 (*c* = 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.94 (dd, *J*= 9.6, 5.6 Hz, 1H), 6.03 (d, *J* = 10.0 Hz, 1H), 5.90-5.72 (br. s., 2H), 4.98 (t, *J* = 3.6 Hz, 1H), 4.50 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.87 (d, *J* = 8.8 Hz, 1H), 3.75-3.56 (m, 2H), 2.44-2.23 (m, 1H), 2.44 (s, 1H), 2.00-1.31 (m, 6H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.01 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.6, 149.5, 134.3, 124.5, 121.0, 108.1, 108.0, 84.4, 82.8, 80.4, 79.6, 73.2, 61.3, 59.4, 39.3, 37.5, 37.2, 28.3, 26.3, 25.9, 25.7, 21.6, 18.3, 18.1, 10.9, -4.6, -5.0, -5.3; **LRMS (ESI$^+$)** expected $[M+\underline{Na}]^+$: 615.4, observed: 615.3; **IR** (thin film, cm^{-1}): 3019, 1521, 1215, 930, 758, 669, 521, 509; **TLC**(97.5:2.5 CH_2Cl_2:MeOH): R_f = 0.72.

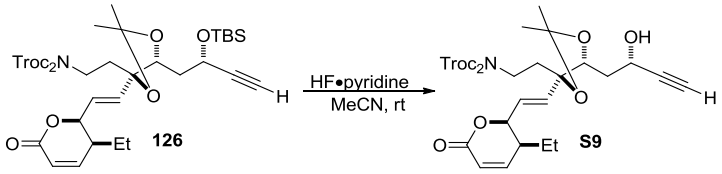


(5S,6S)-6-((E)-2-((4R,5S)-5-((S)-2-((tert-butyldimethylsilyl)oxy)but-3-yn-1-yl)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (S8): A plastic scintillation vial was charged with compound **125** (105 mg, 0.178 mmol, 1.0 equiv) and MeCN (4.0 mL). The solution was cooled to -20 °C in an acetone-ice bath, and HF•pyridine (0.4 mL) was added. After stirring for 2 h at the same temperature, the reaction was determined complete by TLC analysis and was quenched by the dropwise addition of a saturated aqueous sodium bicarbonate solution (3.0 mL). The product was partitioned between diethyl ether and water, and the combined organic extracts were washed with saturated sodium bicarbonate, water, and brine and were dried with magnesium sulfate. Concentration *in vacuo* gave a colorless oil, which was used without additional purification (86 mg, 92%) as a colorless oil. Analytical data: $[\alpha]_D^{25.6}$ = +71.5 (*c* = 0.29, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.96 (dd, *J*= 9.6, 5.2 Hz, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 5.93-5.85 (br. s., 2H), 5.02 (br. s., 1H), 4.50 (br. s., 1H), 3.94 (d, *J* = 9.6 Hz, 1H), 3.82-3.64 (m, 2H), 2.45-2.35 (m, 1H), 2.01-1.49 (m, 6H), 1.49 (s, 3H), 1.41 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.7, 149.9, 133.1, 125.2, 120.8, 108.4, 84.9, 84.0, 80.1, 79.4, 73.4, 61.1, 59.4, 39.1, 37.3, 35.3, 28.0, 26.1, 25.7, 21.5, 18.0, 10.9, -4.6, -5.1; **LRMS (ESI$^+$)** expected $[M+\underline{Na}]^+$: 501.3, observed: 501.2; **IR** (thin film, cm^{-1}): 3410, 3000, 2395, 2260, 2214, 1510, 1375, 1210, 908, 777, 651; **TLC**(50:50 hexanes:EtOAc): R_f = 0.16.



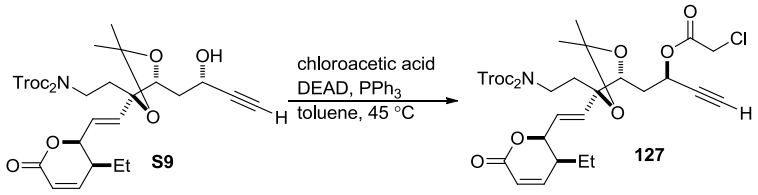
Compound 126: An oven-dried and cooled 20-mL scintillation vial was charged with alcohol **S8** (76 mg, 0.160 mmol, 1.0 equiv), triphenylphosphine (88 mg, 0.336 mmol, 2.1 equiv), and $Troc_2NH$ (77 mg, 0.208 mmol, 1.3 equiv). The vial was purged with N_2, and toluene (4.0 mL) was added. The resulting solution was cooled to -78 °C in an acetone-dry ice bath, and diethylazodicarboxylate (0.050 mL, 56 mg, 0.32 mmol, 2.0 equiv) was added dropwise. The reaction was removed from the cold bath and allowed to warm to room temperature. After stirring at room temperature for 15 min, TLC analysis indicated complete consumption of the starting material, and the reaction was quenched with saturated sodium bicarbonate solution. The solution was concentrated to approximately 2.0 mL *in vacuo*, and the resulting toluene solution was loaded onto a SiO_2 column and was then purified via flash chromatography, eluting with 100:0 to 75:25 hexanes:ethyl acetate, to afford the title compound (112 mg, 85%) as a colorless oil. Analytical data: $[\alpha]_D^{25.4}$ = +33.9 (*c* = 0.34, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.94 (dd, *J*= 9.6, 5.6 Hz, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 5.99 (dd, *J* = 15.2, 4.4 Hz, 1H), 5.86 (d, *J* = 15.6 Hz, 1H), 4.99 (t, *J* = 4.4 Hz, 1H), 4.92 (d, *J* = 12.0 Hz, 2H), 4.76 (d, *J* = 12 Hz, 2H), 4.48 (dd, *J* = 7.6, 4.0 Hz, 1H), 4.07-3.99 (m, 1H), 3.89 (d, *J* = 10.4 Hz, 1H), 3.77-3.69 (m, 1H), 2.40-2.37 (m, 1H), 2.39 (d, *J* = 1.6 Hz, 1H), 2.07-1.40 (m, 6H), 1.48 (s, 3H), 1.40 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.6, 151.4, 149.7, 133.2, 125.7, 120.8, 108.5, 94.2, 84.1, 82.6, 80.2, 79.6, 75.8, 74.8, 73.4, 61.1, 39.1, 37.3, 32.6, 28.2, 26.2, 26.0, 21.5, 18.0, 11.0, -4.6, -5.1; **LRMS (ESI$^+$)** expected $[M+\underline{Na}]^+$: 848.1, observed: 848.2;

IR (thin film, cm^{-1}): 3220, 3019, 2253, 1645, 1383, 1216, 908, 764, 728, 651; **TLC**(50:50 hexanes:EtOAc): R_f = 0.77.



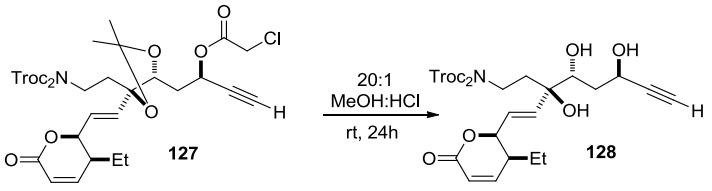
A plastic 20-mL scintillation vial was charged with silyl ether **126** (110 mg, 0.133 mmol, 1.0 equiv) and MeCN (3.0 mL). The resulting solution was cooled to 0 °C, and HF•pyridine (0.3 mL) was added dropwise. After the addition was complete, the reaction was warmed to room temperature. After 45 minutes, TLC analysis indicated complete consumption of the starting material (R_f = 0.77, 50:50 hexanes:EtOAc), and the reaction was quenched by the dropwise addition of a saturated aqueous solution of sodium bicarbonate (3.0 mL). The product was partitioned between diethyl ether and water, and the combined organic extracts were washed with saturated sodium bicarbonate, water, and brine and were dried with magnesium sulfate. Concentration *in vacuo* yielded a colorless oil (95 mg), which was used without additional purification. Analytical data for **S9**: $[\alpha]_D^{24.9}$ = +59.0 (*c* = 0.35, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.98 (dd, *J*= 10.0, 5.6 Hz, 1H), 6.06 (d, *J* = 9.6 Hz, 1H), 5.98 (dd, *J* = 15.6, 4.8 Hz, 1H), 5.90 (d, *J* = 15.2 Hz, 1H), 5.02 (t, *J* = 4.4 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 2H), 4.81 (d, *J* = 12.0 Hz, 2H), 4.55 (dd, *J* = 5.6, 6.8 Hz, 1H), 4.04 (ddd, *J* = 16.4, 14.0, 4.4 Hz, 1H), 3.90 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.73 (ddd, *J* = 13.6, 12.0, 4.0 Hz, 1H), 2.70 (br. s., 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.45-2.39 (m, 1H), 2.08-1.43 (m, 6H), 1.52 (s, 3H), 1.37 (s, 3H), 0.92 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.5, 151.5, 149.7, 133.0, 126.0, 120.9, 109.0 94.3, 83.6, 83.0, 81.4, 79.6, 76.0, 73.5, 61.1, 43.4, 39.2, 36.4, 32. 6, 28.2, 26.4, 21.6, 11.0; **LRMS (ESI$^+$)** expected $[M+\underline{Na}]^+$: 734.0, observed: 734.0;

IR (thin film, cm^{-1}): 3420, 3019, 2400, 2360, 2341, 1520, 1386, 1216, 929, 769, 669; **TLC**(50:50 hexanes:EtOAc): R_f = 0.44.

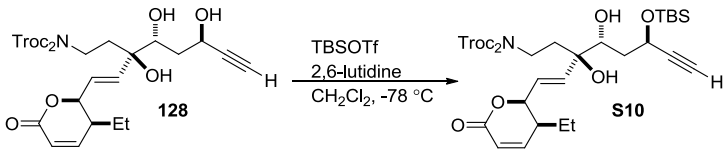


Compound 127: An oven-dried and cooled 20-mL scintillation vial was charged with the crude alcohol **S9** (95 mg, 0.133 mmol, 1.0 equiv), chloroacetic acid (50 mg, 0.533 mmol, 4.0 equiv), and triphenylphosphine (91 mg, 0.346 mmol, 2.6 equiv). The vial was purged with N_2, and dry toluene (4.0 mL) was added. Diethylazodicarboxylate (0.050 mL, 58 mg, 0.333 mmol, 2.5 equiv) was added dropwise, and the reaction was warmed to 45 °C in an oil bath. After 15 minutes at the same temperature, TLC analysis indicated complete consumption of the alcohol, and the reaction was cooled to room temperature and quenched with saturated aqueous ammonium chloride. After concentrating *in vacuo* to approximately 1 mL, the resulting toluene solution was purified via flash chromatography (100:0 to 75:25 hexanes: ethyl acetate) to afford the title compound as a colorless oil (87 mg, 83% over two steps). Analytical data: $[\alpha]_D^{25.0}$ = +70.4 (*c* = 0.79, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.99 (dd, *J*= 10.0, 5.6 Hz, 1H), 6.07 (d, *J* = 9.6 Hz, 1H), 5.99 (dd, *J* = 10.8, 4.8 Hz, 1H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.53 (d, *J* = 6.4 Hz, 1H), 5.03 (br. s, 1H), 4.95 (d, *J* = 12.0 Hz, 2H), 4.82 (d, *J* = 12.0 Hz, 2H), 4.19-3.93 (m, 1H), 4.08 (s, 2H), 3.93-3.67 (m, 2H), 2.54 (d, *J* = 1.6 Hz, 1H), 2.44-2.40 (m, 1H), 2.19-1.53 (m, 6H), 1.51 (s, 3H), 1.33 (s, 3H), 0.95 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 166.1, 163.5, 151.6, 149.7, 132.9, 126.2, 121.0, 108.9, 94.4, 82.6, 79.8, 79.6, 78.9, 76.0, 74.9, 62.9, 43.5, 40.6, 39.3, 34.0, 32.5, 28.2, 26.3, 21.6,

11.0; **IR** (thin film, cm^{-1}): 3444, 2931, 2253, 1805, 1731, 1645, 1518, 1225, 1094, 909, 729, 650; **TLC**(50:50 hexanes:EtOAc): R_f = 0.74.

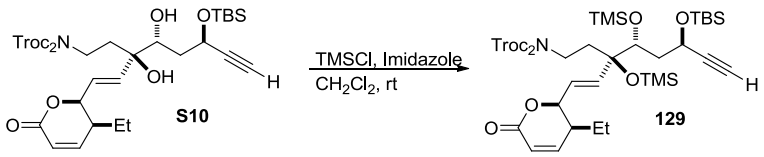


Compound 128: A 20-mL scintillation vial equipped with a magnetic stir bar was charged with **127** (60 mg, 0.076 mmol). A solution of 20:1 MeOH:HCl (2.0 mL) was added, and the reaction was allowed to stir at rt for 24 h. The solution was diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (3x 1.0 mL), water, and brine, and dried with $MgSO_4$. Concentration *in vacuo* afforded a crude yellow oil (50 mg), which was used without further purification. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (dd, *J*= 8.0, 4.0 Hz, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.96 (dd, *J* = 12.0, 4.0 Hz, 1H), 5.89 (d, *J* = 16.0 Hz, 1H), 5.03 (br. s, 1H), 4.92 (d, *J* = 12.0 Hz, 2H), 4.89 (d, *J* = 12.0 Hz, 2H), 4.68 (br. s, 1H), 4.10-3.80 (m, 3H), 3.42 (br. s, 2H), 2.61 (br. s, 1H), 2.49 (s, 1H), 2.44-2.42 (m, 1H), 2.09-1.35 (m, 6H), 0.95 (t, *J* = 8.0 Hz, 3H); **TLC**(95:5 CH_2Cl_2:MeOH): R_f = 0.46.

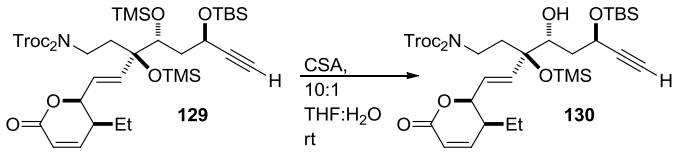


Compound S10: An oven-dried and cooled 20-mL scintillation vial equipped with a magnetic stir bar was charged with crude oil **128** (50 mg, 0.074 mmol, 1.0 equiv). CH_2Cl_2 was added (4 mL), and the resulting solution was cooled to -78 °C in an acetone-dry ice bath. 2,6-lutidine (0.020 mL, 18.4 mg, 0.172 mmol, 2.3 equiv) and TBSOTf (0.020 mL, 23.3 mg,

0.089 mmol, 1.2 equiv) were added sequentially, and the solution was maintained at the same temperature. After 15 min, TLC analysis indicated complete consumption of the triol. The reaction was quenched with MeOH (0.1 mL) and was diluted with Et_2O (10 mL), washed with 1M HCl (3x 5 mL), saturated aqueous $NaHCO_3$ (5 mL), water, and brine and was dried with Na_2SO_4. Concentration *in vacuo* afforded a crude yellow oil (31 mg), which was used without further purification due to its instability.

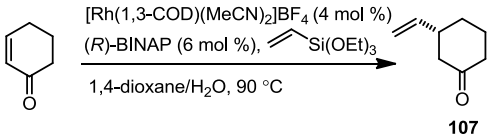


Compound 129: An oven-dried and cooled 20-mL scintillation vial equipped with a magnetic stir bar was charged with crude diol **S10** (31 mg, 0.0394 mmol, 1.0 equiv), and dry CH_2Cl_2 (2 mL) was added. Imidazole (107 mg, 1.576 mmol, 40 equiv) was added in one portion, followed by dropwise addition of TMSCl (0.150 mL, 128 mg, 1.18 mmol, 30 equiv). The reaction vial was sealed with a Teflon-coated cap and stirred at rt for 24 h. The suspension was diluted with Et_2O (10 mL), washed with 1M HCl (3x 5mL), saturated aqueous $NaHCO_3$, water, and brine and dried with Na_2SO_4. Concentration *in vacuo* afforded a crude light yellow oil (35 mg), which was used without further purification. Analytical data: $[\alpha]_D^{24.9}$ = +66.0 (*c* = 0.25, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (dd, *J*= 9.6, 5.2 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 5.91 (d, *J* = 10.0 Hz, 1H), 5.81 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.01 (t, *J* = 4.8 Hz, 1H), 4.91 (s, 4H), 4.41 (d, *J* = 10.4 Hz, 1H), 4.09-3.89 (m, 2H), 3.81 (d, *J* = 10.0 Hz, 1H), 2.39 (d, *J* = 1.6 Hz, 1H), 2.39-2.37 (m, 1H), 2.08-1.43 (m, 6H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.89 (2, 9H), 0.21 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H), 0.13 (9H); δ **LRMS (ESI$^+$)** expected $[M+Na]^+$:952.2, observed: 952.1; **TLC**(75:25 hexanes:EtOAc): R_f = 0.48.



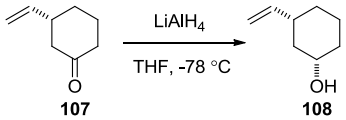
Compound 130: A 20-mL scintillation vial was charged with a magnetic stir bar and crude **129** (35 mg, 0.038 mmol, 1.0 equiv), and a solution of 10:1 THF:H_2O (2 mL) was added. CSA (10 mg, 0.043 mmol, 1.1 equiv) was added, and the reaction was allowed to stir at rt for 1.5 h, at which point TLC analysis indicated complete consumption of the starting material. Saturated aqueous $NaHCO_3$ (0.5 mL) was added, and the reaction was diluted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine and dried with $MgSO_4$. Concentration *in vacuo* afforded a crude yellow oil, which was purified via column chromatography, eluting with 85:15 EtOAc:hexanes, to give the title compound as a clear, colorless oil (23 mg, 35% from **127**). Analytical data: $[\alpha]_D^{25.2}$ = +43.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.98 (dd, *J*= 10.0, 5.5 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 5.98 (d, *J* = 16.0 Hz, 1H), 5.87 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.02 (t, *J* = 4.5 Hz, 1H), 4.92 (d, *J* = 12.0 Hz, 2H), 4.86 (d, *J* = 12.0 Hz, 2H), 4.86 (d, *J* = 5.5 Hz, 1H), 4.09-3.89 (m, 2H), 3.81 (d, *J* = 10.0 Hz, 1H), 4.04-3.85 (m, 2H), 3.12 (s, 1H), 2.44 (d, *J* = 2.5 Hz, 1H), 2.44-2.40 (m, 1H), 2.15-1.43 (m, 6H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.19 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.8, 151.7, 149.8, 135.1, 126.2, 120.9, 94.3, 84.5, 80.2, 79.0, 75.9, 73.8, 73.3, 61.3, 43.8, 39.5, 38.6, 34.6, 25.7, 21.6, 18.0, 11.1, 2.5, -4.7, -5.4 **LRMS (ESI$^+$)** expected $[M+Na]^+$: 880.1, observed: 880.0 **IR** (thin film, cm^{-1}):; **TLC**(75:25 hexanes:EtOAc): R_f = 0.62.

IV. Side Chain Synthesis



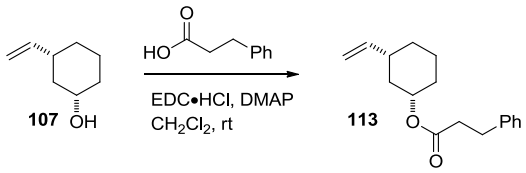
107

(R)-3-vinylcyclohexanone (107): The preparation of the title compound largely followed the procedure of Oi and Inoue.[62] In a dry box, a 100-mL flame-dried and cooled round-bottomed flask equipped with a magnetic stir bar was charged with the rhodium catalyst (157 mg, 0.413 mmol, 0.04 equiv) and (*R*)-BINAP (386 mg, 0.620 mmol, 0.06 equiv). After moving the flask to a fume hood, it was equipped with a reflux condenser and purged thoroughly with N_2. Degassed 1,4-dioxane (20 mL) was added, followed by vinyltriethoxysilane (4.35 mL, 3.93 g, 20.66 mmol, 2.0 equiv), cyclohexen-2-one (1.0 mL, 993 mg, 10.33 mmol, 1.0 equiv), and degassed water (2 mL). The resulting red solution was brought to reflux in an oil bath (temperature 90-100 °C). After refluxing for 24 h, significant solid formation was noted, and the resulting mixture was cooled to rt, diluted with hexanes (100 mL), and vigorously stirred for 30 min. The remaining red solids were filtered off, and the filtrate was concentrated *in vacuo* to give an orange oil, which was purified via column chromatography, eluting with 100:0 to 85:15 petroleum ether:diethyl ether. The title compound was isolated as a colorless oil (576 mg, 45%) whose spectral data matched the reported data.[62] Optical rotation: $[\alpha]_D^{24.0}$ = +23.4 (*c* = 0.24, $CHCl_3$); Literature:[62] $[\alpha]_D^{22}$ = –23.0 (*c* = 0.98, $CHCl_3$), for the (**S**)-enantiomer. The optical purity of the title compound was determined by conversion of alcohol **108** to phenylpropionate **113** (see below).



107 108

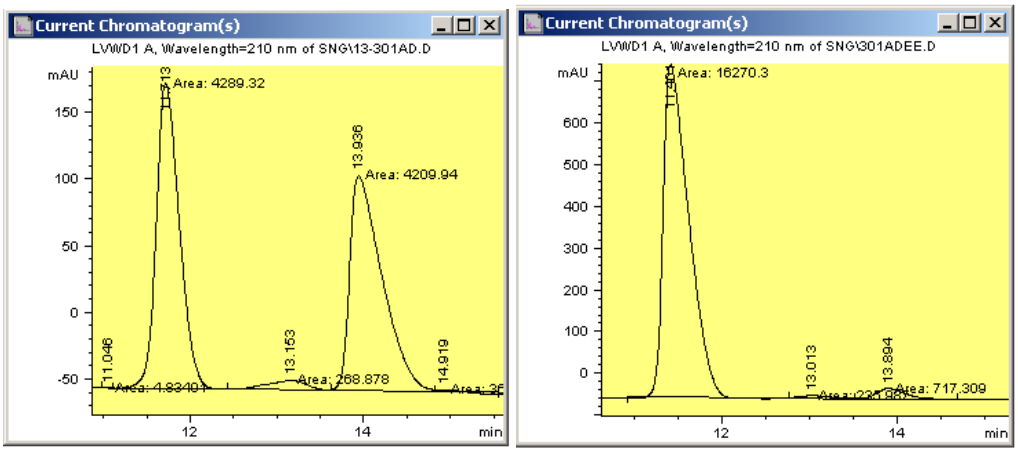
(1S,3R)-3-vinylcyclohexanol (108): A flame-dried and cooled 50-mL round-bottomed flask was charged with vinylcyclohexenone **107** (530 mg, 4.26 mmol, 1.0 equiv) and THF (10 mL). The resulting solution was cooled to -78 °C, and a solution of lithium aluminum hydride (1M in THF, 4.69 mL, 4.69 mmol, 1.1 equiv) was added dropwise. After stirring at the same temperature for 5 min, TLC analysis indicated complete consumption of the ketone, and the reaction was quenched by the addition of MeOH (1.0 mL). The flask was warmed to rt, and diethyl ether (10 mL) and saturated sodium potassium tartrate (10 mL) were added. The resulting biphasic mixture was stirred vigorously for 2 h at rt or until two clear layers were observed. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3x5 mL). The combined organic extracts were washed with water and brine and dried with $MgSO_4$. After concentrating *in vacuo*, the title compound was obtained as a clear, colorless oil which was used without further purification (504 mg, 94%). Analytical data: $[\alpha]_D^{24}$ = +8.0 (*c* = 0.48, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.76 (ddd, *J* = 16.8, 10.4, 6.0 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 4.90 (d, *J* = 10.4 Hz, 1H), 3.63-3.56 (m, 1H), 2.07-1.59 (m, 6H), 1.37-0.87 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 143.2, 112.2, 70.5, 41.5, 40.2, 35.3, 31.4, 23.8; **LRMS (ESI$^+$)** expected 3[M+H]$^+$: 381.3 , observed: 381.3 ; **IR** (thin film, cm^{-1}) 3436, 1638, 1490, 499, 475; **TLC**(85:15 Hexanes:EtOAc): R_f = 0.13.

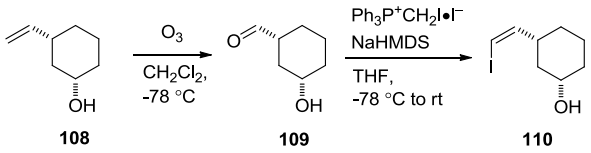


(1S,3R)-3-vinylcyclohexyl 3-phenylpropanoate (113): An oven-dried and cooled vial equipped with magnetic stir bar was charged with alcohol **107** (50 mg, 0.397 mmol, 1.0 equiv), 3-phenylpropionic acid (119mg, 0.794 mmol, 2.0 equiv), and EDC (93 mg, 0.596

mmol, 1.5 equiv). CH_2Cl_2 (3 mL) was added, followed by the addition of DMAP (10 mg, 0.0794 mmol, 0.2 equiv). The vial was sealed, and the resulting solution was stirred at rt for 12 h. The solution was diluted with diethyl ether and water, and the organic layer was washed with water and brine and concentrated *in vacuo* to give a light yellow oil. The crude material was purified via column chromatography, eluting with 92.5:7.5 hexanes:EtOAc, to afford the title compound as a colorless oil (81 mg, 79%). Analytical data: $[\alpha]_D^{25.2}$ = -7.8 (*c* = 0.40, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.20 (m, 5H), 5.76 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.93 (d, *J* = 10.4 Hz, 1H), 4.79-4.71 (m, 1H), 2.95 (t, J = 7.6 Hz, 2H), 2.61 (t, *J* = 8.0 Hz, 1H), 2.08-1.70 (m, 5H), 1.40-1.01 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 172.3, 142.7, 140.6, 128.4, 128.3, 126.2, 112.5, 72.9, 40.0, 37.5, 36.2, 31.4, 31.3, 31.1, 23.7; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 281.2, observed: 281.2; **IR** (thin film, cm^{-1}) 3019, 2400, 1521, 1216, 768, 669; **TLC**(80:20 Hexanes:EtOAc): R_f = 0.56. CSP-SFC analysis of a sample of **113** showed that the product was enriched to 92% ee as determined by CSP-SFC analysis (Chiralpak AD column, 0.5% MeOH, 1.0 mL/min, 150 psi, 24 °C, 210 nm, t_r-major enantiomer: 11.4 min, t_r-minor enantiomer: 13.9 min; CSP-SFC traces for a racemic sample and of the enantioenriched product are attached below.

Racemic Sample: Enantioenriched:

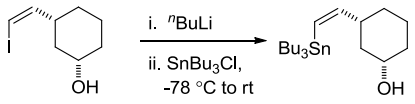




(1S,3R)-3-((Z)-2-iodovinyl)cyclohexanol (110): A 50-mL round-bottomed flask was charged with **108** (430 mg, 3.4 mmol) and CH_2Cl_2 (20 mL). The flask was cooled to -78 °C, and a stream of O_3 was bubbled through the solution until a faint blue color appeared. The contents of the flask were purged with N_2, and dimethylsulfide (1 mL) was added. The flask was allowed to warm to room temperature slowly and was stirred at rt for 16 h. Concentration *in vacuo* afforded a crude oil, which was pushed through a plug of SiO_2, eluting with 70:30 petroleum ether:diethyl ether, to give the crude aldehyde, which was used without additional purification (220 mg).

A flame-dried and cooled 50-mL round-bottomed flask was charged with the Wittig reagent (1.91 g, 3.6 mmol, 2.1 equiv) and THF (8 mL). The resulting suspension was cooled to 0 °C, and a solution of NaHMDS (631 mg, 3.44 mmol, 2.0 equiv) in THF (4 mL) was added via cannula. The resulting red suspension was stirred at rt for 30 min and was then cooled to -78 °C in an acetone-dry ice bath. A solution of the crude aldehyde (220 mg, 1.72

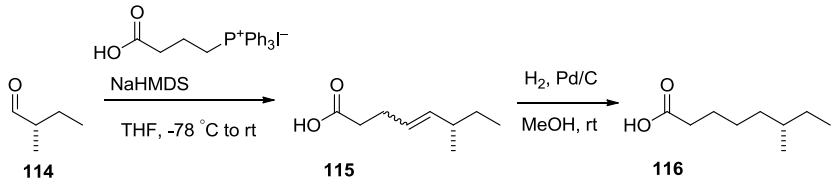
mmol, 1.0 equiv) in THF (3 mL) was added dropwise via cannula. The reaction was stirred at -78 °C for 5 min and was then warmed to rt for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 mL) and was diluted with diethyl ether. After separation of the layers, the aqueous layer was extracted with diethyl ether, and the combined organic extracts were washed with water and brine and dried with $MgSO_4$. After concentration *in vacuo*, the crude material was purified via column chromatography, eluting with 60:40 hexanes:EtOAc, to afford the title compound as a colorless oil (217 mg, 50 %). Analytical data: $[\alpha]_D^{28.6}$ = +33.6 (*c* = 0.24, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.11 (d, *J* = 7.2 Hz, 1H), 5.98 (dd, *J* = 7.6, 4 Hz, 1H), 3.68-3.61 (m, 1H), 2.41-2.33 (m, 1H), 1.97-0.98 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 144.8, 80.4, 69.8, 42.4, 40.1, 34.9, 30.1, 23.6; **IR** (thin film, cm^{-1}) 3435, 2104, 1639, 1510, 1438, 1245, 1180, 1119; **TLC**(60:40 Hexanes:EtOAc): R_f = 0.22.



110 **111**

(1S,3R)-3-((Z)-2-(tributylstannyl)vinyl)cyclohexanol (111): An oven-dried and cooled 20-mL scintillation vial equipped with magnetic stir bar was charged with the vinyl iodide (155 mg, 0.615 mmol, 1.0 equiv) and diethyl ether (5 mL). The vial was cooled to -78 °C in an acetone-dry ice bath, and a solution of ^{n}BuLi (1.5 M in hexanes, 1 mL, 1.48 mmol, 2.4 equiv) was added dropwise. After stirring for 1h at the same temperature, the reaction was allowed to warm to rt for 1.5 h. The reaction was quenched by the addition of 50% saturated aqueous sodium bicarbonate and diluted with 1:1 hexanes:diethyl ether (20 mL total). The organic layer was washed with water and brine and dried with Na_2SO_4. After concentrating *in vacuo*,

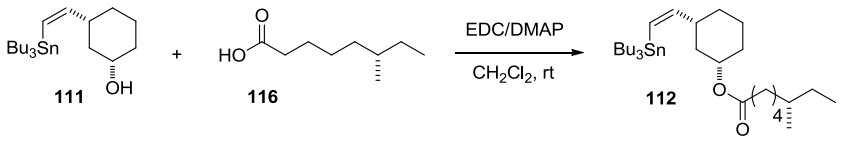
the resulting light yellow oil was purified via column chromatography, eluting with 85:15 to 80:20 hexanes:EtOAc, to afford the title compound as a colorless oil (155 mg, 61%). Analytical data: $[\alpha]_D^{26.2}$ = +29.0 (*c* = 0.16, $CHCl_3$); Literature:[12b] $[\alpha]_D^{22}$ = +29.9 (*c* = 3.49, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.30 (dd, *J* = 12.4, 9.2 Hz, 1H), 5.71 (d, *J* = 12.4 Hz, 1H), 3.57 (ddd, *J* = 14.8, 10.8, 6.4 Hz, 1H), 2.00-1.72 (m, 4H), 1.72-1.38 (m, 8H), 1.38-1.21 (m, 8H), 1.21-0.94 (m, 3H), 0.94-0.68 (m, 14H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 153.2, 126.5, 70.4, 45.4, 42.4, 35.2, 32.2, 29.2, 27.3, 23.9, 13.7, 10.4; **TLC**(60:40 Hexanes:EtOAc): R_f = 0.56.



(S)-6-methyloctanoic acid (116): (*S*)-2-methylbutanal (**114**) was prepared according to the *Organic Syntheses* procedure of Anelli.[64] A 25-mL flame-dried and cooled round-bottomed flask equipped with magnetic stir bar was charged with hexamethyldisilazane (3.61 mL, 2.8 g, 17.33 mmol, 3.1 equiv) and THF (10 mL). The resulting solution was cooled to 0 °C, and a solution of ^{n}BuLi (1.5 M in hexanes, 11.2 mL, 16.8 mmol, 3.0 equiv) was added dropwise. The solution was then stirred for 30 min at rt. A second flame-dried and N_2-purged 50-mL round-bottomed flask was charged with the Wittig reagent (2.4 g, 5.59 mmol, 1.5 equiv) and THF (10 mL), and the resulting suspension was cooled to 0 °C. The solution of NaHMDS was added dropwise via cannula over 5 min to the suspension of the phosphonium salt. After stirring the resulting orange suspension for 30 min at rt, a solution of the aldehyde (28% by mass in CH_2Cl_2, 321 mg, 3.73 mmol, 1.0 equiv) was added dropwise. The suspension was stirred at rt for 1 h and was then quenched by the addition of ammonium chloride (5 mL).

Diethyl ether (20 mL) was added, and the layers were separated. The organic layer was washed with water (2x10 mL) and brine and dried with $MgSO_4$. Concentration *in vacuo* afforded a crude oil, which was purified via column chromatography, eluting with 70:30 hexanes:EtOAc (R_f = 0.35), to afford **115** as a mixture of diastereomers that was used without additional purification.

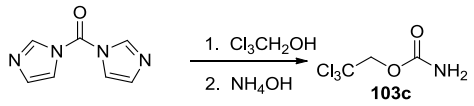
A 50-mL round-bottomed flask equipped with magnetic stir bar was charged with Pd/C (cat.) and purged with N_2. A solution of MeOH (3 mL) and the mixture of alkenes (100 mg, 0.632 mmol) was added, and the flask was purged with H_2. The flask was then equipped with a balloon of H_2 and the MeOH suspension was stirred vigorously at rt for 12 h. The suspension was filtered through Celite to remove all metals, and the filtrate was concentrated *in vacuo* to afford the title compound, which was used without additional purification (100 mg, 99%). The spectral data for the title compound matched those reported in the literature.[68] Optical rotation**:** $[\alpha]_D^{28.7}$ = +8.6 (*c* = 0.38, $CHCl_3$); Literature:[68] $[\alpha]_D^{20}$ = +9.1 (*c* = 1.0, $CHCl_3$).



(S)-(1S,3R)-3-((Z)-2-(tributylstannyl)vinyl)cyclohexyl 3-methylpentanoate (112): An oven-dried 20-mL scintillation vial equipped with a magnetic stir bar was charged with vinyl stannane **111** (44 mg, 0.100 mmol, 1.0 equiv), acid **116** (31 mg, 0.200 mmol, 2.0 equiv), and CH_2Cl_2 (2 mL). EDC (31 mg, 0.200 mmol, 2.0 equiv) and DMAP (4 mg, 0.030 mmol, 0.3 equiv) were added, and the vial was sealed with a Teflon cap. The reaction was allowed to stir at rt for 12 h, at which point it was diluted with hexanes, washed with H_2O (3x5 mL), and

dried with Na_2SO_4. Removal of the solvent *in vacuo* afforded a crude oil, which was pushed through a short silica plug, eluting with 95:5 hexanes:EtOAc, to give the title compound as a colorless oil. The spectral data for the title compound matched those reported in the literature. Optical rotation: $[\alpha]_D^{26.2}$ = +37.0 (*c* = 0.46, $CHCl_3$); Literature:[68] $[\alpha]_D^{21}$= +40.8 (*c* 3.52, $CHCl_3$). Spectral data for the title compound matched those reported in the literature.[12b]

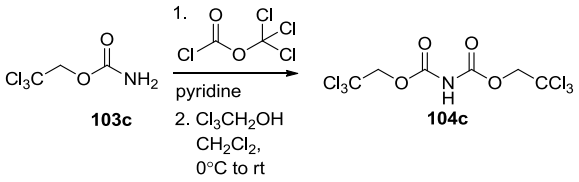
IV. Preparation of Amine Nucleophiles for Mitsunobu Reactions: General Procedure



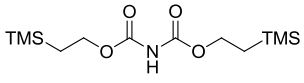
A representative procedure for the preparation of *bis*-carbamate nucleophiles is provided by the synthesis of $Troc_2NH$:

2,2,2-trichloroethyl carbamate: A 25-mL round-bottomed flask equipped with magnetic stir bar was charged with 2,2,2-trichloroethanol (1 mL, 1.56 g, 10.5 mmol, 0.85 equiv) and benzene (10 mL). Carbonyldiimidazole (2.0 g, 12.3 mmol, 1.0 equiv) was added, and the resulting solution was stirred at rt for 6h. A saturated solution of ammonium hydroxide (1.25 mL) was added dropwise, and the reaction was stirred at rt for 12h. The layers were separated, and the aqueous layer was extracted with diethyl ether (3x10 mL). The combined organic extracts were washed with brine and dried with $MgSO_4$ then concentrated *in vacuo* to afford a crude oil, which was triturated with hexanes to afford the desired carbamate (1.4 g, 70%), which was used without additional purification. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.95 (br. s., 2H) 4.73 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 154.7, 95.3, 74.6;

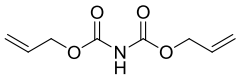
LRMS (ESI$^+$) expected $[M+Na]^+$: 281.2, observed: 281.2; **IR** (thin film, cm^{-1}) 3420, 3032, 2359, 1647, 1388, 1116, 807, 572.



***Bis*-(2,2,2-trichloroethyl)-carbamate (104c):** A flame-dried and cooled 25-mL round-bottomed flask was charged with CH_2Cl_2 (8 mL) and diphosgene (0.180 mL, 297 mg, 1.5 mmol, 0.6 equiv). The resulting solution was cooled to 0 °C in an ice bath. A solution of the carbamate (360 mg, 1.86 mmol, 1.0 equiv) and pyridine (0.400 mL, 389 mg, 4.92 mmol, 2.0 equiv) in CH_2Cl_2 (2 mL) was added dropwise over 5 min to the diphosgene solution. The flask was allowed to warm to rt for 3 h, and the resulting cloudy yellow suspension was recooled to 0 °C. Neat 2,2,2-trichloroethanol (0.471 mL, 735 mg, 4.92 mmol, 2.0 equiv) was added dropwise, and the resulting colorless solution was stirred for an additional 2 h at rt. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x10 mL), and the combined organic extracts were washed with water and brine and dried with Na_2SO_4. Concentration *in vacuo* afforded a crude solid, which was crystallized from hexanes/EtOAc to afford the title compound (290 mg, 42%). Analytical data: melting point: 119-121 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 (br. s., 1H), 4.84 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 148.5, 94.1, 75.0; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 387.8, observed: 387.8; **IR** (thin film, cm^{-1}) 3419, 3031, 2089, 1646, 1362, 1119, 813;

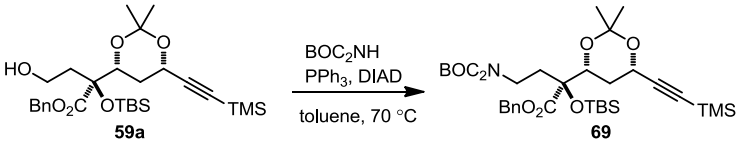


***Bis*-2-(trimethylsilyl)ethyl carbamate (104b):** Compound 104b was prepared according to the general procedure. The title compound was obtained in analytically pure form after purification via column chromatography (70:30 hexanes:EtOAc) as a colorless oil (**104b**, yield = 44% over two steps). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17 (br. s., 1H), 4.23 (t, *J* = 8.8 Hz, 4H), 1.01 (t, *J* = 9.2 Hz, 4H), 0.01 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 151.0, 64.6, 17.4, 1.6; **LRMS (ESI$^+$)** expected $[M+Na]^+$: 328.2, observed: 328.1; **IR** (thin film, cm^{-1}) 3434, 3038, 2089, 1646, 1362, 794, 577; **TLC**(60:40 hexanes:EtOAc): R_f = 0.64.



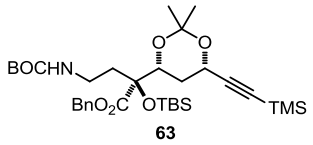
***Bis*-allylcarbamate (104a):** The title compound was prepared according to the general procedure, and the Analytical data matched those reported in the literature.[70] Yield = 24% over two steps.

Additional Compounds of Relevance to Discussions in Section 3.3:



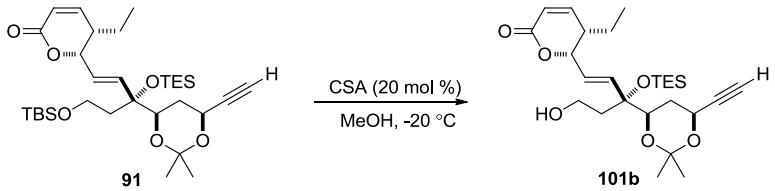
***Bis*-Carbamate 69**: An oven-dried and cooled 20-mL vial equipped with magnetic stir bar was charged with alcohol **59a** (70 mg, 0.131 mmol, 1.0 equiv), BOC_2NH (57 mg, 0.262 mmol, 2.0 equiv), and PPh_3 (72 mg, 0.275 mmol, 2.1 equiv). The vial was purged with N_2, toluene (4 mL) was added, and the reaction was warmed to 70 °C in an oil bath. After 90 min, TLC analysis indicated complete consumption of the starting material (R_f = 0.3, 80:20 hexanes:EtOAc). After cooling to rt, the solution was loaded directly onto a column of silica

and eluted with 100:0 to 90:10 hexanes:EtOAc to afford the desired product as a colorless oil (66 mg, 69%). Analytical data**:** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 5H), 5.40 (d, *J* = 12.0 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.17 (d, *J* = 12.0 Hz, 1H), 3.71 (ddd, *J* = 16.0, 12.0, 4.0 Hz, 1H), 3.45 (ddd, *J* = 16.0, 12.0, 4.0 Hz, 1H), 2.00-1.63 (m, 4H),1.49 (s, 18H), 1.32 (s, 3H), 1.15 (s, 3H), 0.92 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.16 (s, 9H); **TLC**(70:30 hexanes:EtOAc): R_f = 0.50.



63

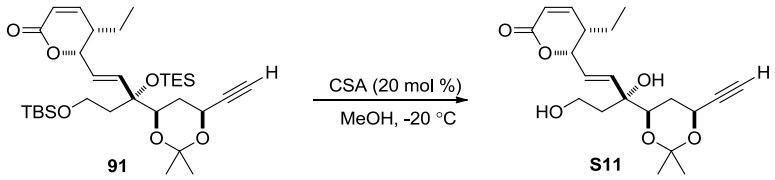
(S)-benzyl 4-((tert-butoxycarbonyl)amino)-2-((4R,6S)-2,2-dimethyl-6-((trimethylsilyl) ethynyl)-1,3-dioxan-4-yl)-2-((triethylsilyl)oxy)butanoate (63): The title compound was obtained as a byproduct in attempted reductions of ester **69** (*vide supra*, Scheme 3-8). Analytical data**:** **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.26 (br. s, 5H), 5.39 (d, *J* = 12.0 Hz, 1H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.66 (s, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.14 (d, *J* = 12.0 Hz, 1H), 3.17 (br. s, 2H), 2.11-1.42 (m, 6H), 1.42 (s, 6H), 0.93 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.16 (s, 9H); **TLC**(80:20 hexanes:EtOAc): R_f = 0.43.



91 **101b**

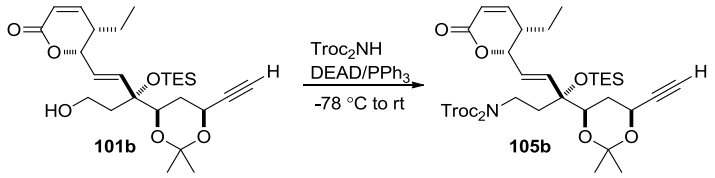
(5S,6S)-5-ethyl-6-((R,E)-3-((4R,6S)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)-5-hydroxy-3-((triethylsilyl)oxy)pent-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one (101b): A 20-mL scintillation vial equipped with a magnetic stir bar was charged with **91** (100 mg, 0.169

mmol, 1.0 equiv) and MeOH (3 mL). The resulting solution was cooled to -20 °C in an isopropanol-dry ice bath, and CSA (7.9 mg, 0.034 mmol, 0.20 equiv) was added. The reaction was stirred for 2 h at rt and was then quenched by the addition of TEA (2 drops). The solvent was removed *in vacuo*, and the crude residue was purified via column chromatography, eluting with 70:30 to 50:50 hexanes:EtOAc, to afford the monoalcohol **101b** (45 mg, 56%; 67% BORSM), diol **S11** (14 mg, 23%; 28% BORSM), and recovered **91** (17 mg, 17%). Analytical data for **101b**: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.95 (dd, *J*= 9.5, 5.0 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 5.83 (d, *J* = 15.5, 6.0 Hz, 1H), 5.04 (t, *J* = 4.5 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 3.78 (dd, *J* = 11.5, 2.0 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 1H), 2.48-2.44 (m, 2H), 2.02-1.20 (m, 6H), 1.45 (s, 3H), 1.42 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); 0.96 (t, *J* = 7.5 Hz, 9H, two coincident resonances), 0.64 (q, *J* = 8.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$)**:** δ 163.9, 149.8, 135.4, 125.4, 120.8, 99.5, 82.2, 80.0, 78.7, 74.0, 73.0, 60.2, 58.7, 40.5, 39.4, 31.8, 29.8, 21.6, 19.2, 11.0, 7.1, 6.9; **TLC**(50:50 hexanes:EtOAc): R_f = 0.35.



(5S,6S)-5-ethyl-6-((R,E)-3-((4R,6S)-6-ethynyl-2,2-dimethyl-1,3-dioxan-4-yl)-3,5-dihydroxypent-1-en-1-yl)-5,6-dihydro-2H-pyran-2-one (S11): Diol **S11** was isolated as a byproduct in selective deprotections of **91**. Analytical data: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.96 (dd, *J*= 9.5, 5.0 Hz, 1H), 6.05 (d, *J* = 9.5 Hz, 1H), 5.98 (dd, *J* = 15.5, 6.0 Hz, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 5.07 (t, *J* = 5.0 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 3.85-3.76 (m, 3H), 2.50-2.46 (m, 1H), 2.46 (d, *J* = 1.5 Hz, 1H), 1.93-1.48 (m, 6H), 1.44 (s, 3H), 1.41 (s, 3H), 0.97 (t, *J* = 7.5 Hz, 3H); **^{13}C**

NMR (100 MHz, $CDCl_3$)**:** δ 164.1, 150.1, 135.4, 125.7, 120.7, 99.5, 82.2, 80.3, 77.1, 73.8, 72.9, 60.0, 59.8, 39.3, 36.6, 31.2, 29.9, 21.6, 19.3, 11.0; **TLC**(50:50 hexanes:EtOAc): R_f = 0.15.



Compound 105b: The general procedure for the synthesis of **126** from **S8** was followed. Yields = 80-85%. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.95 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.06 (d, *J* = 12.0 Hz, 1H), 5.98 (*J* = 16.0 Hz, 1H), 5.91 (dd, *J* = 16.0, 8.0 Hz, 1H), 5.02 (t *J* = 4.0 Hz, 1H), 4.94 (d, *J* = 12.0 Hz, 2H), 4.85 (d, *J* = 12.0 Hz, 2H), 4.61 (d, *J* = 8.0 Hz, 1H), 3.95-3.80 (m, 2H),3.75 (d, *J* = 12.0 Hz, 1H), 2.47 (d, *J* = 2.0 Hz, 1H), 2.46-2.42 (m, 1H), 2.21-1.49 (m, 6H), 1.44 (s, 3H), 1.40 (s, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.68 (dq, *J* = 8.0 Hz, 4.0 Hz, 6H); **TLC**(50:50 hexanes:EtOAc): R_f = 0.75

3.5 References

[1] Hopwood, D. A. *Streptomyces in Nature and Medicine : the Antibiotic Makers.* New York: Oxford University Press, **2007**.

[2] (a) Kohama, T.; Enokita, R.; Okazaki, T.; Miyaoka, H.; Torikata, A.; Inukai, M.; Kaneko, I.; Kagasaki, T.; Sakaida, Y.; Satoh, A.; Shirashi, A. *J. Antibiot.* **1993**, *46*, 1503-1511. (b) Kohama, T.; Nakamura, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *J. Antibiot.* **1993**, *46*, 1512-1519. (c) Matsuhashi, H.; Shimada, K.; *Tetrahedron*, **2002**, *58*, 5619-5626.

[3] (a) Fushimi, S.; Nishikawa, S.; Shimazo, A.; Seto, H. *J. Antibiot.* **1989**, *42*, 1019-1025. (b) Fushimi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1989**, *42*, 1026-1036. (c) Ozasa, T.; Suzuki, K.; Sasamata, M.; Tanaka, K.; Koburi, M.; Kadota, S.; Nagai, K.; Saito, T.; Watanabe, S.; Iwanami, M. *J. Antibiot*. **1989**, *42*, 1331-1338. (d) Ozasa, T.; Tanaka, K.; Sasamata, M.; Kaniwa, H.; Shimizu, M.; Matsumoto, H.; Iwanami, M. *J. Antibiot.* **1989**, *42*, 1339-1343. (e) Shibata, T.; Kurihara, S. Yoda, K.; Haruyama, H. *Tetrahedron* **1995**, *51*, 11999-12012. (f) Sekiyama, Y.; Palaniappan, N.; Reynolds, K. A.; Osada, H. *Tetrahedron*, **2003**, *59*, 7465-7471. (g) Choudhuri, S. D.; Ayers, S.; Soine, W. H.; Reynolds, K. A.; *J. Antibiot.* **2005**, *58*, 573-582. (h) Mizuhara, N.; Usuki, Y.; Ogita, M.; Fujita, K.; Kuroda, M.; Doe, M.; Lio, H.; Tanaka, T. *J. Antibiot*. **2007**, *60*, 762-765.

[4] (a) Lewy, D. S.; Gauss, C. M.; Soenen, D. R.; Boger, D. L.; *Curr. Med. Chem.* **2002**, *9*, 2005-2032. (b) Uramoto, M.; Shen, Y.C.; Takizawa, N.; Kusakabe, H.; Isono, K. *J. Antibiot.* **1985**, *38*, 665-668.

[5] (a) Tunac, J. B.; Graham, B. D.; Dobson, W. E.; *J. Antibiot.* **1983,** *36*, 1595-1600. (b) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983,** *36*, 1601-1605. (c) Boger, D. L.; Hikota, M.; Lewis, B. M. *J. Org. Chem.* **1997**, *62*, 1748-1753.

[6] Koishi, R.; Yoshimura, C.; Kohama, T.; Serizawa, N. *J. Interferon and Cytokine Res.* **2002**, *22*, 343-350.

[7] (a) Kohama, T.; Katayama, T.; Kinoshita, T.; Kaneko, I.; Shiraishi, A. *Microbiol. Immunol.* **1994**, *38*, 741-745. (b) Koishi, R.; Serizawa, N.; Kohama, T. *J. Interferon Cytokine Res.* **1998**, *18*, 863-869.

[8] Kohama, T.; Maeda, H.; Imada-Sakai, J.; Shiraishi, A.; Ymashita, K. *J. Antibiot.* **1996**, *49*, 91-94.

[9] (a) Hertwick, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688-4716. (b) Palaniappan, N.; Kim, B. S.; Sekiyama, Y.; Osada, H. Reynolds, K. A. *J. Biol. Chem.* **2003**, *278*, 35552-35557.

[10] For phoslactomycin B syntheses, see: (a) Wang, Y.-G.; Takeyama, T.; Kobayashi, Y.; *Angew. Chem. Int. Ed.* **2006**, *45*, 3320-3323. (b) Nonaka, H.; Maeda, N.; Kobayashi, Y. *Tetrahedron Lett.* **2007**, *48*, 5601-5604. (c) Shibahara, S.; Fujina, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139-2142. (d) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 935-938. (e) Konig, C. M.; Gebhardt, B.; Schleth, C.; Dauber, M.; Koert, U. *Org. Lett.* **2009**, *11*, 2728-2731. (f) Shibahara, S.; Fujino, M.; Tashiro, Y.; Nanako, O.; Esumi, T.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Synthesis* **2009**, 2935-2953.

[11] Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048-4049.

[12] (a) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *Tetrahedron Lett.* **2007**, *48*, 3829-3833. (b) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *J. Org. Chem.* **2008**, *73*, 5360-5370.

[13] Moise, J.; Sonowane, R. P.; Corsi, C.; Wendeborn, S.V.; Arseniyadis, S.; Cossy, J. *Synlett*, **2008**, 2617-2620.

[14] Matsuhashi, H.; Shimada, K. *Tetrahedron*, **2002**, *58*, 5619-5626.

[15] a) Akai, S.; Naka, T.; Fujita, T.; Takebe, Y.; Tsujino, T.; Kita, Y. *J. Org. Chem.* **2002**, *67*, 411-419. (b) Fadel, A.; Arzel, P. *Tetrahedron:Asymmetry* **1997**, *8*, 283-291.

[16] Ando, K. *J. Org. Chem.* **1997**, *62*, 1934-1939.

[17] Aerssens, M. H. P. J.; van der Heiden, R.; Heus, M.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3421-3425.

[18] Hayakawa, Y.; Wakabayashi, S.; Nobori, T.; Noyori, R. *Tetrahedron Lett.* **1987**, *28*, 2259-2262.

[19] Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

[20] Review: Blakemore, P. R. *J. Chem. Soc. Perkin Trans.I* **2002**, 2563-2585.

[21] Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4573-4576.

[22] (a) Cintas, P.; *Synthesis* **1992**, 248-257. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991-1046.

[23] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410.

[24] Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *48*, 4155-4156.

[25] Brown, H. C.; Hubbard, J. L.; Singaram. B. *Tetrahedron*, **1981**, *37*, 2359-2362.

[26] Review : de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153-1174.

[27] Stork. G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174.

[28] Gololobov, Y. G. *Tetrahedron* **1981**, *37*, 437-472.

[29] For the analogous crotylation, see: Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293-294.

[30] Moise, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 1695-1698.

[31] Greszler, S. N.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3689-3691.

[32] (a) Nelson, S. G.; Wan, Z. Org. Lett. **2000**, *2*, 1883-1886. (b) Nelson, S. G.; Mills, P. M.; Ohshima, T.; Shibasaki, M. *Org. Synth.* **2005**, *82*, 170-174.

[33] Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am Chem. Soc.* **2006**, *128*, 7438-7439.

[34] Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551-2651.

[35] In addition to reference 33, examples of ring-opening of β-lactones via O–CO bond cleavage: (a) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 7317-7320. (b) Shimizu, M.; Ishii, K.; Fujisawa, T. *Chem. Lett.* **1997**, 765-766.

[36] Hu, M.; Li, J.; Yao, S. Q. *Org. Lett.* **2008**, *10*, 5529-5531.

[37] The enantiomeric excess of the β-lactone was determined by Supercritical Fluid Chromatographic (SFC) analysis of the corresponding β-hydroxyketone products (**39, 39′**).

[38] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

[39] Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923-1926.

[40] Jahn,U.; Hartmann, P.; Kaasalainen, E. *Org. Lett.* **2004**, *6*, 257-260.

[41] Picotin, G.; Miginiac, P.; *J. Org. Chem.* **1987**, *52*, 4796-4798.

[42] Kimura, M.; Seki, M. *Tetrahedron Lett.* **2004**, *45*, 1635-1637.

[43] Reviews of Reformatsky reagents: a) Ocampo, R.; Dolbier, W. R. *Tetrahedron* **2004**, *60*, 9325-9374; b) Fürstner, A. *Synthesis* **1989**, 571-590; c) Cozzi, P. G. *Angew. Chem. Int. Ed*. **2007**, *46*, 2568-2571.

[44] Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317-4320.

[45] (a) de Vries, E. F. J.; Brussee, J.; van der Gen, A. *J. Org. Chem.* **1994**, *59*, 7133-7137. (b) Saravanan, P.; Gupta, S.; Gupta, A. D.; Gupta, S.; Singh, V. K. *Synth. Comm.* **1997**, *27*, 2695-2699.

[46] Brown, H. C.; Narasihman, S. *J. Org. Chem.* **1982**, *47*, 1604-1606.

[47] Wadsworth, W. S.; Emmons, W. D., *J. Am. Chem. Soc*. **1961**, *83*, 1733-1738.

[48] (a) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775-777. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902. (C) Crimmins, M. T.; Dechert, A.-M. R. *Org. Lett.* **2009**, *11*, 1635-1638.

[49] Schlessinger, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1999**, *40*, 1257-1260. (b) Schlessinger, R. H.; Li, Y.-J.; Von Langen, D. J. *J. Org. Chem.* **1996**, *61*, 3226-3227.

[50] (a) Bressy, C.; Vors, J.-P.; Hillebrand, S.; Arseniyadis, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 10137-10104. (b) Ono K.; Nagata T.; Nishida, A. *Synlett* **2003**, 1207-1209. (c) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020-2023.

[51] Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, *37*, 3475-3478. (b) Seyferth, D.; Nestle, M. O.; Wehman, A. T. *J. Am. Chem. Soc.* **1975**, *97*, 7417-7426. (c) Greenfield, H.; Sternberg, H. W.; Friedel, R. A.; Wotiz, J. H.; Markby, R.; Wender, I. *J. Am. Chem. Soc.* **1956**, *78*, 120-124.

[52] Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869-1874.

[53] Hayashi, Y.; Yamaguchi, H.; Toyoshima, M.; Okado, K.; Toyo, T.; Shoji, M. *Org. Lett.* **2008**, *10*, 1405-1408.

[54] Chinchilla, R.; Njera, C. *Chem. Rev.* **2007**,*107*, 874-922.

[55] Konosu, T.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2212-2215.

[56] Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095-13096.

[57] Reddy, K. L.; Dress, K. R.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 3667-3670.

[58] Taguchi, M.; Goda, K.-I.; Sugimoto, K.; Akama, T.; Yamamoto, K.; Suzuki, T.; Tomishima, Y.; Nishiguchi, M.; Arai, K.; Takahashi, K.; Kobori, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3681-3684.

[59] Bialy, L.; Waldmann, H. *Chem. Eur. J.* **2004**,*10*, 2759-2780.

[60] Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

[61] Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1998**, *50*, 1-652.

[62] Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97-99.

[63] See Section 3.5 for additional information.

[64] Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212

[65] Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748-2749.

[66] Pozsgay, V. *J. Am. Chem. Soc.* **1995**, *117*, 6673-6681.

[67] Novokshonova, I. A.; *Synthesis* **2008**, 3797-3800.

[68] Milburn, A. H.; *J. Chem. Soc*. **1954**, 3344-3351.

[70] Shen, Ruichao; *J. Org. Chem*. **2005**, *70*, 3686-3692.