COMPLEXITY-BUILDING TRANSFORMATIONS OF SILYL GLYOXYLATES

Daniel Copley Schmitt

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.

Chapel Hill
2011

Approved by

Advisor: Jeffrey S. Johnson

Chair: Michael T. Crimmins

Reader: David A. Nicewicz

Committee Member: Maurice Brookhart

Committee Member: Marcey L. Waters

ABSTRACT

Daniel Copley Schmitt
Complexity-Building Transformations of Silyl Glyoxylates
(Under the direction of Jeffrey S. Johnson)

Silyl glyoxylates are reagents used for the geminal difunctionalization of a glycolic acid junction with nucleophilic and electrophilic species. The research summarized herein describes the development of new reactions that utilize silyl glyoxylates to generate multiple C–C bonds and stereogenic centers. Significant results include: (1) completion of the synthesis of (+)-zaragozic acid C; (2) development of a tandem Brook/Ireland Claisen rearrangement for the synthesis of functionalized γ,δ-unsaturated glycolic acids; (3) development of a nitrile-oxide cycloaddition for the synthesis of 3,4-disubstituted isoxazoles; (4) development of a three component glycolate Michael reaction; (5) application of the glycolate Michael reaction to the synthesis of (±)-trachyspic acid dimethyl ester.

ACKNOWLEDGEMENTS

I would like to thank my advisor, Jeffrey Johnson. Performing research with Jeff has been an extraordinary experience. His passion for chemistry is infectious. It is hard to imagine a more ideal advisor than Jeff; he is incredibly driven and maintains a hunger for results, but is unwaveringly good-natured. This is a rare and desirable combination in the field of organic chemistry. In addition to chemistry, Jeff has taught me much about leadership, perseverance, and attention to detail. I also thank him for providing me with various exciting projects.

I am grateful to Prof. Michael Crimmins for multiple reasons. During Anne-Marie's and my postdoc hunt, he was understanding of our two-body problem, and helped us to find positions together. I appreciate Prof. Crimmins' patience with me when I smashed his ozonator on the brick walkway between Kenan and Caudill. I also appreciate the multiple letters of recommendation Prof. Crimmins has provided me with over the past year. I am also appreciative of my other committee members: Maurice Brookhart, Marcey Waters, and Dave Nicewicz. In particular, I thank Dave for both serving as a reader of this thesis, and for his stellar work on the zaragozic acid project; his experimental results were trustworthy and reproducible, which was a great benefit to Andy and I.

I was fortunate to collaborate with both Andy Satterfield and Leighann Lam during my graduate studies. Andy's mentorship was critical to my development as a chemist. Leighann's pioneering efforts in the development of the enolsilane/nitrile-oxide

[3+2] are greatly appreciated. Her hard-working and eager nature will serve her well as graduate student at Emory.

I would like to express my gratitude to many of my coworkers over the past few years. Kim Steward and Justin Malinowski have continuously brought a high level of intensity from day one. I thank my intramural soccer teammates Michael Corbett and Dung "Lebron James of Soccer" Do; I hope they both continue to excel in the Johnson group and in soccer. In particular, I must thank my fellow silyl glyoxylysts: Steve Greszler, Greg Boyce, and Mike Slade; their independent findings and helpful suggestions had an immense impact on my studies. I also thank Austin Smith for countless thoughtful discussions and the sharing of ideas; his intellectual contributions and friendship are both valued. I am also grateful to former group members Shanina Sanders, Matthew Campbell, Chris Tarr, and Andrew Parsons. I consider it a privilege to have worked with them; they are each talented scientists and have my utmost respect.

My interest in chemistry was first ignited by Dr. James Johnson, my AP Chem teacher at Falmouth High School. Dr. Johnson's love for teaching and chemistry have had a profound influence on my life. My interest in organic chemistry first emerged when I took Prof. James Panek's synthesis class at Boston University. This led to my cautious decision to try undergraduate research in organic chemistry, and from there I was hooked: for the first time in my life, when I glanced at the clock while at work, I actually wished there were *more* hours in the day. I must thank my undergraduate research advisor, Prof. John Porco, and my graduate student mentor, Dr. Sujata Bardhan; they made me want to pursue further education in chemistry.

I acknowledge Chris Franks for his friendship, which dates back to Woods Hole Day Care Coop circa 1987. Our many scientific studies (including the effects of liquid N_2 and tesla coils on spiders, and the design of a chocolate-powered turbo-hopper time machine) made me want to pursue a scientific career. I am also grateful to Matt "Vlade" Kogut, Dan "Senator" Solworth, Ian "Doctor" Pegg, Garrett "GB" Boyd, Matt "Concussed" Rosene, Randy "Grinder" Dodds, and Guam "Matthew" Salas. My relatively new friends, Dr. Troy Knight, Dr. Nicki Knight, and Prof. Henry Taube Knight are thanked for their roles as golf buddy, chef, and entertainer, respectively.

I thank the 2004 Red Sox for showing me that if you believe in yourself, anything is possible. Growing up a Sox fan, while often traumatic, was valuable in preparing me mentally for graduate school. I am also thankful to the '07 Sox, '08 NY Giants, '09 Terrier hockey, and '09 Tar Heel basketball for the joy and goodness they have brought to the world.

My uncle Bruce's influence was certainly a factor in my decision to study chemistry; I also owe him for introducing me to golf (I enjoy it despite my skills). I would like to thank other family members for their constant support. In particular, Gramma and Grandpa Schmitt, uncle Dave and aunt Marti, and the Auler family for making me feel at home in NC. I am grateful to Cris, Judy, Kenzie, and Britton – they have been great friends as well as relatives. I appreciate the support of my brothers, Stephen and Eric. Although we haven't lived in the same house for years now, I have many fond memories of our youth, and I always enjoy our phone conversations.

I would like to thank my in-laws: Charlotte, Randy, and August. I value the time I have spent with you over the past few years. Getting to know them has been a great experience for me. They have made me feel welcome in their family.

My parents have been loving and supportive for my entire life. I'm sure that raising me was no easy task, but they were always patient and kind to me, even when I probably didn't deserve it. They always encouraged me to ask questions about the world around me, which undoubtedly contributed to my interest in chemistry. Thank you for everything.

Finally, I acknowledge my wife Anne-Marie for her love over the past five years. She has been with me through the many highs and lows of research. She has the distinctive ability to both relax me and to motivate me, depending on what I need. She taught me how to study, she contributes regularly to my research, she makes me soup when I'm sick, and she can always make me laugh. The highlight of my days has been when Anne-Marie makes a surprise visit to Caudill 213 (usually with NMR tubes in-hand). Without question, meeting her was my greatest achievement at UNC. Words cannot express my gratitude for everything she's done for me.

In loving memory of my grandparents,
John and Dorothy Copley

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES AND SCHEMES

LIST OF ABBREVIATIONS AND SYMBOLS

2D-NMR	two-dimensional nuclear magnetic resonance
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetate
AIBN	azobisisobutyronitrile
Ar	aryl
aq	aqueous
atm	atmospheres
Bn	benzyl
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
conv	conversion
COSY	correlated spectroscopy
Cp	cyclopentadienyl

*m*CPBA	*meta*-chloroperoxybenzoic acid
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
d.r.	diastereomeric ratio
dt	doublet of triplet
E	*entgegen*
E^+ or El	electrophile
eq	equation
equiv	equivalents
e.r.	enantiomeric ratio

ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
exo	exocyclic
FID	flame ionization detector
G2	Grubbs' second generation catalyst
h	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
n-hexanal	*normal*-hexanal
HOAc	acetic acid
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
ICR	Ireland-Claisen Rearrangement
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
L	liter or ligand
LA	Lewis acid
LAH	lithium aluminum hydride

LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
LRMS	low resolution mass spectroscopy
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
MeMgBr	Methylmagnesium bromide
MeOH	methanol
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz
MIB	3-*exo*-morpholinoisoborneol
min	minutes
mL	milliliter
mmol	millimole
mp	melting point
MPV	Meerwein-Ponndorf-Verley
n	number of atoms or counterions
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
nd	not determined
NHK	Nozaki-Hiyama-Kishi

NMP	*N*-methylpyrrolidone
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
nr	no reaction
Nu	nucleophile
OO	Oppenauer Oxidation
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
^{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
SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
T	temperature
t	triplet
t_r	retention time

TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TEA	triethylamine
TEMPO	tetramethylpiperidine-*N*-oxide
TES	triethylsilyl
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Tr	trityl or triphenylmethyl
triflate	trifluoromethanesulfonate
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 1

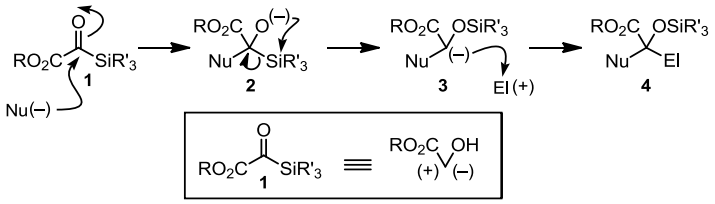
TOTAL SYNTHESIS OF ZARAGOZIC ACID C

1.1 Introduction

1.1.1 Reactivity of Silyl Glyoxylates

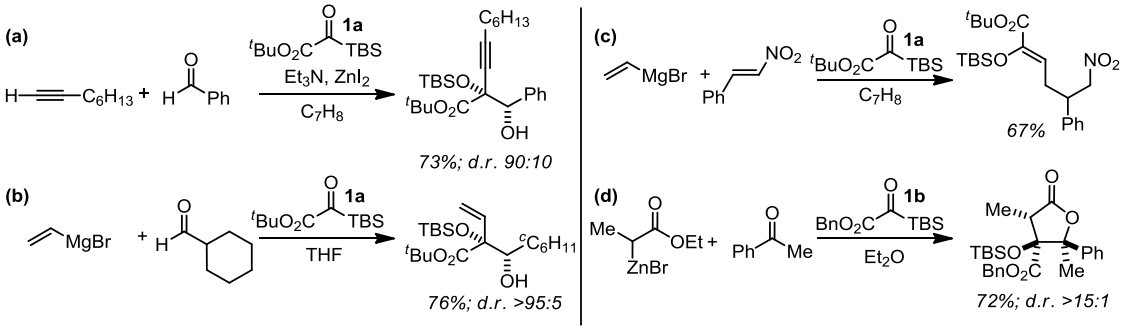
Complex molecule synthesis continues to be revolutionized by the development of cascade sequences. Chemical reactions that generate multiple C–C bonds in a single operation are valuable transformations as they reduce overall step count, providing time and cost effective alternatives to multistep routes.[1] Silyl glyoxylate **1**, an easily accessible reagent developed in our group, has been utilized in such cascade reactions (Scheme 1-1).[2,3] Reagent design hinges on a nucleophile-triggered [1,2]-Brook rearrangement (**2** → **3**) to achieve umpolung reactivity at what was the carbonyl carbon.[4] Trapping the nascent carbanion (enolate, **3**) with an electrophile provides the 2,2-difunctionalized product **4**. Thus, the silyl glyoxylate serves as a useful conjunctive reagent for the one-pot, geminal grafting of both nucleophilic (organometallic species, enolates, and hydride sources) and electrophilic (carbonyl compounds and Michael acceptors) species to a glycolic acid framework.

Scheme 1-1. General Reaction Scheme Involving Silyl Glyoxylates



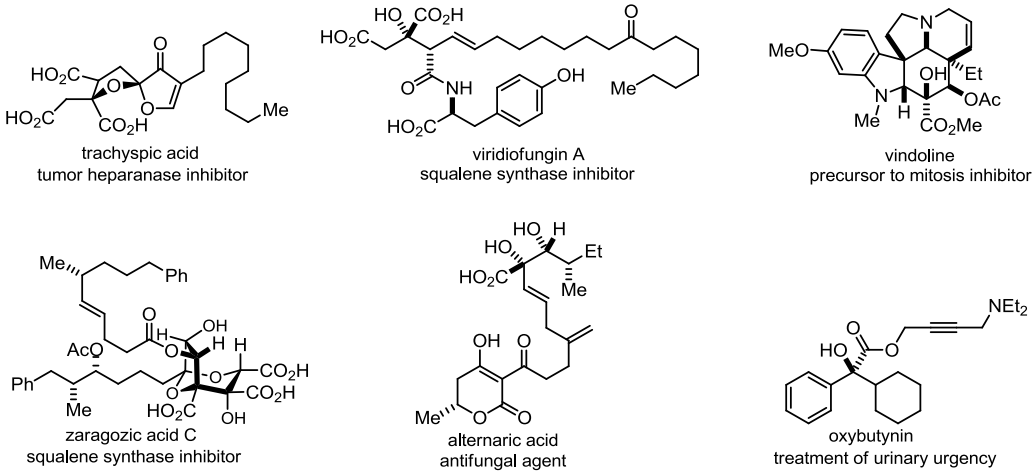
To date, several three component coupling reactions have been developed that rely on silyl glyoxylate to provide molecular complexity from simple, achiral building blocks. Examples of compatible reactants include zinc acetylides or Grignard reagents with aldehydes (a and b, Scheme 1-2),[2] vinyl Grignard reagent with nitroolefins (c),[3] and Reformatsky reagents with ketones (d).[5]

Scheme 1-2. Effective Nucleophile/Electrophile Pairs



The glycolate subunit can be found in several biologically active natural products and therapeutics (Figure 1-1).[6-11] While many elegant syntheses of these bioactive glycolates have been completed, none had the strategic benefit engendered by the silyl glyoxylate. Its ability to undergo geminal difunctionalization allows facile access to challenging targets, with minimal refunctionalization or oxidation state modification. No other general synthetic tactic is known which is applicable to such an abundance of stereochemically-dense, glycolic acid-containing molecules.

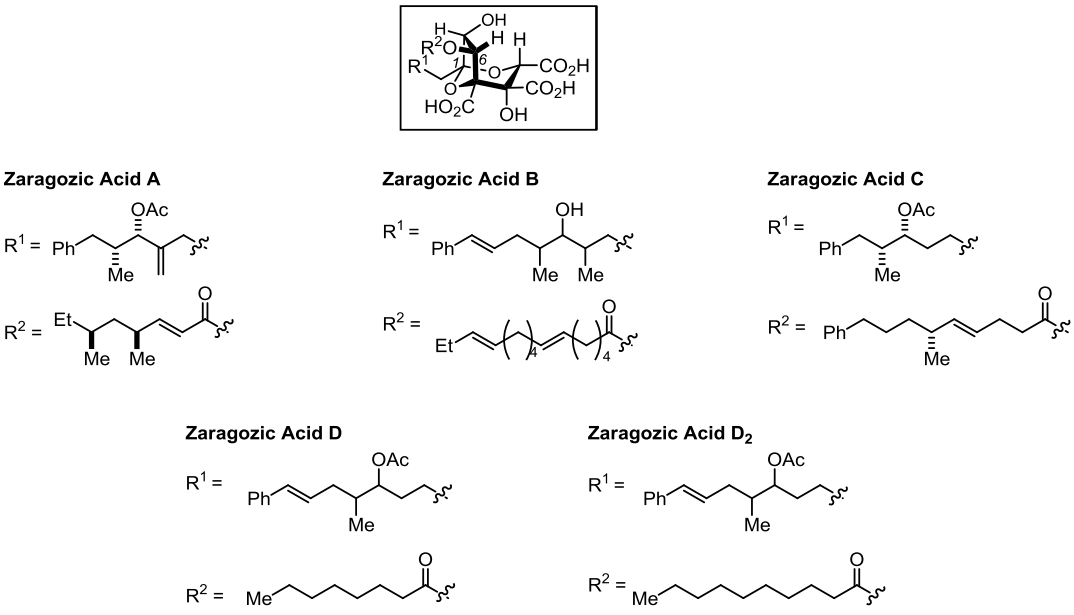
Figure 1-1. The Glycolic Acid Subunit in Biologically-Active Compounds



1.1.2 The Zaragozic Acids

The zaragozic acids and the squalestatins constitute a class of squalene synthase inhibitors isolated from various fungal strains in 1991.[12] In mammals, squalene synthase is responsible for the biosynthesis of cholesterol; therefore, the zaragozic acids have potential as pharmaceutical agents for the treatment of hypercholesterolemia.[9] Structurally, the zaragozic acids all contain a densely functionalized 2,8-dioxabicyclo[3.2.1]octane core, and are differentiated by their C1-alkyl and C6-acyl sidechains (Figure 1-2).

Figure 1-2. Zaragozic Acid Structure



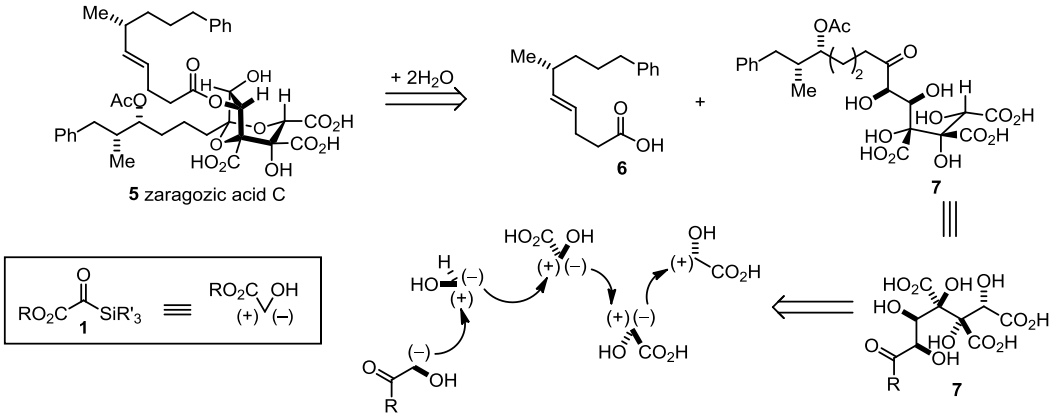
Due to their biological activity and novel structure, the zaragozic acids have attracted significant attention from the synthetic community. The six contiguous chiral centers of the core constitute the principal obstacle to synthesis, and have inspired many unique solutions.[13-29] The first synthesis of zaragozic acid C was completed by Carreira and Du Bois in 1994, requiring 32 linear steps from commercially available starting materials.[14] Prior to our work, the shortest route to zaragozic acid C was reported by the Evans group, involving 23 linear steps from D-tartaric acid.[18] Notably, all prior approaches to the zaragozic acids rely on multistep alterations in functionality and oxidation state. In contrast, we aimed to achieve a "self-consistent synthesis", defined by Hendrickson as a sequence of constructions not requiring any intervening refunctionalizations.[30]

1.1.3 Retrosynthetic Analysis and Multicomponent Coupling

What we found striking about zaragozic acid C was that the global complexity masks an elementary composition of simple building blocks. Analysis of the C1-C7

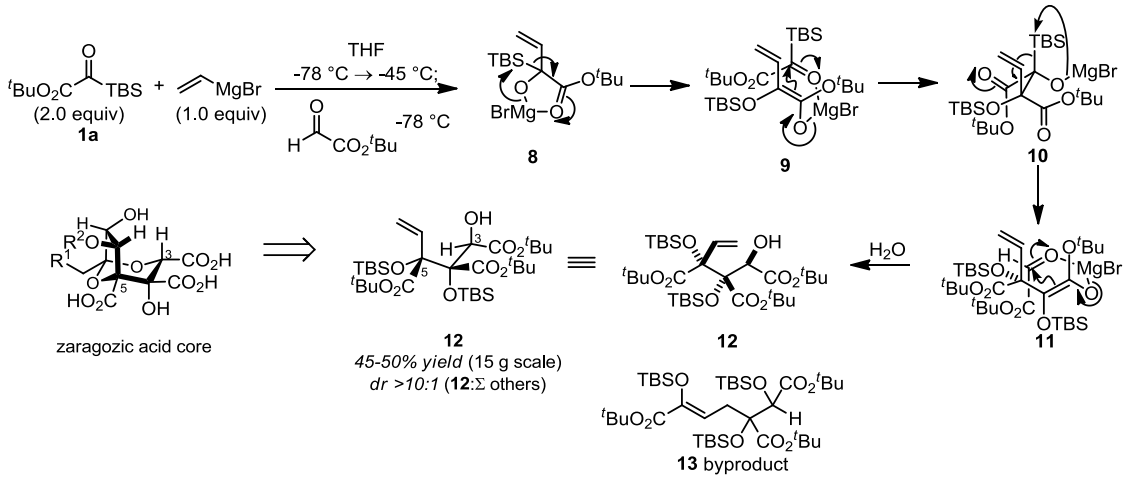
bicyclic ketal by deconstruction into simple synthons reveals a repeating series of glycolic acid fragments (Scheme 1-3). Because silyl glyoxylates serve as geminal dipolar glycolic acid synthons, a trimerization of glycolic acid units represents a reasonable synthetic approach to the zaragozic acid core.

Scheme 1-3. Retrosynthetic Plan Incorporating Geminal Diaddition



David Nicewicz tested the hypothesis that enchainment of multiple equivalents of silyl glyoxylate could assemble most of the zaragozic acid skeleton in one step. Nicewicz found that the addition of one equivalent of vinyl Grignard reagent to two equivalents of **1a** at -78 °C initiated the oligomerization process (Scheme 1-4). In the absence of an alternative secondary electrophile, the glycolate enolate intermediate **9** reacted with a second equivalent of silyl glyoxylate, which underwent Brook rearrangement prior to termination of the oligomerization sequence by addition of *t*-butyl glyoxylate. The multicomponent coupling provided α-hydroxy ester **12** with >10:1 d.r. and up to 50% yield. The major byproduct resulted from vinylogous addition and subsequent enchainment of a third equivalent of silyl glyoxylate to provide enolsilane **13**. This polyaddition reaction introduces the C3-C6 framework in one step with correct establishment of the relative stereochemistry at the most challenging sites: C4 and C5.

Scheme 1-4. Multicomponent Coupling

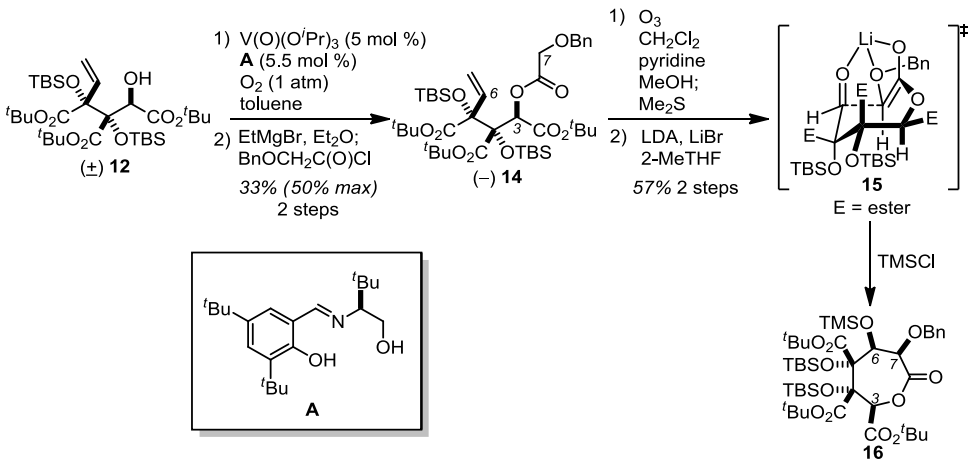


1.2 Total Synthesis of Zaragozic Acid C

1.2.1 Completion of the Dioxabicyclo[3.2.1]octane Core

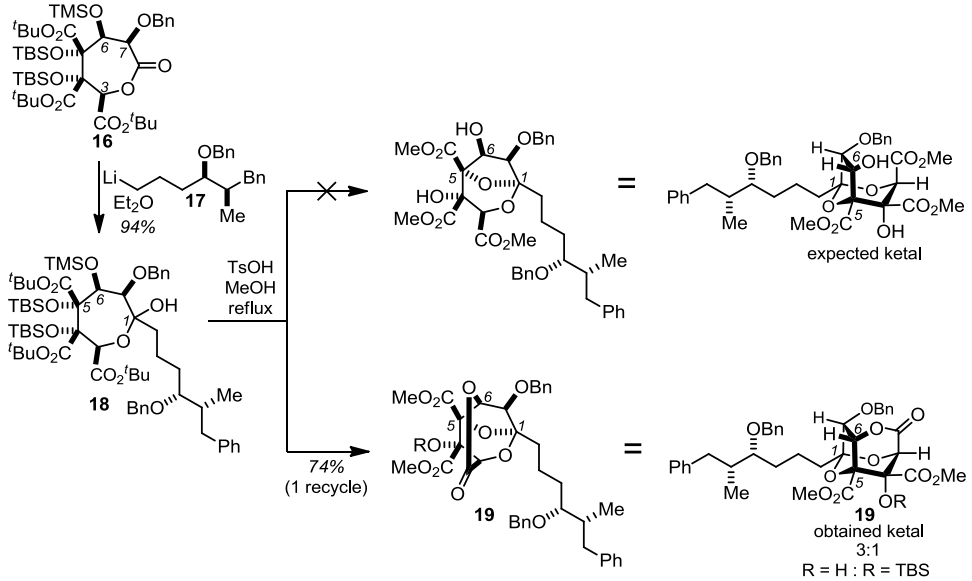
Racemic hydroxy ester **12** was subjected to oxidative kinetic resolution providing (–)-**12** in 90% ee (Scheme 1-5).[31] The C3 alcohol was acylated with benzyloxyacetyl chloride to provide glycolate ester **14**. Subsequent ozonolysis of the terminal olefin revealed the C6 aldehyde. Kinetic enolization with LDA induced an intramolecular glycolate aldol addition to afford **16** after TMSCl trapping of the aldolate. The aldol reaction created the C6 and C7 stereogenic centers, where C6 was generated with undesired stereochemistry. This result can be rationalized by the closed transition state **15**, wherein the C6 aldehyde, the C7 –OBn, and the C1 enolate chelate to the Li counterion. ε-Lactone **16** possesses the full carbon skeleton of the zaragozic acid core, obtained in 5 steps from silyl glyoxylate **1a**.

Scheme 1-5. Synthesis of C1-C7 ε-Lactone



The C1 alkyl sidechain was introduced by means of a nucleophilic addition of the organolithium **17** to lactone **16** (Scheme 1-6). Treatment of the resulting ketol/lactol mixture with TsOH induced the desired ketalization onto C1; however, a δ-lactone was also formed, likely as a consequence of the incorrect stereochemistry at C3 and C6.

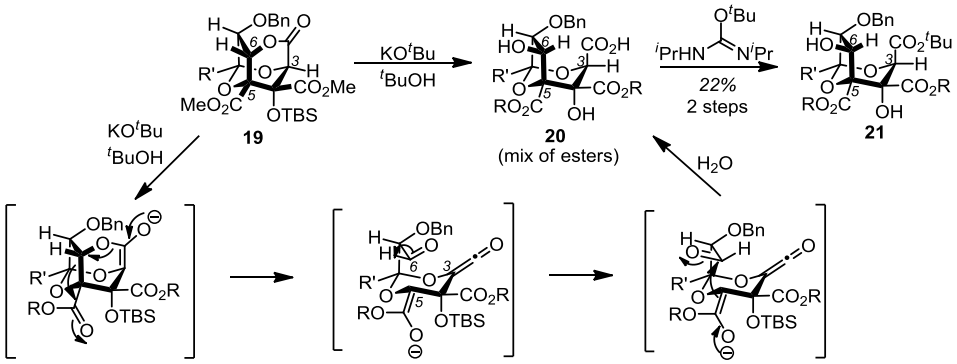
Scheme 1-6. Tricyclic Ketalization



The undesired δ-lactone ultimately served as a means to correct the C6 stereochemistry; treatment of tricycle **19** with KO^{t}Bu in ^{t}BuOH at room temperature

resulted in lactone opening as well as epimerization of C6. The mechanism (Scheme 1-7) of this fortuitous transformation may be initiated by alkoxide addition to the C3 lactone (not shown) or deprotonation of the C3 lactone with subsequent ketene formation. The resulting C6 alkoxide could trigger a retro-aldol fragmentation of the C5-C6 bond, producing a C6 aldehyde and a C5 glycolate enolate. Rotation of the C6 aldehyde, followed by aldol closure of the C5-C6 bond would result in the observed stereochemical correction. If C3 ketene formation is involved, aqueous workup would result in C3 carboxylic acid formation. *t*-Butyl esterification was then performed on the crude mixture to provide triester **21**. Notably, this transformation was only possible because the zaragozic acid core had been assembled in the correct oxidation state from the outset of the synthesis.

Scheme 1-7. Proposed Mechanism of C6 Stereochemical Correction

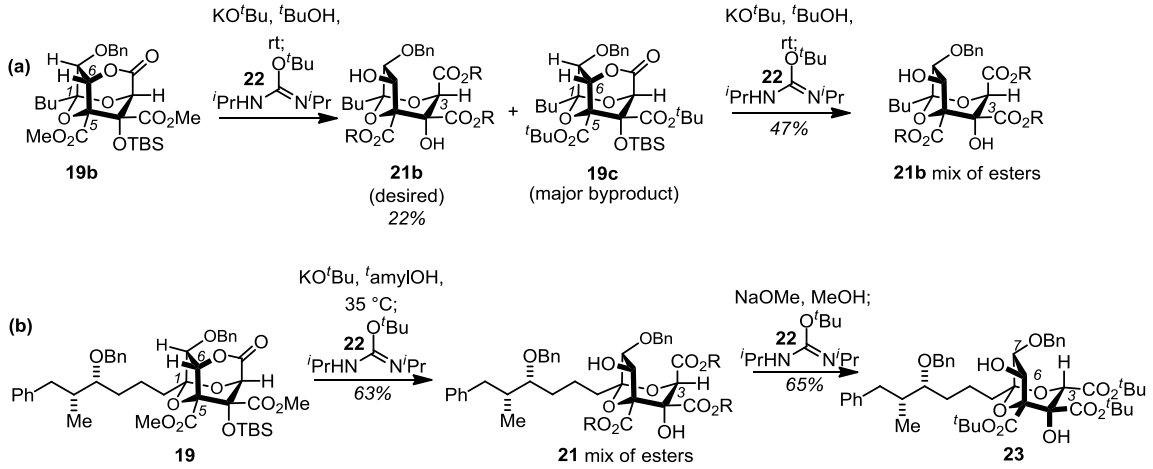


Although this protocol achieved two necessary transformations (lactone opening and C6 epimerization), the yield was only 22%. Before graduating, Nicewicz found that the zaragozic acid core could be completed by inversion of C3 with NaOMe; the only remaining transformations for completion of the synthesis included installation of the C6 sidechain and deprotections. In collaboration with Andrew Satterfield, efforts commenced to finish the synthesis, starting with optimization of the lactone opening.

Initial efforts involved attempts to reductively cleave the lactone, which could likely be reoxidized to the carboxylic acid. $NaBH_4$ and DIBAL both selectively reduced methyl esters in preference to the lactone. Borane reducing agents proved to be unreactive. We next investigated conversion of the lactone to a cleavable vinyl ether, with the expectation that the additional carbon atom could be removed through a haloform reaction. However, both Tebbe and Petasis reagents provided only unreacted starting material when exposed to lactone tricycle **19**.

Efforts then shifted back to optimization of the originally developed conditions of KO^{t}Bu in ^{t}BuOH, using model system **19b**. A major byproduct of this protocol resulted from transesterification of the methyl esters to *t*-butyl esters without lactone opening (**19c**, Scheme 1-8). Resubjection of this transesterified tricycle to the reaction conditions resulted in increased yields of the C6-corrected triester **21b**. Noting that sterically hindered esters underwent cleaner lactone opening, we attempted to saponify the methyl esters of **19b** and then re-esterify them to bulkier esters. Evaluation of various saponification conditions led to the unexpected finding that KO^{t}Bu in *t*-amyl alcohol at 35 °C induced rapid saponification and lactone opening. Treatment of the crude mixture with isourea **22** provided C6-epimerized triester **21** in synthetically useful yield (b, Scheme 1-8). Subsequently, treatment with the previously developed conditions of NaOMe in MeOH resulted in correction of the C3 stereocenter as well as unanticipated saponification to the tricarboxylic acid. This unwanted hydrolysis necessitated re-esterification with isourea **22**, furnishing triester **23**.

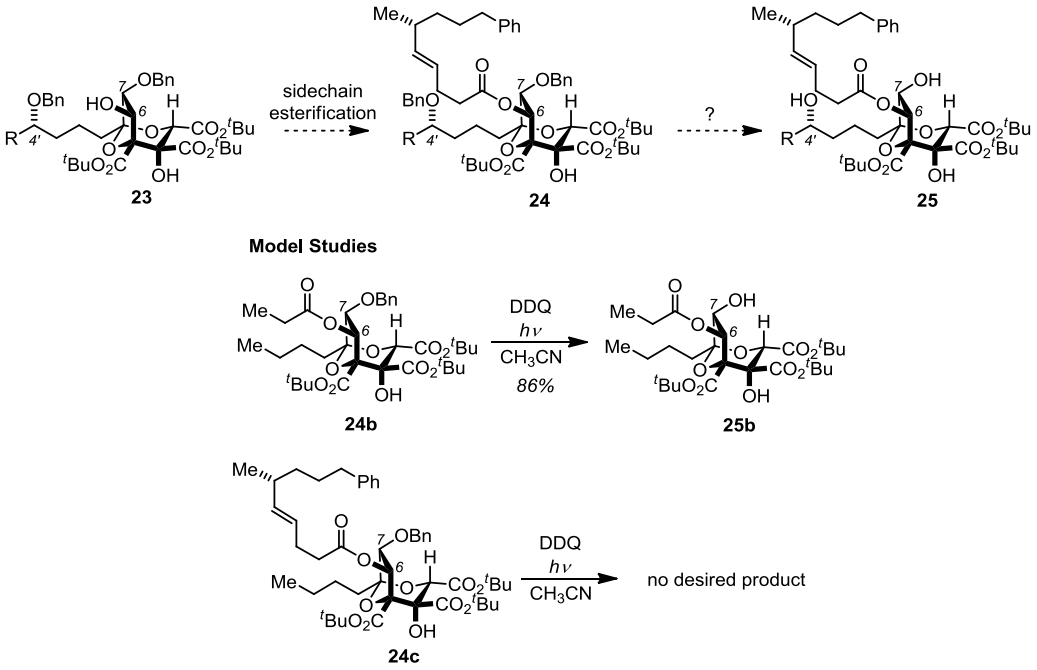
Scheme 1-8. Inversion of C6 and C3



1.2.2 Completion of (+)-Zaragozic Acid C

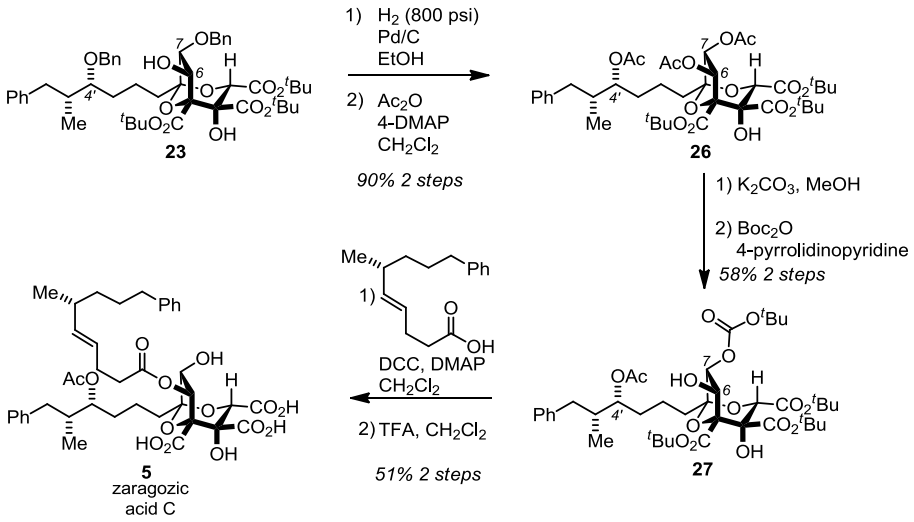
With a scalable route developed for the synthesis of the dioxabicyclooctane core, we shifted our focus towards the completion of zaragozic acid C. The C6 hydroxyl was the sole unprotected secondary alcohol at this stage, providing an opportunity to install the C6 acyl sidechain. However, completion of the synthesis would require deprotection of the benzyl ethers, which would likely involve a process incompatible with the olefin of the C6 sidechain. Alternative benzyl deprotection conditions were tested on simplified substrate **24b** (Scheme 1-9). After a variety of conditions failed to cleanly deprotect the C7 benzyl ether of model substrate **24b**, photoirradiation in conjunction with DDQ provided the desired transformation in high yield.[32,33] When the same procedure was repeated on olefin **24c**, decomposition resulted. As we were unable to deprotect the benzyl ethers in the presence of the C6 sidechain, we sought an alternative completion strategy.

Scheme 1-9. Benzyl Deprotection Incompatible with Olefin



The Carreira synthesis of zaragozic acid C utilizes a series of remarkably selective late-stage modifications that effectively distinguish the three secondary alcohols at C4', C6, and C7.[13] Deprotection of the benzyl ethers of bicyclic ketal **23**, followed by triacetylation of C4', C6, and C7 provided Carreira's triacetate **26** (Scheme 1-10). At this point, we utilized the Carreira protocol for completion of the synthesis, first involving selective deprotection of the C6 and C7 acetates. Presumably, this was possible due to their elevated electrophilicity relative to the C4' sidechain acetate, owing to inductive effects of the highly-oxygenated core. Differentiation of the C6 and C7 alcohols was performed by selective O-Boc protection of the C7 hydroxyl group, which Carreira and Du Bois found to be more reactive than the C6-OH in their model studies on derivatives of zaragozic acid A. Subsequent DCC coupling with the C6 acyl sidechain and treatment with TFA completed the synthesis of (+)-zaragozic acid C.[34]

Scheme 1-10. Completion of Zaragozic Acid C



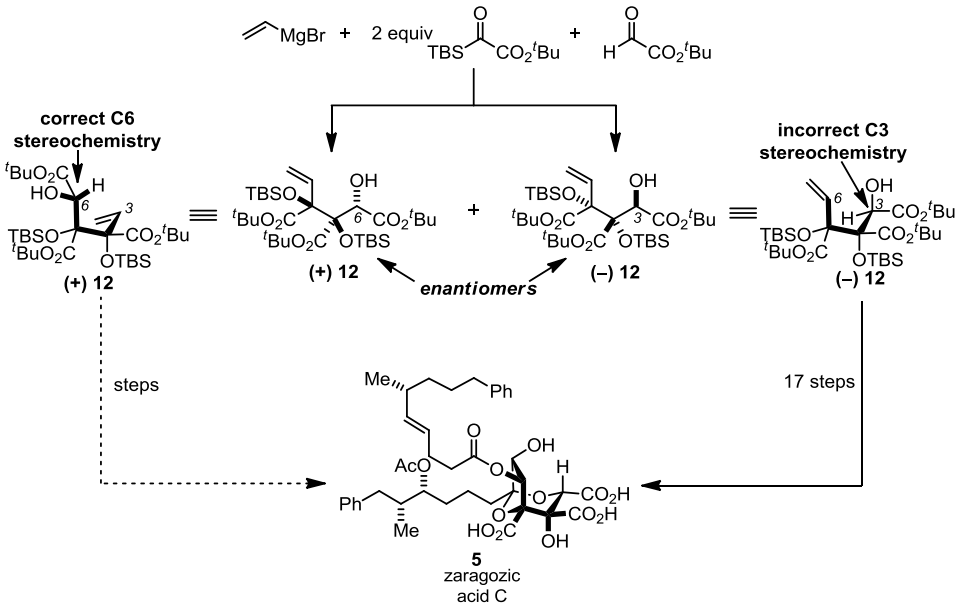
The synthesis of zaragozic acid C was completed in 18 linear steps, constituting the shortest synthesis to date. This was made possible by the rapid buildup of molecular complexity engendered by the silyl glyoxylate multicomponent reaction. Furthermore, the brevity of the sequence is also due in part to its "self-consistent" nature, as there was only one oxidation state modification throughout the synthesis (C6 ozonolysis).

1.3 Efforts Toward a Second-Generation Synthesis

1.3.1 Retrosynthesis Involving a C6 Electrophile

Although our completed synthesis constituted a concise route to zaragozic acid C, we postulated that a shorter synthesis was possible. This premise was based on the stereochemical outcome of the multicomponent coupling step (Scheme 1-11). The first generation synthesis utilized two equivalents of silyl glyoxylate to serve as the C4 and C5 glycolic acid units and *t*-butyl glyoxylate to serve as the C3 glycolic acid. Since the C3 stereocenter is created with undesired relative stereochemistry, multiple correction steps were required. We noticed that the enantiomeric multicomponent coupling product **(+)-12** would provide the correct stereochemistry at C6.

Scheme 1-11. Stereochemistry of Multicomponent Coupling

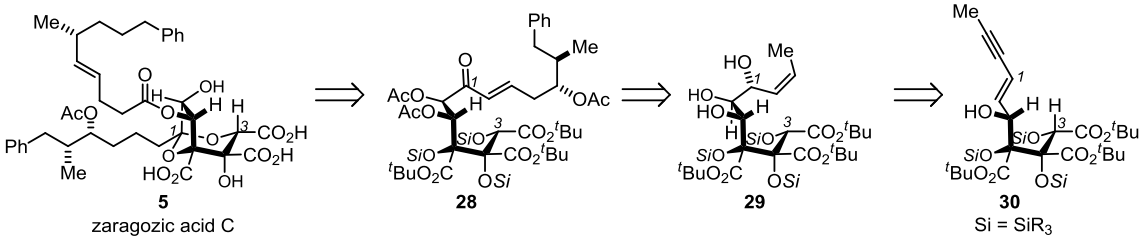


Another improvement would be to utilize an alternative terminal electrophile that would facilitate manipulation of C7 and C1 (an α,β-unsaturated aldehyde). To this end, the cascade reaction was tested with cinnamaldehyde as the terminal electrophile, which provided the multicomponent coupling product in usable 40% yield and >10:1 d.r. with correct C6 stereochemistry. At this juncture, we had established the feasibility of assembling C4-C6 in one step with correct stereochemistry; however, we recognized that the use of vinyl Grignard reagent as the nucleophilic initiator would necessitate substantial modification for the installation of C3 functionality. The ideal C3 nucleophile would be prefunctionalized, initiate silyl glyoxylate dimerization, and generate C3, C4, C5, and C6 with proper relative stereochemistry.

Based on this idealized assembly, a revised retrosynthesis was considered. Zaragozic acid C could potentially be accessed by 1,4-reduction and ketalization of enone **28**. Enone **28** could be accessed by allylic oxidation and cross metathesis from allylic

alcohol **29**. Triol **29** could be prepared by asymmetric dihydroxylation and Lindlar reduction of cascade product **30**. This direct route hinged on the identification of a proper nucleophilic cascade trigger to constitute C3.

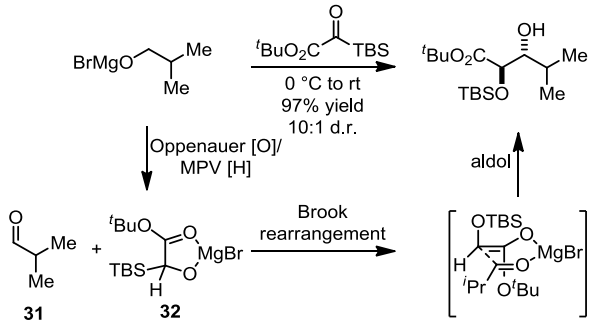
Scheme 1-12. Second-Generation Retrosynthesis of Zaragozic Acid C



1.3.2 MPV-Initiated Multicomponent Couplings

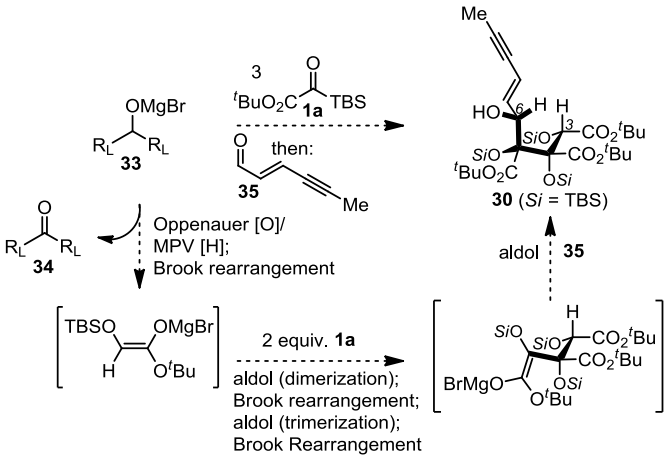
We considered the Meerwein-Ponndorf-Verley (MPV) reduction/aldol sequence developed by former group members Xin Linghu and Andrew Satterfield (eq. 1, Scheme 1-13) as a potential solution to the C3 nucleophile problem.[35] Mechanistically, the reaction is proposed to involve Oppenauer oxidation of a magnesium alkoxide (generating aldehyde **31**), with concurrent MPV reduction of silyl glyoxylate (generating magnesium alkoxide **32**). Subsequent Brook rearrangement generates a glycolate enolate, which undergoes aldol coupling with the aldehyde **31** that was generated *in situ* from the alkoxide.

Scheme 1-13. Aldol Triggered by Oppenauer Oxidation/MPV Reduction



We hypothesized that employing a sterically hindered secondary magnesium alkoxide **33** would permit MPV reduction of the silyl glyoxylate, and would induce aldol addition to a second equivalent of silyl glyoxylate in preference to the sterically hindered ketone **34** (Scheme 1-14). After addition to a second equivalent of silyl glyoxylate **1a** and subsequent Brook rearrangement, enchainment of a third silyl glyoxylate unit would be possible. Finally, a third Brook rearrangement and aldol addition to the terminal electrophile (aldehyde **35**) would provide multicomponent coupling product **30**.

Scheme 1-14. Proposed MPV-Initiated Multicomponent Coupling

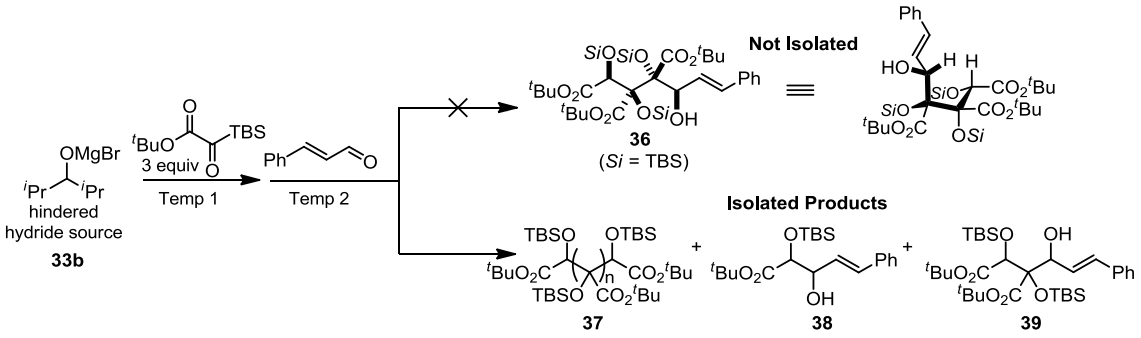


Chemoselectivity could potentially be controlled by stoichiometry and order of reagent addition, but the reaction would need to provide adequate stereoselectivity to be useful. The proposed coupling would install four contiguous stereocenters (C3-C6); while a relevant model for proper establishment of C3 relative stereochemistry was lacking, C4-C6 would preferably be formed with analogous stereochemistry to the parent vinyl Grignard-initiated coupling.

Initial experiments employed hindered magnesium alkoxide **33b**, three equivalents of silyl glyoxylate **1a**, and cinnamaldehyde as a model α,β-unsaturated aldehyde. Reactions where the silyl glyoxylate and the alkoxide were warmed to rt prior

to addition of cinnamaldehyde resulted in uncontrolled silyl glyoxylate oligomerization (entries 1-2, Table 1-1). This indicated that the magnesium alkoxide was effectively inducing MPV reduction of the silyl glyoxylate, and the resulting hindered ketone was not undergoing undesired aldol coupling. In an effort to control the degree of oligomerization, the hindered alkoxide **33b** and the silyl glyoxylate were stirred at -50 °C prior to addition of cinnamaldehyde (entry 3). The product, **38**, resulted from MPV reduction, Brook rearrangement, and addition to cinnamaldehyde. Since only one silyl glyoxylate was incorporated, we next increased the temperature prior to addition of cinnamaldehyde. Dimerization/aldol product **39** was obtained when the reaction was warmed to 0 °C (entry 4). Attempts to incorporate the third silyl glyoxylate unit by holding at -10 °C for extended periods resulted in mixtures of uncontrolled oligomerization products **37** (entry 5). Another attempt (not shown) involved sequential introduction of two equivalents of TBS silyl glyoxylate **1a**, followed by one equivalent of trimethylsilyl glyoxylate. Despite the reduced hindrance of trimethylsilyl glyoxylate, the third silyl glyoxylate was not incorporated.

Table 1-1. Influence of Temperature on MPV-Initiated Cascade



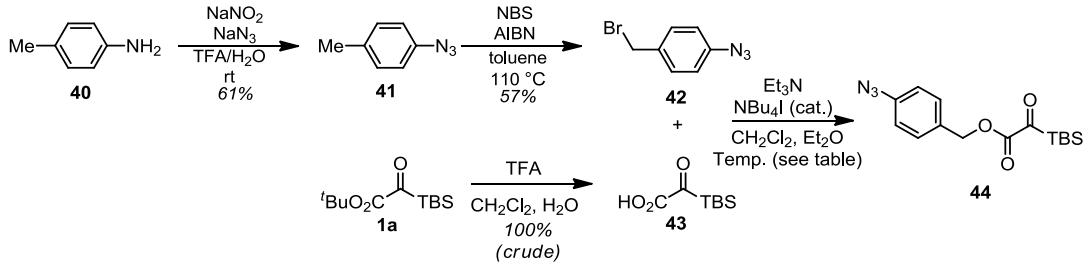
entry	temperature 1	temperature 2	major product
1	rt	rt	**37**
2	-78 °C to rt	-78 °C	**37**
3	-50 °C	-50 °C	**38**
4	-78 to 0 °C	-78 °C	**39**
5	-78 to -10 °C (5 h)	-78 °C	**37**

Due to the challenges associated with controlling the degree of oligomerization, we next investigated an intramolecular cascade using tethered silyl glyoxylates. The first objective was to synthesize a compound comprised of three silyl glyoxylate units. Previous studies in our group had revealed that *t*-butyl silyl glyoxylate could be cleanly modified to the silyl glyoxylic acid by treatment with TFA (Table 1-2, **1a** → **43**). Subsequent triesterification of glycerol with the silyl glyoxylic acid **43** under either Mukaiyama[36] or DCC conditions was unsuccessful, as acylsilane decomposition occurred in each case. Conversion of the silyl glyoxylic acid to the acid chloride was also unsuccessful using oxalyl or thionyl chloride.

We next tried using the silyl glyoxylic acid as a nucleophile to displace a benzylic halide leaving group. *p*-Azido benzyl bromide **42** was employed as the electrophile, due

to its potential for elaboration under mild conditions via Huisgen cycloaddition.[37] Initial nucleophilic esterification attempts resulted in poor yields (Table 1-2). However, heating the reaction to reflux (1:1 CH_2Cl_2:Et_2O) resulted in 55% yield of the benzylic ester **44** (entry 5).

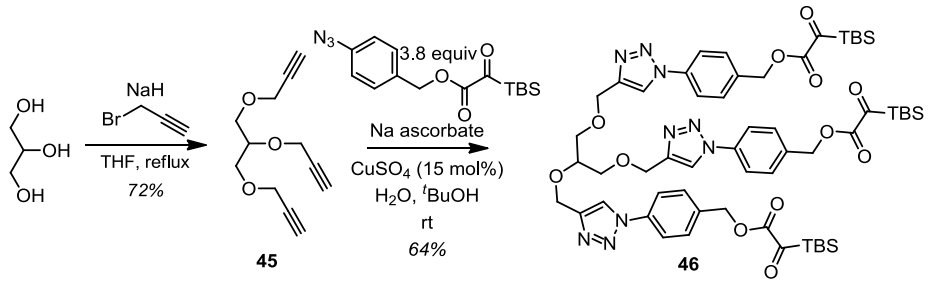
Table 1-2. Optimization of Nucleophilic Esterification



entry	equiv NBu_4I	equiv 42	T (°C)	isolated yield
1	0.01	1.5	0 to rt	15%
2	0.01	3.0	0 to rt	12%
3	0.01	1.5	-78 to rt	<5%
4	0.01	1.5	rt	14%
5	0.01	1.5	reflux	55%
6	0	1.5	reflux	0%

Having developed a scalable route to the azide-containing silyl glyoxylate **44**, we next prepared a triyne for a triple azide/alkyne [3+2] reaction. Glycerol was selected as a readily available triyne precursor; treatment with propargyl bromide and NaH afforded triyne **45**. Subsequent triple Huisgen cycloaddition provided tethered silyl glyoxylate **46**.

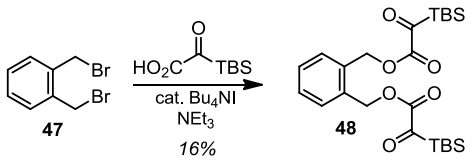
Scheme 1-15. Preparation of Tethered Silyl Glyoxylate for Intramolecular Cascade



Attempts to induce the MPV-initiated intramolecular coupling were met with no success. In order to initiate any reactivity, four equivalents of magnesium alkoxide **33b** were required. This may have been due to coordination of the three triazole moieties to the first three equivalents of magnesium, which would presumably inhibit formation of the six-membered transition state necessary for Oppenauer oxidation/MPV reduction. Nonetheless, using four or more equivalents of the hydride source caused decomposition to occur in each case. The products could not be identified, but may have resulted from multiple MPV reductions of tri-silyl glyoxylate **46**. In some cases, attack of the terminal electrophile (cinnamaldehyde) occurred, but the desired coupling product was never isolated.

In order to be successful, the MPV/double intramolecular aldol/intermolecular aldol cascade will likely require a different tether. Intramolecular silyl glyoxylate coupling with triazole **46** would have required formation of two large rings; a more feasible coupling would involve the closure of smaller rings. In an effort to generate a smaller and more rigid tether, esterification of dibromide **47** was performed (Scheme 1-16). Due to the low yield of formation of di-silyl glyoxylate **48**, we did not attempt analogous triesterification. In an effort to simplify the multicomponent coupling, we next considered prefunctionalization of the initial nucleophile.

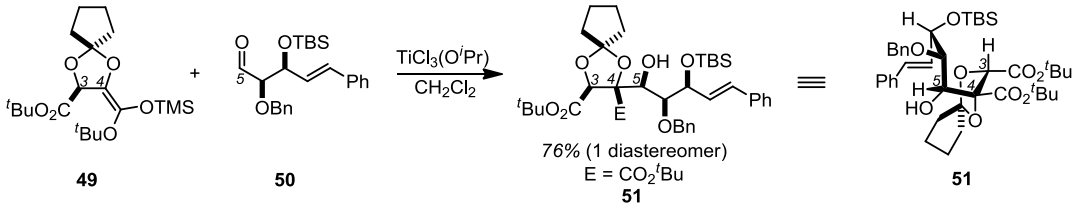
Scheme 1-16. Nucleophilic Esterification of a Benzylic Dibromide



1.3.3 Enolate-Initiated Multicomponent Couplings

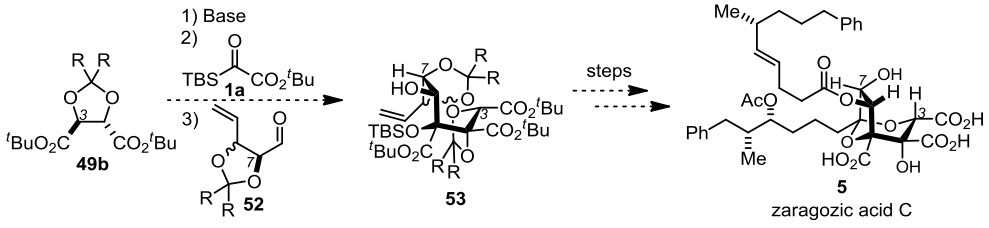
Evans' synthesis of zaragozic acid C established the C4–C5 bond via an aldol reaction between tartrate silyl ketene acetal **49** and aldehyde **50** (Scheme 1-17).[18] The high stereoselectivity at C4 is believed to result from approach of the aldehyde from the less hindered face of the tartrate ketal. We hypothesized that a prefunctionalized nucleophilic initiator, such as **49**, would reduce the number of components necessary in the multicomponent coupling.

Scheme 1-17. Known Stereoselective Aldol with Tartrate Enolate



A three component coupling of a protected tartrate enolate (C3 and C4), a silyl glyoxylate (C5), and an aldehyde (C6) could provide the majority of the zaragozic acid core (Scheme 1-18). Ideally, the C6 aldehyde **52** would be oxygenated at both the α- (C7) and β- (C1) positions, and possess an alkene for installation of the C1 sidechain via cross metathesis. However, for test reactions, benzaldehyde was used.

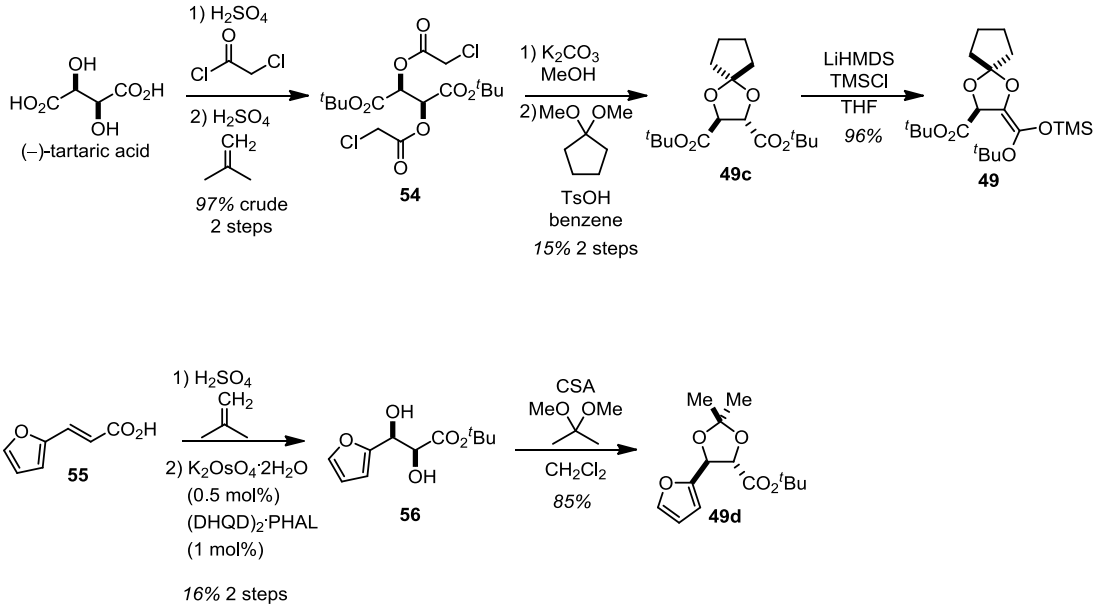
Scheme 1-18. Proposed Three Component Coupling with Tartrate Enolate



A series of protected tartaric acid derivatives were prepared. After direct *t*-butyl esterification of (–)-tartaric acid failed to proceed cleanly, ketals **49** and **49c** were

prepared according to the Evans procedure: (–)-tartaric acid was acylated with chloroacetyl chloride and esterified with condensed isobutylene to furnish tetra-ester **54**.[18] Deprotection of the secondary alcohols and ketalization with 1,1-dimethoxy cyclopentane provided ketal **49c**. Enolization and TMS trapping provided silyl ketene acetal **49**. Additionally, furan **49d** was prepared with the expectation that the 2-furyl substituent could be ozonolyzed to reveal a carboxylic acid later in the synthesis.[38] Beginning with commercially available 3-(2-furyl)acrylic acid **55**, furan **49d** was synthesized via an esterification, asymmetric dihydroxylation, and ketalization sequence.[39]

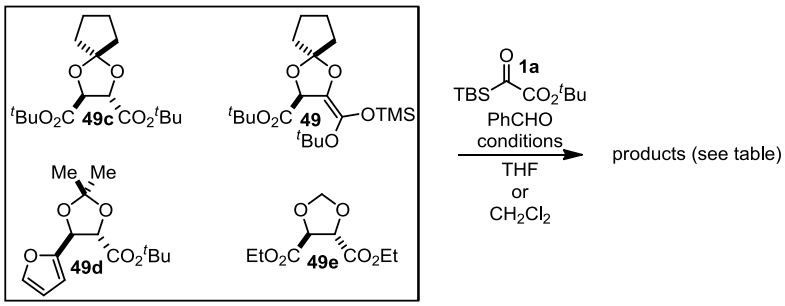
Scheme 1-19. Synthesis of *t*-Butyl Tartrate Derivatives



Cyclopentyl ketal **49c** was used in initial experiments. Stirring ketal **49c** with LiHMDS, followed by sequential addition of silyl glyoxylate and finally benzaldehyde, surprisingly resulted in recovery of ketal **49c** (entry 1, Table 1-3). In an effort to ensure the reactivity of the tartrate enolate, a simple aldol reaction was attempted with benzaldehyde (entry 2). Although the reaction was warmed to room temperature in an effort to increase

conversion, the unreacted tartrate ketal **49c** was the sole identifiable product. Based on this result, we postulated that a retro-aldol reaction was occurring at elevated temperatures, regenerating ketal **49c**. However, holding the temperature at -78 °C for the duration of the reaction still resulted in no conversion of ketal **49c**. We reasoned that enolate formation was a problem, so silyl ketene acetal **49** was prepared. Using a modification of the Evans conditions (entry 4), alcohol **57** was obtained; this product may be formed by MPV reduction of the silyl glyoxylate by $TiCl_3(O^iPr)_3$, with no subsequent Brook rearrangement (Si migration may be blocked by the O–Ti bond). In effort to generate the magnesium tartrate enolate, silyl ketene acetal **49** was reacted with tetrabutylammonium difluorotriphenylsilicate (TBAT) (entry 5). However, this only resulted in regeneration of diester **49c**.

Table 1-3. Tartrate Enolate Initiated Three Component Coupling Attempts



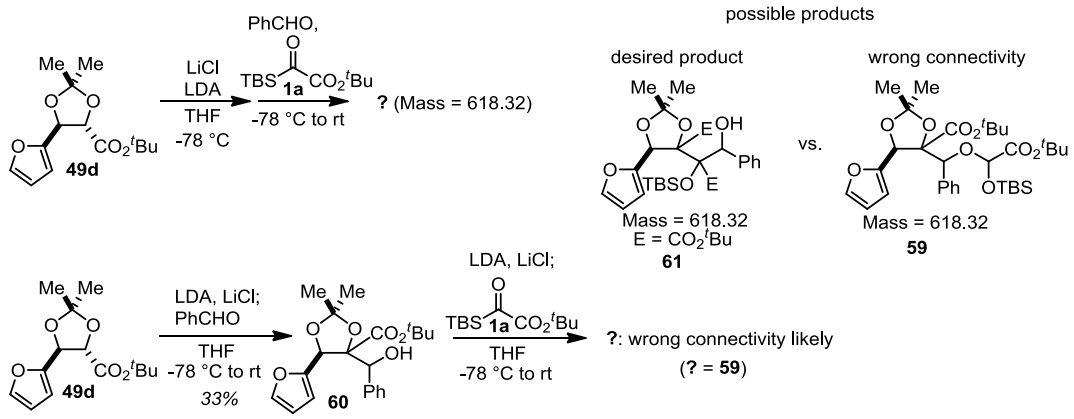
entry	conditions	major product
1	**49c**; LiHMDS; **1a**; PhCHO (-78 °C to rt)	**49c**
2	**49c**; LiHMDS; PhCHO (rt)	**49c**
3	**49c**; LiHMDS; PhCHO (-78 °C)	**49c**
4	**49**; $TiCl_3(O^iPr)$; $MgBr_2$; **1a**; PhCHO (-78 °C to rt)	**57**
5	**49**; $MgBr_2$ + TBAT; **1a**; PhCHO (-78 °C to rt)	**49c**
6	**49d**; LDA; **1a**; PhCHO (-78 °C to rt)	**58**
7	**49d**; LDA; PhCHO + **1a** (-78 °C to rt)	**59** d.r. unclear 1 diastereomer isolated (10% yield)
8	**49e**; LDA; **1a**; PhCHO (-78 °C to rt)	**49e**

We sought to further simplify the proposed reaction by employing a C3-C4 nucleophile with only one enolizable site. Reaction of furan **49d** sequentially with LDA, silyl glyoxylate **1a**, and benzaldehyde resulted in the first observation of addition to the silyl glyoxylate, although the terminal electrophile was not incorporated (entry 6, Table

1-3). Simultaneous addition of benzaldehyde and silyl glyoxylate to a solution of the enolate of **49d** resulted in formation of three component coupling product **59** (entry 7). Initially, this product was believed to be the desired C3-C6 coupling product, as the product's mass and ^{1}H NMR spectrum appeared to be correct.

Further analysis confirmed incorrect connectivity: (1) the IR spectrum revealed no OH stretch, and (2) no exchangeable protons were revealed by ^{1}H NMR after stirring with D_2O. Additionally, preparation of **59** was possible by treatment of alcohol **60** with LDA and silyl glyoxylate (Scheme 1-20). This indicated that the three component product resulted from an aldol reaction between the enolate of **49d** and benzaldehyde, then alkoxide addition to silyl glyoxylate, Brook rearrangement, and a proton quench. We then conjectured that a less hindered tartrate enolate would be necessary, and prepared the formaldehyde acetal of diethyl tartrate.[40] However, treatment of **49e** with LDA, silyl glyoxylate, and benzaldehyde resulted in low conversion (entry 8).

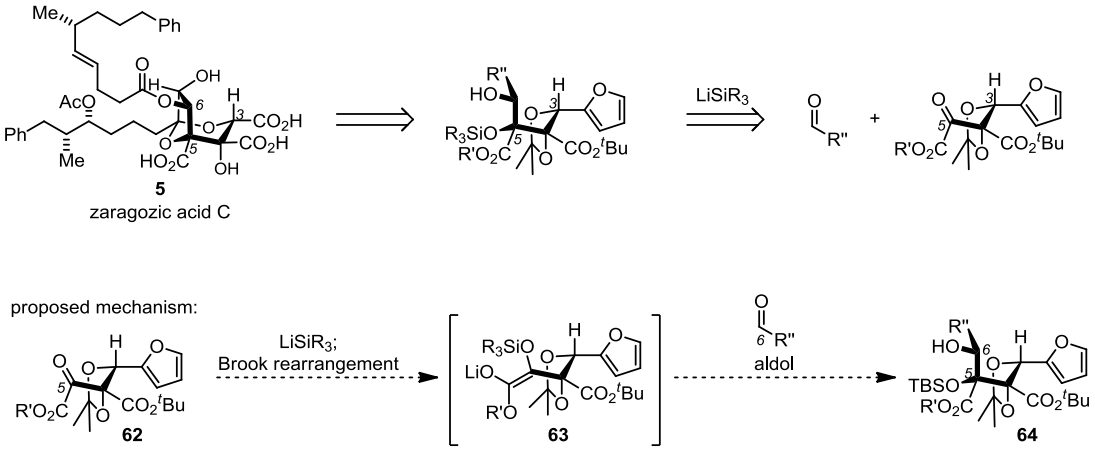
Scheme 1-20. Determination of the Connectivity of Three Component Product **59**



Due to the difficulties associated with the tartrate enolate initiated couplings, we considered an alternative approach. Rather than employing the silyl glyoxylate to link nucleophilic and electrophilic fragments, we investigated an umpolung coupling between

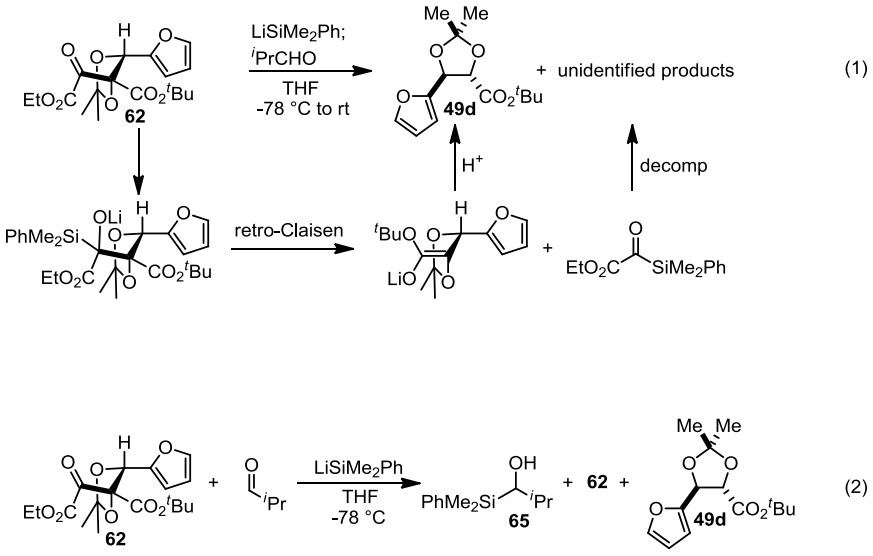
an aldehyde (C6) and ketoester **62** (C3-C5) (Scheme 1-21). In the proposed reaction, a silyl lithium reagent would add to the ketone of **62** and induce Brook rearrangement to form enolate **63**. Aldol reaction between enolate **63** and a C6 aldehyde would provide the desired C5-C6 bond.

Scheme 1-21. Umpolung C5-C6 Strategy



Ketoester **62** was prepared by means of an aldol reaction of furan **49d** with ethyl glyoxylate followed by Dess-Martin oxidation. Treatment of ketoester **62** with $LiSiMe_2Ph$ followed by isobutyraldehyde did not result in any of the desired coupling product; instead, retro-Claisen fragmentation product **49d** was formed (eq. 1, Scheme 1-22). Addition of $LiSiMe_2Ph$ to a premixed solution of ketoester **62** and isobutyraldehyde resulted in poor chemoselectivity for silyl lithium addition (eq. 2, Scheme 1-22). Disilyl zinc nucleophiles were also evaluated without success. Based on the experimental observations, the creation of the C4-C5 bond or the C5-C6 bond will be challenging due to a combination of steric demand and the reversibility of each bond construction.

Scheme 1-22. Attempted Couplings of Ketoester with Isobutyraldehyde.



1.4 Conclusion

In summary, a silyl glyoxylate cascade reaction allowed for the synthesis of (+)-zaragozic acid C in 18 linear steps. In addition to the multicomponent coupling, key steps included an intramolecular aldol reaction, and a one-pot lactone opening/retro-aldol/aldol sequence. The minimization of redox chemistry contributed to both the conciseness of the synthesis and to the unexpected solution for correction of C6 stereochemistry. This work further highlights the utility of silyl glyoxylates as geminal dipolar glycolic acid synthons.

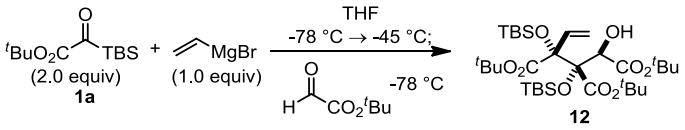
In an effort to complete a shorter, second generation synthesis, various approaches were investigated. A silyl glyoxylate trimerization/aldol cascade initiated by MPV reduction was explored, but the degree of oligomerization was difficult to control. Three component couplings between a tartrate-derived enolate, silyl glyoxylate, and an aldehyde resulted in low conversions, which was likely due to steric hindrance. We are

still interested in an improved synthesis of the zaragozic acids, and the development of new cascade reactions is ongoing.

1.5 Experimental

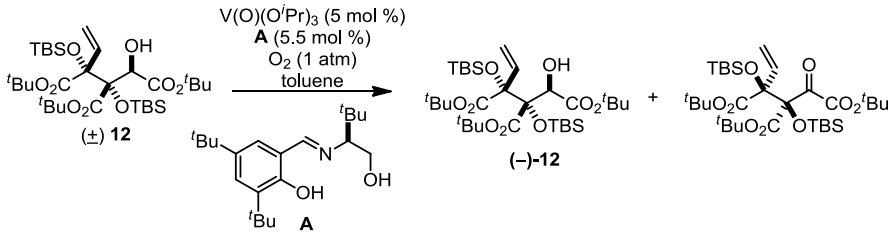
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on either a Bruker model Avance 500 (^{1}H at 500 MHz and ^{13}C NMR at 125 MHz), Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), or a Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.23 ppm; C_6D_6 at 7.15 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm and C_6D_6 at 128.62 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constants (Hz), and integration. Enantiomeric excesses were obtained using a Berger Supercritical Fluid Chromatograph model FCM 1100/1200 equipped with an Agilent 1100 series UV-Vis detector using a Chiralcel Chiralpak AS HPLC column. Samples were eluted with SFC grade CO2 at the indicated percentage of MeOH. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. Yields are reported

for a specific experiment and as a result may differ slightly from those found in the figures, which are averages of at least two experiments. Diethyl ether, tetrahydrofuran, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. Triethylamine was freshly distilled from CaH_2 under Ar prior to use. Side chains **53** and **30** were prepared according to the literature procedure.[34]



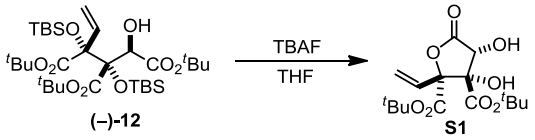
3-*tert*-Butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-2-vinyl-pentanedioic acid di-*tert*-butyl ester (12). A solution of 31.7 mL (31.7 mmol, 1.1 equiv) of vinylmagnesium bromide in THF (150 mL) was cooled to -78 °C and a solution of 15 mL (57.7 mmol, 1.1 equiv) of *tert*-butyl *tert*-butyldimethylsilyl glyoxylate (**1a**) in THF (50 mL) was added via cannula down the wall of the flask over 15 min. Once addition of the silyl glyoxylate was complete, the reaction was slowly warmed to -45 °C over 15 min. Once the cooling bath had reached -45 °C, the reaction was again cooled to -78 °C and 4.9 mL (43.3 mmol, 1.5 equiv) of *tert*-butyl glyoxylate was added via syringe. After stirring for 1 h at -78 °C, the reaction was quenched with 30 mL of saturated aqueous ammonium chloride solution. The two layers were separated and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to furnish the crude product which was purified by flash chromatography (1:2 CH_2Cl_2: petroleum ether linear gradient to 4:1 CH_2Cl_2:petroleum ether) to furnish 8.3 g (44%) of the pure product (**12**). The product

crystallized slowly (ca. 24 h) from a small amount (ca. 15 mL) of petroleum ether and yielded crystals suitable for X-ray analysis. Analytical data for **12**: **IR** (thin film, cm-1) 3534, 2931, 2856, 1734, 1645, 1472, 1393, 1368, 1248, 1147, 1001; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.30 (dd, 18.0, 10.8 Hz, 1H), 5.17 (d, *J* = 11.6 Hz, 1H), 5.17 (d, *J* = 16.8, 1H), 4.56 (d, *J* = 10.4, 1H), 3.64 (d, *J* = 10.8 Hz, 1H), 1.52 (s, 9H), 1.50 (s, 9H), 1.44 (s, 9H), 0.92 (s, 9H), 0.81 (s, 9H), 0.22 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6, 169.2, 169.1, 138.0, 117.2, 83.8, 83.0, 82.1, 77.4, 75.8, 74.7, 28.7, 28.6, 28.4, 26.9, 26.7, 19.7, 19.2, -1.0, -1.1, -1.5, -1.6; **TLC** (5:95 EtOAc: petroleum ether) R*f* 0.33. **Anal.** Calcd for $C_{32}H_{62}O_9Si_2$: C, 59.40; H, 9.66. Found: C, 59.47; H, 9.74.

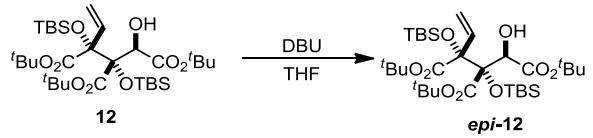


3-*tert*-Butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-2-vinyl-pentanedioic acid di-*tert*-butyl ester (–)-12. A 50 mL round bottomed flask equipped with a stirbar was purged with O_2 and charged with 82.2 mg (0.246 mmol, 0.055 equiv) of the salen ligand **A** in dry toluene (11.3 mL) and treated with 53 μL (0.224 mmol, 0.05 equiv) of VO(O^{i}Pr)$_3$ under a dry O_2 atmosphere. The resultant dark brown solution was stirred for 30 min. A solution of 2.9 g (4.48 mmol, 1.0 equiv) of racemic alcohol **12** in toluene (11.3 mL) was added via cannula to the catalyst solution. After 48 h, the reaction was passed through a plug of silica gel eluted with 1:9 Et_2O:petroleum ether. After concentration of collected fractions *in vacuo*, ^{1}H NMR analysis revealed 50% conversion to α-keto ester. The alcohol was purified by flash chromatography (5:95 Et_2O:petroleum

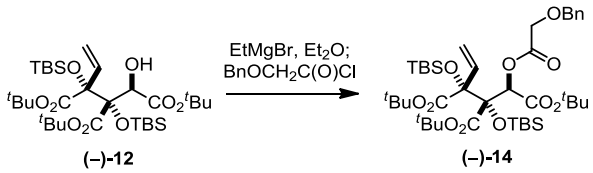
ether) to furnish 1.5 g (51%) of alcohol **(–)-12** (e.r. 90:10). The enantiomer ratio was determined by CSP-SFC analysis of lactone **51**.



3,4-Dihydroxy-5-oxo-2-vinyl-tetrahydrofuran-2,3-dicarboxylic acid di-*tert*-butyl ester (S1). A solution of 150 mg (0.23 mmol, 1.0 equiv) of bis-TBS ether **(–)-12** in THF (3.0 mL) at -45 °C was treated with 0.51 mL (0.51 mmol, 2.2 equiv) of a 1.0 M solution of tetrabutylammonium fluoride in THF. The solution was warmed to -20 °C and maintained at that temperature. After 1 h, 1.0 mL of H_2O was added and the reaction was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to furnish the crude diol which was purified by flash chromatography (2:3 EtOAc: petroleum ether), to furnish 63 mg (80%) of the pure diol (**S1**) as a white foam. Analytical data for **S1**: **IR** (Nujol mull, cm-1) 3525, 3439, 2912, 2858, 1801, 1760, 1729, 1458, 1377, 1304, 1258, 1146, 1124; **[α]Na** -18.8 (c = 1.09, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.49 (d, *J* = 17.0 Hz, 1H), 5.31 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 10.5 Hz, 1H), 4.28 (s, 1H), 3.01 (d, *J* = 11.0 Hz, 1H), 1.52 (s, 9H), 1.47 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.5, 167.7, 164.2, 131.4, 117.5, 88.1, 86.3, 84.8, 80.5, 72.0, 28.1, 28.0; **CSP-SFC** analysis (Chiralpak AS column, 5% MeOH, 1.5 mL/min, 150 psi, 40 °C, 240 nm, *t*r-minor 6.3 min, *t*r-major 18.6 min; **TLC** (30:70 EtOAc: petroleum ether) R*f* 0.17. **Anal.** Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: C, 55.79; H, 7.16.

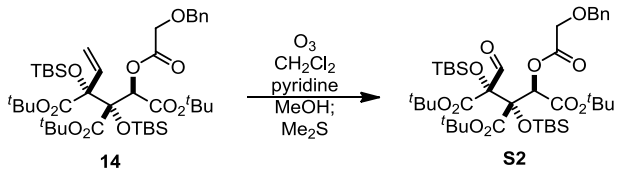


3-*tert*-Butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-2-vinyl-pentanedioic acid di-*tert*-butyl ester (*epi*-12). To a solution of 750 mg (1.15 mmol, 1.0 equiv) of the alcohol (**12**) in THF (10 mL) was added 86 μL (0.57 mmol, 0.5 equiv) of 1,8-diazabicyclo[5.4.0]undec-7-ene. After 5 h, 1 mL of saturated aqueous ammonium chloride was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 8 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude material (5:95 Et_2O: petroleum ether) furnished 551 mg (73%) of the alcohol ***epi*-12** as an oil. Analytical data for ***epi*-12**: **IR** (thin film, cm-1) 3428, 2930, 2857, 1746, 1729, 1713, 1473, 1393, 1369, 1255, 1155; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.49 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.45 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.63 (s, 1H), 4.03 (s, 1H), 1.52 (s, 9H), 1.42 (s, 18H), 0.93 (s, 9H), 0.87 (s, 9H), 0.20 (s, 3H), 0.11 s, 3H), -0.01 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.7, 170.1, 170.0, 137.6, 123.5, 85.5, 83.6, 82.8, 81.4, 74.6, 28.5, 28.2, 26.8, 26.1, 25.8, 19.7, 18.3, -1.8, -2.5, -4.3, -4.5 (two overlapping resonances); **TLC** (5:95 Et_2O: petroleum ether) R*f* 0.29. **Anal.** Calcd for $C_{32}H_{62}O_9Si_2$: C, 59.40; H, 9.66. Found: C, 59.57; H, 9.78.

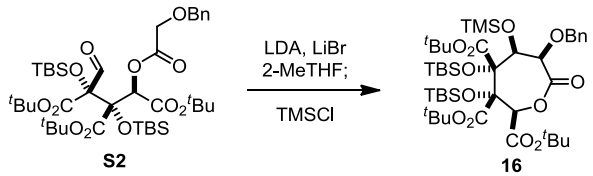


4-(2-Benzyloxy-acetoxy)-3-*tert*-butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-vinyl-pentanedioic acid di-*tert*-butyl ester (14). To a solution of 680 mg

(1.1 mmol, 1.0 equiv) of the alcohol (**12**) in Et_2O (14 mL) at 0 °C was added 1.3 mL of a 1.0 M EtMgBr solution in THF (1.26 mmol, 1.2 equiv). This solution was warmed to 23 °C and resulted in a thick slurry. Following stirring for 1 h, a solution of 0.32 mL (2.1 mmol, 2.0 equiv) of the acid chloride in Et_2O (4 mL) was added via cannula (1 mL rinse). The reaction was stirred at 23 °C for 18 h, then quenched by the addition of 6 mL of saturated aqueous ammonium chloride solution. After the layers were separated, the aqueous layer was extracted with additional Et_2O (3 X 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction revealed 74% conversion of the starting material. Purification of the crude reaction by flash chromatography (5:95 EtOAc: petroleum ether) yielded 540 mg (65%, 88% based on recovered starting material) of the acylated alcohol (**14**). Analytical data for **14**: **IR** (thin film, cm-1) 2930, 2855, 1757, 1744, 1725, 1594, 1369, 1250, 1152; **[α]Hg** -3.8 (c = 2.15, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 6.39 (dd, *J* = 18.0, 11.2 Hz, 1H), 6.17 (s, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 18.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.6, 1H), 4.06 (s, 2H), 1.56 (s, 9H), 1.39 (s, 9H), 1.37 (s, 9H), 0.89 (s, 9H), 0.85 (s, 9H), 0.30 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.3, 168.9, 167.9, 164.7, 137.2, 136.8, 128.7, 128.3, 128.2, 118.4, 87.0, 85.7, 83.9, 83.2, 83.0, 75.7, 73.5, 67.1, 28.7, 28.6, 28.5, 27.5, 26.9, 20.1, 19.4, -0.5, -0.7, -1.4, -1.7; **TLC** (5:95 EtOAc: petroleum ether) R*f* 0.23. **Anal.** Calcd for $C_{41}H_{70}O_{11}Si_2$ C, 61.93; H, 8.87. Found: C, 62.73; H, 9.01.

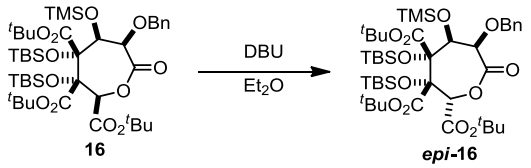


4-(2-Benzyloxy-acetoxy)-3-*tert*-butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-formyl-pentane dioic acid di-*tert*-butyl ester (S2). A solution of 646 mg (0.81 mmol, 1.0 equiv) of alkene **14** in 8.9 mL of CH_2Cl_2/MeOH/pyridine (10:1:1) was cooled to -78 °C. O3 was bubbled slowly through the solution at -78 °C and the reaction was monitored by TLC. After 1 h (reaction complete by TLC), the reaction was purged with Ar for 15 min. Dimethylsulfide (300 μL, 4.1 mmol, 5.0 equiv) was then added via syringe and the reaction was warmed to ambient temperature and stirred for 2 h. Concentration of the crude reaction *in vacuo* followed by flash chromatography (5:95 EtOAc: petroleum ether) afforded 550 mg (85%) of the pure aldehyde (**S2**) as a white foam. Analytical data for **S2**: **IR** (thin film, cm-1) 2977, 2929, 2859, 1758, 1745, 1728, 1473, 1394, 1368, 1253, 1152, 1129; **[α]D** -6.7 (c = 0.73, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.34-7.23 (m, 5H), 6.32 (s, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H); 4.07 (d, *J* = 16.8 Hz, 1H), 4.02 (d, *J* = 16.8 Hz, 1H), 1.51 (s, 9H), 1.37 (s, 18H), 0.90 (s, 9H), 0.81 (s, 9H), 0.29 (s, 3H), 0.11 (s, 3H), 0.067 (s, 3H), 0.034 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.4, 169.0, 166.8, 166.4, 165.2, 137.1, 128.7, 128.3, 128.2, 87.1, 86.2, 84.4, 84.0, 83.9, 74.9, 73.5, 67.1, 28.4, 28.3, 27.0, 26.7, -1.2, -1.4, -1.9, -2.7 (two overlapping resonances); **TLC** (1:9 EtOAc: petroleum ether) R*f* 0.39. **Anal.** Calcd for $C_{40}H_{68}O_{12}Si_2$: C, 60.27; H, 8.60. Found: C, 60.45; H, 8.65.

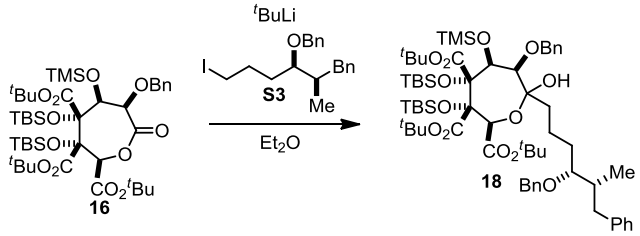


6-Benzyloxy-3,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-7-oxo-5-trimethylsilanyloxy-oxepane-2,3,4-tricarboxylic acid tri-*tert*-butyl ester (16). To a solution of 80 μL of diisopropylamine (0.55 mmol, 2.2 equiv) in 2-methyltetrahydrofuran (0.6 mL) at 0 °C under an Ar atmosphere was added 360 μL of a 1.4 M *n*-butyllithium solution in hexane (0.50 mmol, 2.0 equiv). The LDA solution was stirred for 15 min at 0 °C, then added via cannula to a solution of 200 mg (0.25 mmol, 1.0 equiv) of aldehyde **S2** and 87 mg (1.0 mmol, 4.0 equiv) of LiBr in 2-methyltetrahydrofuran (1.0 mL) at -78 °C. Once addition was complete (0.4 mL wash), the yellow solution was warmed slowly (ca. 15 min) to -45°C and maintained at that temperature. After 1 h, 130 μL of chlorotrimethylsilane was added at -45°C. The reaction was stirred for 15 min, then quenched by the addition of saturated aqueous ammonium chloride solution (1.0 mL). The reaction was extracted with Et_2O (3 x 8 mL) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography (1:9 Et_2O: petroleum ether), to afford 145 mg (67%) of the pure aldol (**16**) as a crystalline solid. Analytical data for **16**: **IR** (thin film, cm-1) 2976, 2929, 2858, 1761, 1733, 1471, 1369, 1252, 1152, 1121, 1004; **[α]D** -6.8 (c = 1.06, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 5.24 (s, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.85 (s, 1H), 4.39 (s, 1H), 4.33 (d, *J* = 10.0 Hz, 1H), 1.53 (s, 9H), 1.50 (s, 9H), 1.47 (s, 9H), 0.99 (s, 9H), 0.81 (s, 9H), 0.34 (s, 3H), 0.28 (s, 3H), 0.18 (s, 3H), 0.14 (s, 3H), 0.049 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 167.0, 166.7, 165.1, 137.2, 128.9, 128.5, 128.2, 87.3, 84.1, 83.7, 83.3, 81.6, 78.5,

77.7, 75.0, 72.9, 28.9, 28.4, 28.2, 27.7, 27.6, 20.4, 20.3, 1.5, -0.008, -0.3, -0.6, -0.8; **TLC** (1:9 Et_2O: petroleum ether) R*f* 0.32. **Anal.** Calcd for $C_{43}H_{76}O_{12}Si_3$: C, 59.41; H, 8.81. Found: C, 59.64; H, 8.87.

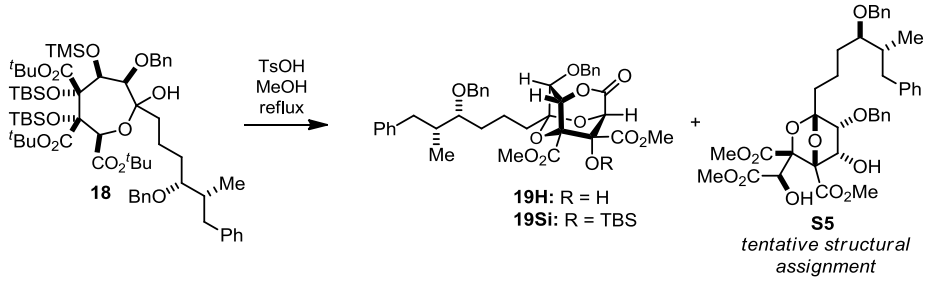


6-Benzyloxy-3,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-7-oxo-5-hydroxy-oxepane-2,3,4-tricarboxylic acid tri-*tert*-butyl ester (*epi*-16). To a solution of 60 mg (0.075 mmol, 1.0 equiv) of lactone **16** in Et_2O (1.0 mL) was added 56 μL (0.38 mmol, 5.0 equiv) of DBU. After 3 h, 0.5 mL of saturated aqueous ammonium chloride was added. The reaction was extracted with Et_2O (3 X 3 mL), dried ($MgSO_4$), and concentrated *in vacuo* to furnish an 85:15 ratio of diastereomers as judged by ^{1}H NMR analysis. Purification of the reaction mixture by flash chromatography (5:95 EtOAc: petroleum ether), afforded 44 mg (73%) of ***epi*-16** as an oil. Analytical data for ***epi*-16**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.23 (m, 5H), 5.16 (d, *J* = 11.6 Hz, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.89 (s, 1H), 4.30 (d, *J* = 9.6 Hz, 1H), 3.91 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.61 (d, *J* = 6.0 Hz, 1H), 1.48 (s, 9H), 1.42 (s, 9H), 1.31 (s, 9H), 0.93 (s, 9H), 0.84 (s, 9H), 0.24 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); **TLC** (1:9 EtOAc: petroleum ether) R*f* 0.39.



(2*R*,3*S*,4*R*,5*S*,6*R*)-tri-*tert*-butyl 6-(benzyloxy)-7-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-3,4-bis(*tert*-butyldimethylsilyloxy)-7-hydroxy-5-

(trimethylsilyloxy)oxepane-2,3,4-tricarboxylate (18). A solution of 94 mg (0.23 mmol, 5.0 equiv) of iodide **S3**[34] in Et_2O (0.6 mL) was cooled to -78 °C under an Ar atmosphere and 220 μL of a 1.7 M solution of *t*Buli (0.368 mmol, 8.0 equiv) was added via syringe. After 5 min, a solution of 40 mg (0.032 mmol, 1.0 equiv) of lactone **16** in Et_2O (0.35 mL) was added via cannula (0.35 mL rinse). After 15 min the reaction was quenched with 1.0 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with Et_2O (3 X 5 mL). The combined extracts were dried dried ($MgSO_4$), and concentrated *in vacuo*. ^{1}H NMR analysis of the unpurified reaction mixture revealed an isomeric mixture of lactols and ketol. The inseparable isomers were purified by flash chromatography (5:95 EtOAc: petroleum ether), to afford 53 mg (94%) of **18** as a mixture of isomers. Analytical data for **18** (reported as a mixture of lactol and ketol isomers): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.10 (m), 4.85-4.55 (m), 4.54-4.42 (m), 4.12-4.09 (m), 3.31-3.18 (m), 2.88-2.71 (m), 2.40-2.14 (m), 2.12-1.95 (m), 1.95-1.82 (m), 1.58 (s), 1.41 (s), 1.20 (s), 1.03 (s), 0.84 (s), 0.45 (s), 0.36 (s), 0.32 (s), 0.29 (s), 0.25 (s), 0.18 (s), 0.16 (s), 0.14 (s), 0.11 (s). 0.07 (s); **TLC** (1:9 EtOAc: petroleum ether) R*f* 0.29.



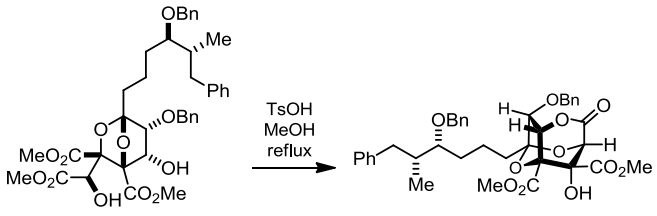
C4 O-*tert*-butyldimethylsilyl tricyclic ketal δ-lactone (19Si). To a solution of 103 mg of **18** (0.089 mmol. 1.0 equiv)) in 7 mL of methanol, 136 mg of *p*-toluenesulfonic acid (0.715 mmol, 8.0 equiv) was added. The reaction flask was fitted with a reflux condenser and heated to reflux for 72 h. Heating was discontinued and the reaction was allowed to

cool to 23 °C. 5 mL of distilled water was added and the MeOH was removed *in vacuo*. The resulting aqueous layer was extracted with EtOAc (4 x 5 mL), the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by flash chromatography (2:8 EtOAc: petroleum ether to 1:1 EtOAc: petroleum ether linear gradient), to afford 10 mg (15%) of silyl-protected lactone (**19Si**), 29 mg (48%) of δ-lactone **19**, and 9 mg (15%) of ketal (**19H**). Analytical data for **19Si**: **IR** (thin film, cm-1) 3566, 2954, 2926, 2857, 2359, 1801, 1772, 1747, 1646, 1496, 1365, 1257, 1028; **[α]Na** -18.7 (c = 0.05, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.24 (m, 12H), 7.17-7.08 (m, 3H), 4.84 (m, 2H), 4.52 (m, 3H), 4.44 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.53 (d, *J* = 7 Hz), 3.25-3.21 (m, 1H), 2.86 (dd, *J* = 13, 4.5 Hz, 1H), 2.23-2.25 (m, 1H), 2.00-1.92 (m, 2H), 1.69-1.65 (m, 1H), 1.53-1.38 (m, 5H), 1.24-1.22 (m, 1H), 0.84 (s, 9H), 0.81 (d, *J* = 7 Hz, 3H), 0.24 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 171.7, 166.2, 165.5, 141.6, 139.1, 136.6, 129.1, 128.7, 128.4, 128.3, 128.2, 127.7, 127.4, 125.7, 107.0, 90.5, 82.2, 80.3, 74.0, 72.4, 71.6, 53.2, 52.8, 38.6, 37.7, 34.1, 30.3, 25.6, 18.9, 18.4, 14.5, -2.28, -4.04; **TLC** (3:7 EtOAc: petroleum ether) R*f* 0.65. **HRMS** (ESI) exact mass calculated for C44H56O11Na [M + Na]+ 811.3489. Found: 811.3390.

C4-hydroxy-tricyclic ketal δ-lactone (19H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 11H), 7.19-7.10 (m, 4H), 4.90 (d, *J* = 6.8, 1H), 4.82 (d, *J* = 12 Hz, 1H), 4.57-4.49 (m, 3H), 4.46 (s, 1H), 4.18 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.55 (d, *J* = 6.8, 1H), 3.27-3.24 (m, 1H), 2.93-2.81 (m, 1H), 2.40-2.30 (m, 1H), 2.01-1.98 (m, 2H), 1.70-1.49 (m, 6H), 0.83 (d, *J* = 6.8 Hz, 3H).

(1*R*,3*S*,4*R*,5*S*,6*R*)-dimethyl 6-(benzyloxy)-1-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-5-hydroxy-3-((*R*)-1-hydroxy-2-methoxy-2-oxoethyl)-2,7-

dioxabicyclo[2.2.1]heptane-3,4-dicarboxylate (S5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35-7.19 (m, 11H), 7.11-7.09 (m, 4H), 5.67 (d, *J* = 5.1 Hz, 1H), 5.00 (s, 1H), 4.76 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 4.8 Hz, 1H), 4.56 (d, *J* = 12 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1 H), 4.32 (d, *J* = 10.8 Hz, 1H), 3.92 (d, *J* = 5.4 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.56-3.52 (m, 1H), 3.23-3.19 (m, 1H), 3.07 (s, 3H), 2.90 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.36-2.32 (m, 1H), 2.05-1.97 (m, 1H), 1.76-1.41 (m, 5H), 0.86 (d, *J* = 5.1 Hz, 3H).

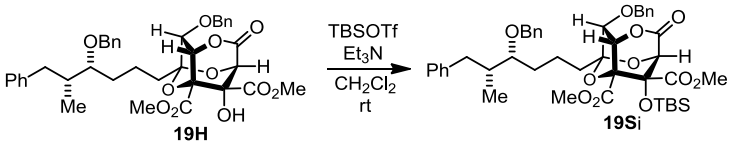


S5

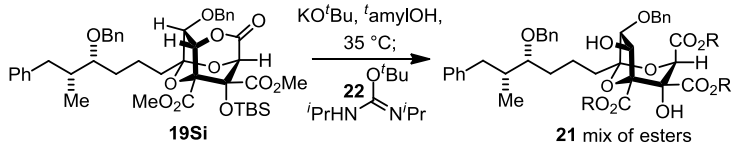
tentative structural assignment

19H

C4-hydroxy-tricyclic ketal δ-lactone (19H). To a solution of 16 mg of **S5** (0.023 mmol, 1.0 equiv) in 3 mL of methanol, 46 mg of *p*-toluenesulfonic acid (0.242 mmol, 8.0 equiv) was added. The reaction flask was fitted with a reflux condenser and heated to reflux for 72 h. Heating was discontinued and the reaction was allowed to cool to 23 °C. Distilled water (5 mL) was added and the MeOH was removed *in vacuo*. The resulting aqueous layer was extracted with EtOAc (4 x 5 mL), the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by flash chromatography (2:8 EtOAc: petroleum ether to 1:1 EtOAc: petroleum ether linear gradient), to afford 11 mg (73%) of δ-lactone **19H**.

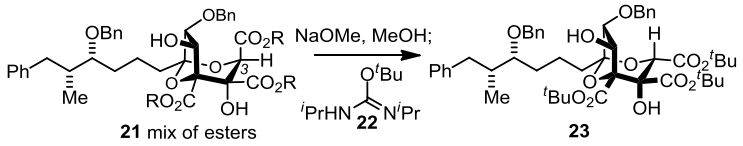


C4 O-*tert*-butyldimethylsilyl tricyclic ketal δ-lactone (19Si): To a solution of 51 mg (0.076 mmol) of tertiary alcohol **19H** in 0.75 mL CH_2Cl_2 at 0 °C under an Ar atmosphere, was added 42 μL (0.308 mmol, 4.0 equiv) of NEt_3, and 35 μL (0.154 mmol, 2.0 equiv) of TBSOTf. The reaction was warmed to 23 °C. After stirring for 15 min, an additional 42 μL (0.308 mmol, 4.0 equiv) of NEt_3, and 35 μL (0.154 mmol, 2.0 equiv) of TBSOTf was added. After 1 h, 0.5 mL of saturated $NaHCO_3$ (aq) was added. The solution was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude silyl ether, which was purified by flash chromatography (1:5 EtOAc: petroleum ether), to furnish 52 mg (87%) of silyl ether δ-lactone **19Si** (characterization data provided above).



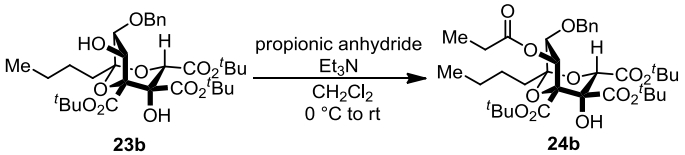
(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-3,4-di-*tert*-butyl 5-methyl 7-(benzyloxy)-1-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-4,6-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (21). To a solution of 15 mg (0.019 mmol, 1.0 equiv) of lactone **19Si** in *t*-amyl alcohol (1.0 mL, freshly distilled from Na) was added a solution of 23 mg KO*t*Bu (0.204 mmol, 11 equiv) in 0.75 mL *t*-amyl alcohol via cannula. The solution was warmed to 35 °C and stirred under an Ar atmosphere for 40 min, at which point it was cooled to 23 °C. The reaction was quenched with 2 mL of 1 M HCl. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and

concentrated *in vacuo*, affording the crude dicarboxylic acid. The crude material was dissolved in 1 mL toluene and 88 μL (0.367 mmol, 19 equiv) of *N*,*N*'-diisopropyl-*O*-*tert*-butylisourea **22** was added. The solution was warmed to 75 °C under an Ar atmosphere and stirred at 75 °C. After 2 h the solution was cooled to 23 °C, diluted with diethyl ether and filtered through celite. Concentration *in vacuo* afforded the crude triester. The crude material was purified by flash chromatography (1:9 EtOAc:petroleum ether to 2:3 EtOAc:petroleum ether, linear gradient), to afford 9.5 mg (63%) of the product as a mixture of esters, and 4.5 mg (27%) of starting material with *t*-butyl esters. Distribution of products: 6.5 mg (43%) of di-*t*-butyl ester; 2.0 mg (13%) of tri-*t*-butyl ester; 1.0 mg of mono-*t*-butyl ester (7%); 90% yield BRSM. Analytical data for **21**: **IR** (thin film, cm-1) 2922, 2851, 1737, 1635, 1456, 1370, 1262, 1151; **[α]Hg**-16.0 (c = 0.135, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 9H), 7.26-7.24 (m, 2H), 7.18-7.10 (m, 3H), 5.09 (dd, *J* = 8.0, 3.5 Hz, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 12.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1 H), 4.46 (s, 1H), 4.14 (s, 1H), 3.81 (s, 3H), 3.61 (d, *J* = 3.5, 1H), 3.25 (s, 1H), 2.85 (dd, J = 13.5, 5.0 Hz, 1 H), 2.37 (m, 1H), 2.00-1.93 (m, 2H), 1.80-175 (m, 2H), 1.56 (s, 9H), 1.52 (m, 3H), 1.45 (s, 9H), 1.21 (m, 1H), 0.84 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 167.4, 167.2, 141.6, 139.3, 137.8, 129.1, 128.4, 128.3, 128.2, 12 8.1, 127.8, 127.6, 127.3, 125.6, 106.4, 94.2, 87.1, 84.9, 82.6, 82.1, 80.6, 72.2, 71.5, 52.4, 39.0, 37.7, 33.9, 30.6, 29.7, 28.1, 28.0, 19.1, 14.2; **TLC** (2:3 EtOAc: petroleum ether) R*f* 0.24. **HRMS** (ESI) exact mass calculated for C45H58O12Na [M+Na]+ 813.3825. Found: 813.3827.



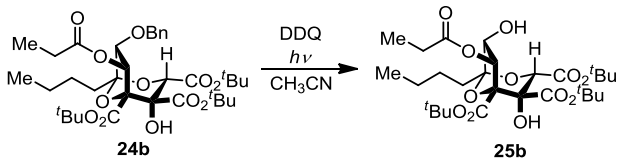
(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 7-(benzyloxy)-1-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-4,6-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (23). 0.75 mL of a 1 M solution of NaOMe in MeOH (distilled from Mg metal) was added to 14 mg (0.019 mmol, 1.0 equiv) of **21**, as a mix of esters, in a shell vial that had been purged with Ar. The solution was stirred for 2 h monitoring by TLC (2:5 EtOAc:petroleum ether) until no starting material remained. The solution was poured into 1 mL of 1 M HCl. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude tricarboxylic acid. The crude material was dissolved in 1 mL of toluene and 81 μL (0.343 mmol, 18 equiv) of *N*,*N*'-diisopropyl-*O*-*tert*-butylisourea was added. The solution was warmed to 75 °C under an Ar atmosphere and stirred at 75 °C. After 2 h the solution was cooled to 23 °C, diluted with diethyl ether and filtered through celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (1:5 EtOAc:petroleum ether to 3:10 EtOAc:petroleum ether, linear gradient) to afford 11 mg (69%) of the product as a mixture of epimers (8:1) in favor of the correct C3-(*S*) configuration. The epimers were separable at the stage of the triacetate **26**. Analytical data for **23**: **IR** (thin film, cm-1) 3443, 3031, 2878, 1697, 1616, 1506, 1395, 1367, 1258, 1198, 1149; **[α]Na** -12.7 (c = 0.16, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33-7.21 (m, 9H), 7.15-7.13 (m, 2H), 7.13-7.09 (d, *J* = 16 Hz, 4H), 5.11 (s, 1H), 4.92 (s, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.47 (d,*J* = 11.5 Hz, 1H), 3.83 (s, 1H), 3.78 (s, 1H), 3.27 (s, 1H), 2.83 (dd, J = 13.0, 4.5 Hz, 1 H),

2.36 (t,*J* = 9.5 Hz, 1H), 2.00-1.80 (m, 3H), 1.60-1.40 (m, 4H), 1.56 (s, 9H), 1.45 (s, 9H), 1.42 (s, 9H), 1.21 (m, 1H), 0.81 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 167.4, 166.6, 141.8, 139.3, 137.3, 129.2, 128.5, 128.3, 128.2, 128.1, 127.7, 127.6, 127.3, 125.5, 104.7, 91.3, 87.7, 84.7, 84.2, 83.0, 82.3, 80.6, 75.3, 74.3, 72.8, 71.5, 39.1, 37.8, 36.2, 34.4, 30.3, 29.7, 28.2, 28.0, 19.5, 14.1; TLC (1:5 EtOAc: petroleum ether) R*f* 0.19. **HRMS** (ESI) exact mass calculated for C48H64O12Na [M+Na]+ 855.4295. Found: 855.4296.

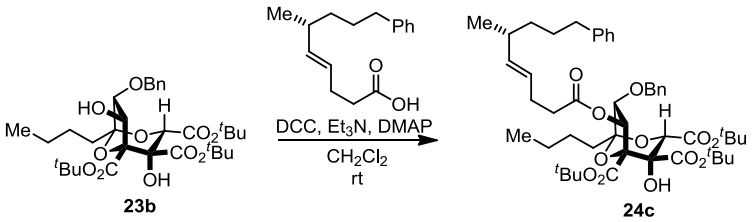


(1*S*,3*R*,4*R*,5*R*,6*R*,7*S*)-tri-*tert*-butyl 7-(benzyloxy)-1-butyl-4-hydroxy-6-(propionyloxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (24b). A dry scintillation vial was purged with Ar for 5 minutes and was charged with 10 mg (0.016 mmol, 1 equiv) of **23b**, a stir bar, and 1 mL of CH_2Cl_2. The solution was cooled to 0 °C. To this solution was added 7 μL (0.05 mmol, 3 equiv) of Et_3N dropwise via syringe, 2 mg (0.016 mmol, 1 equiv) of DMAP and 6 μL (0.05 mmol, 3 equiv) of propionic anhydride dropwise via syringe. The solution was stirred for 3 h. The reaction was quenched with aqueous 1 M KH_2PO_4 (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product purified by flash column (1:5 EtOAc: petroleum ether) to yield 7 mg (64%) of **24b** as a clear oil. Analytical data for **24b**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 5H), 6.48 (s, 1H), 5.07 (s, 1H), 4.82 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.00 (s, 1H), 3.75 (s, 1H), 2.31 – 2.23 (m, 2H),

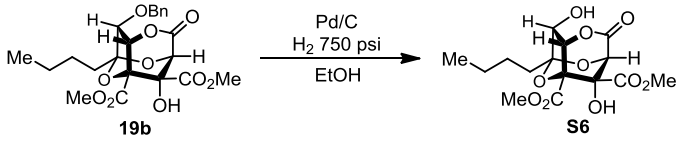
1.94 – 1.76 (m, 2H), 1.47 – 1.35 (m, 27H), 1.35 – 1.18 (m, 4H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); **TLC** (1:5 EtOAc: petroleum ether) R*f* 0.27.



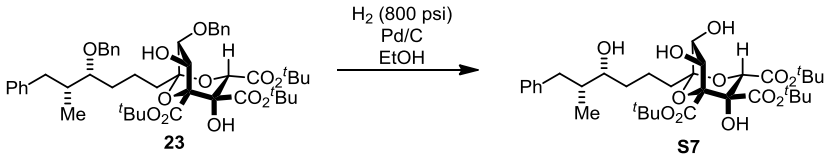
(1*S*,3*R*,4*R*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 1-butyl-4,7-dihydroxy-6-(propionyloxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (25b). A dry scintillation vial was purged with Ar for 5 minutes and was charged with 4 mg (0.006 mmol, 1 equiv) of **24b**, 4 mg (0.012 mmol, 2 equiv) of DDQ, a stir bar, and 0.005 mL of CH_3CN. The solution was then irradiated with a 450 watt 365 nm mercury vapor lamp at a distance of 15 cm for 4 h. To this solution was added 7 μL (0.05 mmol, 3 equiv) of Et_3N dropwise via syringe, 2 mg (0.016 mmol, 1 equiv) of DMAP and 6 μL (0.05 mmol, 3 equiv) of propionic anhydride via syringe. The solution was stirred for 3 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product purified by flash column (1:5 EtOAc: petroleum ether) to yield 3 mg (86%) of **25b** as a clear oil. Analytical data for **25b**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.91 (s, 3H), 4.99 (s, 1H), 3.99 (s, 1H), 2.76 (s, 1H), 2.35 (dd, *J* = 14.2, 7.6 Hz, 2H), 1.95 (t, *J* = 27.8 Hz, 3H), 1.56 (s, 9H), 1.46 (s, 9H), 1.43 (s, 9H), 1.39 – 1.31 (m, 2H), 1.14 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); TLC (1:5 EtOAc: petroleum ether) R*f* 0.30.



(1S,3S,4S,5R,6R,7R)-tri-tert-butyl 7-(benzyloxy)-1-butyl-4-hydroxy-6-(((R,E)-6-methyl-9-phenylnon-4-enoyl)oxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (24c). A solution of acyl side chain acid (7 mg, 0.030 mmol, 2 equiv) and DCC (6 mg, 0.030 mmol, 2 equiv) in 485 µl of CH_2Cl_2 was stirred under Ar for 15 minutes. To a solution of **23b** (9.0 mg, 0.015 mmol, 1.0 equiv) and DMAP (4 mg, 0.035 mmol, 2.3 equiv) in CH_2Cl_2 (1.5 mL,) was added the acyl side chain-DCC solution. The reaction was stirred at 23 °C under Ar in a sealed vial for 40 h. The reaction was quenched with 1.5 mL of 50% aqueous satd. $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (4 x 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude product. The crude material was purified by flash chromatography (1:5 EtOAc:hexanes), to give product **24c** as a colorless film 6.0 mg (50%). Analytical data for **24c**: **IR** (thin film, cm-1) 3398 broad, 2929, 2851, 2347, 1724, 1594, 1451, 1377; 1172; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.08 (m, 10H), 6.47 (s, 1H), 5.30 (s, 2H), 5.05 (s, 1H), 4.80 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.00 (s, 1H), 3.74 (s, 1H), 2.53 (t, *J* = 7.1 Hz, 2H), 2.34 – 2.22 (m, 4H), 2.04 (s, 2H), 1.95 – 1.70 (m, 3H), 1.61 (s, 9H), 1.41 (s, 18H), 1.33 – 1.21 (m, 6H), 0.94 – 0.79 (m, 6H); **TLC** (1:4 EtOAc: petroleum ether) R*f* 0.25.

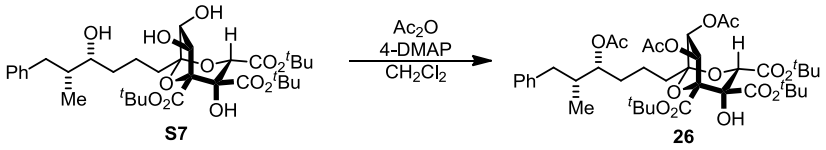


C7 hydroxyl tricyclic ketal δ-lactone (S6). A scintillation vial was charged with 28 mg (0.064 mmol) of lactone **19b**, capped with a rubber septum and purged with Ar for 5 minutes. EtOH (2 mL) was added followed by a spatula tip of 10% Pd/C. The rubber septum was pierced with an 18 gauge needle and the vial was placed in a bomb. The bomb was purged with hydrogen gas 7 times and then pressurized to 750 psi. The reaction was stirred in the bomb at 750 psi for 20 h. The bomb was depressurized and the solution was filtered through celite with diethyl ether. Concentration *in vacuo* afforded the debenzylated diester. The crude material was purified by flash column (20:1 petroleum ether:EtOAc) to give 22 mg (100%) of **S6** as a clear oil. Analytical data for **S6**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.92 (d, *J* = 7.2 Hz, 1H), 4.47 (s, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.94 (d, *J* = 11.9 Hz, 1H), 1.98 – 1.89 (m, 1H), 1.81 – 1.70 (m, 1H), 1.56 – 1.40 (m, 2H), 1.40 – 1.26 (m, 2H), 1.21 (dd, *J* = 8.3, 6.0 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); **TLC** (1:1 EtOAc:petroleum ether) R_f 0.28.



(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 4,6,7-trihydroxy-1-((4*R*,5*R*)-4-hydroxy-5-methyl-6-phenylhexyl)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (S7). A scintillation vial was charged with 11 mg (0.013 mmol) of tri-ester **23**, capped with a rubber septum and purged with Ar for 5 minutes. EtOH (2 mL) was added followed by a spatula tip of 10% Pd/C. The rubber septum was pierced with an 18 gauge needle and the

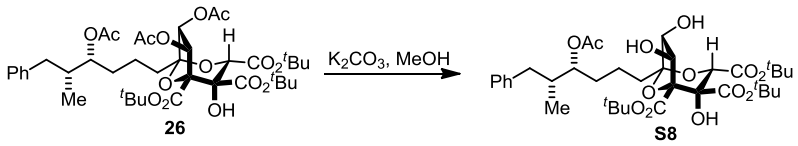
vial was placed in a bomb. The bomb was purged with hydrogen gas 7 times and then pressurized to 800 psi. The reaction was stirred in the bomb at 800 psi for 20 h. The bomb was depressurized and the solution was filtered through celite with diethyl ether. Concentration *in vacuo* afforded the debenzylated triester. The material was pure by 1H NMR spectroscopy and was used in the next step without further purification. Analytical data for **S7**: **IR** (thin film, cm-1) 3443, 3031, 2878, 1697, 1616, 1506, 1395, 1367, 1258, 1198, 1149; **[α]Na** +11.6 (c = 0.09, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 (m, 3H), 7.13 (d, *J* = 7.5 Hz, 2H), 4.98 (s, 1H), 4.91 (s, 1H), 4.09 (s, 1H), 3.96 (s broad, 1H), 3.51 (s broad, 1H), 2.76 (dd, *J* = 13.3, 6.0 Hz, 1 H), 2.39 (dd, *J* = 10.0 Hz, *J* = 9.0 Hz, 1H), 2.00-1.89 (m, 3H), 1.80-1.50 (m, 4H), 1.55 (s, 9H), 1.45 (s, 9H), 1.41 (s, 9H), 0.82 (d, *J* = 4.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.7, 166.4, 166.2, 143.5, 141.3, 129.2, 128.2, 125.7, 105.3, 91.3, 85.1, 84.3, 83.4, 82.4, 78.8, 75.1, 74.3, 74.1, 58.5, 40.7, 39.8, 35.1, 33.8, 30.3, 30.0, 28.3, 28.1, 28.0, 19.7, 13.3; TLC (1:1 EtOAc: petroleum ether) R_f 0.07. HRMS (ESI) exact mass calculated for $C_{34}H_{52}O_{12}Na$ [M+Na]+ 675.3356. Found: 675.3357.



(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 6,7-diacetoxy-1-((4*R*,5*R*)-4-acetoxy-5-methyl-6-phenylhexyl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (26). To a solution of 11.8 mg (0.018 mmol, 1.0 equiv) of triester **S7** and 4 mg (0.036 mmol, 2.0 equiv) of DMAP in dichloromethane (1.5 mL,) was added 17 µl (0.1 mmol, 10 equiv) of acetic anhydride via syringe. The solution was stirred at 23 °C under Ar for 3 h until no starting material remained by TLC (1:1 EtOAc:petroleum ether). The reaction was

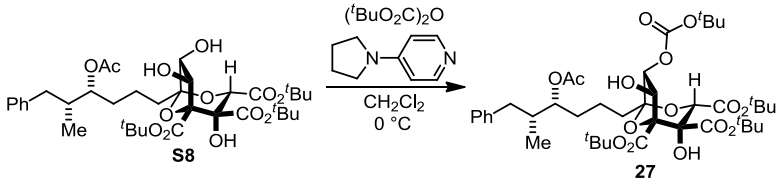
quenched with 1.5 mL aqueous satd. $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude tri-acetate. The crude material was purified by flash chromatography (1:5 EtOAc:petroleum ether to 3:10 EtOAc:petroleum ether, linear gradient), to afford 9 mg (65%) of the desired major diastereomer **26**, and 2.5 mg (18%) of the minor diastereomer. Analytical data for **26**: **IR** (thin film, cm-1) 3434 (br), 2930, 2861, 1724, 1651, 1594, 1374, 1233, 1172, 1034; **[α]Na** +11.1 (c = 0.325, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 7.17 (t, *J* = 7.5 Hz, H), 7.13 (d, *J* = 7.5 Hz, 2H), 6.33 (d, *J* = 1.5 Hz, 1H), 5.08 (d, *J* = 2 Hz, 1H), 4.88 (s, 1H), 4.88-4.86 (m, 1H), 4.07 (s, 1H), 2.76 (dd, J = 13.3, 4.5 Hz, 1 H), 2.30 (dd, *J* = 10.5 Hz, *J* = 13.5 Hz, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.05-1.90 (m, 3H), 1.70-1.50 (m, 4H), 1.61 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H), 0.83 (d, *J* = 7 Hz, 3H); **^{13}C NMR** (125 MHz, CD_3OD) δ 173.0, 171.1, 170.2, 168.7, 167.4, 165.6, 141.9, 130.2, 129.3, 127.0, 105.6, 91.2, 86.4, 85.3, 85.0, 81.6, 77.9 (2 lines), 76.9, 75.6, 40.6, 39.7, 36.5, 32.3, 28.5, 28.4 (3 lines), 21.1, 20.7, 20.5, 20.1, 14.3; (125 MHz, $CDCl_3$) δ 170.9, 169.5, 168.7, 168.5, 165.5, 163.9, 140.7, 129.1, 128.2, 125.8, 104.1, 89.7, 86.1, 84.1, 83.6, 80.4, 76.4, 75.2, 73.8, 39.3, 38.1, 35.7, 30.8, 28.1, 27.9, 21.2, 20.7, 20.6, 19.0, 13.9; **TLC** (1:2 EtOAc:hexanes) R*f* 0.46. **HRMS** (ESI) exact mass calculated for $C_{40}H_{58}O_{15}$ [M+Na]+ 801.3673. Found: 801.3674.

The spectroscopic data match those reported by Carreira.[14]



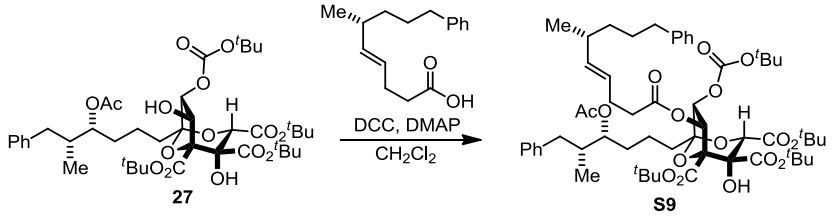
(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 1-((4*R*,5*R*)-4-acetoxy-5-methyl-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (S8). A solution of 6 mg (0.008 mmol, 1.0 equiv) of triacetate **26** in 1.2 mL of 0.2% K_2CO_3 in MeOH was stirred at 23 °C under Ar for 30 minutes. The reaction was quenched with 1.5 mL 0.3 M KH_2PO_4 solution. The aqueous layer was extracted with Et_2O (5 x 3 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude mono-acetate. The crude material was purified by flash chromatography (2:5 EtOAc:hexanes to 1:1 EtOAc:hexanes, linear gradient), to afford 4 mg (75%) of the triol **S8**. Analytical data for **S8**: **IR** (thin film, cm-1) 3460 (broad), 2927, 1732, 1371, 1258, 1159; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.24 (t, *J* = 7.5 Hz, 2H), 7.14-7.15 (m, 3H), 4.97-4.96 (2H), 3.99 (d, *J* = 2.0 Hz, 1H), 2.75 (dd, *J* = 13.5, 5.5 Hz, 1 H), 2.36 (dd, *J* = 9.5 Hz, *J* = 13.3 Hz, 1H), 2.06 (s, 3H), 2.05-2.0 (m, 1H), 1.95-1.70 (m, 2H), 1.70-1.60 (m, 2H), 1.60-1.20 (m, 2H), 1.60 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), one proton obscured by residual water; **^{13}C NMR** (125 MHz, CD_3OD) δ 173.0, 169.8, 168.3, 167.4, 142.0, 130.2, 129.3, 126.9, 106.4, 93.2, 85.4, 84.2 (2 lines), 79.9, 78.2, 76.8, 76.0, 40.6, 39.5, 36.6, 32.5, 28.7, 28.5, 28.4, 21.1, 20.1, 14.2; **TLC** (2:5 EtOAc: petroleum ether) R*f* 0.17. **HRMS** (ESI) exact mass calculated for $C_{36}H_{54}O_{13}Na$ [M+Na]+ 717.3461. Found: 717.3463.

The spectroscopic data match those reported by Carreira.[14]



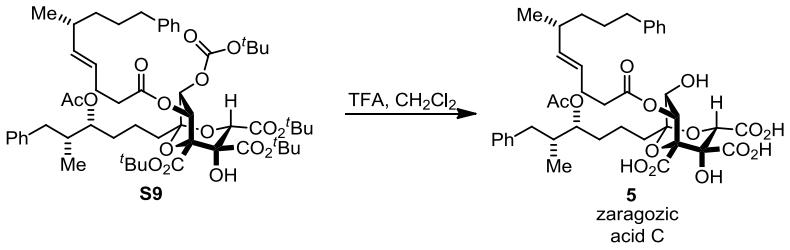
(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 1-((4*R*,5*R*)-4-acetoxy-5-methyl-6-phenylhexyl)-7-(*tert*-butoxycarbonyloxy)-4,6-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (27). A solution of 4 mg (0.006 mmol, 1.0 equiv) of monoacetate **S8** in 0.75 mL of dichloromethane under Ar was stirred and cooled to 0 °C. A solution of 4-pyrrolidinopyridine (0.1 M in CH_2Cl_2, 46 µl, 0.005 mmol, 0.8 equiv) was added followed by a solution of Et_3N (115 µl, 0.2 M in CH_2Cl_2, 0.024 mmol, 4.0 equiv) and a solution of di-*tert*-butyl dicarbonate (66 µl, 0.1 M in CH_2Cl_2, 0.007 mmol, 1.15 equiv). The solution was stirred for 6.5 h at 0 °C. The reaction was quenched with 1.5 mL 1.0 M KH_2PO_4 solution. The aqueous layer was extracted with Et_2O (5 x 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude product. The crude material was purified by flash chromatography (1:4 EtOAc:hexanes to 1:1 EtOAc:hexanes, linear gradient), to afford 3.5 mg (77%) of the boc-protected product **27**. Analytical data for **27**: **IR** (thin film, cm-1) 3433 (broad), 2927, 2851, 1644, 1451, 1378, 1259, 1171, 1113, 1026; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27−7.24 (m, 2H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 2H), 5.11 (d, *J* = 1.5 Hz, 1H), 4.87 (m, 1H), 4.72, (s, 1H), 4.63 (d, *J* = 1.5 Hz, 1H), 3.95 (s, 1H), 2.84 (broad s, 1H), 2.75 (dd, *J* = 13.3, 5.5 Hz, 1 H), 2.30 (dd, *J* = 13.0, 9.5 Hz, 1H), 2.06 (s, 3H), 2.05-1.90 (m, 4H), 1.70-1.30 (m, 4H), 1.58 (s, 9H), 1.50 (s, 9H), 1.48 (s, 9H), 1.45 (s, 9H), 0.83 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.0, 168.7, 165.9, 165.3, 153.8, 140.9, 129.3, 128.4, 125.7, 104.0, 90.9, 85.6, 85.2, 84.1, 84.0, 83.4, 77.4, 75.4, 74.2, 39.5, 38.0, 35.7, 34.4, 31.0, 29.9, 28.3,

28.2, 28.1, 27.8, 21.4, 19.0, 13.9; **TLC** (2:5 EtOAc:petroleum ether) R*f* 0.59. **HRMS** (ESI) exact mass calculated for $C_{41}H_{62}O_{15}Na$ [M+Na]+: 817.3986. Found: 817.3987.



(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 1-((4*R*,5*R*)-4-acetoxy-5-methyl-6-phenylhexyl)-7-(*tert*-butoxycarbonyloxy)-4-hydroxy-6-((*R*,*E*)-6-methyl-9-phenylnon-4-enoyloxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (S9). A solution of acyl side chain acid (12 mg, 0.049 mmol) and DCC (10 mg, 0.049 mmol) in 485 µl of CH_2Cl_2 was stirred under Ar for 15 minutes. To a solution of boc-protected **27** (8.0 mg, 0.010 mmol, 1.0 equiv) and DMAP (4 mg, 0.035 mmol, 3.5 equiv) in CH_2Cl_2 (1.5 mL,) was added 120 µl (1.2 equiv) of the acyl side chain-DCC solution. The reaction was stirred at 23 °C under Ar in a sealed vial for 40 h. The reaction was quenched with 1.5 mL of 50% aqueous satd. $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O (4 x 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*, affording the crude product. The crude material was purified by flash chromatography (1:5 EtOAc:hexanes), to give product **S9** as a colorless film 5.1 mg (51%) and 3 mg (38%) of recovered boc-protected starting material **27**. Analytical data for **S9**: **IR** (thin film, cm-1) 3398 broad, 2929, 2851, 2347, 1724, 1594, 1451, 1377; 1172; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28–7.24 (m, 4H), 7.18-7.12 (m, 6H), 6.40 (d, *J* = 2.0 Hz, 1H), 5.39-5.28 (m, 2H), 4.91 (s, 1H), 4.86 (d, *J* = 2.0 Hz 1H), 4.88-4.86 (m, 1H), 4.07 (s, 1H), 2.76 (dd, *J* = 15.0, 4.5 Hz, 1 H), 2.56 (t, *J* = 7.5 Hz, 1H), 2.32-2.25 (m, 3H), 2.10-1.91 (m, 6H), 2.05 (s, 3H), 1.68-1.25 (m, 8H), 1.61 (s, 9H), 1.47 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H), 0.93 (d, *J*

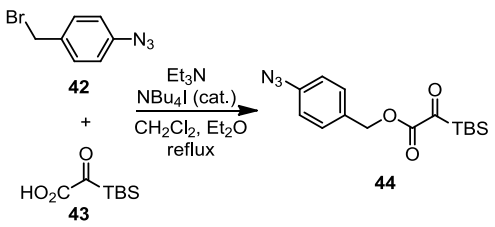
= 6.5 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.8, 170.7, 168.7, 165.6, 164.1, 152.4, 142.8, 140.8, 137.6, 129.2, 128.4, 128.3, 128.2, 126.1, 125.8, 125.6, 103.7, 89.8, 86.1, 84.0, 83.5, 83.4, 83.0, 76.1, 75.2, 73.9, 39.3, 38.0, 36.6, 36.5, 36.1, 35.9, 34.1, 30.8, 29.3, 28.1, 28.2, 28.0, 27.9, 27.73, 27.66, 21.3, 20.6, 18.9, 13.8; **TLC** (1:4 EtOAc: petroleum ether) R*f* 0.29. **HRMS** (ESI) exact mass calculated for $C_{57}H_{82}O_{16}Na$ [M+Na]+: 1045.5500 Found: 1045.5501.



Zaragozic Acid C (1). To a solution of **S9** (5.0 mg, 0.005 mmol, 1.0 equiv) in 2.55 mL of dichloromethane under Ar was added TFA (850 µl). The solution was stirred for 16 h at 23 °C. Volatiles were removed in vacuo. The pale green residue was dissolved in 5 mL of toluene, concentrated in vacuo, and lyophilized from 1.5 mL of benzene to afford 3.6 mg (100%) of the product **5** as a white flocculent solid. Analytical data for **5**: **IR** (thin film, cm-1) 3427 broad, 2929, 2360, 1717, 1646, 1378, 1268, 1171; **[α]Na** +3.81 (c = 0.040, EtOH); **^{1}H NMR** (500 MHz, CD_3OD) δ 7.23−7.21 (m, 4H), 7.14-7.10 (m, 6H), 6.23 (d, *J* = 1.5 Hz, 1H), 5.37 (m, 1H), 5.32 (m, 1H), 5.23 (s, 1H), 4.90 (m, 1H, masked by solvent signal), 4.01 (s, 1H), 2.73 (dd, *J* = 13.5, 5.5 Hz, 1 H), 2.56 (dd, *J* = 7.0 Hz, 12.5 Hz, 2H), 2.36-2.32 (m, 3H), 2.28-2.24 (m, 2H) 2.08-2.00 (m, 2H), 2.05 (s, 3H) 1.92-1.85 (m, 2H), 1.7-1.66 (m, 2H), 1.61-1.52 (m, 4H), 1.40-1.20 (m, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.1, 173.06, 172.7, 170.3, 168.7, 143.9, 142.0, 138.8, 130.2, 129.4, 129.3, 129.27, 127.7, 126.9, 126.6, 107.1,

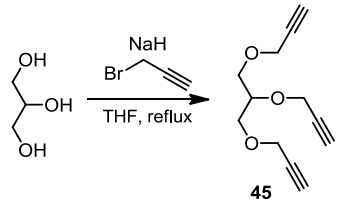
91.1, 82.3, 81.2, 78.1, 76.7, 75.7, 40.5, 39.7, 37.9, 37.6, 36.9, 36.3, 35.4, 32.5, 30.5, 28.8, 21.3, 21.1, 20.1, 14.3; **LRMS** (ESI) exact mass calculated for $C_{40}H_{50}O_{14}$ 754.3 Found: 754.4 (376.2 [M-2H]2-). **HRMS** (ESI) exact mass calculated $C_{40}H_{50}O_{14}Na$ [M+Na]+: 777.3098 Found: 777.3068.

The spectroscopic data match those reported by Carreira and Armstrong. In addition to the published spectral data, we found the scanned spectrum in the Supporting Information for the Armstrong synthesis to be useful for comparison purposes. An authentic sample of zaragozic acid C (<200 μg) was generously provided by Dr. Sheo Singh (Merck Research Laboratories). This sample also contains what we surmise to be the des-acetyl zaragozic acid C (LC-MS analysis). Purification was not feasible due to the quantity provided.

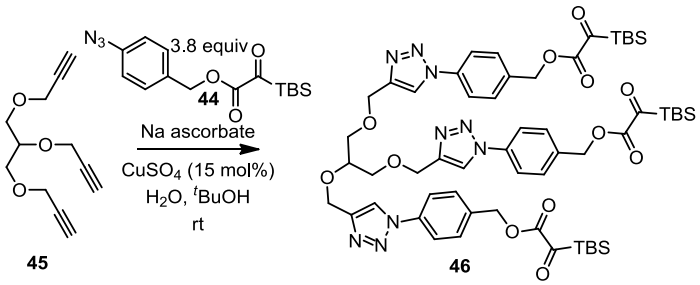


4-Azidobenzyl-tert-butyldimethylsilyl glyoxylate (44). To NBu_4I (388 mg, 1.05 mmol, 0.1 equiv) and **42** (3.35 g, 15.8 mmol, 1.5 equiv) was added a solution of **43** (1.98 g, 10.5 mmol, 1.0 equiv) in CH_2Cl_2 (75 mL), followed by Et_2O (75 mL), and Et_3N (2.05 mL, 14.7 mmol, 1.4 equiv). The solution was heated to reflux for 17 h, and then cooled to room temperature. The reaction was quenched with saturated NH_4Cl (50 mL) and extracted with Et_2O (3 X 500 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography (97:3 petroleum ether:EtOAc) to afford **44** (1.86 g, 5.81 mmol,

55% yield) as a yellow liquid. Analytical data for **44**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 5.21 (s, 2H), 0.92 (s, 9H), 0.24 (s, 6H).

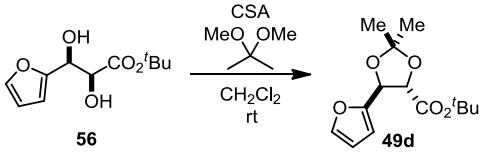


3-((1,3-bis(prop-2-yn-1-yloxy)propan-2-yl)oxy)prop-1-yne (45). To NaH (60% in mineral oil, washed with petroleum ether: 1.09 g, 27.2 mmol, 5.0 equiv) in THF (10 mL) at 0 °C was added glycerol (500 mg, 5.43 mmol, 1.0 equiv). The solution was stirred for 10 min at 0 °C before propargyl bromide (80% solution, 3.98 mL, 38.0 mmol, 7.0 equiv) was added. The solution was heated to reflux for 15 h and then cooled to room temperature. The reaction was quenched with saturated NH_4Cl, and extracted with Et_2O (3 X 100 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (90:10 petroleum ether:EtOAc) to afford **45** (810 mg, 3.93 mmol, 72% yield) as a clear liquid. Analytical data for **45**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.35 (d, *J* = 2.4 Hz, 2H), 4.20 (d, *J* = 2.4 Hz, 4H), 3.96-3.91 (m, 1H), 3.73-3.63 (m, 4H), 2.44 (t, *J* = 2.4 Hz, 3H).

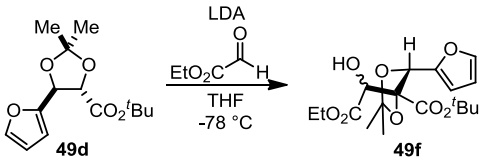


Tris-triazole (**46**). To $CuSO_4$ (45 mg, 0.182 mmol, 0.16 equiv), **44** (1.30 g, 4.07 mmol, 3.8 equiv), and **45** (221 mg, 1.07 mmol, 1.0 equiv) in H_2O (18 mL) and ^{t}BuOH (18 mL)

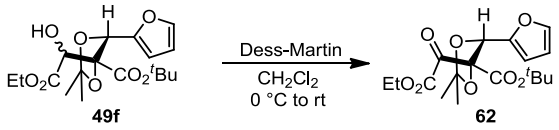
was added Na ascorbate (276 mg, 1.39 mmol, 1.3 equiv). The solution was stirred at room temperature for 18 h and was then diluted with CH_2Cl_2 (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL). The combined organic phases were concentrated under reduced pressure. The crude material was purified by flash chromatography (95:5 CH_2Cl_2:MeOH) to afford **46** (740 mg, 0.635 mmol, 59% yield) as a yellow foam. Analytical data for **46**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.09 (s, 2H), 7.78-7.73 (m, 6H), 7.56-7.51 (m, 6H), 5.30-5.27 (m, 6H), 4.93 (s, 2H), 4.77 (s, 4H), 4.00-3.94 (m, 1H), 3.75 (t, *J* = 3.9 Hz), 0.94 (s, 27H), 0.26 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.6, 146.3, 145.9, 137.1, 135.5, 131.3, 130.0, 121.0, 120.8, 120.6, 120.5, 77.6, 70.6, 66.2, 65.8, 64.9, 63.9, 26.4, 17.0, -6.9. **LRMS** (ESI) exact mass calculated for $C_{57}H_{77}N_9O_{12}Si_3Na$: 1,186.49. Found: 1,186.50.



(4S,5S)-tert-butyl 5-(furan-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (49d). To **56**[39] (4.33 g, 19.0 mmol, 1.0 equiv) in CH_2Cl_2 (85 mL) was added dimethoxypropane (22.99 mL, 186 mmol, 9.8 equiv) and CSA (97 mg, 0.418 mmol, 0.022 equiv). The solution was stirred at room temperature for 26 h. Saturated $NaHCO_3$ (50 mL) was added and the layers were separated. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to afford **49d** (>95% pure by ^{1}H NMR analysis, 4.35 g, 16.2 mmol, 85%). Analytical data for **49d**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 5.09 (d, *J* = 7.8 Hz, 1H), 4.61 (d, *J* = 7.8 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.43 (s, 9H).



Furyl glycolic ester (49f). To $^{i}Pr_2NH$ (0.57 mL, 4.10 mmol, 1.1 equiv) in THF (10 mL) at -78 °C was added ^{n}BuLi (1.5 M solution in hexane, 2.73 mL, 4.10 mmol, 1.1 equiv). The solution was stirred at -78 °C 10 min before a solution of **49d** (1.00 g, 3.73 mmol, 1.0 equiv) in THF (14 mL) was added. The solution was stirred at -78 °C for 15 min before a solution of ethyl glyoxylate (0.76 g, 4.48 mmol, 1.2 equiv) in THF (2 mL) was added dropwise. The solution was stirred at -78 °C for 1 h before it was quenched with saturated NH_4Cl (10 mL). The solution was diluted with CH_2Cl_2 (50 mL), and the phases were separated. The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography (90:10 petroleum ether:EtOAc) to afford **49f** (1:1 mix of two diastereomers: 1.00 g, 2.70 mmol, 72% yield) as a clear liquid. Analytical data for **49f**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.42-6.38 (m, 2H), 5.70 (s, 0.5H), 5.62 (s, 0.5H), 4.71 (d, *J* = 7.2 Hz, 0.5H), 4.53 (d, *J* = 9.9 Hz, 0.5H), 4.33-4.24 (m, 2H), 3.44-3.39 (m, 1H), 1.73 (s, 1.5H), 1.70 (s, 1.5H), 1.52-1.23 (m, 15H).



(4S,5R)-tert-butyl 4-(2-ethoxy-2-oxoacetyl)-5-(furan-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (62). To **49f** (990 mg, 2.67 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at 0 °C was added Dess-Martin periodinane (1.47 g, 3.47 mmol, 1.3 equiv). The solution was slowly warmed to rt over 1 h, then stirred at room temperature for 1 h. The

reaction was quenched with saturated $Na_2S_2O_3$ (5 mL) and stirred 10 min. The solution was extracted with Et_2O (3 X 50 mL) and the combined organic phases were washed with brine (50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography (90:10 petroleum ether:EtOAc) to afford **62** (438 mg, 1.19 mmol, 45% yield) as a clear oil. Analytical data for **62**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.49 (d, *J* = 3 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 5.91 (s, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.76 (s, 3H), 1.39-1.34 (m, 6H), 1.23 (s, 9H).

1.6 References

(1) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197-201.

(2) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170-6171.

(3) Boyce, G. R.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 8930-8933.

(4) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77-84.

(5) Greszler, S. N.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3689-3691.

(6) Shiozawa, H.; Takahashi, M.; Takatsu, T.; Kinoshita, T.; Tanzawa, K.; Hosoya, T.; Furuya, K.; Takahashi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 357-362.

(7) Mandala, S. M.; Harris, G. H. In *Sphingolipid Metabolism and Cell Signaling Part A*; Academic Press, 2000; Vol. Volume 311, pp. 335-348.

(8) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058-1059.

(9) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639-647.

(10) Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Unwin, C. H.; Wright, J. M. *Nature* **1949**, *164*, 534.

(11) Tupker, R. A.; Harmsze, A. M.; Deneer, V. H. M. *Arch. Dermatol.* **2006**, *142*, 1065-1066.

(12) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221-10226.

(13) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825-10826.

(14) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106-8125.

(15) Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; Riccardis, F. D.; Nadin, A.; Leresche, J. E.; La Greca, S.; Yang, Z. *Angew. Chem. Int. Ed.* **1994**, *33*, 2184-2187.

(16) Nicolaou, K. C.; Yue, E. W.; la Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; de Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467-494.

(17) Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Greca, S. L.; Tsuri, T.; Yue, E. W.; Yang, Z. *Angew. Chem. Int. Ed.* **1994**, *33*, 2187-2190.

(18) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111-12112.

(19) Freeman-Cook, K. D.; Halcomb, R. L. *J. Org. Chem.* **2000**, *65*, 6153-6159.

(20) Bunte, J. O.; Cuzzupe, A. N.; Daly, A. M.; Rizzacasa, M. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6376-6380.

(21) Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.-H.; Nakai, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 4502-4505.

(22) Hirata, Y.; Nakamura, S.; Watanabe, N.; Kataoka, O.; Kurosaki, T.; Anada, M.; Kitagaki, S.; Shiro, M.; Hashimoto, S. *Chem. Eur. J.* **2006**, *12*, 8898-8925.

(23) Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337-3340.

(24) Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020-7 032.

(25) Sato, H.; Nakamura, S.-ichi; Watanabe, N.; Hashimoto, S.-ichi *Synlett* **1997**, *1997*, 451-454.

(26) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 5351-5355.

(27) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115-9125.

(28) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

(29) Nakamura, S.; Sato, H.; Hirata, Y.; Watanabe, N.; Hashimoto, S. *Tetrahedron* **2005**, *61*, 11078-11106.

(30) Hendrickson, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 5439-5450.

(31) Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 1090-1091.

(32) Rahim, M. A.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2005**, *46*, 7307-7309.

(33) Satterfield, A. D. [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, University of North Carolina at Chapel Hill, 2009.

(34) Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281-17283.

(35) Linghu, X.; Satterfield, A. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 9302-9303.

(36) Mukaiyama, T. *Angew. Chem. Int. Ed.* **1979**, *18*, 707-721.

(37) Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967**, *100*, 2494-2507.

(38) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259-260.

(39) Barrow, J. C. Ph.D. Thesis. Harvard University, **1996**.

(40) Seebach, D.; Beck, A. K.; Imwinkelzied, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954-974.

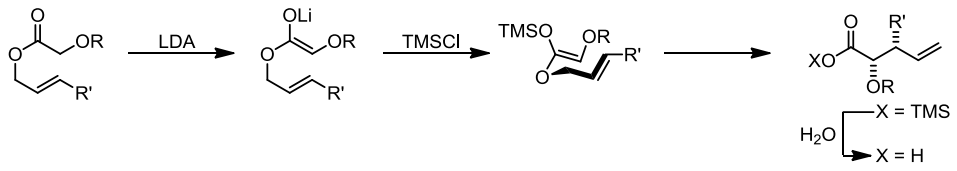
CHAPTER 2

DEVELOPMENT OF A BROOK/IRELAND-CLAISEN REARRANGEMENT SEQUENCE

2.1 Introduction

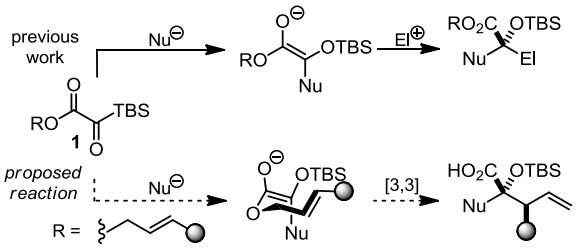
New methods to produce the glycolic acid moiety continue to be important in the creation of small molecule building blocks. γ,δ-Unsaturated glycolic acid derivatives represent a functional group-rich subset of substituted α-hydroxy acids with significant potential for further elaboration. A common approach to the preparation of such compounds is the Ireland-Claisen rearrangement of allyl glycolate esters (Scheme 2-1).[1,2,3] While the standard Ireland-Claisen rearrangement is performed by sequential enolization and silylation of allylic esters, creative alternative approaches to the requisite silyl ketene acetal have been reported. Known methods include 1,4-addition to enoates,[4] silylene transfer followed by 6π-electrocyclization,[5] and Rh-catalyzed reduction of enoates.[6] All of these methods allow for the generation of chiral products from achiral starting materials; however, a glycolate Ireland-Claisen rearrangement that introduces two α-substituents in one step has remained elusive.

Scheme 2-1. Ireland-Claisen Rearrangement of Allyl Glycolate Esters



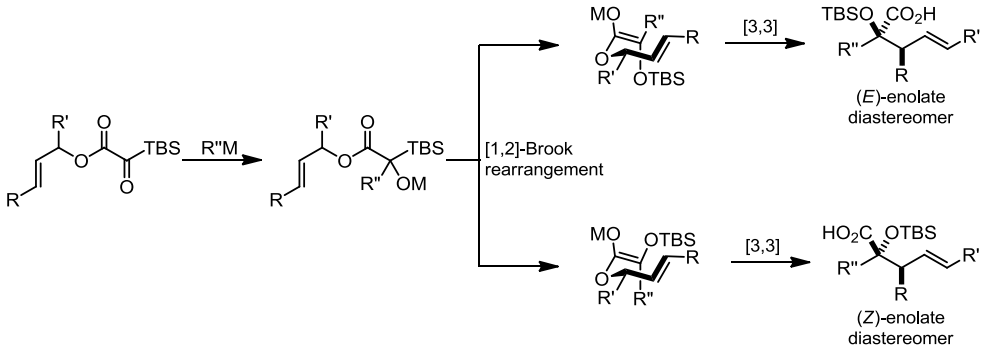
Silyl glyoxylates (**1**, Scheme 2-2) are reagents for the geminal linking of nucleophile/electrophile pairs at a glycolic acid junction (see Chapter 1).[7,8] Since multicomponent couplings involving silyl glyoxylates are believed to proceed by a glycolate enolate intermediate, the use of an allylic ester might allow [3,3]-sigmatropic rearrangement to proceed in preference to intermolecular addition to an electrophile (Scheme 2-2).

Scheme 2-2. Silyl Glyoxylate Reactivity



The Ireland-Claisen rearrangement proceeds via a well-understood transition state wherein the enolate geometry dictates the stereochemistry of the product. The *E*/*Z* geometry of the intermediate glycolate enolate has not been established in reactions of silyl glyoxylates; therefore, determination of enolate geometry would augment our understanding of silyl glyoxylate reactivity and provide mechanistic insight for future endeavors (Scheme 2-3). Furthermore, this process would create two new C–C bonds, allowing access to densely functionalized glycolic acids.

Scheme 2-3. Proposed Rearrangement Cascade



2.2 Results and Discussion

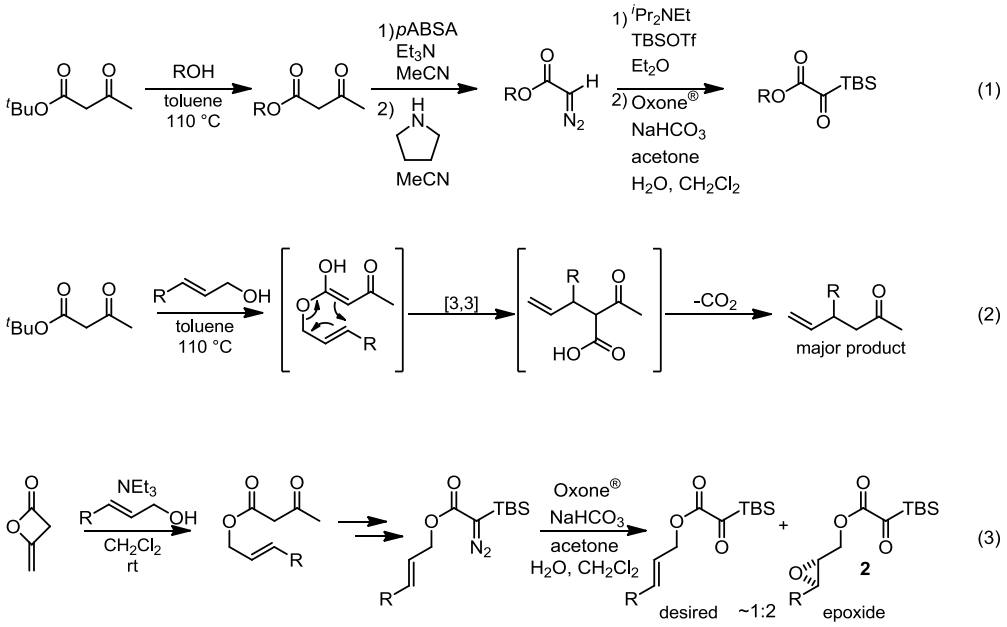
2.2.1 Preparation of Allylic Silyl Glyoxylates

Development of the Brook/Ireland-Claisen rearrangement cascade first required preparation of allylic silyl glyoxylates. The established synthesis of alkyl silyl glyoxylates involves a four step sequence from the alkyl acetoacetate, involving diazo transfer, retro-Claisen fragmentation, silylation, and oxidation (eq. 1, Scheme 2-4).[9] Although allyl acetoacetate is commercially available, the preparation and subsequent Ireland-Claisen rearrangement of simple allyl silyl glyoxylate would not yield useful information regarding the enolate geometry, as only one chiral center would be generated; therefore, substituted allylic silyl glyoxylates (cinnamyl, crotyl, etc.) needed to be prepared. Preparation of cinnamyl acetoacetate proved to be more challenging than originally anticipated.

The preparation of alkyl acetoacetates involves the thermal transesterification of *t*-butyl acetoacetate, driven by distillative removal of *t*-butanol. However, when transesterification of *t*-butyl acetoacetate was attempted with cinnamyl alcohol, an undesired [3,3]-rearrangement followed by decarboxylation (Carroll rearrangement) occurred as a consequence of the allylic ester (eq. 2, Scheme 2-4).[10] Following some

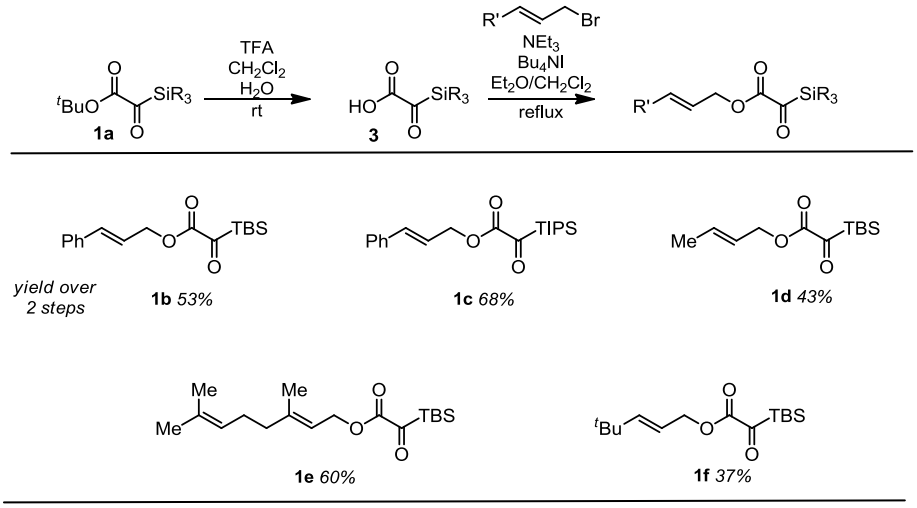
experimentation, allylic alcohol acetoacetylation by treatment with diketene proved to be effective as it did not require elevated temperatures and thus avoided Carroll rearrangement (eq. 3, Scheme 2-4). With cinnamyl acetoacetate in hand, subsequent diazo transfer, retro-Claisen, and *C*-silylation proceeded smoothly. However, in the final step, treatment with Oxone® resulted in competitive overoxidation to epoxide **2**.

Scheme 2-4. Allylic Esters Incompatible with Traditional Silyl Glyoxylate Synthesis



Due to these difficulties, we modified our approach and installed the allylic ester following acylsilane formation. The silyl glyoxylic acid **3** can undergo nucleophilic esterification with allylic bromides (Scheme 2-5) under identical conditions to those developed in Chapter 1 for esterification with benzylic bromides. This method was found to be effective with both TBS and TIPS silyl glyoxylic acids with various allylic bromides.

Scheme 2-5. Nucleophilic Esterification of Silyl Glyoxylic Acids

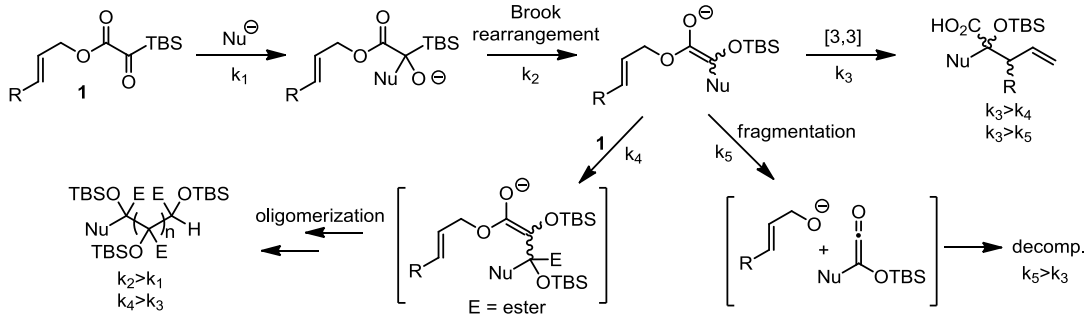


2.2.2 Identification of Competent Nucleophiles

Preliminary work focused on defining a compatible nucleophilic component. Previously employed nucleophiles such as vinylmagnesium bromide and zinc acetylides were found to trigger oligomerization of the silyl glyoxylate. This result underscores the chemoselectivity displayed in previously reported three-component coupling reactions, where the nucleophile reacts selectively with the silyl glyoxylate, rather than the terminal electrophile, and the intermediate glycolate enolate reacts selectively with a terminal electrophile, rather than a second equivalent of silyl glyoxylate. The proposed transformation would need to proceed in the absence of a secondary electrophile (vide infra). We hypothesized that two requirements exist for any given nucleophile to initiate the desired rearrangement cascade (Scheme 2-6): (1) the nucleophile must fully consume the silyl glyoxylate prior to Brook rearrangement in order to prevent oligomerization, and (2) following Brook rearrangement the intermediate glycolate enolate must be stable

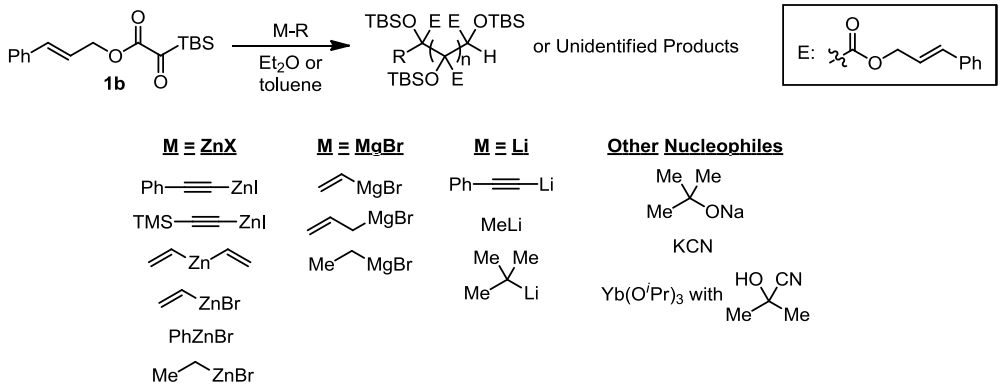
enough to undergo Ireland-Claisen rearrangement in preference to decomposition via ketene formation.

Scheme 2-6. Rate Requirements for the Desired Cascade



In an effort to identify competent nucleophiles, a screen of organometallics was performed. In each case, the result was silyl glyoxylate oligomerization or other forms of decomposition (Figure 2-1). Attempts to inhibit Brook rearrangement by holding the reaction at -78 °C for several hours still resulted in oligomerization; this result may be due to slower nucleophilic addition to silyl glyoxylate at low temperature, leaving behind unreacted silyl glyoxylate that could participate in oligomerization.

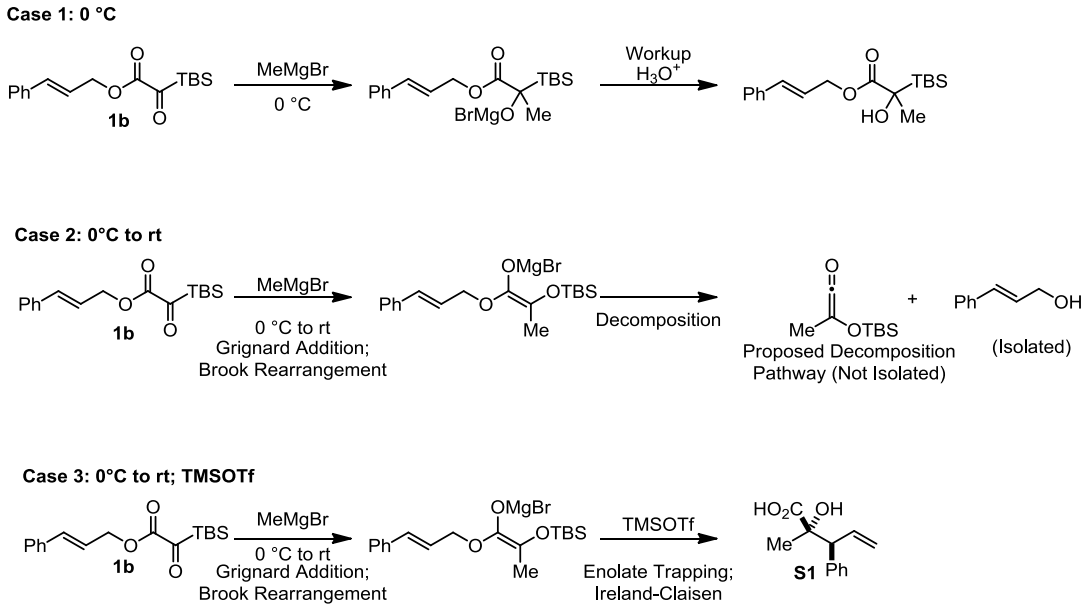
Figure 2-1. Nucleophiles that Generate Oligomers or Unidentified Products



2.2.3 Scope and Limitations

An assessment of Grignard reagents revealed that MeMgBr had potential as an effective nucleophile as it cleanly added to cinnamyl silyl glyoxylate **1b** at 0 °C. In this case, Brook rearrangement did not occur below room temperature (Scheme 2-7). When the reaction was allowed to warm, decomposition was observed within 30 minutes. In an attempt to stabilize the glycolate enolate intermediate, silyl ketene acetal formation was attempted by addition of MeMgBr at 0 °C followed by warming to room temperature and addition of TMSCl; however, this experiment also resulted in decomposition. Given that no TMS incorporation was observed, we turned to TMSOTf, which induced the desired Ireland-Claisen rearrangement and provided the γ,δ-unsaturated glycolic acid **S1** in 55% yield (Scheme 2-7).

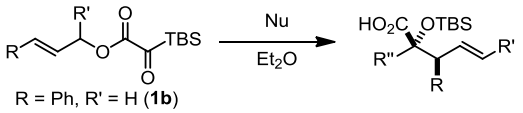
Scheme 2-7. Successful Ireland-Claisen Rearrangement with MeMgBr



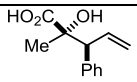
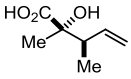
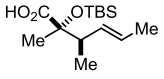
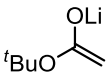
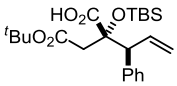
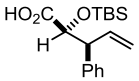
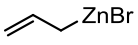
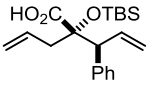
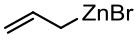
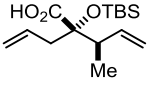
Various organozinc nucleophiles were also found to be effective nucleophilic initiators. $ZnEt_2$ serves as an efficient hydride donor, triggering the sequential Brook and

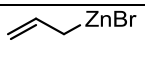
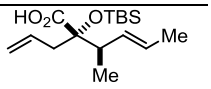
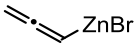
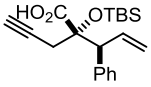
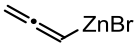
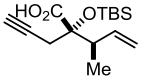
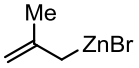
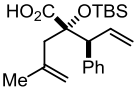
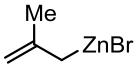
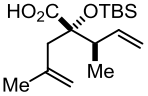
Ireland-Claisen rearrangements, to afford the glycolic acid in 69% yield with good diastereoselectivity (Table 2-1, entry 5). The hydride reduction of α-ketoesters with $ZnEt_2$ or EtMgBr has been previously reported; however, it is typically a minor byproduct to ethyl addition.[11] Allyl zinc bromide and allenyl zinc bromide were useful triggers as well (Table 2-1, entries 6-10).

Table 2-1. Sequenced Brook and Ireland-Claisen Rearrangements



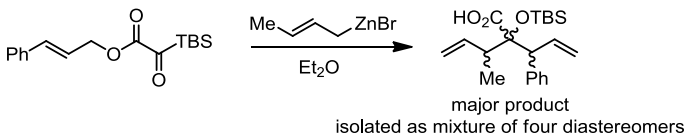
R = Ph, R' = H (**1b**)
R = Me, R' = H (**1d**)
R = Me, R' = Me (**1g**)

entry	silyl glyoxylate	Nu	yield, d.r.
1	**1b**	MeMgBr/TMSOTf	 *55%, 5.0:1*
2	**1d**	MeMgBr/TMSOTf	 *64%, 5.7:1*
3	**1g**	MeMgBr/TMSOTf	 *65%, 4.9:1*
4	**1b**		 *31%, 20:1*
5	**1b**	$ZnEt_2$	 *69%, 12:1*
6	**1b**		 *68%, 1.8:1*
7	**1d**		 *57%, 8.0:1*

8	**1g**		 *67%, 6.0:1*
9	**1b**		 *58%, 2.2:1*
10	**1d**		 *33%, 10:1*
11	**1b**		 *74%, 1:1*
12	**1d**		 *61%, 4.9:1*

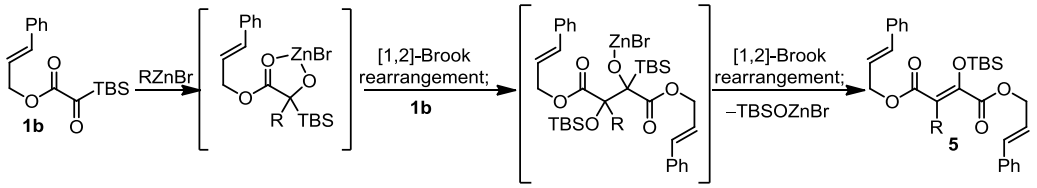
Substituted allylic zinc nucleophiles were also competent initiators. Methallylzinc bromide provided the desired products with slightly diminished diastereoselectivity relative to allylzinc bromide (entries 11-12). Crotyl- and cinnamylzinc reagents provided a complex mixture of diastereomeric products (Scheme 2-8). Notably, none of the organozinc nucleophiles required silyl ketene acetal formation, as the zinc enolate underwent [3,3]-rearrangement spontaneously. The lithium enolate of ^{t}BuOAc also initiated the Brook/Ireland-Claisen sequence without TMS trapping and proceeded with excellent diastereoselectivity (Table 2-1, entry 4).

Scheme 2-8. Crotyl Zinc Bromide Generates Three Adjacent Chiral Centers



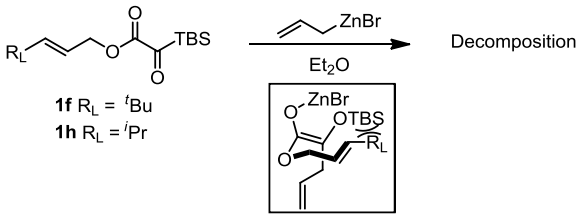
Extension to other organozinc bromides proved challenging. Benzylzinc bromide, propynylzinc bromide, and Reformatsky nucleophiles resulted in alkene dimer **5** (Scheme 2-9). This dimer was cleanly formed by addition of the glycolate enolate to a second equivalent of silyl glyoxylate. The derived alkoxide suffered Brook rearrangement and elimination. It appears that allyl and allenyl zinc bromide nucleophiles consumed the silyl glyoxylate more rapidly and therefore dimerization was not competitive.

Scheme 2-9. Organozinc Bromide Induced Dimerization



The scope of the ester component was also investigated. While cinnamyl (**1b**), crotyl (**1d**), and substituted crotyl (**1g**) silyl glyoxylates were effective, the more hindered silyl glyoxylates **1f** and **1h** failed to undergo the desired transformation (Figure 2-2). This may be due to steric hindrance preventing the approach of the enolate and ester termini, slowing the Ireland-Claisen rearrangement and eventually resulting in enolate decomposition.

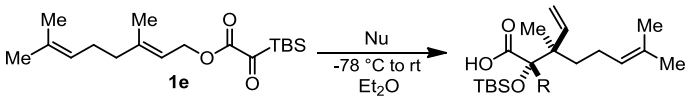
Figure 2-2. Ineffective Silyl Glyoxylates

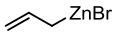
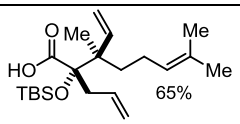
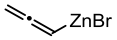
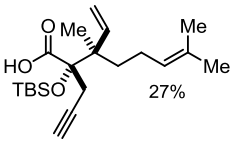
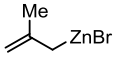
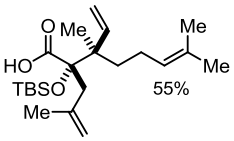


Geranyl silyl glyoxylate **1e** underwent the title transformation when treated with allenyl or allylic zinc bromides, providing glycolic acid derivatives in moderate

diastereoselectivity (Table 2-2). These results demonstrate that the Brook/Ireland-Claisen sequence may show promise for the construction of adjacent chiral quaternary centers.

Table 2-2. Preparation of Contiguous Quaternary Centers



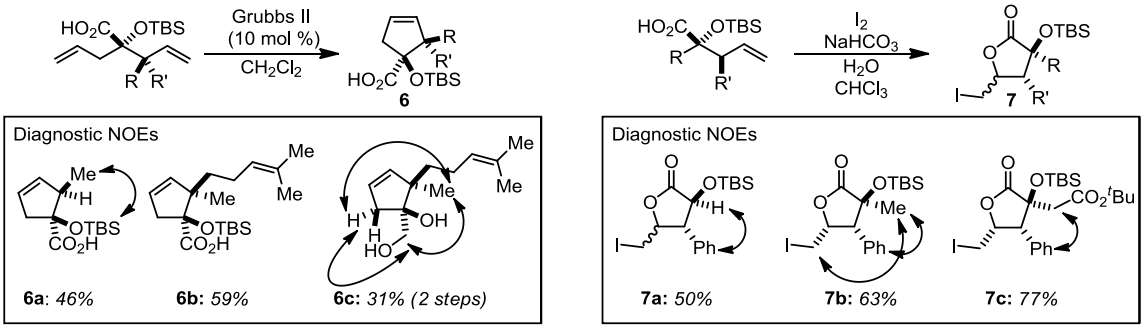
entry	nucleophile	product (yield)	d.r.
1		 65%	3.0:1
2		 27%	3.7:1
3		 55%	2.5:1

2.2.4 Determination of Stereochemistry

Enolate geometry was inferred by examination of the relative stereochemistry of the γ,δ-unsaturated glycolic acid products. The majority of these products were unknown compounds, so derivatization was required in order to allow NOESY analysis for determination of stereochemistry. The γ,δ-unsaturated acids resulting from addition of allyl zinc bromide were treated with Grubbs II catalyst to form cyclopentenes via RCM (**6a**-**6c**, Scheme 2-10). The products of allenyl zinc bromide addition (Table 2-1, entries 9-10), failed to undergo clean enyne RCM, so they were subjected to Lindlar reduction to

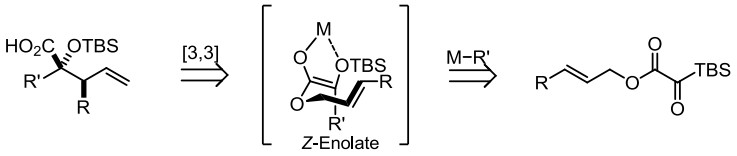
provide the corresponding dienes. NOESY stereochemical analysis of the geraniol derived cyclopentene **6b** was inconclusive, so the carboxylic acid was reduced with LAH to diol **6c**, revealing an additional diagnostic methylene that facilitated NOESY analysis.

Scheme 2-10. Product Derivatization for Stereochemical Determination



Products that possessed only one olefin could be cyclized by iodolactonization to the corresponding γ-lactones **7a-c** (Scheme 2-10). In some other cases, the tertiary silyl ethers of the acyclic products could be deprotected with TBAF to provide known compounds. In each case, the major diastereomer was found to be consistent with a (*Z*)-glycolate enolate, assuming the Ireland-Claisen rearrangement proceeded through a chairlike transition state (Scheme 2-11).

Scheme 2-11. (*Z*)-Glycolate Enolate Intermediate

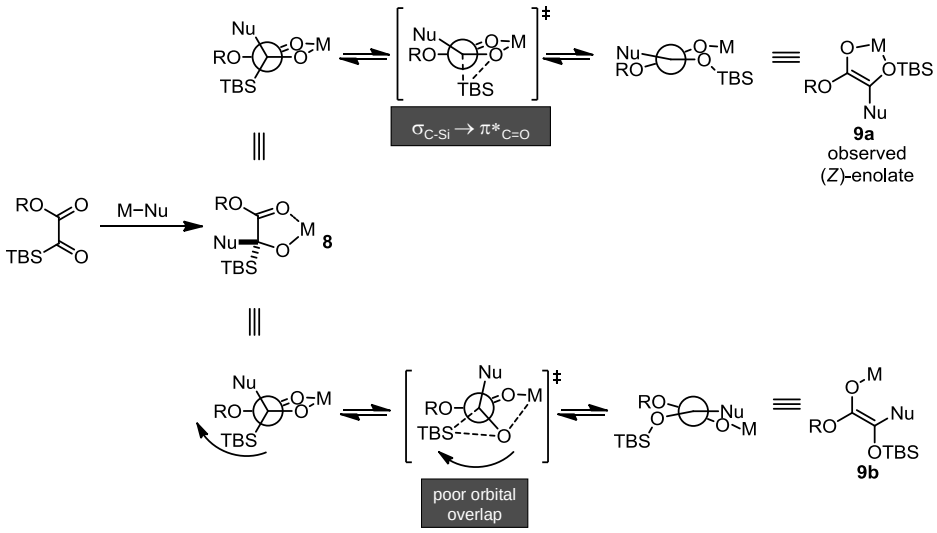


2.2.5 Mechanistic Insight

The degree of diastereocontrol depended on the identity of both the nucleophile and the ester. While cinnamyl silyl glyoxylate **1b** reacted with allylzinc bromide (Table 2-1, entry 6) and allenylzinc bromide (entry 9) with modest diastereocontrol, analogous

reactions with crotyl silyl glyoxylate **1d** resulted in substantially higher d.r.'s (entries 7, 10). The formation of the chelated alkoxide **8** (Scheme 2-12) appears likely in light of the established tendencies for bidentate coordination in α–dicarbonyl electrophiles and the derived addition products.[12] Proper alignment of the C–Si σ orbital with the adjacent C=O π* orbital in tetrahedral intermediate **8** would allow [1,2]-Brook rearrangement to proceed, forming glycolate enolate **9a**. These stereoelectronic considerations would suggest subsequent formation of (*Z*)-enolate **9a** arising from Brook rearrangement (scheme 2-12). Without breaking chelation prior to Brook rearrangement, formation of (*E*)-enolate **9b** would be challenging, as the proper orbital alignment for silyl migration would be inaccessible.

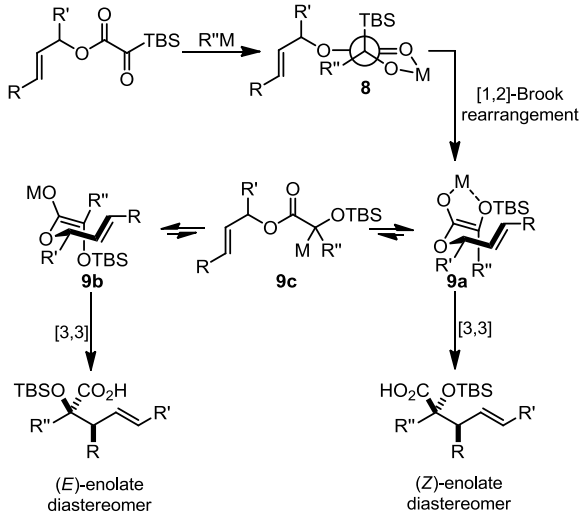
Scheme 2-12. FMO Analysis



Following Brook rearrangement, the resulting silyl ether should dramatically weaken chelation,[13] potentially permitting enolate equilibration (via the C–Zn tautomer **9c**, scheme 2-13 below) to compete with Ireland-Claisen rearrangement from the (*Z*)-isomer. The rate of the sigmatropic rearrangement should be linked to steric demand,

where a less hindered substrate undergoes more rapid [3,3]-rearrangement;[14] therefore, it is hypothesized that the more encumbered **1b** undergoes enolate equilibration to a greater extent prior to sigmatropic rearrangement. The result is an erosion of the initial enolate geometric ratio and a corresponding decrease in product diastereoselectivity. This proposal is consistent with the experimental observations within the organozinc nucleophile series: the product diastereomer ratio increases as nucleophile bulk decreases (hydride > propargyl ≈ allyl > methallyl).[15]

Scheme 2-13. Mechanistic Rationale for Diastereoselectivity Trend

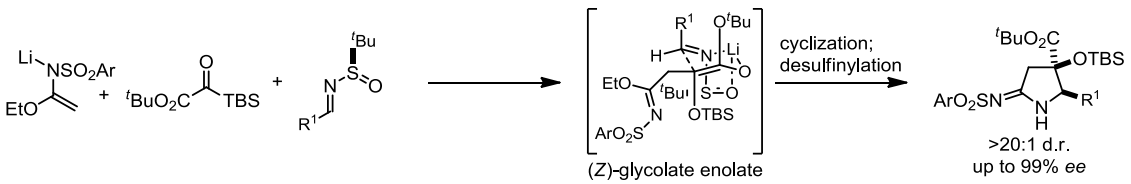


It is notable that MeMgBr initiates Ireland-Claisen rearrangement with diastereoselectivity independent of ester. This may be a result of silyl ketene acetal formation prior to sigmatropic rearrangement. Provided there is no enolate equilibration after TMSOTf trapping, the diastereoselectivity reflects the (*Z*)/(*E*) Mg-enolate ratio at the time of TMSOTf addition. The high diastereoselectivity observed for the Li-enolate (Table 2-1, entry 4) can be explained if generation of the C–Li tautomer **9c** is slow and [3,3]-sigmatropic rearrangement outcompetes enolate equilibration.

2.2.6 Implications of Enolate Geometry

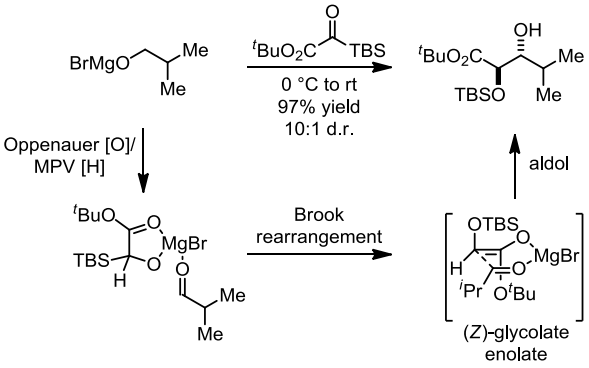
A (*Z*)-glycolate enolate resulting from Brook rearrangement is consistent with the results of other silyl glyoxylate couplings with lithium, magnesium, and zinc counterions. A recent report by Lu describes the synthesis of amidines via three component coupling of lithium aza-enolates, silyl glyoxylates, and aldimines.[16] The high levels of diastereoselectivity can be rationalized by a chairlike transition state wherein the (*Z*)-glycolate enolate approaches the aldimines from the opposite direction of the *t*-butyl group (Scheme 2-14).

Scheme 2-14. Lu's Highly Diastereoselective Couplings via a (*Z*)-Lithium Enolate



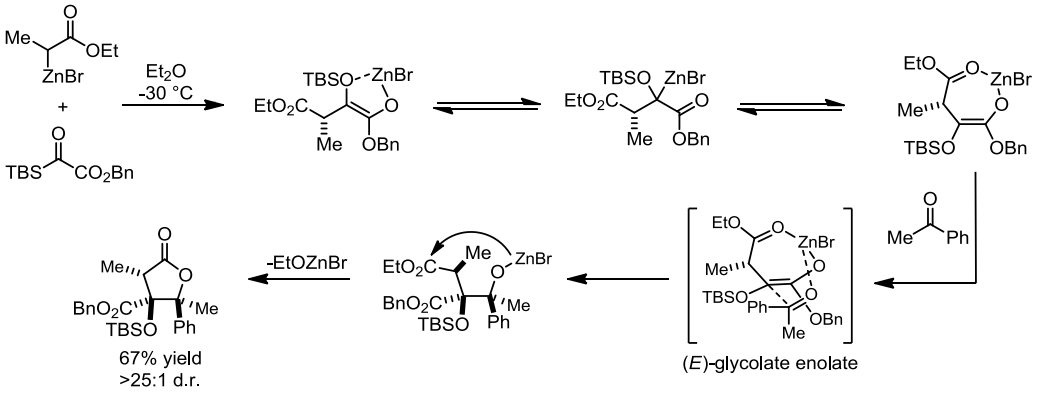
Evidence of a (*Z*)-magnesium enolate intermediate was also obtained from the Meerwein-Ponndorf-Verley initiated aldol reaction previously developed in our group (Scheme 2-15).[17] The resulting *anti* stereochemistry is consistent with a (*Z*)-glycolate enolate reacting via a boatlike transition state, a proposal that follows precedent set by Evans for (*Z*)-magnesium enolate *anti* propionate aldol additions.[18] Further support for a (*Z*)-magnesium enolate was obtained through Boyce and Liu's density functional theory calculations on a related system that reveal a thermodynamic preference of 6.4 kcal/mol relative to the (*E*)-magnesium glycolate enolate.[19]

Scheme 2-15. Linghu's Diastereoselective Aldol via a (*Z*)-Magnesium Enolate



The observed facile equilibration of zinc glycolate enolates further validates Greszler's previously proposed mechanism for the diastereoselective three component couplings of Reformatsky reagents, silyl glyoxylates, and ketones.[20] In that study, propionate nucleophiles provided substantially higher diastereoselectivity than acetate nucleophiles. The stereochemical result is consistent with a boat/twist-boat transition state in which the ethyl ester chelates to the zinc, necessitating isomerization to the (*E*)-glycolate enolate, and approach of the ketone electrophile from the less hindered face (Scheme 2-16).

Scheme 2-16. Greszler's Couplings via Equilibration to the (*E*)-Zn Enolate



2.3 Conclusion

In summary, we have developed a one-pot Brook/Ireland-Claisen rearrangement sequence that generates γ,δ-unsaturated glycolic acids containing two new C–C bonds and two contiguous stereocenters. The reaction is tolerant of various reaction partners, but diastereoselectivity is linked to the identity of the metal cation and the ester. In cases that show good diastereoselectivity, the stereochemical outcome of the reaction is consistent with a (*Z*)-enolate intermediate proceeding through a chairlike transition state. The work suggests that diastereocontrol and enolate geometry in reactions with silyl glyoxylates can be tuned with the judicious selection of metal cation and that the rate of the "second stage" reaction can have an impact.

2.4 Experimental

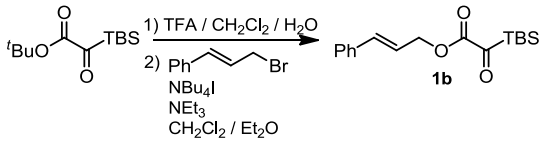
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on either a Bruker model Avance 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz), Bruker model Avance 500 (^{1}H at 500 MHz and ^{13}C NMR at 125 MHz), Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), or a Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; C_6D_6 at 7.15 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm and C_6D_6 at 128.62 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, 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 aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. 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. Diethyl ether, methylene chloride, tetrahydrofuran, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use.[21] Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. Triethylamine, diisopropylamine, and pyridine were freshly distilled from CaH_2 under Ar prior to use.

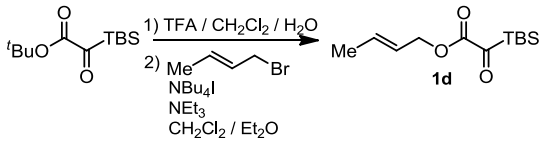
Synthesis of Silyl Glyoxylates

General esterification procedure A for formation of allylic silyl glyoxylates: To *t*-butyl *t*-butyldimethylsilyl glyoxylate,[9] (1.0 equiv) a solution of 20:10:1 CH_2Cl_2:TFA:H_2O (0.5 M) was added. After the yellow solution was stirred at room temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The yellow oil was then dissolved in toluene and again concentrated *in vacuo*. The resulting yellow oil was added to a dry round bottom flask and the allylic bromide (1.3 equiv), and tetrabutylammonium iodide (0.1 equiv) were added. The mixture was dissolved in 1:1 Et_2O:CH_2Cl_2 (0.1 M) and NEt_3 (1.4 equiv) was added. The flask was fitted with a reflux condenser and the solution was heated to reflux for 10-16 h. The reaction was then allowed to cool to room temperature. The reaction was diluted with 30 mL saturated aqueous NH_4Cl solution. The layers were

separated and the aqueous layer was extracted with Et_2O (2 X 30 mL) and then CH_2Cl_2 (2 X 30 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The resulting yellow oil was purified as indicated.

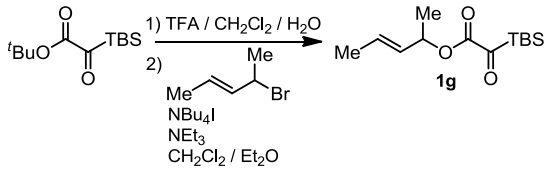


Cinnamyl tert-butyldimethylsilyl glyoxylate (1b). The general esterification procedure was performed using *t*-butyl *t*-butyldimethylsilyl glyoxylate (4.96 g, 20.3 mmol), cinnamyl bromide (5.20 g, 26.4 mmol), tetrabutylammonium iodide (750 mg, 2.03 mmol), and NEt_3 (3.95 mL, 28.4 mmol). Purification by flash chromatography (3:97 Et_2O:petroleum ether) furnished 3.07 g (50%) of **1b** as a yellow liquid: **IR** (thin film, cm^{-1}) 3029, 2930, 2860, 1718, 1654, 1558, 1541, 1254, 968; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 6.73 (d, *J* = 15.6 Hz, 1H), 6.33 (dt, *J* = 15.9, 6.6 Hz, 1H), 4.89 (d, *J* = 6.6 Hz, 2H), 0.97 (s, 9H), 0.30 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 231.9, 162.8, 135.9, 135.7, 128.6, 128.3, 126.7, 121.8, 66.0, 26.4, 17.0, -6.9; **TLC** (5:95 EtOAc: petroleum ether) R_f 0.40. **LRMS** (ESI) exact mass calculated for $C_{17}H_{24}O_3SiNa$: 327.15. Found: 327.13.

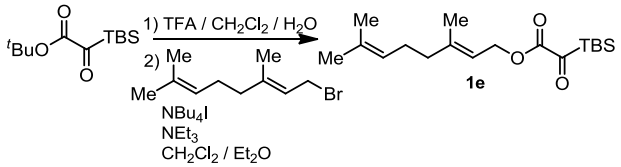


Crotyl tert-butyldimethylsilyl glyoxylate (1d). The general esterification procedure was performed using *t*-butyl *t*-butyldimethylsilyl glyoxylate (780 mg, 3.19 mmol), *trans*-crotyl bromide[22] (559 mg, 4.14 mmol), tetrabutylammonium iodide (118 mg, 0.319

mmol), and NEt_3 (622 μL, 4.47 mmol). Purification by flash chromatography (3:97 Et_2O:petroleum ether) furnished 335 mg (43%) of **1d** as a yellow liquid: **IR** (thin film, cm^{-1}) 2953, 2931, 2886, 2860, 2360, 1719, 1656, 1465, 1254; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.90-5.84 (m, 1H), 5.67-5.59 (m, 1H), 4.64 (d, *J* = 6.8 Hz, 2H), 1.73 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 9H), 0.27 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.8, 133.0, 124.0, 66.1, 27.9, 26.4, 17.7, 16.9, -7.0; **TLC** (5:95 EtOAc: petroleum ether) R_f 0.52. **LRMS** (ESI) exact mass calculated for $C_{12}H_{22}O_3SiNa$: 265.13. Found: 265.12.



(*E*)-pent-3-en-2-yl-*tert*-butyldimethylsilyl glyoxylate (1g). The general esterification procedure was performed using *t*-butyl *t*-butyldimethylsilyl glyoxylate (1.09 g, 4.46 mmol), (*E*)-4-bromopent-2-ene (864 mg, 5.80 mmol), tetrabutylammonium iodide (165 mg, 0.446 mmol), and NEt_3 (870 μL, 6.24 mmol). Purification by flash chromatography (3:97 Et_2O:petroleum ether) furnished 337 mg (29%) of **1g** as a yellow liquid: **IR** (thin film, cm^{-1}) 2954, 2932, 2886, 2860, 1715, 1658, 1558, 1541, 1254; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.85-5.78 (m, 1H), 5.55-5.40 (m, 2H), 1.70 (d, *J* = 6.6, 3H), 1.38 (d, *J* = 6.3 Hz, 3H), 0.95 (s, 9H), 0.27 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 232.1, 162.6, 129.8, 73.2, 26.4, 20.2, 17.5, 16.9, -6.9; **TLC** (5:95 EtOAc: petroleum ether) R_f 0.54. **LRMS** (ESI) exact mass calculated for $C_{13}H_{24}O_3SiNa$: 279.15. Found: 279.13.

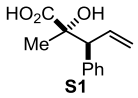


Geranyl tert-butyldimethylsilyl glyoxylate (1e). The general esterification procedure was performed using *t*-butyl *t*-butyldimethylsilyl glyoxylate (1.21 g, 4.94 mmol), geranyl bromide (1.39 g, 6.42 mmol), tetrabutylammonium iodide (182 mg, 0.494 mmol), and NEt_3 (0.96 mL, 6.92 mmol). Purification by flash chromatography (2:98 Et_2O:petroleum ether) furnished 969 mg (60%) of **1e** as a yellow liquid: **IR** (thin film, cm^{-1}) 2930, 2859, 1717, 1660, 1464, 1377, 1365, 1252, 990; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.41 (t, *J* = 6.9 Hz, 1H), 5.09-5.07 (m, 1H), 4.75 (d, *J* = 7.5 Hz, 2H), 2.10-2.03 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 0.96 (s, 9H), 0.27 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 231.9, 163.1, 143.9, 131.9, 123.6, 117.3, 62.2, 39.5, 28.0, 26.4, 26.3, 25.6, 17.6, 17.0, 16.5, -6.9; **TLC** (5:95 EtOAc: petroleum ether) R_f 0.53. **LRMS** (ESI) exact mass calculated for $C_{18}H_{32}O_3SiNa$: 347.21. Found: 347.20.

Synthesis of Glycolic Acid Derivatives (Tables 2-1 and 2-2)

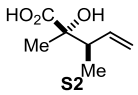
General procedure B for reaction of silyl glyoxylates with MeMgBr: A solution of MeMgBr (1.7 equiv) in Et_2O (3 M) was diluted with Et_2O to 0.18 M. The solution was cooled to 0 °C and a solution of silyl glyoxylate (1.0 equiv) in Et_2O (0.03 M) was added. The ice bath was removed and the reaction was stirred for 1 min. TMSOTf (2.0 equiv) was added and the reaction was stirred at room temperature for 2-8 h. The reaction was diluted with aqueous HCl (1 M, 5 mL). The layers were separated and the aqueous layer

was extracted with CH_2Cl_2 (3 X 10 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The resulting colorless oil was purified as indicated.



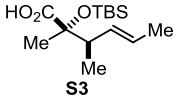
S1

2-hydroxy-2-methyl-3-phenylpent-4-enoic acid (S1). General procedure B was performed using cinnamyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.263 mmol), MeMgBr (3 M in Et_2O, 0.15 mL, 0.447 mmol), and TMSOTf (95 μL, 0.526 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 30 mg (55%) of **S1** as a clear oil that matched analytical data previously reported.[23]



S2

2-hydroxy-2,3-dimethylpent-4-enoic acid (S2). General procedure B was performed using crotyl *t*-butyldimethylsilyl glyoxylate (80 mg, 0.33 mmol), MeMgBr (0.19 mL, 0.561 mmol), and TMSOTf (119 μL, 0.66 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 25 mg (53%) of **S2** as a clear oil that matched analytical data previously reported.[24]

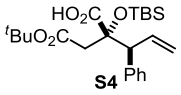


S3

(E)-2-(tert-butyldimethylsilyloxy)-2,3-dimethylhex-4-enoic acid (S3). General procedure B was performed using (E)-pent-3-en-2-yl 2-tert-butyldimethylsilyl glyoxylate

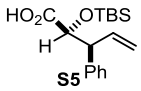
(70 mg, 0.273 mmol), MeMgBr (0.155 mL, 0.464 mmol), and TMSOTf (99 μL, 0.546 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 48 mg (65%) of **S3** as a white solid. Analytical data for **S3**: mp 83 °C; **IR** (thin film, cm^{-1}) 2930, 2857, 1715, 1472, 1462, 1410, 1371, 1282, 1198; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54-5.45 (m, 1H), 5.34-5.26 (m, 1H), 2.46-2.41 (m, 1H), 1.69 (d, *J* = 6.3 Hz, 3H), 1.44 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 130.9, 127.7, 80.8, 46.2, 25.8, 24.2, 18.5, 18.0, 15.7, -2.5, -2.7; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.25. **LRMS** (ESI) exact mass calculated for $C_{14}H_{28}O_3SiNa$: 295.18. Found: 295.17.

Proof of Stereochemistry: Product stereochemistry was determined by conversion to the known 2-hydroxy-2,3-dimethylhex-4-enoic acid. This was accomplished via TBAF deprotection. Spectral data of the minor diastereomer were identical to those reported in the literature (Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H. *J. Am. Chem. Soc.* **1999**, *121*, 1748-1749). Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.63-5.55 (m, 1H), 5.42-5.36 (m, 1H), 2.52-2.47 (m, 1H), 1.72 (d, *J* = 6.4, 3 H), 1.42 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H). Minor diastereomer: (400 MHz, $CDCl_3$) δ 5.63-5.55 (m, 1H), 5.42-5.36 (m, 1H), 2.52-2.47 (m, 1H), 1.67 (d, *J* = 6.4, 3 H), 1.42 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H).



2-(2-tert-butoxy-2-oxoethyl)-2-(tert-butyldimethylsilyloxy)-3-phenylpent-4-enoic acid (S4). To 56 mg LiCl in 2.2 mL THF at 0 °C was added diisopropylamine (55 μL, 0.395 mmol, 1.5 equiv) followed by ^{n}BuLi (1.5 M in hexanes, 0.245 mL, 0.368 mmol, 1.4 equiv). The solution was stirred for 10 min at 0 °C and then warmed to room temperature and stirred 15 min. The solution was then cooled to -78 °C and ^{t}BuOAc (46 μL, 0.342 mmol, 1.3 equiv) was added. The solution was stirred for 1 h at -78 °C. Cinnamyl silyl glyoxylate (80 mg, 0.263 mmol, 1.0 equiv) in 2.0 mL Et_2O was then added via syringe. The solution was slowly warmed to room temperature and stirred for 19 h. The reaction was diluted with 5 mL aqueous HCl (1 M). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (93:6:1 petroleum ether:Et_2O:HOAc) furnished 34 mg (31%) of **S4** as a white solid. Analytical data for **S4**: mp 92 °C; **IR** (thin film, cm^{-1}) 2929, 2855, 1735, 1558, 1541, 1473, 1393, 1368, 1152; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26-7.20 (m, 5H), 6.36-6.24 (m, 1H), 5.27 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.19 (d, *J* = 17.1, 1H), 3.81 (d, *J* = 9.6 Hz, 1H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.72 (d, *J* = 16.8 Hz, 1H), 1.46 (s, 9H), 0.93 (s, 1H), 0.12 (s, 3H), -0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.6, 138.9, 135.9, 129.4, 128.0, 127.2, 118.9, 82.5, 80.9, 57.5, 44.7, 28.1, 26.2, 19.0, -2.6, -2.9; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.14. **LRMS** (ESI) exact mass calculated for $C_{23}H_{36}O_5SiNa$: 443.23. Found: 443.21.

Proof of Stereochemistry: Product stereochemistry was determined by conversion to the iodolactone **7c** and subsequent NOESY analysis. Experimental details are provided below.



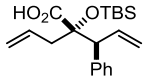
S5

2-(tert-butyldimethylsilyloxy)-3-phenylpent-4-enoic acid (S5). $ZnEt_2$ (1 M in hexanes, 0.39 mL, 0.394 mmol, 1.5 equiv) was diluted with 1.2 mL Et_2O. The solution was cooled to 0 °C and a solution of cinnamyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.263 mmol, 1.0 equiv) in 2.8 mL Et_2O was added. The reaction was warmed to room temperature and allowed to stir for 4 h. The reaction was diluted with 5 mL aqueous HCl (1 M). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 56 mg (69%) of **S5** as a white solid. Analytical data for **S5**: mp 82 °C; **IR** (thin film, cm^{-1}) 3031, 2954, 2929, 2896, 2858, 2360, 1724, 1255, 1134; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 6.19-6.07 (m, 1H), 5.19 (d, *J* = 3.3 Hz, 1H), 5.14 (s, 1H), 4.44 (d, *J* = 5.7 Hz, 1H), 3.71 (dd, *J* = 8.7, 6.0 Hz, 1H), 0.86 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.0, 139.0, 136.9, 128.9, 128.3, 127.1, 117.5, 76.6, 54.6, 25.6, 18.0, -5.4; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.20. **LRMS** (ESI) exact mass calculated for $C_{17}H_{26}O_3SiNa$: 329.17. Found: 329.15.

Proof of Stereochemistry: Product stereochemistry was determined by conversion to the known 2-hydroxy-3-phenylpent-4-enoic acid. This was accomplished via TBAF

deprotection. Spectral data were identical to that reported in the literature (Kaur, P.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 8231-8240). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 5H), 6.27-6.18 (m, 1H), 5.27-5.23 (m, 2H), 4.59 (m, 1H), 3.87-3.86 (m, 1H).

General procedure C for reaction of silyl glyoxylates with allyl zinc bromide and methallyl zinc bromide: A solution of allyl zinc bromide[25] (1.5 equiv) or methallylzinc bromide (1.5 equiv) in THF (0.33 M) was diluted with Et_2O to 0.16 M. The solution was cooled to -78 °C and a solution of silyl glyoxylate (1.0 equiv) in Et_2O (0.10 M) was added. The reaction was allowed to slowly warm to room temperature over 1 h and then stir for 30 min to 2 h at room temperature. The reaction was diluted with 5 mL aqueous HCl (1 M). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The resulting colorless oil was purified as indicated.

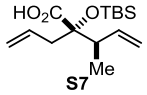


S6

2-allyl-2-(tert-butyldimethylsilyloxy)-3-phenylpent-4-enoic acid (S6). General procedure C was performed using cinnamyl tert-butyldimethylsilyl glyoxylate (40 mg, 0.131 mmol) and allylZnBr (0.33 M, 0.60 mL, 0.197 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 31 mg (68%) of **S6** as a clear oil. Analytical data for **S6** (mix of diastereomers): **IR** (thin film, cm^{-1}) 3079, 3031, 2955, 2928, 2895, 1723, 1254, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H),

6.32-6.21 (m, 1H), 5.87-5.74 (m, 1H), 5.25-4.98 (m, 4H), 3.72-3.66 (m, 1H), 2.63-2.24 (m, 3H), 0.96 (s, 9H), 0.11 (s, 3H), -0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.5, 139.9, 137.3, 136.1, 132.8, 129.8, 129.4, 128.0, 126.9, 119.1, 118.4, 83.3, 57.3, 44.1, 26.3, 19.2, -1.7, -2.7; **TLC** (10:90 EtOAc:petroleum ether) R_f 0.20. **LRMS** (ESI) exact mass calculated for $C_{20}H_{30}O_3SiNa$: 369.20. Found: 369.17.

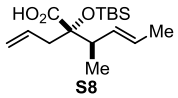
Proof of Stereochemistry: Reaction proceeded with low diastereoselectivity.



S7

2-allyl-2-(tert-butyldimethylsilyloxy)-3-methylpent-4-enoic acid (S7). General procedure C was performed using crotyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.33 mmol) and allylZnBr (0.33 M, 1.52 mL, 0.50 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 54 mg (58%) of **S7** as a clear oil. Analytical data for **S7**: **IR** (thin film, cm^{-1}) 3079, 2956, 2929, 2857, 1719, 1644, 1558, 1254, 1170; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84-5.73 (m, 2H), 5.13-5.07 (m, 4H), 2.63-2.60 (m, 1H), 2.48 (d, *J* = 7.2 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.91 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.0, 138.5, 132.9, 118.8, 116.8, 83.5, 46.2, 43.5, 26.2, 19.1, 16.0, -2.0, -2.5; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.28. **LRMS** (ESI) exact mass calculated for $C_{15}H_{28}O_3SiNa$: 307.18. Found: 307.17.

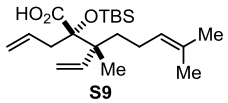
Proof of Stereochemistry: Product stereochemistry was determined by ring closing metathesis and NOESY analysis of the resulting cyclopentene **6a**. Experimental details are provided below.



S8

2-allyl-2-(tert-butyldimethylsilyloxy)-3-methylhex-4-enoic acid (S8). General procedure C was performed using (E)-pent-3-en-2-yl 2-tert-butyldimethylsilyl glyoxylate (80 mg, 0.312 mmol) and allylZnBr (0.33 M, 1.42 mL, 0.468 mmol). Purification by flash chromatography (94:5:1 petroleum ether:Et_2O:HOAc) furnished 61 mg (67%) of **S8** as a clear oil. Analytical data for **S8**: **IR** (thin film, cm^{-1}) 3080, 2956, 2929, 2857, 1642, 1416, 1377, 1277, 1106; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1H), 5.54-5.39 (m, 2H), 5.13-5.07 (m, 2H), 2.59-2.55 (m, 1H), 2.49-2.45 (m, 2H), 1.70 (d, *J* = 6 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.5, 133.0, 131.0, 127.4, 118.6, 83.8, 45.7, 43.5, 26.2, 19.1, 18.1, 16.4, -2.0, -2.5; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.26. **LRMS** (ESI) exact mass calculated for $C_{16}H_{30}O_3SiNa$: 321.20. Found: 321.18.

Proof of Stereochemistry: Product stereochemistry was determined by ring closing metathesis, which provided cyclopentene **6a.** Experimental details are provided below.

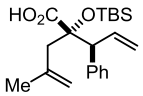


S9

2-allyl-2-(tert-butyldimethylsilyloxy)-3,7-dimethyl-3-vinyloct-6-enoic acid (S9). General procedure C was performed using geranyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.247 mmol) and allylZnBr (0.33 M, 1.12 mL, 0.370 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 59 mg (65%) of **S9** as a clear oil. Analytical data for **S9**: **IR** (thin film, cm^{-1}) 3081, 2956, 2928, 2856, 1714,

1640, 1471, 1415, 1155; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.90 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.77-5.70 (m, 1H), 5.22-5.01 (m, 5H), 2.71 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.43 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.80-1.75 (m, 2H), 1.71-1.61 (m, 1H) 1.67 (s, 3H), 1.56 (s, 3H), 1.40-1.36 (m, 1H), 1.19 (s, 3H), 0.91 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.0, 141.8, 133.9, 133.8, 131.4, 124.6, 119.2, 115.3, 86.9, 48.2, 39.4, 34.7, 26.4, 25.7, 22.9, 19.4, 17.6, 17.1, -1.85, -2.06; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.32. **LRMS** (ESI) exact mass calculated for $C_{21}H_{38}O_3SiNa$: 389.26. Found: 389.24.

Proof of Stereochemistry: Product stereochemistry was determined by ring closing metathesis followed by $LiAlH_4$ reduction and NOESY analysis of the resulting cyclopentene **6c**. See below for experimental details.

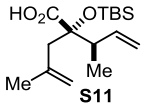


S10

2-(tert-butyldimethylsilyloxy)-4-methyl-2-(1-phenylallyl)pent-4-enoic acid (S10). General procedure C was performed using cinnamyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.263 mmol) and methallylZnBr (0.33 M, 1.19 mL, 0.394 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 70 mg (74%) of **S10** as a clear oil. Analytical data for **S10** (1:1 mix of diastereomers): **IR** (thin film, cm^{-1}) 3077, 3031, 2957, 2928, 2856, 1721, 1646, 1472, 1151; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.21 (m, 5H), 6.39-6.33 (m, 1H), 6.27-6.18 (m, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.17 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 4.0 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J*

= 14.8 Hz, 2H), 4.76 (d, *J* = 49.6 Hz, 2H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.71 (d, *J* = 9.2 Hz, 1H), 2.69 (d, *J* = 13.6 Hz, 1H) , 2.59 (d, *J* = 13.6 Hz, 1H), 2.56 (d, *J* = 13.6 Hz, 1H), 2.21 (d, *J* = 13.6 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 0.97 (s, 9H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H), -0.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.1, 140.0, 139.9, 137.8, 136.6, 129.8, 129.4, 128.2, 127.9, 127.0, 126.9, 118.7, 117.3, 116.8, 116.5, 83.8, 83.1, 60.1, 58.2, 48.0, 47.4, 27.0, 26.8, 26.7, 23.6, 23.5, 19.5, -1.7, -1.8, -2.1, -2.5; TLC (10:90 EtOAc: petroleum ether) R_f 0.21. **LRMS** (ESI) exact mass calculated for $C_{21}H_{32}O_3SiNa$: 383.21. Found: 383.20.

Proof of Stereochemistry: Product was obtained as a 1:1 mixture of diastereomers.

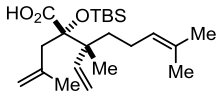


S11

2-(-but-3-en-2-yl)-2-(tert-butyldimethylsilyloxy)-4-methylpent-4-enoic acid (S11). General procedure C was performed using crotyl tert-butyldimethylsilyl glyoxylate (40 mg, 0.165 mmol) and methallylZnBr (0.33 M, 0.75 mL, 0.248 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 30 mg (61%) of **S11** as a clear oil. Analytical data for **S11**: **IR** (thin film, cm^{-1}) 3078, 2957, 2929, 2856, 2360, 1719, 1646, 1472, 1161; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.90-5.81 (m, 1H), 5.14-5.07 (m, 2H), 4.84 (s, 1H), 4.77 (s, 1H), 2.65-2.61 (m, 1H), 2.55 (d, *J* = 14.0 Hz, 1H), 2.46 (d, *J* = 14.0, 1H), 1.71 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.1, 140.4, 138.7, 117.1, 115.7, 83.3,

47.2, 46.8, 26.4, 23.6, 19.3, 16.3, -2.0, -2.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.28. **LRMS** (ESI) exact mass calculated for $C_{16}H_{30}O_3SiNa$: 321.20. Found: 321.18.

Proof of Stereochemistry: Product stereochemistry was assigned by analogy to allylzinc example with crotyl silyl glyoxylate.

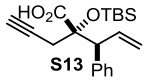


S12

2-(tert-butyldimethylsilyloxy)-3,7-dimethyl-2-(2-methylallyl)-3-vinyloct-6-enoic acid (S12). General procedure C was performed using geranyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.247 mmol) and methallylZnBr (0.33 M, 1.12 mL, 0.370 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 52 mg (55%) of **S12** as a clear oil. Analytical data for **S12**: **IR** (thin film, cm^{-1}) 2960, 2928, 2856, 1712, 1647, 1471, 1414, 1377, 1145; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.94 (dd, *J* = 17.7, 11.1 Jz, 1H), 5.24 (d, *J* = 11.1 Hz, 1H), 5.08-5.03 (m, 2H), 4.85 (s, 1H), 4.77 (s, 1H), 2.74 (d, *J* = 13.5 Hz, 1H), 2.47 (d, *J* = 13.8 Hz, 1H), 1.79-1.72 (m, 2H), 1.67 (s, 6H), 1.56 (s, 3H), 1.36-1.30 (m, 2H), 1.14 (s, 3H), 0.91 (s, 9H), 0.20 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.0, 142.0, 140.4, 131.3, 124.6, 116.9, 115.5, 86.1, 49.0, 43.0, 34.7, 26.9, 25.6, 23.7, 23.1, 19.9, 17.6, 17.1, -1.4, -1.9; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.32. **LRMS** (ESI) exact mass calculated for $C_{22}H_{40}O_3SiNa$: 403.27. Found: 403.25.

Proof of Stereochemistry: Product stereochemistry was assigned by analogy to allylzinc example with geranyl silyl glyoxylate.

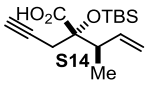
General Procedure D for reaction of silyl glyoxylates with allenyl zinc bromide: A solution of allenyl zinc bromide[26] (1.5 equiv) in THF (0.33 M) was diluted with Et_2O to 0.10 M. The solution was cooled to -78 °C and a solution of silyl glyoxylate (1.0 equiv) in Et_2O (0.10 M) was added. The reaction was allowed to slowly warm to room temperature over 1 h and then stir for 30 min to 2 h at room temperature. The reaction was diluted with 5 mL aqueous HCl (1 M). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated *in vacuo*. The resulting colorless oil was purified as indicated.



2-(tert-butyldimethylsilyloxy)-3-phenyl-2-(prop-2-ynyl)pent-4-enoic acid (S13). General procedure D was performed using cinnamyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.263 mmol) and allenylZnBr (0.33 M, 2.39 mL, 0.525 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 53 mg (58%) of **S13** as a clear oil. Analytical data for **S13**: **IR** (thin film, cm^{-1}) 3310, 3063, 3032, 2954, 2929, 2895, 2856, 1725, 1158; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 6.31-6.22 (m, 1H), 5.26 (d, J = 1.6 Hz), 5.23 (d, *J* = 8.8 Hz, 1H), 3.84 (d, *J* = 9.6 Hz, 1H), 2.79 (d, *J* = 17.2 Hz, 1H), 2.65 (d, *J* = 16.8 Hz, 1H), 2.10 (t, *J* = 2.8 Hz, 1H), 0.96 (s, 9H), 0.19

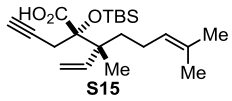
(s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.9, 139.0, 136.5, 135.5, 129.7, 129.2, 128.1, 127.3, 127.2, 118.9, 117.8, 82.4, 79.8, 72.2, 57.6, 29.7, 26.2, 19.0, -2.1, -3.0; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.20. **LRMS** (ESI) exact mass calculated for $C_{20}H_{28}O_3SiNa$: 367.18. Found: 367.16.

Proof of Stereochemistry: Product was formed with low diastereoselectivity.



2-(tert-butyldimethylsilyloxy)-3-methyl-2-(prop-2-ynyl)pent-4-enoic acid (S14). General procedure D was performed using crotyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.330 mmol) and allenylZnBr (0.33 M, 3.0 mL, 0.66 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 31 mg (33%) of **S14** as a clear oil. Analytical data for **S14**: **IR** (thin film, cm^{-1}) 3313, 2955, 2929, 2857, 1725, 1471, 1420, 1254, 1168; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81-5.72 (m, 1H), 5.14 (d, *J* = 14.0 Hz, 2H), 2.71-2.59 (m, 3H), 2.06 (s, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.9, 137.6, 117.6, 82.7, 79.8, 72.1, 46.4, 29.1, 26.1, 18.9, 15.7, -2.2, -2.7; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.18. **LRMS** (ESI) exact mass calculated for $C_{15}H_{26}O_3SiNa$: 305.17. Found: 305.12.

Proof of Stereochemistry: Product stereochemistry was determined by Lindlar reduction to afford 2-allyl-2-(tert-butyldimethylsilyloxy)-3-methylpent-4-enoic acid **S7** characterized above.

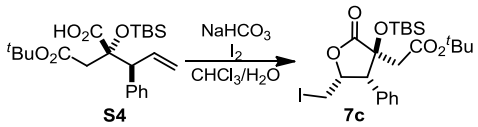


S15

2-(tert-butyldimethylsilyloxy)-3,7-dimethyl-2-(prop-2-ynyl)-3-vinyloct-6-enoic acid (S15). General procedure D was performed using geranyl tert-butyldimethylsilyl glyoxylate (80 mg, 0.247 mmol) and allenylZnBr (0.30 M, 1.64 mL, 0.493 mmol). Purification by flash chromatography (96:3:1 petroleum ether:Et_2O:HOAc) furnished 24 mg (27%) of **S15** as a clear oil. Analytical data for **S15**: **IR** (thin film, cm^{-1}) 3312, 2956, 2928, 2856, 1717, 1471, 1415, 1378, 1150; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (dd, J = 17.6, 10.8 Hz, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 5.06-5.02 (m, 2H), 2.94 (dd, *J* = 16.8, 2.4 Hz, 1H), 2.46 (dd, *J* = 16.8, 2.4 Hz, 1H), 2.00-1.98 (m, 1H), 1.78-1.70 (m, 2H), 1.66 (s, 3H), 1.55 (s, 3H), 1.39-1.31 (m, 1H), 1.10 (s, 3H), 0.94 (s, 9H), 0.28 (s, 3H), 0.23 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.4, 140.8, 131.5, 124.4, 116.0, 86.2, 81.2, 72.1, 48.1, 34.5, 26.3, 25.7, 19.2, 17.6, 17.1, -2.3, -2.4; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.24. **LRMS** (ESI) exact mass calculated for $C_{21}H_{36}O_3SiNa$: 387.24. Found: 387.22.

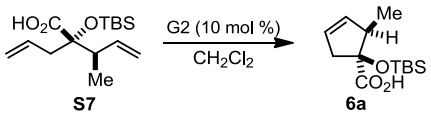
Proof of Stereochemistry: Product stereochemistry was determined by Lindlar reduction to afford 2-allyl-2-(tert-butyldimethylsilyloxy)-3,7-dimethyl-3-vinyloct-6-enoic acid **S9** characterized above.

Experimental Details for Cyclizations



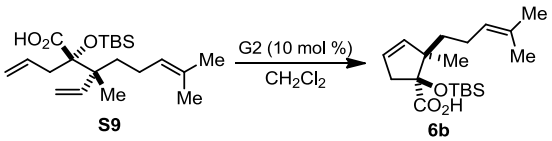
tert-butyl-3-(tert-butyldimethylsilyloxy)-5-(iodomethyl)-2-oxo-4-phenyltetrahydrofuran-3-yl)acetate (7c). To **S4** (12 mg, 0.0285 mmol, 1.0 equiv) in 2.0 mL $CHCl_3$ was added $NaHCO_3$ (20 mg, 0.239 mmol, 8.4 equiv) in 2.0 mL H_2O. The reaction was cooled to 0 °C and iodine (62 mg, 0.245 mmol, 8.6 equiv) was added. The reaction was allowed to warm to room temperature and stirred 24 h. The reaction was diluted with 5 mL CH_2Cl_2 and the layers were separated. The organic phase was washed with 3 mL 10% $Na_2S_2O_3$ (aq), then 3 mL H_2O, then 3 mL brine. The organic phase was dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (90:10 petroleum ether:EtOAc) furnished 12 mg (77%) of **7c**. Analytical data for **7c**: **IR** (thin film, cm^{-1}) 2953, 2930, 2857, 1786, 1737, 1558, 1495, 1257, 1153; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.27 (m, 3H), 7.14-7.12 (m, 2H), 5.25-5.20 (m, 1H), 4.15 (d, *J* = 4.8 Hz, 1H), 3.30 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.83-2.79 (m, 2H), 2.19 (d, *J* = 17.6 Hz, 1H), 1.33 (s, 9H), 0.92 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.4, 167.4, 133.0, 128.6, 128.0, 82.1, 80.9, 80.2, 57.6, 38.1, 28.0, 25.5, 18.3, 0.9, -

3.3, -4.9; TLC (5:95 EtOAc: petroleum ether) R_f 0.30. **LRMS** (ESI) exact mass calculated for $C_{23}H_{35}IO_5SiNa$: 569.13. Found: 569.11.



S7 **6a**

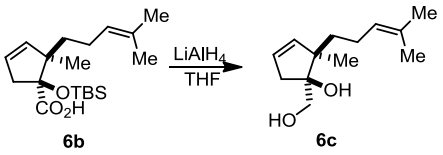
1-(tert-butyldimethylsilyloxy)-2-methylcyclopent-3-enecarboxylic acid (6a). To **S7** (12 mg, 0.0421 mmol, 1.0 equiv) in 1.9 mL CH_2Cl_2 was added Grubbs 2nd generation catalyst (3.6 mg, 0.00421 mmol, 0.10 equiv) in 0.90 mL CH_2Cl_2. The reaction was diluted with 2.8 mL CH_2Cl_2 and stirred at room temperature for 50 h. Approximately 200 mg silica was added and the reaction was stirred for 15 min. The slurry was filtered through a silica plug and concentrated *in vacuo* to afford 5 mg (46%) cyclopentene **6a**. Analytical data for **6a**: **IR** (thin film, cm^{-1}) 2930, 2858, 2349, 1708, 1472, 1256, 1201, 837; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.70-5.69 (m, 1H), 5.56-5.54 (m, 1H), 3.02-2.97 (m, 2H), 2.54 (d, *J* = 18.0 Hz, 1H), 1.05 (d, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 0.31 (s, 3H), 0.30 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.5, 133.9, 126.6, 81.9, 49.1, 46.1, 25.4, 17.7, 15.3, 12.6, -4.9, -5.0; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.27. **LRMS** (ESI) exact mass calculated for $C_{13}H_{24}O_3SiNa$: 279.15. Found: 279.13.



S9 **6b**

1-(tert-butyldimethylsilyloxy)-2-methyl-2-(4-methylpent-3-enyl)cyclopent-3-enecarboxylic acid (6b). To **S9** (24 mg, 0.0654 mmol, 1.0 equiv) in 2.9 mL CH_2Cl_2 was

added Grubbs 2nd generation catalyst (5.6 mg, 0.00654 mmol, 0.10 equiv) in 1.4 mL CH_2Cl_2. The reaction was diluted with 4.3 mL CH_2Cl_2 and stirred at room temperature for 15 h. Approximately 300 mg silica was added and the reaction was stirred for 15 min. The slurry was filtered through a silica plug (CH_2Cl_2) and concentrated *in vacuo.* Purification by flash chromatography (94:5:1 petroleum ether: Et_2O: HOAc) afforded 13 mg (59%) cyclopentene **6b**. Analytical data for **6b**: **IR** (thin film, cm^{-1}) 2926, 2349, 1700, 1684, 1653, 1558, 1541, 1507, 1457; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.65-5.58 (m, 2H), 5.11-5.06 (m, 1H), 3.22 (d, *J* = 17.4 Hz, 1H), 2.54 (dd, *J* = 16.8, 6.3 Hz, 1H), 2.04-1.95 (m, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.54-1.44 (m, 2H), 1.00 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 137.4, 125.2, 124.9, 100.1, 55.5, 42.7, 35.1, 29.7, 25.9, 25.6, 23.7, 22.7, 21.1, 18.5, 17.7, -3.1, -3.6; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.21. **LRMS** (ESI) exact mass calculated for $C_{19}H_{34}O_3SiCs$: 471.13. Found: 471.27.



6b **6c**

1-(hydroxymethyl)-2-methyl-2-(4-methylpent-3-enyl)cyclopent-3-enol (6c). To **6b** (10 mg, 0.0295 mmol, 1.0 equiv) in 0.5 mL THF at 0 °C was added $LiAlH_4$ (44 μL, 0.044 mmol, 1.5 equiv, 1 M in THF). The reaction was allowed to warm to room temperature and stirred 19 h. The reaction was quenched with 1 mL 3 M NaOH (aq). The aqueous layer was extracted with CH_2Cl_2 (3 X 3 mL). The organic extracts were

combined, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (49:50:1 petroleum ether:Et_2O:HOAc) furnished 5 mg (52%) of **6c**. Analytical data for **6c**: **IR** (thin film, cm^{-1}) 2958, 2922, 1771, 1732, 1635, 1558, 1489, 1376, 1078; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.69-5.64 (m, 2H), 5.15-5.11 (m, 1H), 3.79-3.75 (m, 1H), 3.66-3.60 (m, 1H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.35 (d, *J* = 16.8 Hz, 1H), 2.10-1.95 (m, 2H), 1.68 (s, 3H), 1.64 (s, 3H), 1.51-1.46 (m, 2H), 0.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.2, 131.3, 125.7, 125.1, 84.0, 66.3, 52.1, 43.5, 35.0, 25.6, 23.9, 20.0, 17.6; **TLC** (30:70 EtOAc: petroleum ether) R_f 0.15. **LRMS** (ESI) exact mass calculated for $C_{13}H_{22}O_2Na$: 233.26. Found: 233.12.

2.5 References

(1) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889-3901.

(2) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465-3468.

(3) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221-5228.

(4) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905-2928.

(5) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046-2047.

(6) Miller, S. P.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2743-2745.

(7) Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 6170-6171.

(8) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77-84.

(9) Nicewicz, D. A.; Breteche, G.; Johnson, J. S. *Org. Synth.* **2008**, *85*, 278-286.

(10) Carroll, M. F. *J. Chem. Soc.* **1940**, 704-706.

(11) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249-6265.

(12) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686-699.

(13) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265-268.

(14) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636-6642.

(15) Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010**, *12*, 944-947.

(16) Yao, M.; Lu, C.-D. *Org. Lett.* **2011**, *13*, 2782-2785.

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

(18) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127-1130.

(19) Boyce, G. R.; Liu, S.; Johnson, J. S. Unpublished Results.

(20) Greszler, S. N.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3689-3691.

(21) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(22) Haynes, R. K.; Au-Yeung, T.; Chan, W.; Lam, W.; Li, Z.; Yeung, L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem.* **2000**, *2000*, 3205-3216.

(23) Kaur, P.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 8231-8240.

(24) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941-3945.

(25) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366-368.

(26) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530-4535.

CHAPTER 3

SYNTHESIS OF TRACHYSPIC ACID DIMETHYL ESTER

3.1 Introduction

3.1.1 Isolation and Biological Activity

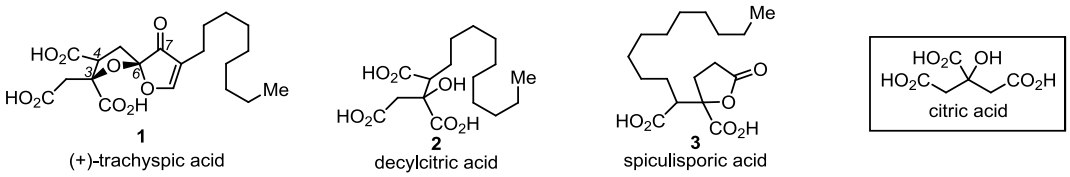
A current area of study in pharmaceutical research is the development of heparanase inhibition agents. Heparanase is an endo-β-D-glucuronidase which cleaves heparan sulfate sidechains and triggers degradation of the extracellular matrix.[1] Breakdown of the extracellular matrix facilitates the spread of metastatic tumor cells and leukocytes by allowing their passage into the bloodstream. Furthermore, the release of short heparan sulfate fragments is believed to induce additional problematic processes. Since inhibition of heparanase would likely prevent extracellular matrix degradation, heparanase inhibitors are of great interest as anti-inflammatory and anti-metastasis therapeutics.

In the course of a screen for heparanase inhibitors, trachyspic acid (**1**) was isolated from the culture broth of *Talaromyces trachyspermus* SANK 12191 (Figure 3-1).[2] The fungal strain SANK 12191 was acquired from a soil sample from Kagoshima Pref., southwest Japan. Trachyspic acid was identified as a potent inhibitor of heparanase with an IC_{50} value 36 μM. The two-dimensional structure was determined in 1995, based on NMR experiments and degradation studies.[2] The relative stereochemistry was

elucidated by Hatakeyama via the racemic total syntheses of trachyspic acid and a diastereomer.[3]

Like other members of the alkyl citrate family of natural products, trachyspic acid is comprised of a substituted citric acid motif. Other structural attributes include an *n*-nonyl sidechain and a furanone ring embedded in a 5,5-spiroketal. The structurally related compounds decylcitric acid **2** and spiculisporic acid **3** are also produced by *Talaromyces trachyspermus* (Figure 3-1). Notably, these molecules both contain a polycarboxylic acid subunit and a hydrophobic alkyl chain, but have not demonstrated heparanase inhibition.[2]

Figure 3-1. Compounds Isolated from *Talaromyces trachyspermus*



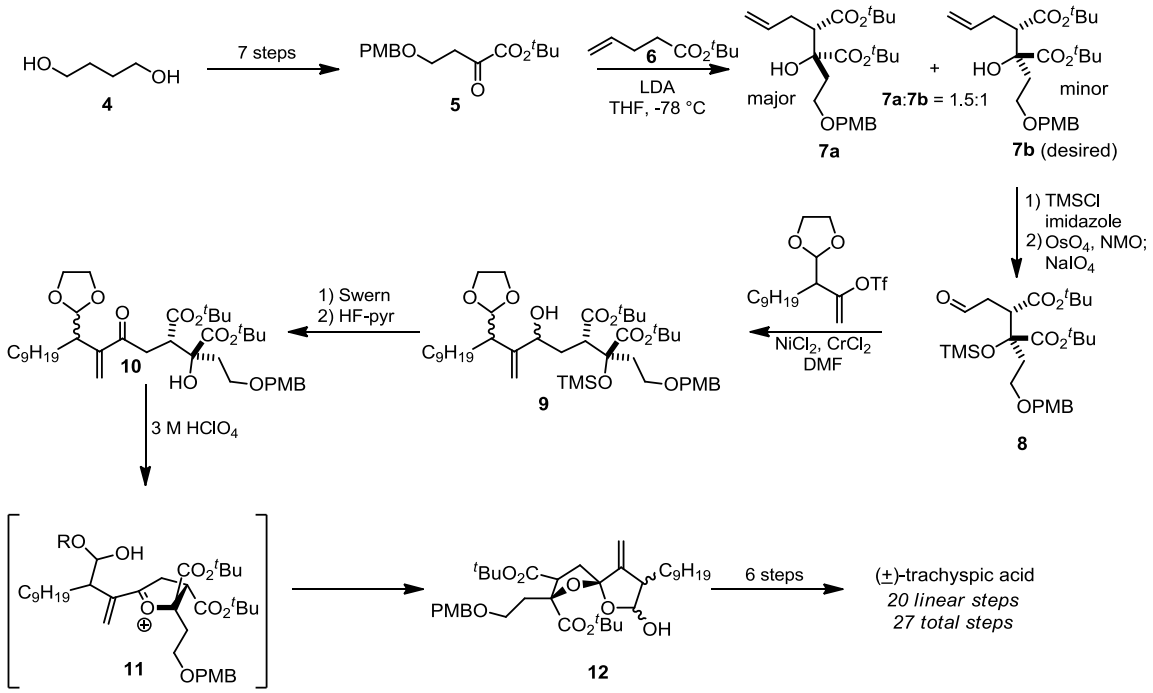
3.1.2 Prior Synthetic Approaches to Trachyspic Acid

Since further biological testing hinges on the development of a scalable synthetic approach to trachyspic acid or analogues thereof, numerous syntheses have been reported to date: trachyspic acid has been the target of four total syntheses and one formal synthesis. Shortly following Hatakeyama's elucidation of the relative stereochemistry, Rizzacasa determined the absolute stereochemistry via total syntheses of the unnatural (–) and the natural (+) enantiomer in 2005 and 2007, respectively.[4] One year later, Hatakeyama also completed an asymmetric synthesis.[5] A formal synthesis of unnatural (–)-trachyspic acid was disclosed in 2009 by Barrett.[6]

Despite its apparent structural simplicity, trachyspic acid has proven itself to be a challenging target with extant syntheses ranging from 18 to 26 linear steps. The primary obstacle to concise synthesis is the contiguous C3 and C4 chiral centers. Installation of these stereocenters has been performed by various methods, including Ireland-Claisen rearrangement, Seebach alkylation, and aldol reaction.[3,4,6]

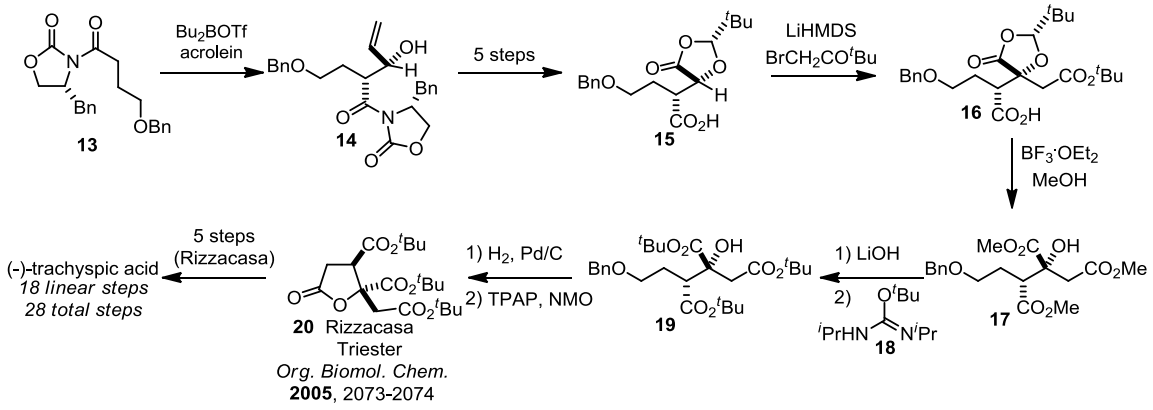
Hatakeyama's first synthesis commenced with the assembly of ketoester **5** from 1,4-butanediol (Scheme 3-1). The C3–C4 bond was then constructed by means of an unselective aldol reaction with ester **6**, completing the C1-C6 carbon skeleton. After subsequent manipulations, the C7-C9 framework was introduced via a Nozaki-Hiyama-Kishi coupling.[7] Oxidation of the resulting C6 alcohol set the stage for spiroketalization with $HClO_4$, which afforded 4:1 diastereoselection at the spirocenter. Trachyspic acid was then completed following a series of deprotections and oxidation state modifications.

Scheme 3-1. Hatakeyama's Racemic Synthesis of Trachyspic Acid



Barrett's formal synthesis of (–)-trachyspic acid constitutes the shortest approach to date.[6] The C3 and C4 stereocenters were set by an Evans aldol reaction with acrolein (Scheme 3-2). The C3 stereocenter was quaternized stereoselectively with *t*-butyl bromoacetate using Seebach's "self-regeneration of stereochemistry".[8] Following cleavage of the Seebach chiral auxiliary and transesterification, C6 was deprotected and oxidized, which induced cyclization to intercept the Rizzacasa lactone **20**. Following Rizzacasa's protocol, completion of the synthesis would require addition of the C7-C9 organolithium (which would require 10 steps in itself to prepare), $HClO_4$ spiroketalization, acetylation of the resulting hemiacetal, ozonolysis of the C7 olefin, and cleavage of the *t*-butyl esters (18 linear steps).

Scheme 3-2. Barrett's Formal Synthesis of Unnatural (-)-Trachyspic Acid

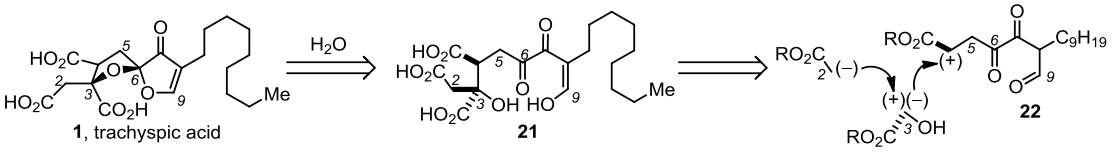


3.1.3 Retrosynthetic Analysis

Silyl glyoxylates were developed in our laboratory as conjunctive reagents for the geminal coupling of nucleophiles and electrophiles to a glycolic acid unit.[9] Multicomponent couplings of silyl glyoxylates have effectively generated high levels of molecular complexity from simple starting materials (see Chapters 1 and 2). Trachyspic acid constitutes a potential application of silyl glyoxylate reactivity due to its C3

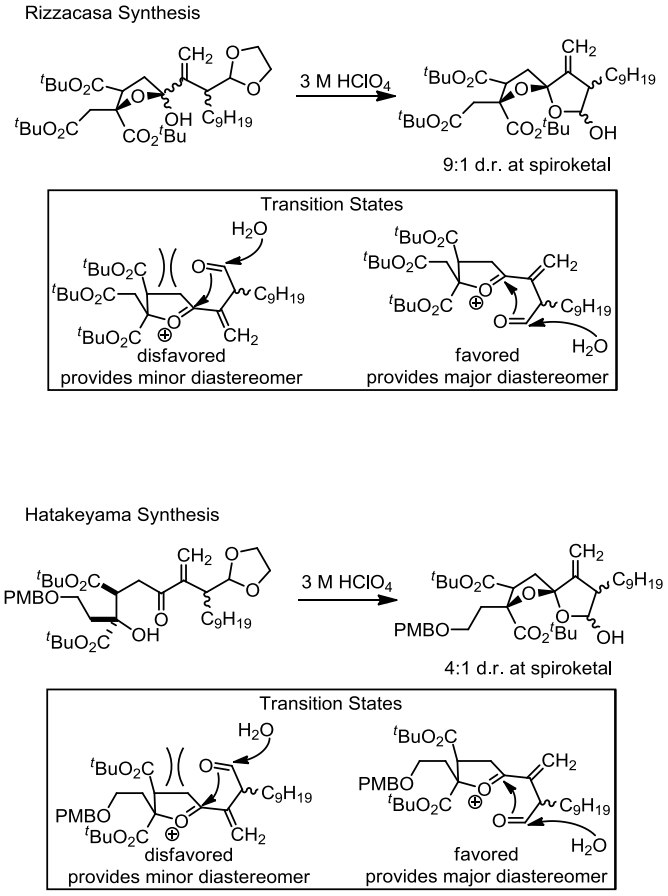
quaternary glycolic acid motif, as a three component coupling approach to trachyspic acid would likely permit its concise synthesis. The open chain form of trachyspic acid reveals a 1,4-relationship between the C3 glycolic acid and the C6 ketone, hinting at a potential Michael addition of the geminally dipolar silyl glyoxylate with a prefunctionalized α,β-unsaturated ketone electrophile (Scheme 3-3). The ideal nucleophilic component for the proposed coupling would be an acetate enolate.

Scheme 3-3. Three Simple Fragments to Access Trachyspic Acid



If this heretofore unknown three component coupling could be developed, then trachyspic acid's spiroketal would likely be accessible from **21** simply by treatment with $HClO_4$, as shown in all prior syntheses.[3,4] The diastereoselectivity of ketalization has been proposed to be dictated by the kinetic preference for cyclization of the C9 oxygen from the less hindered face of the oxocarbenium ion intermediate (Scheme 3-4), resulting in spiroketal stereoselectivity ranging from 4:1 (Hatakeyama) to 9:1 (Rizzacasa) favoring the desired isomer. Thermodynamic spiroketalization is also a possibility in principle, but Rizzacasa notes that no spiroketal epimerization occurs when the spiroketal is treated with acid, indicating that reversibility is not a factor.

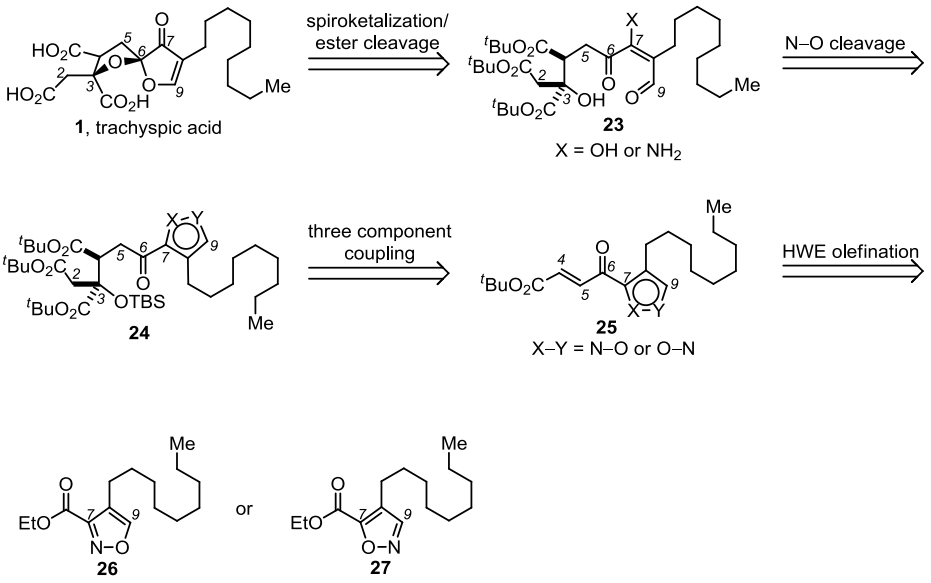
Scheme 3-4. Diastereoselective Spiroketalization



With the expectation that a tandem aldol/Michael three component coupling of an acetate enolate, silyl glyoxylate, and an enone would provide the C1-C6 glycolate Michael skeleton of trachyspic acid, we next considered methods of packaging the remainder of the carbon framework, including the C7-C9 dicarbonyl and the C8 nonyl side chain. The open chain form of trachyspic acid reveals C6, C7, C9 tricarbonyl compound **22** that would pose a significant chemoselectivity challenge in the key three component coupling (Scheme 3-3). We chose to rely on a proven method of masking the 1,3-dicarbonyl subunit in organic synthesis: the incorporation of an isoxazole.[10] The C7-C9 dicarbonyl fragment could be protected as an isoxazole, leaving the C4 enone as the most reactive site on the electrophilic component. Reductive cleavage of the N–O bond

of 3,5-disubstituted isoxazoles has been shown to reveal a β-enamino ketone moiety that may be hydrolyzed to the β-diketone. While N–O reduction of a 3,4-disubstituted isoxazole to reveal a β-enamino aldehyde has not been demonstrated, it was expected to behave analogously. Enone **25** was anticipated to be accessible from simple isoxazoles **26** or **27**. The proposed synthetic approach would allow the efficient construction of trachyspic acid, as the oxidation state of the carbon backbone would be retained throughout the synthesis.

Scheme 3-5. Retrosynthetic Analysis



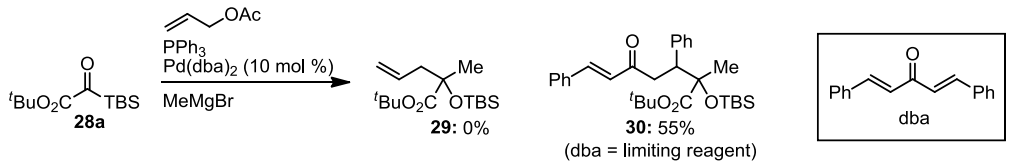
3.2 Development of the Tandem Aldol/Michael Three Component Coupling

3.2.1 The Unexpected Byproduct

In addition to trachyspic acid's unique structure and biological activity, our interest in its synthesis was further solidified by a serendipitous discovery. In an effort to identify new reaction components compatible with silyl glyoxylates, (π-allyl)Pd^{+} was tested as a terminal electrophile. Methyl Grignard reagent was selected as the

nucleophilic trigger for the proposed reaction (Scheme 3-6) due to its relatively unique ability to rapidly add to silyl glyoxylate, thus preventing oligomerization (see section 2.2.2). Catalytic $Pd(dba)_2$ in conjunction with allyl acetate and PPh_3 was selected to generate the electrophilic π-allyl Pd species. Following workup, purification of the crude reaction mixture did not reveal any of the expected γ,δ-unsaturated ester **29**. However, an unexpected three component coupling product, glycolate Michael adduct **30**, was isolated. This product results from coupling of the intermediate glycolate enolate with dibenzylideneacetone (dba) rather than the allyl electrophile. While only a small quantity of **30** was formed, the yield was 55% based on the catalytic amount of dba used. This regioselective 1,4-addition of silyl glyoxylate to an α,β-unsaturated ketone supported the feasibility of our proposed approach to trachyspic acid.

Scheme 3-6. Attempted Three Component Coupling with π-Allyl Palladium

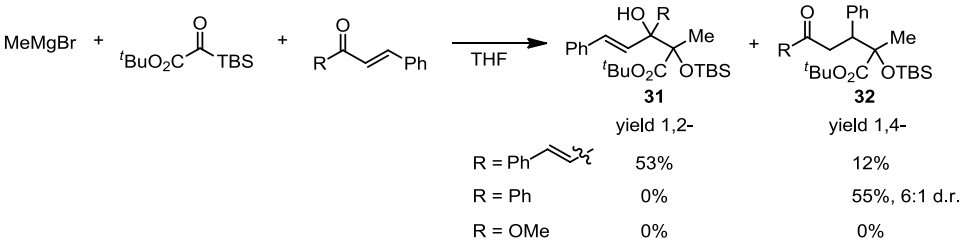


Studies commenced to determine whether the unanticipated Michael reaction required all of the reaction components that were not incorporated into ketone **30**. Mixing methyl Grignard reagent, silyl glyoxylate, and non-Pd-bound dibenzylideneacetone provided three component coupling products; however, the 1,2-addition product **31** was favored (1,2:1,4 = 4.3:1.0). Notably, when the reaction was repeated using $Pd(dba)_2$ as the electrophilic component, approximately equal amounts of 1,2 and 1,4-addition products were formed (1,2:1,4 = 1.0:1.1). While using a Pd-bound

electrophile helped to form the desired 1,4-addition product, the cost associated with stoichiometric levels of Pd precluded this strategy.

Other α,β-unsaturated carbonyl compounds were tested as potential Michael acceptors. Reaction of methyl Grignard reagent, silyl glyoxylate, and methyl cinnamate provided unreacted ester as the sole identifiable compound. On the other hand, chalcone proved to be a good Michael acceptor, affording 55% yield of the 1,4-addition product with 6:1 d.r. and no trace of 1,2-addition (Scheme 3-7). The selectivity for Michael addition to chalcone is particularly striking when compared to dibenzylideneacetone's strong preference for 1,2-addition. This result could be rationalized by chalcone's slightly more hindered carbonyl relative to dibenzylideneacetone. Noting the strong dependence of regioselectivity on substrate structure, our efforts shifted toward the development of a three component coupling more amenable to trachyspic acid's carbon skeleton.

Scheme 3-7. Regioselectivity of Different Michael Acceptors



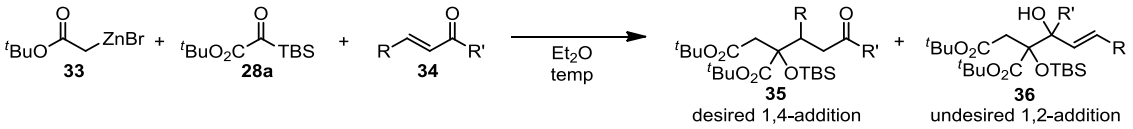
3.2.2 Acetate Enolates as Nucleophilic Triggers

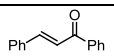
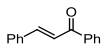
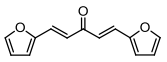
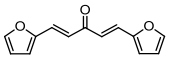
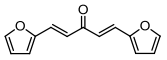
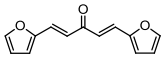
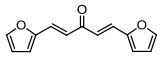
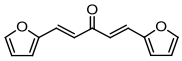
The retrosynthetic plan for trachyspic acid required an acetate enolate to initiate the cascade coupling sequence. Reformatsky reagents had been previously identified as nucleophiles compatible with silyl glyoxylates in Greszler's three component synthesis of

γ-lactones.[11] For this reason, the Reformatsky reagent of *t*-butyl bromoacetate was first selected as the most promising nucleophile.

Addition of a premixed solution of silyl glyoxylate **28a** and chalcone to the Reformatsky reagent afforded 1,2-addition of Reformatsky reagent to chalcone, with no silyl glyoxylate incorporation (entry 1, Table 3-1). Sequential addition of silyl glyoxylate followed by chalcone resulted in three component coupling, but 1,2-addition to chalcone was the major product (entry 2). Difurylideneacetone as the terminal electrophile provided comparable results, with three component 1,2-addition being the major product (entry 3). Running the reaction at -20 °C rather than room temperature provided exclusively 1,2-addition, with incomplete conversion (entry 4). This indicates that the 1,2-addition product could be the kinetic product and the desired 1,4-addition could be the thermodynamic product. However, increasing reaction temperature to 40 °C resulted in a complex mixture. Subsequent reactions were not heated above room temperature.

Table 3-1. Optimization with Reformatsky Nucleophile



entry	enone	addition	additive	temp	ratio 35:36
1		**33**; **34** and **28a**	none	-30 °C to rt	NA[a]
2		**33**; **28a**; **34**	none	-30 °C to rt	1.0 : 2.0
3		**33**; **28a**; **34**	none	-30 °C to rt	1.0 : 4.2
4		**33**; **28a**; **34**	none	-30 °C to -20 °C	1.0 : >20
5		**33**; **28a**; **34**	$ZnCl_2$	-30 °C to rt	1.2 : 1.0
6		**33**; **28a**; **34**	$ZnBr_2$	-30 °C to rt	1.0 : 1.0
7		**33**; **28a**; **34**	ZnI_2	-30 °C to rt	3.3 : 1.0
8		**33**; **28a**; **34**	$Zn(OTf)_2$	-30 °C to rt	1.0 : >20

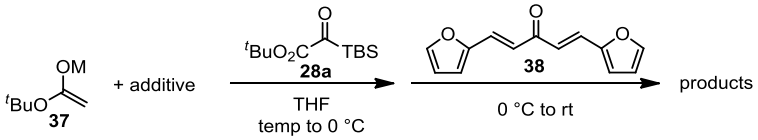
a) Major product was 1,2-addition of acetate enolate to chalcone.

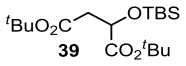
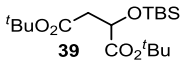
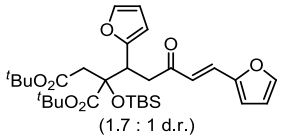
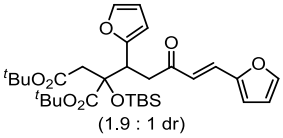
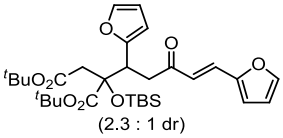
Zinc salt additives were evaluated in an effort to improve conversion via Lewis acid activation of the enone. It was expected that these additives could potentially influence the regioselectivity of the coupling as well. Zinc triflate provided complete regioselection, but was selective for undesired 1,2-addition. Of the zinc salt additives, ZnI_2 demonstrated the best selectivity for Michael addition (3.3:1).

Noting the strong influence of anionic counterions on selectivity, a series of metal cationic counterions were evaluated as well. After a number of metal enolates proved ineffective as nucleophilic triggers, lithium enolates were found to provide exclusively the desired 1,4-addition (Table 3-2). The addition of superstoichiometric lithium chloride

was found to provide optimal conversion and diastereoselectivity, which may be due to altered aggregation of the glycolate enolate or an increased degree of chelation during Michael addition.

Table 3-2. Optimization with Various Metal Enolates



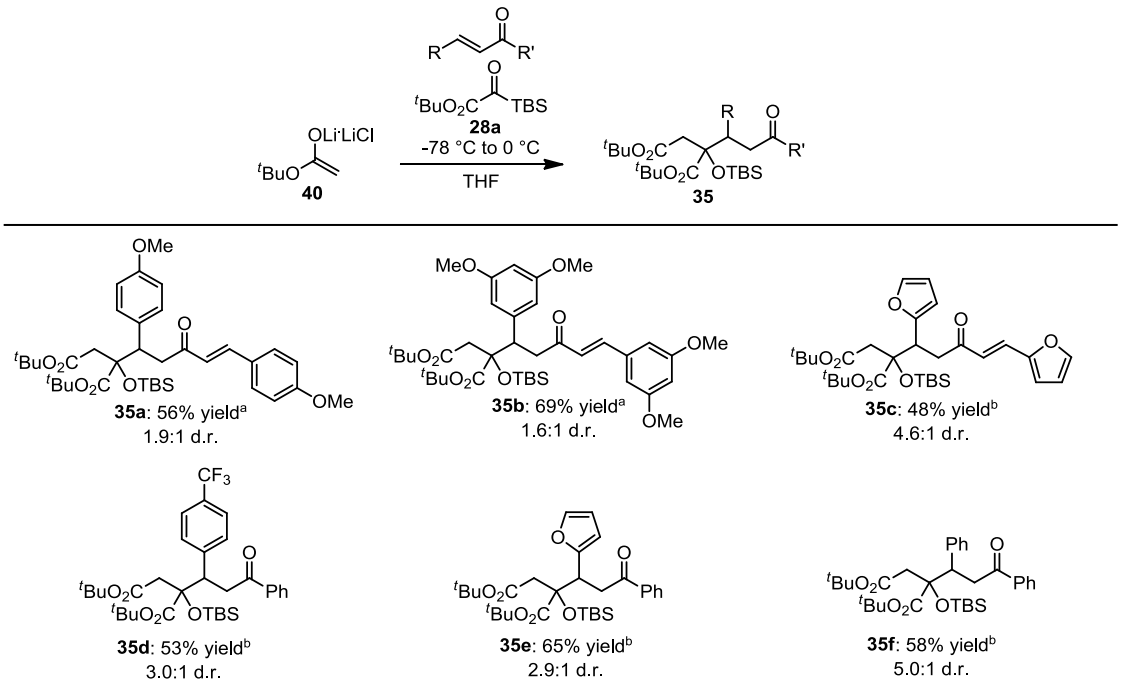
entry	M	additive	major products
1	Li	$MgBr_2$	**38** and decomposed **28a**
2	Li	$TiCl_4$	**38** and decomposed **28a**
3[a]	Li	$MnCl_4Li_2$	**38** and decomposed **28a**
4[b]	Li	$CuCl_2$	**38** and 
5[b]	Li	CuBr	**38** and 
6	Li	none	 (1.7 : 1 d.r.)
7	Na	none	**38** and decomposed **28a**
8	K	none	decomposition
9	Li	LiI	decomposition
10	Li	LiBr	 (1.9 : 1 dr)
11	Li	LiCl	 (2.3 : 1 dr)

Reactions were not purified; yields are unknown. a) $MnCl_4Li_2$ prepared by treatment of $MnCl_2$ with 2 equiv. of LiCl in THF. b) **39** is formed by addition of acetate enolate to **28a**, subsequent Brook rearrangement, and proton quenching.

3.2.3 Scope and Limitations of Three Component Glycolate Michael Reaction

In addition to regioselective multicomponent 1,4-addition to difurylideneacetone, lithium enolates proved to be effective initial nucleophiles in three component couplings with other α,β-unsaturated ketones as well. Both vinyl and aryl enones were effective terminal electrophiles and demonstrated complete 1,4-regioselectivity (Scheme 3-8). The yields were modest due to incomplete conversion; yields based on recovered starting material were >80% in most cases. In some cases, the diastereoselectivity could be increased by adding the Michael acceptor and the silyl glyoxylate simultaneously to a solution of the lithium enolate, rather than sequential reagent addition. Simultaneous reagent addition requires the lithium enolate to chemoselectively react with the silyl glyoxylate in preference to the enone. Certain enones suffered from competitive direct coupling with the acetate enolate using this protocol, including those with imidazoles or isoxazoles adjacent to the ketone.

Scheme 3-8. Enones Compatible with Tandem Aldol/Michael Reaction



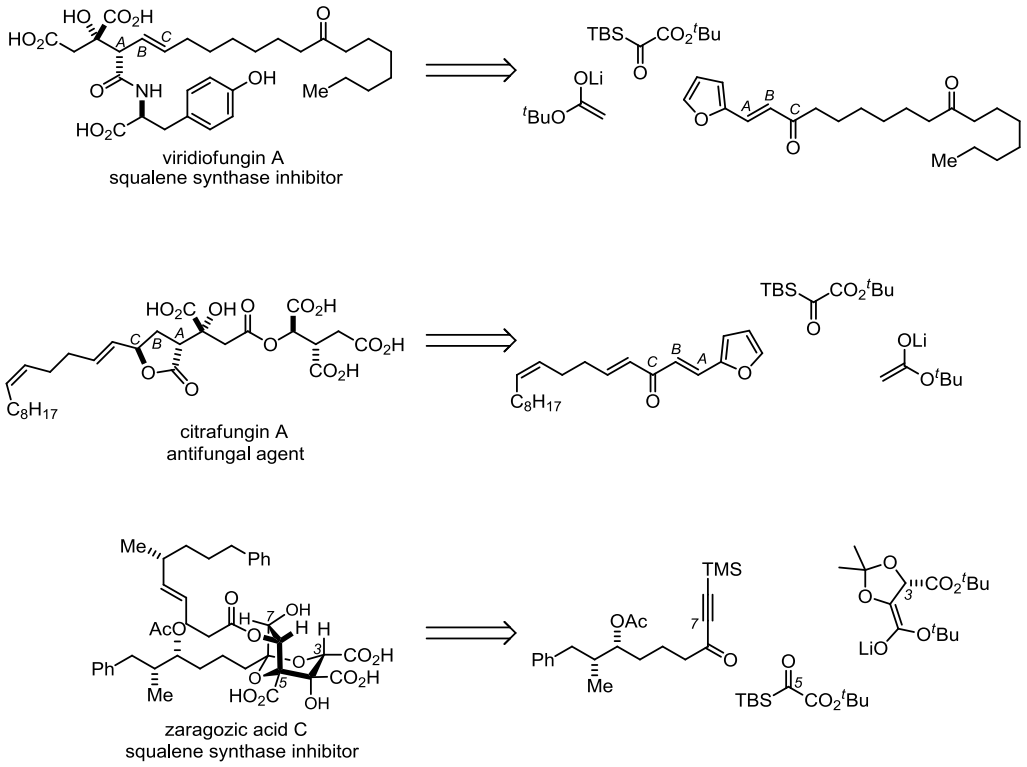
Reagent addition: premixed solution of enone and silyl glyoxylate added to a solution of acetate enolate at -78 °C. a) Yield determined by ^{1}H NMR analysis of crude reaction mixture. b) Isolated yield of analytically pure material.

Ineffective Michael acceptors included those with sterically hindered β-positions and α,β-unsaturated aldehydes, both of which were found to favor three component 1,2-addition. Aliphatic enones did undergo the desired three component coupling but usually suffered from either an additional Dieckmann cyclization or low conversion, which resulted in poor yields. Methyl cinnamate was found to be an unreactive terminal electrophile, as it was in Grignard-initiated couplings (section 3.2.1, Scheme 3-7).

Future studies will involve quenching of the three component coupling reactions with prochiral electrophiles rather than a proton source; these potential four component couplings would further increase the level of molecular complexity accessible in one step. Additional studies could apply the regioselective three component coupling of

enolates, silyl glyoxylates, and α,β-unsaturated ketones to the synthesis of other alkyl citrate natural products, such as the viridiofungins, citrafungins, and zaragozic acids (Scheme 3-9).

Scheme 3-9. Potential Applications of Glycolate Michael Coupling



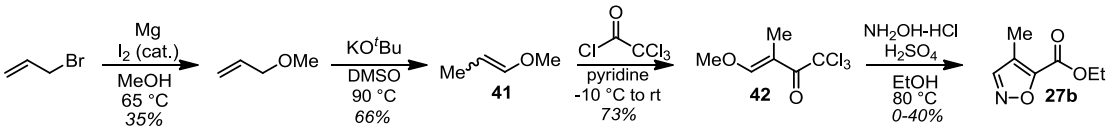
3.3 A Three Component Coupling Approach to Trachyspic Acid Dimethyl Ester

3.3.1 Enone Synthesis

Our retrosynthetic plan called for the preparation of an enone containing the majority of trachyspic acid's carbon framework, including the C8 alkyl side chain (Scheme 3-5). Our initial approach to the C7-C9 isoxazole **27** relied on the hydroxylamine cyclocondensation method developed by Martins.[12] For the purpose of initial test reactions, a methyl group was substituted for the nonyl side chain (Scheme 3-10). Methoxide allylation followed by olefin migration provided enol ether **41**.

Treatment of **41** with trichloromethyl acetyl chloride and pyridine furnished vinylogous ester **42**. Subsequent cyclocondensation occasionally gave desired carboxyisoxazole; however, yields were <20% in most cases. Experimentation with different temperatures and acids did not improve yields. Due to the low reliability of this approach, we sought an alternative synthesis of the C7-C9 isoxazole.

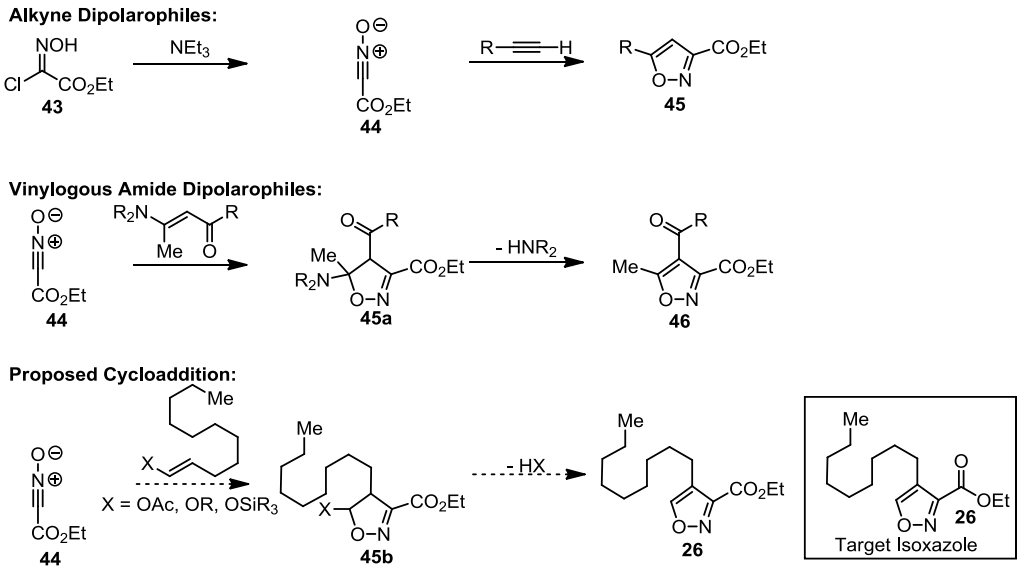
Scheme 3-10. Cyclocondensation Approach to Isoxazole **27b**



Nitrile-oxide cycloaddition with alkynes represents a direct and reliable route to isoxazoles; however, due to steric effects, monosubstituted dipolarophiles always provide the 3,5-disubstituted isoxazoles, the incorrect regioisomer needed for the projected trachyspic acid synthesis (Scheme 3-11).[13] Examples of the preparation of 3,4-disubstituted isoxazoles by nitrile-oxide cycloaddition are scarce. The majority of these approaches rely on a tethered nitrile-oxide[14] or a vinylogous amide directing group (Scheme 3-11).[15]

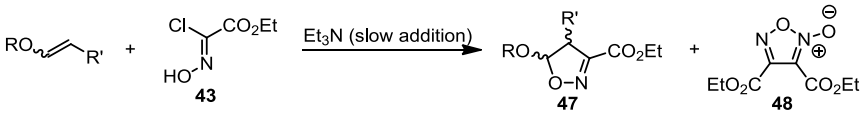
Electronic regiocontrol for the nitrile-oxide cycloaddition appeared to be a prospective strategy for preparation of the C7-C9 isoxazole **26**. While a vinylogous amide dipolarophile would afford 4-acyl isoxazole **46** after aromatization, we postulated that another directing group could potentially provide the necessary 4-alkyl isoxazole **26**. Considerations for the directing group included its ability to serve dually as an electron-donating group for regiocontrol, and as a leaving group for aromatization.

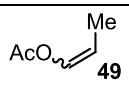
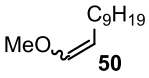
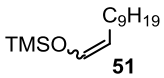
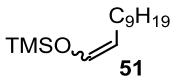
Scheme 3-11. Regiochemistry of Nitrile-Oxide Cycloadditions



For the nitrile-oxide component we selected carboethoxyformonitrile oxide **44** (CEFNO), due to its facile *in situ* preparation from stable ethyl chlorooximidoacetate **43** (Scheme 3-11). While **43** is commercially available, it can also be prepared in one step from ethyl glycine.[16] Initial experiments utilized enol acetate and alkyl enol ether dipolarophiles. In each case, triethylamine was added slowly in an attempt to limit formation of furoxan dimer **48**. Both enol acetate **49** and enol ether **50** provided the furoxan dimer **48** as the major product. We hypothesized that employing a more electron-rich dipolarophile would facilitate cycloaddition with the electron-poor nitrile-oxide; thus, enolsilane **51** was tested. Syringe pump addition of triethylamine over 3 h to a solution of oxime **43** and enolsilane **51** provided 21% yield of a diastereomeric mixture of isoxazoline **47**, wherein the desired cycloaddition had occurred, but aromatization via elimination had not. Addition of triethylamine over 14 h provided increased yield of **47** while limiting yield of dimer **48**. A series of other bases were screened, but were ineffective.

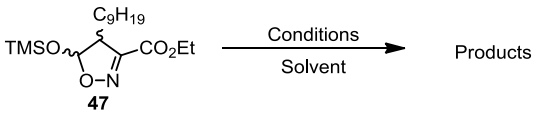
Table 3-3. Enol Ether Dipolarophiles in Nitrile-Oxide Cycloaddition

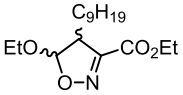
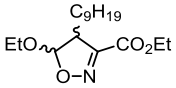
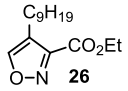


entry	enol	rate of addition of Et_3N	product
1		3 h	**48**
2		4 h	**48**
3		3 h	**47**:**48** = 1:2
4		14 h	**47**

We next sought to develop conditions for the aromatization of isoxazoline **47** to isoxazole **26** (Table 3-4). Heating **47** in toluene failed to induce any change. $BF_3 \cdot OEt_2$ also proved to be unreactive. Heating with HCl or TsOH in ethanol resulted in exchange of the –OTMS substituent for –OEt, without any trace of aromatization. Returning to TsOH but using toluene as a non-nucleophilic solvent, we isolated 83% yield of the desired aromatized **26**. Since isolated yields of isoxazoline **47** were always modest due to its limited stability to silica gel, we attempted a single-pot cycloaddition/aromatization process. Syringe pump addition of triethylamine, followed by addition of TsOH and heating to 70 °C for 24 h resulted in the one-pot synthesis of isoxazole **26** from enolsilane **51**.

Table 3-4. Identification of Isoxazoline Aromatization Conditions

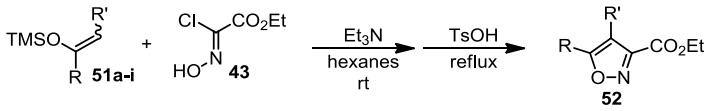


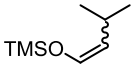
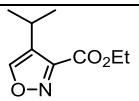
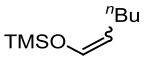
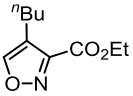
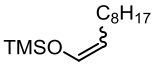
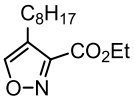
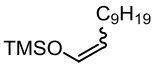
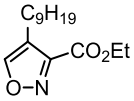
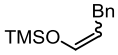
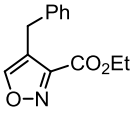
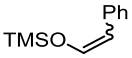
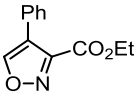
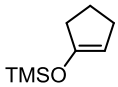
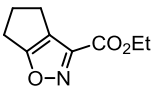
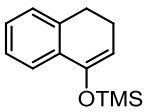
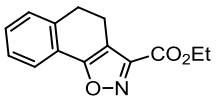
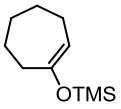
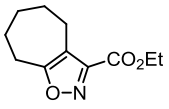
entry	conditions	solvent	products
1	110 °C	PhMe	no reaction
2	$BF_3{\cdot}OEt_2$, NBu_4I	CH_2Cl_2	no reaction
3	TsOH	EtOH	
4	HCl	EtOH	
5	TsOH	PhMe	 **26** 83% yield

Since the preparation of 3,4-disubstituted isoxazoles is an unsolved problem in organic synthesis, we evaluated the scope and limitations of this cycloaddition. Various enolsilanes of aldehydes were effective dipolarophiles, including both aromatic and aliphatic (linear and branched) aldehydes (Table 3-5). The preparation of fused-ring isoxazoles is another challenge to organic chemists that was addressed by this method. Small and medium ring alkynes are unstable due to ring strain, so the preparation of fused-ring isoxazoles has inspired creative methods.[17,18] Five-, six-, and seven-membered ring enolsilanes were found to be competent in the cycloaddition (entries 7-9). The modest yields are believed to be due to ester hydrolysis during the second stage elimination reaction, as well as product volatility. The enolsilanes could be used without

prior distillation in most cases, allowing for the operationally simple preparation of isoxazoles in two steps from carbonyl compounds.

Table 3-5. Scope of Enolsilane Dipolarophiles in Nitrile-Oxide Cycloaddition

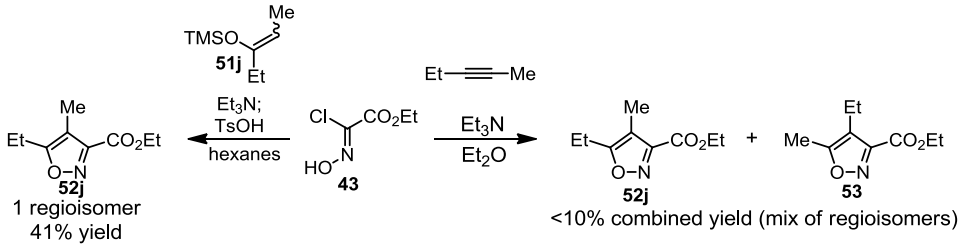


entry	enolsilane 51	product 52	yield[a]
1			34%
2			22%
3			29%
4			44%
5			31%
6[b]			10%
7			40%
8			70%
9			44%

a) Isolated yields (average of at least two experiments). b) Enolsilane purified prior to use (all other enolsilanes used crude).

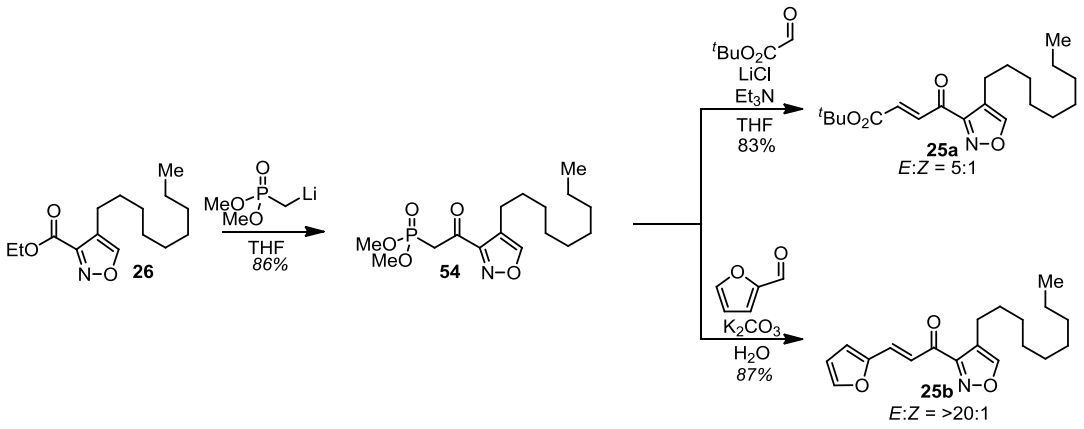
Another advantage of enolsilanes as dipolarophiles over alkynes is their ability to completely control regiochemistry. Disubstituted alkynes with sterically and electronically similar substituents demonstrate poor regiocontrol; direct comparison of the enolsilane **51j** to 2-pentyne revealed complete regiocontrol in the case of the enolsilane, while the alkyne displayed both poor regiocontrol and lower yield (Scheme 3-12).

Scheme 3-12. Direct Comparison of Enolsilane to Alkyne Dipolarophile



Having developed a reliable, scalable method for the preparation of isoxazole **26**, we next pursued the completion of enone **25**. Claisen condensation with lithiated methyl dimethyl phosphonate provided β-ketophosphonate **54** (Scheme 3-13). Subsequent Horner-Wadsworth-Emmons olefination with *t*-butyl glyoxylate furnished enone **25a** as a separable 5:1 *E*:*Z* mixture. Enone **25b** was also prepared with the expectation that the 2-furyl group could ultimately be cleaved oxidatively.[19] Olefination of *t*-butyl glyoxylate proceeded smoothly with triethylamine at room temperature; however, olefination of furfural proved to be more challenging, likely due to its reduced electrophilicity. After screening temperatures, bases, and solvents, K_2CO_3 in refluxing water was found to afford the desired enone **25b** (>20:1 *E*:*Z*).

Scheme 3-13. Preparation of C4-C9 Michael Acceptors



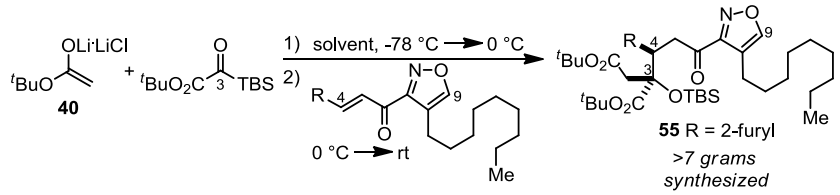
3.3.2 Three Component Coupling with C4-C9 Michael Acceptor

Using the conditions developed for the three component coupling with difurylideneacetone as the terminal electrophile, enones **25a** and **25b** were evaluated. Unfortunately, β-carboxy-enone **25a** was ineffective as a Michael acceptor, producing only decomposition. However, β-furyl-enone **25b** was found to be a viable Michael acceptor, providing the desired three component coupling product with 2.7:1 d.r. Although the desired product was formed, the conversion and yield were poor. Initial experiments employed 1.2 equivalents of both the acetate enolate and silyl glyoxylate relative to the C4-C9 enone as the limiting reagent, which was recovered in substantial quantities due to low conversion. Increasing the equivalents of acetate enolate and silyl glyoxylate to 2.0 was effective at increasing consumption of enone **25b**, providing 100% conversion in most cases.

Solvent was found to have an influence on diastereoselectivity. While THF induced 2.7:1 d.r. favoring the desired isomer, the diastereoselectivity was inverted when toluene (1:1.7), hexanes (1:1.5), or diethyl ether (1:2.0) were utilized. The ability to switch the diastereoselectivity by switching solvents could be an asset for analogue

synthesis. The identity of the ester on the silyl glyoxylate was also found to be important: both ethyl and benzyl esters provided lower diastereoselectivity than the originally used *t*-butyl silyl glyoxylate. Optimized three component coupling conditions gave the chiral ketone **55** in 84% yield and 2.7:1 d.r. (Scheme 3-14). This coupling generates the critical C3 and C4 stereogenic centers and completes the full carbon skeleton of trachyspic acid.

Scheme 3-14. Three Component Coupling with C4-C9 Michael Acceptor

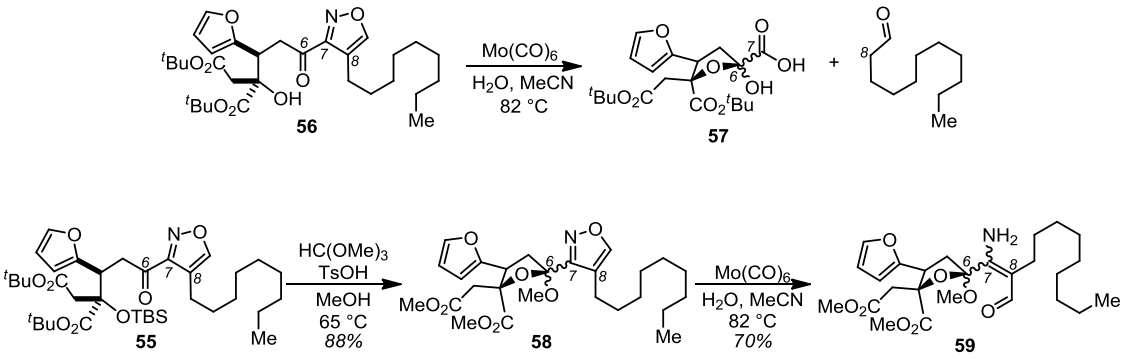


R	solvent	yield (d.r.)
$CO_2{}^t$Bu	THF	0%
2-furyl	THF	84% (2.7:1)
2-furyl	toluene	<50% (1:1.7)
2-furyl	hexanes	<50% (1:1.5)
2-furyl	Et_2O	67% (1:2.0)

3.3.3 Completion of Trachyspic Acid Dimethyl Ester

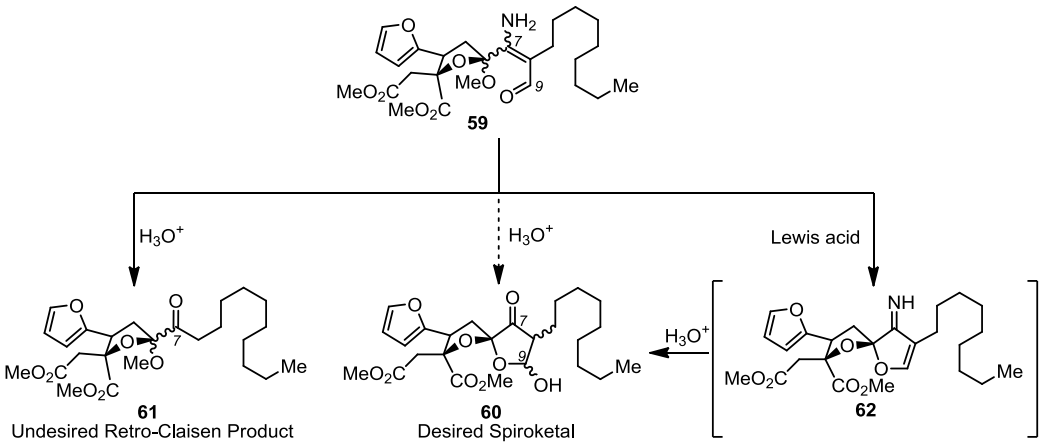
With ketone **55** in hand, remaining synthetic operations included isoxazole N–O cleavage, furan oxidation, and spiroketalization. Treatment of ketone **55** with either oxidative or reductive conditions was ineffective at cleaving the furan or the isoxazole respectively. Isoxazole N–O reduction attempts on alcohol **56** resulted in clean formation of acid **57**, which likely results from retro-Claisen fragmentation of the C7–C8 bond following isoxazole reduction (Scheme 3-15). It was necessary to first form mixed methyl ketal **58**, which underwent successful N–O reduction with $Mo(CO)_6$ to provide enamine **59**.

Scheme 3-15. Synthesis of Spiroketalization Precursor



We expected that Brønsted acid-promoted ketalization of **59** would furnish C6 spiroketal **60**. Following the model of Rizzacasa and Hatakeyama, enamine **59** was treated with 3 M $HClO_4$; however, rather than the expected spiroketal **60**, ketone **61** was generated as the major product. Ketone **61** presumably is formed by enamine hydrolysis and retro-Claisen fragmentation of the C8–C9 bond. Other aqueous Brønsted acids were also found to cause the same undesired fragmentation (Table 3-6, entries 1-3).

Table 3-6. Spiroketalization



entry	conditions	result	entry	conditions	result
1	3 M $HClO_4$, THF, rt	**61**	9	$YbCl_3$, CH_2Cl_2, rt	no reaction
2	$TsOH \cdot H_2O$, 65 °C	**61**	10	BCl_3, CH_2Cl_2, rt	no reaction
3	1 M HCl, rt	**61**	11	$MeAlCl_2$, CH_2Cl_2, rt	no reaction
4	CSA, CH_2Cl_2, rt	taut.[a]	12	$Sc(OTf)_3$, CH_2Cl_2, rt	isom.[b]
5	TfOH, Et_2O, rt	taut.[a]	13	$BF_3 \cdot OEt_2$, MeCN, 82 °C	decomp.
6	$MgCl_2$, CH_2Cl_2, rt	no reaction	14	$SnCl_4$, CH_2Cl_2, rt	decomp.
7	$BaCl_2$, CH_2Cl_2, rt	no reaction	15	$Ti(OiPr)_4$, CH_2Cl_2, rt	x-esterif.[c]
8	$LaCl_3$, CH_2Cl_2, rt	no reaction	16	$TiCl_4$, CH_2Cl_2, rt	**62**

a) "taut." Indicates tautomerization of either the enamine or the aldehyde. b) "isom." Indicates isomerization of enamine olefin geometry. c) "x-esterif." Indicates methyl to isopropyl transesterification.

In an effort to avoid retro-Claisen fragmentation, we tested a series of less nucleophilic ketalization conditions (Table 3-6, entries 4-16). After a number of Lewis acids were found to induce only tautomerization or no reaction, $TiCl_4$ demonstrated the unique ability to promote spiroketalization. The product that directly resulted from treatment with $TiCl_4$ at room temperature followed by aqueous workup is believed to be spirocyclic imine **62**. The proposed imine **62** was incompatible with subsequent furan oxidation attempts and was unstable to flash chromatography, so hydrolysis was

performed to afford ketone **60** as an inseparable mixture of stereoisomers. Ketalization and hydrolysis could be conducted in a single flask, simply by quenching the reaction with 1 M HCl. Since the diastereoselectivity at the C6 spirocenter was difficult to determine at this juncture, we proceeded with the synthetic plan without attempting optimization of the spiroketalization. Cleavage of furan **60** to reveal the C4-CO_2H was successful with both $NaIO_4/RuCl_3$ (cat.) and ozone.[19,20] Ultimately, the catalytic $RuCl_3$ method was found to be superior due to its slightly improved yields as well as increased levels of safety and operational simplicity relative to ozonolysis. With the C1-C4 citric acid motif installed, we aimed to complete trachyspic acid's dimethyl ester via dehydration of hemiacetal **63** (Scheme 3-16). Trifluoroacetic anhydride was found to induce decomposition; however, both acetic anhydride and MsCl were effective at cleanly promoting the desired elimination. Hemiacetal dehydration revealed two separable C6 spirocyclic diastereomers in a varying diastereomeric ratio which ranged from 1.5:1 up to 5:1, with the natural configuration constituting the major diastereomer. Methylation of the C4-CO_2H of the major diastereomer provided a trimethyl ester that was found to be identical to the known trachyspic acid trimethyl ester by ^1H NMR (Figure 3-2) and ^{13}C NMR spectroscopy.

Scheme 3-16. Furan Cleavage and Synthesis of Trachyspic Acid Trimethyl Ester

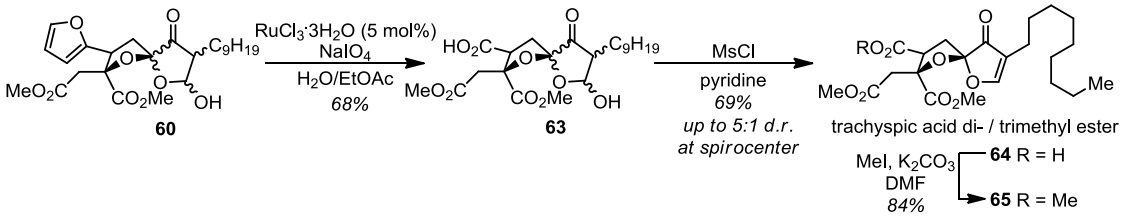
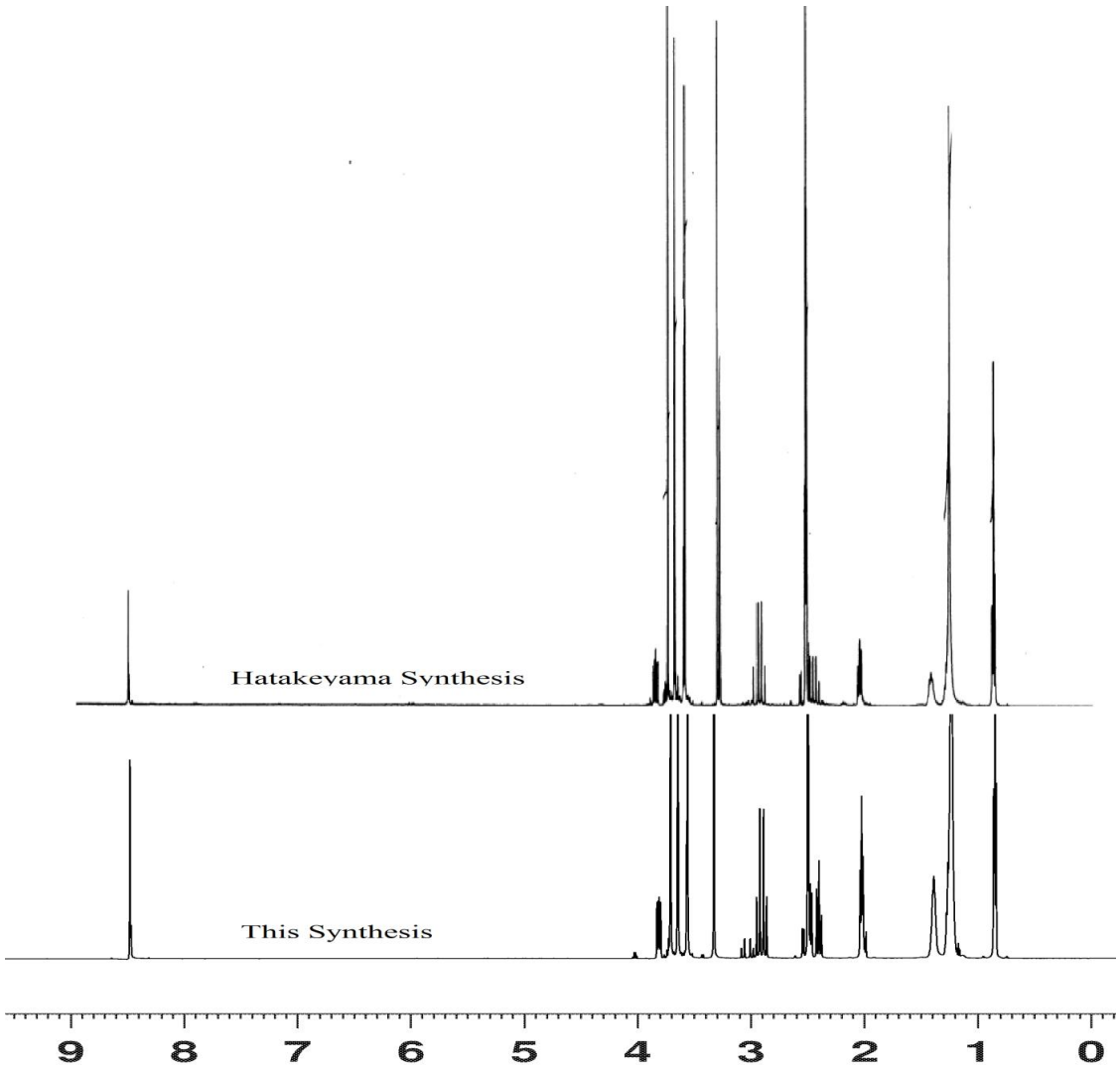


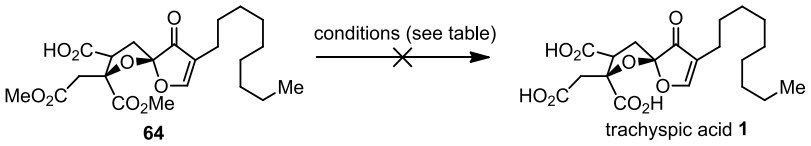
Figure 3-2. ^{1}H NMR Spectral Overlay (DMSO-d_6)



A wide range of conditions were evaluated in an effort to convert the di- or tri-methyl esters to the naturally occurring tri-acid; this transformation proved to be more challenging than originally anticipated (Table 3-7). Saponification attempts with metal hydroxides resulted in formation of unidentifiable product mixtures, possibly resulting from enolization of the least hindered C1-ester, β-elimination resulting in spiroketal opening, and subsequent retro-Claisen fragmentation of the resulting C7-C9 dicarbonyl. Another common approach to methyl ester deprotection is attack of the methyl group by

a discriminating nucleophile, which displaces the carboxylate as the leaving group. These methods typically offer the advantage of being able to react with sterically encumbered methyl esters (like the C3 glycolate ester), presumably since they do not require addition to the congested carbonyl carbon. A series of these reagents proved to be unable to cleanly demethylate diester **64** (entries 8-17).

Table 3-7. Methyl Ester Cleavage Attempts



entry	conditions	result	entry	conditions	result
1	LiOH, THF/H_2O/MeOH	decomp.	10	LiI, EtOAc	decomp.
2	NaOH, H_2O	decomp.	11	BBr_3, CH_2Cl_2	decomp.
3	KOH, H_2O	decomp.	12	$AlBr_3$[a]	decomp.
4	$Ba(OH)_2$, H_2O	no reaction	13	BCl_3, CH_2Cl_2	decomp.
5	LiSEt, THF	no reaction	14	PhSH, Cs_2CO_3, DMF	decomp.
6	LiOOH, THF	epoxidation	15	KOTMS, THF	decomp.
7	Me_3SnOH, DCE	low conv.	16	NaCN, HMPT	decomp.
8	TMSI, CH_3CN	decomp.	17	$LiPPh_2$, THF	low conv.
9	LiI, pyridine	decomp.	18	3.6 M HCl, H_2O	no reaction

Reactions run at 0 °C and monitored by TLC. If no conversion was observed at 0 °C,reactions were warmed as necessary. a) solvent was tetrahydrothiophene.

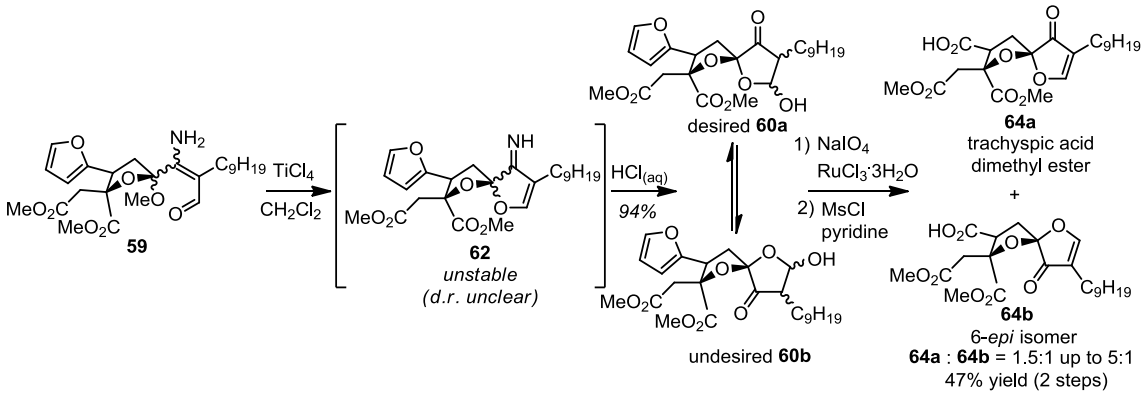
We eventually tried reduction of the tricarboxyl motif to their respective alcohols, which could be re-oxidized to the triacid via Jones Oxidation. Treatment of **64** with five equivalents of DIBAL resulted in a mixture of unidentified products. Using three equivalents of LAH, both ketone and monoester reduction were observed, but one methyl ester remained intact. When increasing the LAH equivalents to 8.0, only decomposition

resulted. Saponification attempts on earlier intermediates in the synthetic sequence were also unsuccessful. While a method for conversion of **64** or **65** to trachyspic acid remains elusive, a synthesis of its dimethyl ester has been achieved in ten steps from commercially available undecanal.

3.3.4 Attempts to Increase the Diastereoselectivity of Spiroketalization

Having completed a concise synthesis of trachyspic acid dimethyl ester **64**, efforts were shifted toward optimization of the spiroketalization step. Multiple repetitions of the synthetic sequence had revealed the sporadic diastereoselectivity of the spiroketalization; in some cases, the C6 spirocenter was formed as a 5:1 mixture of isomers, while in other cases the center was only formed with 1.5:1 d.r. (Scheme 3-17). It was unclear whether the final spiroketal stereochemistry was determined during treatment with $TiCl_4$, or if isomerization was occurring during the subsequent steps; attempts to evaluate the d.r. of the stereoisomeric mixtures by ^1H NMR analysis was challenging due to the presence of eight diastereomers.

Scheme 3-17. Spiroketal Isomerization

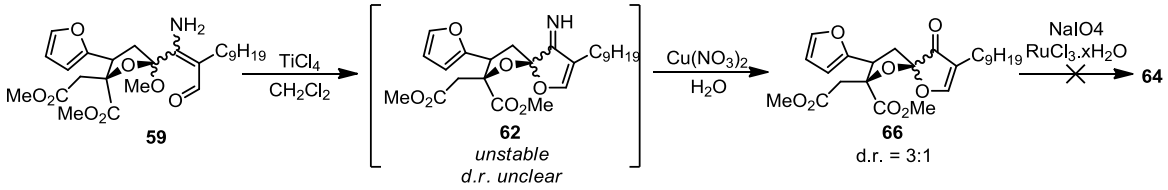


Although Rizzacasa's diastereoselective spiroketalization on a similar substrate was proposed to proceed under kinetic control due to steric constraints,[4] we recognized the possibility that thermodynamic spiroketal equilibration may have been occurring

during the imine hydrolysis step with 1 M HCl. Attempts to increase the degree of equilibration by hydrolysis with stronger acids were ineffective at increasing the diastereomeric ratio. We next tried to alter the d.r. of the spiroketal by "chelation controlled spiroketalization" with zinc chloride, a strategy reported by Dudley for 5,5-spiroketals.[21] Ketalization attempts using solely $ZnCl_2$ resulted in no conversion; Ketalization with $TiCl_4$ and stoichiometric $ZnCl_2$ as an additive did not significantly change the d.r. Assuming the natural spiroketal configuration was the thermodynamic diastereomer, we attempted isomerization following spiroketalization by treatment with Lewis acids, but observed no change.

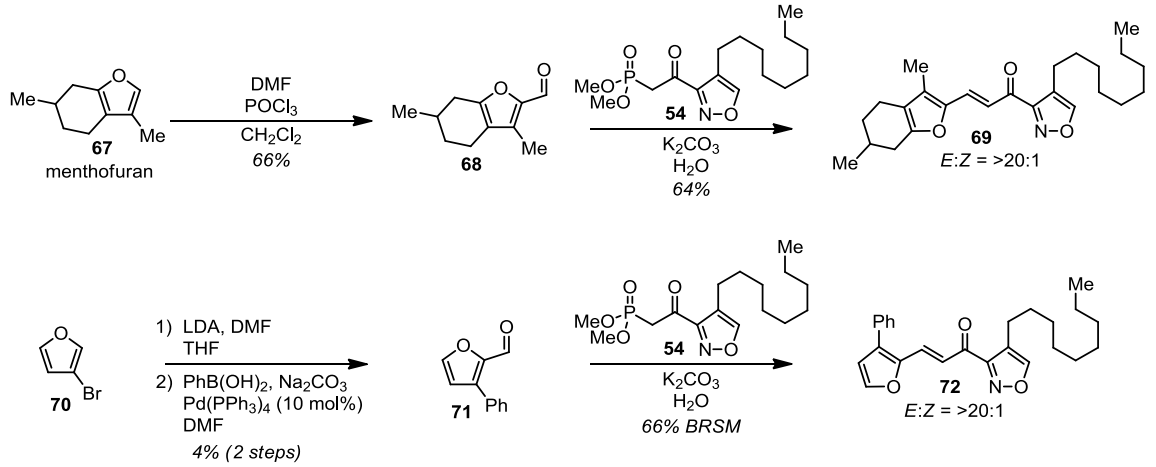
Since it was unclear whether spiroketal isomerization would increase or decrease the d.r., we also attempted to hydrolyze imine **62** under milder conditions which could prevent spiroketal isomerization. Various copper salts were tested as azaphilic lewis acids to promote imine hydrolysis without spiroketal isomerization. 3 M $Cu(NO_3)_{2\ (aq)}$ effectively induced imine hydrolysis without enol ether hydration, allowing a direct readout of ~3:1 d.r. at C6, which may or may not have resulted from spiroketal equilibration during the milder imine hydrolysis. This method was not pursued further since the resulting C8–C9 olefin would likely be incompatible with the subsequent furan oxidation. Having failed to develop a set of conditions for the reproducible, diastereoselective spiroketalization of enamine **59**, we next sought to induce a substrate bias.

Scheme 3-18. Selective Hydrolysis with $Cu(NO_3)_2$



Rizzacasa and Hatakeyama both propose that spiroketalization diastereoselectivity results from the approach of the C9 oxygen from the less hindered face of the intermediate oxocarbenium ion (see section 3.1.3). According to this model, increased steric bulk on the furan would further block the undesired approach and improve spiroketal d.r. (Scheme 3-4). To this end, Michael acceptors **69** and **72** were prepared (Scheme 3-19). Formylation of commercially available menthofuran provided furyl aldehyde **68**. Subsequent Horner-Wadsworth-Emmons olefination with the C5-C9 ketophosphonate **54** provided enone **69**. Enone **72** was prepared in three steps by formylation of 3-bromofuran, Suzuki cross coupling, and olefination.

Scheme 3-19. Preparation of Enones with Hindered Furans

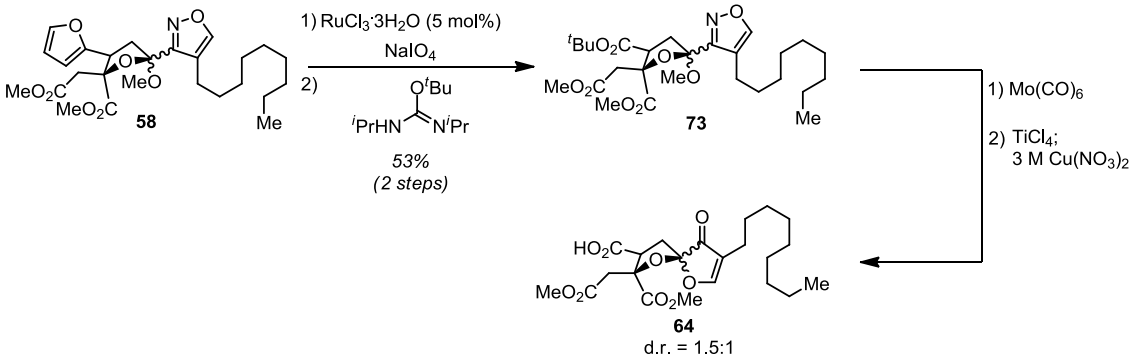


With the bulky β-furyl enones in hand, they were each subjected to three component coupling conditions. Menthofuran-derived enone **69** was found to provide

low conversion (60% conversion after 40 h) and d.r. (1:1). Enone **72** was found to be unreactive in the three component coupling, affording <5% conversion. Three component 1,2-addition products were not identified, but may have been major byproducts. Since these bulky furyl enones provided poor results in the three component coupling, their performance in the spiroketalization was not evaluated.

An alternative strategy to access a spiroketalization precursor with a larger C4 substituent was developed, involving conversion of the furan to a *t*-butyl ester prior to spiroketalization. While furan ozonolysis was found to provide decomposition at every synthetic intermediate besides lactol **63**, $RuCl_3/NaIO_4$ was capable of chemoselective furan oxidation in the presence of the isoxazole (Scheme 3-20). Esterification with isourea **18** afforded triester **73**. Subsequent N–O reduction and one-pot spiroketalization / hydrolysis provided trachyspic acid dimethyl ester **64** with low diastereoselectivity (1.5:1), wherein the *t*-butyl ester had been unexpectedly cleaved, decreasing the intended facial bias in spiroketalization. Having been unsuccessful at improving the spiroketal d.r. by substrate bias, we shifted our focus to the development of an asymmetric route.

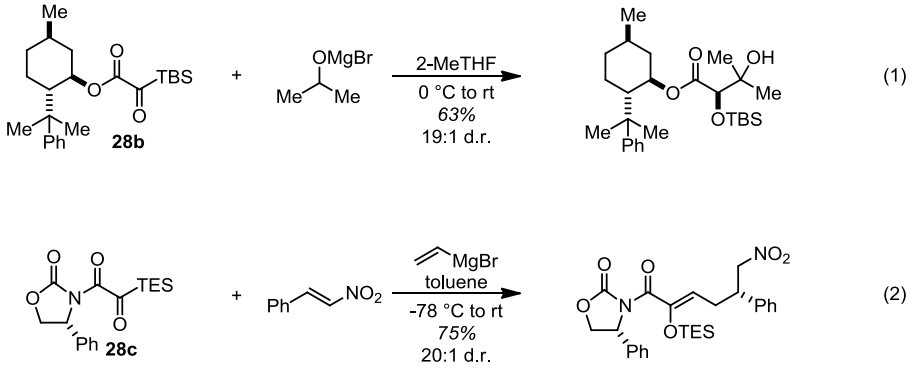
Scheme 3-20. Spiroketalization with C4 *t*-Butyl Ester



3.3.5 Asymmetric Three Component Couplings of Chiral Silyl Glyoxylates

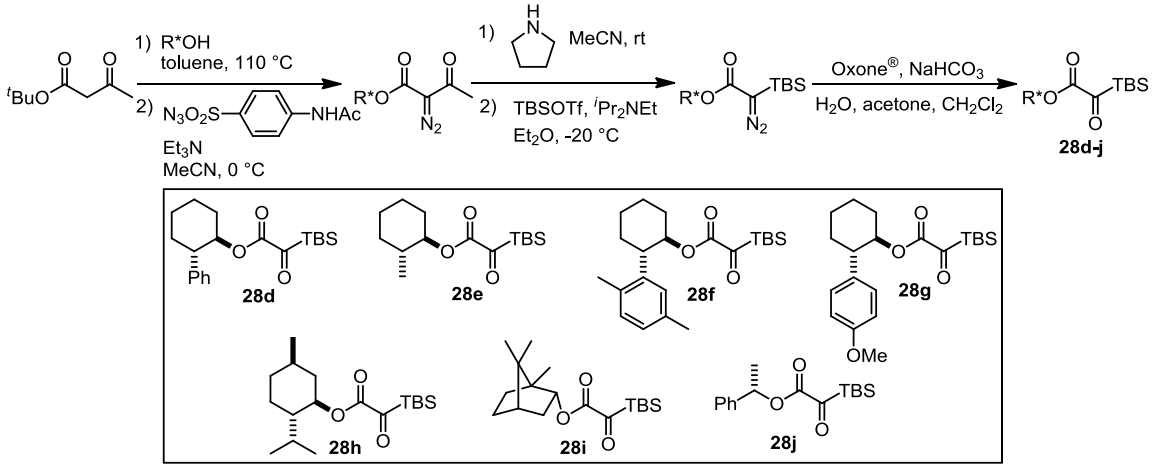
Although silyl glyoxylates have proven to be valuable conjunctive reagents for the rapid production of dense molecular complexity in diverse settings, they have seen limited use in nonracemic reactions. Chiral silyl glyoxylates have been shown to induce asymmetry in two systems to date: Xin Linghu and Andrew Satterfield utilized chiral silyl glyoxylate **28b** in a Meerwein-Ponndorf-Verley/aldol sequence which induced excellent diastereoselectivity (Scheme 3-21, eq. 1).[22] Recently, Gregory Boyce used chiral silyl glyoximide **28c** in a three component coupling with vinylmagnesium bromide and β-nitrostyrene which also provided excellent diastereoselectivity (Scheme 3-21, eq. 2).[23]

Scheme 3-21. Diastereoselective Couplings of Chiral Silyl Glyoxylates



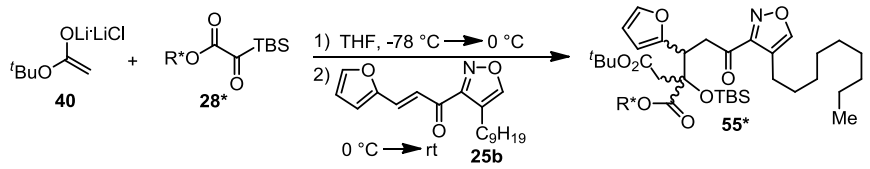
An asymmetric route to trachyspic acid could exploit chiral auxiliary control in the three component coupling. For this reason, a number of chiral silyl glyoxylates were prepared for evaluation in the key step. Silyl glyoxylates **28d-j** were prepared by initial acylation of the chiral alcohols followed by the standard synthetic sequence (Scheme 3-22).[24]

Scheme 3-22. Synthesis of Chiral Silyl Glyoxylates



Following their preparation, the chiral silyl glyoxylates were each tested in the three component coupling with the trachyspic acid C4-C9 Michael acceptor. While **28e**, **28i**, **28j**, and glyoximide **28c** failed to provide any of the desired coupling product, the other silyl glyoxylates all provided the desired chiral ketones **55** as the major product with various levels of diastereoselection (Table 3-8). The best chiral silyl glyoxylate was found to be **28f**, which provided 4.5:1 d.r. (major diastereomer : Σ minor diastereomers).

Table 3-8. Enolate Initiated Couplings of Chiral Silyl Glyoxylates with C4-C9 Enone



entry	silyl glyoxylate	result
1	**28c**	0% conversion
2[a]	**28d**	57% yield, 3.7:1 d.r.[b]
3	**28e**	0% conversion
4[c]	**28f**	87% yield, 4.5:1 d.r.[b]
5[d]	**28g**	3.5:1 d.r.[b]
6[d]	**28h**	1.9:1 d.r.[b]
7	**28i**	0% conversion
8	**28j**	0% conversion

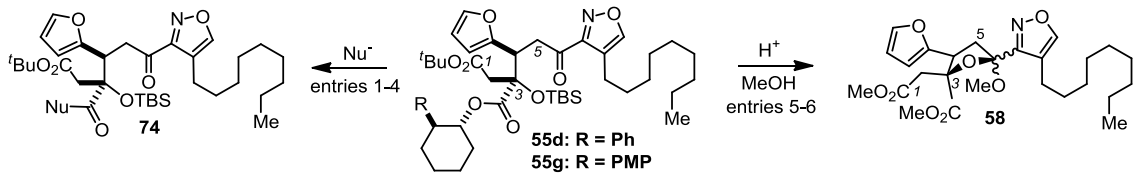
a) Isolated yield of analytically pure material. b) Diastereomeric ratio of major diastereomer to the sum of three minor diastereomers. c) Yield determined by ^{1}H NMR analysis of crude reaction mixture. d) Yield not determined due to inferior diastereoselection.

3.3.6 Chiral Auxiliary Cleavage

In order to apply this asymmetric three component coupling to trachyspic acid, the chiral auxiliary had to be removed. Thiolate, hydroxide, and alkoxide nucleophiles did not provide clean transesterification of the hindered chiral ester (Table 3-9). In most cases no reactivity occurred at room temperature, but heating resulted in formation of complex mixtures. We recalled that acidic conditions removed both t-butyl esters in the racemic synthesis (see Scheme 3-15, section 3.3.3). However, acidic conditions were found to methylate the C1-ester and induce mixed methyl ketal formation, but did not react with the C3 chiral ester. Employing more forcing conditions, we observed the

desired dimethyl ester **58** (entry 6); however, the yield was <10%, as substantial decomposition also occurred.

Table 3-9. Chiral Auxiliary Cleavage Attempts



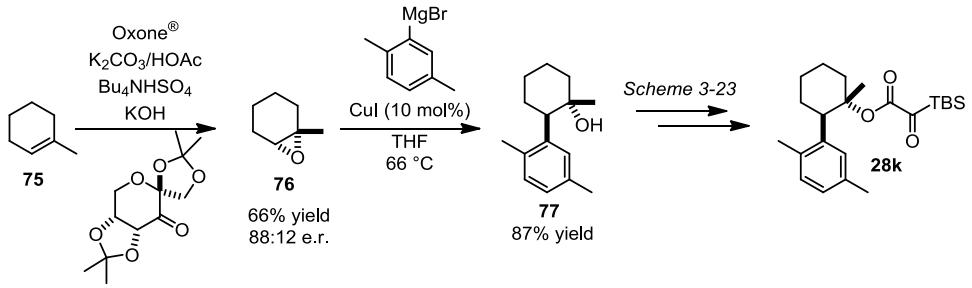
entry	substrate[a]	conditions	temp. (°C)	result
1	**55g**	LiSEt, THF	40	No Reaction
2	**55d**	KOH, H_2O/THF	66	decomposition
3[b]	**55d**	NaOMe, MeOH	65	decomposition
4	**55d**	NaOEt, EtOH	78	decomposition
5	**55d**	$HC(OMe)_3$, TsOH	65	C1-methyl ester
6	**55d**	$HC(OMe)_3$, TsOH	100[c]	**58** (<10% yield)

a) Absolute stereochemistry of C3 and C4 unknown. b) Wolfe successfully cleaved 2-phenylcyclohexanol ester to methyl ester using identical conditions.[25] c) Reaction performed in sealed pressure tube (methanol solvent).

Having previously observed facile cleavage of the C3 *t*-butyl ester with TsOH/MeOH, we hypothesized that the C3 chiral ester was more robust because it was comprised of a secondary alcohol rather than a tertiary alcohol. *t*-Butyl esters are acid-labile due to the relative stability of the resulting tertiary carbocation. Therefore, we speculated that if a chiral tertiary alcohol was employed as the auxiliary, its direct cleavage to mixed methyl ketal **58** would be possible under mild acidic conditions. With this in mind, and in an effort to deviate minimally from optimal secondary auxiliary **28f**, silyl glyoxylate **28k** was prepared from enantioenriched tertiary alcohol **77**. The tertiary

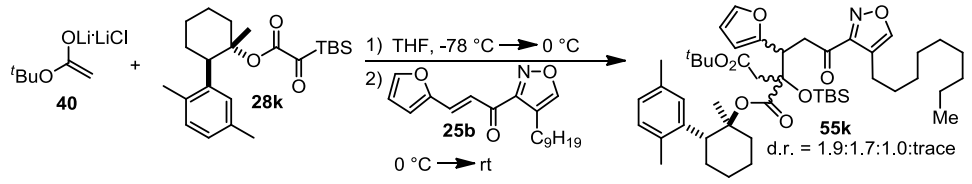
chiral alcohol **77** was prepared by Shi epoxidation and subsequent Cu-catalyzed epoxide opening (Scheme 3-23).

Scheme 3-23. Preparation of Tertiary Chiral Silyl Glyoxylate



After elaboration of chiral tertiary alcohol **77**, silyl glyoxylate **28k** was tested in the three component glycolate Michael coupling. The coupling proceeded cleanly with full conversion of the C4-C9 enone; however the d.r. was unfortunately 1.9:1.7:1.0:trace (compared to 4.5:1 for silyl glyoxylate **28f**). It is likely that the additional methyl group altered the conformation of the glycolate enolate intermediate, preventing the adjacent aryl ring from adequately blocking one face of the enolate.

Scheme 3-24. Poor Diastereoselection with Tertiary Auxiliary



Despite the poor d.r. of the three component coupling, we proceeded with cleavage of the chiral auxiliary by treatment of the diastereomeric mixture with TsOH and $(MeO)_3CH$ in refluxing methanol. As predicted, the tertiary auxiliary underwent facile cleavage to mixed methyl ketal **58** (mixture of *syn* and *anti*, 53% combined yield; compare to <10% yield with auxiliary **55d**). The enantiopurity of the mixed methyl ketal was not tested, but should be ~63:37 e.r. based on the 1.7:1.0 ratio of diastereomers that

are believed to possess the desired relative stereochemistry between C3 and C4. Future work could involve the synthesis of more chiral tertiary silyl glyoxylates for testing in the three component coupling, since we have demonstrated their acid lability.

3.4 Conclusion

In summary, we have developed a three component coupling of enolates, silyl glyoxylates, and enones which demonstrates counterion-dependent regioselectivity. Additionally, we have developed a nitrile-oxide cycloaddition with enolsilane dipolarophiles for the synthesis of isoxazoles that are challenging to access by other means. These new reactions allowed the synthesis of trachyspic acid dimethyl ester in 10 linear steps from undecanal in 4% overall yield (average of >70% yield per step). The three component coupling step may be done asymmetrically by utilizing a chiral silyl glyoxylate. The aim of future work is to evaluate the scope of the tandem aldol/Michael reaction in the context of other alkyl citrate natural products.

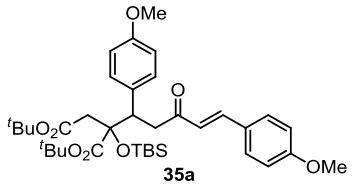
3.5 Experimental

Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on either a Bruker model Avance 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz), Bruker model Avance 500 (^{1}H at 500 MHz and ^{13}C NMR at 125 MHz), Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), or a Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; C_6D_6 at 7.15 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm and C_6D_6 at 128.62 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad

singlet, d = doublet, t = triplet, q = quartet, sept = septet, 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 aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out by flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material. 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. Diethyl ether, methylene chloride, tetrahydrofuran, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use.[21] Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. Triethylamine, diisopropylamine, and pyridine were freshly distilled from CaH_2 under Ar prior to use.

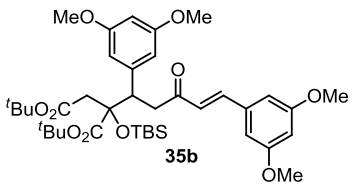
General Procedure A for Aldol/Michael Three Component Couplings: To a solution of LiCl (8.0 equiv, 1.9 M) in THF was added iPr_2NH (2.1 equiv). The solution was cooled to 0 °C and ^{n}BuLi (1.4 M in hexanes, 2.0 equiv) was added. The solution was stirred at 0 °C for 10 min, then stirred at room temperature for 10 min. The solution was cooled to -78 °C and a solution of ^{t}BuOAc (1.9 equiv) in THF (1.1 M) was added. The solution was stirred at -78 °C for 1 h. A solution of α,β-unsaturated ketone (1.0 equiv, 0.2 M) and *t*-butyl *t*-butyldimethylsilyl glyoxylate[23] (2.1 equiv) in THF was added. The solution was allowed to slowly warm to room temperature over 3 h and then stirred at room temperature for 14-24 h. The reaction was diluted with Et_2O (15 mL) and quenched with saturated

NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The organic extracts were combined, washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified as indicated.

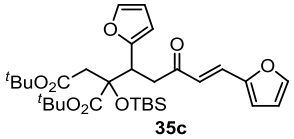


35a

(E)-di-tert-butyl 2-(1,5-bis(4-methoxyphenyl)-3-oxopent-4-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)succinate (35a). General procedure A was performed using dianisylideneacetone (59 mg, 0.200 mmol, 1.0 equiv). Purification by flash chromatography (95:5 to 85:15 petroleum ether:Et_2O gradient) furnished **35a** (52 mg, 0.0794 mmol, 40% yield) as a clear oil. Analytical data for **35a**: **IR** (thin film, cm^{-1}) 2930, 2854, 1740, 1658, 1602, 1513, 1463, 1422, 1393, 1107, 1036; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.37(m, 3H), 7.27-7.25 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 16.4 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.61 (dd, *J* = 2.4, 10.4 Hz, 1H), 3.20 (dd, *J* = 10.8, 16.8 Hz, 1H), 3.06 (dd, *J* = 2.8, 16.8 Hz, 1H), 2.65 (d, *J* = 17.2 Hz, 1H), 2.22 (d, *J* = 16.8 Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H), 0.93 (s, 9H), 0.37 (s, 3H), 0.16 (s, 0.16); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 198.3, 172.3, 169.0, 161.5, 158.5, 142.1, 131.8, 130.9, 130.0, 127.2, 124.3, 114.3, 113.4, 81.6, 80.6, 80.2, 55.4, 55.2, 48.8, 44.3, 42.6, 28.1, 27.8, 26.5, 19.2, -2.1, -2.6; **LRMS** (ESI) exact mass calculated for $C_{37}H_{54}O_8SiNa$: 677.35. Found: 677.37.

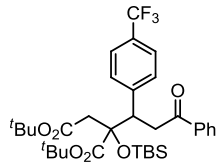


(E)-di-tert-butyl 2-(1,5-bis(3,5-dimethoxyphenyl)-3-oxopent-4-en-1-yl)-2-((tert-butyldimethylsilyl)oxy)succinate (35b). General procedure A was performed using (1E,4E)-1,5-bis(3,5-dimethoxyphenyl)-1,4-pentadien-3-one (60 mg, 0.169 mmol, 1.0 equiv). Purification by flash chromatography (85:15 petroleum ether:Et_2O) furnished **35b** (50 mg, 0.0699 mmol, 41% yield) as a clear oil. Analytical data for **35b**: **IR** (thin film, cm^{-1}) 2929, 2850, 1740, 1651, 1595, 1463, 1428, 1368, 1067; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 1H), 6.61-6.47 (m, 6H) 6.28 (d, *J* = 18.4 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.48 (d, *J* = 7.2 Hz, 1H), 3.26-3.14 (m, 2H), 2.71 (d, *J* = 17.2 Hz, 1H), 2.35 (d, *J* = 17.2 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 0.95 (s, 9H), 0.36 (s, 3H), 0.16 (s, 3H); **LRMS** (ESI) exact mass calculated for $C_{39}H_{58}O_{10}SiNa$: 737.37. Found: 737.39.



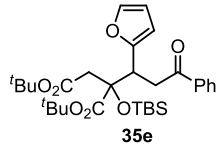
(E)-di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-(1,5-di(furan-2-yl)-3-oxopent-4-en-1-yl)succinate (35c). General procedure A was performed using difurylideneacetone (31 mg, 0.145 mmol, 1.0 equiv). Purification by flash chromatography (97:3 hexanes:Et_2O) furnished **35c** (40 mg, 0.0695 mmol, 48% yield) as a clear oil. Analytical data for **35c**: **IR** (thin film, cm^{-1}) 2855, 1739, 1614, 1555, 1473, 1369, 1150, 1107, 1017; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.30 (d, *J* = 1.2 Hz, 1H), 7.21 (s, 1H), 6.62 (d, *J* = 3.3 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.46 (dd, *J* = 1.8, 3.6 Hz, 1H), 6.25 (dd, *J* = 1.8, 3.0 Hz, 1H), 6.13 (d, *J* = 3.0 Hz, 1H), 3.81 (dd, *J* = 2.7, 11.1 Hz, 1H), 3.23-3.15

(m, 1H), 2.97 (dd, *J* = 2.4, 16.5 Hz, 1H), 2.89 (d, *J* = 16.8 Hz, 1H), 2.42 (d, *J* = 16.8 Hz, 1H), 1.44 (s, 9H), 1.42 (s, 9H), 0.87 (s, 9H), 0.30 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.3, 171.8, 168.9, 152.9, 151.1, 144.8, 141.4, 128.6, 123.2, 115.6, 112.5, 110.2, 108.6, 81.7, 80.3, 79.7, 43.6, 43.4, 40.5, 28.1, 28.0, 27.9, 27.8, 27.7, 26.2, 19.0, -2.5, -2.9; **LRMS** (ESI) exact mass calculated for $C_{31}H_{46}O_8SiNa$: 597.29. Found: 597.30.



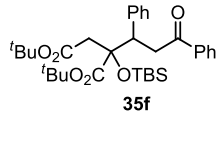
35d

di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-(3-oxo-3-phenyl-1-(4-(trifluoromethyl)phenyl)propyl)succinate (35d). General procedure A was performed using (E)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (40 mg, 0.145 mmol, 1.0 equiv). Purification by flash chromatography (97:3 hexanes:Et_2O) furnished **35d** (49 mg, 0.0769 mmol, 53% yield) as a clear oil. Analytical data for **35d**: **IR** (thin film, cm^{-1}) 2931, 2359, 1741, 1618, 1472, 1394, 1325, 1255, 1222, 1164, 1069, 1019; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.53-7.50 (m, 5H), 7.44-7.40 (m, 2H), 3.88 (dd, *J* = 2.4, 10.2 Hz), 3.58 (t, *J* = 10.2 Hz, 1H), 3.51 (dd, *J* = 3, 18 Hz, 1H), 2.63 (d, *J* = 17.4 Hz, 1H), 2.22 (d, *J* = 17.4 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 9H), 0.93 (s, 9H), 0.39 (s, 3H), 0.18 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 197.5, 171.8, 168.6, 136.8, 133.1, 130.3, 128.6, 127.8, 124.9, 82.1, 80.6, 80.2, 48.6, 44.4, 40.6, 28.1, 27.7, 26.5, 19.2, -2.2, -2.6; **LRMS** (ESI) exact mass calculated for $C_{34}H_{47}F_3O_6SiNa$: 659.30. Found: 659.32.



35e

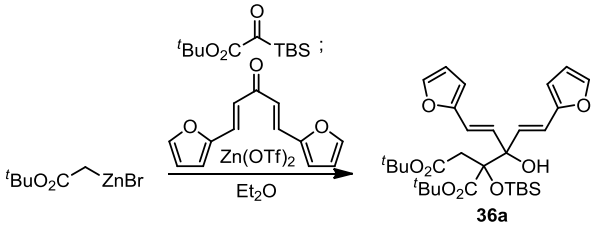
di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-(1-(furan-2-yl)-3-oxo-3-phenylpropyl)succinate (35e). General procedure A was performed using (E)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (29 mg, 0.145 mmol, 1.0 equiv). Purification by flash chromatography (97:3 hexanes:Et_2O) furnished **35e** (53 mg, 0.0948 mmol, 65% yield) as a clear oil. Analytical data for **35e**: **IR** (thin film, cm^{-1}) 2930, 2855, 1741, 1692, 1598, 1472, 1393, 1368, 1251, 1149, 1106, 1012; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = Hz, 2H), 7.53 (t, *J* = 7 Hz, 1H), 7.44-7.40 (m, 2H), 7.28 (s, 1H), 6.24 (d, *J* = 2 Hz, 1H), 6.14 (d, *J* = 3.5 Hz, 1H), 3.95 (dd, *J* = 2, 10.5 Hz, 1H), 3.66 (dd, *J* = 10.5, 17.5 Hz, 1H), 3.31 (dd, *J* = 2, 17 Hz, 1H), 2.92 (d, *J* = 16.5 Hz, 1H), 2.45 (d, *J* = 17 Hz, 1H), 1.43 (s, 9H), 1.39 (s, 9H), 0.87 (s, 9H), 0.33 (s, 3H), 0.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.7, 171.9, 168.9, 153.1, 141.4, 137.0, 132.9, 128.5, 128.0, 110.2, 108.5, 81.7, 80.3, 79.8, 43.6, 43.3, 28.1, 27.7, 26.2, 19.0, -2.4, -2.9; **LRMS** (ESI) exact mass calculated for $C_{31}H_{46}O_7SiNa$: 581.29. Found: 581.31.



35f

di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-(3-oxo-1,3-diphenylpropyl)succinate (35f). General procedure A was performed using *trans*-chalcone (42 mg, 0.200 mmol, 1.0 equiv). Purification by flash chromatography (97:3 petroleum ether:Et_2O) furnished **35f** (67 mg, 0.118 mmol, 59% yield) as a clear oil. Analytical data for **35f**: **IR** (thin film, cm^{-1}) 2929, 2855, 2360, 2124, 1739, 1691, 1607, 1578, 1495, 1017; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 6.6 Hz, 2H), 7.51-7.49 (m 1H), 7.49-7.36 (m, 4H), 7.25-7.19 (m,

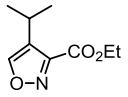
3H), 3.79 (d, *J* = 10.2 Hz, 1H), 3.60 (dd, *J* = 10.2, 18.0 Hz, 1H), 3.47 (d, J = 18.0 Hz, 1H), 2.70 (d, *J* = 16.8 Hz, 1H), 2.24 (d, *J* = 17.4 Hz, 1H), 1.40 (s, 9H), 1.39 (s, 9H), 0.92 (s, 9H), 0.39 (s, 3H), 0.18 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.0, 172.3, 169.0, 140.0, 137.2, 132.8, 130.2, 130.0, 128.5, 128.0, 127.9, 127.5, 126.9, 81.7, 80.5, 80.3, 49.1, 44.4, 40.6, 28.1 (2 peaks), 27.8, 26.5, 26.3, 19.2, -2.1, -2.6; **LRMS** (ESI) exact mass calculated for $C_{15}H_{26}O_3SiNa$: 591.31. Found: 591.33.



di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-((1E,4E)-1,5-di(furan-2-yl)-3-hydroxypenta-1,4-dien-3-yl)succinate (36a). To the Reformatsky reagent of *t*-butyl bromoacetate[11] (0.39 M in Et_2O, 1.5 mL, 0.583 mmol, 2.5 equiv) was added 0.9 mL Et_2O. The solution was cooled to -30 °C and a solution of *t*-butyl *t*-butyldimethylsilyl glyoxylate[24] (142 mg, 0.583 mmol, 2.5 equiv) in Et_2O (1.5 mL) was added. The solution was slowly warmed to 0 °C over 30 min before a solution of $Zn(OTf)_2$ (85 mg, 0.233 mmol, 1.0 equiv) and difurylideneacetone (50 mg, 0.233 mmol, 1.0 equiv) in Et_2O (3.0 mL) was added (Some $Zn(OTf)_2$ would not dissolve and was not transferred into reaction). The solution was slowly warmed to room temperature over 15 h and then saturated NH_4Cl (5 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 X 20 mL). The organic extracts were combined, washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (97:3 to 95:5 petroleum ether:EtOAc gradient) furnished **36a** (56 mg, 0.0974 mmol, 42% yield) as a colorless oil. Analytical data for **36a**: **^{1}H NMR** (400

MHz, $CDCl_3$) δ 7.33 (s, 2H), 6.59-6.52 (m, 3H), 6.38-6.33 (m, 3H), 6.21 (t, *J* = 4.4 Hz, 2H), 3.83 (brs, 1H), 3.17 (d, *J* = 17.6 Hz, 1H), 2.64 (d, *J* = 17.6 Hz, 1H), 1.46 (s, 9H), 1.42 (s, 9H), 0.93 (s, 9H), 0.25 (s, 3H), 0.16 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.7, 169.7, 152.9, 142.0, 128.5, 127.6, 118.1, 117.5, 111.2, 108.0 (2 peaks), 83.1, 82.7, 80.6, 78.8, 41.4, 28.1, 27.9, 26.2, 19.0, -2.5, -2.8.

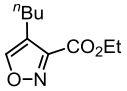
General Procedure B for Dipolar Cycloadditions: To a solution of enolsilane (2.0 to 8.0 equiv) and ethyl chlorooximidoacetate (1.0 equiv, 0.04 M in hexanes) was added a solution of Et_3N (1.5 equiv, 0.1 M in hexanes) via syringe pump over 15 h. The solution was stirred at room temperature for 4-72 h and then $TsOH{\cdot}H_2O$ (4.0 equiv) was added. The flask was fitted with a reflux condenser and the solution was heated to reflux for 4-24 h. The reaction was cooled to room temperature and H_2O was added. The solution was extracted with EtOAc (3X) and the combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting brown oil was purified as indicated.



52a

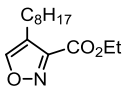
Ethyl 4-isopropylisoxazole-3-carboxylate (52a). General procedure B was performed using the trimethylsilyl enol ether of 3-methylbutyraldehyde (1.69 g, 10.6 mmol, 8.0 equiv), ethyl chlorooximidoacetate (200 mg, 1.32 mmol, 1.0 equiv), Et_3N (0.276 mL, 1.98 mmol, 1.5 equiv), and $TsOH{\cdot}H_2O$ (1.00 g, 5.28 mmol, 4.0 equiv). Purification by flash chromatography (95:5 petroleum ether:Et_2O) furnished **52a** (87 mg, 0.475 mmol, 36% yield) as a clear oil. Analytical data for **52a**: **IR** (thin film, cm^{-1}) 3448, 3114, 2967,

2936, 2874, 1731, 1587, 1468, 1338, 1270, 1163, 1016; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 4.46 (q, *J* = 6.8 Hz, 2H), 3.29-3.22 (m, 1H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.27 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.5, 155.9, 153.3, 128.3, 61.8, 23.0, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.29; **LRMS** (ESI) exact mass calculated for $C_9H_{13}NO_3Na$: 206.08. Found: 206.10.



52b

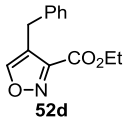
Ethyl 4-butylisoxazole-3-carboxylate (52b). General procedure B was performed using the trimethylsilyl enol ether of hexanal (230 mg, 1.32 mmol, 2.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH{\cdot}H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (97:3 petroleum ether:Et_2O) furnished **52b** (29 mg, 0.147 mmol, 22% yield) as a clear oil. Analytical data for **52b**: **IR** (thin film, cm^{-1}) 2960, 1732, 1457, 1236, 1119; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.58 (m, 2H), 1.45-1.36 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.5, 157.1, 153.8, 121.4, 61.8, 31.6, 22.3, 21.8, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.19; **LRMS** (ESI) exact mass calculated for $C_{10}H_{15}NO_3Na$: 220.10. Found: 220.11.



52c

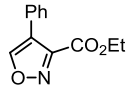
Ethyl 4-octylisoxazole-3-carboxylate (52c). General procedure B was performed using the trimethylsilyl enol ether of decanal (300 mg, 1.32 mmol, 2.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5

equiv), and $TsOH \cdot H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (97:3 petroleum ether:Et_2O) furnished **52c** (49 mg, 0.194 mmol, 29% yield) as a clear oil. Analytical data for **52c**: **IR** (thin film, cm^{-1}) 3115, 2927, 2856, 1732, 1592, 1461, 1390, 1291, 1236, 1173, 1122, 1018; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 4.45 (q, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 6.8 Hz, 3H), 1.34-1.27 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.5, 157.0, 153.9, 121.4, 61.8, 31.8, 29.5, 29.3, 29.2, 22.6, 22.1, 14.1, 14.0; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.33; **LRMS** (ESI) exact mass calculated for $C_{14}H_{23}NO_3Na$: 276.16. Found: 276.17.



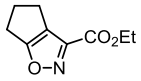
52d

Ethyl 4-benzylisoxazole-3-carboxylate (52d). General procedure B was performed using the trimethylsilyl enol ether of hydrocinnamaldehyde (540 mg, 2.64 mmol, 4.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (97:3 petroleum ether:Et_2O) furnished **52d** (40 mg, 0.172 mmol, 26% yield) as a clear oil. Analytical data for **52d**: **IR** (thin film, cm^{-1}) 2360, 1732, 1456, 1237, 1105, 708; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.36-7.23 (m, 5H), 4.47 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.3, 158.3, 153.6, 138.4, 128.7, 128.6, 126.8, 121.0, 63.6, 62.0, 53.4, 28.5, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.15; **LRMS** (ESI) exact mass calculated for $C_{13}H_{13}NO_3Na$: 254.08. Found: 254.09.



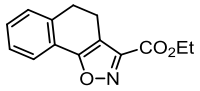
52e

Ethyl 4-phenylisoxazole-3-carboxylate (52e). General procedure B was performed using the trimethylsilyl enol ether of phenylacetaldehyde (250 mg, 1.32 mmol, 2.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (95:5 petroleum ether:Et_2O) furnished **52e** (14 mg, 0.066 mmol, 10% yield) as a clear oil.



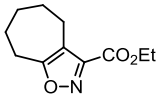
52f

Ethyl 5,6-dihydro-4H-cyclopenta[d]isoxazole-3-carboxylate (52f). General procedure B was performed using the trimethylsilyl enol ether of cyclopentanone (413 mg, 2.64 mmol, 4.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (95:5 petroleum ether:Et_2O) furnished **52f** (77 mg, 0.425 mmol, 64% yield) as a clear oil. Analytical data for **52f**: **IR** (thin film, cm^{-1}) 2981, 1747, 1618, 1434, 1389, 1307, 1239, 1134, 1040; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (q, *J* = 7.2 Hz, 2H), 2.88-2.83 (m, 2H), 2.76-2.69 (m, 4H), 1.41 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 181.7, 160.3, 151.8, 124.5, 61.9, 30.4, 24.6, 21.5, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.17; **LRMS** (ESI) exact mass calculated for $C_9H_{11}NO_3Na$: 204.06. Found: 204.08.



52g

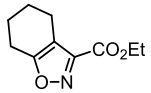
Ethyl 4,5-dihydronaphtho[2,1-d]isoxazole-3-carboxylate (52g). General procedure B was performed using the trimethylsilyl enol ether of tetralone (870 mg, 3.95 mmol, 6.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (95:5 petroleum ether:Et_2O) furnished **52g** (112 mg, 0.461 mmol, 70% yield) as a white solid. Analytical data for **52g**: 1745, 1634, 1596, 1569, 1367, 1350, 1285, 1192, 1018; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.46-7.27 (m, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 3.05-3.00 (m, 4H), 1.44 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.6, 160.3, 153.2, 136.5, 130.1, 128.3, 126.9, 124.3, 121.8, 113.6, 61.7, 28.4, 18.4, 14.0; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.21.



52h

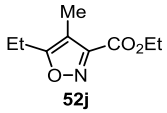
Ethyl 5,6,7,8-tetrahydro-4H-cyclohepta[d]isoxazole-3-carboxylate (52h). General procedure B was performed using the trimethylsilyl enol ether of cycloheptanone (487 mg, 2.64 mmol, 4.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.66 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (0.50 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (97:3 petroleum ether:Et_2O) furnished **52h** (89 mg, 0.421 mmol, 64% yield) as a clear oil. Analytical data for **52h**: **IR** (thin film, cm^{-1}) 1730, 1619, 1452, 1389, 1369, 1348, 1120, 1094, 1074; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.44 (q, *J* = 6.8 Hz, 2H), 2.93 (t, *J* = 6.0 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 1.86-1.83 (m, 2H), 1.77-1.70 (m, 4H), 1.44 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 161.1,

154.3, 117.5, 61.6, 30.4, 27.8, 25.4, 22.1, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.19. **LRMS** (ESI) exact mass calculated for $C_{11}H_{15}NO_3Na$: 232.10. Found: 232.11.



52i

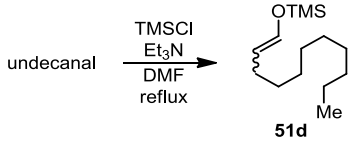
Ethyl 4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxylate (52i). General procedure B was performed using the trimethylsilyl enol ether of cyclohexanone (900 mg, 5.28 mmol, 4.0 equiv), ethyl chlorooximidoacetate (200 mg, 1.32 mmol, 1.0 equiv), Et_3N (0.280 mL, 1.98 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (1.00 g, 5.28 mmol, 4.0 equiv). Purification by flash chromatography (95:5 petroleum ether:Et_2O) furnished **52i** (64 mg, 0.330 mmol, 25% yield) as a clear oil. Analytical data for **52i**: **IR** (thin film, cm^{-1}) 1728, 1630, 1455, 1333, 1272, 1240, 1213, 1177, 1045; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.43 (q, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 6.0 Hz, 2H), 2.67 (t, *J* = 4.4 Hz, 2H), 1.91-1.86 (m, 2H), 1.80-1.76 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.5, 160.8, 153.7, 113.9, 61.6, 22.7, 22.2, 21.9, 20.2, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.17; **LRMS** (ESI) exact mass calculated for $C_{10}H_{13}NO_3Na$: 218.08. Found: 218.09.



52j

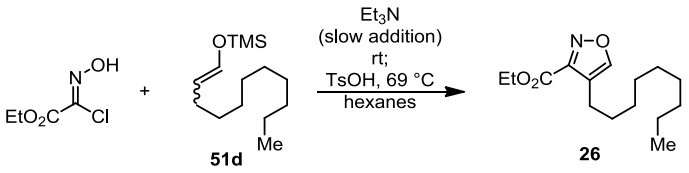
ethyl 5-ethyl-4-methylisoxazole-3-carboxylate (52j). General procedure B was performed using the trimethylsilyl enol ether of 3-pentanone (830 mg, 5.28 mmol, 4.0 equiv), ethyl chlorooximidoacetate (100 mg, 0.660 mmol, 1.0 equiv), Et_3N (0.138 mL, 0.990 mmol, 1.5 equiv), and $TsOH \cdot H_2O$ (0.502 g, 2.64 mmol, 4.0 equiv). Purification by flash chromatography (95:5 petroleum ether:Et_2O) furnished **52j** (49 mg, 0.268 mmol, 41% yield) as a clear oil. Analytical data for **52j**: **IR** (thin film, cm^{-1}) 1731, 1624, 1466,

1454, 1389, 1365, 1328, 1293, 1270, 1201, 1165, 1085, 1019; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (q, *J* = 6.8 Hz, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.14 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 172.1, 160.9, 154.7, 110.3, 61.6, 53.4, 18.8, 14.1, 11.8; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.25; **LRMS** (ESI) exact mass calculated for $C_9H_{13}NO_3Na$: 206.08. Found: 206.09.

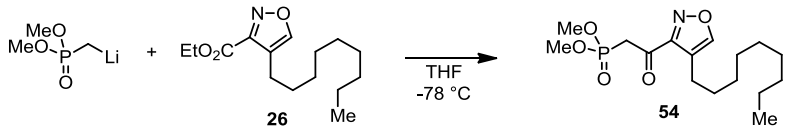


Trimethyl(undec-1-en-1-yloxy)silane (51d). To undecanal (20.0 g, 117 mmol, 1.0 equiv) in 35 mL DMF was added Et_3N (37.6 mL, 270 mmol, 2.3 equiv) followed by TMSCl (17.8 mL, 140 mmol, 1.2 equiv). The flask was fitted with a reflux condenser and stirred at reflux for 46 h and then cooled to room temperature. Water (200 mL) was added, and the solution was extracted with petroleum ether (400 mL). The organic phase was separated and washed with 1 M HCl (3 X 100 mL), followed by saturated aqueous NaHCO3 (3 X 100 mL), followed by brine (1 X 150 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to give trimethyl(undec-1-en-1-yloxy)silane (**51d**) (25.4 g, 105 mmol, 90% yield) as a pale orange liquid. The product was >95% pure by ^{1}H NMR analysis, and was used in the following step without purification. Analytical data for **51d** (~1:1 *Z*:*E*): **IR** (thin film, cm^{-1}) 3029, 2958, 2925, 2854, 2359, 1730, 1659, 1465, 1401, 1253, 1162, 1093; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.21-6.13 (m, 2H), 5.00 (dd, *J* = 6.9, 11.7 Hz, 1H), 4.48 (d, *J* = 6, 13.2 Hz, 1H), 2.08-2.04 (m, 2H), 1.90-1.85 (m, 2H), 1.26 (brs, 28H), 0.88 (t, *J* = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.3, 137.6, 112.2, 111.8, 32.0, 30.5, 29.7, 29.7, 29.6, 29.5, 29.4,

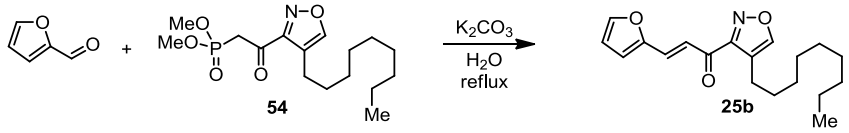
29.3, 29.1, 27.4, 23.6, 22.7, 14.1, -0.5, -0.6; **LRMS** (ESI) exact mass calculated for $C_{14}H_{30}OSiH$: 243.21. Found: 243.23.



Ethyl 4-nonylisoxazole-3-carboxylate (26). To ethyl chlorooximidoacetate (10.2 g, 67.2 mmol, 1.0 equiv) and **51d** (48.9 g, 202 mmol, 3.0 equiv) in hexanes (2.0 L) at room temperature was added slowly a solution of Et_3N (14.1 mL, 101 mmol, 1.5 equiv) and hexanes (10 mL) via syringe pump over 15 h. The solution was stirred at room temperature for an additional 9 h, then TsOH (76.8 g, 404 mmol, 6.0 equiv) was added and the flask was fitted with a reflux condenser and stirred at reflux for 70 h. The reaction was cooled to room temperature and 500 mL of water was added. The solution was extracted with hexanes (3 X 700 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (97:3 petroleum ether:EtOAc) furnished ethyl 4-nonylisoxazole-3-carboxylate (**26**) (8.26 g, 30.9 mmol, 46% yield) as a pale yellow liquid. Analytical data for **26**: **IR** (thin film, cm^{-1}) 3114, 2926, 2856, 1732, 1592, 1460, 1389, 1302, 1236, 1173, 1122, 1018; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 8 Hz, 2H), 1.60-1.54 (m, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.32-1.24 (m, 12H), 0.87 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.4, 157.0, 153.4, 121.3, 61.6, 31.8, 29.5, 29.4, 29.2, 22.5, 22.0, 14.0; **LRMS** (ESI) exact mass calculated for $C_{15}H_{25}NO_3Na$: 290.17. Found: 290.17.

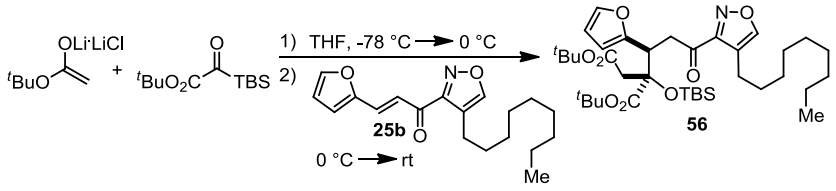


Dimethyl (2-(4-nonylisoxazol-3-yl)-2-oxoethyl)phosphonate (**54**). To dimethyl methylphosphonate (163 μL, 1.50 mmol, 2.0 equiv) in THF (3 mL) at -78 °C was added ^{n}BuLi (1.5 M in hexanes, 1.00 mL, 1.50 mmol, 2.0 equiv) and the solution was stirred at -78 °C for 1 h. A solution of ester **26** (201 mg, 0.752 mmol, 1.0 equiv) in THF (6.7 mL) was added dropwise. The resulting solution was stirred at -78 °C for 1 h, gradually turning dark red. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 X 40 mL). The organic phase was washed with brine (40 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (50:50 petroleum ether:EtOAc) furnished dimethyl (2-(4-nonylisoxazol-3-yl)-2-oxoethyl)phosphonate (**54**) (224 mg, 0.649 mmol, 86% yield) as a clear liquid. Analytical data for **54**: **IR** (thin film, cm^{-1}) 2926, 2855, 1703, 1455, 1263, 1033; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 3.82-3.75 (m, 8H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.56-1.51 (m, 2H), 1.26 (brs, 12H), 0.88 (t, *J* = 6.9 Hz, 3H); **TLC** (50:50 EtOAc: petroleum ether) R_f 0.18; **LRMS** (ESI) exact mass calculated for $C_{16}H_{28}NO_5PNa$: 368.16. Found: 368.17.



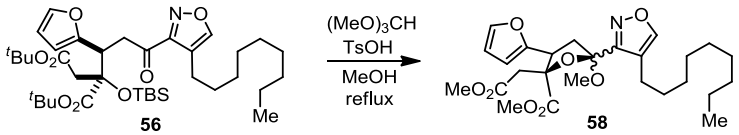
(E)-3-(furan-2-yl)-1-(4-nonylisoxazol-3-yl)prop-2-en-1-one (**25b**). To **54** (2.22 g, 6.43 mmol, 1.0 equiv) and furfural (1.85 g, 19.3 mmol, 3.0 equiv) in H_2O (20 mL) at room temperature was added a solution of K_2CO_3 (1.07 g, 7.71 mmol, 1.2 equiv) in H_2O

(175 mL). The solution was stirred at reflux for 4.5 h and then was cooled to room temperature. The reaction mixture was quenched with 1 M HCl (50 mL) and extracted with Et_2O (3 X 150 mL). The organic phase was washed with brine (75 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (95:5 petroleum ether:EtOAc) furnished (E)-3-(furan-2-yl)-1-(4-nonylisoxazol-3-yl)prop-2-en-1-one (**25b**) (1.76 g, 5.58 mmol, 87% yield) as a yellow solid. Analytical data for **25b**: **MP** 39 °C; **IR** (thin film, cm^{-1}) 2925, 2852, 1672, 1605, 1556, 1431, 1389, 1264, 1202, 1166, 1097, 1014; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.64 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 2H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.52 (dd, J = 2, 3.6 Hz, 1H), 2.71 (t, *J* = 8 Hz, 1H), 1.60-1.56 (m, 2H), 1.35-1.25 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 183.9, 158.9, 156.6, 151.4, 145.5, 131.0, 121.1, 120.7, 116.9, 112.7, 31.8, 29.5, 29.4, 29.3, 29.2, 22.6, 22.2, 14.1; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.35; **LRMS** (ESI) exact mass calculated for $C_{19}H_{25}NO_3Na$: 338.17. Found: 338.17.

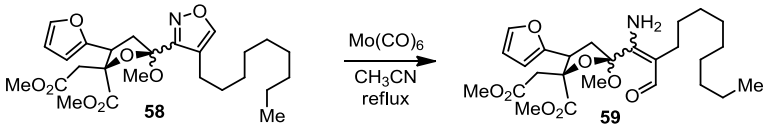


Di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-(1-(furan-2-yl)-3-(4-nonylisoxazol-3-yl)-3-oxopropyl)succinate (**56**). To LiCl (3.97 g, 93.6 mmol, 8.0 equiv) in THF (110 mL) at room temperature was added ^{i}Pr$_2$NH (3.60 mL, 25.7 mmol, 2.2 equiv). The solution was cooled to 0 °C and ^{n}BuLi (1.5 M in hexanes, 16.4 mL, 24.6 mmol, 2.1 equiv) was added. The solution was stirred at 0 °C for 10 min and then the ice bath was removed. The solution was stirred at room temperature for 10 min and

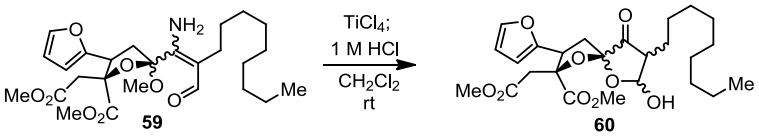
then cooled to -78 °C. A solution of ^{t}BuOAc (3.15 mL, 23.5 mmol, 2.0 equiv) in THF (110 mL) was added and the solution was stirred at -78 °C for 1 h. A solution of *t*-butyl *t*-butyldimethylsilyl glyoxylate[24] (5.74 g, 23.5 mmol, 2.0 equiv) in THF (35 mL) was added and the solution was slowly warmed to 0 °C over 1.5 h. A solution of enone **25b** (3.70 g, 11.7 mmol, 1.0 equiv) in THF (85 mL) was added and the solution was slowly warmed to room temperature over 2 h. The reaction was stirred at room temperature for 21 h and then was quenched with saturated NH_4Cl (100 mL) and extracted with Et_2O (3 X 300 mL). The combined organic extracts were washed with brine (200 mL), dried with $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (97:3 petroleum ether:Et_2O) furnished di-tert-butyl 2-((tert-butyldimethylsilyl)oxy)-2-(1-(furan-2-yl)-3-(4-nonylisoxazol-3-yl)-3-oxopropyl)succinate (**56**) (4.85 g of shown diastereomer, 7.17 mmol; 1.80 g of undesired diastereomer, 2.66 mmol; 84% overall yield) as a clear liquid. Analytical data for **56**: **IR** (thin film, cm^{-1}) 3118, 2928, 2856, 1740, 1705, 1592, 1504, 1471, 1393; 1368; 1252; 1153; 1106; 1012 **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.29 (d, *J* = 1.2 Hz, 1H) 6.24 (t, *J* = 1.2 Hz, 1H), 6.14 (d, *J* = 3.2 Hz, 1H), 3.94 (dd, *J* = 2, 11.2 Hz, 1H), 3.78 (dd, *J* = 11.2 Hz, 17.6, 1H), 3.41 (dd, J = 2.4, 17.6 Hz, 1H), 2.90 (d, *J* = 16.8 Hz, 1H), 2.55-2.48 (m, 3H), 1.42 (s, 9H), 1.38 (s, 9H), 1.25 (brs, 14H), 0.88 (t, J = 6.6 Hz, 3H), 0.85 (s, 9H), 0.29 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 171.6, 168.8, 158.2, 156.6, 152.9, 141.4, 120.4, 110.1, 108.6, 81.6, 80.1, 79.7, 31.8, 29.4, 29.2, 29.2, 29.1, 28.1, 27.6, 26.1, 22.6, 21.9, 18.9, 14.0, -2.6, -3.0; **TLC** (10:90 EtOAc: petroleum ether) R_f 0.45; **LRMS** (ESI) exact mass calculated for $C_{37}H_{61}NO_8SiNa$: 698.41. Found: 698.40.



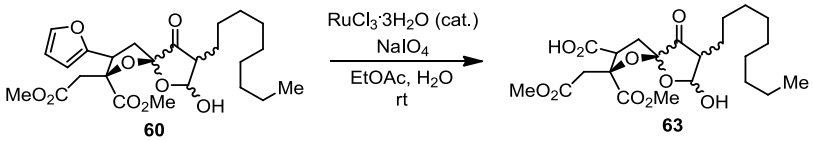
Methyl 3-(furan-2-yl)-5-methoxy-2-(2-methoxy-2-oxoethyl)-5-(4-nonylisoxazol-3-yl)tetrahydrofuran-2-carboxylate (**58**). To **56** (3.48 g, 5.15 mmol, 1.0 equiv) in MeOH (220 mL) at room temperature was added $(MeO)_3CH$ (5.64 mL, 51.5 mmol, 10 equiv) and $TsOH{\cdot}H_2O$ (3.92 g, 20.6 mmol, 4.0 equiv). The solution was stirred at reflux for 42 h and then was cooled to room temperature. The reaction mixture was concentrated under reduced pressure and redissolved in CH_2Cl_2 (200 mL). The solution was washed with saturated $NaHCO_3$ (200 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 X 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (80:20 petroleum ether:EtOAc) furnished a mixture of diastereomers of methyl methyl 3-(furan-2-yl)-5-methoxy-2-(2-methoxy-2-oxoethyl)-5-(4-nonylisoxazol-3-yl)tetrahydrofuran-2-carboxylate (**58**) (2.23 g, 4.54 mmol, 88% yield) as a clear liquid. Analytical data for **58**: **IR** (thin film, cm^{-1}) 2926, 2855, 2359, 1745, 1436, 1359, 1205, 1042; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.33 (t, *J* = 0.6 Hz, 1H), 6.30 (dd, *J* = 1.8, 3 Hz, 1H), 6.17 (d, *J* = 3 Hz, 1H), 4.33 (dd, *J* = 7.5, 11.4 Hz, 1H), 3.84 (s, 3H), 3.56 (s, 3H), 3.28 (s, 3H), 2.85-2.55 (m, 4H), 2.46 (t, *J* = 7.8 Hz, 2H), 1.60-1.54 (m, 2H), 1.25 (brs, 12H), 0.86 (t, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4, 169.7, 160.3, 156.0, 150.5, 142.3, 118.9, 110.5, 108.9, 106.0, 86.6, 52.5, 51.5, 50.9, 43.3, 42.0, 40.0, 31.8, 29.5, 29.4, 29.2, 22.6, 22.3, 14.0; **TLC** (30:70 EtOAc: petroleum ether) R_f 0.50; **LRMS** (ESI) exact mass calculated for $C_{26}H_{37}NO_8Na$: 514.24. Found: 514.18.



Methyl 5-(1-amino-2-formylundec-1-en-1-yl)-3-(furan-2-yl)-5-methoxy-2-(2-methoxy-2-oxoethyl)tetrahydrofuran-2-carboxylate (**59**). To **58** (42 mg, 0.0854 mmol, 1.0 equiv) in MeCN (13 mL) at room temperature was added H_2O (24 μL) and $Mo(CO)_6$ (34 mg, 0.128 mmol, 1.5 equiv). The solution was stirred at reflux for 5 h and then was cooled to room temperature. The reaction mixture was diluted with Et_2O (50 mL). The solution was washed with $NaHCO_3$ (25 mL) and the aqueous phase was extracted with Et_2O (3 X 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (70:30 petroleum ether:EtOAc) furnished a mixture of diastereomers of methyl 5-(1-amino-2-formylundec-1-en-1-yl)-3-(furan-2-yl)-5-methoxy-2-(2-methoxy-2-oxoethyl)tetrahydrofuran-2-carboxylate (**59**) (31 mg, 0.0628 mmol, 74% yield) as a clear oil. Analytical data for **59** (4 diastereomers): **IR** (thin film, cm^{-1}) 3211, 1743, 1600, 1485, 1437, 1360, 1297, 1198, 1076, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.90 (s, 0.28H), 9.26 (s, 0.72H), 7.36 (s, 1H), 6.34 (s, 1H), 6.23-6.19 (m, 1H), 4.27-4.22 (m, 1H), 3.85 (s, 3H), 3.68-3.65 (m, 3H), 3.33 (s, 0.64H), 3.30 (s, 1.67H), 3.23 (s, 0.19H), 3.20 (s, 0.50H), 2.86-2.27 (m, 5H), 1.26 (brs, 14H), 0.86 (t, J = 5.6 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 193.0, 192.6, 171.8, 170.2, 158.1, 157.4, 149.6, 149.2, 142.6, 110.6, 109.3, 109.1, 106.6, 104.0, 85.7, 52.8, 52.1, 51.9, 50.6, 44.2, 42.6, 39.9, 39.2, 33.1, 31.9, 29.8, 29.6, 29.4, 29.3, 27.3, 22.7, 22.6, 14.1; **TLC** (50:50 EtOAc: petroleum ether) R_f 0.53; **LRMS** (ESI) exact mass calculated for $C_{26}H_{39}NO_8Na$: 516.26. Found: 516.24.

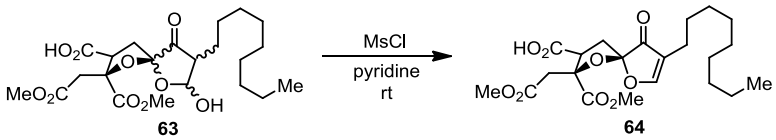


Methyl 3-(furan-2-yl)-7-hydroxy-2-(2-methoxy-2-oxoethyl)-8-nonyl-9-oxo-1,6-dioxaspiro[4.4]nonane-2-carboxylate (**60**). To **59** (1.17 g, 2.37 mmol, 1.0 equiv) in CH_2Cl_2 (275 mL) at room temperature was added a solution of $TiCl_4$ (0.47 mL, 4.27 mmol, 1.8 equiv) in CH_2Cl_2 (20 mL). The solution was stirred at room temperature for 1.5 h and then 1 M HCl (275 mL) was added. The solution was stirred vigorously for 20 h and was extracted with CH_2Cl_2 (2 X 200 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (60:40 petroleum ether:EtOAc) furnished a mixture of diastereomers of methyl 3-(furan-2-yl)-7-hydroxy-2-(2-methoxy-2-oxoethyl)-8-nonyl-9-oxo-1,6-dioxaspiro[4.4]nonane-2-carboxylate (**60**) (1.07 g, 2.23 mmol, 94% yield) as a clear oil. Analytical data for **60** (8 diastereomers): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.37 (m, 1H), 6.35-6.26 (m, 2H), 5.78-5.36 (m, 1H), 4.12-4.07 (m, 1H), 3.86-3.79 (m, 3H), 3.64-3.56 (m, 3H), 2.90-2.15 (m, 5H), 1.62-1.39 (m, 2H), 1.26 (brs, 12 H), 0.88 (t, J = 6.8 Hz, 3H); **LRMS** (ESI) exact mass calculated for $C_{25}H_{36}O_9Na$: 503.23. Found: 503.22.



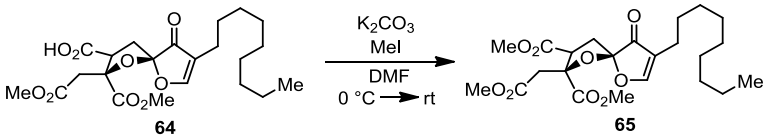
Trachyspic acid dimethyl ester 9-hydrate (**63**). To $NaIO_4$ (1.16 g, 5.43 mmol, 7.0 equiv) in H_2O (18 mL) was added a solution of $RuCl_3{\cdot}3H_2O$ (10 mg, 0.0383 mmol, 0.05 equiv) in H_2O (3.5 mL). The solution was stirred at room temperature for 10 min, and

then a solution of **60** (373 mg, 0.776 mmol, 1.0 equiv) in EtOAc (18 mL) was added. The solution was stirred at room temperature for 5.5 h. Brine (15 mL) was added, and the solution was extracted with EtOAc (3 X 120 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (60:38:2 petroleum ether:EtOAc:HOAc) furnished a mixture of diastereomers of trachyspic acid dimethyl ester 9-hydrate (**63**) (242 mg, 0.528 mmol, 68% yield) as a clear oil. Analytical data for **63** (8 diastereomers): **IR** (thin film, cm^{-1}) 3460, 2954, 2926, 2855, 1744, 1611, 1439, 1366, 1211, 1178, 1136, 1073; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76-5.39 (m, 1H), 3.88-3.78 (m, 3H), 3.71-3.64 (m, 3H), 3.32-2.09 (m, 5H), 1.49-1.39 (m, 2H), 1.25 (brs, 12 H), 0.88 (t, *J* = 6 Hz, 3H); **TLC** (50:50 EtOAc: petroleum ether) R_f 0.16; **LRMS** (ESI) exact mass calculated for $C_{13}H_{22}O_2Na$: 481.22. Found: 481.21.



Trachyspic acid dimethyl ester (**64**). To **63** (467 mg, 1.02 mmol, 1.0 equiv) in pyridine (20 mL) at room temperature was added a solution of MsCl (0.120 mL, 1.53 mmol, 1.5 equiv) in pyridine (5 mL). The solution was stirred for 17 h and then was diluted with Et_2O (100 mL). The solution was washed with 1 M HCl (3 X 50 mL), followed by saturated $CuSO_4$ (50 mL). The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (70:28:2 petroleum ether:EtOAc:HOAc) furnished trachyspic acid dimethyl ester (**64**) (286 mg, 0.649 mmol, 64% yield overall; 5:1 mixture of separable spiroketal diastereomers) as a clear oil. Analytical data for **64**: **IR** (thin film, cm^{-1}) 2926, 2855, 2358, 1746, 1557, 1506, 1437,

1371, 1212; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 3.93-3.82 (m, 1H), 3.89 (s, 3H) 3.68 (s, 3H), 3.17 (d, *J* = 16.4 Hz, 1H), 3.11 (d, *J* = 16.4 Hz, 1H), 2.71 (dd, *J* = 13.4, 17.4 Hz, 1H), 2.39 (dd, *J* = 7.2, 13.6 Hz, 1H), 2.10 (t, *J* = 6.8 Hz, 2H), 1.49-1.39 (m, 2H), 1.25 (brs, 12 H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.9, 172.7, 172.6, 171.3, 169.7, 118.3, 107.8, 86.9, 53.6, 52.2, 48.5, 38.9, 37.4, 31.8, 29.5, 29.3, 27.8, 22.6, 21.1, 14.1; **TLC** (30:70 EtOAc: petroleum ether) R_f 0.12; **LRMS** (ESI) exact mass calculated for $C_{22}H_{32}O_9Na$: 463.20. Found: 463.24.



Trachyspic acid trimethyl ester (**65**). To **64** (52 mg, 0.118 mmol, 1.0 equiv) in DMF (3.0 mL) at 0 °C was added K_2CO_3 (24 mg, 0.177 mmol, 1.5 equiv) followed by a solution of MeI (11 μL, 0.177 mmol, 1.5 equiv) in DMF (0.17 mL). The solution was warmed to room temperature and stirred for 5 h. 1 M HCl (3 mL) was added and the solution was extracted with EtOAc (3 X 10 mL). The combined organic phases were washed with 1 M HCl (4 X 10 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (60:40 petroleum ether:EtOAc) furnished trachyspic acid trimethyl ester (**65**) (45 mg, 0.099 mmol, 84% yield) as a clear oil. Analytical data for **65**: **IR** (thin film, cm^{-1}) 2927, 2855, 2359, 1746, 1613, 1438, 1369, 1210, 1074; **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.48 (s, 1H), 3.81 (dd, *J* = 7.2, 12 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.56 (s, 3H), 2.94 (d, *J* = 16.8 Hz, 1H), 2.91 (d, *J* = 16.8 Hz, 1H), 2.50-2.47 (m, 1H), 2.40 (t, *J* = 13.2 Hz, 1H), 2.03 (t, *J* = 7.8 Hz, 2H), 1.39 (brs, 2H), 1.28 (brs, 12H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 3.91 (dd, *J* = 7.2, 12.4 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.10 (s, 2H),

2.71 (dd, *J* = 12.8, 13.2 Hz, 1H), 2.32 (dd *J* = 7.2, 13.2 Hz, 1H), 2.09 (t, *J* = 7.6 Hz, 2H), 1.50-1.37 (m, 2H), 1.24 (brs, 12H), 0.88 (t, *J* = 6.8 Hz, 3H) **^{13}C NMR** (150 MHz, DMSO-d_6) δ 198.1, 175.1, 170.2, 169.9, 169.5, 117.4, 108.1, 86.9, 53.4, 53.0, 52.2, 48.0, 38.9, 37.7, 31.8, 29.4, 29.2, 27.9, 22.6, 20.9, 14.4; **^{13}C NMR** (125 MHz, $CDCl_3$) 197.7, 172.3, 170.5, 169.8, 169.7, 118.3, 107.9, 87.1, 53.3, 52.7, 52.0, 47.8, 38.7, 37.9, 31.8, 29.5, 29.3, 27.8, 22.7, 21.1, 14.1; **TLC** (50:50 EtOAc: petroleum ether) R_f 0.53; **LRMS** (ESI) exact mass calculated for $C_{23}H_{34}O_9Cs$: 587.13. Found: 587.13.

3.6 References

(1) Ilan, N.; Elkin, M.; Vlodavsky, I. *Int. J. Biochem. Cell Biol.* **2006**, *38*, 2018-2039.

(2) Shiozawa, H.; Takahashi, M.; Takatsu, T.; Kinoshita, T.; Tanzawa, K.; Hosoya, T.; Furuya, K.; Takahashi, S.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 357-362.

(3) Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 857-859.

(4) Zammit, S. C.; Ferro, V.; Hammond, E.; Rizzacasa, M. A. *Org. Biomol. Chem.* **2007**, *5*, 2826-2834.

(5) Morokuma, K.; Taira, Y.; Uehara, Y.; Shibahara, S.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2008**, *49*, 6043-6045.

(6) Calo, F.; Richardson, J.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2009**, *50*, 1566-1567.

(7) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281-5284.

(8) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2708-2748.

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

(10) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816-6826.

(11) Greszler, S. N.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3689-3691.

(12) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293-297.

(13) G. Meyer, A.; J. Easton, C.; F. Lincoln, S.; W. Simpson, G. *Chem. Commun.* **1997**, 1517-1518.

(14) Smith, A. L.; Hwang, C. K.; Pitsinos, E.; Scarlato, G. R.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, *114*, 3134-3136.

(15) Abdelhamid, A. O. *J. Heterocyclic Chem.* **2009**, *46*, 680-686.

(16) Skinner, G. S. *J. Am. Chem. Soc.* **1924**, *46*, 731-741.

(17) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, *5*, 391-394.

(18) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O.; Wenkert, E. *J. Org. Chem.* **1994**, *59*, 2882-2884.

(19) Noji, M.; Sunahara, H.; Tsuchiya, K.-ichi; Mukai, T.; Komasaka, A.; Ishii, K. *Synthesis* **2008**, *2008*, 3835-3845.

(20) Schmid, G. Fukuyama, T. Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259-260.

(21) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698-4701.

(22) Satterfield, A. D. [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, University of North Carolina: Chapel Hill, 2009.

(23) Boyce, G. R.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 8930-8933.

(24) Nicewicz, D. A.; Breteche, Guillaume; Johnson, J. S. *Org. Synth.* **2008**, *85*, 278-286.

(25) Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12556-12557.

(26) Alaimo, P. J. Peters, D. W. Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.