I. [1,2]-Brook Rearrangement: Application of Silyl Glyoxylates In a Novel Glycolate Aldol Reaction and in a Controlled Oligomerization to Complete the Total Synthesis of Zaragozic Acid C

II. Progress Toward The Total Synthesis of Pactamycin

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

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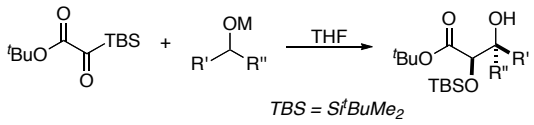
ABSTRACT

ANDREW DUNCAN SATTERFIELD:
I. [1,2]-Brook Rearrangement: Application of Silyl Glyoxylates to a Novel Glycolate Aldol Reaction and in a Controlled Oligomerization to Complete the Total Synthesis of Zaragozic Acid C
II. Progress Towards the Total Synthesis of Pactamycin
(Under the direction of Professor Jeffrey Scott Johnson)

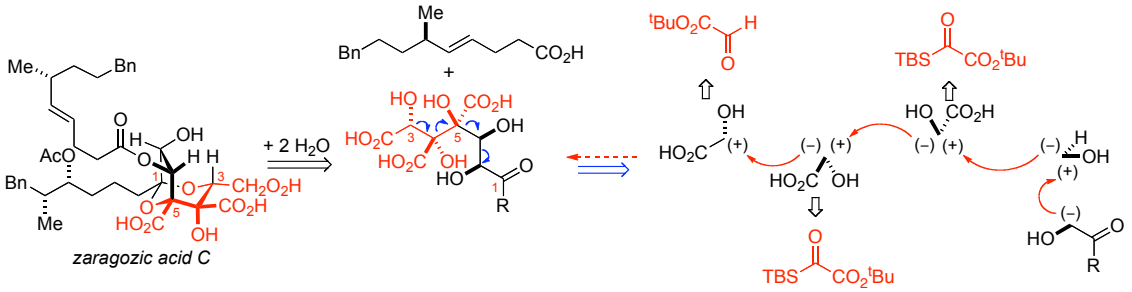
I. Symbiotic Reagent Activation: Oppenauer Oxidation of Magnesium Alkoxides by Silyl Glyoxylates Triggers Second-Stage Aldolization

The treatment of silyl glyoxylates with magnesium alkoxides leads to a Meerwein-Ponndorf-Verley reduction of the silyl glyoxylate and an Oppenauer oxidation of the alkoxide. The symbiotic transfer of a hydride from the alkoxide to the silyl glyoxylate triggers a [1,2]-Brook rearrangement forming an enolate that undergoes an aldol reaction with the carbonyl oxidation product. The magnesium alkoxide can be generated via deprotonation of primary and secondary alcohols with EtMgBr, Grignard addition to aldehydes or CuI-catalyzed alkylation of epoxides. Moderate levels of *anti*-diastereoselectivity were observered with primary aliphatic alkoxides. Stereoselective as well as catalytic versions of this reaction were also investigated.



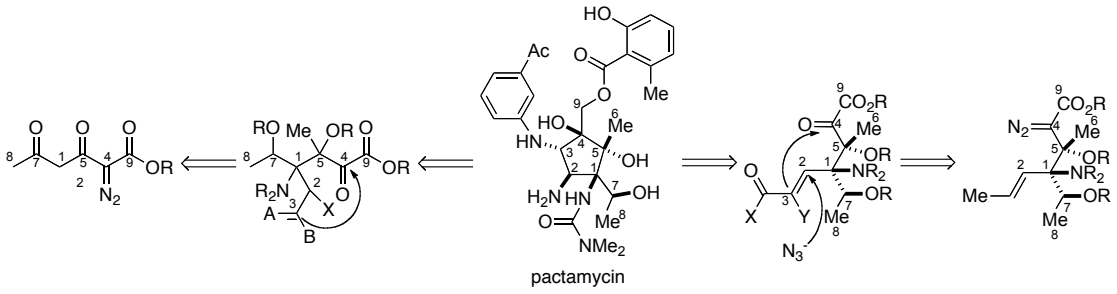
II. Total Synthesis of Zaragozic Acid C via Controlled Oligomerization

Tert-butyldimethylsilyl glyoxylate was used as a dipolar glycolic acid synthon to rapidly assemble the core of zaragozic acid C by means of a controlled oligomerization. This new methodology facilitated a rapid, stereocontrolled construction of the carbon skeleton while minimizing the need for functional group and oxidation state manipulation.



III. Progress Toward the Total Synthesis of Pactamycin

A review of literature covering previous synthetic approaches to the core of pactamycin is presented. Work was done on the construction of precursors to an intramolecular cyclization to form the densely functionalized core of pactamycin. The strategies involved using a diazo group to block reactivity and allow installation of core functionality. Subsequent oxidization would reveal the requisite electrophile for the cyclization.



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I thank professors Maurice S. Brookhart, Erik J. Alexanian, Joseph L. Templeton and Cynthia K. Schauer for serving on my defense committee and Jim Morken for serving on my oral examination committee.

I would also like to thank the peers I've worked with. First and foremost Dave, Dan and Xin for giving me the opportunity to collaborate on projects with them. I'd also like to thank Johnson group members past (Cory, Justin, Roy, Pat and especially Dave for showing me the ropes my first year in the group as well as Xin, Mary Robert, Ashley and Becca) and present (Matthew, Shanina, Austin, Andrew, Kim, Steve, Dan, Chris, Mike, Greg, and Jen). I could always count on a light atmosphere and there was never a dull moment.

I would like to thank my friends for their support and distraction. My lifelong friends Mason, Matt and Chang in Pennsylvania with whom I always have a good time and are always willing to listen. My friends here in North Carolina (Ben, Travis, Kristina, Stephanie, Stuart, Ali, Lindsey, Kayla and Nikki) who I could always count on for support and to be willing to help wipe away a bad day with some pickup soccer or mindless banter over a few drinks. I'd especially like to thank Kristina for all her support this last year.

Most importantly, I'd like to thank my family for their support. Even as a child they always encouraged my interest in chemistry. In particular, I would like to acknowledge my grandfather, Donald Meldrum, who was also a chemist. When I think about what first inspired me to pursue chemistry, the memory I recall was my grandfather taking me on a tour of the chemistry lab named for my great grandfather at Haverford College in the third grade. Without my family I could never have gotten to where I am today. No matter what, they are always there to give me words of encouragement and advice during even the hardest times.

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LIST OF ABBREVIATIONS AND SYMBOLS

Ac	acetate
Ac_2O	acetic anhydride
^{t}amyl	*tert*-amyl
aq.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BOC	butoxycarbonyl
br	broad
^{n}Bu	*n*-butyl
^{n}BuLi	*n*-butyl lithium
^{t}Bu	*tert*-butyl
cat.	catalytic amount or catalyst
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
conv.	conversion
COSY	correlated spectroscopy
*m*CPBA	*m*-chloroperbenzoic acid
18-crown-6	1,4,7,10,13,16-Hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSP	chiral stationary phase
Cy	cyclohexyl
d	doublet or days
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ	2,3-dichloro-5,6-dicyanohydroquinone
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
d.r.	diastereomeric ratio
El^+	electrophile
ee	enantiomeric excess
eq	equation
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
h	hour
^1H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
L	ligand
LA	Lewis acid
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane

LRMS	low resolution mass spectroscopy
M	metal
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
mp	melting point
NaHMDS	sodium hexamethyldisilazane
NMM	*N*-methylmopholine
NMO	*N*-methylmorpholine-*N*-oxide
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
NR	no reaction
Nu	nucleophile
ORTEP	Oak Ridge thermal ellipsoid plot
pABSA	para-acetamidobenzenesulfonyl azide
Ph	phenyl
Piv	pivolate
PMB	*p*-methoxybenzyl
ppm	parts per million
^{i}Pr	isopropyl
rac	racemic

R_f	retention factor
rt	room temperature
Salen	N,N'-Ethylenebis(salicylimine)
SFC	supercritical fluid chromatography
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
Temp	temperature
TEMPO	2,2,6,6-tetramethyl-piperidinyloxy, free radical
OTf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
2-MeTHF	2-methyltetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
t_r	retention time
TsOH	*p*-toluenesulfonic acid
X	anionic ligand
δ	chemical shift
μL	microliter
μm	micrometer

CHAPTER 1

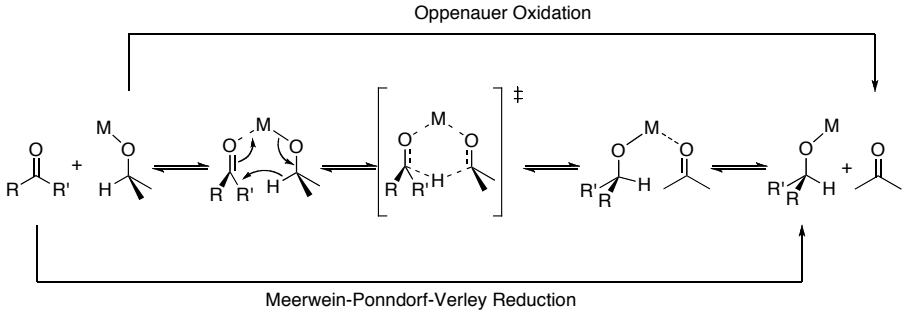
SYMBIOTIC REAGENT ACTIVATION: OPPENAUER OXIDATION OF MAGNESIUM ALKOXIDES BY SILYL GLYOXYLATES TRIGGERS SECOND-STAGE ALDOLIZATION

1.1 Introduction

The aldol reaction is the preeminent method for the introduction of the β hydroxy carbonyl function, and extensive development has made it a valuable tool for organic synthesis.[1] Recent advances have focused on the design of catalysts to achieve a direct aldol reaction selectively forming the nucleophilic enol species in the presence of the carbonyl electrophile.[2-9] This has greatly expanded the synthetic utility, but application of the aldol reaction to the synthesis of complex molecules is often still hampered by the need for additional measures, such as a prior oxidation event, to prepare the requisite electrophile.[10] A more efficient direct aldol reaction would combine formation of the nucleophilic donor, the electrophilic acceptor and the subsequent aldol reaction into one process. The goal of this project was to develop an efficient, direct aldol reaction that formed the requisite electrophile and nucleophile symbiotically using silyl glyoxylates[11] and metal alkoxides.

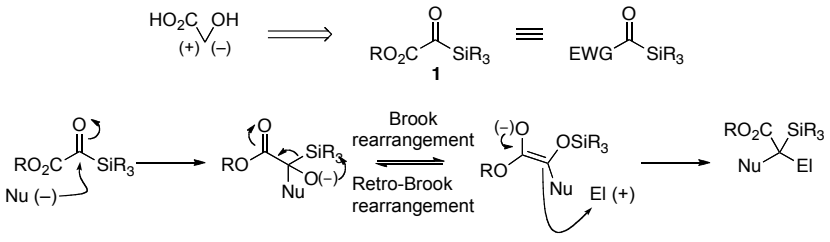
1.2 Background

Scheme 1-1 Oppenauer Oxidation MPV Reduction



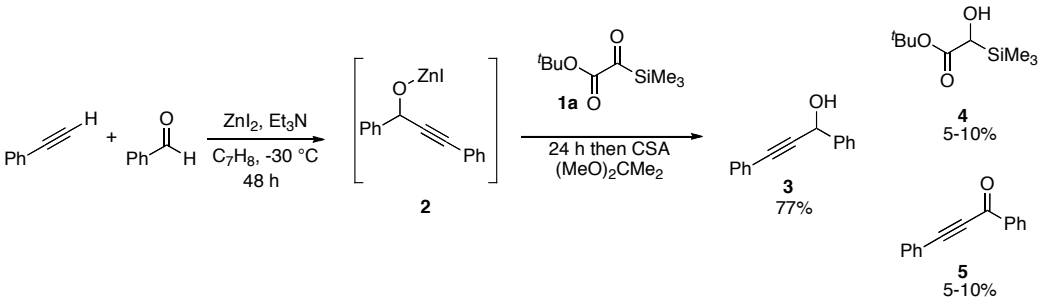
This project combined a classic reaction, the Oppenauer oxidation/Meerwein-Ponndorf-Verley (MPV)[12,13] reduction with the unique properties of silyl glyoxylates to accomplish a second stage aldol reaction between unactivated substrates. The Oppenauer oxidation is the oxidation of a metal alkoxide by a carbonyl species via hydride transfer; the MPV reduction is the reverse process (Scheme **1-1**). The reaction is reversible, but the equilibrium can be shifted to favor complete reduction or oxidation by the selective removal of products. This reaction can be promoted by many metals, including lanthanides, aluminum, and magnesium, but often a stoichiometric amount of metal is required due to the stability of the product alkoxides. Aldehydes, ketones, and in this study silyl glyoxylates, can serve as oxidants with the general trend in reactivity favoring oxidation of secondary over primary alkoxides.

Scheme 1-2 Reactivity of Silyl Glyoxylates



Silyl glyoxylates **1** are acyl silanes with a bound electron withdrawing ester group and function as dipolar glycolic acid synthon (Scheme **1-2**). Nucleophilic attack on the acyl silane portion results in formation of an oxyanion and a subsequent [1,2]-Brook rearrangement,[14] forming a carbanion that can be trapped by an electrophile. Brook rearrangement is driven by the greater stability of the Si-O σ bond (120-130 kcal mol^{-1}) compared the Si-C σ bond (75-85 kcal mol^{-1}) as well as stabilization of the carbanion as an enolate by the pendant ester group. This type of reactivity allows silyl glyoxylates to serve as synthetic linchpins in multicomponent couplings.

Scheme 1-3 MPV/Aldol Origin

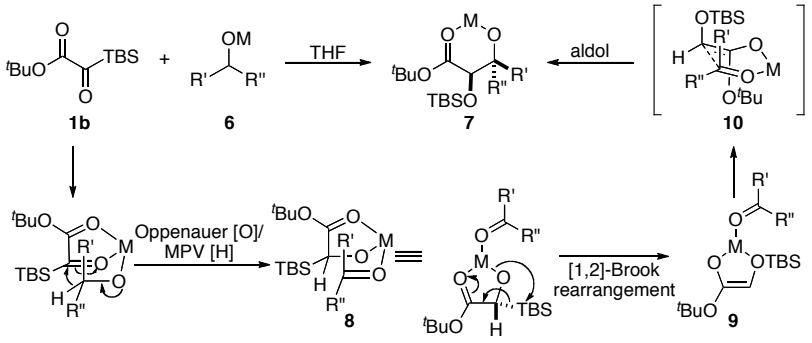


An example of silyl glyoxylates playing the role of conjunctive agent was the use of **1a** in the coupling of alkynylzinc halides and aldehydes.[15] The genesis of the study described herein was the observation of hydroxysilane **4** and ynone **5** as minor byproducts in a reaction between zinc alkoxide **2** and silyl glyoxylate **1a** (Scheme **1-3**) that was designed to probe the mechanism of the aforementioned three-component coupling. While formation of **3** can be explained by proton quench of the expected intermediate zinc alkoxide **2**, it was hypothesized that the byproducts **4** and **5** resulted from an Oppenauer oxidation MPV reduction[6-8] between **2** and **1a**. In contrast to other nucleophiles that react with **1a**, the hydride transfer did not trigger [1,2]-Brook rearrangement.[16,17]

Given the observation of products **4** and **5** we proposed a reaction wherein a metal alkoxide and a silyl glyoxylate react symbiotically under mild conditions to achieve an aldol reaction between unactivated substrates (Scheme **1-4**). If reaction conditions could be suitably modified such that the Oppenauer/MPV process did cause C → O silyl migration (**8** → **9**), the

resulting products from the redox reaction would be a glycolate enolate and ketone or aldehyde poised to undergo aldolization.

Scheme 1-4 Proposed Mechanism

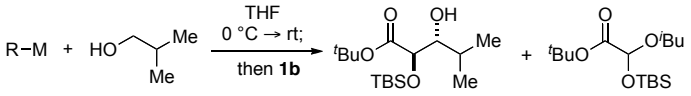


1.3 Results and Discussion

1.3.1 Reaction Scope

It was projected that the identity of the metal cation would be crucial in governing the efficiency of each proposed step; therefore, an evaluation of suitable candidates was initiated. For the initial evaluation of the reaction metal alkoxides were generated via deprotonation of alcohols by organometallic species using THF as a solvent. As commonly employed catalysts for MPV/Oppenauer reactions, aluminum alkoxides provided a logical starting point for this inquiry (Table **1-1**).[18] Surprisingly, no reaction was observed with $MeAlCl_2$ (entry 1). Use of ^{n}BuLi and Bu_3La provided only the direct addition/rearrangement product **12** (entries 2 and 3). Selective generation of desired aldol product **11a** was achieved with a magnesium alkoxide[19] generated in THF (entry 4). Using the conditions from entry 4, this reaction was successfully conducted with a variety of primary and secondary alcohols.[20]

Table 1-1 Evaluation of Metal Alkoxides

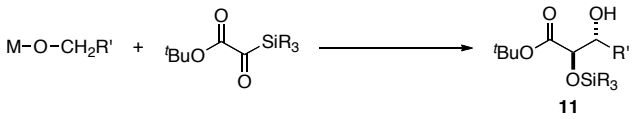


entry	R–M	result	*anti*:*syn*[a]
1	$MeAlCl_2$	no reaction	-
2	*n*-BuLi	40% of **12**[b]	-
3	Bu_3La	58% of **12**[c]	-
4	EtMgBr	71% of **11a**[c]	6:1

[a] Determined by ^{1}H NMR spectroscopy. [b] ^{1}H NMR yield versus an internal standard. [c] Isolated yield.

A more extensive evaluation of reaction variables was undertaken to optimize reaction conditions to maximize yield and improve diastereoselectivity (Table **1-2**). The identity of the metal cation was investigated further (entries 1-6). Aluminum and titanium alkoxides were able to complete the reaction but in lower yields than the magnesium alkoxides (entries 3 and 6). The identity of the halide present in the magnesium alkoxide was varied and while MgCl alkoxides gave comparable yields, the best diastereoselectivity was achieved with MgBr (entries 1, 4 and 5). Variation of the silyl group of the silyl glyoxylate to the less sterically demanding triethylsilyl glyoxylate and the more encumbering triisopropyl silyl resulted in diminished yields compared to the TBS silyl glyoxylate (entries 7 and 8). As the final variable investigated, a screen of solvent systems revealed that a 2:1 mixture of THF/CH_2Cl_2 improved the yield and diastereoselectivity of the reaction (entries 9-20).

Table 1-2 Evaluation of Reaction Variables



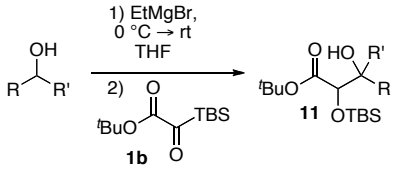
11

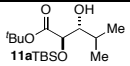
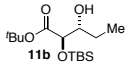
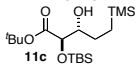
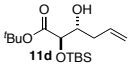
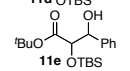
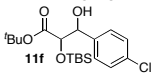
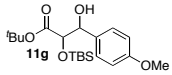
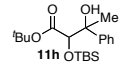
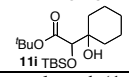
entry	^{i}BuO–M	^{t}BuO$_2$CC(O)SiR$_3$	solvent	yield[a]	*d.r.*[b]
1	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	THF	71%	6:1
2	Me$_2$AlCl (1 equiv)/ ^{i}BuOH	^{t}BuO$_2$CC(O)TBS	THF	0%	n.a.
3	Me$_2$AlCl (0.5 equiv)/	^{t}BuO$_2$CC(O)TBS	THF	42%	5:1
4	^{i}BuO–MgCl	^{t}BuO$_2$CC(O)TBS	THF	≈70%	4.8:1
5	^{i}BuO–MgI	^{t}BuO$_2$CC(O)TBS	THF	<20%	1:1
6	(^{i}PrO)$_4$Ti	^{t}BuO$_2$CC(O)TBS	THF	<10%	n.d.
7	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TES	THF	30%	4.4:1
8	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TIPS	THF	35%	3.7:1
9	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	Dioxane	26%	2.0:1
10	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	CH_2Cl_2	24%	8.0:1
11	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	Et_2O	36%	6.0:1
12	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	Toluene	34%	7.0:1
13	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	MTBE/THF	76%	7.6:1
14	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	MTBE	83%	5.6:1
15	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	2-MeTHF	n.r.	n.a.
16	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	2-MeTHF/THF	56%	7.4:1
17	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	Dioxane/THF	31%	2.8:1
18	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	THF/Et_2O (2:1)	69%	9.1:1
19	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	THF/toluene	57%	10:1
20	^{i}BuO–MgBr	^{t}BuO$_2$CC(O)TBS	THF/CH_2Cl_2	>95%	10.6:1

[a] ^{1}H NMR yield versus an internal standard; isolated yields for entries 7 and 8. [b] Determined by ^{1}H NMR spectroscopy.

The optimized reaction conditions, deprotonation of alcohols in 2:1 THF/CH_2Cl_2 with EtMgBr, were then used to evaluate alcohols as coupling partners (Table **1-3**). The new conditions resulted in a marked improvement in the yields and diastereomer ratio of some substrates compared to results obtained using only THF as the solvent (entries 1-3). Results were good for a variety of alcohols with yields from 63 to 97%. Notably, primary aliphatic alcohols delivered the aldol products with synthetically useful levels of *anti* diastereocontrol (entries 1-4).[21-27] The boat-like transition structure **10** may be construed as a tentative model to explain the observed *anti* isomer (*vide infra*).

Table 1-3 Alchohol Substrate Scope



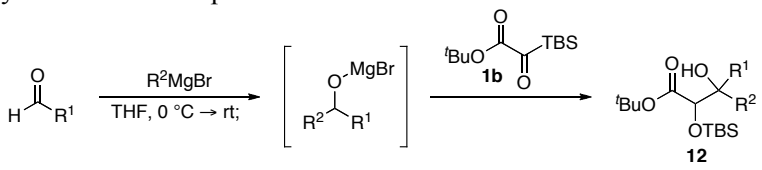
entry	alcohol	product	yield (%)[b]	d.r.[c]
1[d]	Me_2CHCH_2OH		97	10:1
2[d]	$Me(CH_2)_5OH$		86	7:1
3[d]	$TMS(CH_2)_3OH$		88	5:1
4	$CH_2=CH(CH_2)_4OH$		63	5:1
5	$PhCH_2OH$		90	1.2:1
6	$4\text{-}ClPhCH_2OH$		82	1:1
7	$4\text{-}MeOPhCH_2OH$		85	1:1
8	PhCH(OH)Me		67	2.5:1
9	cyclohexanol		68	n.a.

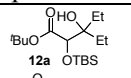
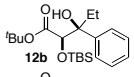
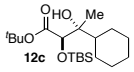
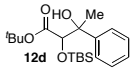
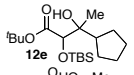
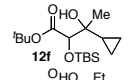
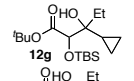
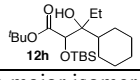
[a] Alcohol (1.5 equiv), EtMgBr (2.0 equiv), THF, 0 °C → rt; then **1** (1.0 equiv). [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy; the major isomer is shown. [d] Reaction solvent: 2:1 THF/CH_2Cl_2

Benzylic alcohols provided the aldol adducts with superior yields but negligible diastereocontrol (entries 5-7). Perhaps most strikingly, secondary alcohols function effectively in

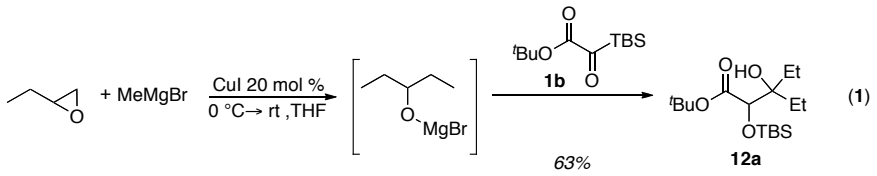
this reaction to deliver highly substituted ketone aldol adducts (entries 8 and 9). The success of these latter reactions led us to evaluate a three-component coupling strategy wherein the requisite secondary alkoxide was formed via Grignard addition to aldehydes (Table **1-4**).[28] This simple one-step protocol facilitated access to more complex ketone aldol adducts with no reduction in reaction efficiency. In the case where significant steric differentiation exists between R^1 and R^2, promising levels of diastereocontrol may be achieved (entry 3). Greater steric bulk of both the Grignard reagent and the aldehyde generally resulted in a decreased yield for the reaction.

Table 1-4 Aldehyde Substrate Scope



entry	R^1	R^2	product	yield (%)[a]	d.r.[b]
1	Et	Et	 **12a**	68	n.a.
2	Ph	Et	 **12b**	81	1.8:1
3	cyclohexyl	Me	 **12c**	67	3.5:1
4	Ph	Me	 **12d**	45	2:1
5	cyclopentyl	Me	 **12e**	39	1.6:1
6	cyclopropyl	Me	 **12f**	35	1.2:1
7	cyclopropyl	Et	 **12g**	25	2.7:1
8	cyclohexyl	Et	 **12h**	15	2.4:1

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopy; the major isomer is shown when determined.



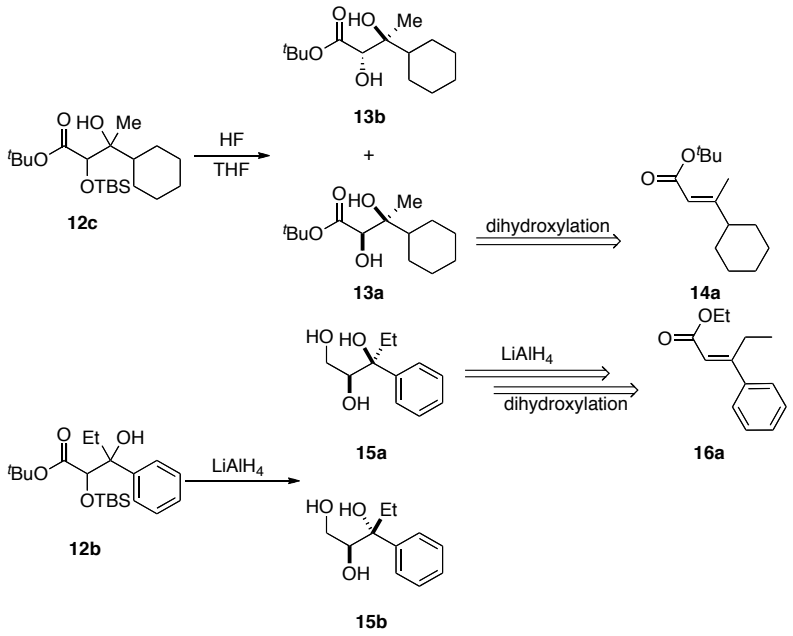
(1)

Epoxides may also serve as the alkoxide progenitor in conjunction with a Cu(I)-catalyzed alkylation (eq **1**). On the basis of the similar yield for **12a** beginning from either an epoxide or an aldehyde (Table **1-3**, entry 1) and the ability to run the reaction stoichiometric in copper, it appears that CuI does not interfere with the subsequent steps.

1.3.2 Identification and Rationalization of Relative Stereochemistry for Aldol Products

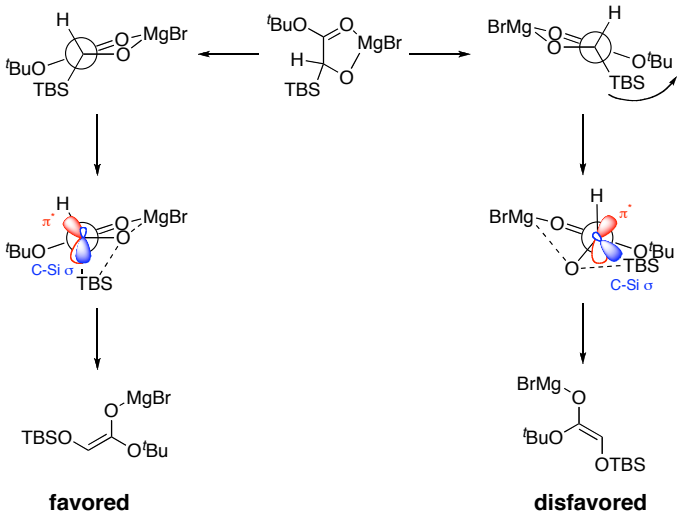
The relative stereochemistry for aldol products resultant from alcohol-derived alkoxides was elucidated previously.[29] Silyl ether deprotection of **12c** with HF gave **13a** and **13b**. Comparison with the ^{1}H NMR spectrum of known *syn* diol **13a** formed from osmium catalyzed dihydroxylation revealed *anti* **13b** as the major diastereomer (Scheme **1-5**). Similarly, reduction of the ester and deprotection of the silyl ether of **12b** in one pot with $LiAlH_4$ gave triols **15a** and **15b**. Comparison of the supercritical fluid chromatography (SFC) trace with that of triol **15a,** with a *syn* configuration of the two secondary alcohols, formed from an osmium catalyzed dihydroxylation and $LiAlH_4$ reduction revealed **15a** as the major diastereomer. The *syn* diol orientation seen in **15** goes against the favored *anti* orientation seen in the aliphatic products. This combined with the general trend of a lack of diastereoselectivity with aryl products may indicate an alternate mechanism.

Scheme 1-5 Stereochemical Proofs



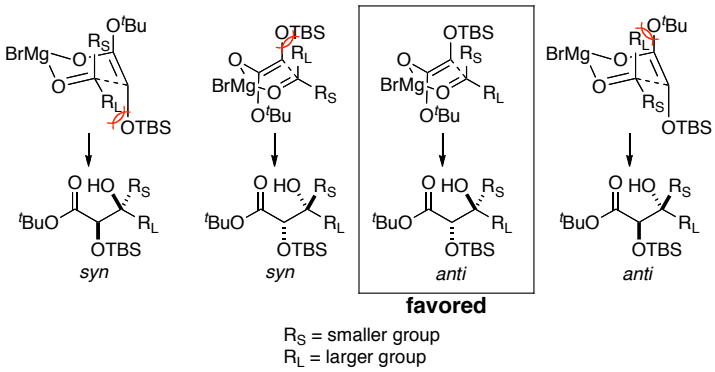
The predominance of the *anti* isomer in aliphatic products is congruent with the recent observation by Evans and co-workers of *anti* propionates from (*Z*)-magnesium enolates.[30] In this system, preference for the (*Z*)-magnesium enolates may be due to a favorable orbital overlap of the C-Si σ bond with the π^* orbital of the ester carbonyl (Scheme **1-6**). This orbital overlap could facilitate formation of the enolate π bond via [1,2]-Brook rearrangement. In order to form the (*E*)-enolate, the C-Si σ bond would have to rotate out of alignment with the π^* orbital in addition to breaking the chelating interaction of magnesium with the two oxygen atoms.

Scheme 1-6 Orbital Overlap



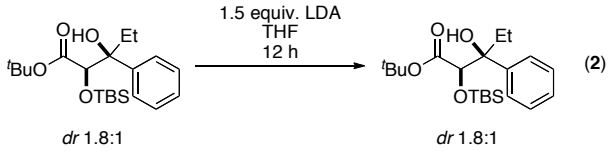
Assuming formation of the (*Z*)-magnesium enolate, the boat-like transition structure **10** may thus be construed as a tentative model for the observed stereochemical outcome (Scheme **1-7**). This boat-like transition structure minimizes the unfavorable steric interactions between the large group of the carbonyl acceptor and the TBS group and *tert*-butyl ester of the enolate and leads to the observed anti diol orientation.

Scheme 1-7 Transition State Models



1.3.3 Attempts to Enhance Selectivity

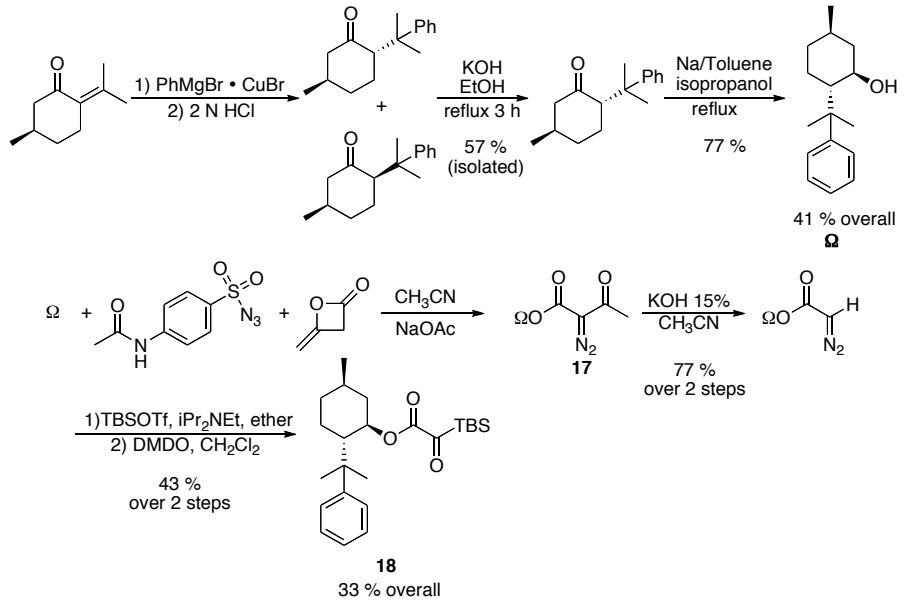
To increase the synthetic utility of this methodology attempts were made to convert the diastereomeric mixture of products to the potentially thermodynamically favored product and increase the selectivity of product formation during the course of the reaction. The mixture of diastereomers resultant from a ketone aldol reaction was subjected to the strong base LDA to investigate the possibility of an epimerization to a thermodynamically favored product (eq **2**). Upon proton quench no change in the diastereomeric ratio of the products was observed.



(**2**)

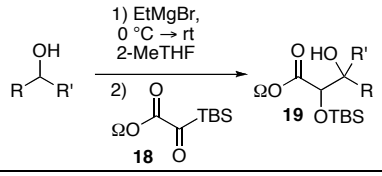
By placing a chiral auxiliary on the silyl glyoxylate we sought to block one face of the intermediate magnesium enolate. The auxiliary (-)-8-phenyl menthol **Ω** was chosen since it was easily synthesized in large quantities from pulegone, a compound available from the chiral pool (Scheme **1-8**). An alternative synthesis using **Ω** was developed to make a chiral silyl glyoxylate. The procedure differed from the conventional synthesis of **1b**[31] by starting with diketene, **Ω** and pABSA to form the diazo malonate **17** in one pot.

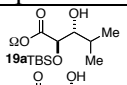
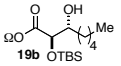
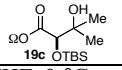
Scheme 1-8 Chiral Silyl Glyoxylate Synthesis



Once in hand, the chiral silyl glyoxylate **18** was evaluated with alcohol substrates (Table **1-5**). Attempts to run the reaction with primary alcohols resulted in product mixtures with limited selectivity for 1 diastereomer over three others (entries 1 and 2). Favorable results were achieved with the secondary alcohol isopropanol (entry 3), with a diastereomeric ratio of 19:1.

Table 1-5 Asymmetric Substrate Scope

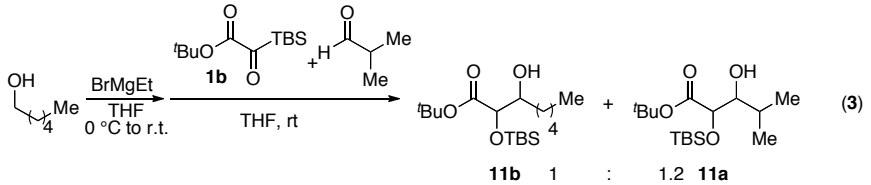


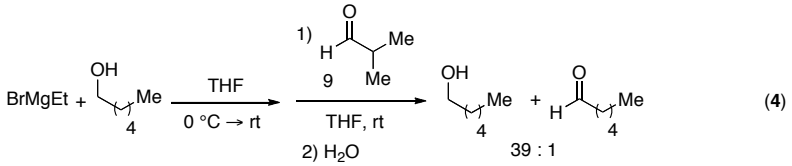
entry	alcohol	product	yield (%)[b]	d.r.[c]
1[d]	Me_2CHCH_2OH		62	1.6:1 (**X**:**Σ** others)
2[d]	$Me(CH_2)_5OH$		54	1.7:1 (**X**:**Σ** others)
3[d]	Me_2CHOH		63	19:1

[a] Alcohol (1.5 equiv), EtMgBr (2.0 equiv), 2-MeTHF, 0 °C → rt; then **1** (1.0 equiv). [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy; the major isomer is shown.

1.3.4 Crossover Experiments

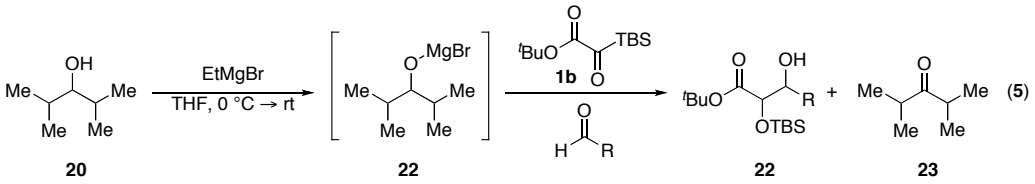
Preliminary conclusions regarding the relative rates of the individual steps of the reaction sequence may be drawn from the crossover experiments shown in eq **3** and **4**. Exposing the magnesium alkoxide of *n*-hexanol to **1b** and isobutyraldehyde resulted in an approximately equimolar mixture of **11b** and **11a**, revealing that dissociation of the aldehyde from the magnesium center is faster than Brook rearrangement and aldolization (eq **3**). The possibility of the origin of **11a** resulting from formation of an intermediate alkoxide by MPV reduction of isobutyraldehyde by *n*-hexanol alkoxide was eliminated in a control experiment exposing isobutyraldehyde to *n*-hexanol alkoxide (eq **4**).

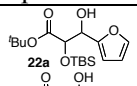
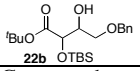




Based on the observations from the crossover experiments, it was hypothesized that by using a sterically hindered hydride donor, it might be possible to expand the scope of the MPV-aldol reaction to include electrophilic coupling partners incapable of reducing a silyl glyoxylate to promote Brook rearrangement (eq **5**). The magnesium alkoxide **21** generated from ethyl Grignard deprotonation of alcohol **20** was able to reduce **1b** and promote Brook rearrangement in the presence of other aldehydes. Presumably, ketone **23** formed from the Oppenauer oxidation is too sterically hindered to undergo an aldol reaction prior to dissociation allowing the association of an alternative aldehyde acceptor to complete aldolization and produce the desired product. The substrates shown in Table **1-6** were inaccessible with the standard MPV reaction protocol.

Table 1-6 Crossover Products

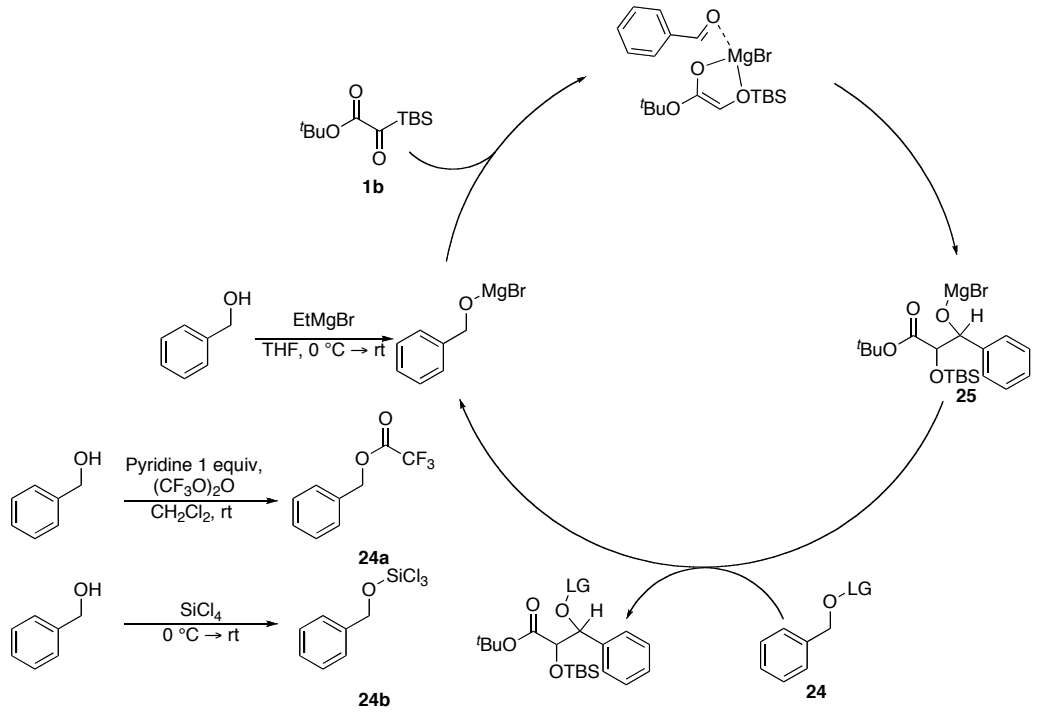


entry	aldehyde	product	yield (%)[b]
1[d]		 **22a**	64
2		 **22b**	33

[a] Alcohol **20** (1.4 equiv), EtMgBr (1.5 equiv), THF, 0 °C → rt; then **1b** (1.0 equiv) and aldehyde (1.0 equiv). [b] Isolated yields of major diastereomer. [c] D.R. not determined.

1.3.5 Catalytic Use of Metal

Scheme 1-9 Proposed Catalytic Cycle

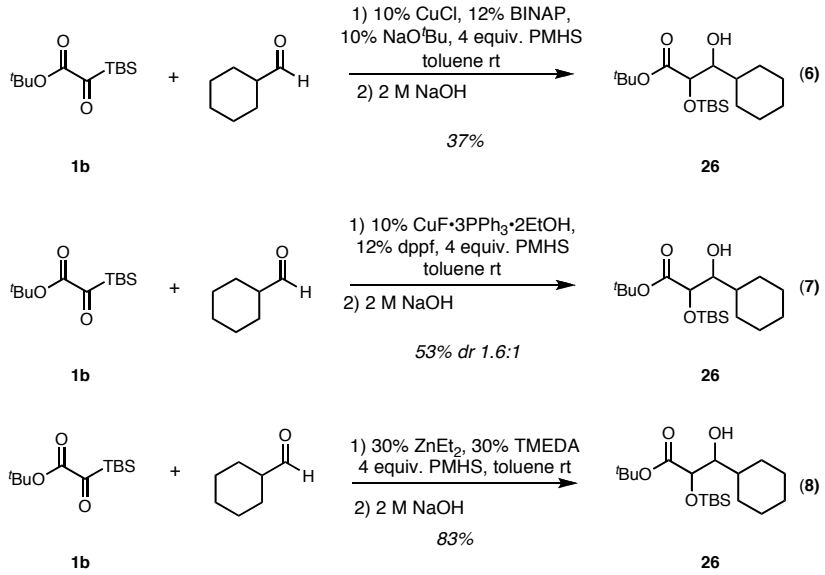


A system catalytic in metal could function as depicted in Scheme **1-9**. The initial magnesium alkoxide would be generated with a substoichiometric amount of alcohol and ethyl Grignard. Addition of silyl glyoxylate **1b** and **24** would initiate the cycle with MPV reduction and Brook rearrangement followed by aldol reaction to form intermediate alkoxide **25**. Regeneration of the starting magnesium alkoxide with **24,** a species capable of displacing the intermediate alkoxide **25,** would facilitate turnover. Compounds **24a**, with a trifluoroacetate leaving group, and **24b**, with a trichlorosilane leaving group, were investigated as possible candidates. With both substrates the resultant desired product was produced from the catalytic amount of magnesium alkoxide.

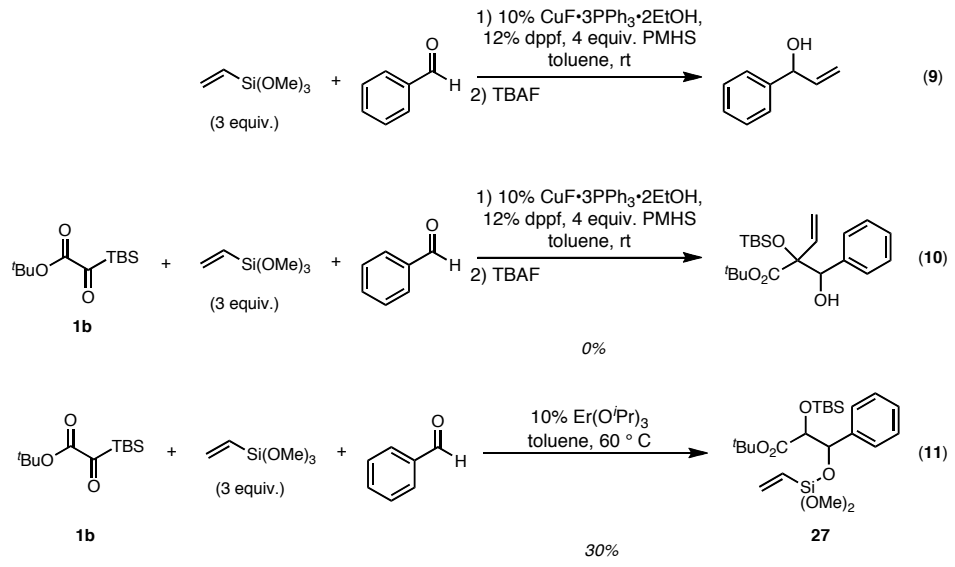
With no success in developing a catalytic MPV cycle with magnesium alkoxides, alternative hydride and vinyl nucleophilic catalyst systems were examined. While this strayed

from the symbiotic nature of the reaction by replacing the MPV reduction of the silyl glyoxylate with an external nucleophile source, it provided the potential for a multicomponent coupling system catalytic in metal and the possibility of employing chiral ligands to develop a stereoselective reaction.

Copper and zinc hydride generated in situ from the stoichiometric hydride source of polymethylhydrosiloxane (PMHS) were investigated with cyclohexylcarboxaldehyde as the electrophilic coupling partner. Using CuCl with a racemic 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (BINAP) ligand and sodium *tert*-butoxide as an initiator resulted in a 37% yield of desired product with poor diastereoselectivity (eq **6**).[32,33] Switching the catalyst to $CuF{\bullet}3PPh_3{\bullet}2EtOH$[34] with 1,1'-Bis(diphenylphosphino)ferrocene (dppf) ligand improved the yield to 53 % with little diastereoselectivity (eq **7**). A system using Zn hydride generated *in situ* from $ZnEt_2$ and PMHS with tetramethylethylene diamine (TMEDA) as a ligand provided the best yield of 83% but with no diastereoselectivity (eq **8**).[35] Besides the poor diastereoselectivities, the PMHS catalyst systems suffer from the requirement of harsh basic conditions to free the desired product from the polymeric backbone of PMHS.



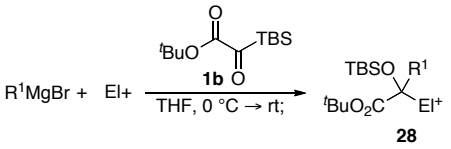
With limited success using metal hydride catalysis, attempts were made to adapt a vinyl copper catalyst system to a multicomponent coupling with silyl glyoxylates and aldehydes. The original conditions used the aforementioned CuF•3PPh$_3$•2EtOH with dppf ligand to generate a vinyl copper species *in situ* with trimethoxyvinylsilane serving as the stoichiometric vinyl source (eq **9**).[36] Initial attempts using the same conditions in the presence of silyl glyoxylate and benzaldehyde resulted in formation of none of the desired product (eq **10**). A number of other metal fluoride sources were also investigated as possible catalysts with no success. A series of lanthanide triisopropoxides were then screened for reactivity with some interesting results. Er(^{i}OPr)$_3$ showed the most promise, forming compound **27** (eq **11**). Formation of **27** could arise from an MPV reduction of silyl glyoxylate by the Er(^{i}OPr)$_3$, Brook rearrangement with Er enolate formation, and then an aldol reaction with benzaldehyde. Catalyst turnover appeared to occur through displacement of the lanthanide alkoxide by trimethoxyvinylsilane. Compound **27** was formed in 30% yield, the maximum theoretical yield given a 10% catalyst loading. This demonstrated the feasibility of an MPV-aldol system catalytic in metal through the use of lanthanide isopropoxides with a silane capable of displacing the intermediate lanthanide alkoxide with concurrent regeneration of the isopropoxide catalyst.

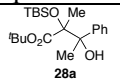
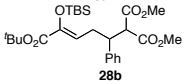
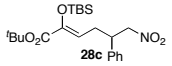
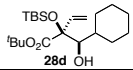


1.3.6 Other Coupling Partners

In addition to hydride nucleophiles to initiate coupling reactions between silyl glyoxylates and electrophiles, success was found using stoichiometric amounts of Grignard reagents as nucleophiles (Table **1-7**). Methylmagnesium bromide successfully coupled silyl glyoxylate with benzaldehyde in a moderate yield with moderate diastereoselectivity (entry **1**). Vinylmagnesium bromide successfully coupled a benzylidine malonate, a nitroalkene and an aldehyde with silyl glyoxylate (entries 2-4). Interestingly, the products observed with the nitro alkene and the benzylidene malonate arose from exclusive addition from the γ position of the enolate. In the case of the aldehyde (entry 4), the high selectivity for the *syn* diol configuration proved useful in a future application of silyl glyoxylates to the synthesis of a complex natural product.

Table 1-7 Grignard Coupling Reactions



entry	R^1	El+	product	yield (%)[a]	selectivity[b]
1	Me		 **28a**	67	d.r. 2.3:1
2	Vinyl		 **28b**	45	1 diastereomer
3	Vinyl		 **28c**	49 (65[c])	only γ addition
4[d]	Vinyl		 **28d**	76	*syn:anti >95:5*

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopy; the major isomer is shown when determined. [c] Reaction run in 2:1 THF:CH_2Cl_2 yield determined by ^{1}H NMR spectroscopy based on the internal standard trimethoxy benzene. [d] Unpublished result from Xin Linghu.

1.4 Conclusions

A new method was developed to efficiently conduct an aldol reaction between silyl glyoxylates and metal alkoxides with no required prior activation or redox manipulation of

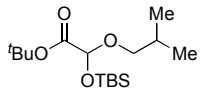
substrates. The reaction is conducted under mild conditions to achieve synthetically useful yields of desired glycolate aldol products with moderate diastereoselectivity in some cases. In addition, the utility of silyl glyoxylate **1** as a conjunctive reagent was explored in the coupling of other nucleophiles and electrophiles. The scope of this new mild aldol reaction was demonstrated as well as the reactivity of the silyl glyoxylate reagent.

1.5 Experimental

General Information. 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 the following instruments: Bruker model Avance 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and Varian Gemini 300 (^{1}H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.24 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet), coupling constants (Hz), and integration. 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 nitrate 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 alcohols for general procedure **(A)** were distilled from magnesium prior to use. All alcohols for general procedure **(C)** were distilled from sodium prior to use. Aldehydes were extracted from an aq. sat. $NaHCO_3$ solution with ether, concentrated, and distilled. THF was distilled from sodium and benzophenone. Analytical chromatography was performed on a Berger Supercritical Fluid Chromatograph (SFC) model FCM 1100/1200 equipped with an Agilent 1100 series UV-Vis detector. Silyl glyoxylate **1** was prepared

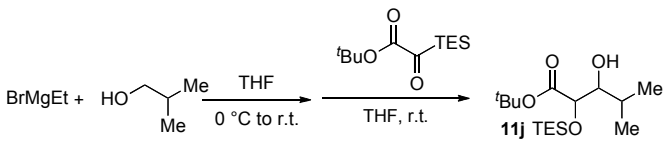
according to the literature procedure.[31,37] (-)-8-phenylmenthol Ω was prepared according to the literature procedure.[38] Yields and diastereomer ratios are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

Representative Procedure (A) for the optimization of reaction conditions (Table 1.1 and Table 1.2). A dry round-bottomed flask with a magnetic stir bar was charged with alcohol (1.5 equiv) and 2 mL of solvent. To the resulting solution, ethylmagnesium bromide (1.0 M in THF) (2.0 equiv) was added *via* syringe at 0 °C under an argon atmosphere. The reaction temperature was allowed to warm to 25 °C for 5 min. To the reaction solution was added dropwise *via* cannula the silylglyoxylate (1.0 equiv., ca. 0.4 mmol) in 2 mL of solvent. The reaction was stirred for 10 min before 5 mL of a saturated NH_4Cl solution and 15 mL of Et_2O were added. The organic layer was separated and the aqueous layer was extracted with two 10 mL portions of Et_2O. The organic extracts were combined, dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. To the crude product was added a known quantity of 1,3,5-trimethoxybenzene as the internal standard, and the yield and the diastereomer ratio of the reaction were determined by ^{1}H NMR spectroscopy.

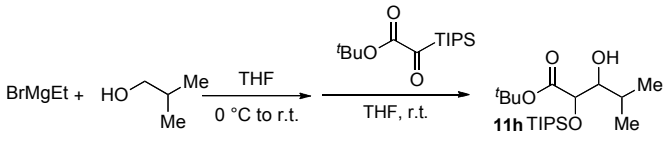


11

***tert*-Butyl-2-*tert*-butyldimethylsilyloxy-2-isobutoxyacetate (11).** Analytical data for title compound: **IR** (thin film, cm^{-1}) 2957, 2930, 2858, 1755, 1472, 1367, 1254, 1130, 1072, 839, 782; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.94 (s, 1H), 3.32 (ABX, J_{AB} = 8.8 Hz, J_{AX} = 6.8 Hz, 2H), 1.87 (sep, J = 6.8 Hz, 1H), 1.48 (s, 9H), 0.92 (s, 9H), 0.91 (d, 6H, one peak overlapped with 0.92 peak), 0.135 (s, 3H), 0.131 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) 168.0, 93.9, 81.6, 73.2, 28.4, 27.9, 25.63, 25.56, 19.3, 18.2, 17.5, -4.6, -4.8



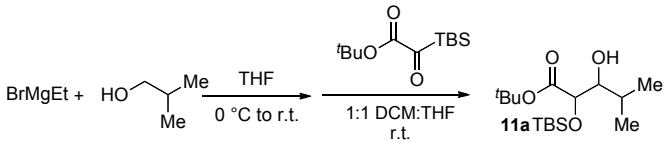
***tert*-Butyl-2-triethylsilyloxy-3-hydroxy-4-methylbutanoate (11j).** The title compound was prepared according to General Procedure **A** using 100 mg (0.41 mmol) of *tert*-butyl triethylsilylglyoxylate in THF (2 mL), 46 mg (0.60 mmol) of isobutanol in THF (2 mL), and 0.7 mL (0.7 mmol) of EtMgBr (1 M in THF). The crude product was extracted with Et_2O and purified by flash chromatography with 15:1 hexanes/EtOAc to afford 40 mg (30%) of the product as a clear oil (4.4:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.11 (d, J = 4.9 Hz, 1H), 3.44 (t, J = 5.7, 1H), 2.45 (br s, 1H), 1.80 (dq, J = 13.4, 6.7 Hz, 1H), 1.46 (s, 9H), 0.94 (t, J = 7.75 Hz, 9H), 0.94 (m, 6H), 0.61 (q, J = 7.79 Hz, 6H).



***tert*-Butyl-2-triisopropylsilyloxy-3-hydroxy-4-methylbutanoate (11h).** The title compound was prepared according to General Procedure **A** using 100 mg (0.41 mmol) of *tert*-butyl triisopropylsilylglyoxylate in THF (2 mL), 46 mg (0.60 mmol) of isobutanol in THF (2 mL), and 0.7 mL (0.7 mmol) of EtMgBr (1 M in THF). The crude product was extracted with Et_2O and purified by flash chromatography with 15:1 hexanes/EtOAc to afford 45 mg (36%) of the product as a clear oil. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.31 (d, J = 3.6 Hz, 1H), 3.40 (dd, J = 8.4, 3.5 1H), 1.72 (sep, J = 8.2 Hz, 1H), 1.45 (s, 12H), 1.2-0.85 (m, 24H).

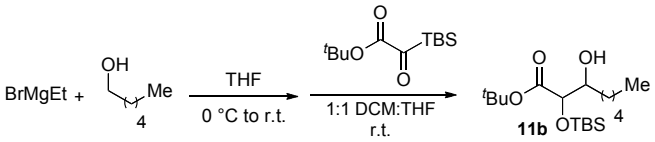
General procedure (B) for tandem Oppenauer oxidation/Brook rearrangement/aldolization (Table 1-3). A dry round bottomed flask with a magnetic stir bar was charged with alcohol (1.5

equiv), and 1-2 mL of solvent. To the resulting solution, ethylmagnesium bromide (1.0 M in THF) (1.75-2.0 equiv) was added *via* syringe at 0 °C under an argon atmosphere. The reaction temperature was allowed to warm to 25 °C for 5 min. To the reaction solution was added dropwise *via* cannula the silylglyoxylate (1.0 equiv, ca. 0.4 mmol) in 1-2 mL of solvent. The reaction was stirred at the same temperature for 10 min before 5 mL of a saturated NH_4Cl solution and 15 mL of Et_2O or CH_2Cl_2 were added. The organic layer was separated and the aqueous layer was extracted with two 10 mL portions of Et_2O or CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). Concentration of the organic phase by rotary evaporation afforded the crude product which was purified by flash chromatography using the specified solvent system.

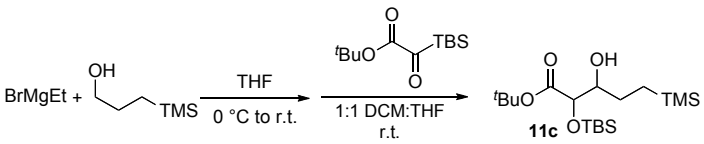


***tert*-Butyl-2-*tert*-butyldimethylsilyloxy-3-hydroxy-4-methylbutanoate (11a).** The title compound was prepared according to General Procedure **B** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in 1:1 (v/v) THF/CH_2Cl_2 (1 mL), 46 mg (0.60 mmol) of isobutanol in 1:1 (v/v) THF/CH_2Cl_2 (1 mL), and 0.7 mL (0.7 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography with 15:1 hexanes/EtOAc to afford 123 mg (95%) of the product as a clear oil (10:1 ratio of two diastereomers). Analytical data for title compound: **IR** (thin film, cm^{-1}) 3502 (br), 2962, 2936, 2859, 1750, 1473, 1392, 1368, 1289, 1253, 1144, 1005, 940, 877, 840, 778; **^{1}H NMR** (300 MHz, $CDCl_3$) (major diastereomer) δ 4.11 (d, *J* = 5.1 Hz, 1H), 3.46 (dd, *J* = 6.0, 5.1 Hz, 1H), 2.37 (br s, 1H), 1.81 (sep, *J* = 6.6 Hz, 1H), 1.46 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.082 (s, 3H), 0.051 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) (major diastereomer) δ 171.0, 81.6, 78.7, 74.1, 29.5, 28.0, 25.7, 19.6, 18.2, 17.5, -4.7, -5.4; TLC (10:1 hexanes/EtOAc)

R_f of major diastereomer 0.25, R_f of minor diastereomer 0.30; **Anal.** Calcd. for $C_{16}H_{34}O_4Si$: C, 60.33; H, 10.76. Found: C, 60.31; H, 10.78.



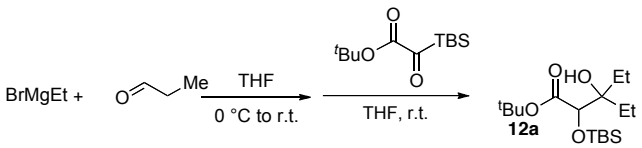
***tert*-Butyl-2-*tert*-butyldimethylsilyloxy-3-hydroxyoctanoate (11b).** The title compound was prepared according to General Procedure **B** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in 1:1 (v/v) THF/CH_2Cl_2 (1 mL), 63 mg (0.61 mmol) of hexanol in 1:1 (v/v) THF/CH_2Cl_2 (1 mL), and 0.7 mL (0.7 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography with 17:1 hexanes/EtOAc to afford 126 mg (89%) of the product as a clear oil (7.5:1 ratio of two diastereomers). Analytical data for title compound: **IR** (thin film, cm^{-1}) 3476 (br), 2955, 2930, 2858, 1750, 1472, 1368, 1254, 1145, 874, 838, 780; **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.03 (d, J = 4.4 Hz, 1H), 3.74 (br m, 1H), 2.25 (br s, 1H), 1.46 (s, 9H), 1.48-1.40 (underneath the peak of 1.46, 2H) 1.36-1.33 (m, 6H), 0.89 (s, 9H), 0.87 (t, J = 6.8 Hz, 3H), 0.085 (s, 3H), 0.048 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) (major diastereomer) δ 170.8, 81.5, 75.7, 73.5, 31.9, 31.7, 28.0, 25.7, 25.3, 22.5, 18.2, 14.0, -4.7, -5.4; TLC (15:1 hexanes/EtOAc) R_f 0.25; **Anal.** Calcd. for $C_{18}H_{38}O_4Si$: C, 62.38; H, 11.05. Found: C, 62.75; H, 10.93.



***tert*-Butyl-2-*tert*-butyldimethylsilyloxy-3-hydroxy-5-trimethylsilylpentanoate (11c).** The title compound was prepared according to General Procedure **B** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in 1:1 (v/v) THF/CH_2Cl_2 (1 mL), 81 mg (0.61 mmol) of 3-trimethylsilylpropanol in 1:1 (v/v) THF/CH_2Cl_2 (1 mL), and 0.7 mL (0.7 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography

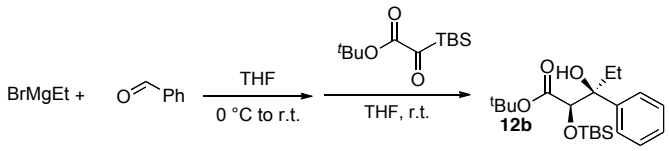
with 17:1 hexanes/EtOAc to afford 130 mg (84%) of the product as a clear oil (5:1 ratio of two diastereomers). Analytical data for title compound: **IR** (thin film, cm^{-1}) 3495 (br), 2952, 2930, 2859, 1748, 1724, 1472, 1368, 1250, 1146, 862, 838, 779; **^{1}H NMR** (300 MHz, $CDCl_3$) (major diastereomer) δ 4.04 (d, *J* = 4.5 Hz, 1H), 3.66 (quint, *J* = 4.5 Hz, 1H), 2.33 (br s, 1H), 1.45 (s, 9H), 0.90 (s, 9H), 0.75-0.63 (m, 2H), 0.50-0.38 (m, 2H), 0.085 (s, 3H), 0.050 (s, 3H), -0.035 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) (major diastereomer) δ 170.9, 81.5, 76.0, 75.4, 28.0, 26.4, 25.7, 18.2, 12.1, -1.86, -4.7, -5.4; TLC (15:1 hexanes/EtOAc) R_f 0.25; **Anal.** Calcd. for $C_{18}H_{40}O_4Si_2$: C, 57.39; H, 10.70. Found: C, 57.71; H, 10.51.

General procedure (E) for reactions in Table 1-4. A dry round bottomed flask with a magnetic stir bar was charged with aldehyde (1.5 equiv), and 2 mL of THF. To the resulting solution, alkylmagnesium bromide (1.0 M in THF) (2.0 equiv) was added *via* syringe at 0 °C under an argon atmosphere. The reaction temperature was allowed to warm to 25 °C for 5 min. To the reaction solution was added dropwise *via* cannula silylglyoxylate (1.0 equiv, ca. 0.4 mmol) in 2 mL of THF. The reaction was stirred at the same temperature for 10 min before 5 mL of a saturated NH_4Cl solution and 15 mL of Et_2O were added. The organic layer was separated and the aqueous layer was extracted with two 10 mL portions of Et_2O. The organic extracts were combined and dried (Na_2SO_4). Concentration of the organic phase by rotary evaporation afforded the crude product which was purified by flash chromatography using the specified solvent system.

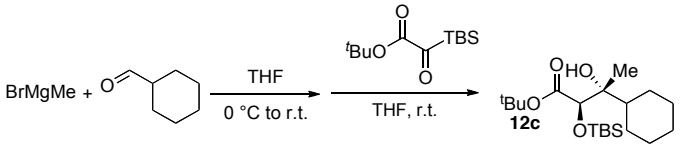


***Tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-ethyl-3-hydroxypentanoate (12a).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 36 mg (0.61 mmol) of propanal in THF (2

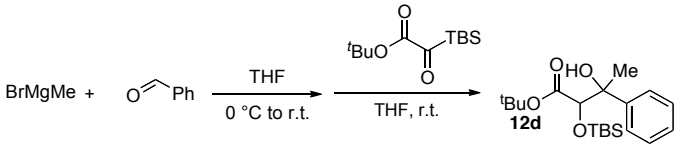
mL), and 0.82 mL (0.82 mmol) of EtMgBr (1 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 93 mg (68%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3567 (br), 2961, 2936, 2887, 2860, 1746, 1472, 1393, 1369, 1253, 1159, 1131, 876, 839, 780; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.98 (s, 1H), 2.68 (s, 1H), 1.4-1.6 (m, 4H), 1.47 (s, 9H), 0.86-0.91 (m, 6H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.0, 81.7, 76.2, 75.8, 28.0, 27.2, 26.8, 25.7, 18.1, 7.7, 7.6, -4.7, -5.4; TLC (20:1 hexanes/EtOAc) R_f 0.26; **Anal.** Calcd. for $C_{17}H_{36}O_4Si$: C, 61.40; H, 10.91. Found: C, 61.05; H, 10.90.



***Tert*-butyl-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-phenylpentanoate (12b).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 65 mg (0.61 mmol) of benzaldehyde in THF (2 mL), and 0.82 mL (0.82 mmol) of EtMgBr (1 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 127 mg (81%) of the product as a clear oil (2:1 ratio of two diastereomers). Analytical data for title compound: **IR** (thin film, cm^{-1}) 3463 (br), 2961, 2932, 2857, 1741, 1694, 1368, 1255, 1137, 876, 839, 780; **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.17-7.46 (m, 5H), 4.17 (s, 1H), 3.73 (d, J = 1.2 Hz, 1 H), 1.98 (sep, J = 7.2 Hz, 2H), 1.27 (s, 9H), 0.84 (s, 9H), 0.70 (t, J = 7.2 Hz, 3H), 0.08 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) (major diastereomer) δ 127.7, 126.2, 82.1, 79.3, 31.1, 27.7, 25.6, 7.5, -5.0, -5.7; TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.33.

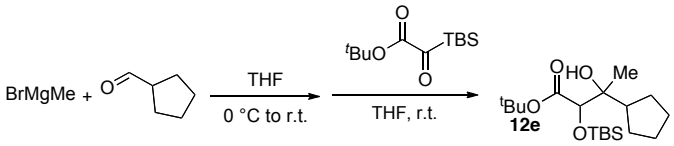


***Tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-cyclohexyl-3-hydroxybutanoate (12c).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 69 mg (0.61 mmol) of cyclohexylcarbaldehyde in THF (2 mL), and 0.82 mL (0.82 mmol) of EtMgBr (1 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 102 mg (67%) of the product as a clear oil (3.5:1 ratio of two diastereomers). Analytical data for title compound: **IR** (thin film, cm^{-1}) 3481 (br), 2928, 2857, 1745, 1723, 1472, 1368, 1257, 1144, 839, 778; **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.01 (s, 1H), 1.60-1.94 (m, 6H), 1.48 (s, 9H), 1.09 (s, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) (major diastereomer) δ 171.3, 81.7, 76.1, 44.1, 26.8, 26.7, 26.6, 25.7, 20.4, 18.1, -5.0, -5.7; TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.33; **Anal.** Calcd. for $C_{20}H_{40}O_4Si$: C, 64.47; H, 10.82. Found: C, 64.25; H, 10.89.

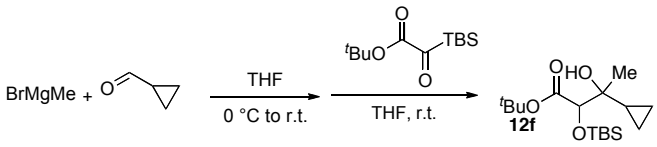


***Tert*-butyl-2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-phenylbutanoate (12d).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 65 mg (0.61 mmol) of benzaldehyde in THF (2 mL), and 0.22 mL (0.66 mmol) of MeMgBr (3 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 67 mg (45%) of the product as a clear oil (2:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.20-7.50 (m, 5H), 4.18 (s, 1H), 3.72 (s, 1 H),

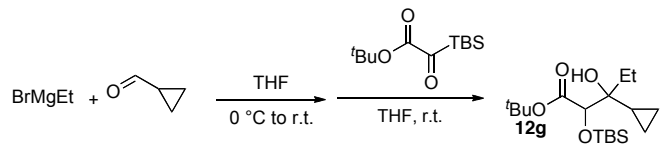
1.53 (s, 3H), 1.31 (s, 9H), 0.83 (s, 9H), -0.03 (s, 3H), -0.17 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.2.



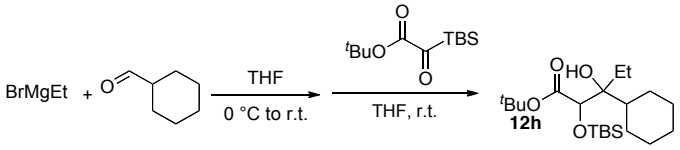
***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-cyclopentyl-3-hydroxybutanoate (12e).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 60 mg (0.61 mmol) of cyclopentanecarboxaldehyde in THF (2 mL), and 0.27 mL (0.66 mmol) of MeMgBr (3 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 52 mg (39%) of the product as a clear oil (1.6:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 3.9 (s, 1H), 2.77 (s, 1 H), 1.95 (td, J = 9.9, 4.65 Hz, 1H), 1.75-1.4 (m, 8H), 1.47 (s, 9H), 1.15 (s, 3H), 0.9 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f 0.22, 0.29.



***tert*-butyl 2-(tert-butyldimethylsilyloxy)-3-cyclopropyl-3-hydroxybutanoate (12f).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 43 mg (0.61 mmol) of cyclopropanecarboxaldehyde in THF (2 mL), and 0.27 mL (0.66 mmol) of MeMgBr (3 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 47 mg (35%) of the product as a clear oil (1.2:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 3.95 (s, 1H), 2.90 (s, 1 H), 1.48 (s, 9H), 1.15 (s, 3H), 0.92 (s, 9H), 0.4-0.28 (m, 5H), 0.07 (s, 3H), 0.05 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.33.



***tert*-butyl 2-(tert-butyldimethylsilyloxy)-3-cyclopropyl-3-hydroxypentanoate (12g).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 43 mg (0.61 mmol) of cyclopropanecarboxaldehyde in THF (2 mL), and 0.8 mL (0.8 mmol) of EtMgBr (1 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 47 mg (35%) of the product as a clear oil (2.7:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.02 (s, 1H), 2.74 (s, 1 H), 1.69-1.64 (m, 2H) 1.48 (s, 9H), 0.93 (m, 3H), 0.91 (s, 9H), 0.41-0.14 (m, 5H), 0.07 (s, 3H), 0.05 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.39.



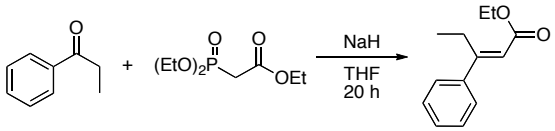
***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-cyclohexyl-3-hydroxybutanoate (12h).** The title compound was prepared according to General Procedure **E** using 100 mg (0.41 mmol) of *tert*-butyl *tert*-butyldimethylsilylglyoxylate in THF (2 mL), 69 mg (0.61 mmol) of cyclohexylcarbaldehyde in THF (2 mL), and 0.82 mL (0.82 mmol) of EtMgBr (1 M in THF). The crude product was purified by flash chromatography with 30:1-20:1 hexanes/EtOAc to afford 27 mg (15%) of the product as a clear oil (2.4:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.14 (s, 1H), 2.77 (s, 1H) 1.60-1.9 (m, 6H), 1.48 (s, 9H), 1.17 (m, 2H), 0.93-0.87 (m, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.33.

General procedure (C) for Horner-Wadsworth-Emmons reactions (step 1 of stereochemical proof for Table 3). A dry round bottomed flask with a magnetic stir bar was charged phosphonoacetate ester (1.0 equiv), and 5 mL of THF. To the resulting solution, sodium hydride (1.1 equiv) was added in one portion. The solution was stirred at room temperature for 30 minutes. To the reaction solution was added dropwise *via* cannula the ketone (1.0 equiv.) in 5 mL of THF. The resulting solution was stirred for 20 h. The product was then extracted from an aq. sat. $NaHCO_3$ solution with 15 mL of ether. The organic layer was separated and the aqueous layer was extracted with two 10 mL portions of Et_2O. The organic extracts were combined and dried ($MgSO_4$). Concentration of the organic phase by rotary evaporation afforded the crude product, which was purified by flash chromatography using the specified solvent system.

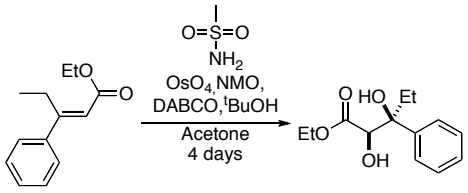
General procedure (D) for lithium aluminum hydride reductions. A dry round bottomed flask with a magnetic stir bar was charged lithium aluminum hydride (5.0 equiv), and 5 mL of THF at 0 ºC. To the resulting solution the ester was added dropwise (1.0 equiv) in 5 mL of THF. The solution was warmed to room temperature and stirred for 1.5 hours. To the solution was added X μL of H_2O where X is equivalent to the number of mg of lithium aluminum hydride used in the reaction. This was followed by the addition of X μL 15% NaOH solution and then 5X μL of additional H_2O. The solid precipitates were filtered. Concentration of the organic phase by rotary evaporation afforded the crude product, which was purified by flash chromatography using the specified solvent system.

General procedure (E) for dihydroxylations. A dry round bottomed flask with a magnetic stir bar was charged with alkene (1.0 equiv), DABCO (0.3 equiv), 4-methylmorpholine N-oxide (2 equiv), methanesulfonamide (1 equiv) and acetone (20 ml). The solution was cooled to 0 °C and potassium osmate dihydrate (0.15 equiv in 1 mL H_2O) was added dropwise followed by addition of t-BuOH (1.5 mL). The reaction was allowed to stir for 4 days and progress was monitored by

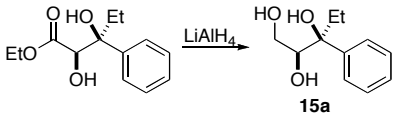
TLC. When all starting material was consumed the homogenous solution was stirred with Na_2SO_3 for 2 hours. The solution was then extracted with three 20 mL portions of CH_2Cl_2. Concentration of the organic phase by rotary evaporation afforded the crude product which was purified by flash chromatography using the specified solvent system.



(*E*)-ethyl 3-phenylpent-2-enoate. The title compound was prepared according to General Procedure **F** using 1 g (7.5 mmol) of propiophenone, 1.69 g (7.5 mmol) of triethylphosphonoacetate, 199 mg NaH (8.3 mmol) and 10 mL of THF. The crude product was purified by flash chromatography with 20:1 hexanes/ether to afford 346 mg (24%) of the product as a clear oil. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.44 (m, 5H), 6.0 (s, 1H), 4.2 (q, J = 7.2 Hz, 2H), 3.09 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H); TLC (20:1 hexanes/ether) R_f (E) 0.29; the ^{1}H NMR spectrum matched that reported previously.[39]



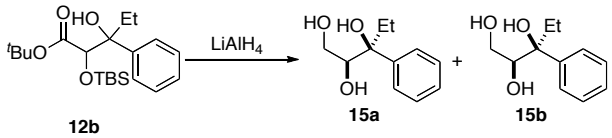
Ethyl 2,3-dihydroxy-3-phenylpentanoate. The title compound was prepared according to General Procedure **H** using 100 mg (0.53 mmol) of alkene, 29 mg (0.08 mmol) of potassium osmate dihydrate, 18 mg (0.15 mmol) of DABCO, 123 mg (1.05 mmol) of NMO, 50 mg (0.53 mmol) of methanesulfonamide, 1.5 mL ^{t}BuOH and 20 mL of acetone. The crude product was purified by flash chromatography with 5:1 hexanes/ether to afford 100 mg (80%) of the product as a clear oil. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20-7.46 (m, 5H), 4.35 (s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 1.99 (dq, J = 7.2 Hz, 1H), 1.93 (dq, J = 7.2 Hz, 1H) 1.14 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H).



15a

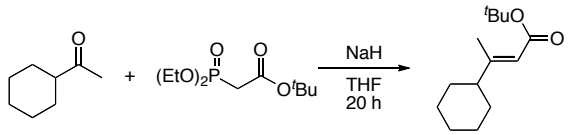
3-phenylpentane-1,2,3-triol (15a). The title compound was prepared according to General Procedure **G** using 100 mg (0.26 mmol) of diol, 50 mg (1.3 mmol) of lithium aluminum hydride, and 1.5 mL of THF. The crude product was purified by flash chromatography with ethyl acetate to afford 35 mg (56%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3410 (br), 2969, 2939, 2881, 1647, 1600, 1447, 1071, 1026, 702; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.2-7.40 (m, 5H), 3.77-3.85 (m, 3H), 3.12 (s, 1H), 2.62-2.68 (m, 2H), 1.83 (q, J = 9.6 Hz, 2H), 0.67 (t, J = 9.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.1, 128.67, 128.54, 128.48, 126.1, 125.9, 79.4, 63.1, 30.5, 7.8; TLC (ethyl acetate) R_f 0.37; CSP-SFC analysis: Chiralpak AS, 0-10% MeOH (ramp 0.5%/min), 1.5 mL/min, 150 bar, 40 °C, 240 nm, t_r 19.8, 20.3 min; **Anal.** Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.03; H, 8.24.

This material was compared (using SFC analysis) to the mixture of **20a/20b** prepared from reduction of **12b**.



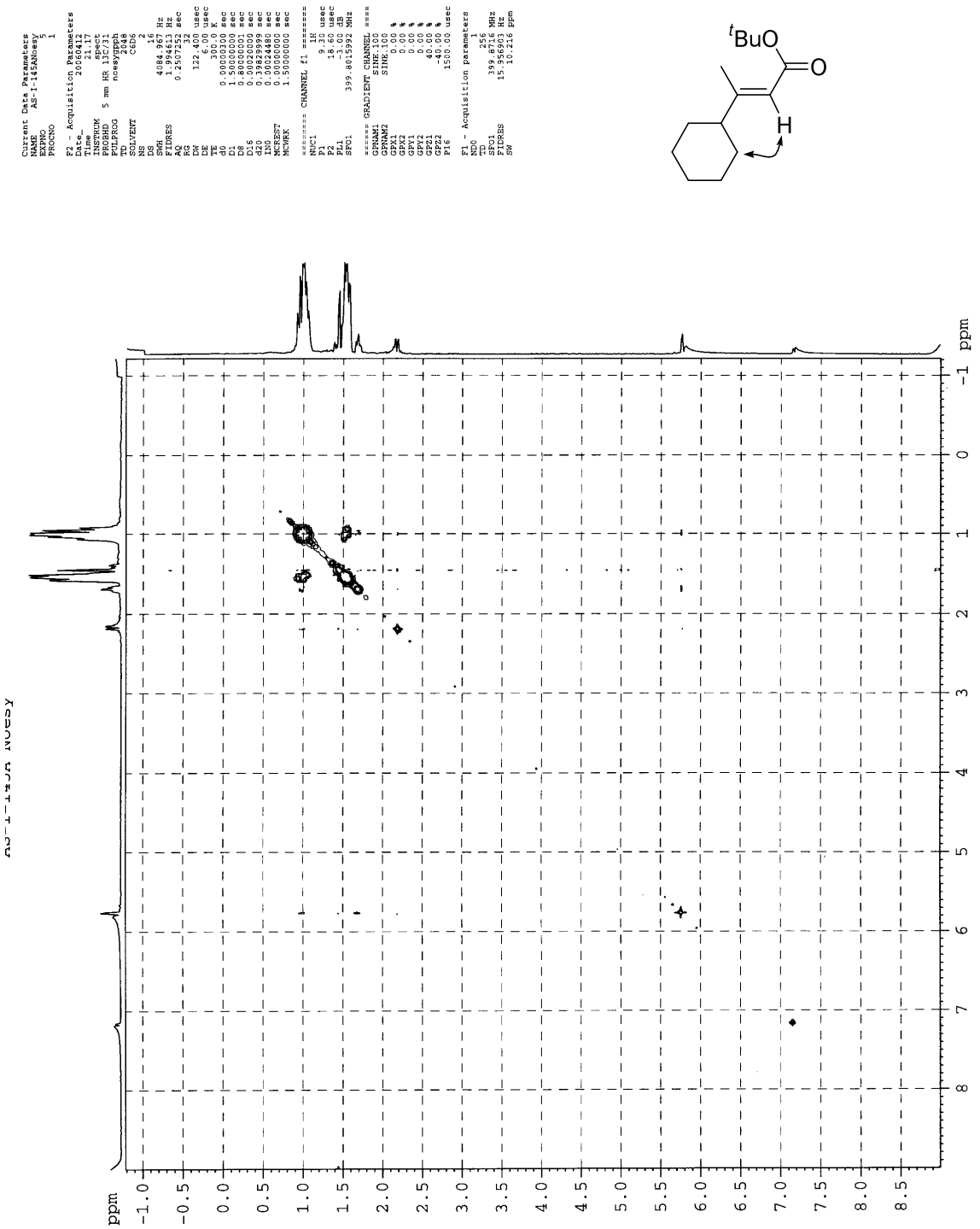
12b 15a 15b

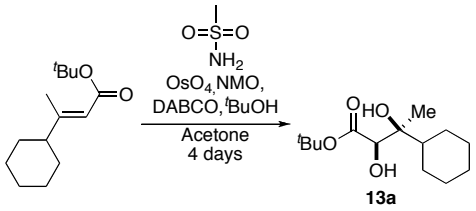
3-phenylpentane-1,2,3-triol (15a/b). The title compound was prepared according to General Procedure **G** using 115 mg (0.30 mmol) of **12b**, 57 mg (1.5 mmol) of lithium aluminum hydride, and 1.5 mL of THF. The crude product was purified by flash chromatography with ethyl acetate to afford 45 mg (63%) of the product as a clear oil. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.2-7.40 (m, 5H), 3.77-3.85 (m, 3H), 3.12 (s, 1H), 2.62-2.68 (m, 2H), 1.83 (q, J = 9.6 Hz, 2H), 0.67 (t, J = 9.6 Hz, 3H); TLC (ethyl acetate) R_f 0.37; CSP-SFC analysis: Chiralpak AS, 0-10% MeOH. (ramp 0.5%/min), 1.5 mL/min, 150 bar, 40 °C, 240 nm, t_r(major) 20.0, 20.6 min, t_r(minor) 17.6, 19.1 min; **Anal.** See above.



(*E*)-*tert*-Butyl 3-cyclohexylbut-2-enoate. The title compound was prepared according to General Procedure **F** using 0.67 g (5.3 mmol) of ketone, 1.34 g (5.3 mmol) of *tert*-Butyl diethyl phosphonoacetate, 146 mg of NaH (6.1 mmol) and 10 mL of THF. The crude product was purified by flash chromatography with 99:1-20:1 hexanes/ether to afford 760 mg (64%) of the product *E* isomer, as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3500 (br), 2977, 2928, 2854, 1720, 1642, 1450, 1366, 1237, 1142; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54 (s, 1H), 2.07 (s, 3H), 1.64-1.94 (m, 6H), 1.45 (s, 9H), 1.1-1.29 (m, 5H), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9, 163.1, 115.7, 79.3, 49.0, 31.3, 30.8, 28.3, 26.5, 26.4, 17.1; TLC (20:1 hexanes/ether) R_f (E) 0.30. For the NOESY spectrum, see below.

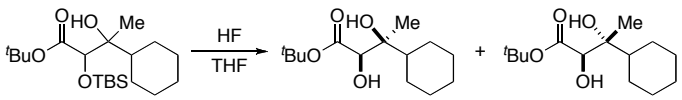
Fig 1-1 NOESY in $CDCl_3$ of (*E*)-*tert*-butyl 3-cyclohexylbut-2-enoate





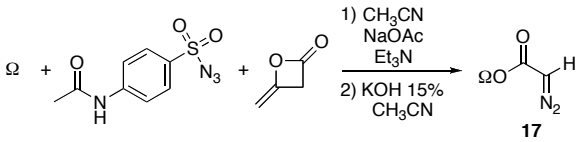
13a

***tert*-butyl 3-cyclohexyl-2,3-dihydroxybutanoate (13a).** The title compound was prepared according to General Procedure **H** using 200 mg (0.89 mmol) of alkene, 49 mg (0.13 mmol) of potassium osmate dihydrate, 30 mg (0.15 mmol) of DABCO, 209 mg (1.05 mmol) of NMO, 84 mg (0.53 mmol) of methanesulfonamide, 2.6 mL ^{t}BuOH and 34 mL of acetone. The crude product was purified by flash chromatography with 5:1 hexanes/ether to afford 147 mg (64%) of the product as a clear oil. Analytical data for title compound: **IR** (thin film, cm^{-1}) 3378 (br), 2974, 2919, 2851, 1729, 1367, 1151; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.04 (d, *J* = 6.8 Hz, 1H), 3.09 (d, *J* = 6.8 Hz, 1H), 2.23 (s, 1H), 1.62-1.88 (m, 6H) 1.50 (s, 9H), 1.13-1.24 (m, 5H), 1.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 74.17, 44.0, 28.06, 27.8, 26.7, 26.6, 26.5, 26.2, 19.3; TLC (10:1 hexanes:EtOAc) R_f 0.2.



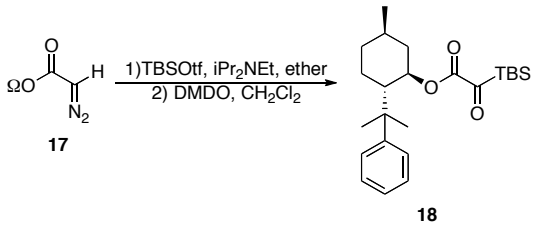
12c **13a** **13b**

***Tert*-butyl 3-cyclohexyl-2,3-dihydroxybutanoate (13a/b).** The title compound was prepared by adding 22 mg (0.06 mmol) of **12c**, 2 mL HF (49% aq.) and 2 mL of THF to a round bottom flask. The solution was stirred overnight and the crude product was isolated as a clear oil. Upon comparison of the ^{1}H NMR spectrum with the spectrum of **13a** derived from dihydroxylation of the (*E*)-alkene, it was determined that the major isomer had the *anti* orientation. ^{1}H NMR data for **13b** (400 MHz, $CDCl_3$) (major diastereomer) δ 3.99 (d, *J* = 6.4 Hz, 1H), 3.07 (m, 1H), 2.23 (s, 1H), 1.62-1.88 (m, 6H) 1.51 (s, 9H), 1.13-1.24 (m, 5H), 1.11(s, 3H); TLC (10:1 hexanes:EtOAc) R_f 0.2.



17

(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-diazoacetate (17). The title compound was prepared by adding 9.92 g (41 mmol) of 4-acetamidobenzenesulfonyl azide, 0.633 g (7.5 mmol) of NaOAc, 6 g (26 mmol) of Ω and 21 mL of CH_3CN to a round bottom flask. The solution was brought to reflux. To the flask 4.34 g (52 mmol) of diketene (distilled from stabilizer prior to use) was added dropwise via syringe in 5 mL of CH_3CN. After addition the reaction was removed from heat and allowed to stir overnight. By TLC reaction was not complete so 3.13 g (31 mmol) of Et_3N and 1.24 g (5 mmol) of 4-acetamidobenzenesulfonyl azide were added. After stirring for an additional 6 h reaction was complete. The solution was diluted with Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The organic layer was then washed with saturated aqueous NH_4Cl (40 mL), washed with brine, dried over $MgSO_4$ and concentrated in vacuo to reveal a yellow oil. The crude material was taken up in CH_3CN (50 mL) and stirred with a 15% aqueous KOH solution (50 mL) overnight. The solution was diluted with Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The organic layer was then washed with saturated aqueous NH_4Cl (40 mL), brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo to yield 6 g (77%) of the product as a pale yellow oil. Crude product was not purified. Analytical data for title compound: ^{1}H NMR data for **21b** (400 MHz, $CDCl_3$) δ 7.28-7.10 (m, 5 H), 4.87 (td, J = 10.73, 4.24 Hz, 1H), 4.2 (s, 1H), 1.98 (ddd, J = 12.25, 6.63, 3.45 Hz, 1H), 1.9 (m, 1H), 1.65 (m, 2H), 1.49-0.85 (m, 4H) 1.3 (s, 3H), 1.21 (s, 3H), 0.85 (d, J = 6.51 Hz, 3H); TLC (10:1 hexanes:EtOAc) R_f 0.3.

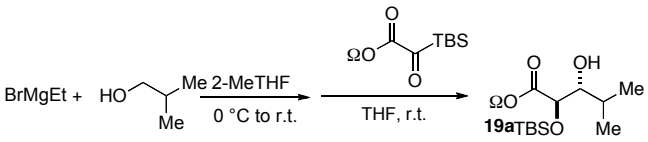


17 18

8-phenylmenthol silyl glyoxylate (18). The title compound was prepared by adding 6 g (20 mmol) of **X** and 75 mL of Et_2O to a round bottom flask under an atmosphere of Ar. To the solution was added 2.85 g (34 mmol) of diisopropylethyl amine. The solution was stirred and cooled to -10 ˚C and 8.15 g (34 mmol) of *tert*-butylsimethylsilyl trifluromethanesulfonate was added slowly via syringe. After addition the solution was allowed to warm slowly to 23 ˚C and stirred for 12 h. When reaction was complete by TLC the solution was filtered to remove salts and concentrated in vacuo. A 1 L, three-necked, round-bottomed flask was fitted with an overhead mechanical stirrer (fitted with a 6.0 x 2.0 cm Teflon paddle) and a thermometer. The flask was charged with sodium bicarbonate (6.7 g, 80 mmol), deionized water (250 mL) and acetone (200 mL) through the open neck. The mixture was mechanically stirred (600 rpm) and cooled to 0 °C in an ice-bath. Oxone® (24.56 g, 40 mmol) was added in several portions. A solution of the crude material from step 1 in dichloromethane (30 mL) was added to the reaction mixture all at once. The resulting yellow mixture was stirred and slowly allowed to warm to 23 °C over 12 h. The progress of the reaction was monitored by TLC until no starting material was present. The insoluble salts were removed by filtration through Celite and the pad was washed with two 25-mL portions of dichloromethane. Deionized water (150 mL) was added to the filtrate and the organic layer was separated and the aqueous phase was extracted with two 50-mL portions of dichloromethane. The combined organic extracts were dried with Na2SO4 (ca. 50 g) for 10 min, then were filtered through a funnel packed with glass wool, and concentrated by rotary evaporation (30 °C bath temperature, 70 torr). The crude product was purified by flash column chromatography with 20:1 petroleum ether/acetone, to yield 3.4 g (43 % for two steps) of

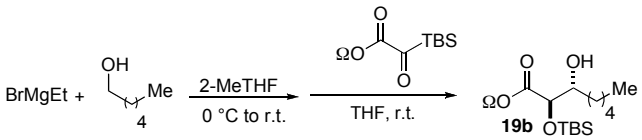
product as a yellow oil. Analytical data for title compound: ^{1}H NMR data for **18** (400 MHz, $CDCl_3$) δ 7.20-7.06 (m, 5 H), 4.86 (td, *J* = 10.76, 4.45 Hz, 1H), 1.98 (ddd, *J* = 12.10, 10.79, 3.31 Hz, 1H), 1.91-0.74 (m, 7H) 1.29 (s, 3H), 1.23 (s, 3H), 0.90 (s, 9H), 0.86 (d, *J* = 6.56 Hz, 3H), 0.23 (s, 3H), 0.20 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 128.0, 125.5, 125.3, 76.5, 50.5, 41.5, 40.0, 34.4, 31.4, 26.9, 26.4, 26.2, 21.7, 16.9, 14.1, 6.7; TLC (20:1 Hexanes:Acetone) R_f 0.35.

General procedure (F) for asymmetric tandem Oppenauer oxidation/Brook rearrangement/aldolization (Table 1-5). A dry round bottomed flask with a magnetic stir bar was charged with alcohol (1.5 equiv), and 1-2 mL of solvent. To the resulting solution, ethylmagnesium bromide (1.0 M in 2-MeTHF) (1.75-2.0 equiv) was added *via* syringe at 0 °C under an argon atmosphere. The reaction temperature was allowed to warm to 25 °C for 5 min. To the reaction solution was added dropwise *via* cannula the silylglyoxylate (1.0 equiv, ca. 0.4 mmol) in 1-2 mL of solvent. The reaction was stirred at the same temperature for 10 min before 5 mL of a saturated NH_4Cl solution and 15 mL of Et_2O or CH_2Cl_2 were added. The organic layer was separated and the aqueous layer was extracted with two 10 mL portions of Et_2O or CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). Concentration of the organic phase by rotary evaporation afforded the crude product which was purified by flash chromatography using the specified solvent system.

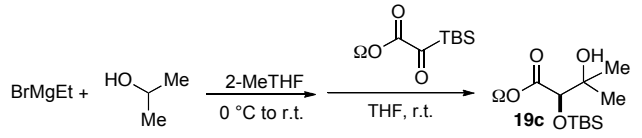


(2*R*,3*R*)-((1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-4-methylpentanoate (19a). The title compound was prepared according to General Procedure **B** using 100 mg (0.2 mmol) of **X** in 2-MeTHF (2 mL), 22 mg (0.30 mmol) of isobutanol in 2-MeTHF (2 mL), and 0.4 mL (0.4 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography

with 20:1 hexanes/EtOAc to afford 51 mg (51%) of the product as a clear oil (1.9:Σ others ratio of four diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.28-7.13 (m, 5 H), 4.80 (td, *J* = 10.68, 4.01 Hz, 1H), 3.66 (d, *J* = 4.36 Hz, 1H), 3.18 (q, *J* = 5.10 Hz, 1H), 2.04 (d, *J* = 5.49 Hz, 1H), 2.13-0.79 (m, 8H) 1.30 (s, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.85 (t, *J* = 6.99 Hz, 6H), 0.80 (d, *J* = 6.79 Hz, 3H), 0.11 (s, 3H), 0.05 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f of mixture diastereomers 0.32.



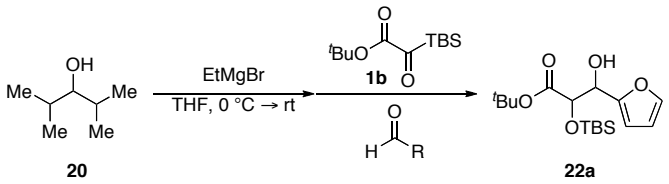
(2*R*,3*R*)-((1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 2-(*tert*-butyldimethylsilyloxy)-3-hydroxyoctanoate (19b). The title compound was prepared according to General Procedure **B** using 100 mg (0.2 mmol) of **X** in 2-MeTHF (2 mL), 30 mg (0.30 mmol) of hexanol in 2-MeTHF (2 mL), and 0.4 mL (0.4 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography with 20:1 hexanes/EtOAc to afford 67 mg (54%) of the product as a clear oil (1.7:Σ others ratio of four diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.28-7.14 (m, 5 H), 4.76 (td, *J* = 10.77, 4.10 Hz, 1H), 3.56 (d, *J* = 3.71 Hz, 1H), 3.43-3.37 (m, 1H), 2.04 (td, *J* = 11.33, 2.64 Hz, 1H), 2.05-0.79 (m, 15H) 1.81, (d, *J* = 7.35 Hz, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 0.90 (s, 9H), 0.88-0.83 (m, 6H), 0.11 (s, 3H), 0.05 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f of mixture diastereomers 0.30.



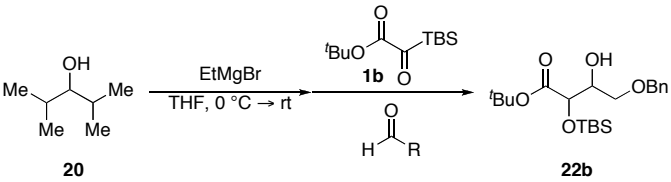
(*R*)-((1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl) 2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-methylbutanoate (19c). The title compound was prepared according to General Procedure **B** using 100 mg (0.2 mmol) of **X** in 2-MeTHF (2 mL), 18 mg (0.30 mmol) of

isopropanol in 2-MeTHF (2 mL), and 0.4 mL (0.4 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography with 20:1 hexanes/EtOAc to afford 72 mg (63%) of the product as a clear oil (19:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.28-7.12 (m, 5 H), 4.76 (td, *J* = 10.75, 4.06 Hz, 1H), 3.29 (s, 1H), 2.58 (s, 1H), 2.14-0.84 (m, 11H) 1.30 (s, 3H), 1.18 (s, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) d 170.8, 151.9, 128, 125.2, 78.17, 76.3872.02, 50.33, 41.25, 39.62, 34.6, 31.37, 27.72, 26.77, 26.68, 25.95, 25.77, 25.39, 25.15, 21.72, 18.26, -4.42, -5.19; TLC (10:1 hexanes/EtOAc) R_f of mixture diastereomers 0.22.

General procedure (G) for crossover tandem Oppenauer oxidation/Brook rearrangement/aldolization (Table 1-6). A dry round bottomed flask with a magnetic stir bar was charged with 2,4-dimethylpentan-3-ol **20** (1.4 equiv), and 1-2 mL of THF. To the resulting solution, ethylmagnesium bromide (1.0 M in 2-MeTHF) (1.5 equiv) was added *via* syringe at 0 °C under an argon atmosphere. The reaction temperature was allowed to warm to 25 °C for 5 min. To the reaction solution was added dropwise *via* cannula the silylglyoxylate (1.0 equiv, ca. 0.4 mmol) and the aldehyde (1 equiv) in 1-2 mL of THF. The reaction was stirred at the same temperature for 1 h before 5 mL of a saturated NH_4Cl solution and 15 mL of Et_2O or CH_2Cl_2 were added. The organic layer was separated and the aqueous layer was extracted with two 10 mL portions of Et_2O or CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). Concentration of the organic phase by rotary evaporation afforded the crude product which was purified by flash chromatography using the specified solvent system.

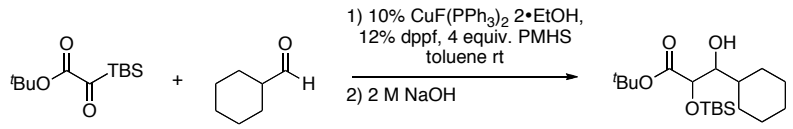


***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-(furan-2-yl)-3-hydroxypropanoate(22a).** The title compound was prepared according to General Procedure **G** using 67 mg (0.57 mmol) of **20** in THF (2 mL), 100 mg (0.4 mmol) of **1b** and 36 mg (0.4 mmol) of furfural in THF (2 mL), and 0.61 mL (0.6 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography with 20:1 hexanes/EtOAc to afford 89 mg (64%) of the product as a clear oil (1 diastereomer isolated). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.34 (t, *J* = 0.83 Hz, 1 H), 6.3 (m, 2H), 4.93 (dd, *J* = 8.37, 3.27 Hz, 1H), 4.38 (dd, *J* = 3.5, 0.24 Hz, 1H), 2.96 (d, *J* = 8.78 Hz, 1H), 1.43 (s, 9H), 0.82 (s, 9H), 0.02 (s, 3H), -0.06 (s, 3H); TLC (10:1 hexanes/EtOAc) R_f of mixture diastereomers 0.22.



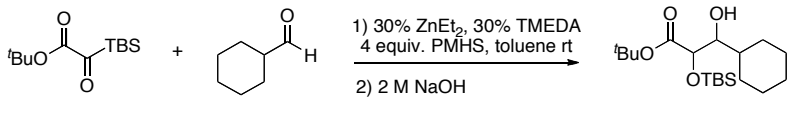
***tert*-butyl 4-(benzyloxy)-2-(*tert*-butyldimethylsilyloxy)-3-hydroxybutanoate (22b).** The title compound was prepared according to General Procedure **G** using 67 mg (0.57 mmol) of **20** in THF (2 mL), 100 mg (0.4 mmol) of **1b** and 62 mg (0.4 mmol) of α-benzloxy acetaldehyde in THF (2 mL), and 0.61 mL (0.6 mmol) of EtMgBr (1 M in THF). The crude product was extracted with CH_2Cl_2 and purified by flash chromatography with 20:1 hexanes/EtOAc to afford 54 mg (33%) of the product as a clear oil (1 diastereomer isolated). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 7.35-7.27 (m, 5 H), 4.55 (d, *J* = 6.14 Hz, 2H), 4.16 (d, *J* = 5.67 Hz, 1H), 4.00 (m, 1H), 3.59 (d, *J* = 4.92 Hz, 2H), 2.5 (d, *J* = 5.84 Hz, 1H),

1.50 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); TLC (10:1 hexanes/EtOAc) R_f of mixture diastereomers 0.15.



1b **26**

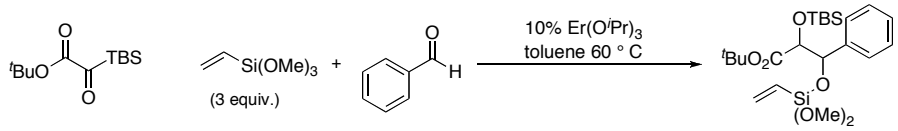
***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-cyclohexyl-3-hydroxypropanoate** (**26**). The title compound was prepared according to following procedure in an inert atmosphere glove box: A flame dried scintillation vial was charged with 38 mg (0.04 mmol) of $CuF(PPh_3)_2$ 2 • EtOH complex[34], 27 mg (0.05 mmol) of diphenylphosphinoferrocene(dppf) and 2 mL of toluene. Solution was stirred for 20 minutes, 107 mg (1 mmol) of PMHS was added and solution was stirred another 20 minutes. A solution of 46 mg (0.4 mmol) of cyclohexylcarboxaldehyde and 100 mg (0.4 mmol) of silyl glyoxylate **1b** in 2 mL of toluene was then added dropwise. Solution was stirred for 16 h and then poured over 2.5 M aqueous NaOH (3 mL) and stirred for 4 h. The aqueous layer was extracted with Et_2O (2 x 5mL). The organic layer was washed with brine (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography with 20:1 hexanes/EtOAc to afford 77 mg (53%) of the product as a clear oil (1.6:1 diastereomer ratio). Analytical data for title compound: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.16 (d, J = 2.6 Hz, 1H), 3.49 – 3.34 (m, 1H), 2.08 (d, J = 9.4 Hz, 1H), 2.01 (d, J = 12.7 Hz, 1H), 1.82 – 1.53 (m, 3H), 1.45 (s, 9H), 1.39 – 0.94 (m, 5H), 0.90 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); TLC (10:1 hexanes/EtOAc) R_f of mixture diastereomers 0.15.



1b **26**

***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-cyclohexyl-3-hydroxypropanoate**(X). The title compound was prepared according to following procedure under an inert atmosphere of Ar: A

flame dried scintillation vial was charged with 0.5 mL of toluene, 54 µL (0.1 mmol) of $ZnEt_2$ (1 M in hexanes) and 14 mg (0.1 mmol) of tetramethylethylenediamine. The solution was stirred for 15 min, 107 mg (1 mmol) of PMHS was added and the solution was stirred another 20 minutes. A solution of 50 mg (0.45 mmol) of cyclohexylcarboxaldehyde and 100 mg (0.4 mmol) of silyl glyoxylate **X** in 1 mL of toluene was then added dropwise. Solution was stirred for 30 min and then poured over 2.5 M aqueous NaOH (3 mL) and stirred for 4 h. The aqueous layer was extracted with Et_2O (2 x 5mL). The organic layer was washed with brine (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography with 20:1 hexanes/EtOAc to afford 121 mg (83%) of the product as a clear oil (1:1 diastereomer ratio). Analytical data for title compound: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.16 (d, *J* = 2.6 Hz, 1H), 3.49 – 3.34 (m, 1H), 2.08 (d, *J* = 9.4 Hz, 1H), 2.01 (d, *J* = 12.7 Hz, 1H), 1.82 – 1.53 (m, 3H), 1.45 (s, 9H), 1.39 – 0.94 (m, 5H), 0.90 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); TLC (10:1 hexanes/EtOAc) R_f of mixture diastereomers 0.15.

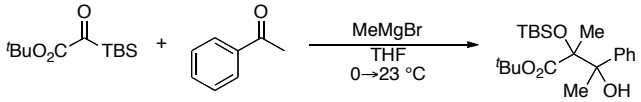


1b **27**

tert-butyl 2-(tert-butyldimethylsilyloxy)-3-(dimethoxy(vinyl)silyloxy)-3-phenylpropanoate (**27**). The title compound was prepared according to following procedure under an inert atmosphere of Ar: A flame dried scintillation vial was charged with 2 mL of toluene, 161 mg (1.2 mmol) of trimethoxyvinyl silane and 14 mg (0.04 mmol) of Erbium triisopropoxide. The solution was stirred for 15 min and a solution of 61 mg (0.45 mmol) of benzaldehyde and 100 mg (0.4 mmol) of silyl glyoxylate **1b** in 2 mL of toluene was then added dropwise. The solution was heated to 60 ˚C and stirred for 3 days. After consumption of starting material was verified by TLC the reaction was concentrated in vacuo. The crude product was purified by flash chromatography with 10:1 hexanes/EtOAc to afford 40 mg (21%) of the product as a clear oil (1.25:1 diastereomer ratio). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ

7.43 – 7.17 (m, 5H), 6.03 (t, *J* = 4.2 Hz, 1H), 5.92 – 5.88 (m, 1H), 5.79 – 5.73 (m, 1H), 4.99 (d, *J* = 7.1 Hz, 1H), 4.08 (d, *J* = 7.2 Hz, 1H), 3.37 (s, 3H), 1.44 (s, 9H), 0.72 (s, 9H), -0.14 (s, 3H), -0.35 (s, 3H).; TLC (20:1 hexanes/EtOAc) R_f of mixture diastereomers 0.30.

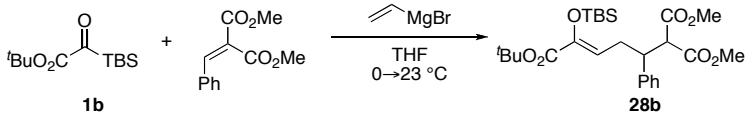
General procedure (H) for multicomponent Grignard initiated multicomponent coupling of silyl glyoxylate and electrophiles (Table 1-7). A dry round bottomed flask with a magnetic stir bar was purged with Ar and charged with silylglyoxylate (1.0 equiv, ca. 0.4 mmol) and the electrophile (1 equiv) in 2 mL of THF. The solution was stirred and Grignard reagent (1.5 equiv) was then added *via* syringe under an argon atmosphere. The solution was stirred until consumption of all starting material by TLC. The reaction was quenched with 3 mL of a saturated NH_4Cl solution and 5 mL of Et_2O were added. The organic layer was separated and the aqueous layer was extracted with two 5 mL portions of Et_2O. The organic extracts were combined and dried (Na_2SO_4). Concentration of the organic phase by rotary evaporation afforded the crude product which was purified by flash chromatography using the specified solvent system.



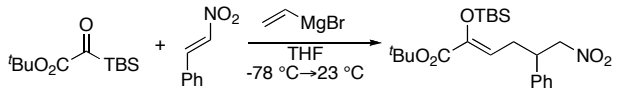
1b **28a**

***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-3-hydroxy-2-methyl-3-phenylbutanoate (28a).** The title compound was prepared according to General Procedure **H** using 100 mg (0.41 mmol) of silyl glyoxylate **1b** and 49 mg (0.4 mmol) of acetophenone in THF (2 mL), and 20 µL (0.6 mmol) of MeMgBr (3 M in THF). The crude product was purified by flash chromatography with 20:1 hexanes/EtOAc to afford 104 mg (67%) of the product as a clear oil (2.4:1 ratio of two diastereomers). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (major diastereomer) δ 4.14 (s, 1H), 2.77 (s, 1H) 1.60-1.9 (m, 6H), 1.48 (s, 9H), 1.17 (m, 2H), 0.93-0.87 (m, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) (both diastereomers) δ 174.13, 144.94, 127.57, 127.12, 127.06, 126.85, 126.79, 82.43, 77.84, 77.73,

27.94, 27.74, 26.16, 26.03, 24.87, 24.24, 22.48, 21.74, 18.57, 18.47, -2.57, -2.79, -2.96. TLC (20:1 hexanes/EtOAc) R_f (both diastereomers) 0.30.



5-*tert*-butyl 1,1-dimethyl 5-(*tert*-butyldimethylsilyloxy)-2-phenylpent-4-ene-1,1,5-tricarboxylate (28b). The title compound was prepared according to General Procedure **H** using 100 mg (0.41 mmol) of silyl glyoxylate **1b** and 90 mg (0.4 mmol) of dimethyl 2-benzylidenemalonate in THF (2 mL), and 0.57 mL (0.6 mmol) of vinyl Grignard (1 M in THF). The crude product was purified by flash chromatography with 10:1 hexanes/EtOAc to afford 88 mg (45%) of the product as a clear oil (1 diastereomer). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (1 diastereomer) δ 7.21 (ddd, J = 21.5, 16.0, 8.3 Hz, 5H), 5.59 (t, J = 7.0 Hz, 1H), 3.87 – 3.76 (m, 1H), 3.71 (s, 3H), 3.54 – 3.44 (m, 1H), 3.40 (s, 3H), 2.67 – 2.57 (m, 1H), 2.50 – 2.38 (m, 1H), 1.38 (s, 9H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f 0.13.



***tert*-butyl 2-(*tert*-butyldimethylsilyloxy)-6-nitro-5-phenylhex-2-enoate (28c).** The title compound was prepared according to General Procedure **H** with the following differences: Reaction was run at a temperature of -78 ˚C for 4 h after addition of vinyl magnesium bromide before being allowed to warm to rt before quenching using 100 mg (0.41 mmol) of silyl glyoxylate **1b** and 61 mg (0.4 mmol) of (*Z*)-(2-nitrovinyl)benzene in THF (2 mL), and 0.57 mL (0.6 mmol) of vinyl magnesium bromide (1 M in THF). The crude product was purified by flash chromatography with 10:1 hexanes/EtOAc to afford 85 mg (49%) of the product as a clear oil (1 diastereomer). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) (1 diastereomer) δ 7.36 – 7.13 (m, 5H), 5.75 (dd, *J* = 8.5, 6.4 Hz, 1H), 4.59 – 4.55 (m, 2H), 3.62 – 3.49 (m, 1H), 2.66

(dt, J = 14.9, 8.2 Hz, 1H), 2.46 (ddd, J = 14.8, 7.2, 6.5 Hz, 1H), 1.45 (s, 9H), 0.97 – 0.95 (m, 9H), 0.17 (s, 3H), 0.14 (s, 3H); TLC (20:1 hexanes/EtOAc) R_f 0.19.

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CHAPTER 2

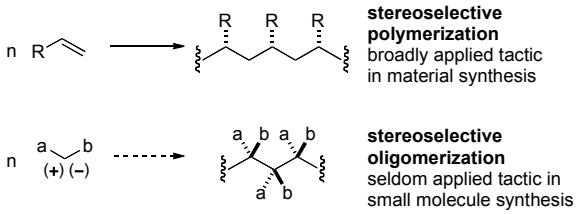
TOTAL SYNTHESIS OF ZARAGOZIC ACID C VIA CONTROLLED OLIGOMERIZATION

2.1 Introduction

The use of small repeating subunits in the construction of complex molecules is ubiquitous in Nature. Many of the structures that make life possible on the molecular level adhere to this synthetic formula: proteins consist of amino acids; DNA and RNA are made up of nucleotides and nucleosides; and oligosaccharides contain saccharides. This efficient synthetic strategy is the result of billions of years of evolution. Many elegant solutions have developed to control construction of the large molecules through facilitated chemical linkage of the small subunits such as ribosomes in the manufacture proteins from the polymerization of amino acids.

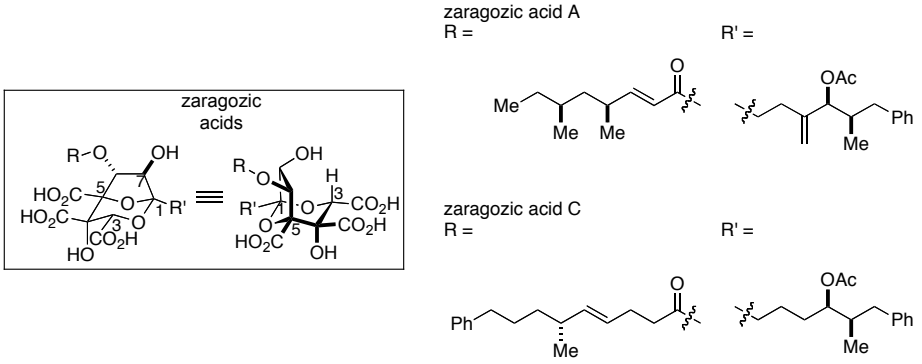
In the realm of materials chemistry this strategy is applied in the preparation of production-scale quantities of stereochemically defined polymers from selective repetitive incorporation of prochiral monomers. While these processes are well suited to making high molecular weight molecules, application of this same strategy to the synthesis of small molecules is a relatively unexplored area. Many chiral natural products such as polyketides, oligosaccharides, and peptides contain repeating subunits. Conventional synthetic strategies to construct these types of molecules would involve stepwise convergent linear routes. A more efficient approach would be a controlled oligomerization of the subunits for the concurrent creation of carbon skeletal frameworks and tetrahedral stereochemistry (Scheme **2-1**). Development of this largely uncultivated tactic for total synthesis could have a drastic impact on the way synthetic chemists construct molecules.[1]

Scheme 2-1 Oligomerization Strategy



2.2 Background

Scheme 2-2 The Zaragozic Acids



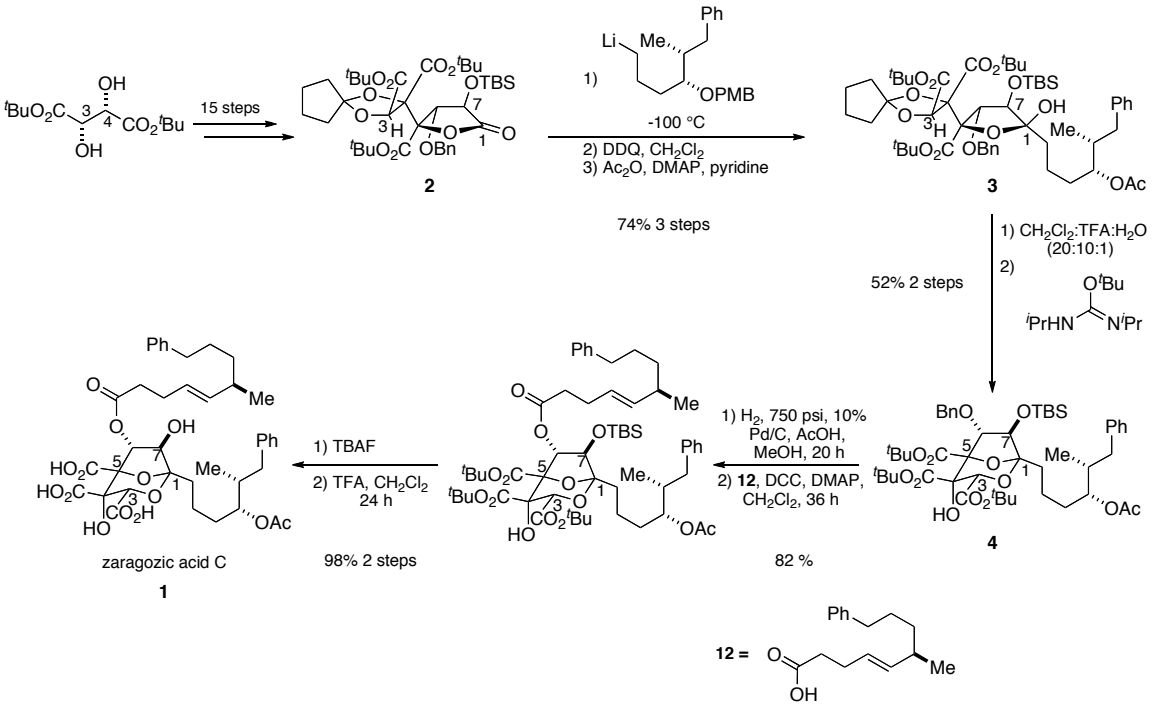
The zaragozic acids are picomolar inhibitors of squalene synthase, the enzyme catalyzing the first committed step in the production of cholesterol.[2,3] The compounds have also been shown to potentiate radiochemotherapy in the destruction of acute myeloid leukemia (AML) cell lines.[4] First isolated from fungal metabolites in 1991 and 1992, the zaragozic acids derive their name from the origin of one of the fungi, ATCC20986, Zaragoza, Spain. Each compound features the same core differing in the makeup of the side chains (Scheme **2-2**).

While the biological activity initially garnered interest for possible pharmaceutical application to lowering cholesterol, the densely functionalized structure of the core has attracted the attention of synthetic chemists. The highly oxygenated 2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core of zaragozic acid C (**1**) features six contiguous asymmetric centers that

comprise the principal obstacle to synthesis. The two fully substituted centers at C4 and C5 in the core have been particularly nettlesome in extant syntheses.[5-25]The synthetic challenges presented by zaragozic acid C have inspired the development of a number of innovative solutions.

A strategy common to many syntheses involves formation of the core through acid catalyzed ketalization of a linear precursor. Two examples of this strategy include a total synthesis completed by Evans and coworkers[11] that was previously the shortest route to zaragozic acid C and a total synthesis completed by Carreira and Dubois[9,10] that is relevant to our study.

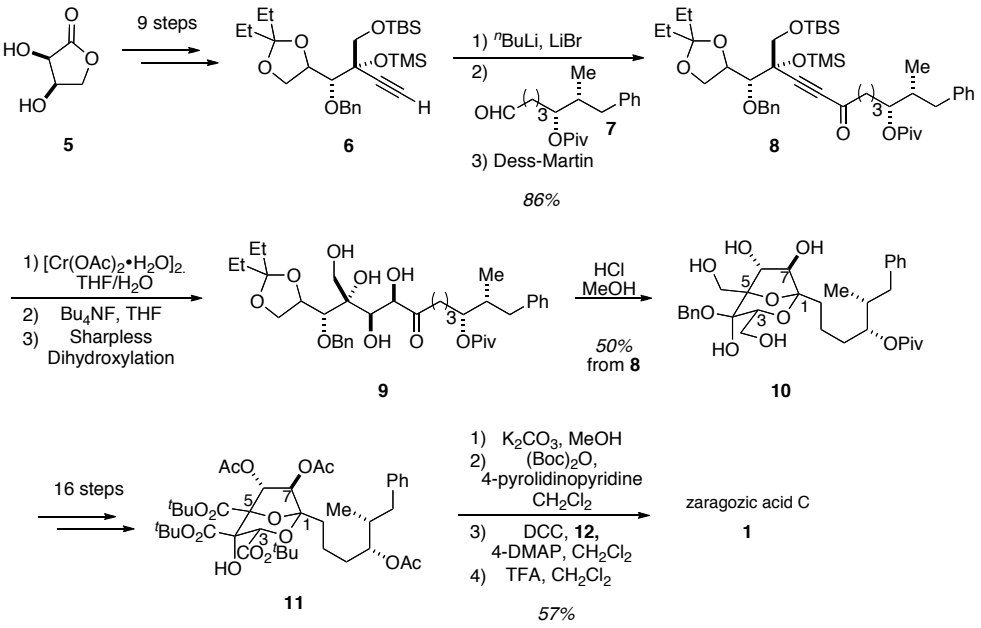
Scheme 2-3 Evans Zaragozic Acid C Total Synthesis



The Evans group started from chiral di-*tert*-butyl-*D*-tartrate and built up the linear precursor to the core in a sequence converging with addition of the alkyl side chain as the organolithium species to lactone **2** (Scheme **2-3**). After 3 subsequent steps the bicyclic core was assembled by acid catalyzed ketalization of **3** to form **4**. The C6 and C7 hydroxyls of **4** are differentiated to allow for selective acylation of the C6 hydroxyl with the acyl side chain.

Differentiating the C6 and C7 hydroxyls is a difficulty commonly encountered in the syntheses of **1** and this problem was solved early in this synthesis. Following benzyl deprotection the acyl side chain was attached and the synthesis of zaragozic acid C was completed in 2 additional steps for a total length of 24.

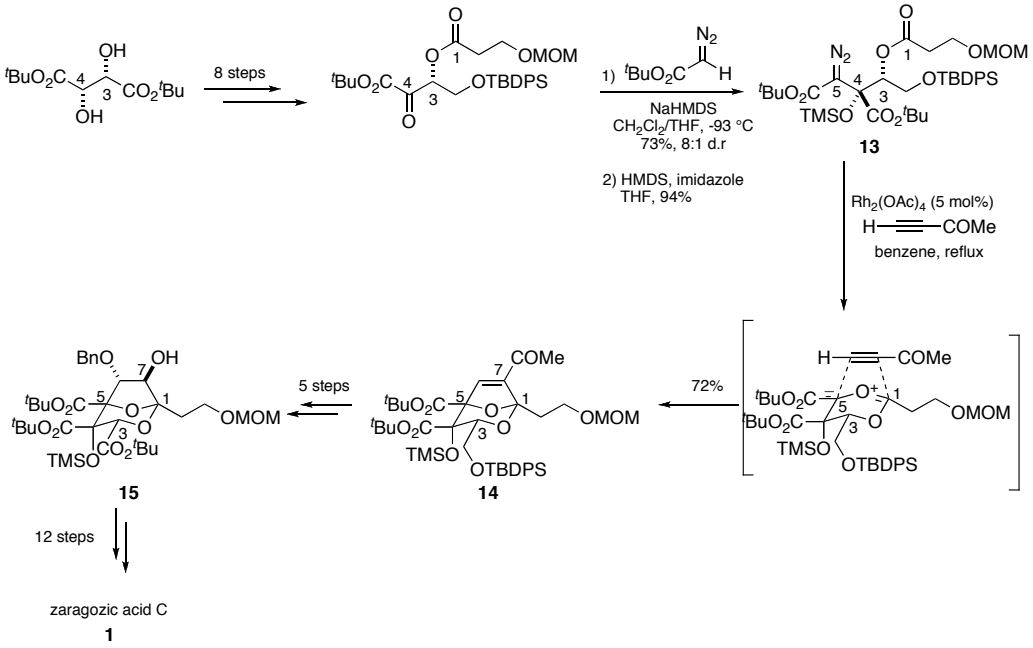
Scheme 2-4 Carreira Total Synthesis



The synthesis completed by Carreira and Du Bois also used acid catalyzed ketalization to form the core of the molecule and served as a useful resource over the course of our study (Scheme **2-4**). Beginning with D-erythronic γ lactone **5**, intermediate **6** was reached in 9 steps. Formation of the organolithium species from **6** and addition to aldehyde **7** followed by Dess-Martin oxidation gave ynone **8**. Semi reduction with $[Cr(OAc)_2 \cdot H_2O]_2$ in aqueous THF was followed by silyl ether deprotection and Sharpless dihydroxylation formed **9**. Exposure of **9** to acid resulted in formation of the desired bicylclic ketal **10**. In 16 additional steps tri-acetate intermediate **11** was reached with all core functionality present in the correct oxidation state. At this stage in the synthesis the problem of C6 and C7 hydroxyl differentiation was addressed. It

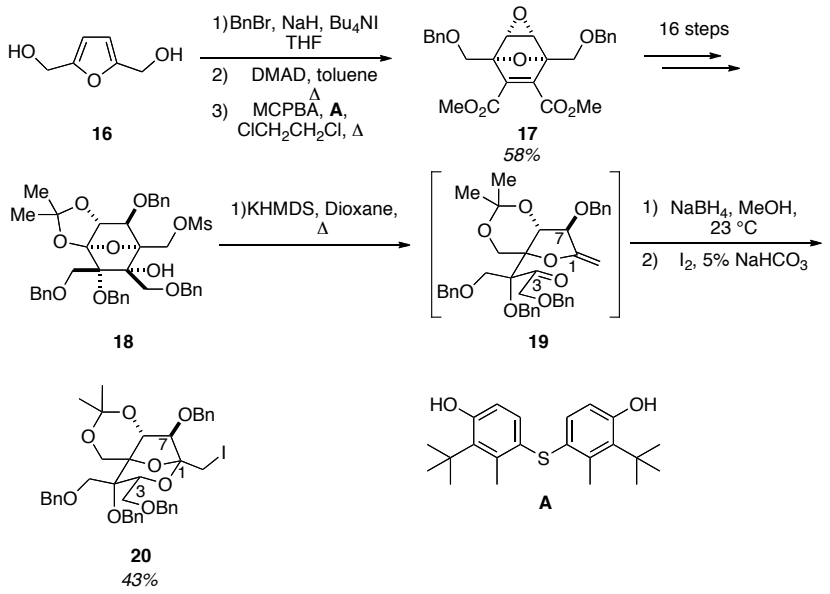
has been observed that the C6 hydroxyl group is more sterically accessible, a result of being oriented away from the core of the molecule, and that the C7 hydroxyl is more acidic due to the electron withdrawing effect of the two ketal oxygens.[21] Upon hydrolysis of the C6 and C7 hydroxyl groups Carierra was able to selectively Boc (*tert*-butoxy carbonyl) protect the C7 hydroxyl using 4-pyrolidinopyridine as an acylation catalyst. The acyl side chain was then attached followed by a global deprotection to complete the synthesis.

Scheme 2-5 Hashimoto Zaragozic Acid C Synthesis



As an alternative to using acid catalyzed ketalization to form the core a few other strategies have been developed. A total synthesis by the Hashimoto group started from chiral di-*tert*-butyl-*D*-tartrate building up to **13**, a diazo precursor to bicyclic core formation in 17 steps (Scheme **2-5**).[14] The core was formed in a rhodium catalyzed 1,3 dipolar cycloaddition using an alkynyl ketone as the dipolarophile. In 5 additional steps intermediate **15** was achieved with desired differentiation of the C6 and C7 hydroxyl groups. From **15** it took 12 steps to reach zaragozic acid C.

Scheme 2-6 Nagaoka Core Synthesis



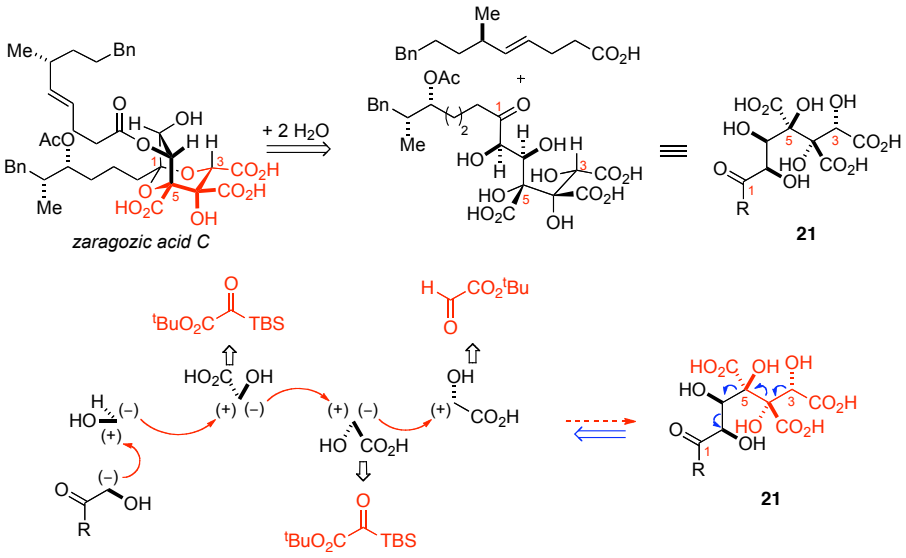
Nagaoka also completed a synthesis of the bicyclic core by means other than acid catalyzed ketalization (Scheme **2-6**).[26] While a total synthesis was not completed, a unique strategy for core formation was developed. Benzyl protection of furan **16** followed by a Diels-Alder reaction with dimethyl acetylenedicarboxylate (DMAD) and selective epoxidation gave **17**. It was possible to differentiate the esters of **17** through an enzyme-catalyzed hydrolysis, which provides the potential for an asymmetric synthesis. With the necessary carbon skeleton present in **17** this synthesis was carried on racemically. The next 16 steps installed the required oxygen functionality to form key intermediate **18**. The core was then formed in one pot through a Grob fragmentation[27]-reduction-iodoacetalisation process. Deprotonation with potassium hexamethyldisilazide (KHMDS) in dioxane led to formation of intermediate **19**, which was reduced with $NaBH_4$ and exposed to iodine to give **20.** Introduction of the side chains and oxidation of the core would complete a racemic total synthesis of **1** from **20**.

As seen in the representative examples of previous syntheses of zaragozic acid C, solutions to the challenges inherent in construction of this densely functionalized oxygenated core commonly involve multistep sequences of oxidation state, functional group, and/or protecting group adjustment. Our goal was to develop a more efficient route based on the concept of a controlled oligomerization to assemble the core with adherence to a synthetic plan predicated on the minimization of oxidation state variance and protecting group manipulation.

2.3 Results and Discussion

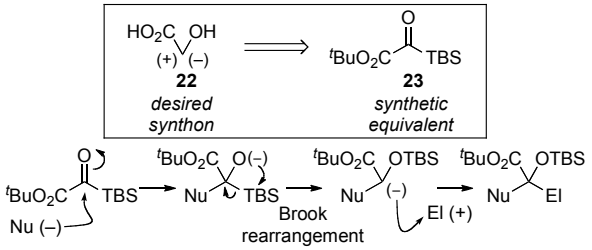
2.3.1 Retrosynthesis and Oligomerization

Scheme 2-7 Retrosynthesis



What we found striking about zaragozic acid C was that the global complexity masks a rather elementary composition of simple building blocks. A retrosynthetic analysis of zaragozic acid C through bond disconnection into its constituent synthons (Scheme **2-7,** blue arrows) reveals a repeating series of glycolic acid fragments.

Scheme 2-8 Silyl Glyoxylate as a Glycolic Acid Synthon

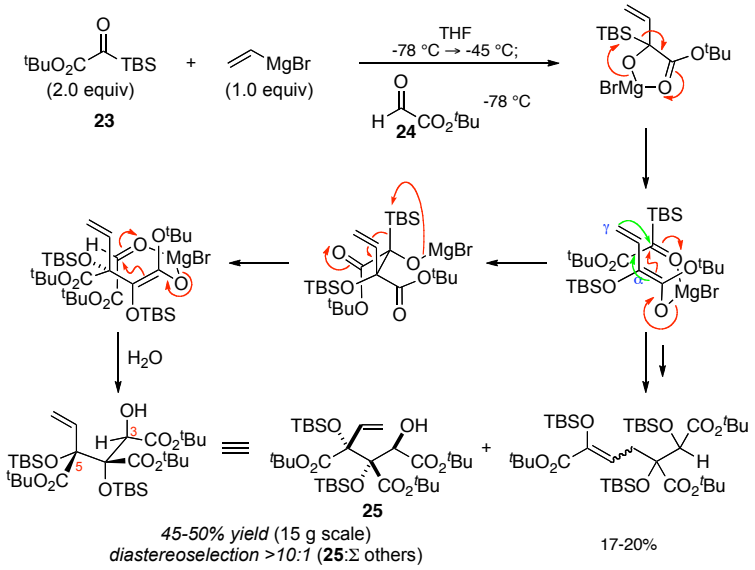


In contemplating efficient connections that would enable the rapid construction of **21** or its equivalent, we were compelled to consider a "self-consistent sequence," one that concurrently merges carbon skeletal buildup with the introduction of stereochemistry, as a method that would be uniquely efficient.[28-30] Thus, a self-consistent synthesis of the zaragozic acid core would be one with connection of the glycolic acid subunits in the correct relative configuration and oxidation state (red arrows). The successful implementation of this strategy requires a synthetic equivalent to the unusual geminal dipolar glycolic acid synthon **22**. We developed the silyl glyoxylate **23** to function as a reagent for the geminal grafting of complementary nucleophilic and electrophilic reagents onto a protected glycolic acid.[31-33] The reactivity pattern exhibited by **23** is summarized in Scheme **2-8**. Nucleophilic attack on the silyl glyoxylate facilitates C→O silicon migration (Brook rearrangement)[34] to form a stabilized carbanion. This nascent enolate reacts with an electrophile giving rise to a product wherein two new bonds have been formed at the same carbon atom.

Given the retrosynthetic analysis presented in Scheme **2-5** and the surrogacy of **23** for **22**, we tested the hypothesis that enchainment of >1 equivalent of **23** could be used to assemble the zaragozic acid backbone in one step (Scheme **2-9**). The addition of one equivalent of vinylmagnesium bromide to two equivalents of **23** at -78 °C initiates the oligomerization detailed in Scheme **2-9**. The initial adduct rearranges to provide a new carbon nucleophile that enchains a

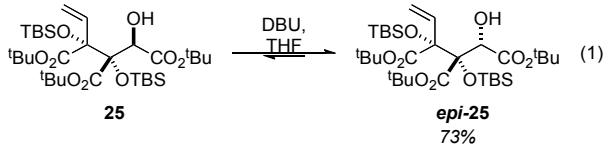
second equivalent of **23**. A second Brook rearrangement delivers the second magnesium enolate of the cascade. The oligomerization of further equivalents of **23** stops at this point, possibly due to steric constraints of the enolate intermediate, and the sequence is terminated via the introduction of tert-butyl glyoxylate (**24**). The α-hydroxy ester **25** was obtained in 45-50% yield on a 15 g scale with a diastereoselection >10:1 (**25**:Σ others), the structure of which was determined from an X-ray diffraction study.[35] The remainder of the mass balance was attributed to γ addition of the initially formed enolate to an additional equivalent of **23** with subsequent enchainment of a third equivalent of **23**. Careful control of the reaction conditions, specifically the regulation of temperature and slow addition of silyl glyoxylate **23** to a solution of vinyl Grignard, allowed us to favor formation of the desired product.

Scheme 2-9 Oligomerization



Three contiguous stereogenic centers of the carbon skeleton were assembled in the correct oxidation state. The direct delivery of the needed functional array meant that no oxidation state adjustment was required in this domain for the remainder of the synthesis. Beyond the native efficiency issues, this attribute was unexpectedly critical for the successful completion of

the synthesis (*vide infra*). Moreover, the reaction achieved its secondary design purpose of providing an ideal protecting group scheme that masked every functional group except the secondary alcohol that would participate in the subsequent reaction.



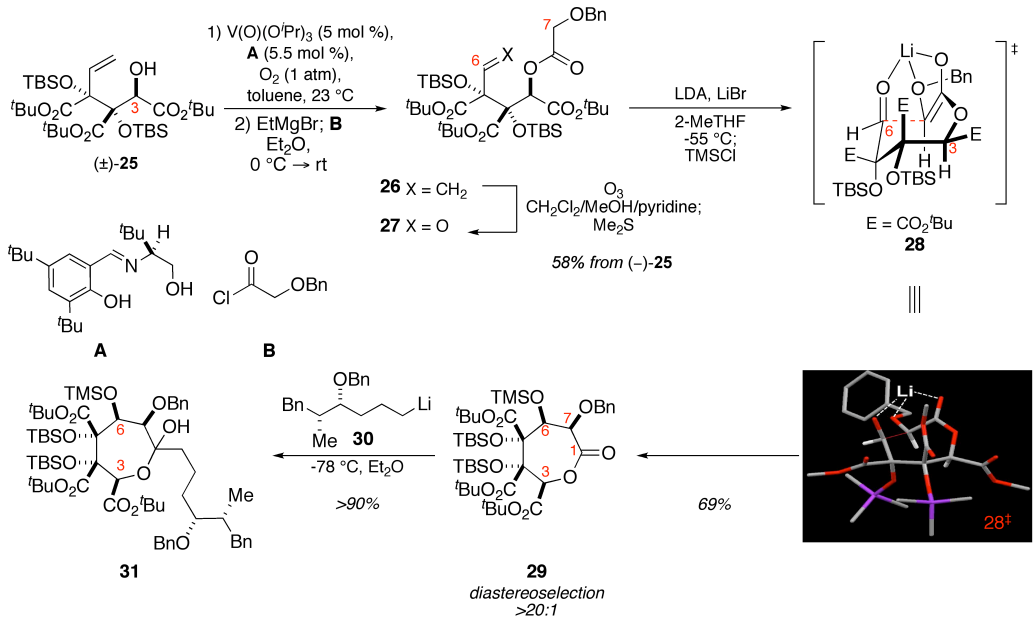
25 ***epi*-25** *73%* (1)

The product obtained possessed the correct relative stereochemistry for the challenging C4 and C5 tertiary alcohols, while the stereocenter that would eventually become C3 of the core required inversion. Epimerization of **25** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was possible at this stage (eq **1**), but multiple downstream operations were unsuccessful with *epi*-**25**. For this reason, compound **25** bearing the incorrect C3 configuration was advanced with the expectation that it could be rectified later in the synthesis.

2.3.2 Intramolecular Aldol Reaction

The racemic α-hydroxy ester (±)-**25** was subjected to a vanadium-catalyzed oxidative kinetic resolution using O_2 as the stoichiometric oxidant (Scheme **2-10**).[36] The resolution yielded 48% (of a maximum 50%) of (−)-**25** with an enantiomer ratio (er) of 90:10. In anticipation of a projected intramolecular aldol reaction to introduce the C6/C7 diol, the C3 hydroxyl group was converted to its derived ester **26** with α-benzyloxyacetyl chloride. Neither the resolution nor the acylation was successful with *epi*-**25**. The requisite C6 electrophile was then revealed through ozonolysis of the vinyl group to provide aldehyde **27**.

Scheme 2-10 Intramolecular Aldol Reaction



A completely diastereoselective intramolecular aldol reaction under carefully prescribed conditions fashioned the C6−C7 bond and led to ε-lactone **29**.[37] Aldolization to form ε-lactones is unusual[38,39] and this case may be assisted by the high level of substitution in the connecting carbon atoms.[40] The ring closure is proposed to proceed via the illustrated transition structure 11‡ (based on the X-ray diffraction study of **29**) and gives the correct stereochemistry at C7 but the incorrect configuration at C6. Epimerization of **29** was possible to correct the C3 stereochemistry at this stage, but once again the correct C3 epimer was found to be unsuitable in subsequent manipulations. The C1 sidechain was appended by means of a nucleophilic addition of the organolithium **30**[41] to the ε-lactone **29** resulting in a mixture of lactol and ketol species. With **14** in hand we were ready to assemble the core of the molecule through an acid catalyzed ketalization.

2.3.3 Acid Catalyzed Ketalization

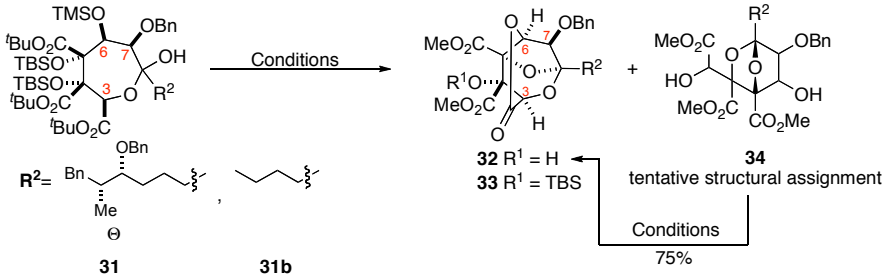
Initially, the ketalization was attempted with conditions similar to those used in previous syntheses of zaragozic acid C involving TFA(trifluoroacetic acid) in CH_2Cl_2 but these conditions proved incompatible with the benzyl ether protecting scheme we were using for the alkyl side chain. Therefore, alternative ketalization conditions were sought (Table **2-1**). The first conditions used to obtain the desired ketalization involved treatment of the ketol/lactol mixture with H_2SO_4 (0.1 M in MeOH) for 72 h and afforded three products: a tricyclic ketal with the tertiary alcohol protected as the TBS ether **33** (13%), the same ketal lacking the silyl ether **32** (50%) as the major product, and an unidentified isomeric ketal **34** (20%) (entry 1). The undesired δ-lactone present in the tricyclic ketal products **32** and **33** was a consequence of the incorrect stereochemical configuration at C3 and C6.

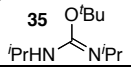
Subsequent findings would show that TBS-protected **33** was the desired product at this stage. The two other products were easily converged to the desired tricyclic ketal **33**. Resubmission of the isomeric ketal to the ketalization conditions, combination with the unprotected tricyclic lactone, and silylation of the C4 hydroxyl group provided an acceptable combined yield of **33**.

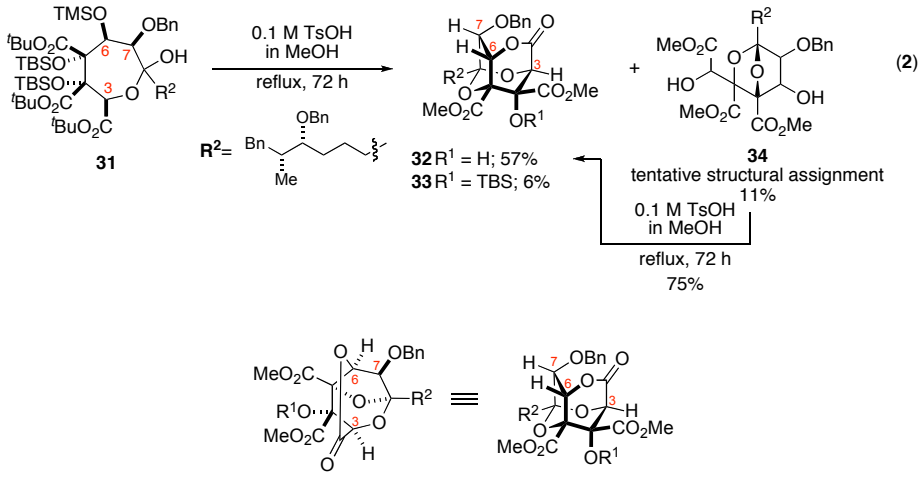
While ketalization with H_2SO_4 provided acceptable yields of the desired product **33** after convergence of products, we sought to optimize this reaction to improve two areas. We desired to minimize efforts needed to channel the material to the desired product **33** and to avoid the transesterification of the *tert*-butyl esters to methyl esters (Table **2-1**). To ease analysis of products as well as limit the unnecessary use of the alkyl side chain a model system with an *n*-butyl side chain **31b**, synthesized from *n*-BuLi addition to **29**, was employed. Attempts to avoid transesterification by using *tert*-butyl alcohol as a solvent or using conditions to saponify the esters followed by re-esterification with isourea[42] **35** were unsuccessful (entries 4 and 5). Camphorsulfonic acid and *p*-toluenesulfonic acid (TsOH) both catalyzed ketalization in methanol

(entries 2 and 3) but TsOH gave the best results forming a mixture of only the desired unprotected lactone **32b** (71%) and the isomeric ketal **34b**. While the TsOH conditions did not form the desired TBS protected lactone it was operationally convenient to isolate and protect **32** rather then deal with a mixture of three products.

Table 2-1 Ketalization Conditions

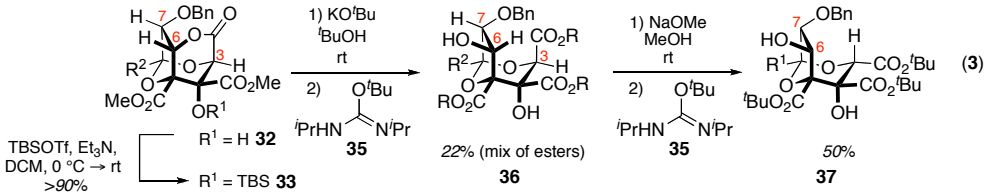


entry	R^2	conditions	**32**	**33**	**34**
1	θ	0.1 M H_2SO_4 in MeOH, reflux 72 h	50%	13%	20%
2	^{n}Bu	0.1 M TsOH, MeOH, reflux 72 h	71%	0%	26%
3	^{n}Bu	0.1 M CSA, dry MeOH, reflux 72 h	52%	0%	26%
4	^{n}Bu	0.1 M H_2SO_4, ^{t}BuOH, reflux 72 h	0%	0%	0%
5	^{n}Bu	1) 0.1M TsOH, THF:H_2O 20:1,reflux 72 h 2) **35** 	0%	0%	0%



Exposure of **31,** with the correct alkyl side chain, to the optimized conditions in a scaled up reaction resulted in a mixture of the three products as seen in the H_2SO_4 ketalization but with better yields: **32**, 57%; **33**, 6%; and **34**, 11% (eq **2**).

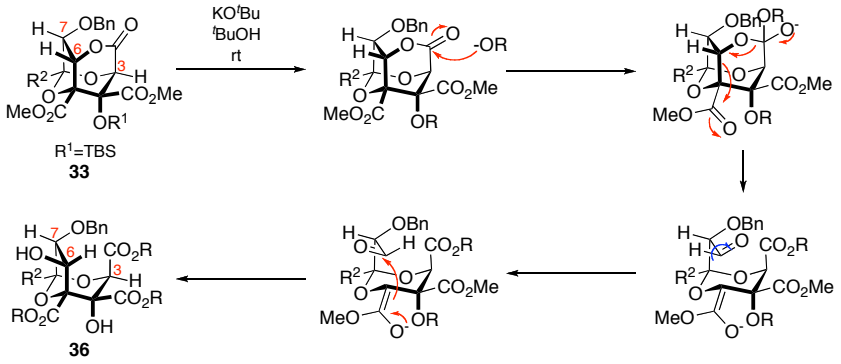
2.3.4 Lactone Opening and Correction of C6 and C3 Stereocenters



The presence of the δ-lactone in **33** highlights the remaining stereochemical problem: the incorrect configurations at C6 and C3. While this lactone was a consequence of the incorrect stereochemistry it also provided a means for resolution of the problem. In initial attempts to open the lactone, by exposure to KO^{t}Bu in ^{t}BuOH followed by re-esterification of the partially saponified esters with **35**, the lactone opened with surprising concomitant inversion of the C6 stereocenter (eq **3**). A retro-aldol/aldol sequence is the probable mechanism accounting for this fortuitous stereochemical correction (Scheme **2-11**).[43] Attack of the alkoxide opens the lactone and initiates a retro-aldol reaction. Rotation about the C6/C7 C-C bond reorients the intermediate aldehyde. An intramolecular aldol reaction between the reoriented aldehyde and the methyl ester

enolate terminates the cascade reforming the C5/C6 bond with C6 in the desired configuration. This unanticipated process would have been impossible in the absence of functional groups in the correct oxidation state. Epimerization of the inconsequential mixture of esters (**36**) with NaOMe in MeOH achieved the desired configuration of the C3 stereocenter. All of the ester groups were unexpectedly cleaved in this reaction; re-esterification of the resulting triacid using **35** gave the zaragozic acid core **37** with the required stereochemistry and in the correct oxidation state. While this process led to formation of the desired core and corrected the stereochemical configurations at C3 and C6 the yield was 11% over the four steps.

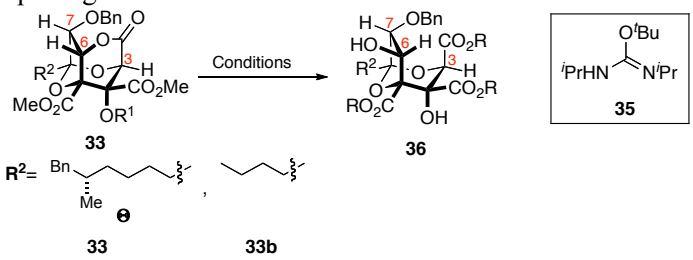
Scheme 2-11 Retro-aldol/Aldol Cascade



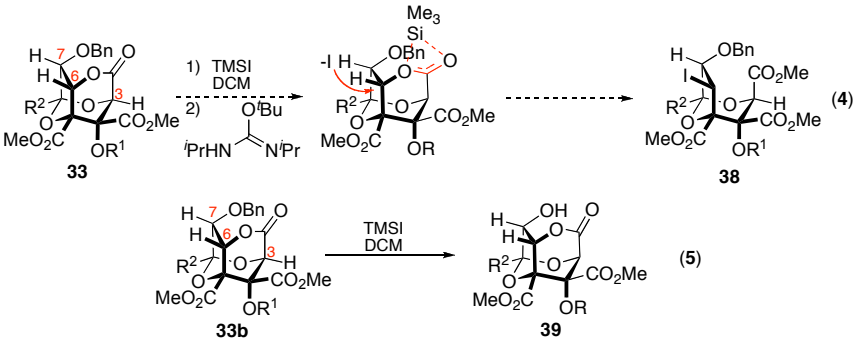
As a consequence of the low yield, a large number of conditions were evaluated to find the optimal way to accomplish this reaction (Table **2-2**). Ideally, lactone opening, the retro-aldol/aldol sequence and epimerization of C3 would all occur in one process with transesterification of the Me esters to desired ^{t}Bu esters. Attempts to open the lactone without protection of the tertiary alcohol as the silyl ether were unsuccessful (entries 1 and 5). An attempt to open the lactone and conduct the epimerization with NaOMe in MeOH resulted in only ester saponification (entry 4). The use of molecular sieves led to lactone opening and C6 inversion but in a lower yield and with saponification (entry 8). Using KO^{t}Bu in different alcoholic as well as ethereal solvents and in the presence of 18-crown-6 (with the aim of increasing alkoxide nucleophilicity), resulted in only saponification or decomposition (entries 3, 6, 7 and 9). Various transesterification protocols including; a KO^{t}Bu complex in ^{t}BuOAc[44], Mg(OMe)$_2$ in MeOH, and

a $La(OTf)_3$ derived catalyst[45,46] had no effect or led to saponification of the esters(entries 5,6 and 12-14). Since saponification seemed inevitable and ^{t}Bu esters were necessary a number of saponification conditions geared toward lactone opening were also evaluated to no avail. We also thought that the strained ring system might be susceptible to photochemical cleavage but upon photoirradiation no reaction was seen (entry 21).

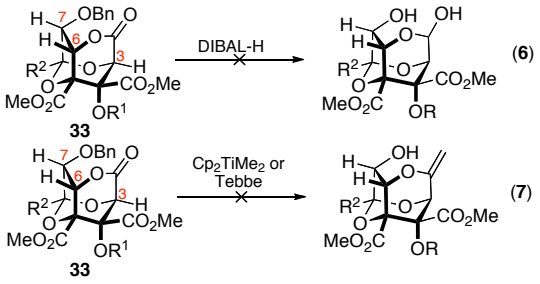
Table 2-2 Lactone Opening



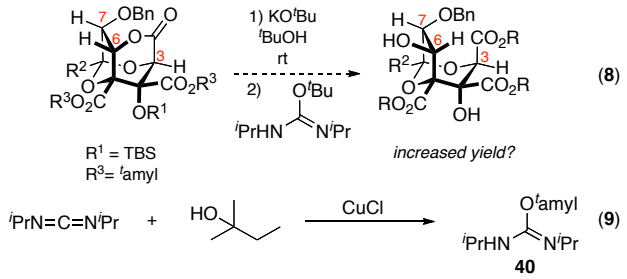
entry	R^1=	R^2=	conditions	result
1	H	θ	5 equiv. KO^{t}Bu, ^{t}BuOAc	Ester saponification
2	TBS	θ	5 equiv. KO^{t}Bu, ^{t}BuOAc	Ester saponification
3	TBS	θ	5 equiv. KO^{t}Bu, ^{t}BuOH, 18-c-6; **35**	Ester saponification
4	TBS	θ	NaOMe. MeOH; **35**	Ester saponification
5	H	^{n}Bu	5 equiv. KO^{t}Bu, ^{t}BuOH	No desired products
6	TBS	^{n}Bu	5 equiv. KO^{t}Bu, ^{t}amyl alcohol; **35**	Ester saponification
7	TBS	^{n}Bu	5 equiv. KO^{t}Bu, EtOH; **35**	Ester saponification
8	TBS	^{n}Bu	4 Å Mol. Sieves, 5 equiv. KO^{t}Bu, ^{t}BuOH; **35**	16% yield **36**
9	TBS	^{n}Bu	5 equiv. KO^{t}Bu, THF	No desired products
10	TBS	^{n}Bu	10 equiv. KO^{t}Bu, 4 equiv. H_2O, Et2O	No desired products
11	TBS	^{n}Bu	Cs_2CO_3, dry MeOH; **35**	No desired products
12	TBS	^{n}Bu	$Mg(OMe)_2$, ^{t}BuOH	Recovered starting material
13	TBS	^{n}Bu	$Mg(OMe)_2$, MeOH, reflux 24 h	Recovered starting material
14	TBS	^{n}Bu	$La(OTf)_2$, NaOMe, MeOH, reflux 24 h	Recovered starting material
15	TBS	^{n}Bu	LiOOH, THF:H_2O; **35**	Recovered starting material
16	TBS	^{n}Bu	LiSEt	No desired prodcuts
17	TBS	^{n}Bu	KOTMS, dry THF, rt; **35**	Ester saponification
18	TBS	^{n}Bu	4.5 equiv. TMSI, DCM	Debenzylation
19	TBS	^{n}Bu	NaI, TMSCl, CH_3CN, reflux	Debenzylation, saponification, TBS deprotection
20	TBS	^{n}Bu	BI_3, Diethylaniline, Benzene; H_2O	No desired products
21	TBS	^{n}Bu	*hv*, solvent	Recovered starting material



One interesting result from the screen occurred with the use of trimethylsilyl iodide (TMSI) (entry 18).[47] The proposed mechanism for lactone opening involved silyl Lewis acid coordination of the lactone with nucleophilic attack at C6 by I^- (eq **4**). This would have led to formation of iodide **38**. In addition to ester cleavage, TMSI is also known to readily cleave benzyl ethers, which was the result obtained upon exposure of the lactone to TMSI (eq **5**). We investigated other conditions, including BI_3 and methods of *in situ* TMSI formation, to effect this kind of lactone opening but all efforts resulted in decomposition of starting materials or ether and methyl ester cleavage (entries 19 and 20).



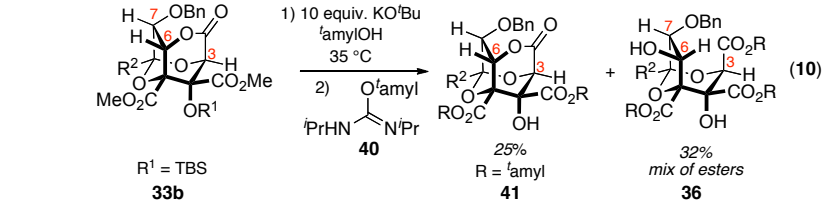
The difficulty in achieving the desired lactone opening and subsequent transformations in synthetically useful yields led us to investigate alternatives. By reducing the lactone to the lactol we thought that it may be possible to induce base promoted lactone opening. When lactone **33** was subjected to DIBAL-H it appeared that TBS ether deprotection and ester reduction occurred prior to reduction of the lactone (eq **6**). We also thought that conversion of the lactone to the vinyl ether may facilitate ring opening but dimethyl titanocene and the Tebbe reagent were unreactive with **33** (eq **7**).

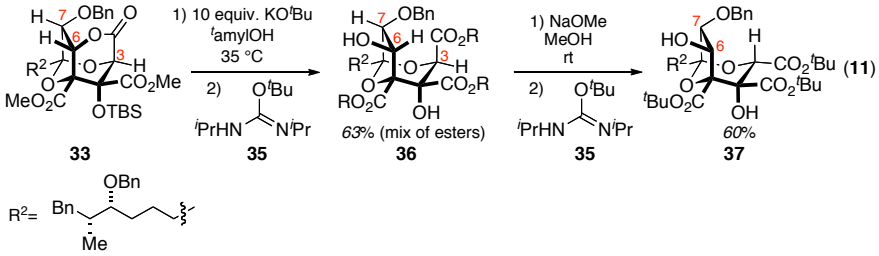


At this point with little success taking other directions we assessed what could be done to best optimize the current lactone opening protocol. Much of the recovered starting material from the evaluation of lactone opening conditions contained a mixture of ^{t}Bu and Me esters following exposure to **35**. During the ongoing search for a better lactone opening protocol, the recovered starting material was being brought through the KO^{t}Bu/^{t}BuOH protocol to work on post lactone opening aspects of the synthesis. A careful examination of the results of these reactions led to the conclusion that when bulkier ^{t}Bu esters were present on the tricyclic lactone the yields for the lactone opening were greater. To test the hypothesis that bulkier esters may improve the yield, ^{t}amyl isourea **40** was synthesized to install ^{t}amyl esters on the saponified δ-lactone.

The best yield of recovered starting material with the most conversion of Me esters to ^{t}Bu esters had been observed with 5 equiv of KO^{t}Bu in ^{t}amyl alcohol followed by exposure of the crude mixture to isourea **35**. To ensure maximum saponification 10 equiv of KO^{t}Bu were used and the reaction was heated gently (eq **10**). Normally, the lactone opening was a slow process taking 12-16 h to complete. In this case, the reaction showed saponification of the starting material in 45 min. Exposure of the crude mixture to **40** and purification revealed an unexpected mixture of products. Desired δ-lactone **41** with ^{t}amyl esters was isolated in a 25% yield but the major product turned out to be the desired opened lactone **36** as a mixture of esters in a 32% yield, a yield higher than previously achieved by any other means. Optimization of the reaction conditions and application to δ-lactone **33** with the correct alkyl side chain resulted in a 63% yield of the desired product **36** as an inconsequential mixture of esters over 2 steps (eq **11**). Epimerization of C3 with NaOMe in MeOH led to complete saponification and formation of **37**

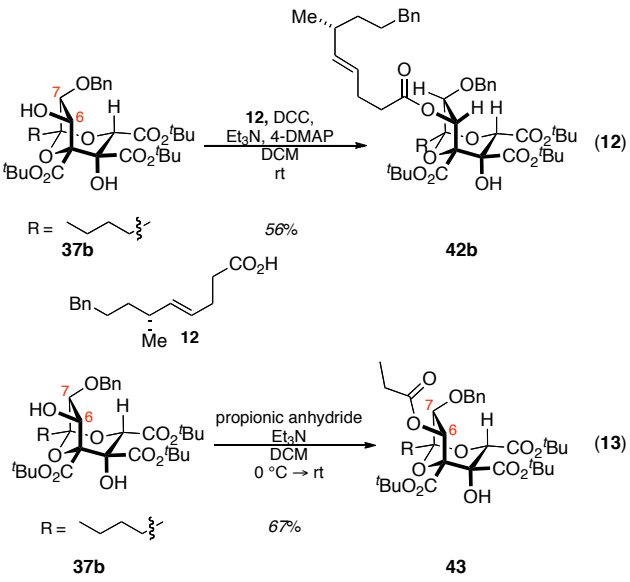
in 60% yield over 2 steps. While the yield was only 38% over 4 steps this was almost a 4 fold improvement over previous results of 11% and the taking into account recovered starting material in formation of **36** the yield was even greater.





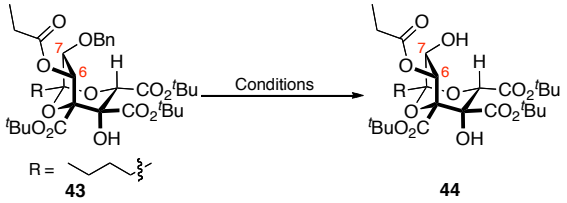
2.3.5 Benzyl Ether Deprotection

At this stage in the synthesis the C6 and C7 alcohols were favorably differentiated with the C7 hydroxyl group protected as a benzyl ether allowing for selective installation of the acyl side chain on the C6 hydroxyl. Compound **37b,** with ^{n}Bu in place of the alkyl side chain, served as a model system for side chain addition. Coupling of the acyl side chain under standard conditions with the coupling agent dicyclohexylcarbodiimide (DCC) was achieved in 56% yield (eq **12**). Compound **43** formed by acylation of the C7 hydroxyl with propionic anhydride was used to screen debenzylation conditions (eq **13**).



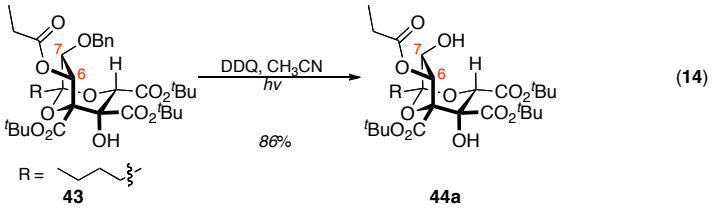
The presence of alkene functionality on the acyl side chain prevented simply using Pd catalyzed hydrogenation to remove the benzyl ethers forcing us to consider alternative deprotection protocols compatible with the presence of olefins. The array of dense functionality on the core of the molecule made this a particularly challenging problem. Single electron reductants lithium napthenalide and lithium 4,4'-di-*tert*-butylbiphenylide (LDBB) were evaluated first and under a variety of conditions led only to decomposition (entries 1 and 2).[48] Lewis acid deprotection was also unsuccessful leading to decomposition (entries 3 and 4). This was not surprising considering the number of Lewis basic sites present in this molecule. TMSI, which selectively cleaved the benzyl ether on the δ-lactone, stripped the molecule of functionality cleaving the benzyl ether, all the esters and removing the acyl side chain (entry 5). Unfortunately TMSI cleavage of the ^{t}Bu esters was more facile than Me esters that existed on the δ-lactone. Based on these results it appears ^{t}Bu ester cleavage occurs at a similar rate to that of benzyl ethers. An attempt to oxidatively cleave the benzyl ether using 2,3 dichloro-5,6-dicyanobenzoquinone (DDQ) was unsuccessful but also was mild enough to allow recovered starting material (entry 6).

Table 2-3 Debenzylation Conditions

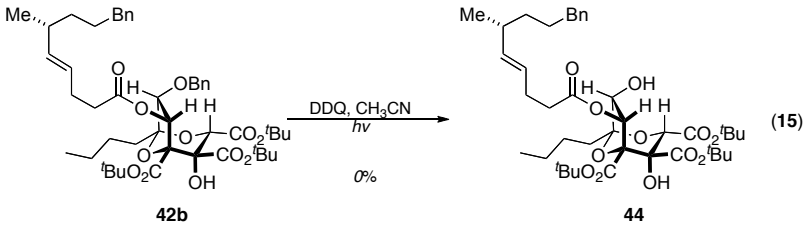


entry	conditions	result
1	lithium napthanelide, THF	Decomposition
2	LDBB, THF	Decomposition
3	$FeCl_3$, CH_2Cl_2, 0 ºC	Decomposition
4	Ph_3C^+ BF_4^-, CH_2Cl_2	Decomposition
5	TMSI, CH_2Cl_2	Saponification, removal of side chain
6	DDQ 1.5 equiv., CH_3CN	Recovered starting material

The use of DDQ in the presence of photoirradiation leads to increased rates of benzyl ether deprotection.[49] When this protocol was applied using compound **43,** deprotection proceeded cleanly giving the product **44** in 86% yield (eq **14**). This protocol is less effective in the presence of alkene functionality and this was apparent when it was applied to compound **42** containing the real acyl side chain as only decomposition resulted.



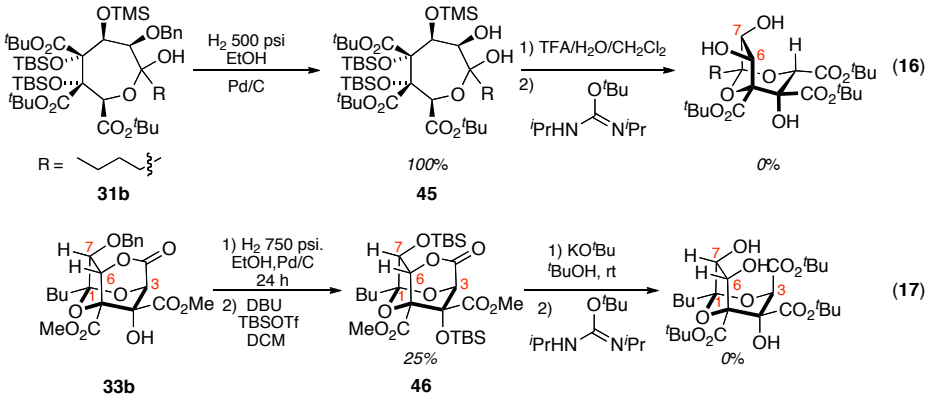
(**14**)



(**15**)

Despite the desirable differentiation of hydroxyl groups present in **37,** installation of the acyl side chain rendered subsequent debenzylation impractical in our hands. Therefore, we investigated removal of the benzyl groups earlier in the synthesis. In the absence of the acyl side chain Pd catalyzed hydrogenation readily cleaved the benzyl ether from the core. Removal of the

benzyl ether from compound **31b** occurred quantitatively but resulted in unsuccessful subsequent ketalization (eq **16**). Removal of the benzyl group and protection of the free alcohols as silyl ethers immediately following ketalization resulted in isolation of only 25% of the desired bis(silylated) product **46** (eq **17**). Attempted lactone opening of **46** was then unsuccessful.

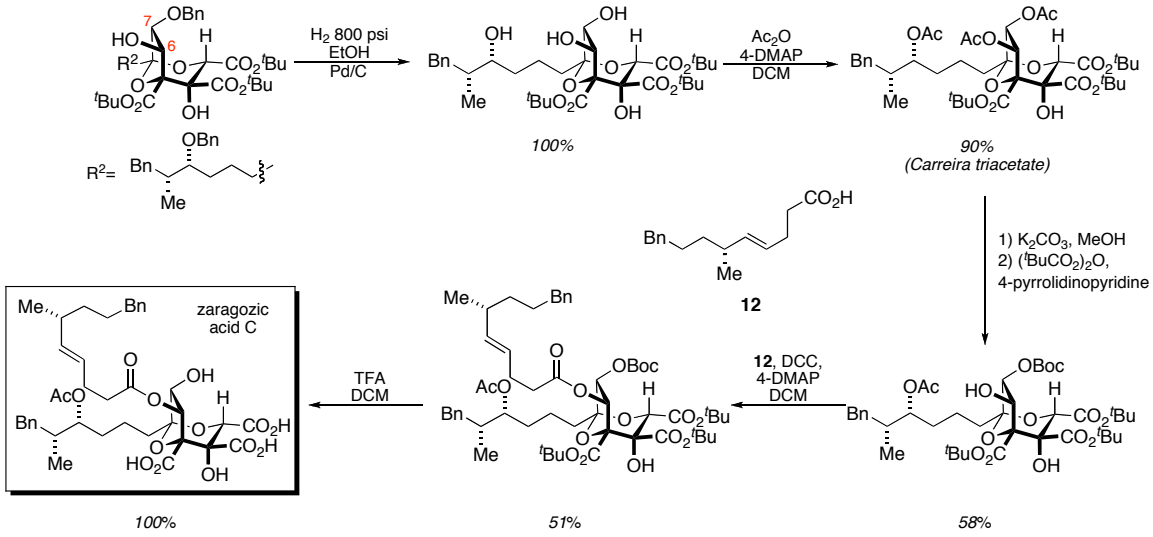


2.3.6 Total Synthesis of Zaragozic Acid C

Given the observed changes in reactivity in the absence of the benzyl ether, it was thought that the use of an alternative protecting group earlier in the synthesis, such as paramethoxybenzyl (PMB) ether, could have a deleterious effect on the subsequent reactions. This led to the final solution for debenzylation of compound **37**. Pd catalyzed hydrogenative debenzylation gave triol **47** in quantitative yield. Acetylation of **47** under standard conditions using DMAP and acetic anhydride formed the triacetate **11**, a compound utilized by Carreira in the total synthesis of zaragozic acid C in 90% yield.[9,10] The analytical data were in full accord with those reported (^{1}H NMR in $CDCl_3$ and ^{13}C NMR in both CD_3OD[10] and $CDCl_3$,[7] IR, TLC, sign of rotation). The preparation of **11** thus constituted a formal synthesis of zaragozic acid C. As illustrated in Scheme **2-10**, we applied the Carreira protocol to complete the synthesis of zaragozic acid C (**1**) in four steps from triacetate **11.** Unreacted starting material was recovered in both the BOC protection and the DCC coupling of the acyl side chain and this is not reflected in the yields seen in Scheme **2-12**. The synthetic material was identical to a sample of natural

material. The total synthesis was accomplished in 18 total steps making it the shortest synthesis of zaragozic acid C to date.

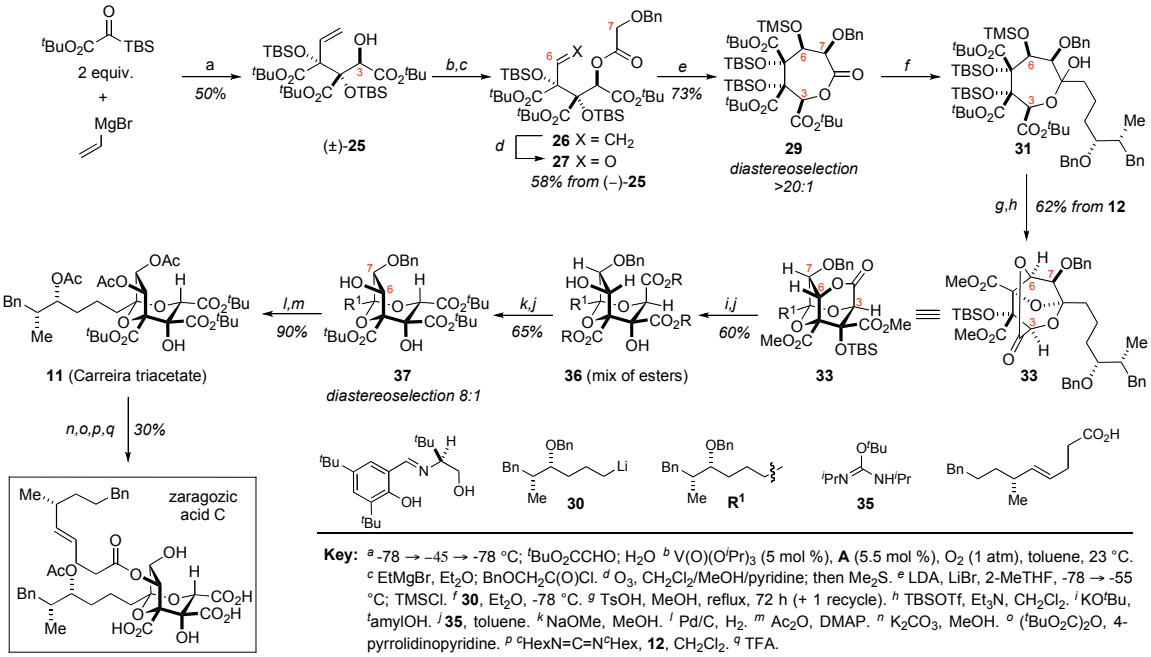
Scheme 2-12 Final Endgame



2.4 Conclusions

The total synthesis of zaragozic acid C was achieved along with the goal of concurrent creation of the carbon skeleton and tetrahedral stereochemistry (Scheme **2-13**). This efficient sequence contained only one oxidation state change (alkene ozonolysis) and no functional group repair in the core synthesis. Adhering to these ideals made this an efficient "self-consistent" synthesis and made possible key reactions such as the retro-aldol/aldol sequence which would not have occurred without the presence of the core functionality in the correct oxidation state. This study highlights the utility of silyl glyoxylates as glycolic acid synthons and demonstrates application of controlled oligomerization to small molecule synthesis. The brevity of this sequence is a testament to the efficiency possible when employing the tactic of controlled oligmerization.

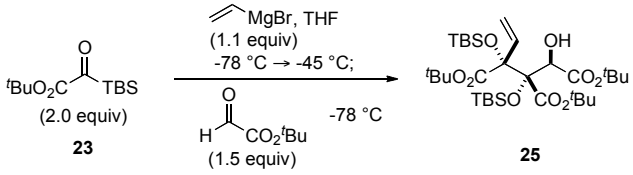
Scheme 2-13 Total Synthesis of Zaragozic Acid C



2.5 Experimental

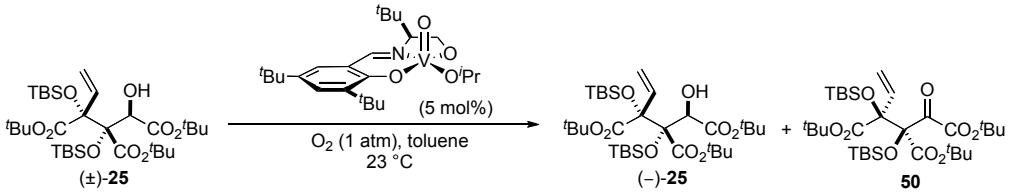
Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on either a Bruker model Avance 500 (^{1}H at 500 MHz and ^{13}C NMR at 125 MHz), Bruker model 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.[41]



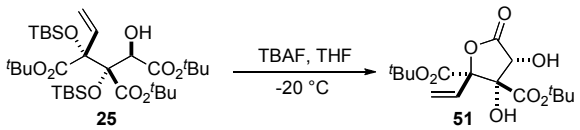
3-*tert*-Butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-2-vinyl-pentanedioic acid di-*tert*-butyl ester (25). A solution of 31.7 mL (31.7 mmol, 1.1 equiv) of vinylmagnesium bromide in THF (150 mL) was cooled to -78 °C and a solution of 15 mL (57.7 mmol, 1.1 equiv) of *tert*-butyl *tert*-butyldimethylsilyl glyoxylate (**23**) 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 (**25**). 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 **7**: **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.

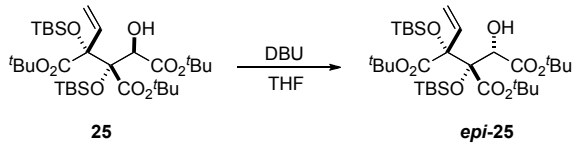


3-*tert*-Butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-2-vinyl-pentanedioic acid di-*tert*-butyl ester (25). A 50 mL round bottomed flask equipped with a stirbar was purged with O2 and charged with 82.2 mg (0.246 mmol, 0.055 equiv) of the salen ligand in dry toluene (11.3 mL) and treated with 53 μL (0.224 mmol, 0.05 equiv) of $VO(O^iPr)_3$ under a dry O2 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 **7** 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 **50**. The alcohol was purified by flash

chromatography (5:95 Et_2O:petroleum ether) to furnish 1.5 g (51%) of alcohol **7** (e.r. 90:10). The enantiomer ratio was determined by CSP-SFC analysis of lactone **51**.

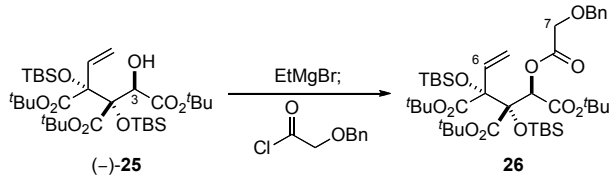


3,4-Dihydroxy-5-oxo-2-vinyl-tetrahydrofuran-2,3-dicarboxylic acid di-*tert*-butyl ester (51). A solution of 150 mg (0.23 mmol, 1.0 equiv) of bis-TBS ether **7** in THF (3.0 mL) at -45 °C was treated with 0.51 mL (0.51 mmol, 2.2 equiv) of a 1.0 M solution of tetrabutylammonium fluoride in THF. The solution 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 (Na2SO4) 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 (**22**) as a white foam. Analytical data for **51**: **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.



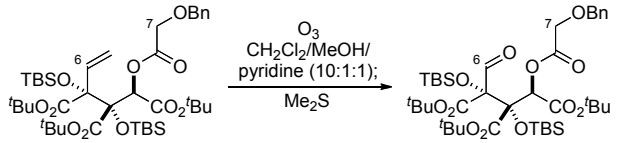
3-*tert*-Butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-2-vinyl-pentanedioic acid di-*tert*-butyl ester (*epi*-25). To a solution of 750 mg (1.15 mmol, 1.0 equiv)

of the alcohol (**7**) 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*-7** as an oil. Analytical data for ***epi*-25**: **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 (26). To a solution of 680 mg (1.1 mmol, 1.0 equiv) of the alcohol (**25**) 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

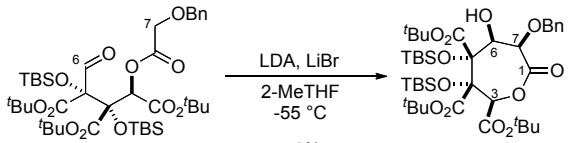
the crude reaction revealed 74% conversion of the starting material. Purification of the crude reaction by flash chromatography (5:95 EtOAc: petroleum ether) yielded 540 mg (65%, 88% based on recovered starting material) of the acylated alcohol (**26**). Analytical data for **26**: **IR** (thin film, 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.



26 **27**

4-(2-Benzyloxy-acetoxy)-3-*tert*-butoxycarbonyl-2,3-bis-(*tert*-butyl-dimethyl-silanyloxy)-2-formyl-pentane dioic acid di-*tert*-butyl ester (27). A solution of 646 mg (0.81 mmol, 1.0 equiv) of alkene **26** 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 (**27**) as a white foam. Analytical data for **27**: **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* =

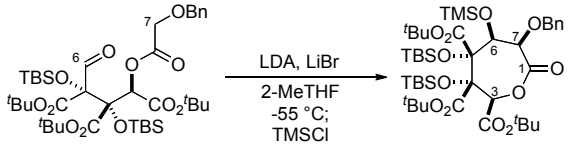
12.0 Hz, 1H); 4.07 (d, *J* = 16.8 Hz, 1H), 4.02 (d, *J* = 16.8 Hz, 1H), 1.51 (s, 9H), 1.37 (s, 18H), 0.90 (s, 9H), 0.81 (s, 9H), 0.29 (s, 3H), 0.11 (s, 3H), 0.067 (s, 3H), 0.034 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.4, 169.0, 166.8, 166.4, 165.2, 137.1, 128.7, 128.3, 128.2, 87.1, 86.2, 84.4, 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.



27 **52**

6-Benzyloxy-3,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-7-oxo-5-hydroxy-oxepane-2,3,4-tricarboxylic acid tri-*tert*-butyl ester (52). To a solution of 41 µL of diisopropylamine (0.29 mmol, 2.2 equiv) in 2-methyltetrahydrofuran (0.8 mL) at 0 °C under an Ar atmosphere was added 180 µL of a 1.5 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 105 mg (0.13 mmol, 1.0 equiv) of aldehyde **27** and 46 mg (0.53 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 -50 °C. After 1 h, the reaction was quenched at -50 °C by the addition of 1.5 mL of a saturated aqueous ammonium chloride solution. The reaction was extracted with Et_2O (3 x 5mL) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash chromatography (5:95 EtOAc: petroleum ether), to afford 80 mg (76%) of the pure aldol (**52**) as white solid. Analytical data for **52**: **IR** (thin film, cm-1) 3943, 2930, 2858, 1766, 1706, 1471, 1371, 1255, 1138, 1004; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6.8 Hz, 2H), 7.32-7.22 (m, 3H), 5.39 (d, *J* = 11.6 Hz, 1H), 5.28 (s, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.67 (d, *J* = 1.6 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.34 (dd, *J* = 12.0, 2.0 Hz, 1H), 1.59 (s, 9H), 1.51 (s, 9H), 1.47 (s, 9H), 0.87 (s, 9H), 0.82 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H),

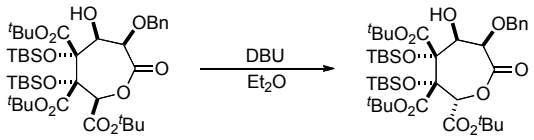
0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 167.8, 167.5, 164.4, 137.2, 129.0, 128.6, 128.3, 87.4, 86.8, 85.2, 83.8, 83.0, 77.3, 76.8, 74.1, 72.9, 28.6, 28.2, 28.1, 27.1, 27.0, 19.9, 19.8, -0.8, -1.0 (four overlapping resonances); **TLC** (1:9 EtOAc: petroleum ether) R*f* 0.29. **Anal.** Calcd for $C_{40}H_{68}O_{12}Si_2$: C, 60.27; H, 8.60. Found: C, 60.51; H, 8.66.



27 **29**

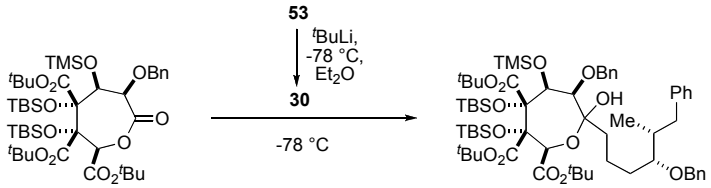
6-Benzyloxy-3,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-7-oxo-5-trimethylsilanyloxy-oxepane-2,3,4-tricarboxylic acid tri-*tert*-butyl ester (29). To a solution of 80 µL of diisopropylamine (0.55 mmol, 2.2 equiv) in 2-methyltetrahydrofuran (0.6 mL) at 0 °C under an Ar atmosphere was added 360 µL of a 1.4 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 **27** 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 (**29**) as a crystalline solid. Analytical data for **29**: **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.



52 ***epi*-52**

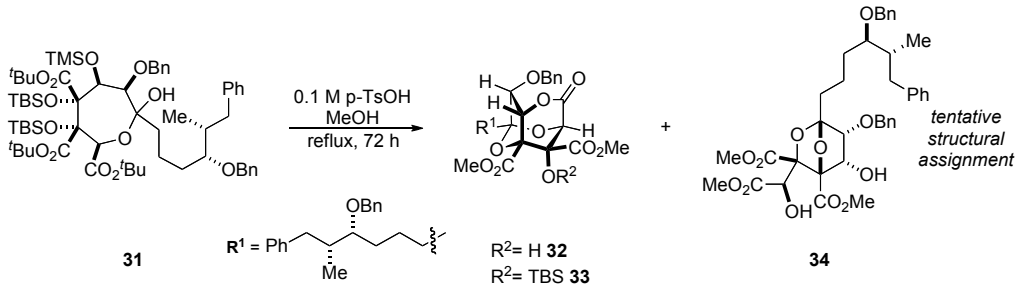
6-Benzyloxy-3,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-7-oxo-5-hydroxy-oxepane-2,3,4-tricarboxylic acid tri-*tert*-butyl ester (*epi*-52). To a solution of 60 mg (0.075 mmol, 1.0 equiv) of lactone **52** in Et_2O (1.0 mL) was added 56 µL (0.38 mmol, 5.0 equiv) of DBU. After 3 h, 0.5 mL of saturated aqueous 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*-52** as an oil. Analytical data for ***epi*-52**: **^{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.



29 **31**

(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 (31). A solution of 94 mg (0.23 mmol, 5.0 equiv) of iodide **53** 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 **29** 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 **31** as mixture of isomers. Analytical data for **31** (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.

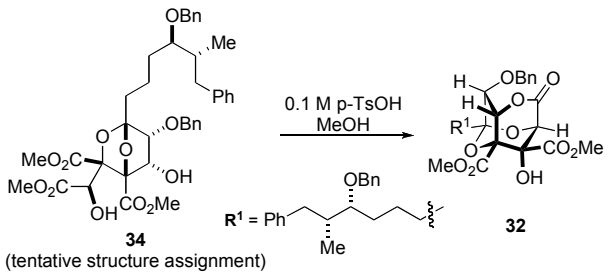


C4 O-*tert*-butyldimethylsilyl tricyclic ketal δ-lactone (33). To a solution of 103 mg of **31** (0.089 mmol. 1.0 equiv)) in 7 mL of methanol, 136 mg of *p*-toluenesulfonic acid (0.715 mmol, 8.0 equiv) was added. The reaction flask was fitted with a reflux condenser and heated to reflux for 72 h. Heating 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 (Na2SO4), 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 (**33**), 29 mg (48%) of δ-lactone **32**, and 9 mg (15%) of ketal (**34**). Analytical data for **116**: **IR**

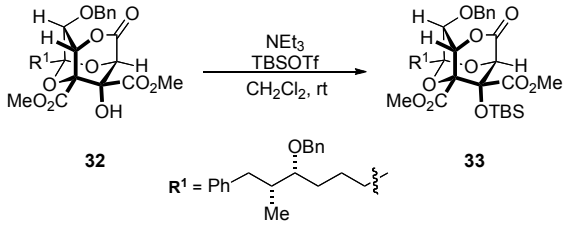
(thin film, cm-1) 3566, 2954, 2926, 2857, 2359, 1801, 1772, 1747, 1646, 1496, 1365, 1257, 1028; **[α]Na** -18.7 (c = 0.05, CH_2Cl_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.24 (m, 12H), 7.17-7.08 (m, 3H), 4.84 (m, 2H), 4.52 (m, 3H), 4.44 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.53 (d, *J* = 7 Hz), 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 (32). ^{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).

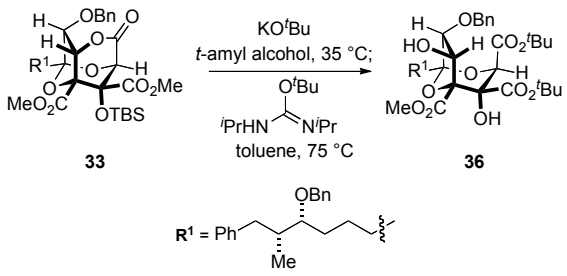
(1*R*,3*S*,4*R*,5*S*,6*R*)-dimethyl 6-(benzyloxy)-1-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-5-hydroxy-3-((*R*)-1-hydroxy-2-methoxy-2-oxoethyl)-2,7-dioxabicyclo[2.2.1]heptane-3,4-dicarboxylate (34). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (m, 11H), 7.11-7.09 (m, 4H), 5.67 (d, *J* = 5.1 Hz, 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).



C4-hydroxy-tricyclic ketal δ-lactone (32). To a solution of 16 mg of **34** (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 (Na2SO4), 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 **32**.

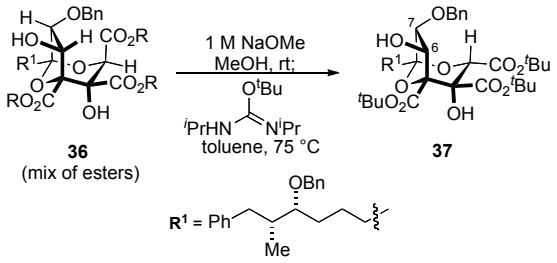


C4 O-*tert*-butyldimethylsilyl tricyclic ketal δ-lactone (33): To a solution of 51 mg (0.076 mmol) of tertiary alcohol **32** in 0.75 mL CH_2Cl_2 at 0 °C under an Ar atmosphere, was added 42 μL (0.308 mmol, 4.0 equiv) of NEt3, and 35 μL (0.154 mmol, 2.0 equiv) of TBSOTf. The reaction was warmed to 23 °C. After stirring for 15 min, an additional 42 μL (0.308 mmol, 4.0 equiv) of NEt3, and 35 μL (0.154 mmol, 2.0 equiv) of TBSOTf was added. After 1 h, 0.5 mL of saturated NaHCO3 (aq) was added. The solution was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na2SO4) 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 **33**.



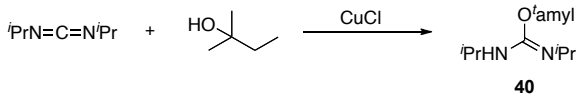
(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*)-3,4-di-*tert*-butyl 5-methyl 7-(benzyloxy)-1-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-4,6-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (36). To a solution of 15 mg (0.019 mmol, 1.0 equiv) of lactone **33** in *t*-amyl alcohol (1.0 mL, freshly 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 (Na2SO4) 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 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 **36**; 2.0 mg (13%) of tri-*t*-butyl ester; 1.0 mg of mono-*t*-butyl ester (7%); 90% yield BRSM. Analytical data for **36**: **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.



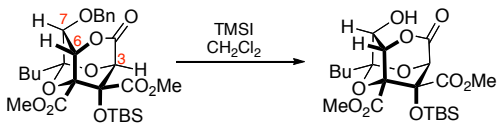
(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 7-(benzyloxy)-1-((4*R*,5*R*)-4-(benzyloxy)-5-methyl-6-phenylhexyl)-4,6-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (37). 0.75 mL of a 1 M solution of NaOMe in MeOH (distilled from Mg metal) was added to 14 mg (0.019 mmol, 1.0 equiv) of **36**, as a mix of esters, in a shell vial that had been purged with Ar. The solution was stirred for 2 hours 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 **11**. Analytical data for **37**: **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.



40

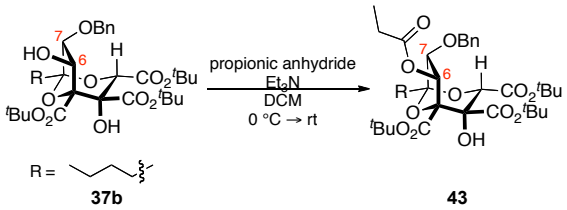
***tert*-pentyl N,N'-diisopropylcarbamimidate (40)**. A round-bottomed flask was flame dried and purged with Ar for 5 minutes. The flask was charged with a stir bar, 5 mL (32 mmol, 1 equiv) of N,N'-diisopropyldicarbodiimide, 320 mg (37 mmol, 0.1 equiv) of CuCl and 3.74 mL (37 mmol, 1.15 equiv) of *tert*-amyl alcohol. The solution was stirred for 5 days. Hexane (15 mL) was added to the solution forming a solid precipitate. The solution was filtered using a fine frit and concentrated *in vacuo*. The crude product was distilled under reduced pressure (10 torr) with a bp of 75-80 °C to yield 2.48g (36%) of **40**. Analytical data for **40**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 – 3.57 (m, 1H), 3.25 – 2.99 (m, 1H), 1.78 (q, *J* = 7.5 Hz, 2H), 1.41 (s, 6H), 1.06 (d, *J* = 6.4 Hz, 6H), 1.00 (d, *J* = 6.1 Hz, 6H), 0.84 (t, *J* = 7.5 Hz, 3H).



33b **39**

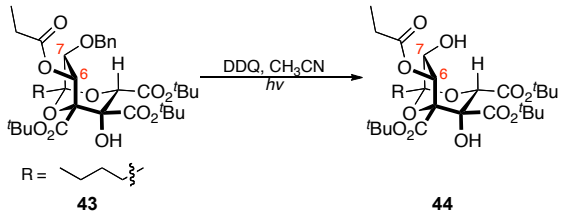
C4 O-*tert*-butyldimethylsilyl C7 hydroxyl tricyclic ketal δ-lactone (39). A dry scintillation vial was purged with Ar for 5 minutes and was charged with 10 mg (0.018 mmol, 1 equiv) of

33b, a stir bar, and 1 mL of CH_2Cl_2. To this solution was added 11 µL (0.08 mmol, 4 equiv) of TMSI dropwise via syringe. The solution was stirred in the absence of light for 12 h. The reaction was quenched with H_2O (1 mL). The layers were separated and the organic layer was extracted with saturated aqueous $NaHCO_3$ (1 mL), aqueous $Na_2S_2O_8$ (1 mL) and brine (1 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 4.5 mg (56%) of **39** as a clear oil. Analytical data for **39**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.89 (d, *J* = 7.2 Hz, 1H), 4.44 (s, 1H), 3.95 – 3.88 (m, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.79 (d, *J* = 12.7 Hz, 1H), 1.91 (dd, *J* = 16.9, 8.9 Hz, 1H), 1.77 (dd, *J* = 14.8, 5.7 Hz, 1H), 1.44 (d, *J* = 39.6 Hz, 1H), 1.40 – 1.16 (m, 4H), 0.96 – 0.85 (m, 2H), 0.83 (s, 9H), 0.20 (s, 3H), 0.00 (s, 3H); TLC (1:5 EtOAc: petroleum ether) R*f* 0.16.

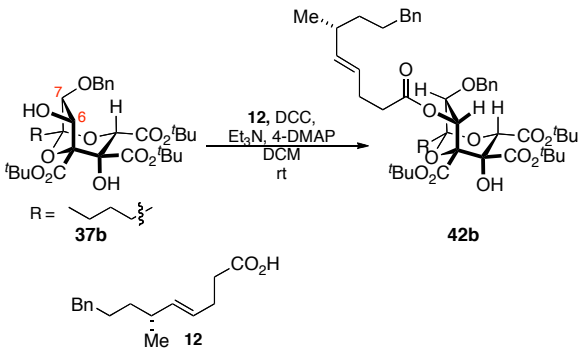


(1*S*,3*R*,4*R*,5*R*,6*R*,7*S*)-tri-*tert*-butyl 7-(benzyloxy)-1-butyl-4-hydroxy-6-(propionyloxy)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (43). A dry scintillation vial was purged with Ar for 5 minutes and was charged with 10 mg (0.016 mmol, 1 equiv) of **37b**, a stir bar, and 1 mL of CH_2Cl_2. 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 aqueuous 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 **43** as a clear oil. Analytical data for **43**: **^{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

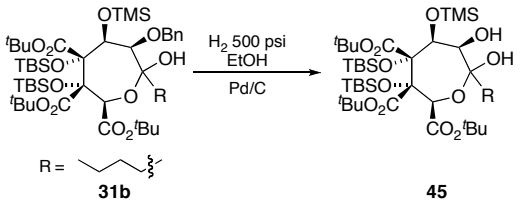
(m, 27H), 1.35 – 1.18 (m, 4H), 1.13 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H); TLC (1:5 EtOAc: petroleum ether) R*f* 0.27.



(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 (44a). A dry scintillation vial was purged with Ar for 5 minutes and was charged with 4 mg (0.006 mmol, 1 equiv) of **43**, 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 365nm 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 dropwise 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 aqueuous 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 **44** as a clear oil. Analytical data for **27a**: **^{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.

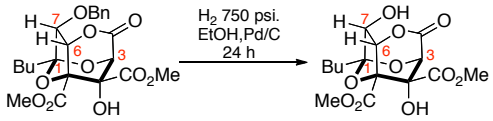


A solution of acyl side chain acid **12** (7 mg, 0.030 mmol, 2 equiv) and DCC (6 mg, 0.030 mmol, 2 equiv) in 485 µl of CH_2Cl_2 was stirred under Ar for 15 minutes. To a solution of **37b** (9.0 mg, 0.015 mmol, 1.0 equiv) and DMAP (4 mg, 0.035 mmol, 2.3 equiv) in CH_2Cl_2 (1.5 mL,) was added the acyl side chain-DCC solution. The reaction was stirred at 23 °C under Ar in a sealed vial for 40 hours. The reaction was quenched with 1.5 mL of 50% aqueous satd. NaHCO3 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 **42b** as a colorless film 6.0 mg (50%). Analytical data for **42b**: **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.



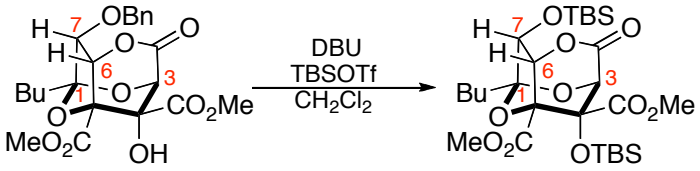
(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-tri-*tert*-butyl 4,6,7-trihydroxy-1-((4*R*,5*R*)-4-hydroxy-5-methyl-6-phenylhexyl)-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylate (45). A scintillation vial was charged with 28 mg (0.030 mmol) of ketol/lactol mixture **31b**, capped with a rubber septum and purged 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 hours. The bomb was depressurized and the solution was filtered through celite with diethyl ether. Concentration *in vacuo* afforded the debenzylated triester. The material was analyzed by 1H NMR spectroscopy and to reveal a complex mixture of lactol/ketol isomers but contained no benzyl ether peaks. The ketol/lactol mixture was used in the next step without further purification. Analytical data for **45**: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1H NMR (300 MHz, CDCl3) δ 5.00 (d, J = 3.6 Hz, 1H), 4.93 (s, 1H), 3.80 (d, J = 5.0 Hz, 1H), 3.76 – 3.61 (m, 4H), 3.08 (s, 5H), 1.66 – 1.16 (m, 97H), 1.00 – 0.76 (m, 58H), 0.35 (s, 2H), 0.30 – -0.05 (m, 27H); **TLC** (2:5 EtOAc: petroleum ether) R_f 0.3 (mixture of products).



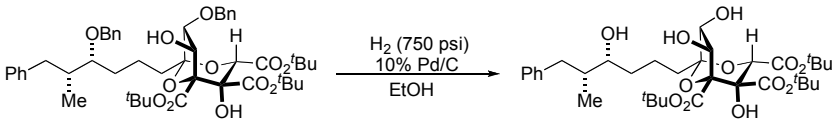
33b **54**

C7 hydroxyl tricyclic ketal δ-lactone (54). A scintillation vial was charged with 28 mg (0.064 mmol) of lactone **33b**, 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 hours. The bomb was depressurized and the solution was filtered through celite with diethyl ether. Concentration *in vacuo* afforded the debenzylated triester. The crude material was purified by flash column (20:1 petroleum ether:EtOAc) to give 22 mg (100%) of **54** as a clear oil. Analytical data for **54**: **^{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.



53 **46**

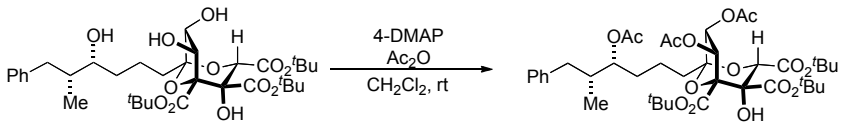
C4 O-*tert*-butyldimethylsilyl tricyclic ketal δ-lactone (46): To a solution of 11 mg (0.076 mmol) of diol **53**in 0.5 mL CH_2Cl_2 at 0 °C under an Ar atmosphere, was added 27 μL (0.1 mmol, 4.0 equiv) of DBU, and 15 μL (0.05 mmol, 2.0 equiv) of TBSOTf. The reaction was warmed to 23 °C. After stirring for 15 min, an additional 27 μL (0.308 mmol, 4.0 equiv) of DBU, and 15 μL (0.05 mmol, 2.0 equiv) of TBSOTf was added. After 2 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 5 mg (27%) of bissilyl ether δ-lactone **46**. Analytical data for **46**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.75 (s, 1H), 4.41 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 1.93 – 1.82 (m, 1H), 1.70 – 1.62 (m, 1H), 1.57 – 1.17 (m, 4H), 0.90 (s, 9H), 0.88 (s, 3H), 0.81 (s, 9H), 0.20 (s, 3H), 0.12 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).; **TLC** (2:5 EtOAc: petroleum ether) R_f 0.35.



37 **47**

(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 (47). A scintillation vial was charged with 11 mg (0.013 mmol) of tri-ester 17, 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 hours. 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 **47**: 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, CDCl3) 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.

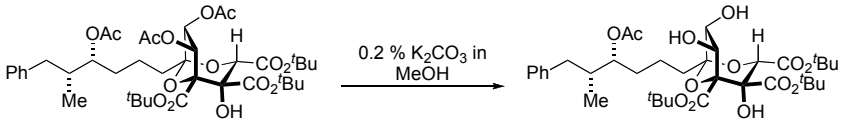


47 **11** (Carreira triacetate)

(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 (11). To a solution of 11.8 mg (0.018 mmol, 1.0 equiv) of triester **47** 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 hours until no starting material remained by TLC (1:1 EtOAc:petroleum ether). The reaction was quenched with 1.5 mL aqueous satd. NaHCO3 solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried (Na2SO4) 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 **11**, and 2.5 mg (18%) of the minor diastereomer. Analytical data for **11**: **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[10] and Rizzacasa[7].

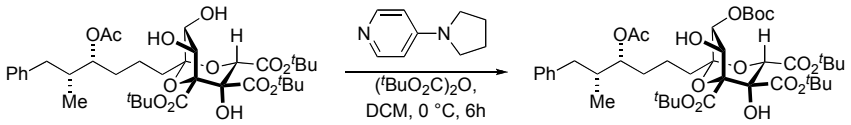


11 **55**

(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 (55). A solution of 6 mg (0.008 mmol, 1.0 equiv) of triacetate **11** 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 **55**. Analytical data for **55**: **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.[10] 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.[5]

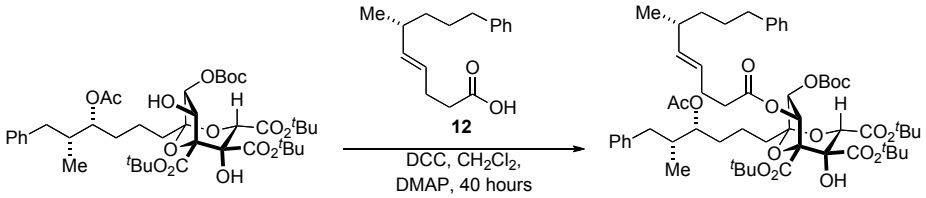


55 **48**

(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 (48). A solution of 4 mg (0.006 mmol, 1.0 equiv) of monoacetate **55** 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 Et3N (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 hours 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 **48**. Analytical data for **48**: **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.

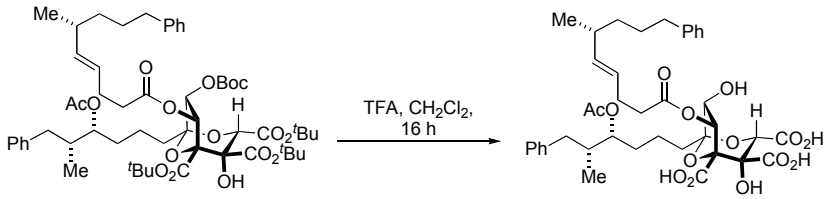
The spectroscopic data match those reported by Carreira9 and Armstrong.11 In addition to the published spectral data, we found the scanned spectrum in the Supporting Information for the Armstrong synthesis to be useful for comparison purposes.



(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 (48). A solution of acyl side chain acid **12** (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 **48** (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 hours. The reaction was quenched with 1.5 mL of 50% aqueous satd. NaHCO3 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 **49** as a colorless film 5.1 mg (51%) and 3 mg (38%) of recovered boc-protected starting material **48**. Analytical data for **49**: **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.

The spectroscopic data match those reported by Carreira[10] and Armstrong[5]. 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.



49 zaragozic acid C (**1**)

Zaragozic Acid C (1). To a solution of **49** (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 hours 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 **1** as a white flocculent solid. Analytical data for **1**: 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. The overlay spectra of the synthetic and natural material are provided below.

Fig 2.1 ^{1}H NMR Spectra Zaragozic Acid C

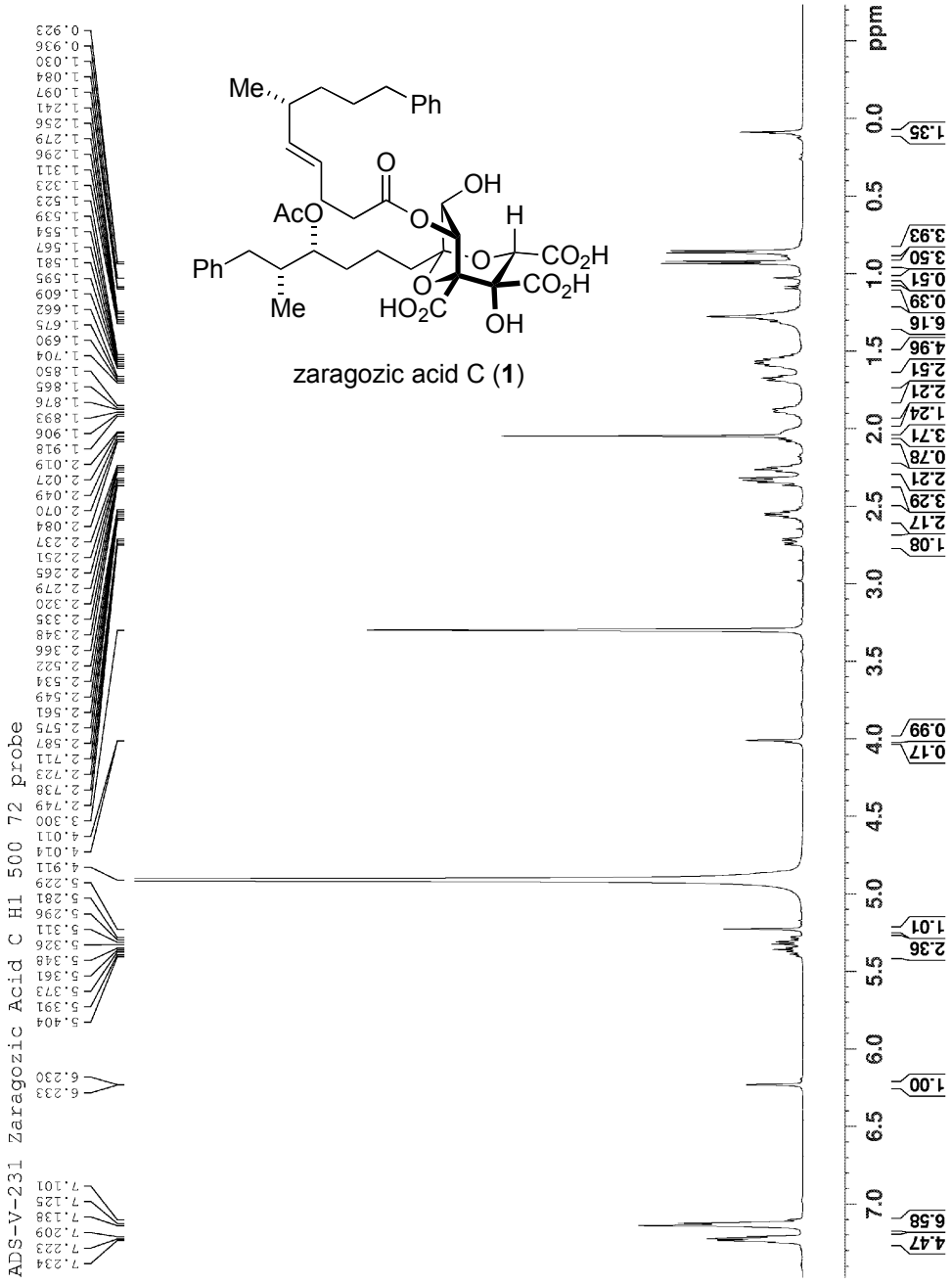


Fig 2.2 ^{13}C NMR Spectra Zaragozic Acid C

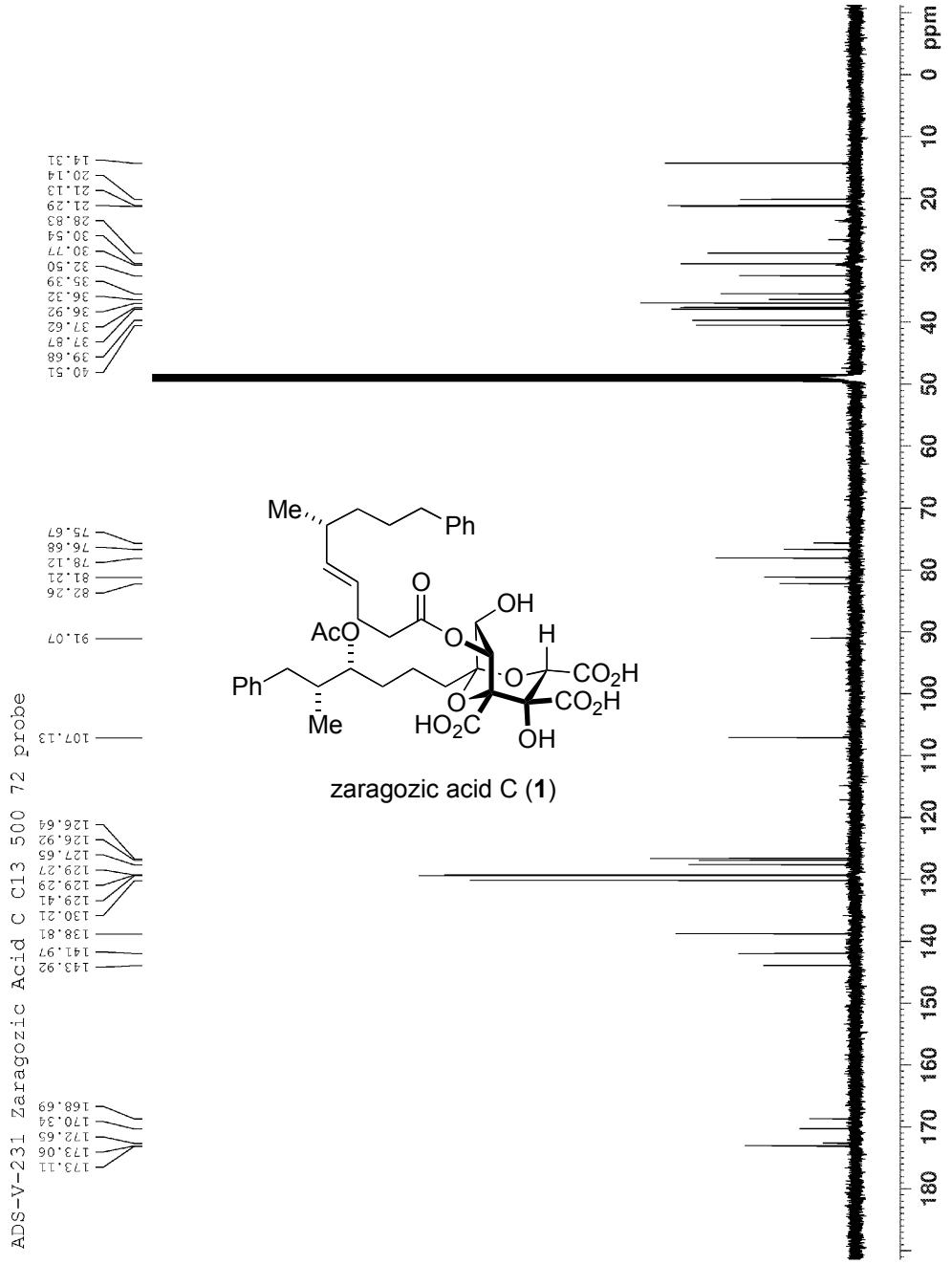
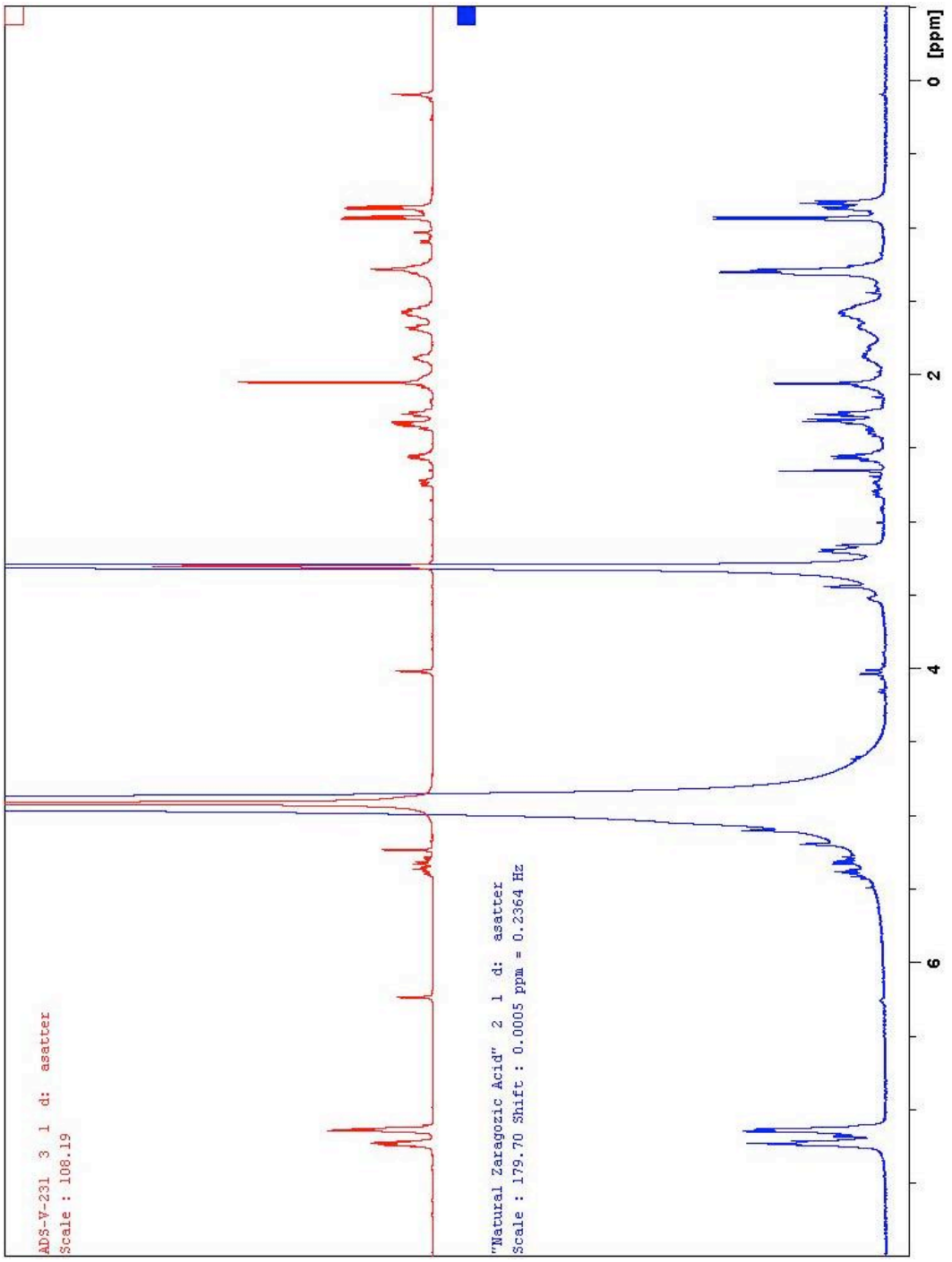


Fig 2.3 ^{1}H NMR Spectra Overlay: Synthetic Sample with Natural Sample



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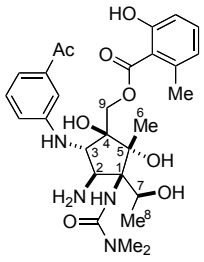
CHAPTER 3

PROGRESS TOWARD THE TOTAL SYNTHESIS OF PACTAMYCIN

3.1 Introduction

Scheme 3-1 Pactamycin

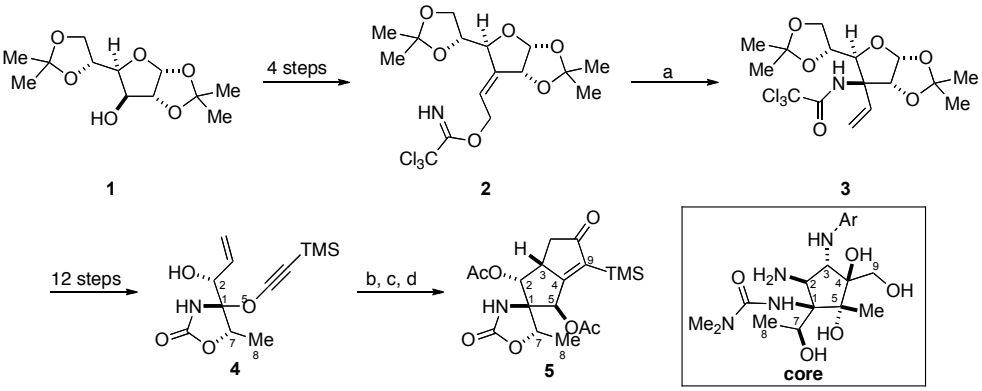


pactamycin

Pactamycin was first isolated from a fermentation broth of *Streptomyces pactum var pactum*.[1-3] It exhibits potent cytotoxicity showing *in vivo* and *in vitro* antitumor activity as well as antimicrobial activity.[2,4] This biological activity is a consequence of the inhibition of protein synthesis. Pactamycin exerts this effect through interaction with the small ribosomal subunit disrupting the action of translocation.[5-7] The structure of pactamycin was first determined by NMR analysis in 1969[8] and then corrected by X-ray crystal structure in 1972.[9]

The unique structure of pactamycin seen in Scheme **3-1** consists of a densely functionalized cyclopentane core. Stereocenters exist at all five carbons of the cyclopentane including three contiguous quaternary carbons that each contain O or N functionality. Despite its potent biological activity and distinctive complex structure, little has been done in regards to the synthesis of pactamycin. Currently, partial syntheses of the cyclopentane core by two groups represent the only efforts towards an artificial synthesis of this molecule.[10,11]

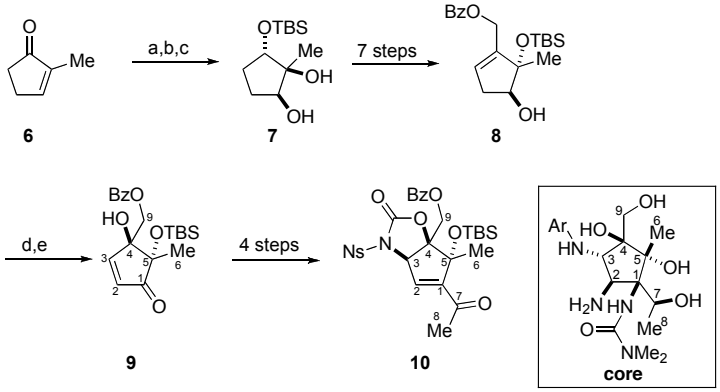
Scheme 3-2 Isobe Partial Core Synthesis



Key: [a] K_2CO_3, *p* - xylene, reflux. [b] $Co_2(CO)_8$, CH_2Cl_2, rt. [c] MeCN, 70 °C. [d] Ac_2O, pyridine, rt.

Isobe synthesized a key intermediate to a proposed total synthesis that contains some of the core functionality in 20 steps (Scheme **3-2**). Starting with a commercially available diacetonide-D-glucose **1**, intermediate **2** was formed in four steps setting up formation of the quaternary C1 by means of an Overman rearrangement.[12] Key enyne intermediate **4** is achieved in 12 subsequent steps. The core cyclopentane was then formed with an intramolecular Pauson-Khand reaction, isolated after 3 steps as bisacetate **5**.[13,14] The amino alcohol functionality at C1 and C7 has been installed in the correct configuration but additional synthetic manipulation would be needed to finish construction of the core of pactamycin as well as the rest of the molecule.

Scheme 3-3 Knapp Partial Core Synthesis



Key: [a] (*R*)-2-methyl-CBS-oxazaborolidine, BH_3, THF. [b] TBSCl, imidazole. [c] OsO_4, NMO, aq acetone. [d] *m*-CPBA, CH_2Cl_2, -20 °C, 60 h. [e] TPAP, NMO, CH_2Cl_2.

A second synthesis undertaken by Knapp reaches a proposed precursor to the core of pactamycin in 16 steps (Scheme **3-3**). The main strategy was to conduct cyclopentane-face-selective-transformations to setup the core configuration. Stereochemistry was initially established with an asymmetric reduction of commercially available 2-methyl-2-cyclopenten-1-one **6** using borane and catalytic (*R*)-2-methyl-CBS-oxazaborolidine.[15] Protection of the alcohol as the *tert*-butyldimethyl silyl (TBS) ether allowed for a facially selective dihydroxylation establishing C5 of the core. Subsequent manipulations then formed intermediate **8** that contained the necessary configuration for a directed epoxidation. Epoxidation was followed by oxidation of the C1 hydroxyl, which occurred with concurrent epoxide opening to form the α,β-unsaturated ketone **9** with C4 in the correct configuration. Additional steps bring the synthesis to a conclusion at **10**, another proposed precursor to the pactamycin core. As in the Isobe synthesis, additional synthetic transformation would be required to finish construction of the core from this point.

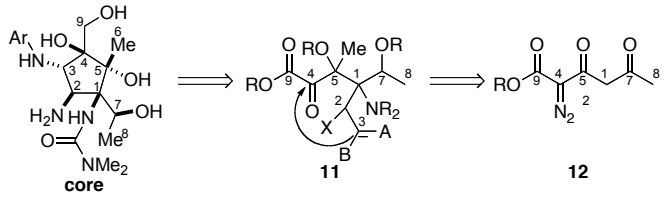
Given the lack of synthetic attention pactamycin has received and the possible challenges associated with construction of such a densely functionalized molecule, pactamycin is an ideal target for total synthesis. The goal of our synthesis is to efficiently assemble pactamycin in a

manner that rapidly builds complexity while minimizing functional group manipulation. Key to our synthesis will be formation of the cyclopentane ring through an intramolecular cyclization.

3.2 Results and Discussion

3.2.1 Retrosynthetic Analysis

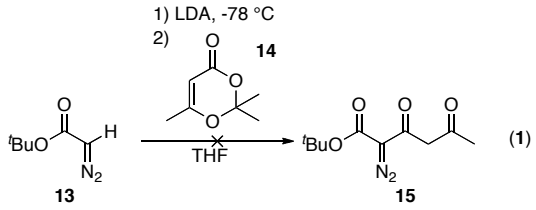
Scheme 3-4 Retrosynthetic Analysis of Pactamycin



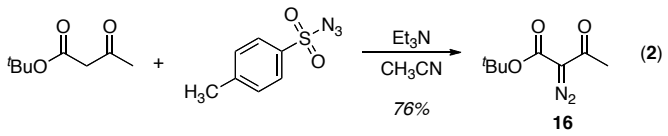
Our initial retrosynthetic analysis envisioned formation of the core by means of an intramolecular attack of a carbanion at C3 on a carbonyl at C4 initiated by deprotonation of a functionalized precursor such as **11**, which would originate from synthetic manipulation of diazo compound **12**. It was envisioned that diazo functionality at C4 could work as a blocking group to allow functionalization of the rest of the molecule prior to formation of the requisite carbonyl at C4 by oxidation. The stereocenter at C1 could be formed with two Michael additions of the diketone moiety of **12**. The first Michael addition to an azodicarboxylate would form the C–N bond at C1. The second Michael addition to a nitroalkene would install C2 and C3. The nitrate at C3 would provide the required C–N bond at C3 and act as an electron-withdrawing group to facilitate formation of a carbanion for the intramolecular cyclization. Methylation with an organometallic species such as MeMgBr and selective reduction would establish C5 and C7 respectively. This proposed strategy begins with a simple compound and rapidly builds up molecular complexity.

3.2.2 Diazo Blocking Strategy

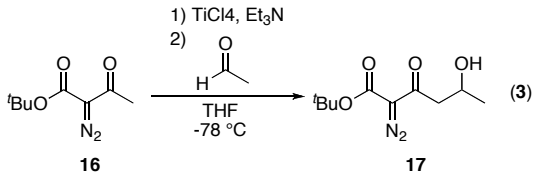
Investigation of our initial strategy began with the synthesis of **15**. Direct formation by means of organolithium addition to diketene surrogate **14** was unsuccessful (eq **1**).



Opting to try a less direct approach starting from commercially available *tert*-butylacetoacetate, diazo functionality was simply installed using tosyl azide and triethylamine in acetonitrile to give **16** in a 76% yield (eq **2**).

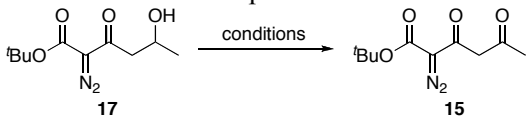


Attempts to homologate the additional carbonyl group in the correct oxidation state in one step proved unsuccessful. Deprotonation of **16** with strong bases such as NaH and lithium diisopropyl amide (LDA) with subsequent addition to Weinreb or morpholine amides gave no formation of **15**. Instead, addition of the titanium enolate of **16** to acetaldehyde formed **17**, which could be oxidized to **15**, in 73% yield (eq **3**).



A survey of oxidation protocols led to identification of Dess-Martin periodinane[16] as being uniquely capable of forming compound **15** in a 56% yield (**Table 3-1**).

Table 3-1 Oxidation Conditions for Diazo Compound

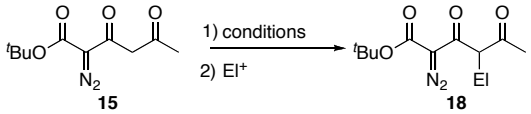


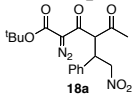
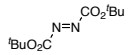
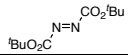
17 **15**

entry	conditions	result
1	MnO_2, CH_2Cl_2, rt	no desired product
2	PCC	no desired product
3	$Ba(MnO_4)_2$, CH_2Cl_2, rt	no desired product
4	Et_3N, SO_3, pyridine, DMSO 0 ° C → rt	no desired product
5	DMP	56% yield

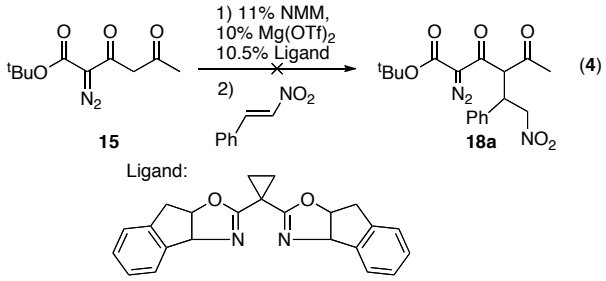
With **15** in hand, Michael addition of the diketone moiety was pursued (**Table 3-2**). Since **15** appeared to exist as a mixture of tautomers, as indicated by the presence of enol by ^1H NMR analysis, Michael addition was attempted by stirring **15** with a suitable electrophile. This resulted in no reactivity. Attempted deprotonation of **15** with both weak (entry 1) and strong (entries 2-5) bases followed by exposure to an electrophile yielded desired products only when the alkoxide base NaOMe was used in benzene. These conditions gave desired product **18a** in a 41% yield as a 1:1 ratio of diastereomers.

Table 3-2 Michael Addition of diazo **15**

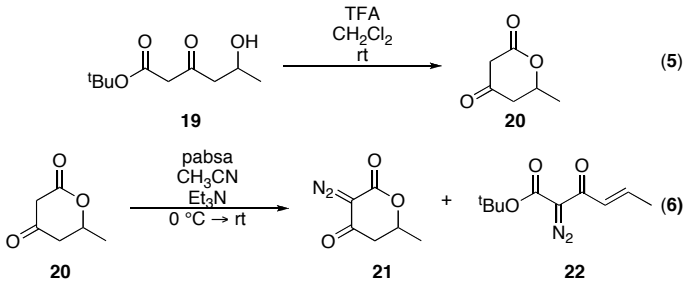


entry	conditions	El+	result
1	Et_3N, THF		no desired product
2	LDA, THF		no desired product
3	NaH, THF		no desired product
4	NaOMe, benzene		 41% yield, 1:1 dr
5	NaH, THF		no desired product
6	NaOMe, benzene		no desired product

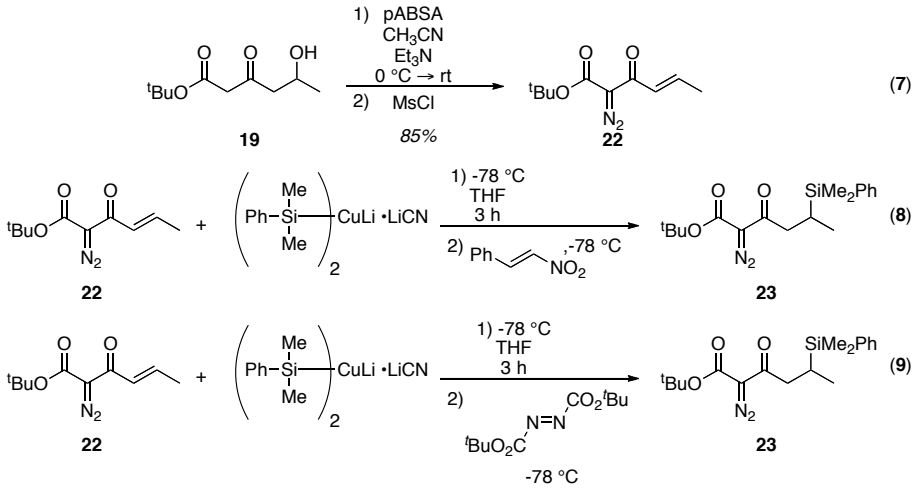
With limited success using base promoted Michael addition, a Lewis acid approach using a system developed by Barnes was investigated.[17] The original conditions, employing a $Mg(OTf)_2$ catalyst with a spiro bis(oxazoline) ligand in the presence of the base N-methyl morpholine (NMM) in chloroform were unsuccessful. Subsequent attempts using either benzene or toluene with copper triflate as the metal catalyst also led to no product formation.



While Michael addition of **15** was being investigated, we also explored the same possibility with lactone **21**. Formation of lactone **20** was achieved in good yield using trifluoroacetic acid in CH_2Cl_2 (eq **5**). Installation of the diazo functionality with para-acetamidobenzenesulfonyl azide (pABSA) led to formation of a mixture of the desired diazo lactone **21** and the elimination product **22** (eq **6**).



Observation of **22** made it appear likely that attempted deprotonation of the lactone would lead to elimination. So instead we decided to pursue Michael addition to the α,β-unsaturated ketone **22** followed by electrophilic trapping of the intermediate enolate. The elimination product **22** was obtained from **19** in an 85% yield by adding mesyl chloride to the reaction mixture following diazo transfer (eq **7**). A silyl cuprate was used as the nucleophile for the initial Michael addition[18] in the hope that the C–Si bond formed could later be oxidized with a Tamao-Fleming oxidation to install the necessary oxygen functionality at that position. This reaction was attempted with a nitro alkene and *tert*-butylazodicarboxylate as the secondary electrophile, and in both cases only successful 1,4-addition was observed with no desired capture of the enolate (eq **8** and **9**).

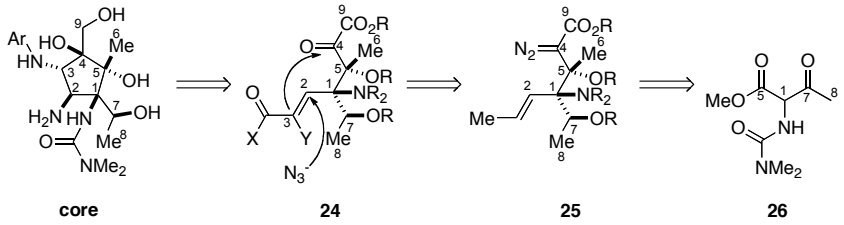


At this point it became apparent that this route was not a viable strategy for the synthesis of pactamycin. Bis-substitution of **15** seemed unlikely given the poor results we observed with

mono-substitution, and development of a conjugate addition was unnecessarily complicating the synthesis. Therefore we decided to pursue another line of attack.

3.2.3 Second Generation Retrosynthesis

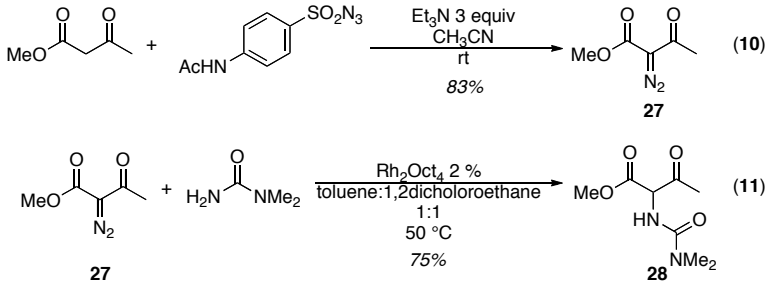
Scheme 3-5 Second Generation Retrosynthesis



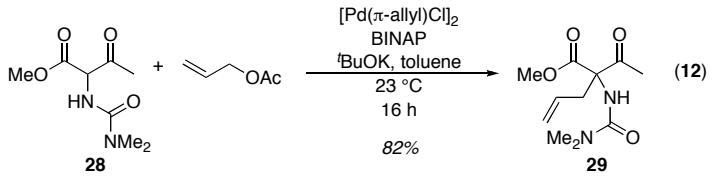
Our second-generation retrosynthesis again focuses on forming the cyclopentane core through the cyclization of a fully functionalized linear compound (Scheme **3-5**). The new strategy calls for an intramolecular cascade reaction initiated by Michael addition of an azide nucleophile to **24**. Subsequent intramolecular attack of the resultant enolate on the C4 ketone would result in successful formation of a pactamycin core precursor with the three contiguous quaternary centers at C4, C5 and C1 established. The proposed synthesis begins with **26**. A stereoselective allylation, developed by Ito for a compound analogous to **26,** would provide C1 in the correct configuration.[19] From there, **25** could be transformed into **24** through a diastereoselective reduction of the ketone at C7, conversion of the C5 ester to the methyl ketone, and a diastereoselective addition of an organolithium diazo compound. Manipulation of the allyl group on C1 would provide the Michael acceptor while the carbonyl at C4 would be revealed through diazo oxidation to give **24**. This revised synthesis again rapidly builds up functionality from a simple starting material. While the proposed cyclization may be difficult in such a complex system there is the possibility that Thorpe-Ingold effects may promote the intramolecular reaction.[20,21]

3.2.4 Synthesis of the Cyclization Precursor

Starting with methylacetoacetate diazo transfer was accomplished with pABSA to form **27** in 83% yield (eq **10**). Compound **28** was then synthesized by rhodium(II)-catalyzed N–H insertion of the diazo compound into *N*,*N*-dimethyl urea in 75% yield (eq **11**).[22] Catalyst loading in the reaction was 2 mol%, but it is possible to run the reaction with as little as 0.3 mol% over a longer period of time.

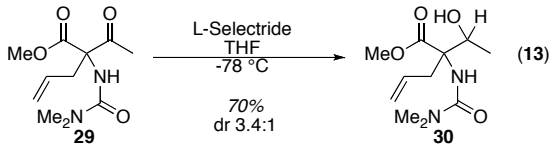


Application of **28** to the Ito protocol proved successful. The reaction uses a π-allyl Pd^{II} chloride dimer with the chiral bisphosphine ligand 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) to form the π-allyl electrophile from allyl acetate. The nucleophile is formed by potassium *tert*-butoxide deprotonation of **28**. The stereoselective reaction calls for chiral BINAP ligand and a temperature of -30 °C. At the time of writing there was greater interest in throughput than selectivity so the reaction was run at room temperature with a racemic ligand to give the racemic product **29** in 82% yield.



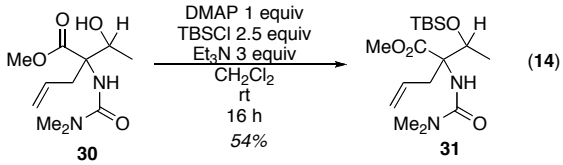
The next step of the synthesis is diastereoselective reduction of the ketone. Ito was able to reduce a substrate similar to **28** with an acetamide rather than a 1,1-dimethylurea in good yield and high diastereoselectivity with L-Selectride. Application of these conditions achieved successful reduction in a 70% yield, but with a diastereomeric ratio of only 3.4:1. If the relative configuration of the major diastereomer matches the similar substrate Ito used it should give us

the correct configuration at C1 and C7. The diastereomers of **30** are easily separated by flash column chromatography but other methods for reduction will need to be investigated to improve the diastereomeric ratio.

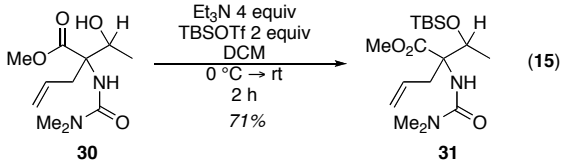


(**13**)

Protection of alcohol **30** as the silyl ether was accomplished with standard conditions using 4-dimethylaminopyridine (DMAP), TBSCl and triethylamine in CH_2Cl_2 over 16 h in 54% yield (eq **14**). Alternate conditions using triethylamine with TBSOTf, which have tended to work better for sterically hindered alcohols, improved the yield of the protection to 71% and shortened the reaction time to 2 h (eq **15)**.



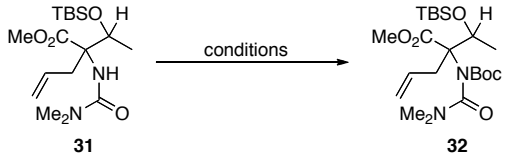
(**14**)



(**15**)

We next sought to protect the free amide nitrogen of **31** as the N-*tert*-butoxycarbonyl (Boc) derivative. Conditions involving di-*tert*-butyl dicarbonate(Boc_2O) used to protect amides adjacent to quaternary carbons were employed for the protection (Table **3-3**).[23,24] This hindered amide was unreactive and starting material was recovered in all cases.

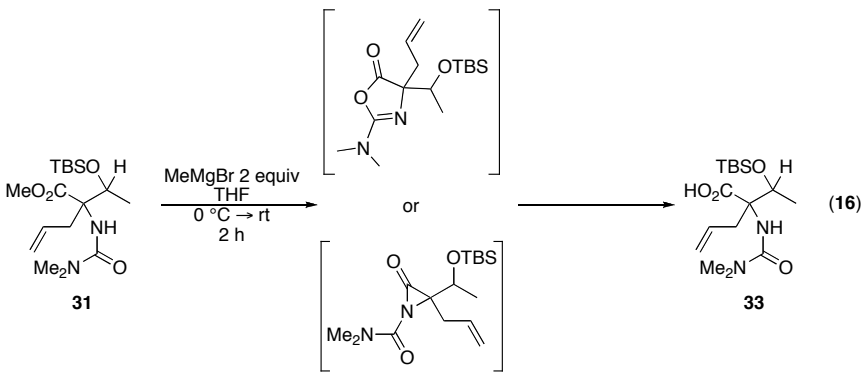
Table 3-3 Attempted Amide Protection



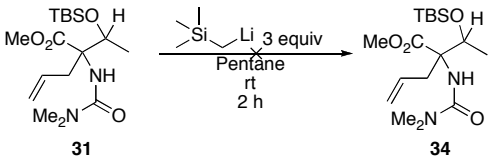
31 32

entry	conditions	result
1	Boc_2O 2 equiv, 10 % DMAP, THF	recovered starting material
2	Boc_2O 2 equiv, 1 equiv DMAP, 1 equiv Et_3N, THF	recovered starting material
3	Boc_2O 2 equiv, 1 equiv Me_4N^+ ^-OH, CH_3CN	recovered starting material

Since the hindered amide appeared to be shielded from reactivity we postulated that protection might be unnecessary. Initial attempts to form the methyl ketone directly from **31** with MeMgBr appeared to lead to saponification of the methyl ester based on ^1H NMR analysis (eq **16**). Saponification may occur because of the intermediate formation of an α-lactam or oxazolinone between the methyl ester and the free urea that becomes hydrolyzed upon aqueous workup. Formation of the methyl ketone from **31** was also attempted using trimethylsilylmethyl lithium (eq **17**).[25] This would form the α-silyl ketone that could easily be hydrolyzed to the desired methyl ketone under acidic or basic conditions, but the reaction led only to the recovery of starting material.


TBSO H
MeO2C
NH
Me2N O
31
MeMgBr 2 equiv
THF
0 °C → rt
2 h
O
OTBS
O
N
N
or
O
OTBS
N
Me2N
O
TBSO H
HO2C
NH
Me2N O
33

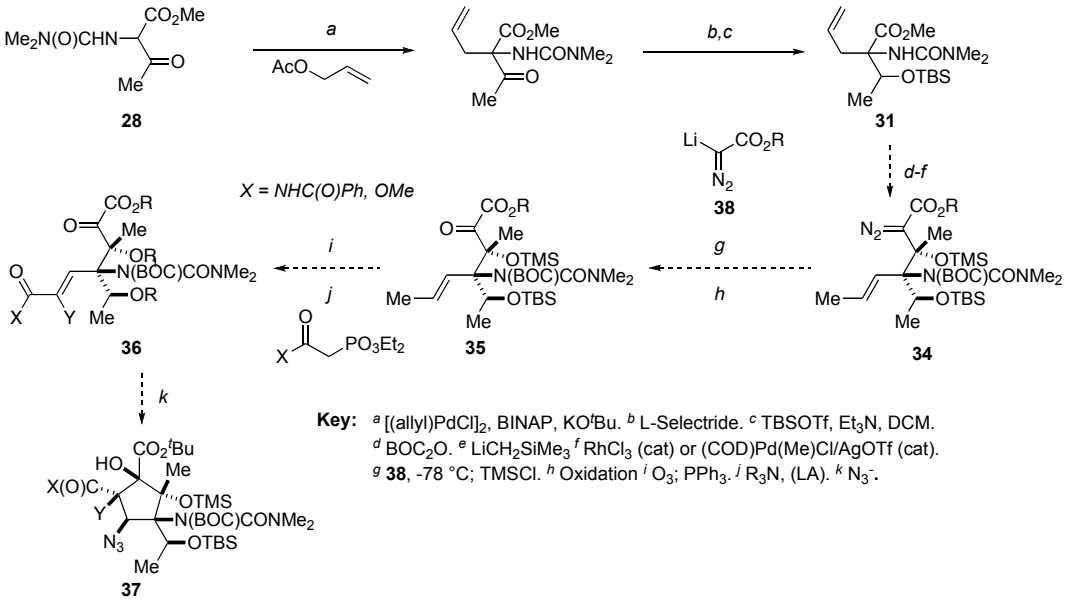
(**16**)


TBSO H
MeO2C
NH
Me2N O
31
Si
Li 3 equiv
Pentane
rt
2 h
TBSO H
MeO2C
NH
Me2N O
34

(**17**)

3.3 Conclusions and Future Directions

Scheme 3-6 Status and Future Directions



Currently the synthesis of pactamycin is in the early stages (Scheme **3-6**). Attempts to use diazo compound **15** as a nucleophile for a Michael addition were unsuccessful. This led to development of a second approach. We began with an application of an allylation protocol to our desired substrate **28** which formed the challenging quaternary center at C1. A diastereoselective reduction with L-Selectride formed **30**, which should contain the correct the configuration of C7. Further optimization of this reduction is necessary to boost the selectivity and increase the yield of the desired diastereomer. Protection of the hydroxyl group of **30** as the TBS ether has proven to be facile, but efforts to protect the urea have thus far been unsuccessful. Protection of the urea seems necessary based on observations made during attempts to transform the methyl ester to the methyl ketone in the presence of the free amide.

Assuming successful urea protection and formation of the methyl ketone, the next step will be to test addition of **38** to the methyl ketone and subsequent oxidative conversion of the

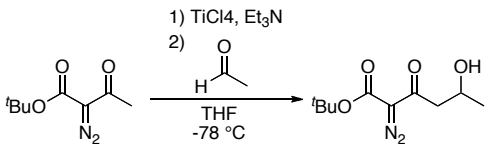
diazo moiety to a ketone. If we can achieve this we could then follow the plan proposed in Scheme **3-5**. The allyl group would be isomerized using a transition metal catalyst to form the internal olefin[26,27], which would then be cleaved oxidatively by ozonolysis. Formation of the Michael acceptor through a Wittig reaction would then bring us to the desired precursor to the cyclization. There are a number of methods we could use to achieve azide Michael addition such as $TMSN_3$ in the presence of F^- or various (salen)Cr-N_3 and (salen)Al-N_3 complexes.[28-30]

The current work represents a promising start and once core formation has been achieved the total synthesis of pactamycin will be pursued. The hindered nature of this molecule represents a synthetic challenge but realization of the proposed synthesis would efficiently form the core of pactamycin. It would also represent a new strategy for the formation of densely functionalized cyclopentane rings.

3.4 Experimental

General Information. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on the following instruments: Bruker model Avance 400 (^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz) and Varian Gemini 300 (^1H NMR at 300 MHz and ^{13}C at 75 MHz) spectrometers with solvent resonance as the internal standard (^1H NMR: $CDCl_3$ at 7.24 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = 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, aqueous $KMnO_4$ solution followed by heating 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). Air sensitive reactions

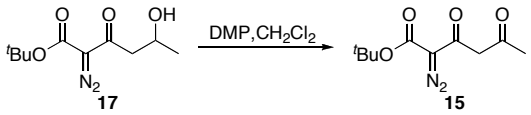
were carried out under an atmosphere of nitrogen in oven-dried glassware. Yield refers to isolated yield of analytically pure material. Toluene, CH_2Cl_2 and pentane were dried by passage through a column of neutral alumina under nitrogen prior to use.[31] Et_3N and 1,2 dichloroethane was distilled from CaH_2 prior to use. Benzene was distilled from sodium prior to use. Potassium *tert*-butoxide was sublimed prior to use. Lactone **20** was prepared according to the literature procedure.[32] Silyl cuprates were prepared according to the literature procedure.[33] *Tert*-butyl diazo acetate was prepared according to the literature procedure.[34] (*E*)-(2-nitrovinyl)benzene was prepared according to the literature procedure.[35] Dess-Martin periodinane was prepared according to the literature procedure.[36,37] Yields and diastereomer ratios are reported for a specific experiment and as a result may differ slightly from those found in the tables, which may be averages of at least two experiments. Unless otherwise noted, reagents were obtained from commercial sources and used without further purification.



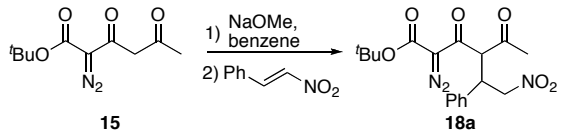
16 **17**

***tert*-butyl 2-diazo-5-hydroxy-3-oxohexanoate (17).** A round bottomed flask equipped with a stirbar, purged with nitrogen and charged with 500 mg (2.7 mmol, 1 equiv) of **16** and dry CH_2Cl_2 (18 mL). The solution was cooled to -78 °C and treated with 302 µL (3 mmol, 1.1 equiv) of Et_3N and 327 µL (3 mmol, 1.1 equiv) of $TiCl_4$ dropwise via syringe. The resultant red solution was stirred for one hour and then 254 µL (2.7 mmol, 1 equiv) of acetaldehyde in CH_2Cl_2 (2 mL) was added via cannula. The resultant solution was stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) stirring for 30 min while warming to 23 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (5:1 petroleum ether:EtOAc) to furnish 469 mg (76%) of diazo compound **17**.

Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.29 – 4.20 (m, 1H), 3.07 (dd, *J* = 17.5, 2.2 Hz, 1H), 2.84 (dd, *J* = 17.5, 9.3 Hz, 1H), 1.51 (s, 9H), 1.22 (d, *J* = 6.3 Hz, 3H); TLC (5:1 petroleum ether/EtOAc) R_f of 0.20.

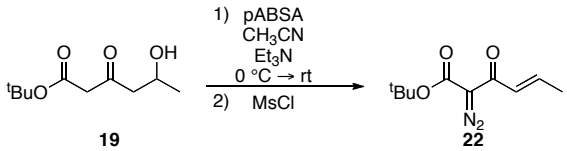


***tert*-butyl 2-diazo-3,5-dioxohexanoate (15).** A round bottomed flask equipped with a stirbar, purged with nitrogen and charged with 50 mg (0.2 mmol, 1 equiv) of **17** and dry CH_2Cl_2 (3 mL). The solution was stirred and treated with 139 mg (0.3 mmol, 1.5 equiv) of Dess-Martin periodinane. The resultant solution was stirred for 2 h. The reaction was quenched with 1:1 saturated aqueous $NaHCO_3$/aqueous $Na_2S_2O_3$ (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (10:1 petroleum ether:EtOAc) to furnish 28 mg (56%) of diazo compound **15**. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 14.93(enol) (s, 1H), 6.39(enol) (s, 1H), 3.92 (s, 2H), 2.23 (s, 3H), 2.00(enol) (s, 3H), 1.48(enol) (s, 9H), 1.47 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.46, 180.50, 160.36, 96.85, 83.53, 83.16, 54.66, 29.66, 28.25, 28.21, 22.28; TLC (10:1 petroleum ether/EtOAc) R_f of 0.25.



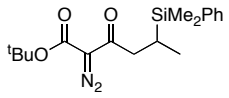
***tert*-butyl 4-acetyl-2-diazo-6-nitro-3-oxo-5-phenylhexanoate (18a).** A flame dried shell vial was equipped with a stirbar, purged with nitrogen and charged with 25 mg (0.11 mmol, 1 equiv) of **15**, 6 mg (0.11 mmol, 1 equiv) of NaOMe, 16,4 mg (0.11 mmol, 1 equiv) of (*E*)-(2-nitrovinyl)benzene and dry CH_2Cl_2 (3 mL). The solution was stirred and monitored by TLC for 16 h. The reaction was quenched with distilled H_2O (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried (Na_2SO_4) and

concentrated *in vacuo*. The crude product was purified by flash chromatography (5:1 petroleum ether:EtOAc) to furnish 17 mg (41%) of diazo compound **18a** as a 1:1 mixture of diastereomers(determined by ^{1}H NMR). Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.19 (m, 4H), 5.29 (d, *J* = 8.9 Hz, 1H), 4.86 (dd, *J* = 13.1, 9.8 Hz, 1H), 4.71 (dd, *J* = 13.1, 4.1 Hz, 1H), 4.30 (td, *J* = 9.4, 4.1 Hz, 1H), 1.97 (s, 3H), 1.47 (s, 9H); TLC (10:1 petroleum ether/EtOAc) R_f of 0.30.



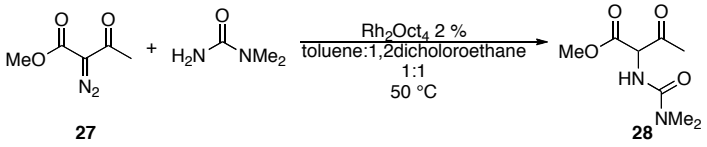
19 22

***tert*-butyl 2-diazo-3-oxohex-4-enoate (22).** A round bottomed flask was equipped with a stirbar, and charged with 400 mg (2 mmol, 1 equiv) of **19**, 475 mg (2 mmol, 1 equiv) of pABSA and CH_3CN (20 mL). The solution was cooled to 0 °C and 1.1 mL (8 mmol, 4 equiv) of Et_3N was added and the solution was stirred and slowly warmed to 23 °C. After 16 h of stirring, 453 mg (4 mmol, 2 equiv) of mesyl chloride were added and stirring was continued for 3 h. The crude reaction mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (5:1 petroleum ether:EtOAc) to furnish 354 mg (85%) of diazo compound **22**. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 – 6.86 (m, 2H), 1.85 (d, *J* = 6.7 Hz, 3H), 1.46 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.80, 160.45, 142.67, 126.61, 82.95, 28.11, 18.19; TLC (10:1 petroleum ether/EtOAc) R_f of 0.25.

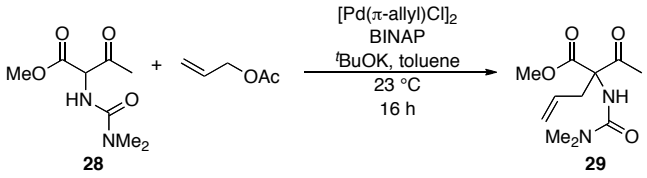


23

***tert*-butyl 2-diazo-5-(dimethyl(phenyl)silyl)-3-oxohexanoate (23).** Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 – 7.28 (m, 5H), 2.80 (dd, *J* = 16.3, 3.9 Hz, 1H), 2.66 (dd, *J* = 16.3, 10.6 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.48 (s, 9H), 0.92 (d, *J* = 7.3 Hz, 3H), 0.27 (d, *J* = 2.1 Hz, 6H).; TLC (20:1 petroleum ether/EtOAc) R_f of 0.30.

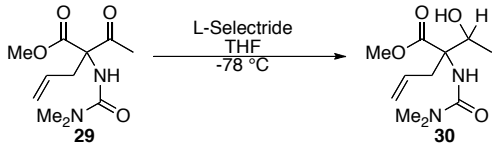


methyl 2-(3,3-dimethylureido)-3-oxobutanoate (28). An oven-dried round bottomed flask was equipped with a stirbar, and charged with 290 mg (2 mmol, 1 equiv) of **27**, 268 mg (3 mmol, 1.5 equiv) of N,N-dimethyl urea and 1:1 toluene/1,2 dichloroethane (20 mL). The suspension was stirred and heated to 80 °C. A suspension of 32 mg (0.04 mmol, 0.02 equiv) of rhodium octanoate dimer in toluene (4 mL) was added to the solution in portions over 10 minutes. During addition a gas was evolved. The solution was stirred for 50 min during which time the color changed from green to yellow. The crude reaction mixture was cooled to 23 °C and concentrated *in vacuo*. The crude product was purified by flash chromatography (1:1 petroleum ether:EtOAc with 3% Et_3N) to furnish 299 mg (75%) of compound **28**. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.55 (d, J = 6.0 Hz, 1H), 5.03 (d, J = 6.5 Hz, 1H), 3.64 (s, 3H), 2.79 (s, 6H), 2.21 (s, 3H).; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.57, 167.43, 156.62, 63.99, 52.65, 35.74, 27.51; TLC (1:1 petroleum ether/EtOAc) R_f of 0.2; **HRMS** (ESI) exact mass calculated $C_8H_{14}N_2O_4Na$ [M+Na]+: 225.0845 Found: 225.0851.



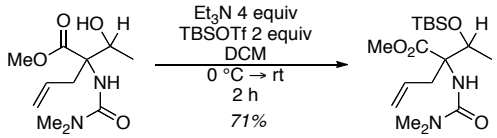
methyl 2-acetyl-2-(3,3-dimethylureido)pent-4-enoate (29). An oven-dried round bottomed flask was purged with nitrogen, equipped with a stirbar, and charged with 0.9 mg (0.002 mmol, 0.005 equiv) of allyl palladium chloride, 3 mg (0.005 mmol, 0.010 equiv) of BINAP and toluene (1 mL). A separate oven-dried round bottomed flask was equipped with a stirbar purged with nitrogen and charged with 100 mg (0.5 mmol, 1 equiv) of **28**, 67 mg (0.6 mmol, 1.2 equiv) of KO^{t}Bu and toluene (1 mL). The suspensions were stirred at 23 °C for 10 minutes and then 74 mg

(0.7 mmol, 1.5 equiv) of allyl acetate was added via syringe to the palladium catalyst solution. Stirring was continued for an additional 10 minutes and then the catalyst solution was transferred to the suspension of substrate via cannula transfer (0.5 mL wash). The solution was stirred for 16 h. Upon consumption of starting material, as indicated by TLC, the reaction was quenched with 1 N HCl (1 mL). The aqueous layer was extracted with EtOAc (3 x 3 mL). The organic layer was washed with brine (3 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The crude product was purified by flash chromatography (3:1 petroleum ether:acetone) to furnish 98 mg (82%) of compound **29**. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.56 – 5.35 (m, 1H), 5.10 – 4.96 (m, 2H), 3.71 (s, 3H), 3.11 (dd, J = 14.6, 6.8 Hz, 1H), 2.94 (dd, J = 14.7, 7.8 Hz, 1H), 2.87 (s, 6H), 2.12 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.97, 169.47, 156.02, 131.60, 119.19, 71.94, 53.15, 36.83, 35.99, 24.54; TLC (3:1 petroleum ether/acetone) R_f of 0.25; **HRMS** (ESI) exact mass calculated $C_{11}H_{18}N_2O_4Na$ [M+Na]+: 265.1161 Found: 225.1164.

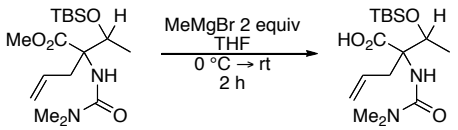


methyl 2-(3,3-dimethylureido)-2-(1-hydroxyethyl)pent-4-enoate (30). An oven-dried round bottomed flask was purged with nitrogen, equipped with a stirbar, and charged with 50 mg (0.2 mmol, 1.0 equiv) of **29** and THF (1.5 mL). The solution was stirred, cooled to -78 °C and 0.31 mL (0.3 mmol, 1.5 equiv) of L-Selectride (1 M in THF) was added dropwise via syringe. The solution was stirred for 2 h. Upon consumption of starting material, as indicated by TLC, the reaction was quenched with, in order, 0.2 mL H_2O, 0.2 mL EtOH, 0.2 mL NaOH (3 M), and 0.2 mL H_2O_2 (30% aqueous solution). The solution was stirred for 10 min at 23 °C. Excess H_2O_2 was quenched with saturated aqueous $Na_2S_2O_8$ (1 mL) and the reaction was diluted with H_2O. The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layer was washed with brine (3 mL), dried (Na_2SO_4) and concentrated in *vacuo*. The crude product was purified by flash

chromatography (3:1 petroleum ether:acetone) to furnish 27 mg (54%) of compound **30** (major diastereomer) and 8 mg (16%) of compound **30** (minor diastereomer). Analytical data for title compound (major diastereomer): **^{1}H NMR** (400 MHz, $CDCl_3$)δ 6.15 (d, *J* = 10.3 Hz, 1H), 5.64 – 5.50 (m, 1H), 5.18 (dd, *J* = 21.2, 13.3 Hz, 2H), 4.85 (s, 1H), 4.04 (dq, *J* = 12.9, 6.4 Hz, 1H), 3.76 (s, 3H), 2.91 (s, 6H), 2.74 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.34 (dd, *J* = 13.7, 10.0 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.80, 158.71, 132.62, 120.66, 71.48, 68.23, 52.55, 40.24, 36.67, 18.18; TLC (5:2 petroleum ether/acetone) R_f of major 0.45, minor 0.55.



methyl 2-(1-(tert-butyldimethylsilyloxy)ethyl)-2-(3,3-dimethylureido)pent-4-enoate (31). An oven-dried round bottomed flask was purged with nitrogen, equipped with a stirbar, and charged with 81 mg (0.33 mmol, 1.0 equiv) of **29** and CH_2Cl_2 (1.5 mL). The solution was stirred, cooled to 0 °C and 0.18 mL (1.3 mmol, 4 equiv) of Et_3N followed by 175 mg (0.66 mmol, 2 equiv) of TBSOtf were added dropwise via syringe. The solution was stirred for 2 h. Upon consumption of starting material, as indicated by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was dried (Na_2SO_4) and concentrated in *vacuo*. The crude product was purified by flash chromatography (5:1 petroleum ether:acetone) to furnish 102 mg (86%) of compound **31**. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 5.89 – 5.74 (m, 1H), 5.31 (s, 1H), 5.06 – 4.91 (m, 2H), 3.71 (s, 3H), 3.06 – 2.96 (m, 1H), 2.87 (s, 6H), 2.76 (d, *J* = 8.0 Hz, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.59, 117.27, 72.09, 52.25, 36.21, 35.46, 25.67, 18.81, 17.81, -4.02, -5.04; TLC (10:1 petroleum ether/acetone) R_f of major 0.15.



31 **33**

2-(1-(tert-butyldimethylsilyloxy)ethyl)-2-(3,3-dimethylureido)pent-4-enoic acid (33). An oven-dried round bottomed flask was purged with nitrogen, equipped with a stirbar, and charged with 27 mg (0.08 mmol, 1.0 equiv) of **31** and THf (1.0 mL). The solution was stirred, cooled to 0 °C and 0.05 mL (0.15 mmol, 2 equiv) of MeMgBr (3 M in THF) was added dropwise via syringe. The solution was stirred for 2 h. Upon consumption of starting material, as indicated by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layer was dried ($MgSO_4$) and concentrated in *vacuo*. The crude product was relatively pure and 24 mg (100%) of compound **33** was recovered. Analytical data for title compound: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.73 – 5.55 (m, 1H), 5.16 – 4.97 (m, 2H), 3.98 (q, J = 6.2 Hz, 1H), 3.75 – 3.66 (m, 1H), 2.90 (d, J = 17.3 Hz, 6H), 2.41 – 2.32 (m, 2H), 1.22 – 1.14 (m, 3H), 0.79 (s, 9H), -0.01 (t, J = 7.8 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.45, 131.86, 119.27, 78.13, 77.32, 77.00, 76.68, 72.20, 37.98, 36.80, 25.53, 17.77, 17.65, -5.39.; TLC (5:1 petroleum ether/acetone) R_f of major 0.63.

3.5 References

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