I. MECHANISTIC STUDIES OF A COPPER-CATALYZED ELECTROPHILIC AMINATION OF DIORGANOZINC REAGENTS BY *O*-BENZOYL *N,N*-DIALKYLHYDROXYLAMINES

II. DEVELOPMENT OF A 3-EXO-DIG CYCLIZATION FOR THE PREPARATION OF VINYLIDENE CYCLOPROPANES

III. TOTAL SYNTHESIS OF (+)-POLYANTHELLIN A

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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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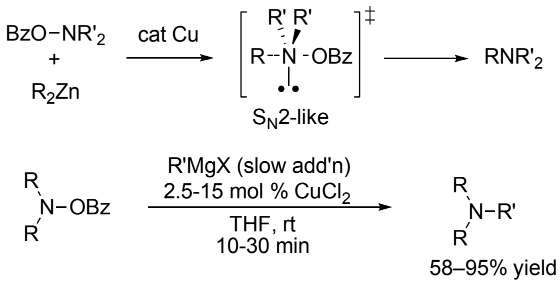
ABSTRACT

MATTHEW JAMES CAMPBELL:
I. Mechanistic Studies of a Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents by *O*-Benzoyl *N,N*-Dialkylhydroxylamines
II. Development of a 3-*Exo*-*Dig* Cyclization for the Preparation of Vinylidene Cyclopropanes
III. Total Synthesis of (+)-Polyanthellin A
(Under the direction of Professor Jeffrey Scott Johnson)

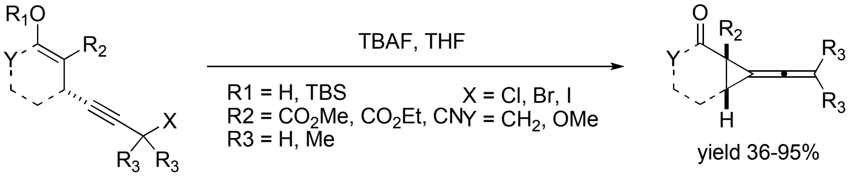
I. Mechanistic Studies of a Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents by *O*-Benzoyl *N,N*-Dialkylhydroxylamines

The mechanism of the Cu-catalyzed amination of R_2Zn reagents by *O*-benzoyl *N,N*-dialkylhydroxylamines has been investigated. An S_N2 pathway has been supported because : (i) stoichiometrically generated cuprates were used to prove zinc is not essential in the C–N bond forming step; (ii) the configuration at the reacting carbon is retained through the reaction, ruling out a radical pathway; (iii) the endocyclic restriction test proceeded without intramolecular amination. A Cu-catalyzed amination of Grignard reagents was realized after experiments determined the relative rates of *O*-acylation, transmetalation, and C–N bond formation were favorable. *O*-Mesitoyl *N,N*-dialkylhydroxylamines were found to be suitable $R_2N(+)$ synthons for the uncatalyzed amination of Grignard reagents, including unhindered vinyl Grignard reagents.


BzO−NR'$_2$
+
R$_2$Zn
cat Cu
R' R'
R--N -OBz
‡
S$_N$2-like
RNR'$_2$
R
N−OBz
R
R'MgX (slow add'n)
2.5-15 mol % CuCl$_2$
THF, rt
10-30 min
R
N−R'
R
58–95% yield

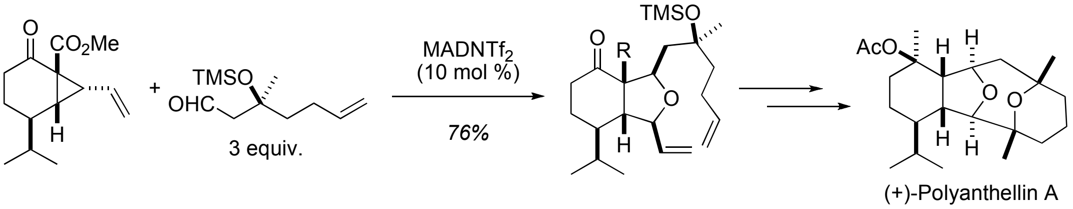
II. Development of a 3-*Exo-Dig* Cyclization for the Preparation of Vinylidene Cyclopropanes

The first all-carbon 3-*exo-dig* cyclization was developed. These cyclizations lead to vinylidene cyclopropanes with electron-withdrawing substituents, products that are not available using carbene chemistry. Both cyclic and acyclic precursors can be used with equal efficacy, although high dilution conditions were necessary to enable cyclization of the latter. The products were amenable to a number of common derivatizations, including halogenation, hydrogenation, and hydroboration.


R$_1$O
Y
R$_2$
X
R$_3$ R$_3$
TBAF, THF
R1 = H, TBS
R2 = CO$_2$Me, CO$_2$Et, CN
R3 = H, Me
X = Cl, Br, I
Y = CH$_2$, OMe
O
Y
R$_2$
H
R$_3$
R$_3$
yield 36-95%

III. Total Synthesis of (+)-Polyanthellin A

(+)-Polyanthellin A was synthesized in 15 linear steps from methallyl alcohol in 2% overall yield, with an average yield of 77% per step. This synthesis demonstrates the utility of the [3+2]-cycloaddition between cyclopropanes and aldehydes in a complex setting. The use of the hindered catalyst, MADNTf$_2$, was essential to ensure a successful cyclization, and has extended the scope of the cycloaddition to include sensitive protected β-hydroxyaldehydes. Other key steps included a Cu-catalyzed cyclopropanation, ring-closing metathesis, selective alkene oxidation, and an iodoetherification.



CO2Me
H
TMSO
OHC
3 equiv.
MADNTf2
(10 mol %)
76%
TMSO
R
O
H
AcO
H
H
(+)-Polyanthellin A

ACKNOWLEDGEMENTS

I would first like to acknowledge Professor Jeff Johnson for guiding my research during the five years I've been here at UNC. As I matured as a chemist, he was more than willing to let me research in my own style, but still would nudge me back on track if I started to stray away from straightforward and simple solutions. I was able to work on diverse projects throughout my tenure here that have opened me up a number of unrelated areas in synthetic chemistry. For this opportunity, I am truly grateful as I realize this is not generally true for organic students. I'm also appreciative of Jeff's ability to not pass judgment, even when I'm arguing against reason, and for humoring the bad ideas I've come up with over the years.

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LIST OF ABBREVIATIONS AND SYMBOLS

18-c-6	1,4,7,10,13,16-hexaoxacyclooctadecane
2D-NMR	two-dimensional nuclear magnetic resonance
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetate
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
Ar	aryl
aq.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
BQ	benzoquinone
br	broad
n-Bu	*normal*-butyl
s-BuLi	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
cat.	catalytic amount or catalyst
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
conv.	conversion
mCPBA	*meta*-chloroperbenzoic acid

c-Hex	cyclohexyl
COSY	correlated spectroscopy
Cp	cyclopentadienyl
c-Pr	cyclopropyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dba	dibenzylidene acetone
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DET	diethyltartrate
DIBAL-H	diisobutylaluminum hydride
dig	digonal
DMA	*N,N*-dimethylacetamide
DMAP	4-*N,N*-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
endo	endocyclic
ent	enantiomer

eq	equation
equiv	equivalents
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
exo	exocyclic
FID	flame ionization detector
GLC	gas-liquid chromatography
hr	hour
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HMPA	hexamethylphosphoramide
HOAc	acetic acid
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
(+)-iPCBH	(+)-diisopinocampheylborane
IR	infrared spectroscopy
J	coupling constant
kPa	kilopascal

LA	Lewis acid
LDA	lithium diisopropylamide
LRMS	low resolution mass spectroscopy
LUMO	lowest unoccupied molecular orbital
M	metal or molarity
m	multiplet
Me	methyl
MeCN	acetonitrile
2-MeTHF	2-methyltetrahydrofuran
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
mmol	millimole
mp	melting point
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
nOe	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy

oct	octuplet or octanoate
ORTEP	Oak Ridge thermal ellipsoid plot
PDC	pyridinium dichromate
Ph	phenyl
Ph_2CO	benzophenone
pin	pinacolato
Piv	pivolate
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
i-Pr	*iso*-propyl
n-Pr	*normal*-propyl
q	quartet
quint	quintuplet
R	alkyl or aryl
rac	racemic
RCM	ring closing metathesis
rt	room temperature
s	singlet
sept	septuplet
S_N2	bimolecular nucleophilic substitution
T	temperature
t	triplet

TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
tet	tetrahedral
Tf	trifluoromethanesulfonyl
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMCDA	*N,N,N′,N′*-tetramethyl-1,2-diaminocyclohexane
TMP	2,2,6,6-tetramethylpiperidine
TPAP	tetrapropyl ammonium peruthenate
TLC	thin layer chromatography
Tr	triphenylmethyl (trityl)
trig	trigonal
Ts	*para*-toluenesulfonyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine
X	anionic ligand
δ	chemical shift
μL	microliter

CHAPTER ONE

MECHANISTIC STUDIES OF A COPPER-CATALYZED ELECTROPHILIC AMINATION OF DIORGANOZINC REAGENTS BY *O*-BENZOYL *N,N*-DIALKYLHYDROXYLAMINES

1.1 Introduction

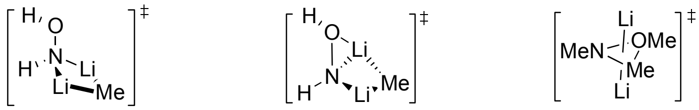
Normal and reverse polarity (umpolung) strategies are powerful methods for carbon-nitrogen bond formation. Normal polarity couplings use nucleophilic nitrogen sources with pre-oxidized carbon donors in the form of alkyl or aryl halides and pseudohalides, while umpolung chemistry dictates electrophilic nitrogen donors undergo reaction with a nucleophilic organometallic.[1] Although utilized less frequently in organic synthesis, much attention has been devoted to developing suitable $R_2N(+)$ synthons that typically contain N-heteroatom single or multiple bonds.[2,3] Methods exist to aminate both stabilized[4] and unstabilized[5] carbanions. Initial research with the latter utilized strongly basic RLi and RMgX reagents, taking advantage of their potent reactivity. Unfortunately, this property precluded their use in systems containing sensitive functionality. Improvements in transition metal catalyzed nucleophilic aminations, such as the Buchwald-Hartwig coupling,[6-8] benefited from a detailed mechanistic understanding that allowed reaction parameters to be rationally modified. This success stimulated research to develop analogous catalytic electrophilic aminations, but these are not yet competitive in scope or efficiency. This chapter will delineate the mechanism of the copper-catalyzed amination of diorganozinc reagents with *O*-benzoyl *N,N*-dialkylhydroxylamines, with the goal that this insight will enable catalytic electrophilic amination technology to expand.

1.2 Background

1.2.1 Mechanistic Studies of Uncatalyzed Electrophilic Aminations

The mechanism of uncatalyzed electrophilic aminations is well studied, in part because of curiosity surrounding the coupling of seemingly repulsive entities: negatively charged carbanions and anionic lithium *O*-alkyl hydroxylamides. Beak and coworkers utilized both endo- and exocyclic restriction tests to support an S_N2-like polar mechanism for the reaction of unstabilized and stabilized organolithium reagents with both anionic lithium *O*-methyl hydroxylamides and neutral *O*-phosphinyl *N,N*-dialkylhydroxylamines.[9-11] Boche and Wagner,[12] Armstrong,[13] and McKee[14] conducted computational experiments confirming Beak's assumption and provided transition states to account for a substitution mechanism (Figure 1-1). The salient feature is two N–Li–C bridging interactions that bring the carbanion and electrophilic nitrogen in close proximity with one another. Similar interactions have been proposed for the amination of Gilman cuprates with *N,O*-bis(trimethylsilyl)hydroxylamine, which is deprotonated during the reaction, by correlating the hardness of various alkyl and aryl cuprates with their propensity to undergo competitive hydroxylation and amination.[15]

Figure 1-1. Calculated Transition States for Methyllithium with Hydroxylamine Derivatives

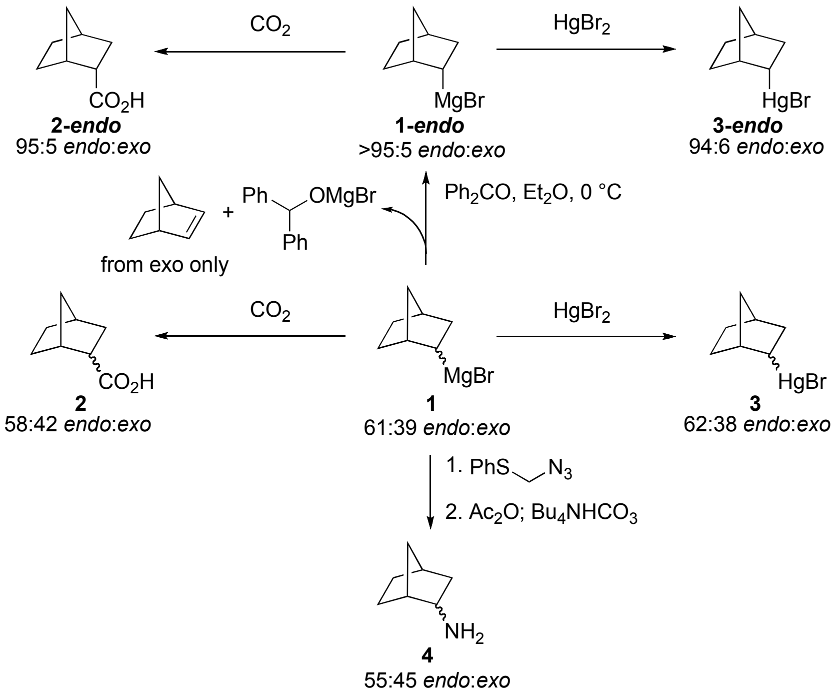


Boche and Wagner Armstrong *et. al.* McKee

Configurationally defined carbon nucleophiles have been used to test between radical and polar mechanisms in organometallic reactions, using the hypothesis that polar reactions will preserve the stereocenter at the reacting carbon, while mechanisms involving radical species will result in epimerization. Jensen and Nakamaye introduced this technique with the development of the diastereomerically enriched Grignard reagent, *endo*-2-norbornylmagnesium bromide (**1-*endo***), resolved by reaction of a 59:41 *endo*:*exo* mixture with benzophenone, which accepts a hydride from only the *exo* diastereomer.[16,17] In the seminal report, reaction with both CO_2 and $HgBr_2$ led to the isolation of highly enriched acid **2-*endo*** and mercurial **3-*endo***, supporting a polar mechanism for both carboxylation and mercuration (Scheme 1-1). To control against diastereoselectivity-induced bias, the same reactions were conducted using an equilibrium mixture of **1** and proceeded with preservation of the ratio.

In the context of electrophilic amination, this system was employed by Trost and Pearson to evaluate the reaction of Grignard reagents with azidomethyl phenyl sulfide, although only the unresolved mixture was aminated.[18] The amine **4** was obtained as a 55:45 *endo*:*exo* mixture, in support of a polar mechanism.

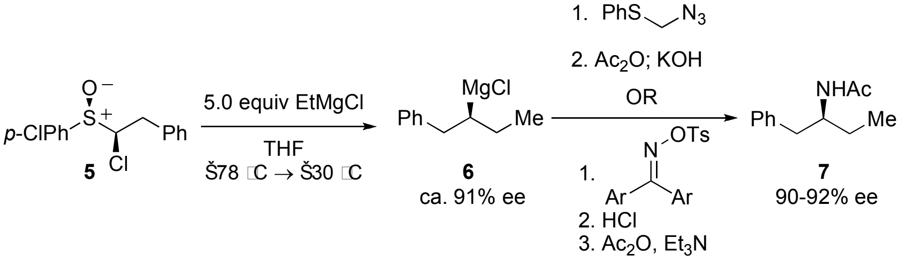
Scheme 1-1. Resolution of 2-Norbornylmagnesium Bromide (**1**) and Reaction with $HgBr_2$, CO_2, and Azidomethyl Phenyl Sulfide



CO2
HgBr2
CO2H
2-endo
95:5 endo:exo
MgBr
1-endo
>95:5 endo:exo
HgBr
3-endo
94:6 endo:exo
+
Ph
OMgBr
Ph
from exo only
Ph2CO, Et2O, 0 °C
CO2
HgBr2
CO2H
2
58:42 endo:exo
MgBr
1
61:39 endo:exo
HgBr
3
62:38 endo:exo
1. PhS N3
2. Ac2O; Bu4NHCO3
NH2
4
55:45 endo:exo

An enantiomerically enriched Grignard reagent was developed by Hoffmann and coworkers, which has an advantage over diastereomerically enriched reagents.[19,20] The lack of adjacent stereocenters allows unambiguous analysis of the reaction of interest. The optically enriched Grignard **6** is prepared by reaction of enantiomerically pure α-chlorosulfoxide **5** with EtMgCl at low temperature. This reagent has been used to elucidate the mechanism of a variety of oxidation and addition reactions.[19,21] Amination with azidomethyl phenyl sulfide or an oxime tosylate provided the acetamide **7** with complete retention of configuration, supporting a polar mechanism for these reactions (Scheme 1-2).[22]

Scheme 1-2. Reaction of Hoffmann's Enantiomerically Enriched Grignard Reagent with Electrophilic Nitrogen Species

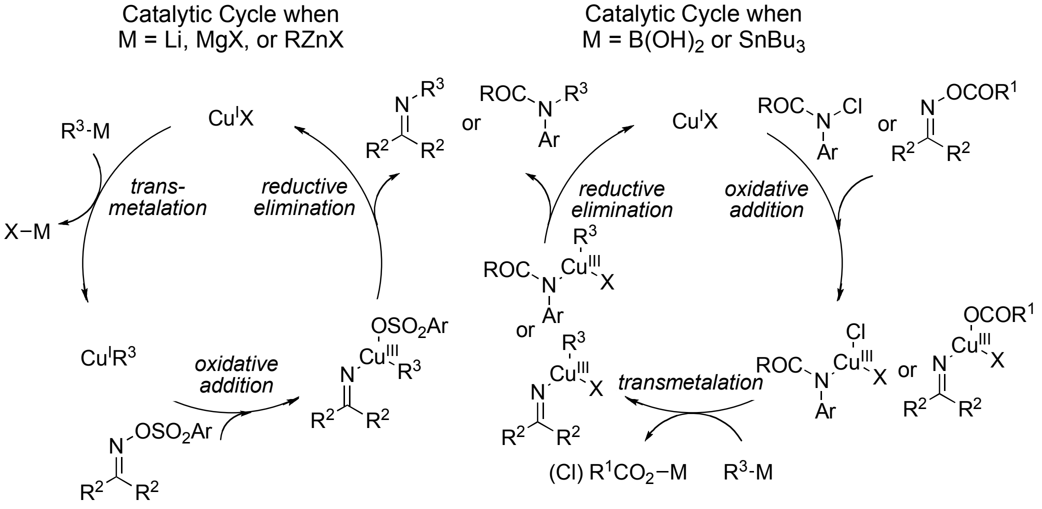


1.2.2 Mechanistic Studies of Copper-Catalyzed Electrophilic Aminations

Catalytic electrophilic aminations were pioneered by Narasaka[23,24] and Erdik.[25-27] These protocols used copper catalysis to couple organolithium, -magnesium, and -zincate reagents with *O*-sulfonyloximes, forming imines. Because of continued reliance on reactive carbanion donors or harsh hydrolysis conditions (12 M HCl), these reactions were still subject to the same limitations inherent with uncatalyzed aminations. More recently, copper-catalyzed and -promoted aminations have been developed with weakly or nonbasic carbon donors such as organozinc reagents, boronic acids, and stannanes. Varied sources of electrophilic nitrogen have been used, including *O*-acyl hydroxylamines[28-30] and hydroxamic acids,[31] *N*-chloroamides,[32] *O*-acyloximes,[33] and iminoesters.[34] Resulting from the mild reaction conditions employed, all enjoy wide functional group compatibility.

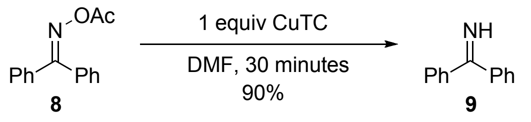
Erdik conducted the first mechanistic study concerning the amination of a neutral electrophilic nitrogen species, acetone *O*-(mesitylenesulfonyl)oxime, under copper catalysis.[35] Using competitive kinetic studies, a nucleophilic oxidative addition mechanism was supported for both stoichiometric and catalytic cuprates. The proposed catalytic cycle for this reaction involves transmetalation of organolithium, -magnesium, or -zinc reagents to form an organocopper (M=MgX) or higher order cuprate (M=Li, ZnX). A nucleophilic oxidative addition into the oxime N–O bond then occurs to generate a putative (amido)organocopper(III) intermediate that rapidly undergoes reductive elimination to generate the product imine, regenerating the copper(I) catalyst (Scheme 1-3, left).

Scheme 1-3. Catalytic Cycles for the Electrophilic Amination of Organometallics

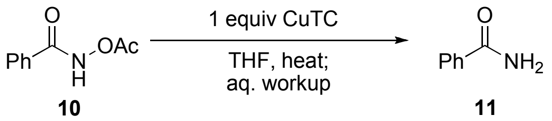

Catalytic Cycle when
M = Li, MgX, or RZnX
Catalytic Cycle when
M = B(OH)2 or SnBu3
R3-M
X–M
CuIX
trans-
metalation
reductive
elimination
CuIR3
oxidative
addition
OSO2Ar
CuIII
R3
N
R2
R2
N
OSO2Ar
R3
or
ROC
Ar
oxidative
addition
Cl
OCOR1
transmetalation
(Cl) R1CO2–M
R3-M
X

Weak carbon donors such as boronic acids and stannanes have been aminated successfully with *N*-chloroamides and *O*-acyloximes using copper catalysis.[32,33] Although employing stoichiometric CuTC, the amination of *O*-acyl hydroxamic acids is mechanistically similar.[31] With these weak carbon donors, mechanistic studies point to oxidative addition preceding transmetalation (Scheme 1-3, right), in direct contrast to aminations with stronger carbon donors (M = Li, MgX, ZnX).

Evidence cited for N–O oxidative addition to Cu(I)X prior to transmetalation includes the production of benzophenone imine (**9**) and benzamide (**11**) by reacting *O*-acetylbenzophenone oxime (**8**) and *N*-acetoxybenzamide (**10**), respectively, with stoichiometric CuTC (eq 1 and 2).[31,33] Lei conducted the most comprehensive mechanistic study thus far.[32] The reaction of arylboronic acids with *N*-chloroamides was monitored by *in situ* IR spectroscopy. Upon the addition of CuCl to a solution of **12**, peaks corresponding to a new species were observed, with complete disappearance of **12** after 80 minutes. Phenylboronic acid and Na_2CO_3 were then added, which led to the immediate appearance of diarylbenzamide **13** (Scheme 1-4). They also reacted PhCu prepared from PhMgBr and CuI with **12** to give only biphenyl and the dechlorinated *N*-arylbenzamide **14**, without detection of **13**. These experiments not only support the hypothesis that N–O oxidative addition occurs prior to transmetalation, but imply it is a requirement when using *N*-chloroamides to prevent a role change from $R_2N(+)$ donor to general oxidant.

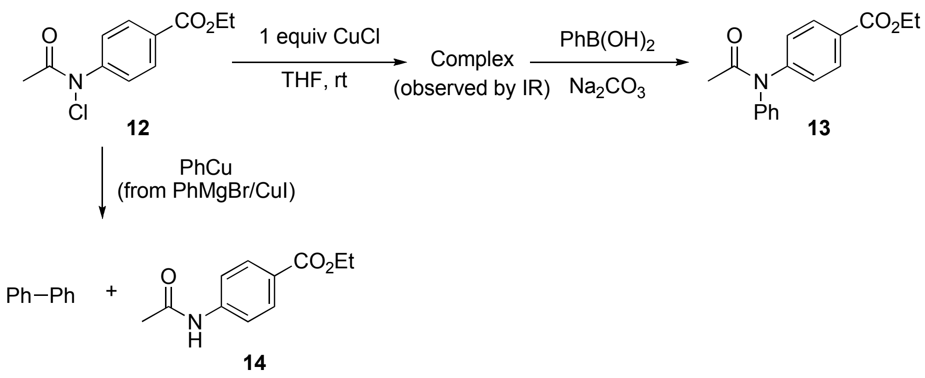

N
OAc
Ph
Ph
8
1 equiv CuTC
DMF, 30 minutes
90%
NH
Ph
Ph
9

(1)

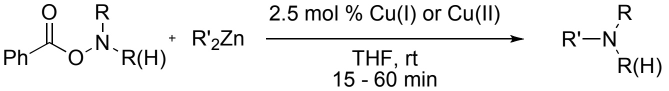

O
Ph
N
H
OAc
10
1 equiv CuTC
THF, heat;
aq. workup
O
Ph
NH2
11

(2)

Scheme 1-4. Mechanistic Experiments Conducted by Lei and Coworkers


O
N
Cl
CO2Et
12
1 equiv CuCl
THF, rt
Complex
(observed by IR)
PhB(OH)2
Na2CO3
O
N
Ph
CO2Et
13
PhCu
(from PhMgBr/CuI)
Ph−Ph
+
O
N
H
CO2Et
14

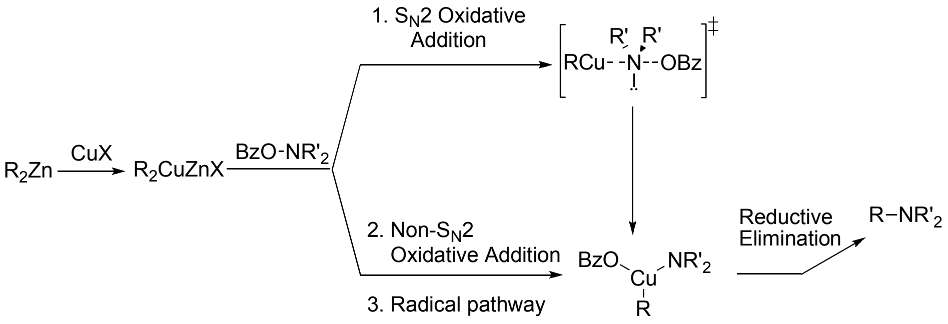
Our laboratory has recently developed an efficient copper-catalyzed electrophilic amination, coupling diorganozinc reagents with *O*-benzoyl *N,N*-dialkyl- and *N*-alkylhydroxylamines to directly provide tertiary and secondary amines (eq 3).[28-30] A number of features render this methodology attractive from a synthetic perspective, including fast reaction under mild reaction conditions (<1 hr, r.t.), tolerance of a wide variety of sensitive functional groups, use of both aryl and alkyl organozinc nucleophiles, ease of product isolation by acid/base extraction, and a high steric tolerance with respect to both reaction partners.[36] Additionally, the *O*-benzoyl hydroxylamines are easily prepared in one step via the oxidation of amines with benzoyl peroxide and are stable enough to be stored in the freezer for extended periods of time.[30,37]



(3)

In an effort to improve our general understanding of this amination, we wished to conduct experiments to elucidate the mechanism. This particular mechanism interested us because it lies at the crossroads of two well-understood scenarios. As described, aminations of RLi and RMgX reagents have been reported to proceed through a substitution mechanism, as oxidative addition/reductive elimination is not possible for Li and Mg. Cu, however, can form C–N bonds by reductive elimination. We wished to discriminate between the mechanisms that can be invoked to lead to the formation of the necessary copper-amido bond.[38,39] Particularly, copper could: (i) displace the benzoate leaving group through an S_N2 reaction; (ii) oxidatively add across the N–O bond in a non-S_N2 process; or (iii) add though a radical process (Figure 1-2).

Figure 1-2. Possible Pathways for the Formation of a Copper-amido Complex from Cuprates and *O*-Benzoyl Hydroxylamines



R2Zn
CuX
R2CuZnX
BzO-NR'2
1. SN2 Oxidative Addition
RCu--N--OBz
R' R'
‡
2. Non-SN2 Oxidative Addition
3. Radical pathway
BzO Cu NR'2
R
Reductive Elimination
R−NR'2

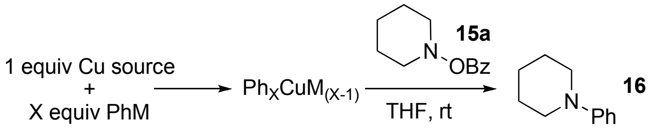
This chapter will detail mechanistic studies directed toward understanding this unique reaction, revealing that an S_N2-type oxidative addition pathway is operative, by using stoichiometric cuprates, the endocyclic restriction test, and by following configurationally-defined carbon nucleophiles through the reaction. Inspired as a consequence of these studies, this chapter will also describe the development of both Cu-catalyzed and direct uncatalyzed aminations of Grignard reagents by *O*-acyl *N,N*-dialkylhydroxylamines. This chapter has been previously published.[40]

1.3 Results and Discussion

1.3.1 Amination with Stoichiometric Cuprates

We first sought to determine whether copper alone can effect the amination or if a synergistic effect with zinc is involved. The results of the amination of **15a** with stoichiometrically generated phenylcuprates to prepare amine **16** are listed in Table 1-1. The suitability of RLi and RMgBr compounds in this reaction as precursors of the cuprate (entries 1-3,5,6) establishes that the presence of ZnX_2 is not integral for the C–N bond forming event. Li_2CuCl_3 was used in addition to the $CuBr•SMe_2$ complex because we found its high solubility in THF made the formation of the cuprate (especially monophenylcopper) more facile. Its use resulted in more consistent results and marginally higher yields (compare entries 3 and 6). Under no set of conditions was the yield obtained by the Cu-catalyzed amination of diphenylzinc matched (entry 8). In some reactions, a small amount of piperidine (<5%) was produced. In these reactions, we also observed the production of biphenyl; presumably, the N–O bond can serve as an oxidant to Cu, promoting biaryl coupling.

Table 1-1. Amination of 4-(Benzoyloxy)piperidine with Phenylcuprates



entry	Cu source	M	Equiv. PhM	% yield[d]
1[b]	$CuBr \cdot SMe_2$	Li	1	55
2[b]	$CuBr \cdot SMe_2$	Li	2	68
3[b]	$CuBr \cdot SMe_2$	MgBr	1	56
4[b]	$CuBr \cdot SMe_2$	ZnBr[e]	2	68
5[c]	Li_2CuCl_3	Li	2	72
6[c]	Li_2CuCl_3	MgBr	1	68
7[c]	Li_2CuCl_3	ZnBr[e]	2	78
8	0.05 eq CuCl	ZnPh	1.1	88

[a]Conditions: 1 equiv "Cu", 1 equiv $R_2NOC(O)Ph$, 0.25 M THF. [b]Cuprate preformed at 0 °C for 30 min. [c]Cuprate preformed at –15 °C for 1 hr. [d]Isolated yields (average of at least two experiments). [e]Prepared from Rieke zinc and bromobenzene. Yield is based on the starting $R_2NOC(O)Ph$.

1.3.2 Amination of Stereodefined Organozinc Reagents

We next sought to determine the fate of a stereodefined $R_2{}^*Zn$ reagent when subjected to the amination conditions. The established Grignard reagents **1-*endo***[16] and **6**[19] were chosen to conduct the study. Though conveniently prepared, the use of **1-*endo*** is not completely unbiased, as the reaction of interest must proceed through diastereomeric transition states. This limitation has been overcome through the pioneering work of Hoffmann, who has developed and used the unbiased chiral Grignard reagent **6**.

Transmetalation of an equilibrium mixture of **1** to zinc and further reaction with an excess of **15b** yielded a 65:35 *endo*:*exo* mixture of amine **17** in 55% yield (Scheme 1-5). This is similar to published ratios obtained for carbonation, mercuration, and amination (*vide supra*). After establishing that both isomers react similarly, we turned our attention to the resolved isomer. The resolution is performed by adding benzophenone to the mixture, which preferentially reacts with **1-*exo***. The use of **1-*endo*** resulted in predominately amine **17-*endo***, supporting retention of configuration during the amination. Both isomers were assigned using NOESY spectroscopy (Figure 1-3).

Scheme 1-5. Amination of 2-Norbonylmagnesium Bromide

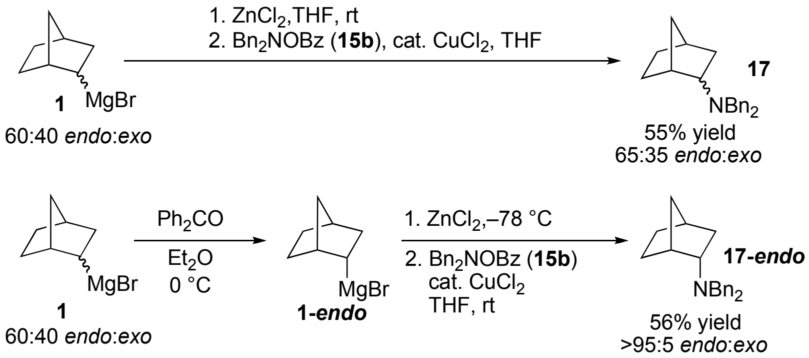
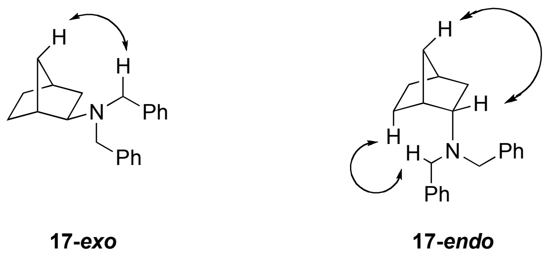

1 MgBr
60:40 endo:exo
1. ZnCl2,THF, rt
2. Bn2NOBz (15b), cat. CuCl2, THF
17
NBn2
55% yield
65:35 endo:exo
MgBr
1
60:40 endo:exo
Ph2CO
Et2O
0 °C
MgBr
1-endo
1. ZnCl2,–78 °C
2. Bn2NOBz (15b)
cat. CuCl2
THF, rt
17-endo
NBn2
56% yield
>95:5 endo:exo

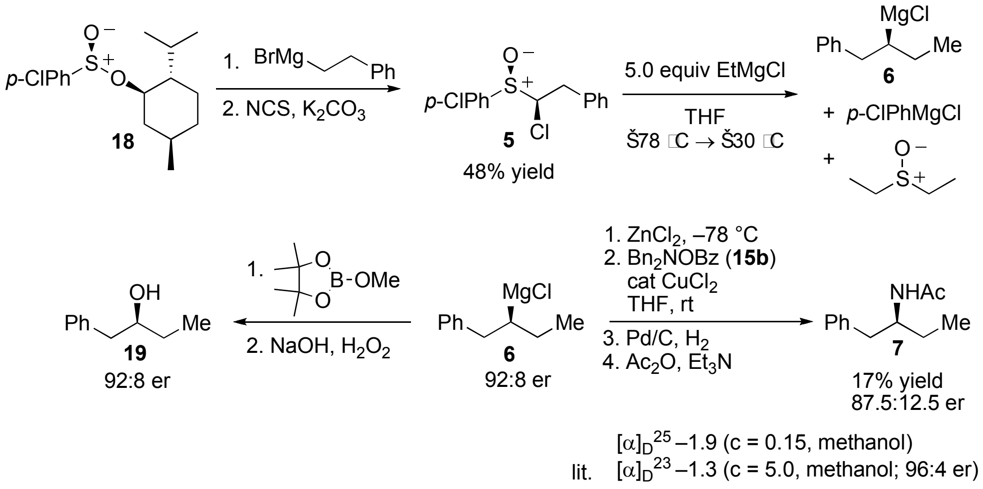
Figure 1-3. Diagnostic nOe Enhancements for Dibenzylnorbornyl Amines


H
H
N
Ph
Ph
H
H
H
H
N
Ph
Ph

17-*exo* **17-*endo***

The enantioenriched Grignard **6** was prepared according to the literature by first converting the enantio- and diastereomerically pure menthyl sulfinate **18** into the α-chlorosulfoxide **5** (Scheme 1-6).[19] Treatment with an excess of EtMgCl at low temperature induces a Mg-sulfoxide exchange followed by a carbenoid homologation to afford **6**. The er was determined by converting **6** to (*S*)-1-phenylbutan-2-ol (**19**) with an oxidation known to proceed with complete chirality transfer. Transmetalation of **6** to zinc followed by amination with **15b** formed the corresponding tertiary amine. This amine was transformed to the acetamide **7** by hydrogenolysis and subsequent acetylation to provide a known derivative that could be identified as the (*S*)-enantiomer of 87.5:12.5 er, as determined by GLC and optical rotation. In a reaction of relevance reported by Hoffmann, sequential transmetalation of **6** to zinc and copper followed by conjugate addition to mesityl oxide resulted in 6% racemization.[21] The 9% racemization that we observe is comparable and we conclude that this amination transfers chirality to the same extent as the conjugate addition of cuprates to enones. Taken together with the retention observed in the norbornyl system, we conclude that a polar mechanism is at least dominant, if not exclusive. A radical mechanism can be eliminated, since considerable racemization would accompany such an intermediate.

Scheme 1-6. Formation and Reactions with Enantioenriched Grignard **6**

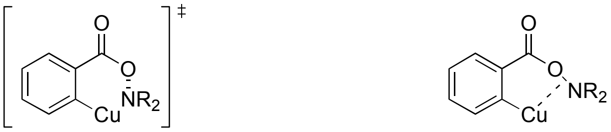


18
1. BrMg Ph
2. NCS, K2CO3
p-ClPh
5
48% yield
5.0 equiv EtMgCl
THF
Š78 □C → Š30 □C
MgCl
Ph
Me
6
+ p-ClPhMgCl
+
1. ZnCl2, –78 °C
2. Bn2NOBz (15b)
cat CuCl2
THF, rt
3. Pd/C, H2
4. Ac2O, Et3N
NHAc
7
17% yield
87.5:12.5 er
92:8 er
1. B-OMe
2. NaOH, H2O2
OH
19
92:8 er
[α]D25 –1.9 (c = 0.15, methanol)
lit. [α]D23 –1.3 (c = 5.0, methanol; 96:4 er)

1.3.3 Endocyclic Restriction Test

We used the endocyclic restriction test[9-11,41] to differentiate between an S_N2 oxidative addition and non-S_N2 oxidative addition of the N–O bond. Using this test allows one to obtain a general picture of the transition state geometry. When the system is a six-membered ring, an intramolecular S_N2 process is forbidden because the 6-*endo-tet* transition state (**20**) is prohibitively strained (Figure 1-4). A non-S_N2 oxidative addition process into the pendant N–O bond would proceed to give a oxametalacyclopentane. This intermediate is geometrically attainable because the precursor σ-bond complex **21** is not strained; the intramolecular cross-coupling is therefore feasible via this mechanism.

Figure 1-4. Transition State and Complex for Possible Mechanisms of N–O Oxidative Addition



∠CuNO < 180°

S_N2 not geometrically attainable

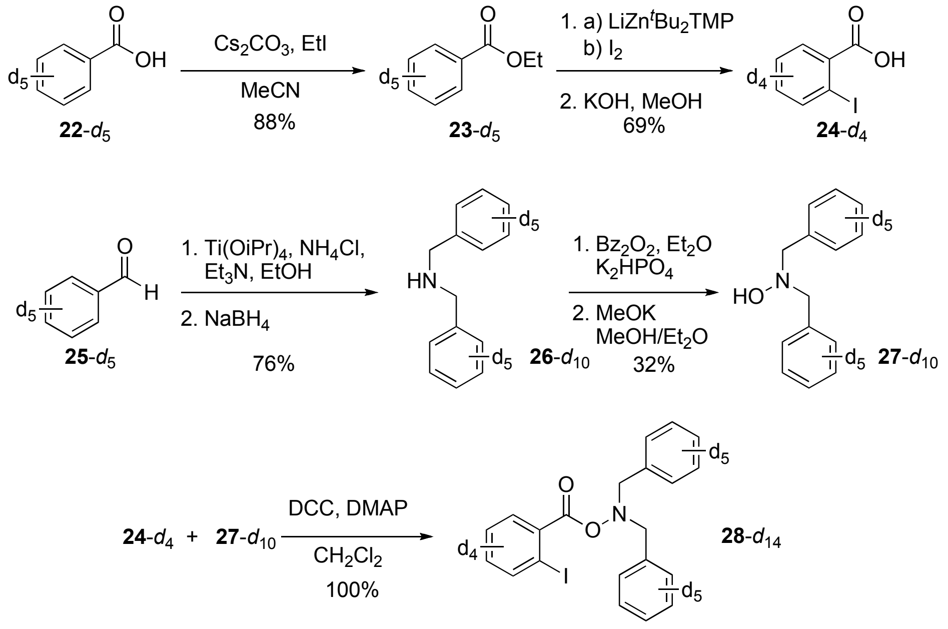
20

Direct O.A. geometrically attainable

21

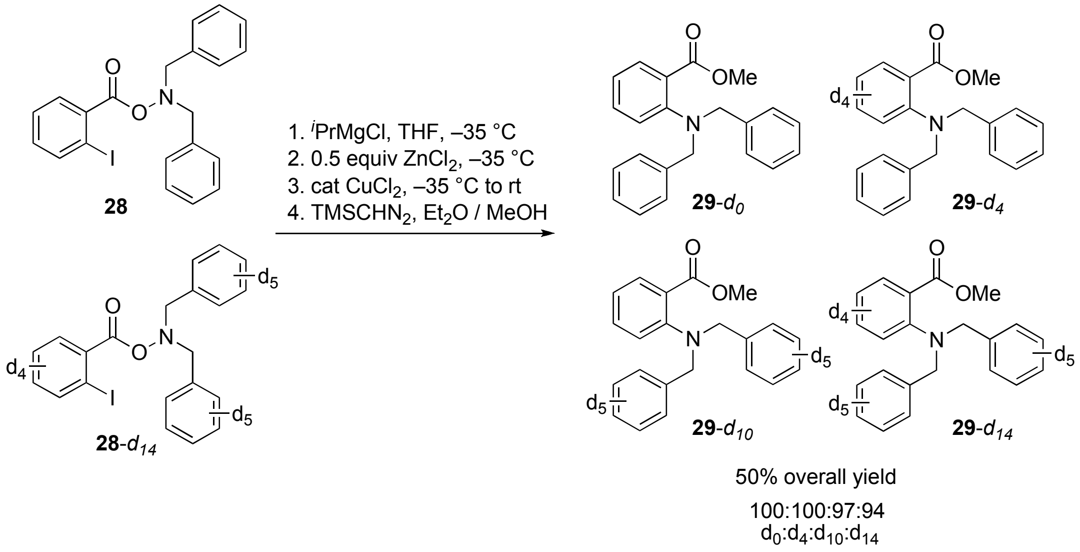
We chose the system **28**, because the deuterated analog **28**-*d*$_{14}$ could be prepared from benzoic acid-*d*$_5$ and benzaldehyde-*d*$_5$ (Scheme 1-7). Both of these precursors are easily synthesized from benzene-*d*$_6$ in one step by deprotonating with Schlosser's superbase and treating with CO_2 or DMF, respectively.[42] Benzoic acid-*d*$_5$ (**22**-*d*$_5$) was esterified with Cs_2CO_3 and EtI to give **23**,[43] converted to the iodide using a TMP-zincate and iodine,[44] and hydrolyzed to yield 2-iodobenzoic acid-*d*$_4$ (**24**-*d*$_4$) in 61% overall yield. Reductive amination of benzaldehyde-*d*$_5$ (**25**-*d*$_5$) with ammonia,[45] oxidation with benzoyl peroxide,[37] and methanolysis gave dibenzylhydroxylamine-*d*$_{10}$ (**27**-*d*$_{10}$). DCC coupling of **24**-*d*$_4$ and **27**-*d*$_{10}$ led to the doubly-labeled substrate **28**-*d*$_{14}$ in quantitative yield. Undeuterated **28** was prepared via an analogous sequence using commercially available 2-iodobenzoic acid and dibenzylamine.

Scheme 1-7. Synthesis of Endocyclic Restriction Test Substrates


22-d5
Cs2CO3, EtI
MeCN
88%
23-d5
1. a) LiZntBu2TMP
b) I2
2. KOH, MeOH
69%
24-d4
25-d5
1. Ti(OiPr)4, NH4Cl, Et3N, EtOH
2. NaBH4
76%
26-d10
1. Bz2O2, Et2O K2HPO4
2. MeOK MeOH/Et2O
32%
27-d10
24-d4 + 27-d10
DCC, DMAP
CH2Cl2
100%
28-d14

This system provides isotopes **29**-*d*$_0$ and **29**-*d*$_{14}$ as non-crossover products and **29**-*d*$_4$ and **29**-*d*$_{10}$ as crossover products, analyzed easily by mass spectrometry (MS). Low temperature iodine/magnesium exchange[46] of an equimolar mixture of **28** and **28**-*d*$_{14}$ provided the functionalized Grignard reagents which were converted to the corresponding diorganozincs. The addition of catalytic CuCl$_2$ and warming to room temperature provided the amino acids that were converted to the methyl esters **29** using TMSCHN$_2$.[47] Deiodinated starting material could be recovered by hydrolyzing the intermediate diorganozinc with no detectable amination prior to the addition of CuCl$_2$. Analysis of the products by MS revealed a near statistical mixture of the four isotopomers, meaning the amination is occuring intermolecularly (Scheme 1-8). This is in support of a transition state that has a large bond angle (Cu–N–OBz ~ 180°), such as S$_N$2.

Scheme 1-8. Endocyclic Restriction Test

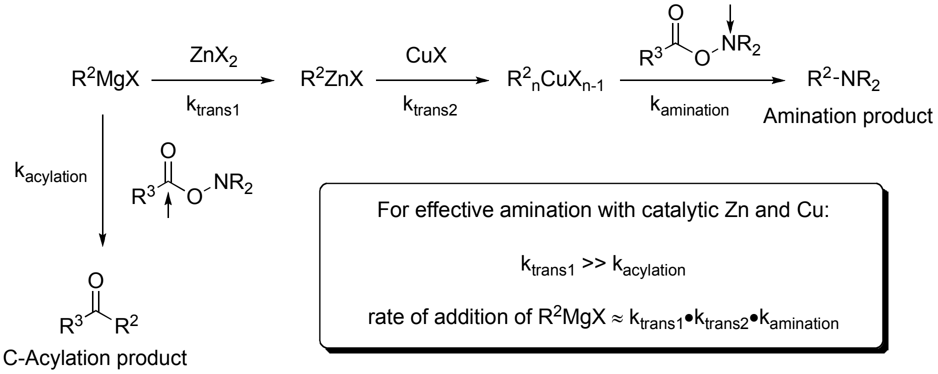

28
28-d14
1. iPrMgCl, THF, –35 °C
2. 0.5 equiv ZnCl2, –35 °C
3. cat CuCl2, –35 °C to rt
4. TMSCHN2, Et2O / MeOH
29-d0
29-d4
29-d10
29-d14
50% overall yield
100:100:97:94
d0:d4:d10:d14

1.3.4 Development of Copper-Catalyzed and Uncatalyzed Amination of Grignard Reagents with *O*-Acyl *N,N*-Dialkylhydroxylamines

Based upon the successful amination of stoichiometric cuprates in the absence of zinc ions (*vide supra*), we reinitiated our previous efforts toward devising a procedure that would eliminate the need to pregenerate the diorganozinc reagent.[30] Eliminating the cost of acquiring and handling stoichiometric amounts of an anhydrous zinc salt would be beneficial for large-scale reactions.

The dominant side reaction when Grignard reagents react with *O*-acylhydroxylamines is *C*-acylation to form ketones and subsequent reduction to alcohols. We postulated that a Zn/Cu-catalyzed amination of Grignard reagents could occur if certain rate criteria were met (Scheme 1-9). Specifically, if k_{trans} to form a non-nucleophilic organozinc or cuprate is faster than $k_{acylation}$, then the C-acylation pathway will be avoided. A further requirement is the rate of addition of RMgX must not exceed the overall of rate of amination (k_{trans1}•k_{trans2}•$k_{amination}$), as uncatalyzed acylation will occur if the catalysts are saturated.

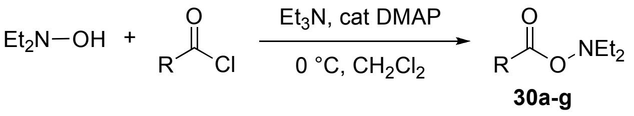
Scheme 1-9. Competing Amination and Acylation Pathways



R^2MgX
ZnX_2
k_{trans1}
R^2ZnX
CuX
k_{trans2}
$R^2_nCuX_{n-1}$
$k_{amination}$
R^2-NR_2
Amination product
$k_{acylation}$
C-Acylation product
For effective amination with catalytic Zn and Cu:
$k_{trans1} >> k_{acylation}$
rate of addition of $R^2MgX \approx k_{trans1}$•$k_{trans2}$•$k_{amination}$

We hypothesized that modification of the reaction conditions would not be able to significantly increase k_{trans}, if initially found to be slow, while $k_{acylation}$ could be decreased by modifying the acyl moiety. Thus, several analogs of **30** were prepared that contain either electron-rich or sterically bulky substituents on the acyl moiety to deter C-acylation. The derivatives were synthesized by reacting commercially available *N,N*-diethylhydroxylamine with the appropriate acyl chloride (Scheme 1-10).

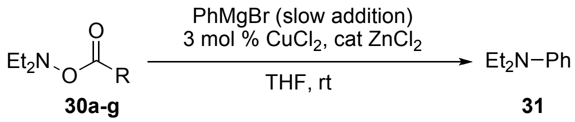
Scheme 1-10. Preparation of *O*-Acyl *N,N*-Diethylhydroxylamines



R =		
Ph	**30a**	99%
4-MeOPh	**30b**	99%
4-Me$_2$NPh	**30c**	27% (from acid)
2-MePh	**30d**	89%
2,4,6-Me$_3$Ph	**30e**	63%
t-Bu	**30f**	85%
OEt	**30g**	79%

Table 1-2 displays the relevant experiments that were conducted using 3 mol % CuCl$_2$ with or without catalytic ZnCl$_2$. PhMgBr was added by syringe pump over seven minutes to ensure reproducibility. Higher yields were realized when ZnCl$_2$ was omitted altogether. The use of 2.2 equivalents of the Grignard was not necessary (entry 7). All analogs except **30g** were equally capable of providing amine **31** (entry 13).

Table 1-2. Amination of *O*-Acyl-*N,N*-diethylhydroxylamines with Phenylmagnesium Bromide Catalyzed by ZnCl$_2$ and CuCl$_2$



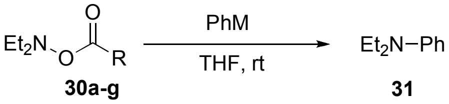
entry	R	equiv. PhMgBr	equiv. ZnCl$_2$	% yield[b]
1	Ph (**30a**)	2.2	0.1	84
2	4-MeOPh (**30b**)	2.2	0.1	62
3	4-Me$_2$NPh (**30c**)	2.2	0.1	81
4	2-MePh (**30d**)	2.2	0.1	74
5	2,4,6-Me$_3$Ph (**30e**)	2.2	0.1	75
6	Ph (**30a**)	2.2	-	87
7	Ph (**30a**)	1.1	-	89
8	4-MeOPh (**30b**)	2.2	-	79
9	4-Me$_2$NPh (**30c**)	2.2	-	79
10	2-MePh (**30d**)	2.2	-	89
11	2,4,6-Me$_3$Ph (**30e**)	2.2	-	82
12	^{t}Bu (**30f**)	2.2	-	83
13	EtO (**30g**)	2.2	-	27

[a] Conditions: PhMgBr added via syringe pump (0.15 mmol/min), 1 equiv R$_2$NOC(O)Ph, 0.03 equiv CuCl$_2$, 0.16 M **30** in THF. [b] Yields determined by GLC. Yield is based on the starting Et$_2$NOC(O)R.

Evidently, the Mg to Cu transmetalation and resulting amination occurs much faster than C-acylation regardless of the relative reactivity of the carbonyl towards nucleophilic attack. This observation parallels the copper-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated ketones. To gauge the relative reactivity of the two electrophilic sites, aminations were conducted in the absence of $CuCl_2$ (Table 1-3).

In the absence of Cu, the predominant products were benzophenone, benzhydrol, and triphenylmethanol for the benzoyl derivative **30a**. Electron-rich and moderately sterically encumbered substrates provided a slight improvement over **30a** (entries 2-4, compare to 1); however, it was not until large acyl groups were used that **31** became the major product (entries 5,9). Attempts to increase the yield using **30f** by varying the temperature were unsuccessful. PhLi reacts with **30e** to give modest yields that increased as the temperature was decreased (entries 6-8).

Table 1-3. Amination of *O*-Acyl-*N,N*-Diethylhydroxylamines with Phenylmagnesium Bromide

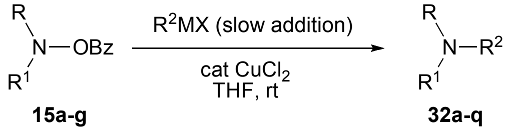


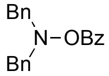
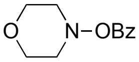
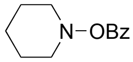
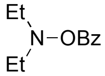
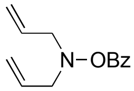
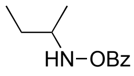
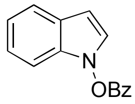
entry	R	PhM	Temperature	% yield[b]
1	Ph (**30a)**	1.1 PhMgBr	rt	9
2	4-MeOPh (**30b)**	1.1 PhMgBr	rt	17
3	4-Me_2NPh (**30c)**	1.1 PhMgBr	rt	21
4	2-MePh (**30d)**	1.1 PhMgBr	rt	18
5	2,4,6-Me_3Ph (**30e)**	1.1 PhMgBr	rt	85
6	2,4,6-Me_3Ph (**30e)**	2.2 PhLi	rt	36
7	2,4,6-Me_3Ph (**30e)**	2.2 PhLi	0 °C	46
8	2,4,6-Me_3Ph (**30e)**	2.2 PhLi	–30 °C	50
9	^{t}Bu (**30f)**	2.2 PhMgBr	rt	54
10	^{t}Bu (**30f)**	2.2 PhMgBr	0 °C	37
11	^{t}Bu (**30f)**	2.2 PhMgBr	44 °C	57
12	EtO (**30g)**	2.2 PhMgBr	Rt	14

[a]Conditions: 1 equiv $R_2NOC(O)Ph$, 0.16 M **30** in THF. [b]Yields determined by GLC. Yield is based on the starting $Et_2NOC(O)R$.

The use of other *O*-2,4,6-trimethylbenzoyl hydroxylamines was not extensively evaluated because they are not as easily accessed as the benzoyl derivatives. Instead, we investigated the scope of the Cu-catalyzed amination of RMgX compounds (Table 1-4). The yields for tertiary amines **32a-q** were moderate to excellent for the majority of cases investigated. For a number of cases, it was necessary to increase the catalyst loading to achieve synthetically useful yields. The benefit of this increase was substrate dependent (compare entries 6,7 to entries 11,12) and high catalyst loadings were ultimately detrimental (entries 17-20). Secondary amines were not successfully prepared. Instead, deprotonation to the Mg amide occurred (entry 22). As predicted by an S_N2 pathway, **15g** was unable to provide *N*-phenylindole by this methodology (entry 23).[48]

Table 1-4. Copper-catalyzed Amination of *O*-Acyl-*N,N*-Diethylhydroxylamines with Grignard Reagents



entry	R(R^1)NOBz	R^{2}MgX (equiv) (product)	mol% CuCl$_2$	% yield^b
1	 **15b**	Et (1.1) **(32a)**	2.5	95
2	**15b**	^{c}Hex (1.1) **(32b)**	2.5	88
3	**15b**	^{t}Bu (1.1) **(32c)**	2.5	88
4	**15b**	^{c}Pr (1.5) **(32d)**	15	59
5	**15b**	Ph (1.6) **(32e)**	5	20^c
6	**15b**	Ph (1.6) **(32e)**	10	92
7	**15b**	4-FPh (2.2) **(32f)**	10	58
8	 **15c**	Ph (1.6) **(32g)**	2.5	37
9	**15c**	Ph (1.6) **(32g)**	10	68
10	**15c**	2-MePh (1.1) (**32h)**	2.5	7
11	 **15a**	Ph (1.1) **(32i)**	2.5	52
12	**15a**	Ph (1.1) **(32i)**	10	64
13	**15a**	2-MePh (1.1) (**32j)**	2.5	75
14	**15a**	2,4,6-Me$_3$Ph (1.2) (**32k)**	2.5	61
15	 **15d**	2-MePh (1.1) (**32l)**	2.5	61
16	**15d**	2,4,6-Me$_3$Ph (1.2) (**32m)**	2.5	80
17	**15d**	4-MeOPh (1.7) (**32n)**	5	65^d
18	**15d**	4-MeOPh (1.7) (**32n)**	10	75
19	**15d**	4-MeOPh (1.7) (**32n)**	25	26^d
20	**15d**	4-MeOPh (1.7) (**32n)**	50	8^d
21	 **15e**	^{c}Hex (1.1) **(32o)**	2.5	84
22	 **15f**	Ph (2.2) **(32p)**	5	trace
23	 **15g**	Ph (2.2) **(32q)**	2.5	0

[a]Conditions: RMgX added via syringe pump (0.15 mmol/min), 1 equiv R$_2$NOC(O)Ph. [b]Isolated yields of product of purity ≥95% based on ^{1}H NMR spectroscopy (average of at least two experiments) unless noted. [c]Yield determined by ^{1}H NMR spectroscopy

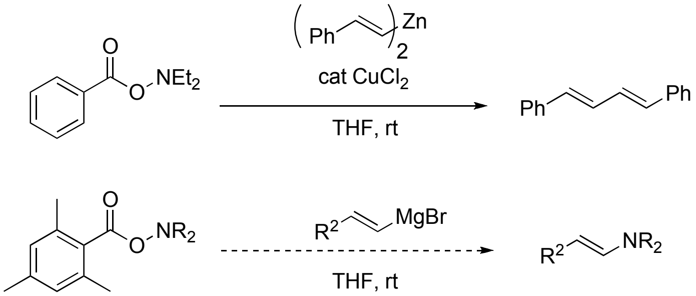
(dodecane = internal standard). [d]Yield determined by GLC (dodecane = internal standard). Yield is based on the starting $R_2NOC(O)Ph$.

1.3.5 Uncatalyzed Amination of Vinyl Grignard Reagents with *O*-Mesitoyl *N,N*-Diethylhydroxylamine

While exploring the scope of the Cu-catalyzed amination of R_2Zn reagents, we found that divinylzinc reagents were not suitable nucleophiles as symmetrical butadienes were produced as major products (Scheme 1-11). Evidently, vinyl cuprates are unstable at room temperature and efficient oxidative coupling occurs rapidly, with the *O*-benzoyl hydroxylamine serving as a general oxidant. In the previous section, *O*-mesitoyl hydroxylamines were found to be effective for the uncatalyzed amination of RMgX.

They were not used because their synthesis from the amine requires three steps, while benzoyl derivatives are easily accessed in a single step. We hypothesized that the amination of vinylmagnesium reagents with *O*-mesitoyl hydroxylamines would proceed smoothly in the absence of Cu. We hoped the use of stereodefined vinyl Grignard reagents would proceed with stereochemical transfer and, in particular, allow access to (*Z*)-enamines, a problem in organic synthesis which lacks a general solution.

Scheme 1-11. Failed Copper-Catalyzed Amination of a Divinylzinc Reagent and Proposed Amination via Uncatalyzed Electrophilic Amination



Initial experiments were promising as (*E*)-styrylmagnesium bromide produced (*E*)-enamine **33** in 70% yield after precipitation of the Mg salts with hexanes, filtration, and removal of solvent. Unfortunately, (*Z*)-styrylmagnesium bromide also provided (*E*)-enamine **33**; evidently, the reaction conditions promote isomerization of the products (Scheme 1-12). The reaction did not prove to be general, as enamines were not formed when (*Z*)-2-alkyl-, 1-aryl-, and 1,2-dialkylmagnesium bromides were used (Figure 1-5). The uncatalyzed amination does not exhibit the high steric tolerance found for the Cu-catalyzed amination of R_2Zn.

Scheme 1-12. Formation of **(*E*)-33** from both (*E*)- and (*Z*)-Styrylmagnesium Bromide

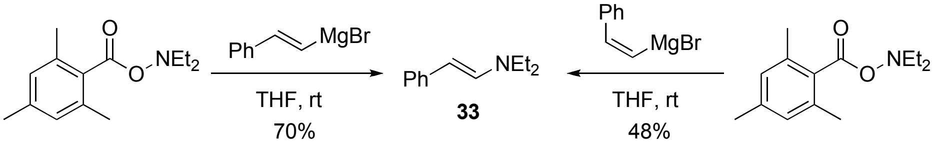
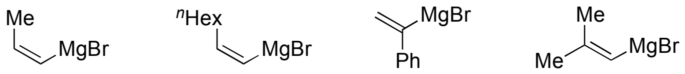


Figure 1-5. Unsuccessful Nucleophiles



1.4 Conclusion

In conclusion, we can support an S_N2 pathway for the Cu-catalyzed amination of R_2Zn reagents because we have : (i) used stoichiometrically generated cuprates to prove zinc is not essential in the C–N bond forming step; (ii) showed that the configuration at the reacting carbon is retained through the reaction, ruling out a radical pathway; (iii) and employed the endocyclic restriction test. We were able to develop a Cu-catalyzed amination of Grignard reagents after realizing the relative rates of *O*-acylation, transmetalation, and C–N bond formation were favorable. The scope for this reaction does not have the breadth of our previous protocol employing diorganozinc compounds, but it does permit the exclusion of anhydrous zinc salts. The use of extremely hindered *O*-mesitoyl *N,N*-dialkylhydroxylamines were found to be suitable $R_2N(+)$ synthons for the uncatalyzed amination of Grignard reagents, including unhindered vinyl Grignard reagents, which was previously unattainable using *O*-acylhydroxylamines.

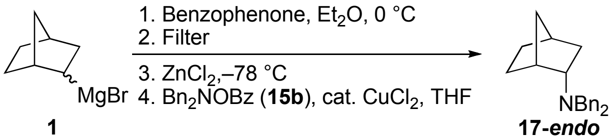
1.5 Experimental.

Materials and Methods: General. Infrared (IR) spectra were obtained using a Nicolet 560-E.S.P. infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model Avance 400 or a Bruker 300Mhz (^{1}H NMR at 400 MHz or 300Mhz and ^{13}C NMR at 100 MHz) spectrometer with tetramethylsilane or solvent resonance as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250°C) or a J&W DB-1701 column (30 m x .249 mm) with helium gas as carrier. 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, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating.

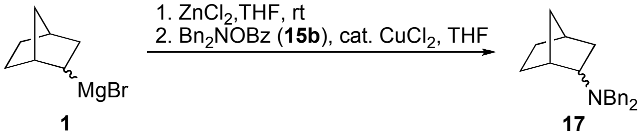
Purification of the reaction products was carried out either by acid/base extractive work-up or flash chromatography using Sorbent Technologies silica gel 60 (32-63 μm). All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use.[49] 4-(Benzoyloxy)morpholine (15c), 4-(benzoyloxy)piperidine (15a), *O*-benzoyl-*N,N*-dibenzylhydroxylamine (15b), *O*-diethyl-*N,N*-diethylhydroxylamine (15d), and *O*-benzoyl-*N,N*-diallylhydroxylamine (15e) were prepared as described previously.[30] Anhydrous zinc chloride was prepared by melting reagent grade zinc chloride and letting it solidify under high vacuum three times. Triethylamine was freshly distilled from calcium hydride. All other reagents were obtained from commercial sources and used without further purification.

General Procedure (A) for the amination of organocuprates with 4-(benzoyloxy)piperidine (15a).

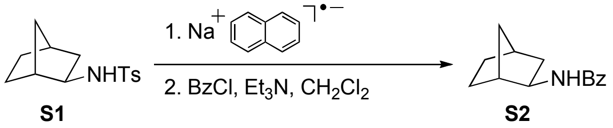
A flame-dried vial equipped with magnetic stir bar was charged with the copper salt (1.00 mmol), anhydrous tetrahydrofuran (4.0-x mL), and the solution was cooled to 0 °C. A solution of PhMX (x mL, 0.5, 1.0 or 2.0 M in THF or dibutyl ether, 1.00 or 2.00 mmol) was slowly added and the reaction mixture was stirred at 0 °C for 30 minutes. A second flame-dried vial equipped with magnetic stir bar was charged with 4-(benzoyloxy)piperidine (**15a**) (1.00 mmol) and anhydrous tetrahydrofuran (5.0 mL). The contents of the second vial were cannulated to the first vial and the reaction mixture was allowed to warm to room temperaure. The vial was stirred at this temperature for 90 minutes. The reaction mixture was quenched with 10 mL 3.0 M ammonium hydroxide solution and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layer was washed with 3.0 M ammonium hydroxide solution (2 x 10 mL), saturated sodium chloride solution (1 x 10 mL), and the solvents were evaporated under reduced pressure. The resulting residue was taken up in diethyl ether (10 mL) and washed with a 1M hydrochloric acid solution (2 x 10 mL), the aqueous layer was basified with a 10% sodium hydroxide solution and extracted with dichloromethane (2 x 10 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed under reduced pressure, affording N-phenyl-piperidine (**16**).


MgBr
1
1. Benzophenone, Et_2O, 0 °C
2. Filter
3. $ZnCl_2$, –78 °C
4. Bn_2NOBz (**15b**), cat. $CuCl_2$, THF
NBn_2
17-*endo*

endo*-*N,N*-Dibenzylbicyclo[2.2.1]heptane-2-amine (17-*endo*).** *endo*-2-Norbornylmagnesium bromide (**1**) was prepared according to Jensen's method[16] with slight modification: a flame-dried vial equipped with magnetic stir bar was charged with benzophenone (0.062 g, 0.34 mmol), anhydrous diethyl ether (1.0 mL), and the solution was cooled to –30 °C. A second flame-dried vial equipped with magnetic stir bar was charged with 2-norbornylmagnesium bromide (mixture of isomers, 0.68 M in diethyl ether, 0.68 mmol, 1.00 mL) and cooled to –30 °C. The contents of the first vial were cannulated to the second vial and stirred at 0 °C for 10 minutes. The solution turns red immediately, and slowly fades to nearly colorless along with copious formation of a white precipitate. The solution was decanted via cannula to a flame-dried vial equipped with a magnetic stir bar and charged with anhydrous zinc chloride (0.022 g, 0.16 mmol) and anhydrous tetrahydrofuran (2.00 mL) cooled to –78 °C. The pale yellow solution was stirred for 1 hour at this temperature. The solution was then cannulated to a flame-dried vial equipped with magnetic stir bar charged with *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.159 g, 0.50 mmol) and anhydrous tetrahydrofuran (3.00 mL) and stirred at room temperature for 2 hours. The reaction mixture was quenched with 10 mL 3.0 M ammonium hydroxide solution and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layer was washed with 3.0 M ammonium hydroxide solution (2 x 10 mL), saturated sodium chloride solution (1 x 10 mL), dried with magnesium sulfate, and the solvents were evaporated under reduced pressure. The residue was purified via flash chromatography, eluting the column with 5% triethylamine/hexanes prior to loading the column and eluting with hexanes, to afford 0.053 g of **17-*endo of a pale yellow oil (0.18 mmol, 56% yield, >95:5 endo:exo). Analytical data for the **17-*endo***: **IR** (thin film, cm^{-1}) 3086, 3061, 3028, 2950, 2864, 2809, 1601, 1494, 1452, 1379, 1344, 1160, 1123, 1076, 944; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 8H), 7.27-7.20 (m, 2H), 3.69 (d, J = 14.4 Hz, 2H), 3.55 (d, J = 14.4 Hz, 2H), 2.85 (dt, J = 3.7, 10.0 Hz, 1H), 2.45 (br s, 1H), 2.21 (br s, 1H), 2.12-2.02 (m, 1H), 1.83-1.74 (m, 1H), 1.60-1.50 (m, 1H), 1.43-1.27 (m, 4H), 1.079 (ddd, J = 12.0, 4.5, 2.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.0, 129.2, 127.9, 126.5, 64.0, 55.1, 40.1, 37.9, 37.1, 36.4, 30.7, 21.0. **Anal.** Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.54. Found: C, 86.58; H, 8.79.

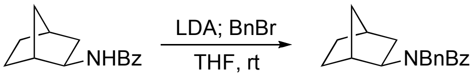


***N,N*-Dibenzylbicyclo[2.2.1]heptane-2-amine (17).** A flame-dried vial equipped with magnetic stir bar was charged with anhydrous zinc chloride (0.068 g, 0.50 mmol) and anhydrous tetrahydrofuran (4.00 mL). A solution of 2-norbornylmagnesium bromide (**1**) (mixture of isomers, 1.00 M in diethyl ether, 1.00 mmol, 1.00 mL) was added by syringe. The pale yellow solution was stirred for 1 hour at room temperature. The solution was then transferred via cannula to a flame-dried vial equipped with magnetic stir bar charged with *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.476 g, 1.50 mmol) and anhydrous tetrahydrofuran (5.00 mL) and stirred at room temperature for 2 hours. The reaction mixture was quenched with 10 mL 3.0 M ammonium hydroxide solution and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layer was washed with 3.0 M ammonium hydroxide solution (2 x 10 mL), saturated sodium chloride solution (1 x 10 mL), dried with magnesium sulfate, and the solvents were evaporated under reduced pressure. The residue was purified via flash chromatography, eluting the column with 5% triethylamine/hexanes prior to loading the column and eluting with hexanes, to afford 0.165 g of **17** a pale yellow oil (0.57 mmol, 57% yield, 65:35 endo:exo).



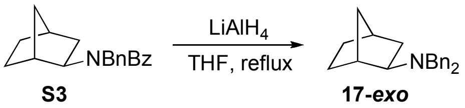
***exo-N*-bicyclo[2.2.1]heptan-2-yl-benzamide (S2).** A flame-dried round bottom flask was charged with thinly rolled sodium metal (0.303 g, 13.2 mmol), naphthalene (1.759 g, 13.5 mmol), and dimethoxyethane (distilled from sodium/benzophenone, 20.0 mL). The dark green mixture was stirred vigorously for 1 hour at room temperature. A second flame-dried round bottom flask was charged with endo-*N,N*-bicyclo[2.2.1]heptan-2-yl)-4-methylbenzenesulfonamide[50] (**S1)** (0.928 g, 5.3 mmol) and anhydrous dimethoxyethane (15 mL) and cooled to –78 °C. The contents of the first flask were transferred via cannula to the second flask over 20 minutes until the sulfonamide disappeared by TLC (~3/4 of sodium naphthalide solution). The reaction was quenched with saturated aqueous sodium bicarbonate (1.0 mL). When the dark green color disappeared, potassium carbonate (5.0 g) was added. The mixture was stirred and allowed to reach room temperature. The solids were removed by filtration, washed with diethyl ether (2 x 10 mL), and the solvent was removed under reduced pressure The resulting residue was taken up in diethyl ether (20 mL) and washed with a 1M hydrochloric acid solution (3 x 5 mL), the aqueous layer was basified with a 10% sodium hydroxide solution and extracted with dichloromethane (3 x 10 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in anhydrous dichloromethane (5.0 mL) in a flame-dried vial equipped with a stir bar. Triethylamine (distilled from calcium hydride, 0.500 mL, 3.6 mmol) and benzoyl chloride (0.400 mL, 3.5 mmol) were added sequentially by syringe. The solution was stirred at room temperature for 1 hour. The crude mixture was concentrated under vacuum and directly purified by flash chromatography, eluting with 15% ethyl acetate/hexanes, to yield the title compound (0.110 g, 0.5 mmol, 19% yield) as a white solid. Analytical data for **S2**:

^{1}H NMR (400 MHz, CDCl$_3$). δ 7.73 (d, *J* = 7.3 Hz, 2H), 7.52-7.38 (m, 3H), 5.93 (br s, 1H), 3.95-3.91 (m, 1H), 2.38-2.30 (m, 2H), 1.95-1.87 (m, 1H), 1.65-1. 40 (m, 2H), 1.38-1.10 (m, 4H); mp = 148-149 °C; lit. mp = 150-150.5 °C. (JACS, 1978, 100, 2176 – 2180)

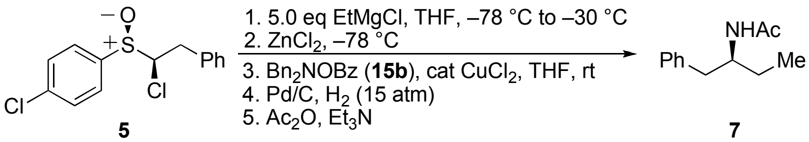


S2 **S3**

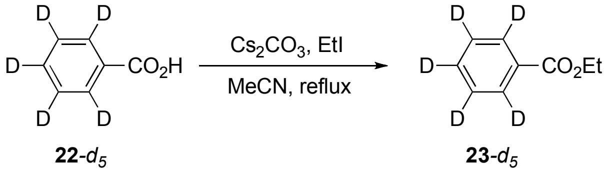
***exo*-*N*-benzyl-*N*-(bicyclo[2.2.1]heptan-2-yl)benzamide (S3).** A flame-dried vial equipped with magnetic stir bar was charged with *N,N*-diisopropylamine (0.069 mL, 0.48 mmol) and anhydrous tetrahydrofuran (2.0 mL). The vial was cooled to 0 °C. Then, *n*-butyllithium (1.4 M in hexanes, 0.345 mL, 0.48 mmol) was added slowly via syringe. The solution was stirred at 0 °C for 25 minutes, and then cooled to –78 °C. A second flame-dried vial equipped with magnetic stir bar was charged with *exo*-N-bicyclo[2.2.1]heptan-2-yl-benzamide (**S2**) (0.080 g, 0.37 mmol) and anhydrous tetrahydrofuran (2.0 mL). This solution was transferred to the first vial via cannula and stirred at –78 °C for 20 minutes. To the yellow solution is added benzyl bromide (0.132 mL, 1.11 mmol) drop wise via syringe. After stirring for 45 minutes, the solution is allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with water (2.0 mL) and diluted with diethyl ether (20 mL). The mixture is transferred to a separatory funnel and washed sequencially with 1M hydrochloric acid solution (10 mL), saturated aqueous sodium bicarbonate solution (10 mL), and saturated aqueous sodium chloride solution (5 mL). The organic layer is dried with magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography, eluting with 20% ethyl acetate/hexanes to yield the title compound as a viscous yellow oil (0.094 g, 0.31 mmol, 83% yield). Analytical data for the **S3**: **IR** (thin film, cm^{-1}) 3085, 3064, 3028, 2956, 2872, 1633, 1496, 1451, 1434, 1416, 1375, 1349, 1304, 1260, 1137, 1076, 1028, 966, 921; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44-7.14 (m, 10H), 4.80 (br d, J = 14.0 Hz, 1H), 4.62 (d, J = 16.5 Hz, 1H), 3.94 (br s, 1H), 2.22 (br s, 2H), 1.85-1.62 (br s, 1H), 1.62-1.50 (m, 2H), 1.30-1.46 (m, 2H), 1.15 (d, J = 9.8 Hz, 1H), 1.03 (br s, 2H); **^{13}C NMR** (50 °C, 100 MHz, $CDCl_3$) δ 173.0, 139.4, 137.9, 129.1, 128.5, 128.3, 126.8, 126.6, 126.4, 61.0, 47.3, 40.8, 39.6, 37.2, 35.8, 28.9, 27.9. **Anal.** Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; O, 5.24. Found: C, 82.64; H, 7.70; O, 5.49.



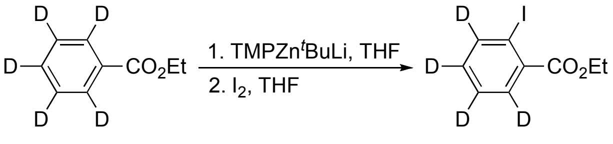
exo-*N,N*-Dibenzylbicyclo[2.2.1]heptane-2-amine (17-*exo*). A flame-dried round bottom flask equipped with a magnetic stir bar and reflux condenser was charged with lithium aluminum hydride (0.155 g, 4.1 mmol). A solution of exo-*N*-benzyl-*N*-(bicyclo[2.2.1]heptan-2-yl)benzamide (**S3**) (0.052 g, 0.17 mmol) in anhydrous tetrahydrofuran (3.0 mL) was added via syringe. The mixture was refluxed until the starting material disappeared by TLC (75 minutes). The reaction was allowed to cool to room temperature, after which it was cooled to 0 °C. Water (0.150 mL) was added cautiously via syringe, followed by 15% w/v aqueous sodium hydroxide solution (0.150 mL). The mixture was stirred briefly. Then another portion of water (0.450 mL) was added and the mixture was allowed to reach room temperature with stirring over 30 minutes. Magnesium sulfate was added, removed by filtration, and the solvents were removed under reduced pressure. The residue was purified via flash chromatography, eluting with 2.5% ethyl acetate/hexanes, to yield the title compound (0.039 g, 0.13 mmol, 79% yield) as a colorless oil. Analytical data for the **17-*exo***: **IR** (thin film, cm^{-1}) 3085, 3061, 3027, 2951, 2869, 1714, 1601, 1494, 1453, 1354, 1265, 1119, 1076, 1028, 988; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.0 Hz, 4H), 7.30 (t, J = 7.6 Hz, 4H), 7.22 (t, J = 7.1 Hz, 2H), 3.71 (d, J = 14.4 Hz, 2H), 3.54 (d, J = 14.4 Hz, 2H), 2.58 (dd, J = 6.6, 4.9 Hz, 1H), 2.42 (br s, 1H), 2.29 (br s, 1H), 1.67-1.57 (m, 2H), 1.52-1.45 (m, 3H), 1.12-1.02 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.3, 128.7, 128.0, 126.4, 66.1, 55.0, 38.6, 38.1, 36.3, 35.7, 28.5, 28.2. **Anal.** Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.54. Found: C, 86.43; H, 8.74.


5
1. 5.0 eq EtMgCl, THF, –78 °C to –30 °C
2. ZnCl$_2$, –78 °C
3. Bn$_2$NOBz (**15b**), cat CuCl$_2$, THF, rt
4. Pd/C, H$_2$ (15 atm)
5. Ac$_2$O, Et$_3$N
NHAc
Ph
Me
7

(*N*)-(1-Phenyl-2-butyl)-acetamide (7). A flame-dried shell vial equipped with magnetic stir bar was charged with (R,R)-*p*-chlorophenyl-1-chloro-2-phenylethyl sulfoxide (**5**) (0.060 g, 0.20 mmol) and anhydrous tetrahydrofuran (0.40 mL) and cooled to –78 °C. Ethylmagnesium chloride (1.88 M in tetrahydrofuran, 0.532 mL, 1.00 mmol) was added drop wise down the side of the vial over 15 minutes. The solution was allowed to warm at a constant rate (~0.5 °C/min) ending at –30 °C after 90 minutes. The solution was cooled to –78 °C. A solution of anhydrous zinc chloride (0.056 g, 0.41 mmol) in 0.60 mL anhydrous tetrahydrofuran was added slowly via cannula and stirred for 80 minutes. *O*-benzoyl-*N,N*-dibenzylhydroxylamine (0.317 g, 1.00 mmol) and copper (I) chloride (0.0003 g, 0.003 mmol) were dissolved in 2.0 mL anhydrous tetrahydrofuran and added via cannula to the first vial. The mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution (5.0 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (5.0 mL) and saturated aqueous sodium chloride solution (5.0 mL), dried with magnesium sulfate, filters, and the solvents removed under reduced pressure. The residue was placed in a vial equipped with a magnetic stir bar and dissolved in 5.0 mL absolute ethanol. 10% Palladium on carbon (0.040 g) was added and the vial was placed in a high pressure hydrogenation bomb at 15 atm hydrogen for 2 hours. The mixture was filtered through Celite and the solvents were evaporated under reduced pressure. The residue was dissolved in anhydrous dichloromethane (2.0 mL) in a vial equipped with a magnetic stir bar. Triethylamine (distilled from calcium hydride, 0.500 mL, 3.6 mmol) and acetic anhydride (0.500 mL, 5.3 mmol) were added sequentially via syringe. The solution was stirred at room temperature for 1 hour. The reaction was quenched with water (1.0 mL) and diluted with diethyl ether (20 mL). The organic layer was washed with 1M hydrochloric acid solution (5 mL), saturated aqueous sodium bicarbonate solution (5 mL), and saturated aqueous sodium chloride solution (5 mL), dried with magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified with flash chromatography, eluting first with dichloromethane and second with 5% methanol/dichloromethane, to afford **7** (0.006 g, 0.04 mmol, 18% yield): $[\alpha]_D^{28.2} = -1.9$ ($c = 0.15$, methanol). The product was analyzed by chiral gas chromatography (160 °C) providing an ee of 75%.

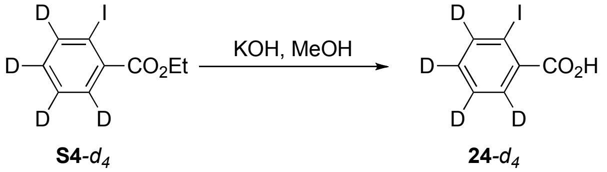


Ethyl benzoate-d_5 (23-d_5). The title compound was prepared according to Lee's method[51] with slight modification: a round bottom flask equipped with a magnetic stir bar and reflux condenser was charged with benzoic acid-d_5[42] (**22-**d_5) (99.5% D, 0.915 g, 7.2 mmol, cesium carbonate (3.519 g, 10.8 mmol), and acetonitrile (60 mL). Iodoethane (2.88 mL, 36.0 mmol) was added via syringe and the mixture was refluxed open to the atmosphere for 90 minutes. After cooling the mixture to room temperature, the solids were filtered through a glass frit. The solvents were removed under reduced pressure. The residue was taken up in dichloromethane (60 mL) and washed with saturated aqueous sodium bicarbonate solution (30 mL). The aqueous layer was back extracted with dichloromethane (30 mL). The combined organic layers were dried with sodium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified via flash chromatography, eluting with 10% ethyl acetate/hexanes to yield the title compound (0.983 g, 6.4 mmol, 88%) as a clear, colorless oil. Analytical data for the **23-**d_5: **IR** (thin film, cm^{-1}) 2981, 2938, 2905, 2298, 2279, 1718, 1569, 1466, 1396, 1382, 1241, 1082, 1040, 851, 819, 729; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 132.1 (t, J_{CD} = 24 Hz), 130.2, 129.0 (t, J_{CD} = 25 Hz), 127.6 (t, J_{CD} = 25 Hz), 60.7, 14.2. **HRMS** (ESI) calcd for $C_9H_5D_5O_2$+Na 178.089, found 178.092.



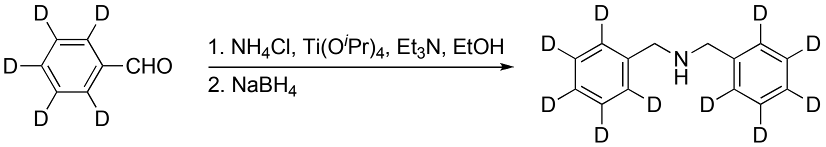
23-d_5 **S4**-d_4

Ethyl 2-iodobenzoate-d_5 (S4-d_4). The title compound was prepared according to Kondo's method[52] with slight modification: A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 2,2,6,6-tetramethylpiperidine (0.851 mL, 5.0 mmol) and anhydrous tetrahydrofuran (25.0 mL) and cooled to –78 °C. *n*-Butyllithium (1.5 M in hexanes, 3.03 mL, 4.6 mmol) was added drop wise via syringe. Afterwards, the solution was allowed to stir at 0 °C for 40 minutes. A flame-dried vial equipped with a magnetic stir bar was charged with anhydrous zinc chloride (1.04 M in tetrahydrofuran, 5.25 mL, 5.5 mmol) and cooled to –78°C. *t*-Butyllithium (1.7 M in pentane, 6.42 mL, 10.9 mmol) was added drop wise via syringe with stirring. After the addition, the mixture was allowed to warm to room temperature over 15 minutes. The first flask was cooled to –78°C. The solution of di-*t*-butylzinc was transferred to the flask via cannula. After the addition, the flask was warmed to room termperature and stirred for 30 minutes. A solution of ethyl benzoate-d_5 (**23-d_5**) (0.353 g, 2.3 mmol) in anhydrous tetrahydrofuran (10.0 mL) was added at once and stirred at room temperature for 15 hours. The solution changed from yellow to reddish-orange. A solution of iodine (4.615 g, 18.2 mmol) in anhydrous tetrahydrofuran (25.0 mL) was added at once via syringe. A slight exotherm developed and the solution was stirred for 100 minutes. The reaction was quenched with saturated aqueous sodium thiosulfate solution (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL), dried with magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The residue was purified via flash chromatography, eluting with 2.5→5.0% ethyl acetate/hexanes to yield the title compound (0.472 g, 1.7 mmol, 74%) as a clear, yellow oil. Analytical data for the **S4-*d*$_4$**: **IR** (thin film, cm^{-1}) 2981, 2936, 2904, 2291, 1724, 1555, 1531, 1464, 1444, 1392, 1377, 1322, 1277, 1235, 1077, 1017, 989; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.37 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 140.7 (t, J_{CD} = 25 Hz), 135.2, 131.9 (t, J_{CD} = 25 Hz), 130.3 (t, J_{CD} = 25 Hz), 127.3 (t, J_{CD} = 25 Hz), 93.7, 61.6, 14.1. **HRMS** (ESI) calcd for $C_9H_5D_4IO_2$+Na 302.979, found 302.980.



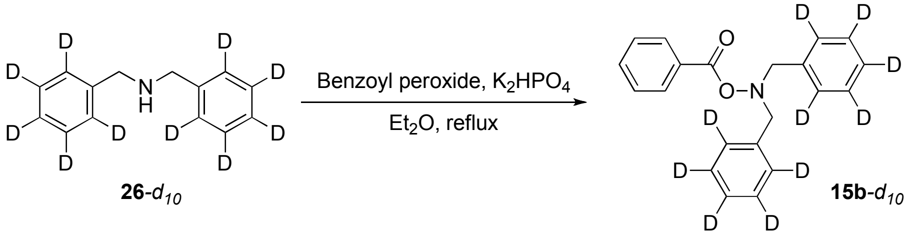
2-Iodobenzoic acid-*d*$_4$ (24-*d*$_4$). A round bottom flask equipped with a magnetic stir bar was charged with ethyl 2-iodobenzoate-*d*$_4$ (**S4**-*d*$_4$) (0.300 g, 1.1 mmol) and methanol (10 mL). Potassium hydroxide pellets (0.300 g, 5.4 mmol) were added and the mixture was stirred for 16 hours at room temperature. The solvents were removed under reduced pressure and the residue was taken up in water (30 mL) and washed with dichloromethane (2 x 5 mL). The aqueous later was then acidified to pH 1 with 10% hydrochloric acid solution. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried with sodium sulfate, filtered, and the solvents were removed under reduced pressure to afford the title compound (0.251 g, 1.0 mmol, 93%) as a slightly yellow solid. Analytical data for **24-*d*$_4$**: **IR** (KBr, cm^{-1}) 2962,

2772, 2716, 2679, 2645, 2590, 1678, 1555, 1529, 1417, 1358, 1312, 1287, 1244, 1079, 993, 906, 785, 660, 615, 579, 534; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.3 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 141.5 (t, J_{CD} = 25 Hz), 133.0 (t, J_{CD} = 24 Hz), 131.7 (t, J_{CD} = 25 Hz), 127.5 (t, J_{CD} = 25 Hz), 94.6, 61.6. **mp** 157.5-159.5 °C. **HRMS** (ESI) calcd for $C_7HD_4IO_2$+Na 274.948, found 274.945.



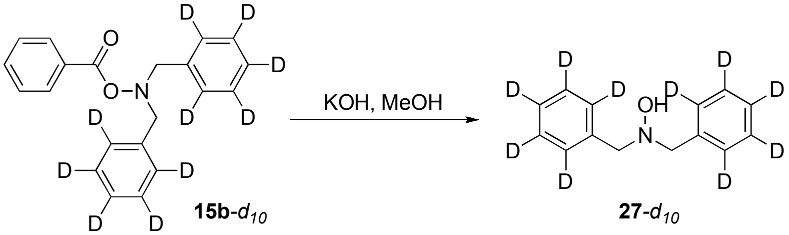
25-*d*$_5$ **26**-*d*$_{10}$

Dibenzylamine-*d*$_{10}$ (26-*d*$_{10}$). The title compound was prepared according to Williamson's method[45] with slight modification: a vial equipped with magnetic stir bar was charged with benzaldehyde-*d*$_5$[42] (**25-***d*$_5$) (99.5% D, 0.421 g, 3.6 mmol), ammonium chloride (0.385 g, 7.2 mmol) and absolute ethanol (5.0 mL). Titanium(IV) isopropoxide (2.13 mL, 7.2 mmol) and triethylamine (distilled from calcium hydride, 1.11 mL, 7.2 mmol) were added sequentially via syringe and the yellow solution was stirred at room temperature for 22 hours. Sodium borohydride (0.204 g, 5.4 mmol) was then added and the mixture was stirred for 10 hours. The mixture was diluted with diethyl ether (10 mL) and poured onto 3M aqueous ammonium hydroxide solution (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried with magnesium sulfate, filtered, and the solvents removed under reduced pressure. The residue was purified via flash chromatography, eluting the column with 10% triethylamine/hexanes prior to loading the column and eluting with 15% ethyl acetate/hexanes, to afford the title compound (0.286 g, 1.4 mmol, 76% yield) as a clear, colorless oil. Analytical data for **26-*d*$_{10}$**: **IR** (thin film, cm^{-1}) 3337, 2917, 2827, 2370, 2321, 2274, 1570, 1452, 1362, 1159, 1100, 1047, 873, 841, 819, 796, 738, 712; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 3.87 (s, 4H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 140.0, 127.8 (t, J_{CD} = 24 Hz), 127.6 (t, J_{CD} = 24 Hz), 126.3 (t, J_{CD} = 23 Hz), 53.0. **HRMS** (ESI) calcd for $C_{14}H_5D_{10}N$+H 208.190, found 208.191.

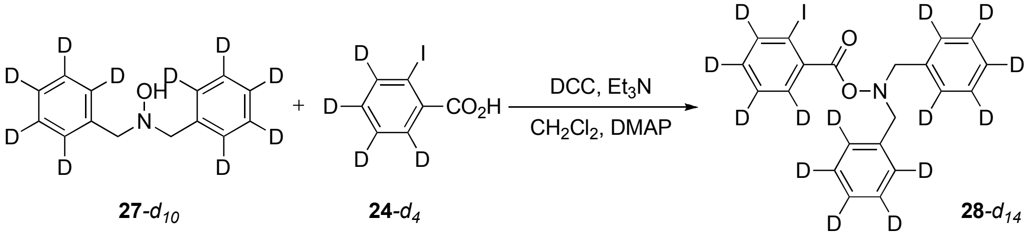


***O*-Benzoyl-*N,N*-dibenzylamine-*d*$_5$ (15b-*d*$_{10}$).** The title compound was prepared according to Ganem's method[37] with slight modification: a round bottom flask equipped with a magnetic stir bar and reflux condenser was charged with dibenzylamine-*d*$_{10}$ (**26-*d*$_{10}$**) (0.226 g, 1.1 mmol), potassium hydrogen phosphate (0.950 g, 5.5 mmol), benzoyl peroxide (0.291 g, 1.2 mmol), and diethyl ether (15 mL). The reaction was refluxed for 3 days. The mixture was shaken with saturated aqueous sodium carbonate solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and the solvents removed under reduced pressure. The residue was purified via flash chromatography two times, eluting with 7.5% ethyl acetate/hexanes, followed by recrystallization from methanol (5 mL) to afford the title compound (0.170 g, 0.5 mmol, 48% yield) as colorless crystals. Analytical data for **15b-*d*$_{10}$**: **IR** (thin film, cm^{-1}) 2954, 2924, 2853, 1727, 1462, 1377, 1263, 1254, 1095, 1069, 1046, 1026, 1000,

961, 941, 836, 819, 706; **^{1}H NMR** (400 MHz, CD_3CN) δ 7.79 (d, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 2H), 4.20 (s, 4.20); **^{13}C NMR** (100 MHz, CD_3CN) δ 165.3, 137.3, 134.0, 130.2, 129.9 (t, J_{CD} = 24 Hz), 129.8, 129.5, 128.6 (t, J_{CD} = 24 Hz), 128.0 (t, J_{CD} = 24 Hz), 63.0. **mp** 94-95 °C. **HRMS (ESI)** calcd for $C_{21}H_9D_{10}NO_2$+Na 350.193, found 350.196.

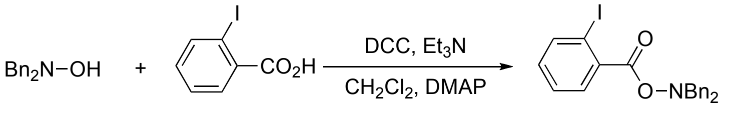


***N,N*-Dibenzylhydroxylamine-*d*$_{10}$ (27-*d*$_{10}$).** The title compound was prepared according to Ganem's method[37] with slight modification: a vial equipped with a magnetic stir bar was charged with anhydrous methanol (distilled from magnesium methoxide, 4.0 mL). The vial was cooled to 0 °C and potassium metal (washed with hexanes, 0.026 g, 0.66 mmol) was added. *O*-Benzoyl-*N,N*-dibenzylhydroxylamine-*d*$_{10}$ (**15b-*d*$_{10}$**) (0.131 g, 0.40 mmol) was dissolved in diethyl ether (6.0 mL) in a flame-dried vial, and cannula transferred to the potassium methoxide solution and stirred at room temperature for 36 hours. The mixture was partitioned between water (20 mL) and diethyl ether (10 mL). The organic layer was separated and washed with 1M hydrochloric acid solution (10 mL). A white precipitate formed immediately. The solid was collected by filtration and washed with diethyl ether (2 x 10 mL). The solid was added to a separatory funnel containing diethyl ether (20 mL) and a saturated aqueous sodium bicarbonate solution (20 mL) and shaken vigorously until nearly all solid dissolved. The layers were separated and the aqueous layer was extracted with diethyl ether (20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and the solvents removed under reduced pressure to afford the title compound (0.059 g, 0.26 mmol, 66% yield) as a colorless solid. Analytical data for **27-*d*$_{10}$**: **IR** (KBr, cm^{-1}) 3219, 2898, 2858, 2269, 1610, 1465, 1450, 1333, 1089, 1053, 1001, 964, 928, 874, 839, 822, 783, 636, 548, 483; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 6.58 (br s, 1H), 3.72 (s, 4H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 137.0, 129.3 (t, J_{CD} = 24 Hz), 127.7 (t, J_{CD} = 25 Hz), 126.9 (t, J_{CD} = 23 Hz), 63.7; **mp** 117.5-119.0 °C. **HRMS** (ESI) calcd for $C_{14}H_5D_{10}NO$+Na 246.167, found 246.170.



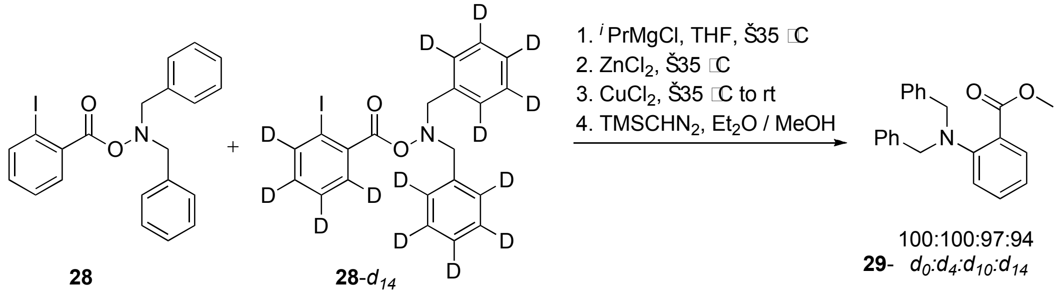
***O*-2-Iodobenzoyl-*N,N*-dibenzylhydroxylamine-*d*$_{14}$ (28-*d*$_{14}$).** A vial equipped with a magnetic stir bar was charged with 2-iodobenzoic acid-*d*$_4$ (**24-*d*$_4$**) (0.038 g, 0.15 mmol), *N,N*-dibenzylhydroxylamine-*d*$_{10}$ (**27-*d*$_{10}$**) (0.030 g, 0.14 mmol), 4-(dimethylamino)pyridine (0.003 g, 0.03 mmol), and dichloromethane (4.0 mL). Dicyclohexylcarbodiimide (0.031 g, 0.15 mmol) was added and the solution stirred for 20 minutes. Additional portions of the benzoic acid (0.004 g) and DCC (0.010 g) were added and the reaction was stirred for a further 30 minutes. The solvents were removed under reduced pressure and the residue purified via flash chromatography, eluting with 7.5% ethyl acetate/hexanes to afford the title compound (0.063 g, 0.14 mmol, 100% yield) as a colorless oil. Analytical data for **28-*d*$_{14}$**: **IR** (thin film, cm^{-1}) 2925, 2850, 2275, 1749, 1554, 1530, 1436, 1373, 1314, 1274, 1197, 1042, 972, 845, 820, 738, 666; **^{1}H NMR** (400

MHz, $CDCl_3$) δ 4.24 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.5, 140.0 (t, J_{CD} = 25 Hz), 135.8, 135.5, 131.5 (t, J_{CD} = 25 Hz), 129.3 (t, J_{CD} = 25 Hz), 128.9 (t, J_{CD} = 24 Hz), 127.8 (t, J_{CD} = 24 Hz), 127.2 (t, J_{CD} = 24 Hz), 127.1 (t, J_{CD} = 25 Hz), 93.1, 62.3. **HRMS** (ESI) calcd for $C_{21}H_4D_{14}INO_2$+Na 480.114, found 480.117.



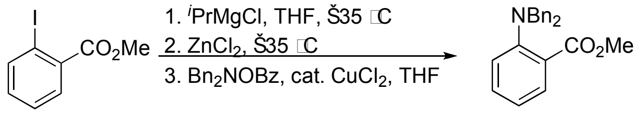
27 **24** **28**

***O*-2-Iodobenzoyl-*N,N*-dibenzylhydroxylamine (28).** A vial equipped with a magnetic stir bar was charged with 2-iodobenzoic acid (**24**) (0.063 g, 0.25 mmol), *N,N*-dibenzylhydroxylamine[37] (**27**) (0.053 g, 0.25 mmol), 4-(dimethylamino)pyridine (0.006 g, 0.05 mmol), and dichloromethane (5.0 mL). Dicyclohexylcarbodiimide (0.052 g, 0.25 mmol) was added and the solution stirred for 40 minutes. The mixture was filtered through a glass frit and washed with dichloromethane (15 mL). The solvents were removed under reduced pressure and the residue purified via flash chromatography, eluting with 7.5% ethyl acetate/hexanes to afford the title compound (0.097 g, 0.22 mmol, 88% yield) as a colorless oil. Analytical data for **28**: **IR** (thin film, cm^{-1}) 3088, 3064, 3030, 2920, 2848, 1751, 1583, 1496, 1465, 1454, 1429, 1283, 1237, 1124, 1088, 1039, 1015, 990, 738, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.1 Hz, 4H), 7.32 (t, J = 7.0 Hz, 4H), 7.28-7.22 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 6.99 (dd, J = 7.7, 1.6 Hz, 1H), 6.95 (dd, J = 7.7, 1.5 Hz, 1H), 4.21 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.5, 140.4, 135.9, 135.6, 132.0, 129.6, 129.3, 128.3, 127.7, 127.6, 93.2, 62.3. **HRMS** (ESI) calcd for $C_{21}H_{18}INO_2$+Na 466.028, found 466.029.


1. ^{i}PrMgCl, THF, Š35 □C
2. ZnCl$_2$, Š35 □C
3. CuCl$_2$, Š35 □C to rt
4. TMSCHN$_2$, Et$_2$O / MeOH
100:100:97:94

28 **28**-d_{14} **29**- d_0:d_4:d_{10}:d_{14}

Procedure for the endocyclic restriction test. To a flame-dried vial equipped with magnetic stir bar was added a solution of O-2-iodo-benzoyl N,N-dibenzylhydroxylamine-d_{14} (**28**-d_{14}) in anhydrous tetrahydrofuran (0.033 M, 1.00 mL, 0.033 mmol) and a solution of O-2-iodobenzoyl N,N-dibenzylhydroxylamine (**28**) (0.033 M, 1.00 mL, 0.033 mmol) via syringe. The total volume was reduced to 1.0 mL under a stream of argon. The vial was cooled to –78 °C. *i*-Propylmagnesium chloride (1.2 M in tetrahydrofuran, 0.058 mL, 0.07 mmol) was added drop wise by syringe. The solution was stirred at –35 °C for 70 minutes. The solution was cooled to –78 °C , after which zinc chloride (1.04 M in tetrahydrofuran, 0.032 mL, 0.033 mmol) was added drop wise. The solution was stirred at –35 °C for 40 minutes. Copper(II) chloride (0.004 M in tetrahydrofuran, 0.300 mL, 0.0001 mmol) was added via syringe at once. The cooling bath was removed and the solution was stirred for 60 minutes. The reaction was quenched with saturated aqueous sodium bicarbonate solution (4 mL) and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layer was dried with sodium sulfate, filtered, and the solvents were removed by rotary evaporation. The residue was dissolved in methanol (distilled from magnesium methoxide, 1.0 mL) and anhydrous diethyl ether (1.0 mL) in a flame-dried vial equipped with a magnetic stir bar. (Trimethylsilyl)diazomethane (2.0 M in diethyl ether, 0.100 mL, 0.2 mmol) was added via syringe. The yellow solution was stirred for 30 minutes. The solvents were removed by rotary evaporation and the residue was purified by flash chromatography with 10% ethyl acetate/hexanes to yield a clear oil (0.011 g, 0.033 mmol, 50%). Analysis by mass spectrometry indicated a 100:100:97:94 mixture of d_0:d_4:d_{10}:d_{14} containing methyl 2-(dibenzylamino)benzoate (**29**). Analytical data for **29**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71-7.68 (m, 0.5H), 7.30-7.18 (m, 5.5H), 6.96-6.92 (m, 1H), 4.24 (s, 4H), 3.88 (s, 3H).

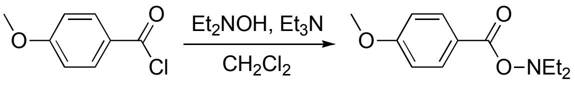


29

Methyl 2-(dibenzylamino)benzoate (29). A flame-dried round bottom flask equipped with magnetic stir bar was charged with methyl 2-iodobenzoate (0.314 g, 1.20 mmol), anhydrous tetrahydrofuran (6.0 mL), and the solution cooled to –35 °C. A tetrahydrofuran solution of *i*-propylmagnesium bromide (1.2 M, 1.32 mL, 1.32 mmol) was slowly added along the edges of the flask and the reaction mixture was stirred at –35 °C for 75 minutes. The solution was cooled to –78 °C and a tetrahydrofuran solution of zinc(II) chloride (1.04 M, 0.635 mL, 0.66 mmol) was slowly added along the edges of the flask and the reaction mixture was stirred at –35 °C for 15 minutes. An oven-dried vial equipped with magnetic stir bar was charged with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (0.190 g, 0.60 mmol), copper(II) chloride (0.001 g, 0.01 mmol), and anhydrous tetrahydrofuran (4.0 mL). The contents of the vial were cannula transferred to the first flask at –35 °C and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water (1.0 mL), diluted with diethyl ether (10 mL), and washed with a 1M hydrochloric acid solution (3 x 5 mL). The aqueous layer was basified with a 10% sodium hydroxide solution and extracted with dichloromethane (2 x 10 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed under reduced pressure, affording the title compound (0.162 g, 0.49 mmol, 81%) as a thick, colorless oil. Analytical data for **29**: **IR** (thin film, cm^{-1}) 3085, 3063, 3030, 2949, 2838, 1718, 1596, 1489, 1452, 1297, 1254, 1121, 762, 733, 699; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71-7.68 (m, 1H), 7.30-7.18 (m, 11H), 6.96-6.92 (m, 2H), 4.24 (s, 4H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.9, 150.8, 137.9, 131.8, 131.2, 129.2, 127.0, 124.9, 121.3, 120.8, 56.8, 52.0. **HRMS** (ESI) calcd for $C_{22}H_{21}NO_2$+Na 354.147, found 354.148.

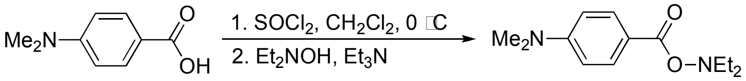
General Procedure (B) for the preparation of substituted *O*-acyl-*N,N*-diethylhydroxylamines.

An oven-dried round bottom flask equipped with magnetic stir bar and addition funnel was charged with *N,N*-diethylhydroxylamine (1.05 eq), triethylamine (distilled from calcium hydride, 1.0 g, 1.4 mL, 10 mmol), and anhydrous dichloromethane and cooled to 0 C. The acyl chloride (1.0 eq) was dissolved in anhydrous dichloromethane and added slowly by syringe over 5 minutes. The reaction was stirred for the indicated time at room temperature. The reaction mixture was diluted with dichloromethane (20 mL) and the organic layer was separated, washed with 1M hydrochloric acid solution (2 x 10 mL), dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography, eluting with the indicated solvent mixture, to afford the *O*-acyl-*N,N*-diethyl-hydroxylamine. The products were stored at -35°C under anhydrous conditions.



30b

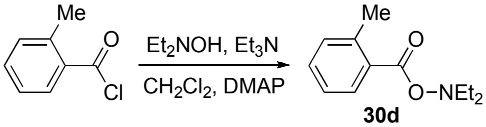
***O*-4-Methoxybenzoyl-*N,N*-diethylhydroxylamine (30b).** The title compound was prepared according to General Procedure **B** using *N,N*-diethylhydroxylamine (0.770 mL, 7.4 mmol) and triethylamine (1.020 mL, 7.4 mmol) in anhydrous dichloromethane (5.0 mL) and 4-methoxybenzoyl chloride (0.974 mL, 7.0 mmol) in anhydrous dichloromethane (5.0 mL) with stirring for 45 minutes to yield *O*-4-methoxybenzoyl-*N,N*-diethylhydroxylamine (**30b**) (1.549 g, 6.9 mmol, 99% yield) as a yellow oil after flash chromatography with 20%→30%→40% ethyl acetate/hexanes. Analytical data for **30b**: **IR** (thin film, cm^{-1}) 2980, 2940, 2842, 2363, 1734, 1700, 1653, 1605, 1559, 1540, 1507, 1457, 1419, 1378, 1316, 1252, 1169, 1070, 1029, 1009, 873, 865, 845, 767; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 2.96 (q, *J* = 7.0 Hz, 4H), 1.11 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.5, 163.2, 131.3, 121.2, 113.5, 55.2, 53.3. 11.7. **HRMS** (ESI) calcd for $C_{12}H_{17}NO_3$+Na 246.111, found 246.113.



30c

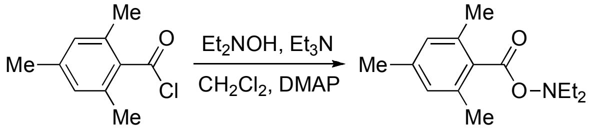
***O*-4-Dimethylaminobenzoyl-*N,N*-diethylhydroxylamine (30c).** A flame-dried vial equipped with magnetic stir bar was charged with 4-(dimethylamino)benzoic acid (1.500 g, 8.9 mmol) and anhydrous dichloromethane (5.0 mL) and cooled to 0°C. The argon line was replaced with a drying tube containing calcium sulfate and thionyl chloride (0.650 mL, 8.9 mmol) was added. The solution was stirred at 0 °C for 3 hours. Triethylamine

(1.300 mL, 9.3 mmol) and *N,N*-diethylhydroxylamine (0.980 mL, 9.3 mmol) were added sequentially via syringe with stirring at 0 °C. Anhydrous dichloromethane (10 mL) was added to aid stirring. The mixture was stirred for 1 hour and then quenched with 1M aqueous sodium hydroxide solution (10 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 20 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (10 mL), dried with sodium sulfate, filtered and the solvents were removed under reduced pressure. The residue was purified via flash chromatography with 30%→40% ethyl acetate/hexanes to yield *O*-4-dimethylaminobenzoyl-*N,N*-diethylhydroxylamine (**30c**) (0.560 g, 2.4 mmol, 27% yield) as a yellow solid. Analytical data for **30c**: **IR** (thin film, cm^{-1}) 2980, 2939, 2873, 2837, 1733, 1618, 1556, 1464, 1436, 1373, 1316, 1264, 1232, 1185, 1065, 1001, 823, 764, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 2.97-2.93 (m, 10H), 1.12 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2, 153.1, 131.0, 155.4, 110.5, 53.3., 39.8, 11.7. **mp** 59.0-60.5 °C. **HRMS** (ESI) calcd for $C_{13}H_{20}N_2O_2$+Na 259.142, found 259.140.



30d

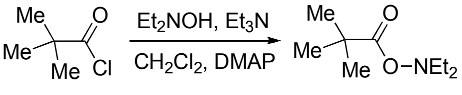
***O*-2-Methylbenzoyl-*N,N*-diethylhydroxylamine (30d).** The title compound was prepared according to General Procedure **B** using *N,N*-diethylhydroxylamine (0.770 mL, 7.4 mmol) and triethylamine (1.020 mL, 7.4 mmol), and 4-(dimethylamino)pyridine (0.030 g, 0.3 mmol) in anhydrous dichloromethane (5.0 mL) and *o*-toluoyl chloride (0.922 mL, 7.0 mmol) in anhydrous dichloromethane (5.0 mL) with stirring for 3 hours to yield *O*-2-methylbenzoyl-*N,N*-diethylhydroxylamine (**30d**) (1.293 g, 6.2 mmol, 89% yield) as a yellow oil after flash chromatography with 20%→30% ethyl acetate/hexanes →100% diethyl ether. Analytical data for **30d**: **IR** (thin film, cm^{-1}) 2978, 2939, 2877, 2845, 1747, 1602, 1577, 1458, 1379, 1286, 1236, 1134, 1044, 874, 823, 794, 736; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.26-7.20 (m, 2H), 3.04 (q, *J* = 7.1 Hz, 4H), 2.57 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.0, 139.6, 131.7, 131.5, 129.7, 129.2, 125.6, 53.3., 21.4, 11.9. **HRMS** (ESI) calcd for $C_{12}H_{17}NO_2$+Na 230.116, found 230.114.



30e

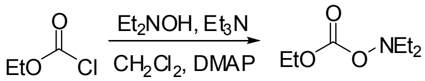
***O*-2,4,6-Trimethylbenzoyl-*N,N*-diethylhydroxylamine (30e).** The title compound was prepared according to General Procedure **B** using *N,N*-diethylhydroxylamine (0.770 mL, 7.4 mmol) and triethylamine (1.020 mL, 7.4 mmol), and 4-(dimethylamino)pyridine (0.030 g, 0.3 mmol) in anhydrous dichloromethane (5.0 mL) and 2,4,6-trimethylbenzoyl chloride (1.305 g, 7.0 mmol) in anhydrous dichloromethane (5.0 mL) with stirring for 30 minutes to yield 2,4,6-trimethylbenzoyl-*N,N*-diethylhydroxylamine (**30e**) (1.042 g, 6.9 mmol, 63% yield) as a yellow oil after flash chromatography with 20% ethyl acetate/hexanes. Analytical data for **30e**: **IR** (thin film, cm^{-1}) 2980, 2939, 2874, 1749, 1612, 1450, 1381, 1243, 1168, 1053, 866, 852; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 (s, 2H), 3.05 (q, *J* = 7.1 Hz, 4H), 2.32 (s, 6H), 2.27 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 6H); **^{13}C**

NMR (100 MHz, CDCl$_3$) δ 169.2, 139.4, 135.0, 129.8, 128.3, 52.4, 21.1, 19.7, 11.7. **HRMS** (ESI) calcd for $C_{14}H_{21}NO_2$+Na 258.147, found 258.147.



30f

***O*-Trimethylacetyl-*N,N*-diethylhydroxylamine (30f).** The title compound was prepared according to General Procedure **B** using *N,N*-diethylhydroxylamine (1.320 mL, 12.6 mmol) and triethylamine (1.750 mL, 12.6 mmol), and 4-(dimethylamino)pyridine (0.030 g, 0.3 mmol) in anhydrous dichloromethane (5.0 mL) and trimethylacetyl chloride (1.490 mL, 12.0 mmol) in anhydrous dichloromethane (5.0 mL) with stirring for 20 minutes to yield *O*-trimethylacetyl-*N,N*-diethylhydroxylamine (**30f**) (1.769 g, 10.2 mmol, 85% yield) as a yellow oil with no further purification necessary. Analytical data for **30f**: **IR** (thin film, cm^{-1}) 2978, 2941, 2874, 2844, 1758, 1481, 1464, 1395, 1367, 1271, 1168, 1142, 1107, 1028, 760; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 2.89 (q, *J* = 7.1 Hz, 4H), 1.23 (s, 9H), 1.10 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 176.5, 52.8, 38.1, 26.9, 11.3. **HRMS** (ESI) calcd for $C_9H_{19}NO_2$+Na 196.131, found 196.133.



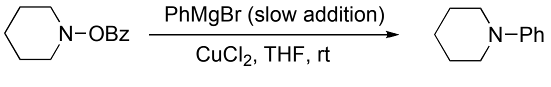
***O*-(Ethoxycarbonyl)-*N,N*-diethylhydroxylamine (30g).** The title compound was prepared according to General Procedure **B** using *N,N*-diethylhydroxylamine (1.320 mL, 12.6 mmol) and triethylamine (1.750 mL, 12.6 mmol), and 4-(dimethylamino)pyridine (0.030 g, 0.3 mmol) in anhydrous dichloromethane (15.0 mL) and ethyl chloroformate (1.150 mL, 12.0 mmol) in anhydrous dichloromethane (5.0 mL) with stirring for 30 minutes to yield *O*-(ethoxycarbonyl)-*N,N*-diethylhydroxylamine (**30g**) (1.372 g, 9.5 mmol, 79% yield) as a yellow oil after bulb to bulb distillation at 15 mbar. Analytical data for **30g**: **IR** (thin film, cm^{-1}) 2982, 2941, 2878, 2849, 2360, 1764, 1455, 1368, 1309, 1233, 1157, 1131, 1051, 999, 982, 908, 883, 828, 784; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.1 Hz, 2H), 2.93 (q, *J* = 7.1 Hz, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 6H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 155.7, 64.3, 53.5, 14.2, 11.7. **HRMS** (ESI) calcd for $C_7H_{15}NO_3$+Na 184.095, found 184.097.

General Procedure (C) for the copper and zinc-catalyzed amination of organomagnesium and organolithium reagents with *O*-acyl-*N,N*-diethylhydroxylamines.

A flame-dried vial equipped with magnetic stir bar was charged with copper(II) chloride, zinc(II) chloride, the *O*-acyl-*N,N*-ethylhydroxylamine (0.50 mmol), dodecane (internal standard) and anhydrous tetrahydrofuran (2.0 mL). A solution of phenylmagnesium bromide or phenyllithium compound in anhydrous tetrahydrofuran or dibutyl ether was slowly added (0.15 mmol/minute) to the reaction mixture via syringe pump and stirred for a further 15 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL) and 3.0 M ammonium hydroxide solution (5 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and the solution analyzed by GC (120 °C, 80 kPa for 11 minutes, then ramp to 180°C at 60 °C/minute).

General Procedure (D) for the copper-catalyzed amination of organomagnesium with *O*-benzoyl-*N*,*N*-dialkyl hydroxylamines.

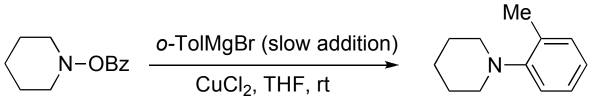
A flame-dried vial equipped with magnetic stir bar was charged with copper(II) chloride, the *O*-benzoyl-*N*,*N*-dialkyl hydroxylamine (0.50 mmol), and anhydrous tetrahydrofuran (4.0 mL). A solution of the organomagnesium compound in anhydrous tetrahydrofuran was slowly added (0.15 mmol/minute) to the reaction mixture via syringe pump and stirred for a further 15 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL) and 3.0 M ammonium hydroxide solution (5 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layer was washed with a 10% hydrochloric acid solution (3 x 5 mL), the aqueous layer was basified with a 10% sodium hydroxide solution and extracted with dichloromethane (3 x 5 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed under reduced pressure to afford the desired amine in ≥95% purity, as determined by ^{1}H NMR.



15a **32i**

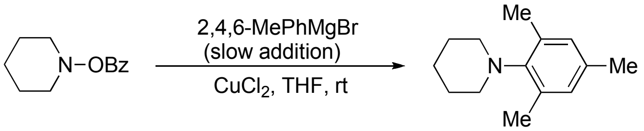
1-Phenylpiperidine (32i). The title compound was prepared according to General Procedure **D** using 1-benzoyloxypiperidine (**15a**) (0.1031 g, 0.50 mmol), copper(II) chloride (0.0013 g, 0.01 mmol), and a tetrahydrofuran solution of phenylmagnesium bromide (1.0 M, 0.800 mL, 0.80 mmol) to yield 1-phenylpiperidine (**32i**) (0.041 g, 0.25

mmol, 51% yield) as a yellow oil. The 1H NMR spectrum was consistent with that reported in the literature.[53]



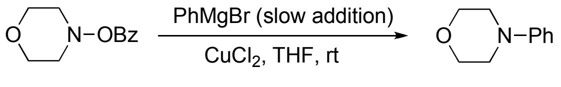
15a **32j**

1-*o*-Tolylpiperidine (32j). The title compound was prepared according to General Procedure **D** using 1-benzoyloxypiperidine (**15a**) (0.1044 g, 0.50 mmol), copper(II) chloride (0.0017 g, 0.01 mmol), and a tetrahydrofuran solution of *o*-tolylmagnesium bromide (0.85 M, 0.650 mL, 0.55 mmol) to yield 1-*o*-tolylpiperidine (**32j**) (0.064 g, 0.37 mmol, 73% yield) as a yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[54]



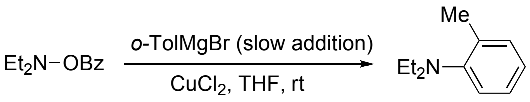
15a **32k**

1-Mesitylpiperidine (32k). The title compound was prepared according to General Procedure **D** with the exception that the more extractions using 10% hydrochloric acid solution (6 x 10 mL) were done. The reaction was conducted using benzoyloxypiperidine (**15a**) (0.1026 g, 0.50 mmol), copper(II) chloride (0.0016 g, 0.01 mmol), and a tetrahydrofuran solution of 1-mesitylmagnesium bromide (0.90 M, 0.670 mL, 0.60 mmol) to yield 1-*o*-tolylpiperidine (**32k**) (0.065 g, 0.32 mmol, 64% yield) as a yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[55]


N–OBz
PhMgBr (slow addition)
CuCl2, THF, rt
N–Ph

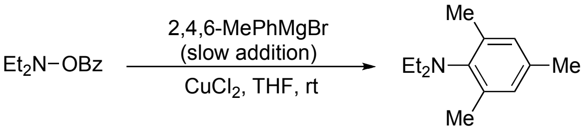
15c **32g**

4-Phenylmorpholine (32g). The title compound was prepared according to General Procedure **D** using 4-benzoyloxymorpholine (**15c**) (0.1038 g, 0.50 mmol), copper(II) chloride (0.0067 g, 0.05 mmol), and a tetrahydrofuran solution of phenylmagnesium bromide (1.0 M, 0.800 mL, 0.80 mmol) to yield 1-phenylmorpholine (**32g**) (0.054 g, 0.33 mmol, 66% yield) as a white solid. The ^{1}H NMR spectrum was consistent with that reported in the literature.[53]


Et2N–OBz
o-TolMgBr (slow addition)
CuCl2, THF, rt
Me
Et2N

15d **32l**

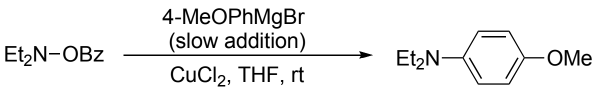
***N,N*-Diethyl-2-methylbenzenamine (32l).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-diethylhydroxylamine (**15d**) (0.0957 g, 0.50 mmol), copper(II) chloride (0.015 g, 0.01 mmol), and a tetrahydrofuran solution of *o*-tolylmagnesium bromide (0.85 M, 0.650 mL, 0.55 mmol) to yield *N,N*-diethyl-2-methylbenzenamine (**32l**) (0.051 g, 0.31 mmol, 62% yield) as a yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[56]


Et2N–OBz
2,4,6-MePhMgBr
(slow addition)
CuCl2, THF, rt
Me
Et2N
Me
Me

15d **32m**

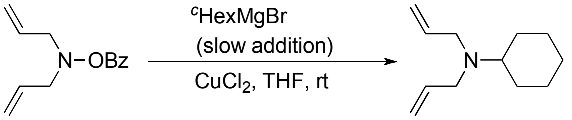
***N,N*-Diethyl-2,4,6-trimethylbenzenamine (32m).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-diethylhydroxylamine (**15d**)

(0.0960 g, 0.50 mmol), copper(II) chloride (0.016 g, 0.01 mmol), and a tetrahydrofuran solution of 2-mesitylmagnesium bromide (0.90 M, 0.670 mL, 0.60 mmol) to yield *N,N*-diethyl-2,4,6-trimethylbenzenamine (**32m**) (0.074 g, 0.39 mmol, 77% yield) as a yellow oil. Analytical data for **32m**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 3.09 (q, *J* = 7.1 Hz, 4H), 2.29 (s, 6H), 2.28 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 145.0, 138.1, 134.1, 129.3, 47.4, 20.7, 19.4, 14.8. For additional analytical data (UV-Vis spectrum), see Grammaticakis.[57]



15d **32n**

***N,N*-Diethyl-4-methoxybenzenamine (32n).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-diethylhydroxylamine (**15d**) (0.0986 g, 0.50 mmol), copper(II) chloride (0.0038 g, 0.03 mmol), and a tetrahydrofuran solution of 4-methoxymagnesium bromide (0.85 M, 0.850 mL, 0.85 mmol) to yield *N,N*-diethyl-4-methoxybenzenamine (**32n**) (0.068 g, 0.38 mmol, 74% yield) as a yellow oil. The ^{1}H NMR spectrum was consistent with that reported in the literature.[58]

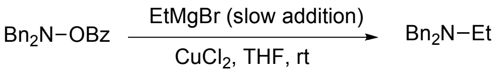


15e **32o**

***N,N*-Diallylcyclohexanamine (32o).** The title compound was prepared according to General Procedure **D** using *O*-benzoyl-*N,N*-diallylhydroxylamine (**15e**) (0.1079 g, 0.50 mmol), copper(II) chloride (0.015 g, 0.01 mmol), and a tetrahydrofuran solution of cyclohexylmagnesium bromide (1.20 M, 0.460 mL, 0.55 mmol) to yield *N,N*-diallylcyclohexanamine (**32o**) (0.067 g, 0.37 mmol, 75% yield) as a yellow oil. Analytical data for **32o**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.4, 6.3 Hz, 2H), 5.13 (d, *J* = 17.1 Hz, 2H), 5.04 (d, *J* = 10.1 Hz, 2H), 3.10 (d, *J* = 6.2 Hz, 4H), 2.58-2.52 (m, 1H), 1.80-1.70 (m, 4H), 1.65-1.55 (m, 1H), 1.18-1.08 (m, 4H), 1.07-0.97 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.5, 116.3, 58.9, 52.9, 29.0, 26.4, 26.1.

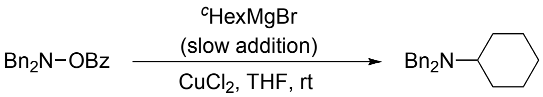
General Procedure (E) for the copper-catalyzed amination of organomagnesium with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine.

A flame-dried vial equipped with magnetic stir bar was charged with the copper(II) chloride, the *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**15b**) (0.50 mmol), and the specified amount of anhydrous tetrahydrofuran. A solution of the organomagnesium compound in anhydrous tetrahydrofuran was slowly added (0.15 mmol/minute) to the reaction mixture via syringe pump and stirred for a further 15 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL) and 3.0 M ammonium hydroxide solution (5 mL) and diluted with diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The organic extracts were combined, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with the indicated solvent system, to afford the desired amine in ≥95% purity, as determined by ^{1}H NMR.


Bn$_2$N−OBz
EtMgBr (slow addition)
CuCl$_2$, THF, rt
Bn$_2$N−Et

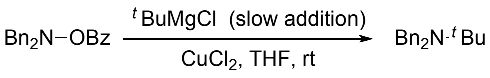
15b **32a**

***N,N*-Dibenzylethanamine (32a).** The title compound was prepared according to General Procedure **E** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.1595 g, 0.50 mmol), copper(II) chloride (0.019 g, 0.01 mmol), anhydrous tetrahydrofuran (4.0 mL), and a tetrahydrofuran solution of ethylmagnesium bromide (1.00 M, 0.550 mL, 0.55 mmol) to yield *N,N*-dibenzylethanamine (**32a**) (0.106 g, 0.47 mmol, 94% yield) as a white solid after no further purification. The ^{1}H NMR spectrum was consistent with that reported in the literature.[59]


Bn$_2$N−OBz
^{c}HexMgBr
(slow addition)
CuCl$_2$, THF, rt
Bn$_2$N

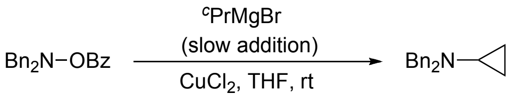
15b **32b**

***N,N*-Dibenzyl-2-methylpropan-2-amine (32b).** The title compound was prepared according to General Procedure **E** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.1586 g, 0.50 mmol), copper(II) chloride (0.017 g, 0.01 mmol), and a tetrahydrofuran solution of *t*-butylmagnesium chloride (1.00 M, 0.550 mL, 0.55 mmol) to yield *N,N*-dibenzyl-2-methylpropan-2-amine (**32b**) (0.113 g, 0.45 mmol, 89% yield) as a white solid after flash chromatography with 1% diethyl ether/pentane, eluting the silica with 3% triethylamine/pentane prior to loading. The ^{1}H NMR spectrum was consistent with that reported in the literature.[60]


Bn$_2$N−OBz
^{t}BuMgCl (slow addition)
CuCl$_2$, THF, rt
Bn$_2$N-^{t}Bu

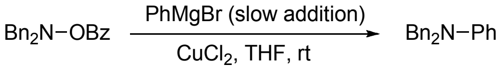
15b **32c**

***N,N*-Dibenzylcyclohexanamine (32c).** The title compound was prepared according to General Procedure **E** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.1607 g, 0.50 mmol), copper(II) chloride (0.015 g, 0.01 mmol), anhydrous tetrahydrofuran (4.0 mL), and a tetrahydrofuran solution of cyclohexylmagnesium bromide (1.20 M, 0.460 mL, 0.55 mmol) to yield *N,N*-dibenzylcyclohexanamine (**32c**) (0.125 g, 0.45 mmol, 88% yield) as a white solid after flash chromatography with 1% diethyl ether/pentane, eluting the silica with 3% triethylamine/pentane prior to loading. The ^{1}H NMR spectrum was consistent with that reported in the literature.[61]



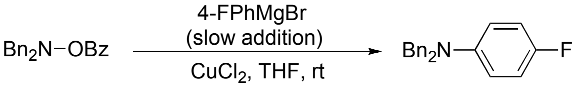
15b **32d**

***N,N*-Dibenzylcyclopropanamine (32d).** The title compound was prepared according to General Procedure **E** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.156.6 g, 0.50 mmol), copper(II) chloride (0.097 g, 0.15 mmol), anhydrous tetrahydrofuran (4.0 mL), and a tetrahydrofuran solution of cyclopropylmagnesium bromide (0.50 M, 2.00 mL, 1.00 mmol) to yield *N,N*-dibenzylcyclopropanamine (**32d**) (0.070 g, 0.30 mmol, 61% yield) as a white solid after flash chromatography with 2.5% ethyl acetate/hexanes, eluting the silica with 5% triethylamine/hexanes prior to loading.. The ^{1}H NMR spectrum was consistent with that reported in the literature.[62]



15b **32e**

***N,N*-Dibenzylbenzenamine (32e).** The title compound was prepared according to General Procedure **E** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.1580 g, 0.50 mmol), copper(II) chloride (0.063 g, 0.05 mmol), anhydrous tetrahydrofuran (2.0 mL) and a tetrahydrofuran solution of phenylmagnesium bromide (1.00 M, 0.800 mL, 0.80 mmol) to yield *N,N*-dibenzylbenzenamine (**32e**) (0.116 g, 0.43 mmol, 92% yield) as a white solid after flash chromatography with 1.25% ethyl acetate/hexanes. The ^{1}H NMR spectrum was consistent with that reported in the literature.[63]



15b **32f**

***N,N*-Dibenzyl-4-fluorobenzenamine (32f).** The title compound was prepared according to General Procedure **E** using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**15b**) (0.1587 g, 0.50 mmol), copper(II) chloride (0.067 g, 0.05 mmol), anhydrous tetrahydrofuran (2.0 mL) and a tetrahydrofuran solution of 4-fluorophenylmagnesium chloride (1.20 M, 0.920 mL, 1.10 mmol) to yield *N,N*-dibenzyl-4-fluorobenzenamine (**32f**) (0.084 g, 0.29 mmol, 58% yield) as a pale yellow oil after flash chromatography with 2.5→5.0% ethyl acetate/hexanes. Analytical data for **32f**: **IR** (thin film, cm^{-1}) 3087, 3061, 3025, 2913, 2863, 1605, 1508, 1495, 1450, 1398, 1364, 1227, 1107, 1072, 1028, 957, 814, 737, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.30-7.24 (m, 6H), 6.89 (t, J = 8.7 Hz, 2H), 6.58 (dd, J = 9.1, 5.3 Hz, 2H), 4.63 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.4 (d, J_{CF} = 234 Hz), 145.7, 138.4, 128.6, 126.9, 126.7, 115.5 (d, J_{CF} = 22 Hz), 113.7 (d, J_{CF} = 7 Hz), 55.0.

1.6 References

(1) Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239-258.

(2) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281-1286.

(3) Greck, C.; Genèt, J. P. *Synlett* **1997**, 741-748.

(4) Erdik, E. *Tetrahedron* **2004**, *60*, 8747-8782.

(5) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947-1980.

(6) Hartwig, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046-2067.

(7) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599-1626.

(8) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805-818.

(9) Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016-6023.

(10) Beak, P.; Li, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 2796-2797.

(11) Beak, P.; Selling, G. *J. Org. Chem.* **1989**, *54*, 5574-5580.

(12) Boche, G.; Wagner, A. V. *J. Chem. Soc., Chem. Commun.* **1984**, 1591-1592.

(13) Armstrong, D. R.; Snaith, R.; Walker, G. T. *J. Chem. Soc., Chem. Commun.* **1985**, 789-791.

(14) McKee, M. C. *J. Am. Chem. Soc.* **1985**, *107*, 859-864.

(15) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620-5623.

(16) Jensen, F. R.; Nakamaye, K. L. *J. Am. Chem. Soc.* **1966**, *88*, 3437-3438.

(17) Morrison, J. D.; Lambert, G. *J. Org. Chem.* **1972**, *37*, 1034-1037.

(18) Pearson, W. H. Ph.D. Thesis, University of Wisconsin, Madison, WI, 1982.

(19) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3072-3074.

(20) Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3359-3365.

(21) Hoffmann, R. W.; Hölzer, B. *J. Am. Chem. Soc.* **2002**, *124*, 4204-4205.

(22) Hoffmann, R. W.; Hölzer, B.; Knopff, O. *Org. Lett.* **2001**, *3*, 1945-1948.

(23) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317-318.

(24) Tsutsui, H.; Ichikawa, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1869-1878.

(25) Erdik, E.; Ay, M. *Synth. React. Inorg. Met.-Org. Chem* **1989**, *19*, 663-668.

(26) Erdik, E.; Daskapan, T. *Synth. Commun.* **1999**, *29*, 3989-3997.

(27) Erdik, E.; Daskapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139-3142.

(28) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680-5681.

(29) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364-366.

(30) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219-224.

(31) Zhang, Z. H.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005-3008.

(32) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 6414-6417.

(33) Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947-1950.

(34) Dickstein, J. S.; Kozlowski, M. C. *Chem. Soc. Rev.* **2008**, *37*, 1166-1173.

(35) Erdik, E.; Omur, O. *Appl. Organomet. Chem* **2005**, *19*, 887-893.

(36) Berman, A. M.; Johnson, J. S. *Org. Synth.* **2006**, *83*, 31-37.

(37) Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537-538.

(38) Barton, D. H. R.; Doris, E. *Tetrahedron Lett.* **1996**, *37*, 3295-3298.

(39) Lindley, J. *Tetrahedron* **1984**, *40*, 1433-1456.

(40) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521-1524.

(41) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215-222.

(42) Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633-5648.

(43) Lee, J. C.; Oh, Y. S.; Cho, S. H.; Lee, J. I. *Org. Prep. Proced. Int.* **1996**, *28*, 480-483.

(44) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539-3540.

(45) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463-1471.

(46) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302-4320.

(47) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475-1478.

(48) Acheson, R. M.; Benn, M. H.; Jacyno, J.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 2* **1983**, 497-500.

(49) Alaimo, P. J.; W., P. D.; Arnold, J.; Bergman, R. G. *J. Chem. Educ.* **2001**, *78*, 64-67.

(50) Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561-3564.

(51) Lee, J. C.; Oh, Y. S.; Cho, S. H.; J.I., L. *Org. Prep. Proced. Int* **1996**, *28*, 480-483.

(52) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539-3540.

(53) Ishikawa, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, *66*, 186-191.

(54) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829-12842.

(55) Akula, M. R.; Kabalka, G. W. *Synth. Commun.* **1998**, *28*, 2063-2070.

(56) Yoder, C. H.; Kaduk, B. A.; Hess, R. E. *Tetrahedron Lett.* **1970**, *11*, 3711-3714.

(57) Grammaticakis, P. *Bull. Soc. Chim. Fr.* **1949**, 134-144.

(58) Conesa Lerma, I.; Cawley, M. J.; Cloke, F. G. N.; Arentsen, K.; Scott, J. S.; Pearson, S. E.; Hayler, J.; Caddick, S. *J. Organomet. Chem.* **2005**, *24-25*, 5841-5848.

(59) Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, *1989*, 225-232.

(60) Suzuki, K.; Okano, K.; Nakai, K.; Terao, Y.; Sekiya, M. *Synthesis* **1983**, 723-725.

(61) Ratcliff, M. A.; Kochi, J. K. *Tetrahedron* **1972**, *28*, 4467-4481.

(62) Wiedemann, S.; Frank, D.; Winsel, H.; de Meijere, A. *Org. Lett.* **2003**, *5*, 753-755.

(63) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403-1412.

CHAPTER TWO

DEVELOPMENT OF A 3-*EXO*-*DIG* CYCLIZATION FOR THE PREPARATION OF VINYLIDENE CYCLOPROPANES FROM ELECTRON-POOR OLEFINS

2.1 Introduction

Baldwin's rules are routinely used as a first round of analysis to predict the propensity for a given system to undergo cyclization.[1-3] These stereoelectronic guidelines continue to occupy a prominent and useful role in synthetic planning, despite the abundance of exceptions in the literature.[4-9] In particular, the rules of digonal cyclization modes should be viewed with skepticism, because they were formulated using an incorrect angle of attack. Still, only isolated examples of the "disfavored" 3-*exo*-*dig* cyclization have been reported in the literature, with all involving nucleophilic attack of a heteroatom onto a pendant alkyne. This chapter explores the development of a 3-*exo*-*dig* substitution reaction, initially proposed in the context of a natural product synthesis, employing an all-carbon variant of this rare cyclization mode.

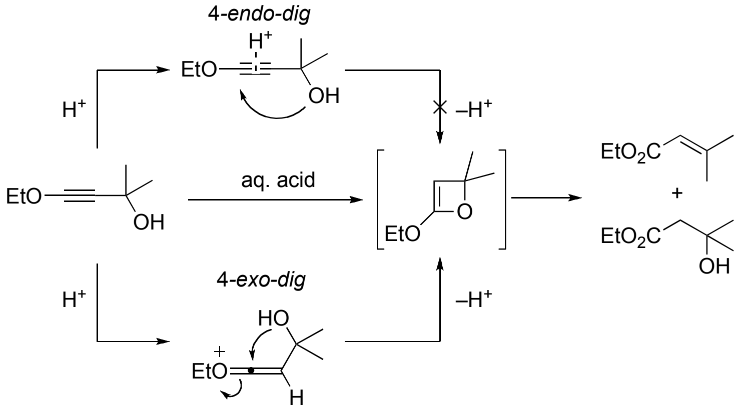
2.2 Background

2.2.1 3-*Exo*-*Dig* Cyclizations

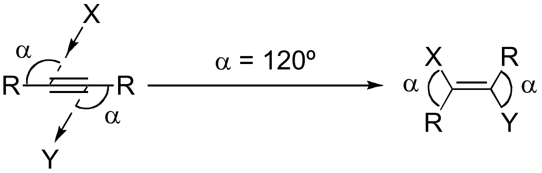
Examples of 3-*exo-dig* cyclizations are rare in the literature. The first was reported in 1992 by Torii and coworkers.[10] Only four examples were known prior to our work, and all involved heteroatom attack onto a pendant alkyne.[11-13] The only cyclization that occurs in the absence of an electrophilic activator or light involves nucleophilic attack by phosphorus, a period 3 element that has less stringent geometrical constraints than period 2 elements, and is thus not formally an exception to the guidelines.

Baldwin's rules for predicting the outcome of cyclizations are based upon the competition of possible cyclization modes in a given system. Thus, one might expect the alternative "favorable" cyclization mode, 4-*endo-dig*, to occur regularly with substrates primed for a 3-*exo-dig* process. However, to our knowledge, there are no reported examples of 4-*endo-dig* cyclizations that occur in the absence of strong acids or mercury(II) salts.[14,15] These catalysts cause re-hybridization of alkynes to occur, giving intermediates resembling vinyl cations. The example of a 4-*endo-dig* cyclization cited by Baldwin in his seminal communication, the acid-catalyzed hydrolysis of (ethoxyethynyl)carbinols, is more appropriately classified as a "disfavored" 4-*exo-dig* cyclization (Scheme 2-1).[16] It is credible that these formal 4-*endo-dig* acid-catalyzed cyclizations, coupled with the complete absence of 3-*exo-dig* cyclizations in 1984, led Baldwin to erroneously categorize 4-*endo-dig* cyclization as a favorable process. This led to a miscalculation of the geometry of nucleophilic attack for digonal systems. It was assumed by Baldwin that the angle of attack would be similar to the angle found between substituents of the product olefin ($\alpha \approx 120^{\circ}$, Scheme 2-2), a supposition that is true for trigonal cyclizations, but not for digonal systems.

Scheme 2-1. Cited Example of 4-*Endo-Dig* Cyclization



Scheme 2-2. Baldwin's Hypothesized Angle of Attack for Digonal Systems



The actual angle of attack has been the subject of computational studies by Houk[17] and Dunitz,[18] both of whom found the angle was considerably smaller (~60°). This angle of approach places the nucleophile in close proximity with the acetylenic substituent, but Houk's computation asserts the terminal hydrogen of acetylene can distort 24° from linearity, even when accommodating a small hydride nucleophile. This bending concurrently decreases the LUMO energy of the alkyne, due to σ_{CH}–π^*_{CC} orbital mixing. A related study presents a crystal structure of **1** showing incipient attack of an *N*-oxide onto a diazonium, a group isoelectric with alkynes and nitriles.[19] The structure is homologous with the aforementioned computational data for hydride delivery to acetylene.

Figure 2-1. Calculated Transition State for Hydride Delivery to Acetylene

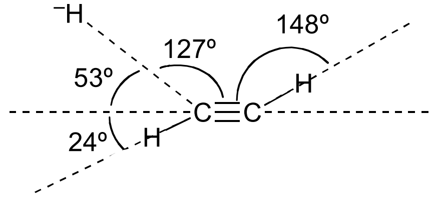
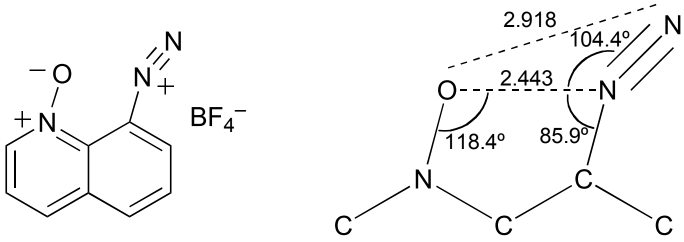


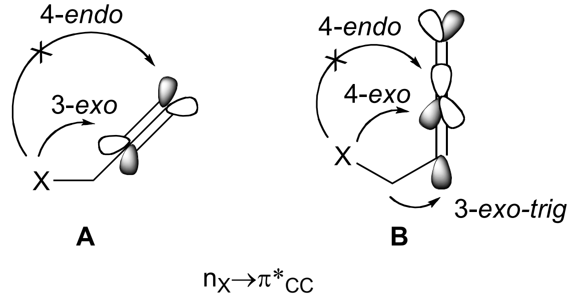
Figure 2-2. Relevant Bond Angles and Lengths from Crystal Structure of **1**



1

Reinspection of the geometries required for 3-*exo-dig* and 4-*endo-dig* cyclizations makes predictions contrary to Baldwin's rules. The nucleophile's lone pair must overlap with a π* orbital of the alkyne for the reaction to occur. 4-*Endo-dig* cyclization onto an alkyne seems geometrically unattainable (Figure 2-3, A), while the corresponding 3-*exo*-dig cyclization would be strained, but is plausible. The rarity of these cyclizations may be because unstable products are formed that are prone to the ring-opening or decomposition. The alignment for a 4-*endo-dig* cyclization onto an allene is improved over the prior case, though still does not appear feasible because the nucleophile is oriented orthogonal to the π* orbital (Figure 2-3, B). Both alternatives, 4-*exo-dig* and 3-*exo-trig*, are appropriately aligned.

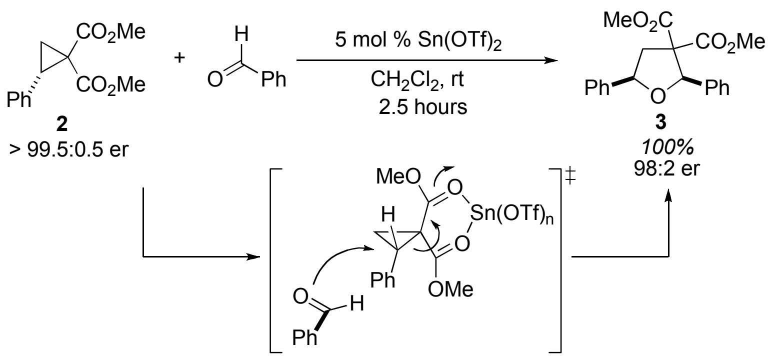
Figure 2-3. Required Orbital Interactions for Small Ring Cyclizations


4-endo
3-exo
X
A
4-endo
4-exo
X
3-exo-trig
B
$n_X \rightarrow \pi^*_{CC}$

2.2.2 Retrosynthesis of the Cladiellin Core

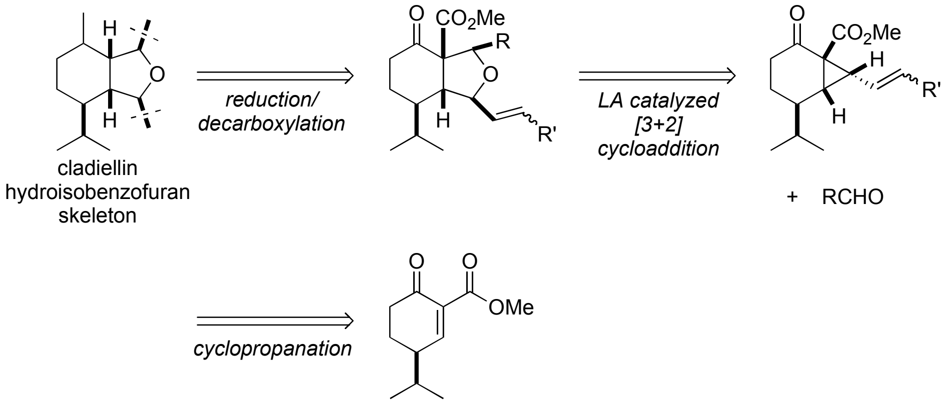
Our laboratory has previously described the Lewis acid-catalyzed cycloaddition between donor-acceptor cyclopropanes and aldehydes to produce 2,5-disubstituted tetrahydrofurans with high levels of *cis*:*trans* diastereoselectivity.[20-22] The reaction proceeds with nearly complete transfer of chirality when enantioenriched cyclopropanes are used, resulting from inversion of the cyclopropane stereocenter during the cycloaddition (Scheme 2-3). This result and subsequent studies support a mechanism in which nucleophilic attack of the aldehyde on the cyclopropane leads to an open chain zwitterion. A diastereoselective aldol reaction occurs rapidly to furnish the substituted THF.

Scheme 2-3. $Sn(OTf)_2$-Catalyzed [3+2] Cycloaddition of **2** with Benzaldehyde


CO_2Me
CO_2Me
Ph
2
> 99.5:0.5 er
+
H
O
Ph
5 mol % $Sn(OTf)_2$
CH_2Cl_2, rt
2.5 hours
MeO_2C
CO_2Me
Ph
O
Ph
3
100%
98:2 er
MeO
O
$Sn(OTf)_n$
H
O
Ph
OMe
O
H
Ph
‡

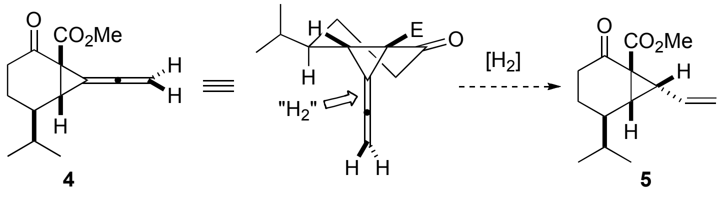
We saw the potential to rapidly assemble the hydroisobenzofuran core contained by members of the cladiellin diterpene family using this methodology (Scheme 2-4).[23, 24] The key disconnection constructs the hydroisobenzofuran via the cycloaddition of an aldehyde with a bicyclo[4.1.0]heptanone, which contains the requisite donor-acceptor vinyl cyclopropane. To form the correct diastereomer of the core, it is essential the vinyl substituent be on the sterically congested concave (α) face of the bicycle.

Scheme 2-4. Retrosynthetic Analysis of the Cladiellin Core


H
O
H
cladiellin
hydroisobenzofuran
skeleton
reduction/
decarboxylation
O
CO2Me
R
O
H
R'
LA catalyzed
[3+2]
cycloaddition
O
CO2Me
H
R'
H
+ RCHO
cyclopropanation
O
O
OMe

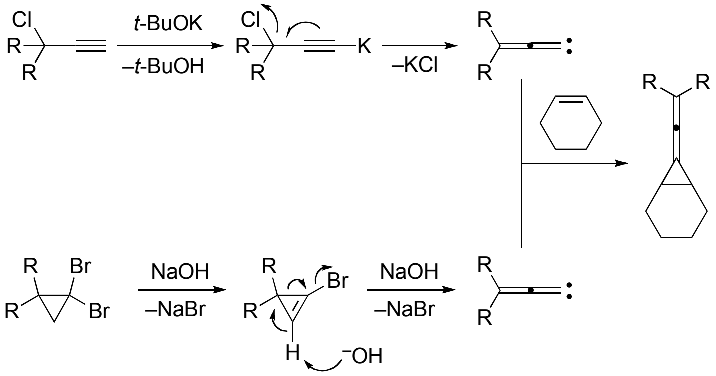
Forming the requisite diastereomer of the bicycle proved synthetically challenging. A Corey–Chaykovsky cyclopropanation[25] with the ylide derived from dimethyl(2-oxopropyl)sulfonium chloride provided an unfavorable 2.3:1 β:α mixture of cyclopropyl ketones. Efforts to effect epimerization were stymied by facile retro-Michael ring opening of the cyclopropane. An alternate strategy used a conjugate addition, followed by a 3-*exo-trig* S_N2' reaction to furnish the vinyl cyclopropane directly, but exclusively provided the β-vinylcyclopropane in low chemical yield. Analysis of the system led to the hypothesis that access to vinylidene cyclopropane **4** would allow delivery of hydrogen from the unhindered convex face of the bicycle to form the desired vinyl cyclopropane **5** (Scheme 2-5). It was hoped the use of a poisoned catalyst would enable the hydrogenation of the strained internal olefin while preserving the terminal alkene.

Scheme 2-5. Proposed Synthesis of Vinyl Cyclopropane **5**



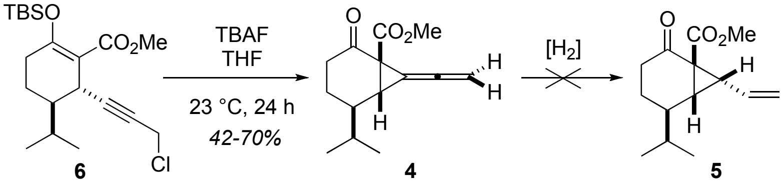
Vinylidene cyclopropanes are synthesized by the reaction of vinylidene carbenes and electron-rich olefins. The carbenes are generated from the treatment of terminal propargylic halides[26,27] or 1,1-dibromocyclopropanes[28] with alkali bases (Scheme 2-6). We presumed these electrophilic carbenes would not react with the electron-poor enone necessary for the synthesis, which led us to consider alternative methods of preparation.

Scheme 2-6. Generation of Vinylidene Carbenes



The simplest solution is to perform a conjugate addition of propargyl chloride to the enone, followed by a 3-*exo-dig* cyclization. Undaunted by the paucity of examples for 3-*exo-dig* reactions, we proceeded with this strategy. One-pot procedures were unsuccessful at providing the vinylidene cyclopropane, so the conjugate addition product was isolated as the TBS-silyl enol ether **6** and later subjected to cyclization conditions. We found TBAF was able to promote the reaction in variable yields, but selective hydrogenation of **4** proved unsuccessful. All conditions examined led to decomposition, presumably due to ring opening through a facile β-carbon elimination process (Scheme 2-7).

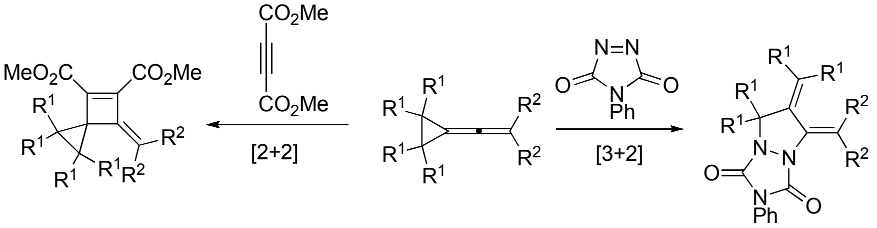
Scheme 2-7. Formation and Unsuccessful Hydrogenation of **4**



2.2.3 Synthetic Utility of Vinylidene Cyclopropanes

The combination of reactive allene and cyclopropane functionalities found in vinylidene cyclopropanes has drawn the attention of numerous synthetic groups. Pasto[29,30] and Sasaki[31] investigated cycloadditions, and used molecular orbital theory to explain the unusual reactivity patterns. They postulated that both [2+2] and [3+2] (8 electron) cycloadditions with electron-poor acetylenes and diazenes, respectively, occur in a concerted fashion. The difference in cycloaddition mode is a consequence of in-plane (for [3+2]) or perpendicular approach (for [2+2]) of the reaction partner with respect to the cyclopropane ring of the vinylidene cyclopropane (Scheme 2-8).

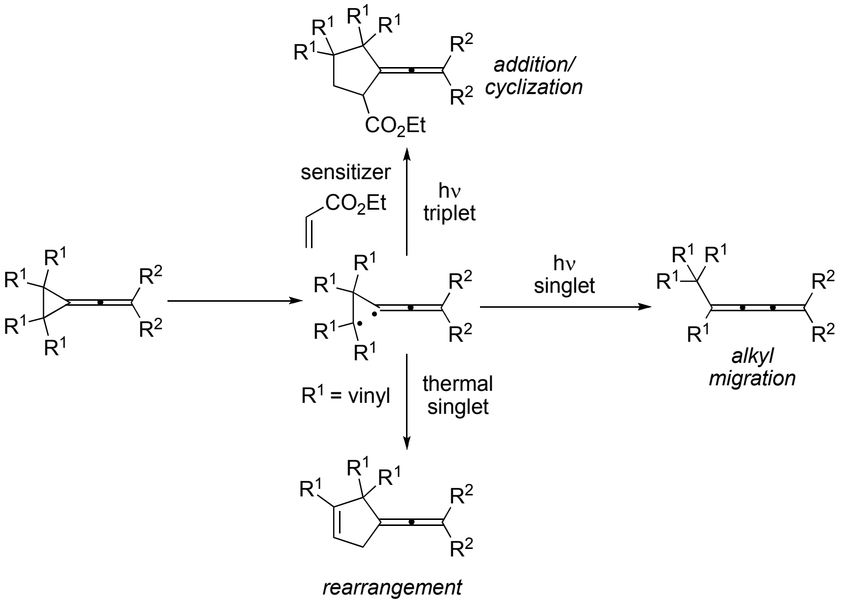
Scheme 2-8. Cycloadditions of Vinylidene Cyclopropanes



Vinylidene cyclopropanes can be thermally or photochemically excited to promote homolytic bond cleavage of the cyclopropane. Typically, the bond proximal to the allene is broken to afford vinyl-alkyl biradicals, though homolytic cleavage of the distal bond to give alkyl-alkyl biradicals has been exploited to allow isomerization of the ring substituents.[32] Thermolysis of vinyl-substituted vinylidene cyclopropanes produces a singlet biradical, which recombines after rearrangement to form vinylidene cyclopentenes (Scheme 2-9).[33] The high torsional and ring strains of vinylidene cyclopropanes allow the reaction to occur at temperatures nearly 100 ºC less than for simpler vinyl cyclopropanes.

Photochemical excitation can produce singlet or triplet biradicals. Singlet biradicals have been implicated in the rearrangement to butatrienes with concurrent alkyl migration;[34] however, they do not participate in intermolecular radical cyclizations. Mizuno was able to achieve these transformations by including sensitizers, such as benzophenone or Michler's ketone, to promote the formation of triplet biradicals. These biradicals are stable enough to allow intermolecular addition and cyclization to nitriles[35] and electron-deficient olefins[36] to occur (Scheme 2-9).

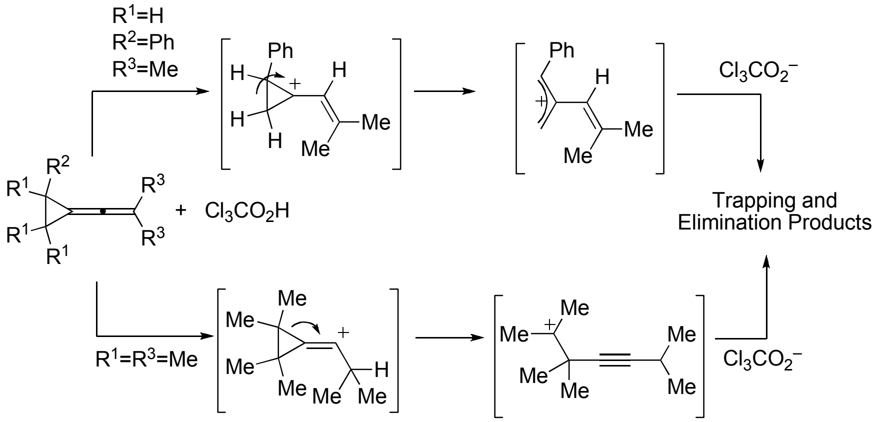
Scheme 2-9. Biradical Reactions of Vinylidene Cyclopropanes



addition/ cyclization
sensitizer
hν triplet
hν singlet
alkyl migration
R1 = vinyl
thermal singlet
rearrangement

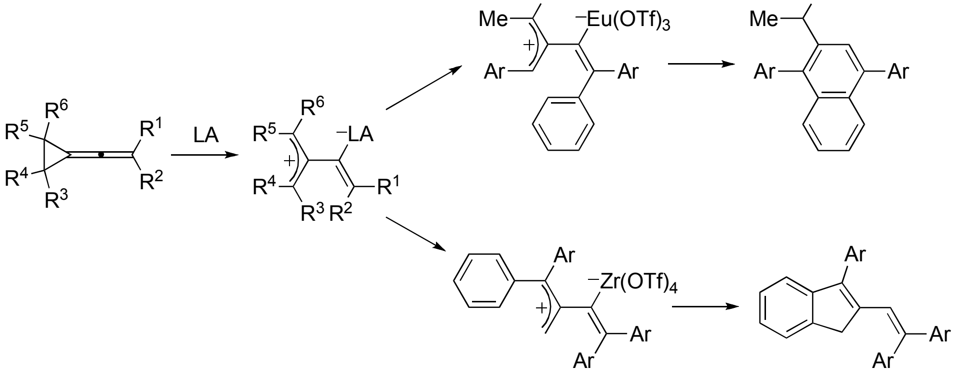
Pasto and coworkers studied the protonation of vinylidene cyclopropanes with Cl_3CO_2H.[37] They found that the site of protonation is dependent on the cyclopropane substituents. The presence of an aryl substituent favored protonation of the internal allenyl carbon, with fast ring-opening to form a stabilized allyl cation (Scheme 2-10). Conversely, the presence of alkyl substituents proceeded with protonation at the terminal allenyl carbon. Rearrangement of the vinyl cation by ring-opening to a tertiary carbocation was terminated by competitive elimination and nucleophilic trapping.

Scheme 2-10. Acid-Catalyzed Reactions of Vinylidene Cyclopropanes


R^1=H
R^2=Ph
R^3=Me
R^1=R^3=Me
+ Cl_3CO_2H
$Cl_3CO_2^-$
$Cl_3CO_2^-$
Trapping and
Elimination Products

Research using protic acids provided the foundation for current work with Lewis acid catalysis. Lewis acid-catalyzed reactions of the more readily available methylidene cyclopropanes are well-studied processes. The Shi group has recently begun analogous work with vinylidene cyclopropanes and reported rearrangements to substituted naphthalenes and indenes (Scheme 2-11).[38] The reactions proceed by Lewis acid-assisted ring opening into stabilized zwitterions, which are substrates for intramolecular Friedel-Crafts reactions. The course of a particular reaction is determined by the choice of Lewis acid and the substitution pattern and electronics of the starting material.

Scheme 2-11. Lewis Acid-Catalyzed Reactions of Vinylidene Cyclopropanes


LA
$^-$LA
$^-$Eu(OTf)$_3$
$^-$Zr(OTf)$_4$

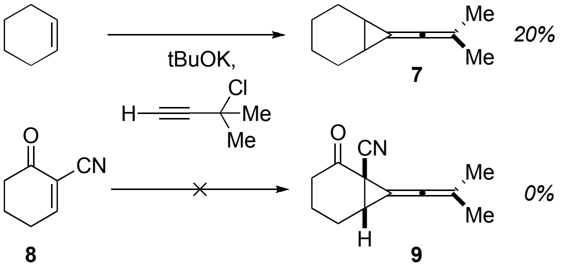
In this chapter, a rare example of the 3-*exo-dig* cyclization mode will be presented as a method to prepare vinylidene cyclopropanes from electron-poor alkenes. Because these compounds have not been available via standard carbene technology, their chemistry will also be topically explored. This chapter has been previously published.[39]

2.3 Results and Discussion

2.3.1 Attempted Synthesis via Carbene Methodology

We established that the carbene generated from potassium tert-butoxide and 3-chloro-3-methylbut-1-yne was unreactive towards an electron-poor olefin. First, cyclohexene was reacted using the standard protocol to afford a 20% yield of the vinylidene cyclopropane **7** (Scheme 2-12). Ketonitrile **8** was subjected to identical conditions, but the formation of vinylidene cyclopropane **9** was not observed.

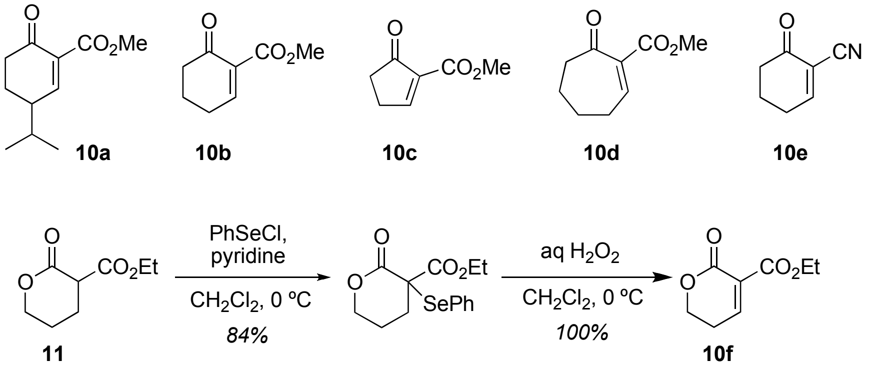
Scheme 2-12. Synthesis of Vinylidene Cyclopropanes via Carbenes



2.3.2 Synthesis of Cyclic Propargyl Chlorides

The electron-poor olefins **10a-e** were prepared via α-selenoxide elimination as previously described (Scheme 2-13).[40-42] The unsaturated lactone ester **10f** was prepared using analogous chemistry in 84% yield over two steps from the known lactone **11**.[43]

Scheme 2-13. Synthesis of Electron-Poor Olefins

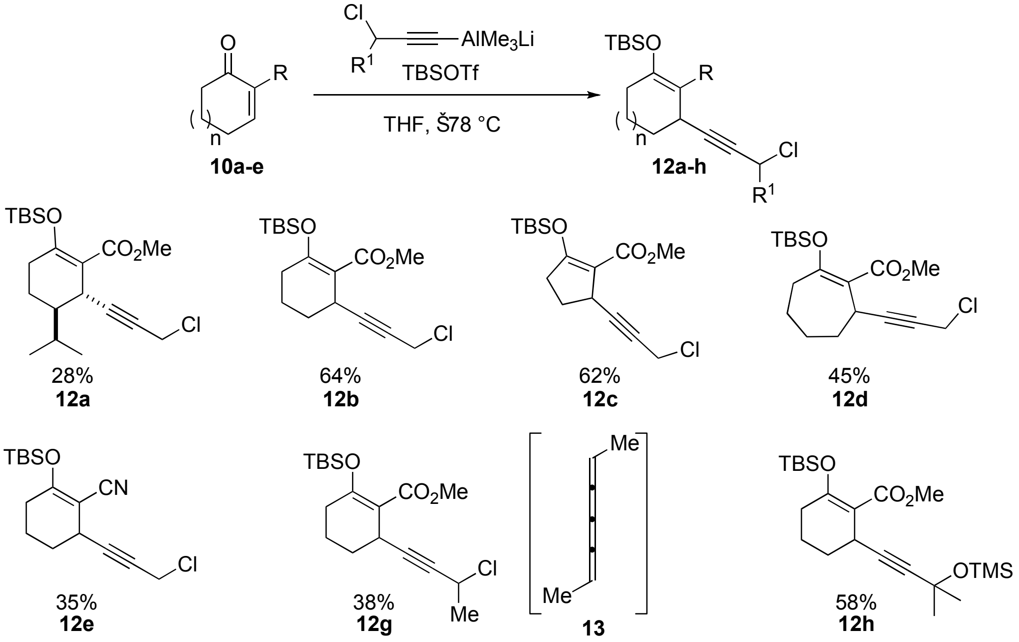


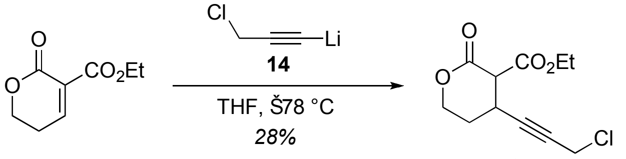
10a **10b** **10c** **10d** **10e**

11 **10f**

The conjugate addition of propargyl chlorides to enones was conducted using a modification of Kim's method.[44] The TBSOTf-promoted addition of acetylides via trimethylaluminates proceeded in moderate to good yields for enones **10a-e** (Figure 2-4). The aluminate was unreactive toward the lactone ester **10f**. The hindered substrate **10a** and ketonitrile **10e** were poor substrates for the addition of propargyl chloride. The use of a secondary propargyl chloride was complicated by competitive carbene formation and dimerization to form the cumulene **13**, resulting in a lower yield relative to the addition of propargyl chloride. This problem was insurmountable when using a tertiary chloride; the corresponding TMS-protected alcohol was used to prepare **12h** with the hope that subsequent interconversion to a leaving group would be possible. While the reaction of lithium acetylide **14** with enones resulted in 1,2-addition, its reaction with **10f** provided the conjugate addition product **12f**, albeit in low yield (eq 1). Nickel and copper-based catalysts are known to be effective for the conjugate addition of unfunctionalized acetylenes (i.e. phenylacetylene), but these systems were unsuitable for the delivery of either propargyl halides or silyl-protected propargyl alcohols.

Figure 2-4. Conjugate Addition of Propargyl Chlorides to Enones **10a-e**


Cl
AlMe3Li
R1
TBSOTf
THF, Š78 °C
10a-e
12a-h
TBSO
R
n
CO2Me
CN
OTMS
Me
28%
12a
64%
12b
62%
12c
45%
12d
35%
12e
38%
12g
13
58%
12h


Cl
Li
14
THF, Š78 °C
28%
CO2Et
O

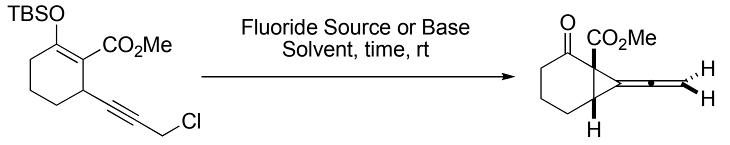
10f **12f** (1)

2.3.3 Optimization of 3-*Exo-Dig* Cyclizations with Propargyl Chlorides

We found during studies toward the synthesis of the cladiellin skeleton that TBAF promoted the 3-*exo-dig* cyclization of **12a** in variable yield. In an attempt to expand the scope of this transformation, we were surprised to find silyl enol ether **12b**, which lacks the 4-isopropyl substituent, was considerably more resistant to cyclization with TBAF in THF, yielding only 13% of **15b** (Table 2-1, entry 1). Seeking improvement, a number of weak bases and fluoride sources were examined. Best results were obtained using carbonates and phosphates in conjunction with a non-coordinating cation, such as Cs^+ or

K^+/18-crown-6. The optimal solvent was found to be DMF, as the use of other polar aprotic solvents resulted in diminished yields.

Table 2-1. Optimization of 3-*Exo-Dig* Cyclization Reaction Variables with Chloride **12b**



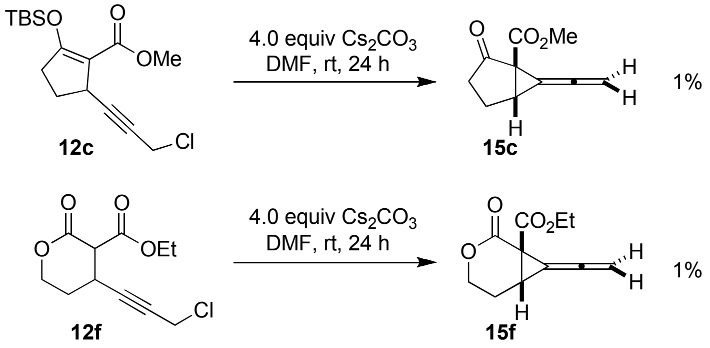
12b **15b**

entry	Reagent	time (h)	solvent	yield (%)[b]
1	TBAF	22	THF	13
2	CsF	22	MeCN	25
3	Cs_2CO_3	22	DMF	35
4	Cs_2CO_3	20	DMA	17
5	Cs_2CO_3	22	MeCN	33[c]
6	K_2CO_3/18-c-6	23	DMF	43
7	K_2CO_3/18-c-6	28	THF	4
8	K_2CO_3/18-c-6	24	Toluene	0
9	K_3PO_4/18-c-6	28	DMF	38

[a] Conditions: Silyl enol ether **12b** (1.0 equiv), reagent (3.0 equiv) in solvent (0.03 M) at room temperature. [b] Yield determined by GLC analysis against an internal standard. [c] Yield determined by isolation. 18-c-6 =1,4,7,10,13,16-hexaoxacyclooctadecane. TBAF = tetrabutylammonium fluoride.

Although disappointed the optimized procedure provided only a moderate yield of the vinylidene cyclopropane **15b**, **12c** and **12f** were exposed to Cs_2CO_3 in DMF. Unfortunately, these conditions were unsatisfactory and only trace quantities of bicycles **15c** and **15f** were obtained (Scheme 2-14). Skeptical that further modifications to the reaction conditions would significantly increase the efficiency of cyclization, we sought to prepare more active substrates, focusing on the identity of the leaving group.

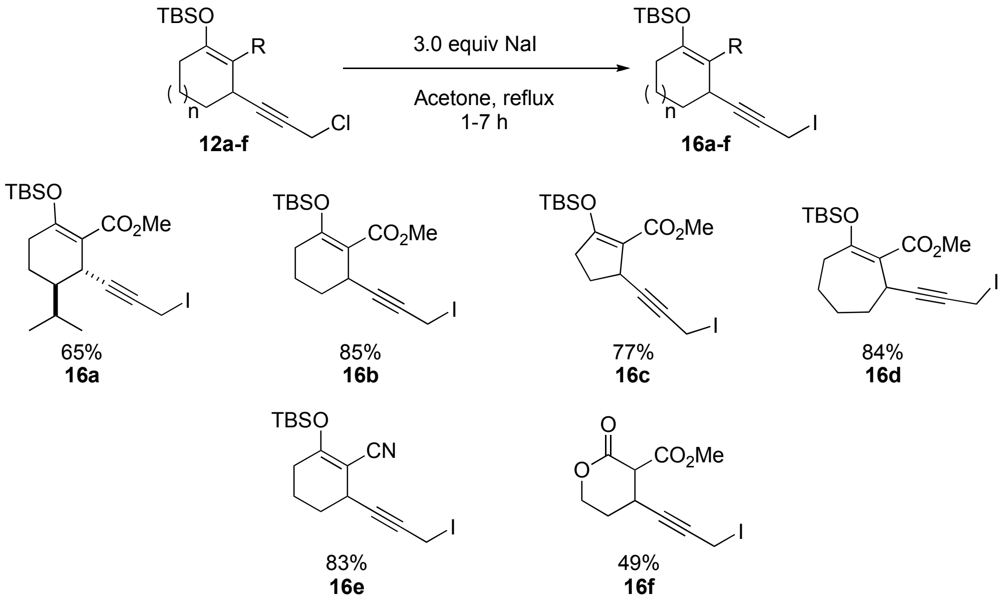
Scheme 2-14. Extension to Alternative Ring Systems


TBSO
O
OMe
4.0 equiv Cs_2CO_3
DMF, rt, 24 h
O
CO_2Me
H
H
H
1%
12c
Cl
15c
O
O
O
OEt
4.0 equiv Cs_2CO_3
DMF, rt, 24 h
O
CO_2Et
O
H
H
H
1%
12f
Cl
15f

2.3.4 Synthesis of Propargylic Iodides

Because we had a viable route to propargyl chlorides, the Finkelstein reaction was used to easily access the corresponding iodides.[45] The substitution reactions proceeded quickly in good yields using the classic conditions, although the secondary chloride **12g** did not provide the respective iodide (Figure 2-5).

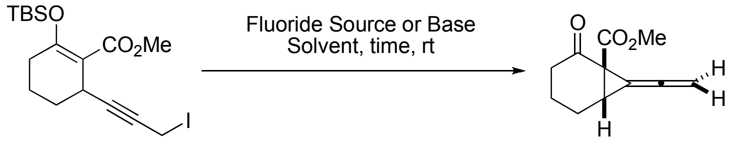
Figure 2-5. Preparation of Iodides using the Finkelstein Reaction


TBSO
R
n
Cl
12a-f
3.0 equiv NaI
Acetone, reflux
1-7 h
TBSO
R
n
I
16a-f
TBSO
CO_2Me
I
65%
16a
TBSO
CO_2Me
I
85%
16b
TBSO
CO_2Me
I
77%
16c
TBSO
CO_2Me
I
84%
16d
TBSO
CN
I
83%
16e
O
O
CO_2Me
I
49%
16f

2.3.5 Optimization of 3-*Exo-Dig* Cyclizations with Propargyl Iodides

Preliminary examination of iodide **16b** indicated that the use of a better nucleofuge was beneficial for the cyclization. Weak, non-coordinating bases in DMF were again effective, with reaction times being significantly shorter than with **12b** (Table 2-2, entries 6-11). Converse to that found with the chloride, fluoride sources were the most effective promoters (Table 2-2, entries 1-7). The best reagent/solvent combinations were TBAF in THF or MeCN and TBAT in DMF or MeCN; however, TBAF in THF was chosen for further experiments because of the combination of efficiency and rapid reaction rate that these conditions engendered.

Table 2-2. Optimization of 3-*Exo-Dig* Cyclization Reaction Variables with Iodide **16b**



16b **15b**

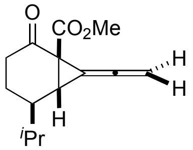
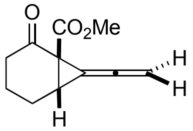
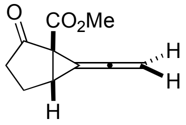
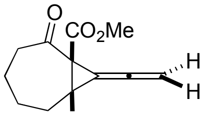
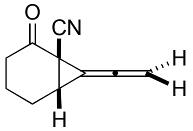
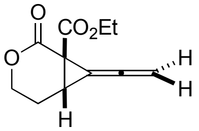
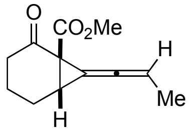
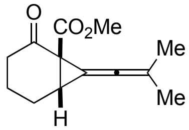
entry	reagent	time (h)	solvent	yield (%)[b]
1	TBAF	0.1	THF	78[c]
2	TBAF	0.5	MeCN	77
3	TBAF	0.3	DMF	13
4	TBAT	4	THF	51
5	TBAT	3	MeCN	77
6	TBAT	2	DMF	82
7	TASF	0.3	DMF	61
8	Cs_2CO_3	2.5	DMF	59
9	K_2CO_3/18-c-6	5	DMF	46
10	K_3PO_4/18-c-6	4	DMF	64
11	Ag_2CO_3	24	DMF	58

[a] Conditions: Silyl enol ether **16b** (1.0 equiv), reagent (3.0 equiv) in solvent (0.03 M) at room temperature. [b] Yield determined by GLC analysis against an internal standard. [c] Yield determined by isolation. 18-c-6 =1,4,7,10,13,16-hexaoxacyclooctadecane. TBAF = tetrabutylammonium fluoride. TBAT = tetrabutylammonium triphenyldifluorosilicate. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate

2.3.6 Substrate Scope with Propargylic Iodides

Using the propargylic iodides, a variety of vinylidene cyclopropanes could be prepared from the corresponding silyl enol ethers in fair to excellent yields in 5 minutes (Table 2-3). We found TBAF to be equally effective in promoting the cyclization from unsilylated precursors, as silyl ketene acetals were not used for diester substrates. Unexpectedly, replacement of the keto ester moiety with a lactone ester or keto nitrile attenuated the efficiency of the cyclization (entries 5 and 6). It was not possible to prepare the secondary iodide from **12f** using the Finkelstein reaction or the tertiary iodide from **12g** using standard reagents. The tertiary bromide could be prepared using PBr_3, although it was not stable to silica gel chromatography. Therefore, the secondary chloride and tertiary bromide were subjected to the reaction conditions directly. Fortunately, both cyclized successfully with TBAF, although the reactions were more sluggish, requiring 9 and 0.75 hours, respectively. We believe these hindered halides are less prone to intermolecular side-reactions than the primary halides, leading to efficient intramolecular cyclizations.

Table 2-3. Scope of the 3-*Exo-Dig* Cyclization of Propargyl Halides[a]

entry	halide	product		yield (%)[b]
1	I		**15a**	95
2	I		**15b**	78
3	I		**15c**	55
4	I		**15d**	58
5	I		**15e**	36
6	I		**15f**	40
7[c]	Cl		**15g**	66 (*d.r.* 1.5:1.0)
8[c,d]	OH, Br		**15h**	23

[a] Conditions: Silyl enol ether (1.0 equiv) and TBAF (1.2 equiv) in THF (0.05 M) at room temperature unless otherwise noted. [b] Isolated yields (average of at least two experiments). [c] TBAF (2.0 equiv). [d] The bromide was unstable to isolation. The yield given is over two steps, beginning with conversion of the alcohol to the bromide with PBr_3 in Et_2O at –5 ºC.

2.3.7 Structural Assignment

The products were unambiguously confirmed as vinylidene cyclopropanes by obtaining a crystal structure of the 2,4-dinitrophenylhydrazone **17**. The hydrazone was obtained as a mixture of (*Z*) and (*E*) isomers in 84% overall yield (eq 2), from which crystals of the (*Z*) isomer were obtained for single crystal X-ray analysis (Figure 2-6).[46,47]

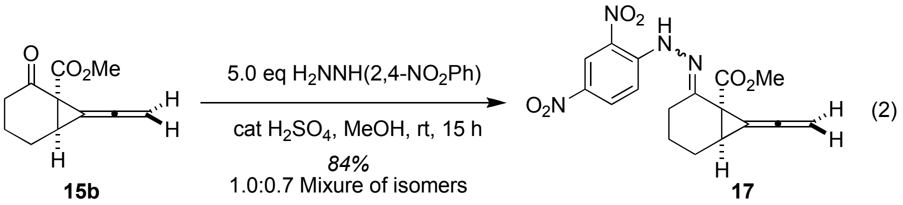
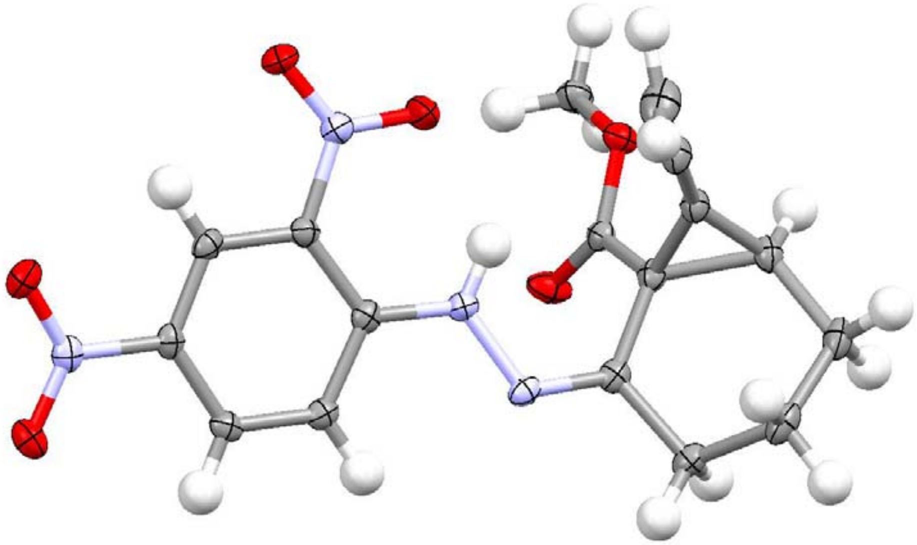

O
CO2Me
H
H
H
15b
5.0 eq H2NNH(2,4-NO2Ph)
cat H2SO4, MeOH, rt, 15 h
84%
1.0:0.7 Mixure of isomers
NO2
H
N
N
O2N
CO2Me
H
H
H
17
(2)

Figure 2-6. ORTEP of **(*Z*)-17**



2.3.8 Stereoelectronic Considerations

Analysis of the pertinent orbital interactions predicts that the 3-*exo-dig* cyclization will occur when the dihedral angle between the π-systems of the enol ether and alkyne is near 90º (Figure 2-7). This model can explain the beneficial influence of the 4-isopropyl substituent of **12a** relative to the parent system **12b** (Figure 2-8). The two half-chairs shown are hypothesized to be the lowest energy conformations for both compounds, with the alkyne in either an unreactive psuedoequatorial or reactive psuedoaxial position. K_{eq} is expected to be larger for **12a** as a consequence of an unfavorable *gauche* interaction between the isopropyl and alkynyl substituents in the diequatorial conformation. This results in a higher concentration of the reactive diaxial conformation, and thus increases the rate and efficiency of cyclization, in accordance with the experimental data.

Figure 2-7. Required Orbital Interactions for Cyclization (Alkyne π_{CC} Omitted for Clarity)

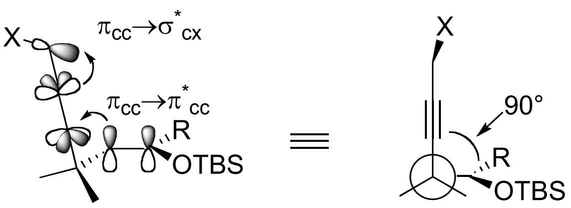
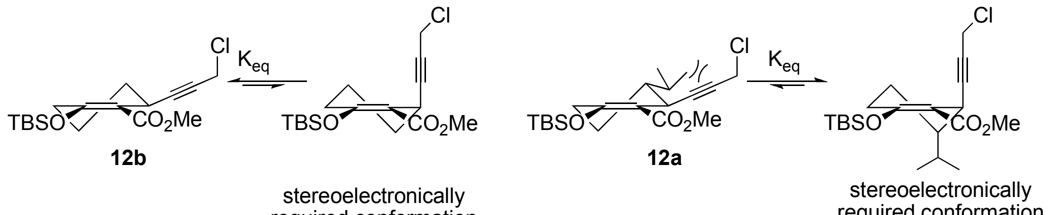

X
$\pi_{cc}\rightarrow\sigma^*_{cx}$
$\pi_{cc}\rightarrow\pi^*_{cc}$
R
OTBS
X
90°
R
OTBS

Figure 2-8. Conformation Analysis of Cyclization for **12a** and **12b**



12b

12a

stereoelectronically
required conformation
for cyclization

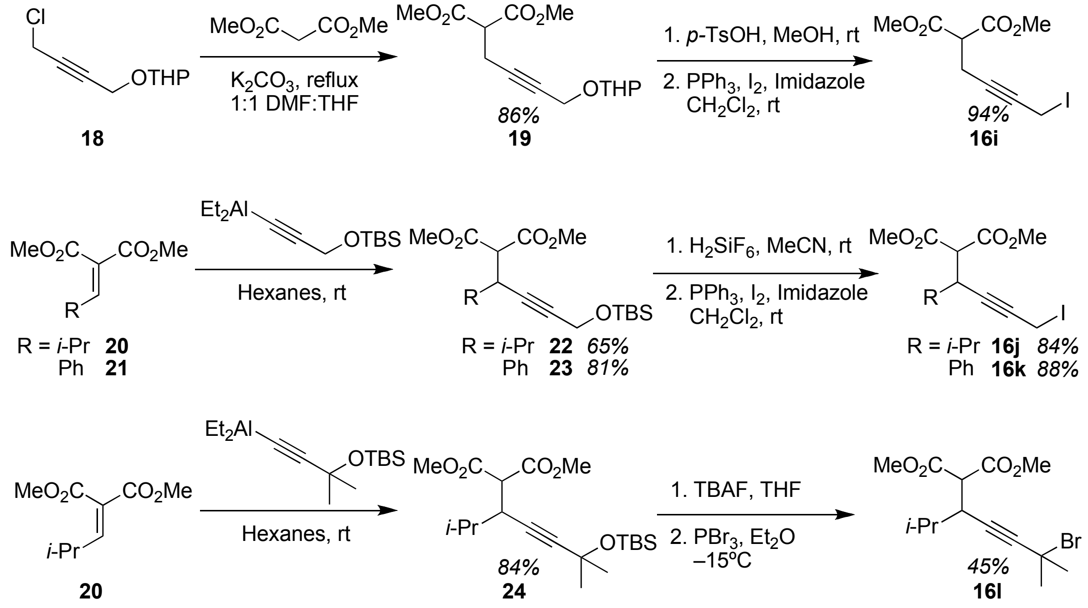
stereoelectronically
required conformation
for cyclization

2.3.9 Synthesis of Acyclic Propargyl Halides

In order to explore the scope of the cyclization further, we prepared several acyclic precursors. Only malonate-derived substrates were used; acyclic keto esters were avoided, because we hypothesized the ketone carbonyl would engage in competitive 5-*exo-dig* cyclization in the absence of the conformational constraints intrinsic to the cyclic systems. To prepare the simplest substrate, lacking substitution at the 3-position, we alkylated dimethyl malonate with the known propargyl chloride **18**[48] (Scheme 2-15). THP removal under acidic conditions and conversion to the iodide proceeded cleanly to form iodide **16i** in 81% overall yield from dimethyl malonate. Conjugate additions of TBS-protected propargyl alcohols to Knoevenagel products **20** and **21** were used to incorporate additional substituents. Propargyl alanes were excellent nucleophiles and provided the adducts **22**, **23**, and **24** in high yields.[49] The use of a tertiary silyl ether was well tolerated. After TBS-removal, primary iodides **16j** and **16k** were prepared from PPh_3/I_2, while the tertiary alcohol was treated with PBr_3 to afford the bromide **16l** in moderate yield.

Compared to the cyclic systems, the conjugate addition route used to prepare **16j** and **16k** is considerably more efficient. The use of protected propargyl alcohols as iodide precursors may be superior to the route taken for the cyclic substrates, but this strategy was not explored.

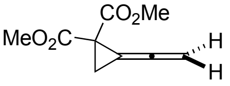
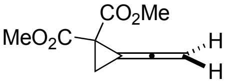
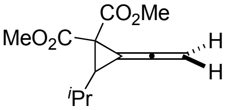
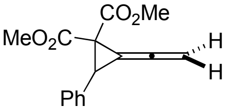
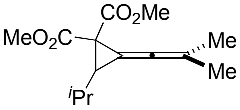
Scheme 2-15. Synthesis of Acyclic Propargyl Halides **16i-l**


Cl
OTHP
18
MeO2C CO2Me
K2CO3, reflux
1:1 DMF:THF
MeO2C CO2Me
OTHP
86%
19
1. p-TsOH, MeOH, rt
2. PPh3, I2, Imidazole
CH2Cl2, rt
MeO2C CO2Me
I
94%
16i
MeO2C CO2Me
R
R = i-Pr 20
Ph 21
Et2Al
OTBS
Hexanes, rt
MeO2C CO2Me
R
OTBS
R = i-Pr 22 65%
Ph 23 81%
1. H2SiF6, MeCN, rt
2. PPh3, I2, Imidazole
CH2Cl2, rt
MeO2C CO2Me
R
I
R = i-Pr 16j 84%
Ph 16k 88%
MeO2C CO2Me
i-Pr
20
Et2Al
OTBS
Hexanes, rt
MeO2C CO2Me
i-Pr
OTBS
84%
24
1. TBAF, THF
2. PBr3, Et2O
−15°C
MeO2C CO2Me
i-Pr
Br
45%
16l

2.3.10 Reaction Development using Acyclic Propargyl Halides

Initial experiments were discouraging as only 8% of **15i** was formed when TBAF was added to a solution of **16i** in THF, with oligomers being the main byproducts (Table 2-4, entry 1). Therefore, modification of the reaction conditions was required to extend this methodology to acyclic systems. We reasoned that intermolecular alkylation was dominant without the conformational constraints found in the cyclic systems that orient the alkyne in the reactive conformation. The use of high dilution conditions was predicted to disfavor intermolecular alkylation and select for the desired intramolecular cyclization. Because of the fast cyclization rate, we were able to use syringe pump addition of the iodide to a solution of TBAF in THF over 40 minutes. The volume of THF was kept at a manageable level while still operating under low substrate concentrations ($[\text{R–I}]_t \sim 10^{-4}$ M). All the linear substrates cyclized in high yields using this procedure.

Table 2-4. Scope of the 3-*Exo-Dig* Cyclization of Acyclic Propargyl Halides[a]

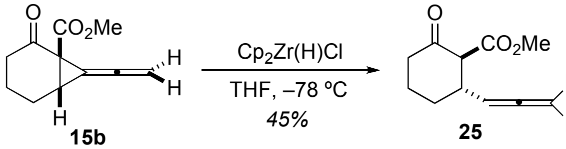
entry	halide	product		yield (%)[b]
1	I		**15i**	8
2[c]	I		**15i**	62
3[c]	I		**15j**	90
4[c]	I		**15k**	79
5[d]	Br		**15l**	82

[a] Conditions: Silyl enol ether (1.0 equiv) and TBAF (1.2 equiv) in THF (0.05 M) at room temperature unless otherwise noted. [b] Isolated yields (average of at least two experiments). [c] Syringe pump addition (0.04 mmol/min) of iodide **16**, TBAF (2.0 equiv) in THF (0.07 M). [d] TBAF (2.0 equiv).

2.3.11 Derivatization of Vinylidene Cyclopropanes

Although research groups have explored the synthetic utility of vinylidene cyclopropanes, we wanted to gauge the reactivity of the compounds we prepared. We were interested primarily because substrates bearing electron-withdrawing groups were previously unavailable, and thus were not the object of study, in the past; however, we wished to explore simple derivatizations, especially those that would leave the cyclopropane intact, because of our continued synthetic interest towards the preparation of the cladiellin core with [3+2] cycloaddition chemistry (*vide supra*).

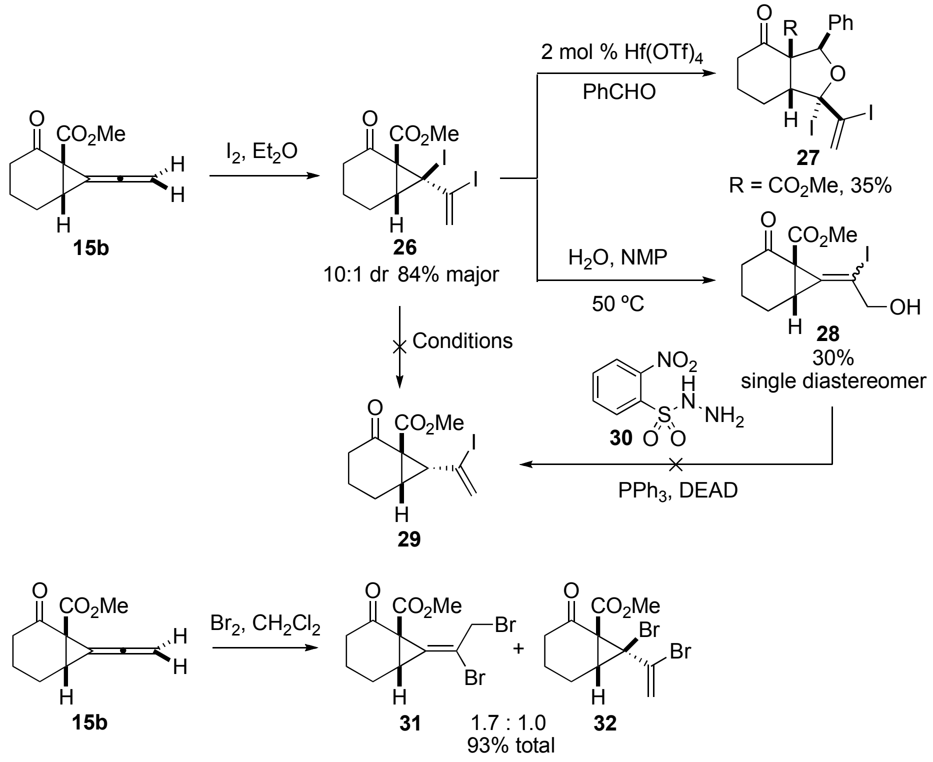
Early attempts to selectively hydrogenate **15a** using transition metal catalysis were met with decomposition, hypothesized to originate from β-carbon elimination, but no products were isolated to support this claim. The product of ring opening (**25**) was isolated in 45% during the reaction of **15b** with Schwartz's reagent, proving the feasibility of this pathway (eq 3). Future experiments were chosen judiciously, avoiding the use of transition metals.



(3)

Treatment of **15b** with iodine was effective at producing the diiodide **26**, with 84% of the major diastereomer isolated.[50] Bromination was also possible, but proceeded with poor regioselectivity to afford a 1.7:1.0 mixture of **31**:**32**. The diiodide **26** could be used in the [3+2] cycloaddition with benzaldehyde to produce an unoptimized 35% of **27**; the stereochemistry expected is shown but 2D-NMR experiments were not conclusive. Water could be used as a nucleophile in the polar aprotic solvents NMP and HMPA,[51] but yields were low, presumably due to the general instability of the diiodide. The iodide **29** was a target of interest, which we felt might be attainable by direct reduction of diiodide **26** or reductive allylic transposition of the alcohol **28**. Exposure of **26** to either radical or Lewis acid-catalyzed conditions led to intractable mixtures with the vinylidene cyclopropane **15b** occasionally produced in low yield. Reductive allylic transposition failed, as **28** was surprisingly resistant to substitution by hydrazide **30** under Mitsunobu conditions.[52] Efforts to directly displace the iodide with hydrazides was not fruitful.

Scheme 2-16. Halogenation and Subsequent Reactions of **15b**

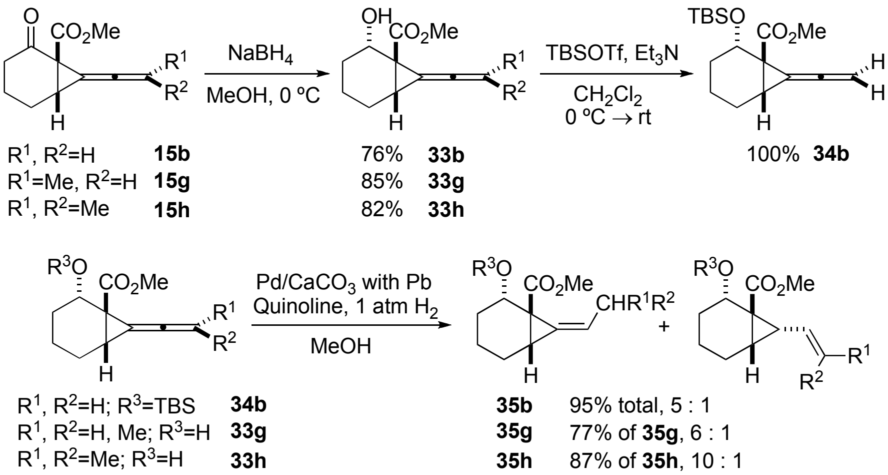

15b
I2, Et2O
26
10:1 dr 84% major
2 mol % Hf(OTf)4
PhCHO
27
R = CO2Me, 35%
H2O, NMP
50 °C
28
30%
single diastereomer
Conditions
30
PPh3, DEAD
29
Br2, CH2Cl2
31
1.7 : 1.0
93% total
32

Metal-free hydrogenations with diimide were investigated with both bicyclic and monocyclic vinylidene cyclopropanes, **15b** and **15i**. Several diimide precursors were used, but regio- and stereoselectivity were poor under all conditions.[53,54] Reactions stopped after partial conversion usually contained substantial amounts of starting material with both partially and exhaustively hydrogenated products.

To decrease the propensity of β-carbon elimination during transition metal catalyzed processes, we selectively reduced the keto esters **15b**, **15g**, and **15h** with $NaBH_4$,[55] hoping this would allow transition metal-catalyzed processes to be used (Scheme 2-17). We first investigated selective hydrogenations, and found that Lindlar's catalyst was able to produce alkylidene cyclopropanes with good regioselectivity. **33b** was converted to the TBS ether to enhance the regioselectivity of the hydrogenation from

3:1 to 5:1. In all examples, NMR analysis showed that the alkylidene cyclopropanes **35b**, **35g**, and **35h** possessed only the olefin geometry shown. Other typical hydrogenation catalysts produced unselective product mixtures, and no set of conditions produced a vinyl cyclopropane as the major product.

Scheme 2-17. Selective Hydrogenation with Lindlar's Catalyst

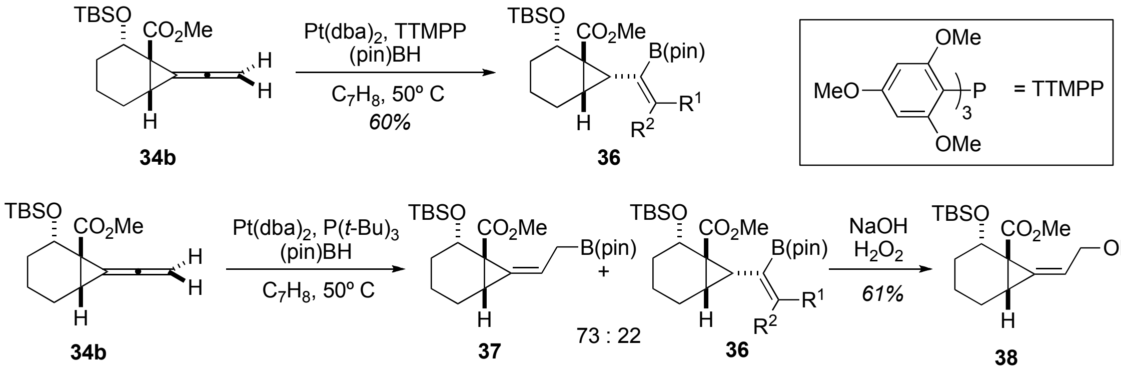


O
CO2Me
R1
R2
H
NaBH4
MeOH, 0 °C
OH
CO2Me
R1
R2
H
TBSOTf, Et3N
CH2Cl2
0 °C → rt
TBSO
CO2Me
H
H
H
R1, R2=H 15b
R1=Me, R2=H 15g
R1, R2=Me 15h
76% 33b
85% 33g
82% 33h
100% 34b
R3O
CO2Me
R1
R2
H
Pd/CaCO3 with Pb
Quinoline, 1 atm H2
MeOH
R3O
CO2Me
CHR1R2
H
+
R3O
CO2Me
R1
R2
H
R1, R2=H; R3=TBS 34b
R1, R2=H, Me; R3=H 33g
R1, R2=Me; R3=H 33h
35b 95% total, 5 : 1
35g 77% of 35g, 6 : 1
35h 87% of 35h, 10 : 1

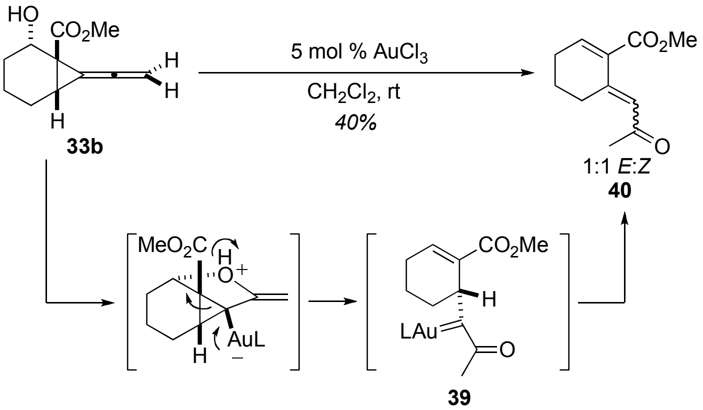
Initial experiments using uncatalyzed hydroborations were disappointing, and we were ultimately attracted to metal-catalyzed hydroborations of dialkoxyboranes. Miyaura developed two complementary Pt-based systems, each selectively producing one of the two possible vinyl boronates from terminal allenes.[56] They reported the bulky phosphine, P(*t*-Bu)$_3$, promotes hydroboration of the internal olefin, while the basic, bulky aryl phosphine, TTMPP, leads to reaction with the terminal olefin. Using the TBS-protected alcohol **34b**, we found both conditions were selective, but for unexpected regioisomers. Using TTMPP, vinyl boronate **36** was produced as the only regioisomer in 60% isolated yield, opposite to Miyaura's results. Several attempts to perform Suzuki couplings resulted in complex product mixtures. Instead of producing the complementary vinyl boronate as expected, the use of P(*t*-Bu)$_3$ formed allyl and vinyl boronates **37** and **36** in

~3:1 selectivity. Chromatography caused partial decomposition of **37**, so the crude mixture was subjected to oxidative conditions, which furnished alcohol **38** in 61% yield. The use of other ligands with Pt(dba)$_2$ led to reduced selectivity, with hydrogenation occurring when bidentate ligands such as bipyridine and BINAP were used. Other metals used commonly for hydroborations, such as Rh- and Ir-complexes, were screened and found to be less effective than Pt. Rh complexes were particularly unsuitable and led exclusively to hydrogenation products.

Scheme 2-18. Hydroboration of **34b** using Pt(dba)$_2$ and Pinacolborane


TBSO
CO2Me
H
H
H
34b
Pt(dba)2, TTMPP
(pin)BH
C7H8, 50° C
60%
TBSO
CO2Me
B(pin)
R1
R2
H
36
OMe
MeO
P
3
OMe
= TTMPP
TBSO
CO2Me
H
H
H
34b
Pt(dba)2, P(t-Bu)3
(pin)BH
C7H8, 50° C
TBSO
CO2Me
B(pin)
H
37
+
73 : 22
TBSO
CO2Me
B(pin)
R1
R2
H
36
NaOH
H2O2
61%
TBSO
CO2Me
OH
H
38

Exposing alcohol **33b** to AuCl$_3$ resulted in an atom-transfer reaction to form a 1:1 mixture of enones in low yield (eq 4). A possible mechanism is that formation of gold carbene **39** occurs concurrently with ring opening and elimination of the enol. The carbene is quenched by a [1,2]-hydride transfer/elimination sequence to afford **40**. Appropriately substituted substrates could prevent the unproductive hydride transfer and utilize the gold carbene in conjunction with other tethered functionality to quickly generate complex carbon skeletons.



(4)

2.4 Conclusion

In summary, we have developed the first example of an all-carbon 3-*exo-dig* cyclization. These cyclizations lead to vinylidene cyclopropanes with electron-withdrawing substituents, products that are not available using carbene chemistry. Both cyclic and acyclic precursors can be used with equal efficacy, although high dilution conditions were necessary to enable cyclization of the latter. A comprehensive reactivity study of the products was beyond the scope of this investigation, but the products were amenable to a number of common derivatizations, including halogenation, hydrogenation, and hydroboration. The pitfall of β-carbon elimination was avoided by partial reduction of keto esters, allowing transition metal-catalyzed processes to be used. Further studies into the reactivity of these vinylidene cyclopropanes should prove fruitful.

2.5 Experimental

Materials and Methods: General. Infrared (IR) spectra were obtained using an ASI ReactIR 1000. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C

NMR) were recorded on a Bruker model DRX 400 or a Bruker AMX 300 (^{1}H NMR at 400 MHz or 300Mhz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250°C) or a J&W DB-1701 column (30 m x .249 mm) with helium gas as carrier. Combustion analyses were performed by Atlantic Microlab Inc., Norcross, GA. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out either by acid/base extractive work-up or flash chromatography using Silia-P flash silica gel (40-63 µm) purchased from Silicycle. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. Hexanes were dried by distillation from sodium metal immediately prior to use. Pyridine and triethylamine were freshly distilled from calcium hydride. All other reagents were obtained from commercial sources and used without further purification.

General Procedure (A) for the conjugate addition of propargyl chlorides to enones. The conjugate addition was conducted according to Kim's method[44] with slight modification: a flame-dried round bottom flask equipped with a magnetic stir bar and a Teflon-coated thermocouple was charged with the propargyl chloride (1.7 equiv), anhydrous tetrahydrofuran (3.0 mL/mmol enone), and the solution was cooled to –78 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 1.5 equiv) was slowly added down the side of the flask, keeping the internal temperature < –70 °C, and the reaction mixture was stirred at –78 °C for 45 minutes. A solution of trimethylaluminum (2.0 M in hexanes, 1.5 equiv) was slowly added down the side of the flask, keeping the internal temperature < –70 °C, and the reaction mixture was stirred at –78 °C for 1 hour. A solution of the enone in anhydrous tetrahydrofuran (1.0 equiv, 0.50 M) was then added slowly keeping the internal temperature < –70 °C, followed by *tert*-butyldimethylsilyl triflate, again keeping the internal temperature < –70 °C. The flask was stirred at –78 °C for the indicated time period. The reaction mixture was quenched by pouring onto saturated aqueous sodium bicarbonate solution (10 mL/mmol enone) and diluted with diethyl ether (10 mL/mmol enone). The combined layers were filtered through a pad of Celite, washing with additional diethyl ether (20 mL/mmol enone). The aqueous layer was further extracted with diethyl ether (5 mL/mmol enone). The combined organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL/mmol enone), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (B) for the conversion of propargyl chlorides to propargyl iodides.

A reaction tube equipped with a magnetic stir bar was charged with the propargyl chloride (1.0 equiv), reagent grade acetone (6.0 mL/mmol propargyl chloride), and then sodium iodide (3.0 equiv). The tube was sealed and the solution heated to 60 °C for the indicated time. The reaction mixture was cooled to room temperature, diluted with diethyl ether (15 mL/mmol propargyl chloride), and passed through a 1 inch silica plug, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (C) for the cyclization of cyclic propargyl iodides.

A vial equipped with a magnetic stir bar was charged with the propargyl iodide (1.0 equiv) and degassed tetrahydrofuran (20.0 mL/mmol propargyl iodide). A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) was then added at a rate of ~1 drop/second. The solution was stirred for 5 minutes further, after which the solution was diluted with diethyl ether (60 mL/mmol propargyl iodide), and passed through a 1 inch silica plug, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (D) for the conjugate addition of *tert*-butyldimethylsilyl protected propargyl alcohols to alkylidene malonates.

The conjugate addition was conducted according to Trost's method[49] with slight modification: a flame-dried round bottom flask equipped with a magnetic stir bar and a Teflon-coated thermocouple was charged with the *tert*-butyldimethylsilyl protected propargyl alcohol (1.2 equiv), anhydrous hexanes (4.5 mL/mmol alkylidene malonate), and the solution was cooled to –78 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 1.1 equiv) was added quickly, keeping the internal temperature < 0 °C, and the reaction mixture was stirred at 0 °C for 15 minutes. The solution was cooled to –78 °C and a solution of diethylaluminum chloride (1.0 M in hexanes, 1.1 equiv) was added quickly, keeping the internal temperature < 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes. The alkylidene malonate was added neat at 0 °C, and the reaction was stirred at room temperature for 3 hours. The reaction mixture was quenched by pouring onto saturated sodium bicarbonate solution (10 mL/mmol enone) and diluted with hexanes (10 mL/mmol enone). The biphasic mixture was stirred vigorously until the mixture solidified into a gel (~5 minutes). The combined layers were filtered through a pad of Celite, washing with additional hexanes (20 mL/mmol enone). The aqueous layer was further extracted with hexanes (2 x 5 mL/mmol enone). The combined organic layer was washed with saturated sodium bicarbonate solution (1 x 5 mL/mmol enone), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (E) for the deprotection of primary *tert*-butyldimethylsilyl protected propargyl alcohols.

The deprotection was conducted according to DeShong's method.[57] A polyethylene Erlenmeyer flask equipped with a magnetic stir bar was charged with the *tert*-butyldimethylsilyl protected propargyl alcohol (1.0 equiv) and reagent grade acetonitrile (8.0 mL/mmol substrate). A solution of fluorosilicic acid (25% in H_2O, 0.2 equiv) was then added at once, and the solution was stirred for 1 hour at room temperature. The reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate solution (1 mL/mmol substrate). The solvent was removed under reduced pressure. The residue was taken up in diethyl ether (5 mL/mmol substrate) and deionized water (2 mL/mmol substrate). The layers were separated and the aqueous layer was extracted with diethyl ether (1 x 5 ml/mmol substrate). The combined organic layer was washed with deionized water (2 x 2 mL/mmol substrate), saturated aqueous sodium chloride solution (1 x 2 mL/mmol substrate), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (F) for the conversion of primary propargyl alcohols to propargyl iodides.

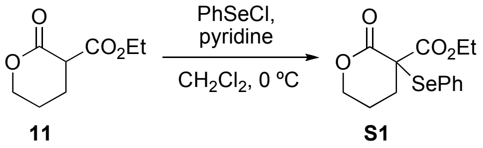
A flame-dried round bottom flask equipped with a magnetic stir bar was charged with the triphenylphosphine (1.4 equiv) and imidazole (1.4 equiv). Anhydrous dichloromethane (10 mL/mmol alcohol) was added and the mixture was briefly stirred until the majority of solids were in solution. Iodine (1.4 equiv) was then added at once and the mixture was stirred for 15 minutes at room temperature until a homogeneous orange mixture was obtained. A solution of the alcohol in anhydrous dichloromethane (1.0 equiv, 0.50 M) was added at once and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with dichloromethane (10 mL/mmol alcohol) and washed with saturated aqueous sodium thiosulfate solution (5 mL/mmol alcohol). The aqueous layer was extracted with dichloromethane (3 x 3 mL/mmol alcohol). The combined organic layer was washed with saturated aqueous sodium chloride solution (1 x 3 mL/mmol alcohol), dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (G) for the cyclization of acyclic propargyl iodides.

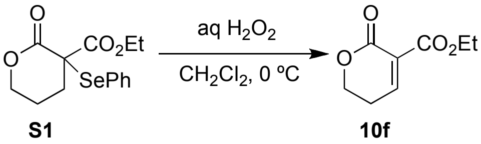
A round bottom flask equipped with a magnetic stir bar was charged with degassed tetrahydrofuran (15.0 mL/mmol propargyl iodide) and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 2.0 equiv). A solution of the propargyl iodide in degassed tetrahydrofuran (1.0 equiv, 0.10 M) was then slowly added (0.04 mmol/minute) via syringe pump. After the addition was complete, the solution was stirred for 5 minutes further, after which the solution was concentrated to ~5 mL/mmol iodide under reduced pressure. The residue was then diluted with diethyl ether (15 mL/mmol propargyl iodide), and passed through a 1 inch silica plug, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with the indicated solvent system.

General Procedure (H) for the reduction of keto esters with sodium borohydride. A round bottom flask equipped with a magnetic stir bar was charged with reagent grade methanol (15.0 mL/mmol keto ester) and the keto ester. The solution was cooled to 0 °C in an ice bath. Sodium borohydride (0.4 equivalents) was added at once and the solution was stirred at 0 °C. The reaction was monitored by TLC and additional sodium borohydride (0.4 equivalents) was added after 30 minutes if needed. The residue was then quenched with aqueous hydrochloric acid (1M, 10 mL/mmol keto ester) and allowed to warm to room temperature. The reaction was diluted with saturated aqueous sodium chloride solution (50 mL/mmol keto ester) and extracted with ethyl acetate (3 x 75 mL/mmol keto ester). The extracts were washed with saturated aqueous sodium chloride (1 x 25 mL/ mmol keto ester) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with the indicated solvent system.

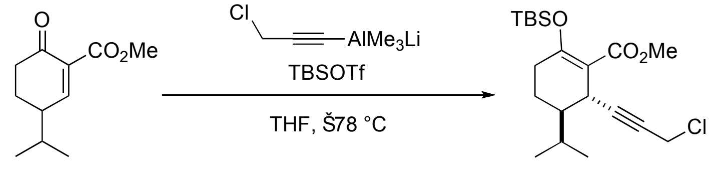
General Procedure (I) for the selective hydrogenation of vinylidene cyclopropanes. A vial equipped with a magnetic stir bar was charged with the requisite vinylidene cyclopropane, palladium on calcium carbonate poisoned with lead (5.0% Pd, 3.5% Pb, 0.05 equiv), quinoline (2.0 equiv), and reagent grade methanol (25.0 mL/mmol vinylidene cyclopropane). The vial was purged with hydrogen gas. The hydrogen balloon was left affixed to the vial and stirred at the desired temperature. When the reaction was deemed complete by TLC, the reaction mixture was filtered through celite, eluting with methanol. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with the indicated solvent system.



Ethyl 2-oxo-3-(phenylselanyl)tetrahydro-2*H*-pyran-3-carboxylate (S1). A flame-dried round bottom flask equipped with a magnetic stir bar was charged with phenylselenyl chloride (1.510 g, 7.9 mmol). Anhydrous dichloromethane (25.0 mL) and pyridine (0.693 mL, 8.6 mmol) were added sequentially, after which the solution was cooled to 0 °C. A solution of ethyl 2-oxotetrahydro-2*H*-pyran-3-carboxylate[43] (**11**) (1.234 g, 7.2 mmol) in anhydrous dichloromethane (2.0 mL) was added dropwise over 5 minutes, and the solution was stirred at 0 °C for 75 minutes. The reaction mixture was washed with 10% aqueous hydrochloric acid solution (2 x 20 mL) and saturated aqueous sodium bicarbonate solution (1 x 20 mL). The combined organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with 50% diethyl ether/hexanes to leave the title compound (1.968 g, 6.0 mmol, 84% yield) as a white solid. Analytical data for **S1**: mp 85-86 °C; **IR** (thin film, cm^{-1}) 1733, 1706, 1291, 1264, 1246, 1196, 1158, 1079, 1025, 961, 868, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H), 7.30 (t, J - 7.2 Hz, 2H), 4.26-4.12 (m, 4H), 2.35 (dt, *J* = 14.0, 5.6 Hz, 1H), 2.10-1.95 (m, 1H), 1.95-1.82 (m, 1H), 1.82-1.67 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8, 167.5 138.1, 129.8, 128.7, 125.8, 68.8, 62.5, 52.6, 30.3, 20.9, 13.7; TLC (50% Et_2O/hexanes) R_f 0.23; **Anal.** Calcd. for $C_{14}H_{16}O_4Se$: C, 51.39; H, 4.93. Found: C, 51.34; H, 5.00.

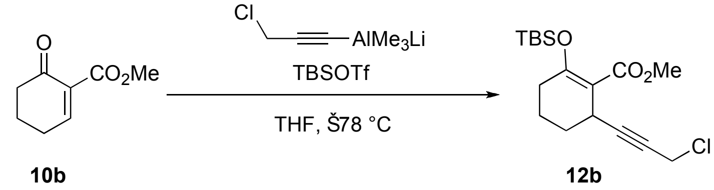


Ethyl 2-oxo-5,6-dihydro-2H-pyran-3-carboxylate (10f). An Erlenmeyer flask equipped with a magnetic stir bar was charged with ethyl 2-oxo-3-(phenylselanyl)tetrahydro-2*H*-pyran-3-carboxylate (**S1**) (0.982 g, 3.0 mmol), reagent grade dichloromethane (10.0 mL), and cooled to 0 °C. A solution of hydrogen peroxide (30% w/v, 0.680 mL, 6.0 mmol) was diluted in 1.20 mL deionized water. This solution was then added in three portions over 5 minutes. The reaction was stirred for 30 minutes at 0 °C, after which the ice bath was removed and the reaction was stirred for 1 hour at room temperature. The reaction mixture was diluted in dichloromethane (10 mL) and washed with saturated aqueous sodium bicarbonate solution (1 x 15 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL), dried over sodium sulfate, and the solvent was removed under reduced pressure to leave the title compound (0.507 g, 3.0 mmol, 100% yield) as a yellow oil. Analytical data for **10f**: **IR** (thin film, cm^{-1}) 2983, 2944, 2908, 1748, 1474, 1449, 1405, 1372, 1356, 1281, 1260, 1204, 1181, 1098, 1082, 1057, 1025, 986; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 4.4 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.53 (td, *J* = 6.0, 4.4 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.4, 159.2, 152.2, 125.6, 65.5, 61.0, 24.3, 13.7; **LRMS** (ESI) Calcd. for $C_8H_{10}O_4$+Na 193.1, Found 193.0.

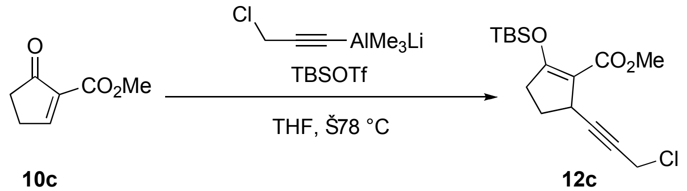


10a **12a**

***trans*-Methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylate (12a).** The title compound was prepared according to General Procedure **A** using methyl 3-isopropyl-6-oxocyclohex-1-enecarboxylate[41] (**10a**) (0.870 g, 4.4 mmol), propargyl chloride (0.545 mL, 7.5 mmol), *n*-butyllithium (1.5 M in hexanes, 4.43 mL, 6.7 mmol), trimethylaluminum (2.0 M in hexanes, 3.33 mL, 6.7 mmol), and *tert*-butyldimethylsilyl triflate (1.22 mL, 5.3 mmol) with stirring for 2.5 hours at –78 °C to yield *trans*-methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylate (**12a**) (0.470 g, 1.2 mmol, 28% yield) as a pale yellow oil after flash chromatography with 3% ethyl acetate/hexanes. The oil solidifies upon standing at –30 °C. Analytical data for **12a**: mp 43-45 °C; **IR** (thin film, cm^{-1}) 2228, 1723, 1693, 1627, 1472, 1464, 1435, 1377, 1292, 1259, 1209, 1136, 1078, 1062, 1010, 943, 899, 841, 814, 782, 693; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.08 (d, J = 2.0 Hz, 2H), 3.74 (s, 3H), 3.64 (br s, 1H), 2.18-2.06 (m, 2H), 1.93 (dddd, J = 13.5, 7.5, 7.5, 3.0 Hz, 1H), 1.74-1.64 (m, 1H), 1.57 (dddd, J = 12.5, 6.0, 6.0, 6.0 Hz, 1H), 1.52-1.45 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.91 (s, 9H), 0.86 (d, J = 6.5 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.5, 159.3, 108.6, 90.1, 75.1, 51.3, 44.7, 31.4, 31.3, 29.6, 27.1, 25.7, 21.6, 21.2, 19.1, 18.4, -3.6, -3.8; TLC (2.5% EtOAc/petroleum ether) R_f 0.15; **Anal.** Calcd. for $C_{20}H_{33}ClO_3Si$: C, 62.39; H, 8.64. Found: C, 62.68; H, 8.72.

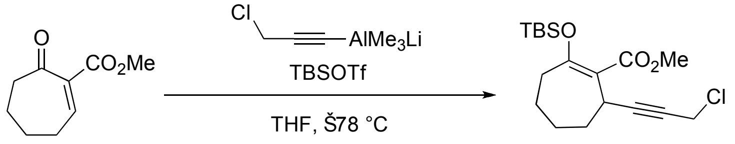


Methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)cyclohex-1-enecarboxylate (12b). The title compound was prepared according to General Procedure **A** using methyl 6-oxocyclohex-1-enecarboxylate[40] (**10b**) (0.950 g, 6.2 mmol), propargyl chloride (0.787 mL, 10.9 mmol), *n*-butyllithium (1.6 M in hexanes, 6.00 mL, 9.6 mmol), trimethylaluminum (2.0 M in hexanes, 4.80 mL, 9.6 mmol), and *tert*-butyldimethylsilyl triflate (1.76 mL, 7.7 mmol) with stirring for 1 hour at –78 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)cyclohex-1-enecarboxylate (**12b**) (1.415 g, 4.1 mmol, 67% yield) as a white solid after flash chromatography with 10% diethyl ether/hexanes. Analytical data for **12b**: mp 68-70 °C; **IR** (thin film, cm^{-1}) 2952, 2935, 2860, 1719, 1692, 1623, 1436, 1376, 1262, 1208, 1133, 1082, 1061, 917, 834; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 (d, J = 2 Hz, 2H), 3.74 (s, 3H), 3.75-3.70 (m, 1H), 2.22-2.15 (m, 2H), 2.00-1.95 (m, 2H), 1.80-1.67 (m, 1H), 1.65-1.53 (m, 1H), 0.94 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 160.2, 109.3, 89.4, 74.9, 51.2, 31.8, 31.2, 28.3, 27.9, 25.6, 19.3, 18.3, -3.7, -3.8; TLC (25% Et_2O/hexanes) R_f 0.61; **LRMS** (ESI) Calcd. for $C_{17}H_{27}ClO_3Si$+Na 365.1, Found 365.2.



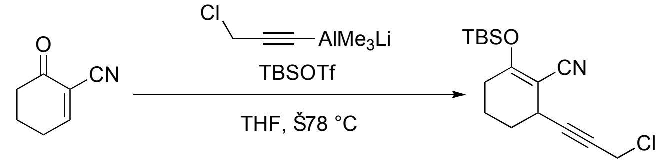
10c **12c**

Methyl 2-(tert-butyldimethylsilyloxy)-5-(3-chloroprop-1-ynyl)cyclopent-1-enecarboxylate (12c). The title compound was prepared according to General Procedure **A** using methyl 5-oxocyclopent-1-enecarboxylate[40] (**10c**) (0.170 g, 1.0 mmol), propargyl chloride (0.123 mL, 1.7 mmol), *n*-butyllithium (1.6 M in hexanes, 0.94 mL, 1.5 mmol), trimethylaluminum (2.0 M in hexanes, 0.75 mL, 1.5 mmol), and *tert*-butyldimethylsilyl triflate (0.276 mL, 1.2 mmol) with stirring for 3 hours at –78 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-5-(3-chloroprop-1-ynyl)cyclopent-1-enecarboxylate (**12c**) (0.204 g, 0.62 mmol, 62% yield) as a yellow oil after flash chromatography with 10% diethyl ether/hexanes. Analytical data for **12c**: **IR** (thin film, cm^{-1}) 2948, 2931, 2860, 1717, 1625, 1437, 1387, 1262, 1231, 1192, 1164, 1129, 1050, 940, 843, 785, 691; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 4.10 (d, J = 2.0 Hz, 2H), 3.75-3.65 (m, 1H), 3.69 (s, 3H), 2.64 (dt, J = 16.8, 8.4 Hz, 1H), 2.32 (ddd, J = 16.8, 9.2, 3.6 Hz, 1H), 2.32 (ddd, J = 16.8, 9.2, 3.6 Hz, 1H), 2.00-1.90 (m, 1H), 0.94 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 166.3, 164.4, 108.8, 89.3, 75.0, 50.6, 34.4, 32.9, 31.2, 27.6, 25.3, 18.1, -4.1, -4.2; TLC (10% Et$_2$O/hexanes) R_f 0.29; **LRMS** (ESI) Calcd. for $C_{16}H_{25}ClO_3Si$+Na 351.1, Found 351.2.



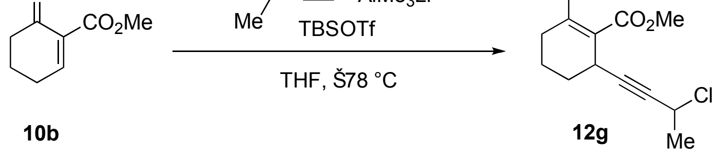
10d **12d**

(Z)-Methyl 2-(*tert*-butyldimethylsilyloxy)-7-(3-chloroprop-1-ynyl)cyclohept-1-enecarboxylate (12d). The title compound was prepared according to General Procedure **A** using methyl 7-oxocyclohept-1-enecarboxylate[40] (**10d**) (0.544 g, 3.2 mmol), propargyl chloride (0.389 mL, 5.4 mmol), *n*-butyllithium (1.6 M in hexanes, 3.00 mL, 4.8 mmol), trimethylaluminum (2.0 M in hexanes, 2.40 mL, 4.8 mmol), and *tert*-butyldimethylsilyl triflate (0.869 mL, 3.7 mmol) with stirring for 4 hours at –78 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-7-(3-chloroprop-1-ynyl)cyclohept-1-enecarboxylate (**12d**) (0.515 g, 1.4 mmol, 45% yield) as a pale yellow oil after flash chromatography with 2.5% ethyl acetate/hexanes. Analytical data for **12d**: **IR** (thin film, cm^{-1}) 2934, 2860, 2239, 1718, 1683, 1613, 1436, 1378, 1262, 1200, 1143, 1092, 1050, 1019, 872, 842, 811, 784; **^{1}H NMR** (300 MHz, CDCl$_3$) δ 4.18 (d, *J* = 2.1 Hz, 2H), 4.20-4.05 (m, 1H), 3.74 (s, 3H), 3.08 (dd, *J* = 15.0, 14.0 Hz, 1H), 2.17 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.10-1.70 (m, 4H), 1.60-1.35 (m, 2H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 168.1, 167.1, 113.4, 87.3, 77.3, 51.2, 36.4, 31.2, 31.0, 29.0, 26.3, 25.5, 24.4, 18.1, -3.8, -4.1; TLC (5% EtOAc/hexanes) R_f 0.30; **LRMS** (ESI) Calcd. for $C_{18}H_{29}O_3Si$+H 357.2, Found 357.3.



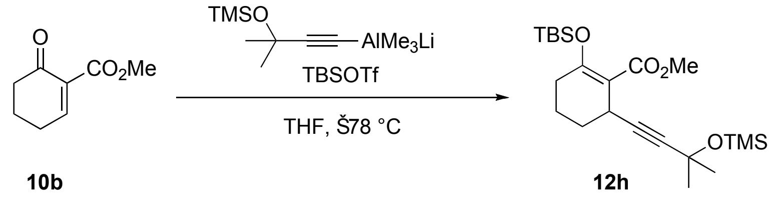
10e **12e**

2-(*tert*-Butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)cyclohex-1-enecarbonitrile (12e). The title compound was prepared according to General Procedure **A** using 3-isopropyl-6-oxocyclohex-1-enecarbonitrile[42] (**10e**) (1.210 g, 10.0 mmol), propargyl chloride (1.23 mL, 17.0 mmol), *n*-butyllithium (1.5 M in hexanes, 10.00 mL, 15.0 mmol), trimethylaluminum (2.0 M in hexanes, 7.50 mL, 15.0 mmol), and *tert*-butyldimethylsilyl triflate (2.75 mL, 12.0 mmol) with stirring for 1 hour at –78 °C to yield 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)cyclohex-1-enecarbonitrile (**10e**) (1.070 g, 3.5 mmol, 35% yield) as a pale yellow oil after flash chromatography with 10% diethyl ether/hexanes that slowly solidfies into a dark solid. Analytical data for **12e**: mp 53-55 °C **IR** (thin film, cm^{-1}) 2954, 2931, 2861, 2211, 1630, 1474, 1465, 1372, 1299, 1262, 1245, 1208, 1156, 1092, 1156, 1092, 1073, 971, 932, 863; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.14 (d, *J* = 1.6 Hz, 2H), 3.36 (br s, 1H), 2.24-2.06 (m, 2H), 1.94-1.82 (m, 1H), 1.82-1.64 (m, 3H), 0.95 (s, 9H), 0.22 (s, 3H), 0.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.1, 117.6, 91.3, 86.6, 76.8, 30.6, 30.5, 28.5, 28.1, 25.3, 19.4, 18.0, -3.8, -3.8; TLC (10% Et_2O/hexanes) R_f 0.33; **LRMS** (ESI) Calcd. for $C_{16}H_{24}ClNOSi$+H 310.1, Found 310.2.

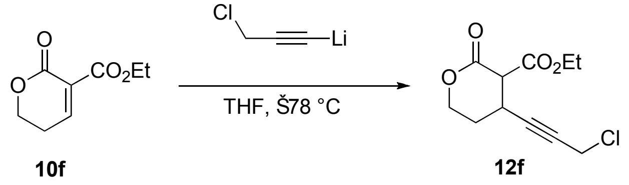


10b **12g**

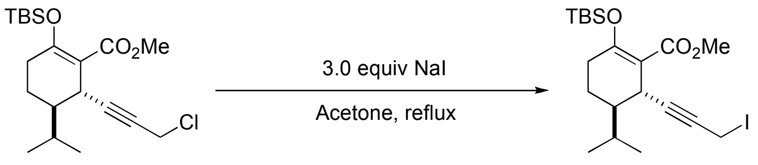
Methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chlorobut-1-ynyl)cyclohex-1-enecarboxylate (12g). The title compound was prepared according to General Procedure **A** using methyl 6-oxocyclohex-1-enecarboxylate[40] (**10b**) (0.880 g, 5.71 mmol), 3-chlorobut-1-yne (0.877 g, 9.91 mmol), *n*-butyllithium (1.5 M in hexanes, 5.80 mL, 8.70 mmol), trimethylaluminum (2.0 M in hexanes, 4.35 mL, 8.70 mmol), and *tert*-butyldimethylsilyl triflate (1.61 mL, 7.04 mmol) with stirring for 3.5 hours at –78 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chlorobut-1-ynyl)cyclohex-1-enecarboxylate (**12g**) (0.770 g, 2.16 mmol, 38% yield) as a pale yellow oil after flash chromatography with 5%→10% diethyl ether/hexanes. Analytical data for **12g**: **IR** (thin film, cm^{-1}) 2952, 2885, 1739, 1723, 1679, 1621, 1463, 1437, 1368, 1316, 1252, 1221, 1208, 1146, 1086, 1067, 949, 917, 866, 834, 782; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 4.62 (dd, *J* = 6.7, 1.8 Hz, 1H), 4.59 (dd, *J* = 6.7, 1.8 Hz, 1H), 3.73 (s, 3H), 2.25-2.08 (m, 2H), 1.97-1.81 (m, 2H), 1.75-1.65 (m, 1H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.59 (tdd, *J* = 12.8, 5.2, 2.8 Hz, 1H), 0.94 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 167.2, 167.2, 159.9, 109.6, 109.6, 88.3, 88.3, 79.7, 51.1, 44.7. 31.8, 28.3, 27.8, 26.9, 25.6, 19.4, 18.3, -3.7, -3.9; TLC (10% Et_2O/hexanes) R_f 0.41; **LRMS** (ESI) Calcd. for $C_{18}H_{29}ClO_3Si$+H 357.2, Found 357.2.



Methyl 2-(tert-butyldimethylsilyloxy)-6-(3-methyl-3-(trimethylsilyloxy)but-1-ynyl)cyclohex-1-enecarboxylate (12h). The title compound was prepared according to General Procedure **A** using methyl 6-oxocyclohex-1-enecarboxylate[40] (**10b**) (0.486 g, 3.15 mmol), trimethyl(2-methylbut-3-yn-2-yloxy)silane (0.838 g, 5.36 mmol), *n*-butyllithium (1.5 M in hexanes, 3.13 mL, 4.70 mmol), trimethylaluminum (2.0 M in hexanes, 3.15 mL, 6.30 mmol), and *tert*-butyldimethylsilyl triflate (0.868 mL, 3.80 mmol) with stirring for 20 minutes at –78 °C to yield methyl 2-(tert-butyldimethylsilyloxy)-6-(3-methyl-3-(trimethylsilyloxy)but-1-ynyl)cyclohex-1-enecarboxylate (**12h**) (0.595 g, 1.40 mmol, 44% yield) as a pale yellow oil after flash chromatography with 4%→5% diethyl ether/hexanes. Analytical data for **12h**: **IR** (thin film, cm^{-1}) 2935, 2858, 1730, 1622, 1444, 1367, 1305, 1251, 1205, 1166, 1035, 958, 842, 780, 687; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.70-3.66 (m, 1H), 3.69 (s, 3H), 2.25-2.05 (m, 2H), 1.98-1.77 (m, 2H), 1.75-1.64 (m, 1H), 1.59 (tdd, J = 12.5, 5.2, 2.8 Hz, 1H), 1.40 (s, 6H), 0.93 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.14 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 159.1, 110.2, 85.3, 66.5, 50.9, 33.4, 33.4, 31.8, 28.6, 27.8, 25.7, 19.5, 18.3, 1.8, –3.7, –3.8; TLC (5% Et_2O/hexanes) R_f 0.21; **LRMS** (ESI) Calcd. for $C_{22}H_{40}O_4Si_2$+K 463.3, Found 462.3.

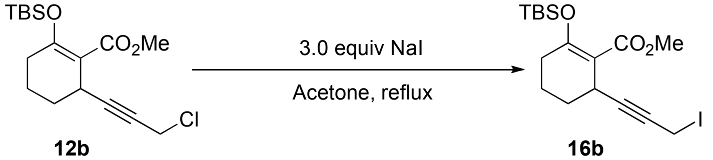


Ethyl 4-(3-chloroprop-1-ynyl)-2-oxotetrahydro-2H-pyran-3-carboxylate (12f). A flame-dried vial equipped with a magnetic stir bar and a Teflon-coated thermocouple was charged with propargyl chloride (0.344 mL, 4.8 mmol), anhydrous tetrahydrofuran (2.0 mL), and the solution was cooled to –78 °C. A solution of *n*-butyllithium (1.6 M in hexanes, 2.60 mL, 4.0 mmol) was slowly added down the side of the flask, keeping the internal temperature < –70 °C, and the reaction mixture was stirred at –78 °C for 60 minutes. A solution of ethyl 2-oxo-5,6-dihydro-2*H*-pyran-3-carboxylate (**10f**) (0.216 g, 1.3 mmol) in anhydrous tetrahydrofuran (3.0 mL) was then added slowly over 5 minutes, keeping the internal temperature < –70 °C. The vial was stirred at –78 °C for 15 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with 30%→35% ethyl acetate/hexanes to leave ethyl 4-(3-chloroprop-1-ynyl)-2-oxotetrahydro-2H-pyran-3-carboxylate (**12f**) (0.089 g, 0.36 mmol, 28%) as a pale yellow oil. Analytical data for **12f**: **IR** (thin film, cm^{-1}) 2984, 2930, 1725, 1475, 1447, 1370, 1320, 1266, 1154, 1073, 1031, 942, 915, 733, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.47 (ddd, *J* = 11.4, 6.8, 4.4 Hz, 1H), 4.35 (ddd, *J* = 11.6, 7.6, 4.0 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.09 (d, *J* = 1.6 Hz, 2H), 3.54 (d, *J* = 8.4 Hz, 1H), 3.45-3.35 (m, 1H), 2.26-2.16 (m, 1H), 1.94 (dddd, J = 14.2, 7.9, 7.4, 4.5 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 165.2, 84.7, 78.7, 67.5, 62.3, 53.0, 30.0, 27.3, 27.3, 14.0; TLC (35% EtOAc/hexanes) R_f 0.38; **LRMS** (ESI) Calcd. for $C_{11}H_{13}ClO_4$+H 245.1, Found 245.1.



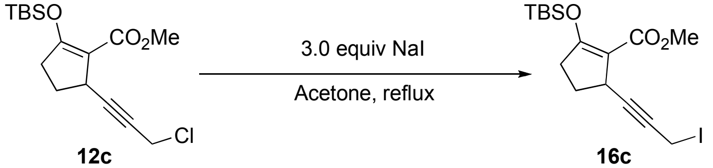
12a **16a**

***trans*-Methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylate (16a).** The title compound was prepared according to General Procedure **B** using *trans*-methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylate (**12a**) (0.230 g, 0.60 mmol) and sodium iodide (0.269 g, 1.80 mmol) with stirring for 7 hours at 60 °C to yield *trans*-methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylate (**16a**) (0.186 g, 0.39 mmol, 65% yield) as a pale yellow oil after flash chromatography with 5% diethyl ether/hexanes. Analytical data for **16a**: **IR** (thin film, cm^{-1}) 2953, 2930, 2895, 2856, 1722, 1691, 1629, 1463, 1436, 1378, 1293, 1254, 1208, 1150, 1061, 1011, 942, 899, 838, 784, 733; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.65 (d, J = 2.4 Hz, 2H), 5.59 (br s, 1H), 2.20-2.04 (m, 2H), 1.91 (dddd, J = 13.6, 6.9, 6.8, 2.7 Hz, 1H), 1.69 (sext, J = 6.7 Hz, 1H), 1.60-1.50 (m, 1H), 1.50-1.42 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.92 (s, 9H), 0.86 (d, J = 6.4 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 167.3, 158.9, 108.5, 89.1, 77.1, 51.2, 44.6, 31.6, 29.6, 27.1, 25.6, 21.4, 21.1, 18.9, 18.2, -3.7, -3.9, -16.7; TLC (2.5% Et_2O/petroleum ether) R_f 0.15; **LRMS** (ESI) Calcd. for $C_{20}H_{33}IO_3Si$+Na 499.1, Found 499.2.



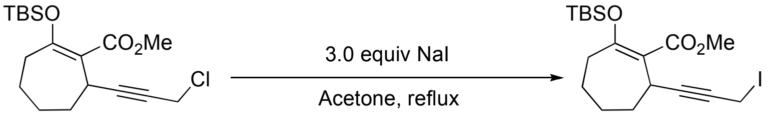
12b **16b**

Methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)cyclohex-1-enecarboxylate (16b). The title compound was prepared according to General Procedure **B** using methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)cyclohex-1-enecarboxylate (**12b**) (0.440 g, 1.28 mmol) and sodium iodide (0.500 g, 3.34 mmol) with stirring for 3.5 hours at 60 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)cyclohex-1-enecarboxylate (**16b**) (0.470 g, 1.08 mmol, 85% yield) as a pale yellow oil after flash chromatography with 5% diethyl ether/hexanes. The product solidifies to yield a yellow solid upon standing at –30 °C. Analytical data for **16b**: mp 32-33 °C; **IR** (thin film, cm^{-1}) 2948, 2935, 2858, 1719, 1690, 1625, 1436, 1376, 1266, 1250, 1206, 1187, 1156, 1138, 1082, 1061, 917; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.70-3.60 (m, 1H), 3.66 (s, 2H), 2.25-2.05 (m, 2H), 1.95-1.80 (m, 2H), 1.75-1.65 (m, 1H), 1.62-1.50 (m, 1H), 0.91 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 159.9, 109.4, 88.6, 77.1, 51.2, 31.8, 28.2, 28.1, 25.6, 19.3, 18.3, -3.7, -3.8, -16.7; TLC (10% Et_2O/hexanes) R_f 0.40; **LRMS** (ESI) Calcd. for $C_{17}H_{27}IO_3Si$+Na 457.1, Found 457.2.



12c **16c**

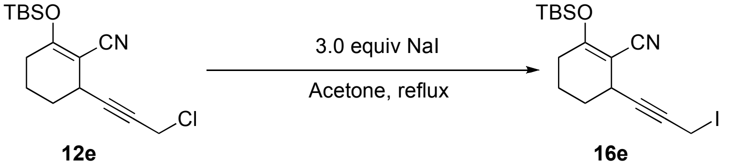
Methyl 2-(tert-butyldimethylsilyloxy)-5-(3-iodoprop-1-ynyl)cyclopent-1-enecarboxylate (16c). The title compound was prepared according to General Procedure **B** using methyl 2-(*tert*-butyldimethylsilyloxy)-5-(3-chloroprop-1-ynyl)cyclopent-1-enecarboxylate (**12c**) (0.132 g, 0.40 mmol) and sodium iodide (0.180 g, 1.20 mmol) with stirring for 1 hour at 60 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-5-(3-iodoprop-1-ynyl)cyclopent-1-enecarboxylate (**16c**) (0.129 g, 0.31 mmol, 77% yield) as a pale yellow oil after flash chromatography with 7.5% diethyl ether/hexanes. Analytical data for **16c**: **IR** (thin film, cm^{-1}) 2949, 2899, 2856, 1702, 1625, 1463, 1440, 1390, 1254, 1231, 1193, 1150, 1131, 1050, 938, 842, 811, 784; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.70 (d, *J* = 3.2 Hz, 2H), 3.72-3.62 (m, 1H), 3.68 (s, 3H), 2.64 (dt, *J* = 16.9, 7.5 Hz, 1H), 2.32 (ddd, *J* = 16.4, 9.2, 3.3 Hz, 1H), 2.20-2.05 (m, 1H), 1.92.1.83 (m, 1H), 0.95 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.1, 164.3, 109.0, 88.5, 77.2, 50.6, 34.4, 33.3, 27.5, 25.4, 18.2, -4.0, -4.1, -16.8; TLC (7.5% Et_2O/hexanes) R_f 0.28; **LRMS** (ESI) Calcd. for $C_{16}H_{25}IO_3Si$+Na 443.1, Found 443.1.



12d **16d**

(Z)-Methyl 2-(*tert*-butyldimethylsilyloxy)-7-(3-iodoprop-1-ynyl)cyclohept-1-enecarboxylate (16d). The title compound was prepared according to General Procedure **B** using methyl 2-(*tert*-butyldimethylsilyloxy)-7-(3-chloroprop-1-ynyl)cyclohept-1-enecarboxylate (**12d**) (0.385 g, 1.08 mmol) and sodium iodide (0.504 g, 3.36 mmol) with stirring for 4 hours at 60 °C to yield methyl 2-(*tert*-butyldimethylsilyloxy)-7-(3-iodoprop-

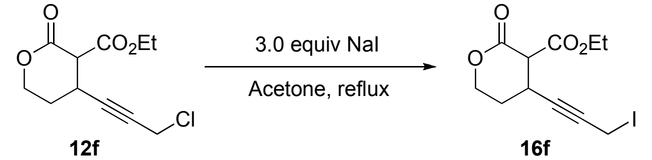
1-ynyl)cyclohept-1-enecarboxylate (**16d**) (0.405 g, 0.90 mmol, 84% yield) as a pale yellow oil after flash chromatography with 5% ethyl acetate/hexanes. Analytical data for **16d**: **IR** (thin film, cm^{-1}) 2934, 2860, 1718, 1683, 1613, 1463, 1436, 1378, 1285, 1258, 1200, 1154, 1092, 1051, 1019, 872, 842, 811, 784, 737; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 6.0, 2.3 Hz, 1H), 3.73 (d, *J* = 2.2 Hz, 2H), 3.68 (s, 3H), 3.08 (dd, *J* = 14.0, 12.2 Hz, 1H), 2.15 (dd, *J* = 14.9, 7.8 Hz, 1H), 2.10-1.70 (m, 4H), 1.53 (tt, *J* = 13.4, 2.5 Hz, 1H), 1.50-1.30 (m, 1H), 0.93 (s, 9H), 0.15 (s, 3H), 0.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 167.1, 113.5, 86.8, 79.3, 51.3, 36.3, 31.3, 29.2, 26.4, 25.6, 24.6, 18.2, -3.8, -4.0, -16.7; TLC (5% EtOAc/hexanes) R_f 0.30; **LRMS** (ESI) Calcd. for $C_{18}H_{29}IO_3Si$+H 449.1, Found 449.2.



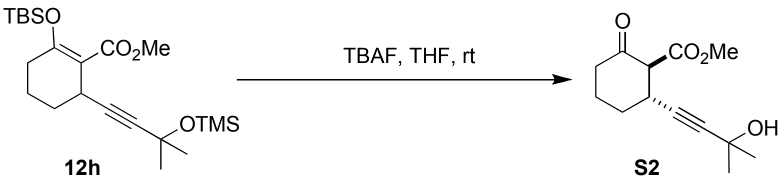
12e **16e**

2-(*tert*-Butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)cyclohex-1-enecarbonitrile (16e). The title compound was prepared according to General Procedure **B** using 2-(*tert*-butyldimethylsilyloxy)-6-(3-chloroprop-1-ynyl)cyclohex-1-enecarbonitrile (**12e**) (0.500 g, 1.60 mmol) and sodium iodide (0.726 g, 4.80 mmol) with stirring for 1 hour at 60 °C to yield 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)cyclohex-1-enecarbonitrile (**16e**) (0.530 g, 1.30 mmol, 83% yield) as a pale yellow oil after flash chromatography with 10% diethyl ether/hexanes. The product was used immediately, as it was found to be unstable even at –30 °C. Analytical data for **16e**: **IR** (thin film, cm^{-1}) 2952, 2927, 2856, 2211, 1625, 1461, 1370, 1258, 1156, 1073, 969, 932, 841, 828, 785; **^{1}H NMR** (400 MHz,

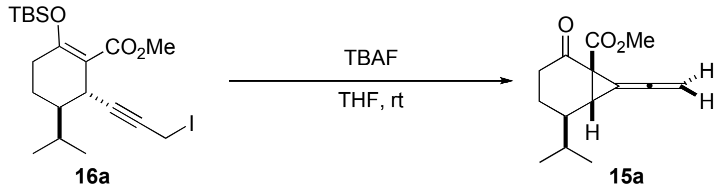
$CDCl_3$) δ 3.72 (d, *J* = 2.2 Hz, 2H), 3.36 (br s, 1H), 2.25-2.08 (m, 2H), 1.95-1.85 (m, 1H), 1.80-1.66 (m, 3H), 0.98 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 117.6, 91.4, 85.4, 79.0, 30.4, 28.6, 28.0, 25.3, 19.4, 17.9, -3.8, -3.8, -18.1; TLC (10% Et_2O/hexanes) R_f 0.33; **LRMS** (ESI) Calcd. for $C_{16}H_{24}INOSi$+H 402.1, Found 402.1.



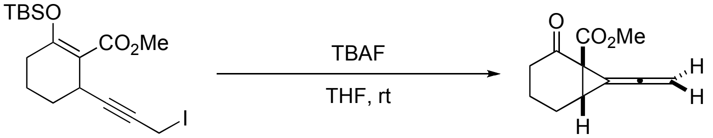
Ethyl 4-(3-iodoprop-1-ynyl)-2-oxotetrahydro-2H-pyran-3-carboxylate (16f). The title compound was prepared according to General Procedure **B** using ethyl 4-(3-chloroprop-1-ynyl)-2-oxotetrahydro-2H-pyran-3-carboxylate (**12f**) (0.085 g, 0.35 mmol) and sodium iodide (0.156 g, 1.04 mmol) with stirring for 45 minutes at 60 °C to yield ethyl 4-(3-iodoprop-1-ynyl)-2-oxotetrahydro-2H-pyran-3-carboxylate (**16f**) (0.058 g, 0.17 mmol, 49% yield) as a pale yellow oil after flash chromatography with 35% ethyl acetate/hexanes. Analytical data for **16f**: **IR** (thin film, cm^{-1}) 2984, 2930, 1725, 1475, 1444, 1409, 1370, 1336, 1262, 1177, 1073, 1031, 942; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.47 (ddd, *J* = 11.4, 6.8, 4.5 Hz, 1H), 4.36 (ddd, *J* = 11.6, 7.6, 4.1 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.64 (d, *J* = 1.6 Hz, 2H), 3.54 (d, *J* = 8.0 Hz, 1H), 3.45-3.35 (m, 1H), 2.26-2.16 (m, 1H), 1.94 (dddd, *J* = 13.9, 7.6, 7.2, 4.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.3, 165.3, 83.4, 81.0, 67.6, 62.3, 53.0, 27.6, 27.2, 14.1, -19.5; TLC (35% EtOAc/hexanes) R_f 0.38; **LRMS** (ESI) Calcd. for $C_{11}H_{13}IO_4$+Na 359.0, Found 359.1.



Methyl 2-(3-hydroxy-3-methylbut-1-ynyl)-6-oxocyclohexanecarboxylate (S2). A vial equipped with a magnetic stir bar was charged with methyl 2-(tert-butyldimethylsilyloxy)-6-(3-methyl-3-(trimethylsilyloxy)but-1-ynyl)cyclohex-1-enecarboxylate (**12h**) (0.460 g, 1.08 mmol) and degassed tetrahydrofuran (3 mL). A tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 3.25 mL, 3.25 mmol) was then added at once, and the solution was stirred for 30 minutes at room temperature. The reaction mixture was poured into deionized water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layer was washed with deionized water (2 x 10 mL), saturated aqueous sodium chloride solution (1 x 10 mL), dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with 30%→40% ethyl acetate/hexanes to yield a 1:1 mixture of the keto and enol forms of the title compound (0.221 g, 0.93 mmol, 86%) as a clear, colorless oil. Analytical data for **S2**: **IR** (thin film, cm^{-1}) 2935, 2873, 1739, 1715, 1653, 1444, 1383, 1274, 1220, 1174, 1066, 958, 826, 726; **^{1}H NMR** (400 MHz, $CDCl_3$), 1:1 enol:keto δ 12.21 (br s, 1H), 3.74-3.67 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.46-3.41 (m, 1H), 3.35 (dd, J = 9.5, 0.9 Hz, 1H), 3.14 (td, J = 9.5, 3.4 Hz, 1H), 2.45-2.15 (m, 4H), 2.10-1.60 (m, 8H), 1.53 (tdd, J = 12.9, 5.2, 2.7 Hz, 1H), 1.40 (s, 6H), 1.39 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$, 1:1 keto:enol) δ 203.6, 172.8, 172.2, 168.9, 99.1, 88.3, 84.7, 84.6, 81.2, 65.0, 64.7, 62.2, 52.1, 51.3, 40.4, 32.9, 31.6, 31.3, 29.4, 28.8, 28.7, 24.9, 23.9, 18.1; TLC (25% EtOAc/hexanes) R_f 0.14; **LRMS** (ESI) Calcd. for $C_{13}H_{18}O_4$+K 277.1, Found 277.1.

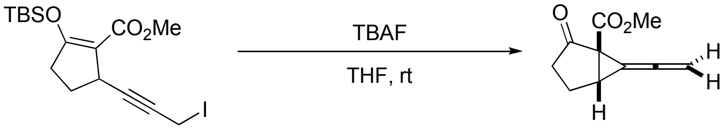


Methyl 5-isopropyl-2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (15a). The title compound was prepared according to General Procedure **C** using *trans*-methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)-5-isopropylcyclohex-1-enecarboxylate (**16a**) (0.099 g, 0.21 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.23 mL, 0.23 mmol) to yield methyl 5-isopropyl-2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**15a**) (0.045 g, 0.19 mmol, 92% yield) as a clear, colorless oil after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for **15a**: **IR** (thin film, cm^{-1}) 2958, 2875, 2021, 1742, 1698, 1463, 1451, 1435, 1389, 1369, 1347, 1328, 1307, 1273, 1232, 1200, 1178, 1137, 1065, 1025, 981, 942, 853, 777; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.16 (dd, J = 11.2, 4.4 Hz, 1H), 5.10 (dd, J = 10.8, 4.4 Hz, 1H), 3.70 (s, 3H), 2.94 (br s, 1H), 2.37-2.10 (m, 2H), 1.97-1.55 (m, 4H), 1.02 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 193.7, 167.7, 85.6, 82.5, 52.7, 43.1, 39.2, 35.1, 34.3, 29.9, 22.7, 20.7, 20.7; TLC (10% EtOAc/petroleum ether) R_f 0.16; **Anal.** Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.96; H, 7.67.



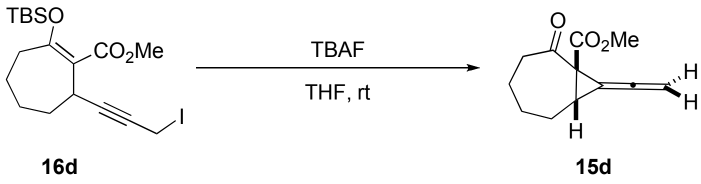
16b **15b**

Methyl 2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (15b). The title compound was prepared according to General Procedure **C** using methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)cyclohex-1-enecarboxylate (**16b**) (0.101 g, 0.23 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.28 mL, 0.28 mmol) to yield methyl 2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**15b**) (0.037 g, 0.19 mmol, 83% yield) as a clear, colorless oil after flash chromatography with 50% diethyl ether/hexanes. Analytical data for **15b**: **IR** (thin film, cm^{-1}) 2952, 2018, 1740, 1698, 1457, 1436, 1339, 1326, 1304, 1268, 1233, 1169, 1065, 1055, 874, 855; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.21 (dd, *J* = 11.2, 4.4 Hz, 1H), 5.13 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.72 (s, 3H), 2.99 (br s, 1H), 2.43 (dt, *J* = 17.2, 3.6 Hz, 1H), 2.20-2.05 (m, 2H), 2.05-1.90 (m, 1H), 1.78-1.60 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.7, 194.4, 167.9, 82.7, 82.5, 52.7, 42.5, 38.3, 30.4, 31.8, 18.0; TLC (30% EtOAc/hexanes) R_f 0.39; **Anal.** Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.44; H, 6.31.

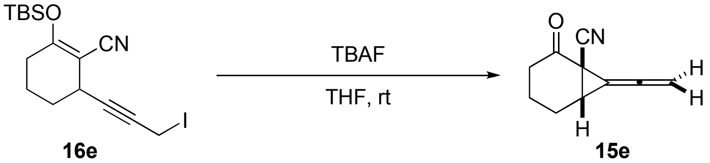


16c **15c**

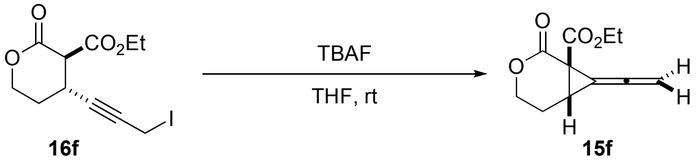
Methyl 2-oxo-6-vinylidenebicyclo[3.1.0]hexane-1-carboxylate (15c). The title compound was prepared according to General Procedure **C** using methyl 2-(*tert*-butyldimethylsilyloxy)-5-(3-iodoprop-1-ynyl)cyclopent-1-enecarboxylate (**16c**) (0.050 g, 0.12 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.14 mL, 0.14 mmol) to yield methyl 2-oxo-6-vinylidenebicyclo[3.1.0]hexane-1-carboxylate (**15c**) (0.011 g, 0.06 mmol, 53% yield) as a clear, colorless oil after flash chromatography with 50% diethyl ether/hexanes. Analytical data for **15c**: **IR** (thin film, cm^{-1}) 2954, 2018, 1752, 1735, 1437, 1412, 1374, 1302, 1246, 1208, 1173, 1079, 1038, 1015, 872, 855, 733; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.24 (dd, *J* = 11.6, 4.0 Hz, 1H), 5.15 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.74 (s, 3H), 3.37 (br q, *J* = 4.0 Hz, 1H), 2.50-2.35 (m, 1H), 2.33-2.15 (m, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 203.2, 193.0, 166.0, 85.9, 83.3, 52.4, 43.5, 35.3, 33.6, 21.9; TLC (30% EtOAc/hexanes) R$_f$ 0.31; **Anal.** Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.20; H, 5.75.



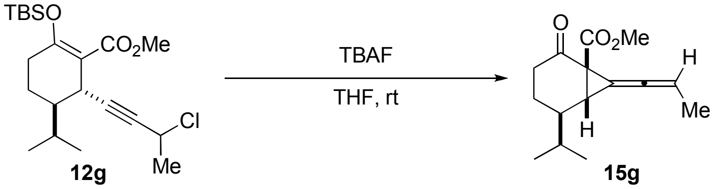
Methyl 2-oxo-8-vinylidenebicyclo[5.1.0]octane-1-carboxylate (15d). The title compound was prepared according to General Procedure **C** using methyl 2-(*tert*-butyldimethylsilyloxy)-7-(3-iodoprop-1-ynyl)cyclohept-1-enecarboxylate (**16d**) (0.079 g, 0.18 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.19 mL, 0.19 mmol) to yield methyl 2-oxo-8-vinylidenebicyclo[5.1.0]octane-1-carboxylate (**15d**) (0.011 g, 0.06 mmol, 53% yield) as a clear, colorless oil after flash chromatography with 20% ethyl acetate/hexanes. Analytical data for **15d**: **IR** (thin film, cm^{-1}) 2934, 2860, 2023, 1710, 1436, 1320, 1285, 1247, 1177, 1085, 996, 926, 849, 772; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.17 (dd, *J* = 11.2, 4.8 Hz, 1H), 5.13 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.74 (s, 3H), 2.78 (m, 1H), 2.60 (m, 2H), 2.28-2.18 (m, 1H), 1.76-1.43 (m, 5H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 202.7, 194.1, 168.6, 86.7, 81.7, 52.7, 46.3, 42.4, 29.7, 28.5, 25.3, 24.8; TLC (30% EtOAc/hexanes) R$_f$ 0.55; **Anal.** Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.61; H, 6.92.



2-Oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carbonitrile (15e). The title compound was prepared according to General Procedure **C** using 2-(*tert*-butyldimethylsilyloxy)-6-(3-iodoprop-1-ynyl)cyclohex-1-enecarbonitrile (**16e**) (0.168 g, 0.42 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.50 mL, 0.50 mmol) to yield 2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carbonitrile (**15e**) (0.036 g, 0.16 mmol, 38% yield) as a colorless solid after flash chromatography with 40% ethyl acetate/hexanes. Analytical data for **15e**: mp 108-109 °C; **IR** (thin film, cm^{-1}) 2952, 2939, 2925, 2242, 2018, 1702, 1493, 1480, 1461, 1443, 1378, 1331, 1293, 1266, 1102, 1071, 1055, 872; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.43 (dd, *J* = 12.0, 4.5 Hz, 1H), 5.34 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.24-3.19 (m, 1H), 2.53 (dt, *J* = 19.2, 4.0 Hz, 1H), 2.27-2.13 (m, 2H), 2.06-1.96 (m, 1H), 1.83-1.75 (m, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 195.9, 194.6, 116.3, 85.2, 82.7, 36.3, 32.2, 30.3, 21.5, 17.2; TLC (30% EtOAc/hexanes) R$_f$ 0.33; **Anal.** Calcd. for $C_{10}H_9NO_3$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.63; N, 8.88.

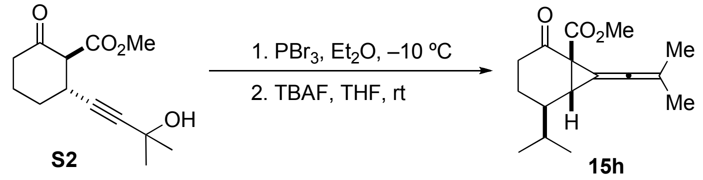


Ethyl 2-oxo-7-vinylidene-3-oxabicyclo[4.1.0]heptane-1-carboxylate (15f). The title compound was prepared according to General Procedure **C** using ethyl 4-(3-iodoprop-1-ynyl)-2-oxotetrahydro-2H-pyran-3-carboxylate (**16f**) (0.054 g, 0.16 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.32 mL, 0.32 mmol) to yield ethyl 2-oxo-7-vinylidene-3-oxabicyclo[4.1.0]heptane-1-carboxylate (**15f**) (0.013 g, 0.06 mmol, 39% yield) as a colorless oil after flash chromatography with 40% ethyl acetate/hexanes. Analytical data for **15f**: **IR** (thin film, cm^{-1}) 2952, 2018, 1740, 1698, 1457, 1436, 1339, 1326, 1304, 1268, 1233, 1169, 1065, 1055, 874, 855; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.32 (dd, *J* = 11.6, 4.0 Hz, 1H), 5.25 (dd, *J* = 11.8, 4.2 Hz, 1H), 4.34-4.24 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.07 (br s, 1H), 2.27 (dddd, *J* = 14.4, 11.6, 5.8, 3.0 Hz, 1H), 2.13 (dq, *J* = 14.4, 2.4 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.2, 165.6, 164.0, 83.3, 80.7, 64.9, 62.0, 35.8, 27.7, 21.2, 13.9; TLC (40% EtOAc/hexanes) R$_f$ 0.30; **LRMS** (ESI) Calcd. for $C_{11}H_{12}O_4$+Na 231.1, Found 231.1.

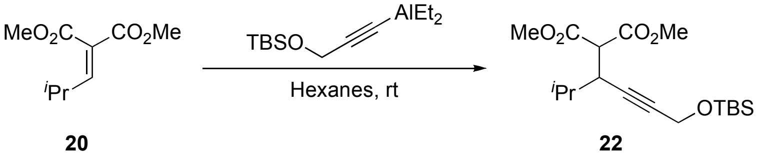


Methyl 2-oxo-7-(prop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (15g). A round bottom flask equipped with a magnetic stir bar was charged with methyl 2-(*tert*-butyldimethylsilyloxy)-6-(3-chlorobut-1-ynyl)cyclohex-1-enecarboxylate (**12g**) (0.169 g, 0.47 mmol) and degassed tetrahydrofuran (20.0 mL). A tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 0.94 mL, 0.94 mmol) was then added at once. The solution was stirred for 9 hours at room temperature, after which the solution was concentrated to ~5 mL under reduced pressure. The residue was diluted with diethyl ether (15 mL), and passed through a 1 inch silica plug, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with 30% ethyl acetate/hexanes to yield methyl 2-oxo-7-(prop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (**15g**) (0.080 g, 0.39 mmol, 69%) as a clear, colorless oil that slowly solidifies to a colorless solid. Analytical data for **15g**: mp 57-66 °C; **IR** (thin film, cm^{-1}) 2950, 2916, 2856, 2256, 2012, 1740, 1698, 1457, 1436, 1326, 1285, 1260, 1246, 1227, 1065, 978, 951, 938, 917, 870, 789, 731, 648; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.58 (dd, J = 7.2, 4.0 Hz, 1H), 5.51 (dd, J = 7.2, 4.0 Hz, 1H), 3.69 (s, 6H), 2.94-2.89 (m, 2H), 2.40 (dt, J = 3.5, 17.3 Hz, 2H), 2.19-2.02 (m, 4H), 1.99-1.88 (m, 2H), 1.78-1.64 (m, 4H), 1.74 (d, J = 7.2 Hz, 3H), 1.72 (d, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 199.0, 198.9, 190.6, 190.5, 168.1, 168.0, 94.5, 83.6, 83.5, 52.5, 42.2, 42.0, 38.3, 38.2, 29.8, 29.7, 21.8, 21.7, 18.0, 18.0, 14.7, 14.5; TLC (30%

EtOAc/hexanes) R_f 0.32; **Anal.** Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.94; H, 6.84.

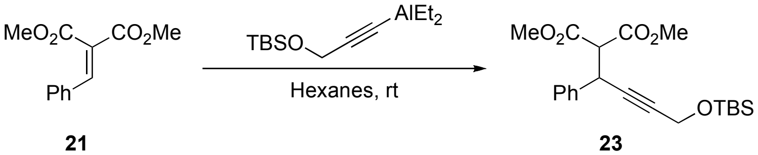


Methyl 7-(2-methylprop-1-enylidene)-2-oxobicyclo[4.1.0]heptane-1-carboxylate (15h). A flame-dried vial equipped with a magnetic stir bar was charged with methyl 2-(3-hydroxy-3-methylbut-1-ynyl)-6-oxocyclohexanecarboxylate (**S2**) (0.2.05 g, 0.86 mmol), anhydrous diethyl ether (10.0 mL), and cooled to –10 °C. Phosphorous tribromide (0.041 mL, 0.43 mmol) was added at once and the reaction was stirred for 22 hours at –10 °C. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (1 x 10 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure to leave a yellow oil. The residue was immediately dissolved in anhydrous tetrahydrofuran (5.0 mL). A tetrahydrofuran solution of tetrabutylammonium fluoride (2.0 mL, 2.0 mmol) was added at once and the reaction was stirred at room temperature for 45 minutes. The solution was concentrated to ~5 mL under reduced pressure. The residue was then diluted with diethyl ether (15 mL), and passed through a 1 inch silica plug, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with 25% ethyl acetate/hexanes to the yield the title compound (0.043 g, 0.20 mmol, 23% from alcohol) as a clear, colorless oil. Analytical data for **15h**: **IR** (thin film, cm^{-1}) 2935, 2858, 2021, 1745, 1699, 1437, 1321, 1282, 1236, 1159, 1066; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 2.91 (dd, J = 3.1, 2.7 Hz, 1H), 2.42 (dt, J = 17.2, 3.7 Hz, 1 Hz), 2.17-2.05 (m, 2H), 1.99-1.87 (m, 1H), 1.79-1.67 (m, 2H), 1.78 (s, 3H), 1.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.2, 187.5, 168.3, 105.2, 83.0, 52.4, 42.1, 38.3, 29.4, 21.9, 20.9, 20.7, 18.2; TLC (25% EtOAc/hexanes) R_f 0.31; **LRMS** (ESI) Calcd. for $C_{13}H_{16}O_3$+H 221.1, Found 221.1.

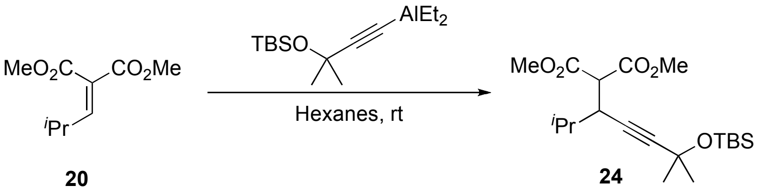


Dimethyl 2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-4-yn-3-yl)propanedioate (22). The title compound was prepared according to General Procedure **D** using dimethyl 2-(2-methylpropylidene)propanedioate[58] (**20**) (2.40 g, 12.88 mmol), *tert*-butyldimethyl(prop-2-ynyloxy)silane[59] (3.06 g, 17.97 mmol), *n*-butyllithium (1.5 M in hexanes, 11.10 mL, 16.70 mmol), and diethylaluminum chloride (1.0 M in hexanes, 16.70 mL, 16.70 mmol) to yield dimethyl 2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-4-yn-3-yl)propanedioate (**22**) (2.97 g, 8.33 mmol, 65% yield) as a clear, yellow oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **22**: **IR** (thin film, cm^{-1}) 2962, 2935, 2860, 1760, 1744, 1465, 1436, 1372, 1324, 1258, 1196, 1164, 1146, 1109, 1088, 1067, 837, 780, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.26 (d, *J* = 1.9 Hz, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.52 (d, *J* = 10.9 Hz, 1H), 3.16 (ddt, *J* = 10.9, 3.6, 1.8

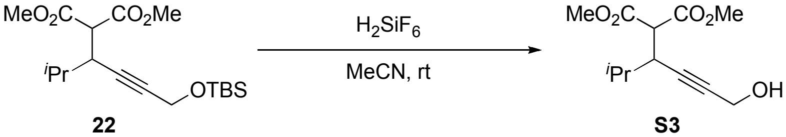
Hz, 1H), 1.70 (dsept, *J* = 6.7, 3.7 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 167.9, 167.9, 83.1, 81.5, 54.8, 52.6, 52.5, 51.6, 38.7, 28.9, 25.7, 21.6, 18.1, 16.8, -5.3; TLC (10% EtOAc/hexanes) R$_f$ 0.26; **LRMS** (ESI) Calcd. for $C_{18}H_{32}O_5Si$+H 356.2, Found 356.3.



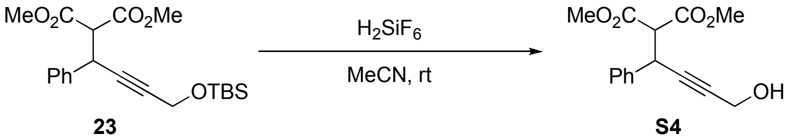
Dimethyl 2-(4-(*tert*-butyldimethylsilyloxy)-1-phenylbut-2-ynyl)propanedioate (23). The title compound was prepared according to General Procedure **D** using dimethyl 2-benzylidenepropanedioate (**21**) (1.00 g, 4.54 mmol), *tert*-butyldimethyl(prop-2-ynyloxy)silane[59] (0.928 g, 5.45 mmol), *n*-butyllithium (1.5 M in hexanes, 3.33 mL, 5.00 mmol), and diethylaluminum chloride (1.0 M in hexanes, 5.00 mL, 5.00 mmol) to yield dimethyl 2-(4-(*tert*-butyldimethylsilyloxy)-1-phenylbut-2-ynyl)propanedioate (**23**) (1.43 g, 3.66 mmol, 81% yield) as a clear, yellow oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **23**: **IR** (thin film, cm^{-1}) 2956, 2931, 2887, 2858, 1744, 1455, 1436, 1331, 1316, 1254, 1194, 1142, 1084, 837, 782, 735, 700; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.40-7.24 (m, 5H), 4.44 (dt, *J* = 10.6, 1.9 Hz, 1H), 4.32 (d, *J* = 2.0 Hz, 2H), 3.81 (d, *J* = 10.6 Hz, 1H), 3.80 (s, 3H), 3.52 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 167.3, 166.9, 137.7, 128.5, 128.3, 128.1, 127.6, 83.1, 82.8, 59.0, 52.7, 52.4, 51.7, 37.7, 25.7, 18.2, -5.3; TLC (30% EtOAc/hexanes) R$_f$ 0.36; **LRMS** (ESI) Calcd. for $C_{21}H_{30}O_5Si$+H 391.2, Found 391.3.


MeO2C
CO2Me
iPr
20
TBSO
AlEt2
Hexanes, rt
MeO2C
CO2Me
iPr
OTBS
24

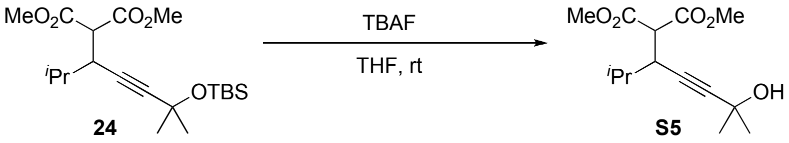
Dimethyl 2-(6-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-yn-3-yl)propanedioate (24). The title compound was prepared according to General Procedure **D** using dimethyl 2-(2-methylpropylidene)propanedioate[58] (**20**) (2.40 g, 12.89 mmol), *tert*-butyldimethyl(2-methylbut-3-yn-2-yloxy)silane[60] (3.57 g, 18.00 mmol), *n*-butyllithium (1.5 M in hexanes, 11.10 mL, 16.70 mmol), and diethylaluminum chloride (1.0 M in hexanes, 16.70 mL, 16.70 mmol) to yield dimethyl 2-(6-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-yn-3-yl)propanedioate (**24**) (4.16 g, 10.82 mmol, 84% yield) as a clear, pale yellow oil after flash chromatography with 7.5% ethyl acetate/hexanes. Analytical data for **24**: **IR** (thin film, cm^{-1}) 2923, 2850, 1764, 1744, 1434, 1358, 1324, 1245, 1194, 1164, 1044, 913, 837, 810, 778, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.73 (s, 3H), 3.52 (d, *J* = 11.1 Hz, 1H), 3.17 (dd, *J* = 11.0, 3.6 Hz, 1H), 1.72 (dsept, *J* = 6.7, 3.6 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 9H), 0.12 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.9, 90.1, 79.2, 66.2, 54.9, 52.6, 52.5, 38.6, 33.3, 28.9, 25.6, 21.7, 17.8, 16.8, -3.1; TLC (15% EtOAc/hexanes) R_f 0.55; **LRMS** (ESI) Calcd. for $C_{20}H_{36}O_5Si$+H 407.2, Found 407.3.


MeO2C
CO2Me
iPr
OTBS
22
H2SiF6
MeCN, rt
MeO2C
CO2Me
iPr
OH
S3

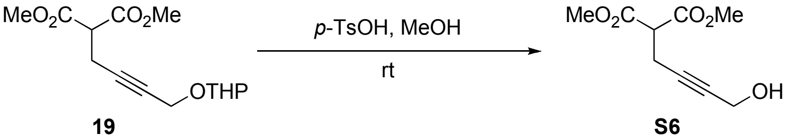
Dimethyl 2-(6-hydroxy-2-methylhex-4-yn-3-yl)propanedioate (S3). The title compound was prepared according to General Procedure **E** using dimethyl 2-(6-(*tert*-butyldimethylsilyloxy)-2-methylhex-4-yn-3-yl)propanedioate (**22**) (1.900 g, 5.33 mmol) and fluorosilicic acid (25% in H_2O, 0.51 mL, 1.07 mmol) to yield dimethyl 2-(6-hydroxy-2-methylhex-4-yn-3-yl)propanedioate (**S3**) (1.087 g, 4.49 mmol, 85% yield) as a clear, pale yellow oil after flash chromatography with 30%→40% ethyl acetate/hexanes. Analytical data for **S3**: **IR** (thin film, cm^{-1}) 3435, 2964, 2873, 1739, 1436, 1355, 1326, 1264, 1196, 1148, 1106, 1077, 1023, 978, 913, 839, 796, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 5.5, 1.9 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.51 (d, *J* = 10.5 Hz, 1H), 3.13 (ddt, *J* = 3.8, 1.9 Hz, 1H), 2.48 (d, *J* = 5.4 Hz, 1H), 1.70 (dsept, *J* = 6.6, 4.1 Hz, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 167.8, 82.9, 82.4, 54.6, 52.7, 52.7, 50.8, 38.6, 28.8, 21.5, 16.9; TLC (30% EtOAc/hexanes) R_f 0.20; **LRMS** (ESI) Calcd. for $C_{12}H_{18}O_5$+Na 265.1, Found 265.2.



Dimethyl 2-(4-hydroxy-1-phenylbut-2-ynyl)propanedioate (S4). The title compound was prepared according to General Procedure **E** using dimethyl 2-(4-(*tert*-butyldimethylsilyloxy)-1-phenylbut-2-ynyl)propanedioate (**23**) (1.32 g, 3.38 mmol) and fluorosilicic acid (25% in H_2O, 0.31 mL, 0.68 mmol) to yield dimethyl 2-(4-hydroxy-1-phenylbut-2-ynyl)propanedioate (**S4**) (0.90 g, 3.25 mmol, 95% yield) as a clear, pale yellow oil after flash chromatography with 30%→40% ethyl acetate/hexanes. Analytical data for **S4**: **IR** (thin film, cm^{-1}) 3435, 3031, 2954, 1756, 1739, 1495, 1455, 1436, 1333, 1316, 1272, 1250, 1196, 1158, 1025, 756, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 4.43 (dt, *J* = 10.2, 1.8 Hz, 1H), 4.24 (dd, *J* = 5.8, 1.9 Hz, 2H), 3.79 (d, *J* = 10.2 Hz, 1H), 3.77 (s, 3H), 3.51 (s, 3H), 2.20 (t, *J* = 5.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 167.0, 137.5, 128.6, 128.1, 127.8, 84.1, 82.6, 58.9, 52.8, 52.5, 51.0, 37.7; TLC (40% EtOAc/hexanes) R_f 0.27; **LRMS** (ESI) Calcd. for $C_{15}H_{16}O_5$+Na 299.1, Found 299.2.

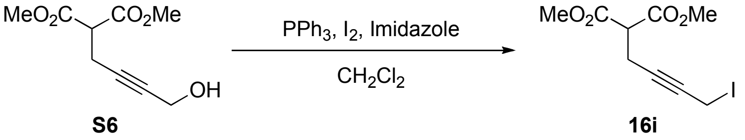


Dimethyl 2-(6-hydroxy-2,6-dimethylhept-4-yn-3-yl)propanedioate (S5). A round bottom flask equipped with a magnetic stir bar was charged with dimethyl 2-(6-(*tert*-butyldimethylsilyloxy)-2,6-dimethylhept-4-yn-3-yl)propanedioate (**24**) (2.00 g, 5.20 mmol) and degassed tetrahydrofuran (25 mL). A tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 15.6 mL, 15.6 mmol) was then added at once, and the solution was stirred for 24 hours at room temperature. The reaction mixture was poured into deionized water (100 mL) and extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (1 x 25 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography, eluting with 25% ethyl acetate/hexanes to yield the title compound (1.05 g, 3.88 mmol, 75%) as a clear, colorless oil. Analytical data for **S5**: **IR** (thin film, cm^{-1}) 2923, 2850, 1764, 1744, 1434, 1358, 1324, 1245, 1194, 1164, 1044, 913, 837, 810, 778, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.72 (s, 3H), 3.50 (d, *J* = 10.7 Hz, 1H), 3.13 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.32 (br s, 1H), 1.72 (dsept, *J* = 6.7, 3.9 Hz, 1H), 1.45 (s, 6H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.1, 167.9, 89.8, 78.8, 65.0, 54.8, 52.6, 52.6, 38.5, 31.5, 31.5, 28.8, 21.6, 16.9; TLC (30% EtOAc/hexanes) R_f 0.32; **LRMS** (ESI) Calcd. for $C_{14}H_{22}O_5$+Na 293.2, Found 293.2.

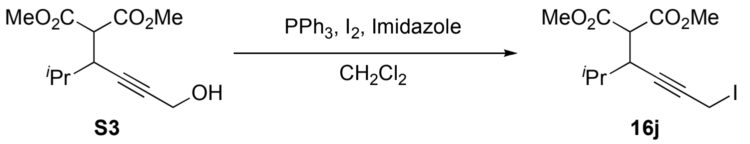


Dimethyl 2-(4-hydroxybut-2-ynyl)propanedioate (S6). A round bottom flask equipped with a magnetic stir bar was charged with dimethyl 2-(4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-ynyl)propanedioate[61] (**19**) (2.98 g, 10.48 mmol) and reagent grade methanol (30 mL). *p*-Toluenesulfonic acid hydrate (0.120 g, 0.63 mmol) was added. An exothermic reaction takes place initially, afterwhich the reaction is stirred at room temperature for 5 hours. A saturated aqueous sodium bicarbonate solution (5 mL) is then added and the solvents are removed under reduced pressure. The residue is taken up in dichloromethane (50 mL) and washed successively with a saturated aqueous sodium bicarbonate solution (1 x 10 mL) and a saturated aqueous sodium chloride solution (1 x 10 mL). The organic layer is dried with sodium sulfate, and the solvents are removed under reduced pressure. The residue was purified via flash chromatography, eluting with 40% ethyl acetate/hexanes to yield the title compound (2.02 g, 10.09 mmol, 96%) as a clear, pale yellow oil. Analytical data for **S6**: **IR** (thin film, cm^{-1}) 3423, 3006, 2958, 2871, 1750,

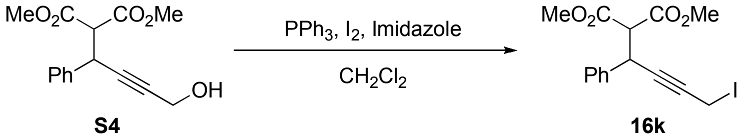
1739, 1437, 1347, 1283, 1243, 1202, 1160, 1138, 1069, 1021, 974, 917, 849; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 4.11 (br s, 2H), 3.69 (s, 6H), 3.52 (t, *J* = 7.7 Hz, 1H), 2.93 (br s, 1H), 2.73 (dt, *J* = 7.7, 2.1 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 168.3, 80.9, 80.6, 52.7, 50.7, 50.5, 18.5; TLC (40% EtOAc/hexanes) R$_f$ 0.26; **LRMS** (ESI) Calcd. for $C_9H_{12}O_5$+Na 223.1, Found 223.1.



Dimethyl 2-(4-iodobut-2-ynyl)propanedioate (16i). The title compound was then prepared according to General Procedure **F** using dimethyl 2-(4-hydroxybut-2-ynyl)propanedioate (**S6**) (0.961 g, 4.80 mmol), triphenylphosphine (1.76 g, 6.72 mmol), imidazole (0.46 g, 6.72 mmol, and iodine (1.70, 6.72 mmol) to yield dimethyl 2-(4-iodobut-2-ynyl)propanedioate (**16i**) (1.460 g, 4.71 mmol, 98% yield) as a clear, yellow oil after flash chromatography with 20% ethyl acetate/hexanes. Analytical data for **16i**: **IR** (thin film, cm^{-1}) 3006, 2956, 2846, 1752, 1737, 1436, 1345, 1281, 1241, 1194, 1171, 1069, 1030; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 3.76 (s, 3H), 3.62 (t, *J* = 2.4 Hz, 2H), 3.56 (t, *J* = 7.7 Hz, 1H), 2.78 (dt, *J* = 7.7, 2.4 Hz, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 168.2, 81.4, 79.2, 52.8, 50.5, 19.1, -18.3; TLC (40% EtOAc/hexanes) R$_f$ 0.50; **LRMS** (ESI) Calcd. for $C_9H_{11}IO_4$+Na 333.0, Found 333.0.

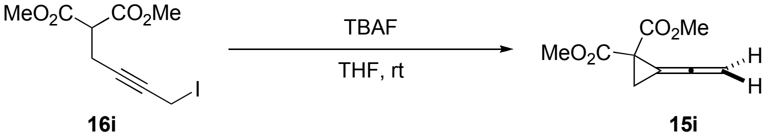


Dimethyl 2-(6-iodo-2-methylhex-4-yn-3-yl)propanedioate (16j). The title compound was prepared according to General Procedure **F** using dimethyl 2-(6-hydroxy-2-methylhex-4-yn-3-yl)propanedioate (**S3**) (0.987 g, 4.07 mmol), triphenylphosphine (1.50 g, 5.70 mmol), imidazole (0.39 g, 5.70 mmol, and iodine (1.45, 5.70 mmol) to yield dimethyl 2-(6-iodo-2-methylhex-4-yn-3-yl)propanedioate (**16j**) (1.428 g, 4.06 mmol, 99% yield) as a clear, pale yellow oil after flash chromatography with 20% ethyl acetate/hexanes. Analytical data for **16j**: **IR** (thin film, cm^{-1}) 2952, 2873, 1760, 1739, 1725, 1463, 1434, 1389, 1370, 1353, 1324, 1258, 1243, 1194, 1150, 1081, 1023, 980, 913, 733; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 3.77 (s, 3H), 3.72 (s, 3H), 3.66 (d, J = 2.4 Hz, 2H), 3.52 (d, J = 10.7 Hz, 1H), 3.15 (ddt, J = 10.7, 3.8, 2.4 Hz, 1H), 1.77 (dsept, J = 6.7, 3.9 Hz, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 167.9, 167.7, 83.2, 81.2, 54.3, 52.8, 52.7, 38.9, 29.2, 21.6, 16.9, -18.1; TLC (15% EtOAc/hexanes) R$_f$ 0.33; **LRMS** (ESI) Calcd. for $C_{12}H_{17}IO_4$+Na 375.0, Found 375.1.



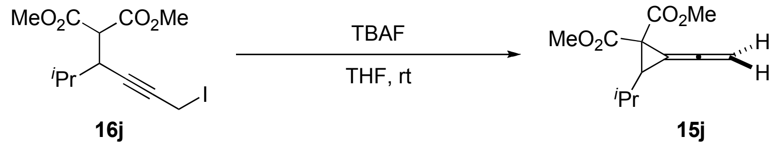
Dimethyl 2-(4-iodo-1-phenylbut-2-ynyl)propanedioate (16k). The title compound was prepared according to General Procedure **F** using dimethyl 2-(4-hydroxy-1-phenylbut-2-

ynyl)propanedioate (**S4**) (1.890 g, 6.84 mmol), triphenylphosphine (3.59 g, 13.69 mmol), imidazole (0.93 g, 13.69 mmol, and iodine (3.47, 13.69 mmol) to yield dimethyl 2-(4-iodo-1-phenylbut-2-ynyl)propanedioate (**16k**) (2.450 g, 6.34 mmol, 93% yield) as a clear, yellow oil after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for **16k**: **IR** (thin film, cm^{-1}) 3064, 3031, 3004, 2954, 1756, 1746, 1495, 1455, 1434, 1331, 1312, 1295, 1270, 1246, 1194, 1165, 1150, 1028, 938, 913, 756, 735, 700; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.21 (m, 5H), 4.43 (dt, *J* = 10.3, 2.0 Hz, 1H), 3.83 (s, 3H), 3.78 (d, *J* = 10.3 Hz, 1H), 3.69 (d, *J* = 2.3 Hz, 2H), 3.54 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 166.8, 137.4, 128.6, 128.1, 127.8, 84.0, 81.1, 58.7, 52.9, 52.3, 37.9, -18.5; TLC (15% EtOAc/hexanes) R_f 0.28; **LRMS** (ESI) Calcd. for $C_{15}H_{15}IO_4$+H 387.0, Found 387.1.

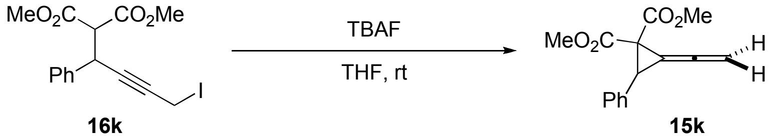


Dimethyl 2-vinylidenecyclopropane-1,1-dicarboxylate (15i). The title compound was prepared according to General Procedure **G** using dimethyl 2-(4-iodobut-2-ynyl)propanedioate (**16i**) (0.521 g, 1.68 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 3.36 mL, 3.36 mmol) to yield dimethyl 2-vinylidenecyclopropane-1,1-dicarboxylate (**15i**) (0.195 g, 1.07 mmol, 64% yield) as a clear, colorless oil after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for **15i**: **IR** (thin film, cm^{-1}) 3072, 3002, 2954, 2036, 1739, 1437, 1353, 1314, 1254, 1194, 1111, 1054, 880, 853; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.16 (t, *J* = 5.0 Hz, 2H), 3.72

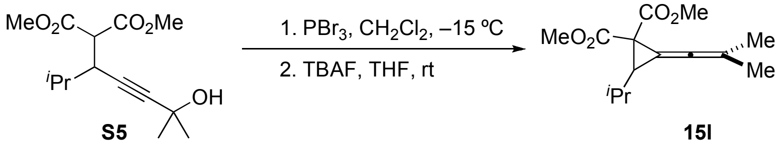
(s, 6H), 2.41 (t, *J* = 5.0 Hz, 2H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 193.2, 167.3, 83.2, 83.0, 52.8, 35.0, 19.8; TLC (15% EtOAc/hexanes) R$_f$ 0.31; **LRMS** (ESI) Calcd. for $C_9H_{10}O_4$+H 183.1, Found 183.1.



Dimethyl 2-isopropyl-3-vinylidenecyclopropane-1,1-dicarboxylate (15j). The title compound was prepared according to General Procedure **G** using dimethyl 2-(6-iodo-2-methylhex-4-yn-3-yl)propanedioate (**16j**) (0.590 g, 1.68 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 3.36 mL, 3.36 mmol) to yield dimethyl 2-isopropyl-3-vinylidenecyclopropane-1,1-dicarboxylate (**15j**) (0.331 g, 1.48 mmol, 88% yield) as a clear, colorless oil after flash chromatography with 15% ethyl acetate/hexanes. Analytical data for **15j**: **IR** (thin film, cm^{-1}) 2962, 2871, 2026, 1737, 1436, 1297, 1281, 1254, 1192, 1142, 1108, 919, 845, 758, 735, 673; ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 5.16 (dd, *J* = 10.9, 5.0 Hz, 1H), 5.10 (dd, *J* = 10.9, 4.9 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.57 (dt, *J* = 10.1, 5.0 Hz, 1H), 1.46 (dsept, *J* = 10.2, 6.7 Hz, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 193.3, 167.9, 166.5, 85.6, 81.9, 52.8, 52.6, 40.8, 39.2, 29.1, 21.8, 21.2; TLC (15% EtOAc/hexanes) R$_f$ 0.38; **LRMS** (ESI) Calcd. for $C_{12}H_{16}O_4$+H 225.1, Found 225.1.

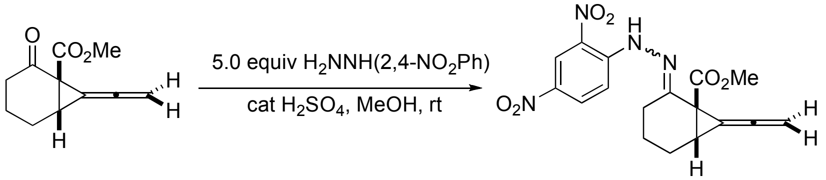


Dimethyl 2-phenyl-3-vinylidenecyclopropane-1,1-dicarboxylate (15k). The title compound was prepared according to General Procedure **G** using dimethyl 2-(4-iodo-1-phenylbut-2-ynyl)propanedioate (**16k**) (0.649 g, 1.68 mmol) and a tetrahydrofuran solution of tetrabutylammonium fluoride (1.0 M, 3.36 mL, 3.36 mmol) to yield dimethyl 2-phenyl-3-vinylidenecyclopropane-1,1-dicarboxylate (**15k**) (0.380 g, 1.32 mmol, 79% yield) as a yellow oil that was ~90% pure by ^{1}H NMR after flash chromatography with 15% ethyl acetate/hexanes on silica that was deactivated prior to use with 5% triethylamine/hexanes. The product decomposes quickly at room temperature. Analytical data for **15k**: **IR** (thin film, cm^{-1}) 3064, 3031, 3008, 2954, 2034, 1729, 1602, 1497, 1451, 1436, 1306, 1291, 1246, 1194, 1106, 1030, 932, 853, 747, 699; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.33-7.23 (m, 5H), 5.42 (dd, *J* = 11.3, 5.0 Hz, 1H), 5.31 (dd, *J* = 11.3, 4.9 Hz, 1H), 4.08 (t, *J* = 4.9 Hz, 1H), 3.82 (s, 3H), 3.37 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 195.2, 167.3, 164.9, 133.0, 128.3, 128.1, 127.8, 84.4, 82.8, 53.0, 52.2, 43.3, 35.6; TLC (15% EtOAc/hexanes) R$_f$ 0.40; **LRMS** (ESI) Calcd. for $C_{15}H_{14}O_4$+Na 281.1, Found 281.1.



Dimethyl 2-isopropyl-3-(2-methylprop-1-enylidene)cyclopropane-1,1-dicarboxylate (15l). A flame-dried round bottom flask equipped with a magnetic stir bar was charged with dimethyl 2-(6-hydroxy-2,6-dimethylhept-4-yn-3-yl)propanedioate (**S5**) (0.400 g, 1.48 mmol), anhydrous diethyl ether (12.0 mL), and cooled to –15 °C. Phosphorous tribromide (0.056 mL, 0.59 mmol) was added at once and the reaction was stirred for 28 hours at –15 °C. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with saturated aqueous sodium chloride solution (1 x 10 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure to leave 0.390 of a yellow oil. The residue was found to consist of 76% dimethyl 2-(6-bromo-2,6-dimethylhept-4-yn-3-yl)propanedioate by mass (0.296 g, 0.89 mmol, 60% yield). The residue was immediately dissolved in anhydrous tetrahydrofuran (36.0 mL). A tetrahydrofuran solution of tetrabutylammonium fluoride (1.78 mL, 1.78 mmol) was added at once and the reaction was stirred at room temperature for 45 minutes. The solution was concentrated to ~5 mL under reduced pressure. The residue was then diluted with diethyl ether (15 mL), and passed through a 1 inch silica plug, eluting with diethyl ether. The solvent was removed under reduced pressure and the residue was purified via flash chromatography, eluting with dichloromethane to the yield the title compound (0.204 g, 0.81 mmol, 91% from bromide) as a clear, colorless oil. Analytical data for **15l**: **IR** (thin film, cm^{-1}) 2958, 2910, 2869, 2020, 1739, 1463, 1436, 1364, 1246, 1192, 1160, 1133, 1094, 1021, 965, 944, 928, 901, 785, 760, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.74 (s, 3H), 2.53 (d, *J* = 10.0 Hz, 1H), 1.84 (s, 3H), 1.79 (s, 3H), 1.46 (dsept, *J* = 10.0, 6.7 Hz, 1H), 1.04 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (100

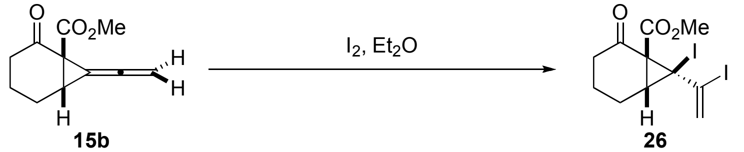
MHz, $CDCl_3$) δ 185.7, 168.6, 167.1, 104.1, 85.8, 52.6, 52.4, 39.7, 38.1, 29.1, 21.8, 21.3, 21.1, 20.8; TLC (CH_2Cl_2) R_f 0.43; **LRMS** (ESI) Calcd. for $C_{14}H_{20}O_4$+H 253.1, Found 253.2.



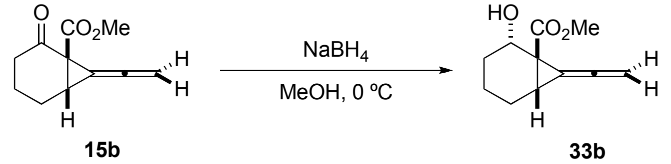
15b **17**

Methyl 2-(2-(2,4-dinitrophenyl)hydrazono)-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (17). A vial equipped with a magnetic stir bar was charged with methyl 2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**15b**) (0.041 g, 0.21 mmol), reagent grade methanol (6.0 mL), and cooled to 0 °C. Then, 2,4-dinitrophenylhydrazine (0.302 g, 1.07 mmol) and sulfuric acid (0.052 g, 0.53 mmol) were added sequentially. The reaction was stirred at 0 °C for 30 minutes, and room temperature for 90 minutes. The reaction was diluted with diethyl ether (15 mL) and run through a 1 inch silica plug, eluting with diethyl ether. The solvents were removed under reduced pressure and the residue was purified by flash chromatography, eluting with 20% ethyl acetate/hexanes to yield the title compound (0.066 g, 0.18 mmol, 84%) in a 1.0:0.7 mixture of isomers as an orange solid. The mixture was recrystallized from 95% aqueous ethanol to obtain crystals suitable for x-ray diffraction. Analytical data for **17**: mp 104-119 °C; **IR** (thin film, cm^{-1}) 3107, 2953, 2872, 2366, 2019, 1729, 1617, 1594, 1505, 1336, 1312, 1278, 1235, 1139, 1112, 1081, 923, 834, 741; **^{1}H NMR** (400 MHz, $CDCl_3$, two diastereomers) δ 11.35 (s, 1H), 11.20 (s, 1H), 9.15-9.10 (m, 2H), 8.33-8.27 (m, 2H), 7.95-7.90 (m, 2H), 5.24-5.18

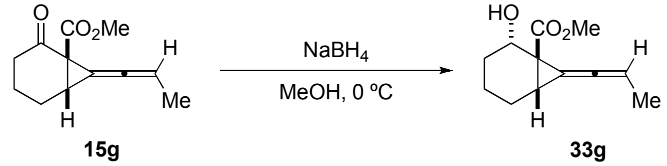
(m, 2H), 5.11 (dd, *J* = 11.2, 4.4 Hz, 1H), 5.03 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.00-2.94 (m, 1H), 2.90-2.84 (m, 1H), 2.75-2.65 (m, 1H), 2.65-2.55 (m, 1H), 2.30-1.65 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$, two diastereomers) δ 194.6, 192.7, 168.9, 167.9, 153.2, 152.1, 144.8, 144.6, 137.9, 137.7, 129.8, 129.6, 129.2, 123.2, 123.0, 166.6, 116.3, 84.2, 82.9, 82.6, 81.3, 53.0, 52.5, 37.6, 32.1, 31.5, 29.1, 28.9, 24.1, 22.3, 21.5, 19.9, 16.9; TLC (30% EtOAc/hexanes) R_f 0.50; **Anal.** Calcd. for $C_{17}H_{16}N_4O_6$: C, 54.84; H, 4.33; N, 15.05. Found: C, 55.19; H, 4.45; N, 14.72.



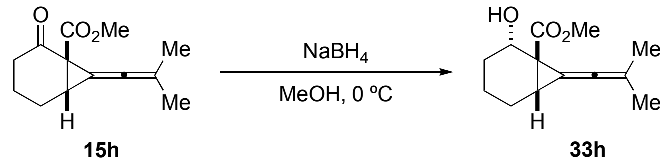
Methyl 7-iodo-7-(1-iodovinyl)-2-oxobicyclo[4.1.0]heptane-1-carboxylate (26). To a vial equipped with a mangetic stir bar was added methyl 2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**15b**) (0.030 g, 0.15 mmol) and reagent grade diethyl ether (2.0 mL). After dissolution, iodine (0.045 g, 0.18 mmol) was added. The reaction was stirred at room temperature for 15 minutes. The reaction was quenched with a saturated aqueous sodium thiosulfate solution (2 mL) and extracted with diethyl ether (3 x 5 mL). The organic layer was dried with magnesium sulfate and the solvents removed under vacuum. The residue was purified by flash column chromatography, eluting with 25% ethyl acetate/hexanes to yield the title compound (0.056 g, 0.126 mmol, 84% yield) as a clear, colorless oil. Analytical data for **26**: **IR** (thin film, cm^{-1}) 2950, 2873, 1746, 1730, 1699, 1437, 1321, 1274, 1259, 1236, 1159, 1066, 1012, 981, 950, 873, 734; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.49 (d, J = 10.1 Hz, 1H), 4.26 (dd, J = 10.1, 1.4 Hz, 1H), 3.75 (s, 3H), 2.59 (br s, 1H), 2.39 (td, J = 17.6, 3.8 Hz, 1H), 2.33 (dtd, J = 13.9, 3.5, 2.8 Hz, 1H), 2.10 (ddd, J = 18.4, 12.8, 5.8 Hz, 1H), 1.92 (tt, J = 13.4, 4.1 Hz, 1H), 1.84-1.73 (m, 1H), 1.56 (qt, J = 13.2, 4.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.2, 166.4, 130.8, 92.5, 52.9, 46.4, 38.3, 31.0, 19.5, 17.9, 12.4; TLC (25% EtOAc/hexanes) R_f 0.25; **LRMS** (ESI) Calcd. for $C_{11}H_{12}I_2O_3$+K 484.8, Found 484.9.



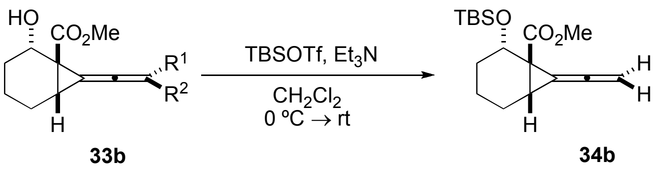
Methyl 2-hydroxy-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (33b). The title compound was prepared according to General Procedure **H** using methyl 2-oxo-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**15b**) (0.475 g, 2.47 mmol) and two portions of sodium borohydride (2 x 0.038 g, 0.99 mmol) to yield methyl 2-hydroxy-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**33b**) (0.365 g, 1.88 mmol, 76% yield) as a colorless solid after flash chromatography with 25%→30% ethyl acetate/hexanes. Analytical data for **33b**: **IR** (thin film, cm^{-1}) 2935, 2866, 2024, 1722, 1599, 1444, 1274, 1244, 1143, 1104, 1066, 842; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.06 (d, J = 4.7 Hz, 2H), 4.58 (dd, J = 8.6, 5.5 Hz, 1H), 3.74 (s, 3H), 2.85-2.77 (m, 1H), 2.58 (br s, 1H), 1.99-1.88 (m, 1H), 1.80-1.66 (m, 2H), 1.64-1.52 (m, 1H), 1.40-1.18 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.7, 172.5, 85.6, 80.1, 66.5, 52.3, 37.7, 28.9, 28.5, 22.3, 19.6; TLC (30% EtOAc/hexanes) R_f 0.25; **LRMS** (ESI) Calcd. for $C_{11}H_{14}O_3$+Na 217.1, Found 217.1.



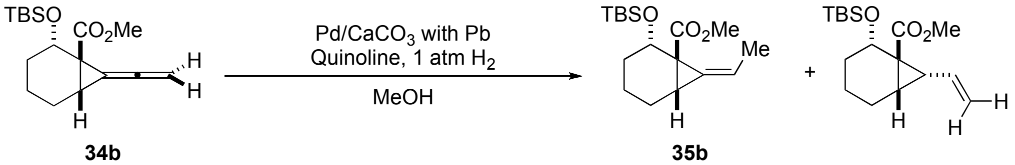
Methyl 2-hydroxy-7-(prop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (33g). The title compound was prepared according to General Procedure **H** using methyl 2-oxo-7-(prop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (**15g**) (0.260 g, 1.26 mmol) and two portions of sodium borohydride (2 x 0.019 g, 0.50 mmol) to yield methyl 2-hydroxy-7-(prop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (**33g**) (0.223 g, 1.07 mmol, 85% yield) as a pale yellow oil after flash chromatography with 25% ethyl acetate/hexanes. Analytical data for **33g**: **IR** (thin film, cm^{-1}) 2935, 2866, 2016, 1715, 1437, 1244, 1143, 1066, 966, 841, 803; **^{1}H NMR** (400 MHz, CDCl$_3$) δ major diastereomer : 5.45 (q, J = 7.1 Hz, 1H), 4.62-4.52 (m, 1H), 3.71 (s, 3H), 2.80-2.73 (m, 1H), 2.52 (d, J = 4.7 Hz, 1H), 1.96-1.85 (m, 1H), 1.80-1.50 (m, 3H), 1.79 (d, J = 7.1 Hz, 3H), 1.45-1.15 (m, 2H); minor diastereomer : 5.46 (q, J = 7.1 Hz, 1H), 4.62-4.52 (m, 1H), 3.73 (s, 3H), 2.80-2.73 (m, 1H), 2.52 (d, J = 4.7 Hz, 1H), 1.96-1.85 (m, 1H), 1.80-1.50 (m, 3H), 1.76 (d, J = 7.1 Hz, 3H), 1.45-1.15 (m, 2H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ major diastereomer : 188.6, 172.8, 91.9, 86.7, 66.2, 52.1, 36.9, 28.7, 28.1, 22.5, 19.3, 15.0; minor diastereomer : 188.7, 172.9, 91.9, 86.8, 66.6, 52.1, 36.7, 28.8, 28.1, 22.3, 19.4, 14.8; TLC (30% EtOAc/hexanes) R*f* 0.31; **LRMS** (ESI) Calcd. for $C_{12}H_{16}O_3$+Na 231.1, Found 231.0.



Methyl 2-hydroxy-7-(2-methylprop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (33h). The title compound was prepared according to General Procedure **H** using methyl 7-(2-methylprop-1-enylidene)-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**15h**) (0.039 g, 0.18 mmol) and one portion of sodium borohydride (0.003 g, 0.08 mmol) to yield methyl 2-hydroxy-7-(2-methylprop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (**33h**) (0.033 g, 0.15 mmol, 82% yield) as a clear, colorless oil after flash chromatography with 25% ethyl acetate/hexanes. Analytical data for **33h**: **IR** (thin film, cm^{-1}) 2935, 2858, 1722, 1652, 1545, 1522, 1442, 1267, 1174; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 4.54 (dt, J = 8.2, 4.9 Hz, 1H), 3.67 (s, 3H), 2.67 (dd, J = 7.3, 1.9 Hz, 1H), 2.52 (d, J = 4.7 Hz, 1 Hz), 1.90-1.56 (m, 3H), 1.77 (s, 3H), 1.74 (s, 3H), 1.39-1.25 (m, 1H), 1.25-1.11 (m, 1H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 185.4, 173.1, 102.1, 85.9, 66.2, 52.0, 36.1, 29.0, 27.4, 22.5, 21.2, 20.9, 19.2; TLC (25% EtOAc/hexanes) R_f 0.31; **LRMS** (ESI) Calcd. for $C_{13}H_{18}O_3$+K 261.1, Found 261.1.

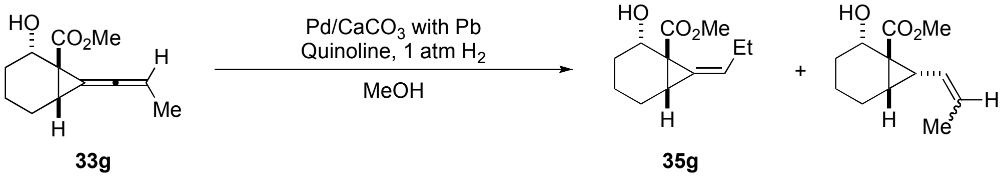


Methyl 2-(tert-butyldimethylsilyloxy)-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (34b). To a flame-dried vial equipped with a mangetic stir bar was added methyl 2-hydroxy-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**33b**) (0.051 g, 0.26 mmol) and anhydrous dichloromethane (5.0 mL). Triethylamine (0.106 g, 0.146 mL, 1.04 mmol) was added and the solution was cooled to 0 °C. *Tert*-butyldimethylsilyl trifluoromethanesulfonate (0.135 g, 0.118 mL, 0.52 mmol) was then added dropwise over two minutes. The reaction was allowed to warm to room temperature and was stirred for 75 minutes. The solvents were removed under reduced pressure and the residue was directly purified by flash column chromatography, eluting with 7.5% ethyl acetate/hexanes to yield the title compound (0.081 g, 0.26 mmol, 100% yield) as a pale yellow oil. Analytical data for **34b**: **IR** (thin film, cm^{-1}) 2951, 2927, 2024, 1722, 1460, 1437, 1359, 1274, 1251, 1151, 1104, 1066, 1027, 896, 834, 780, 703; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.97 (dd, J = 10.1, 4.7 Hz, 1H), 4.92 (dd, J = 10.1, 4.7 Hz, 1H), 4.81 (t, J = 5.5 Hz, 1H), 3.67 (s, 3H), 2.69-2.62 (m, 1H), 1.86-1.70 (m, 2H), 1.58-1.32 (m, 3H), 1.27-1.15 (m, 1H), 0.84 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.1, 172.6, 85.2, 79.1, 65.2, 52.0, 37.4, 29.6, 25.7, 22.9, 18.0, 17.3, –4.8; TLC (30% EtOAc/hexanes) R_f 0.83; **LRMS** (ESI) Calcd. for $C_{17}H_{28}O_3Si$+K 347.1, Found 347.1.

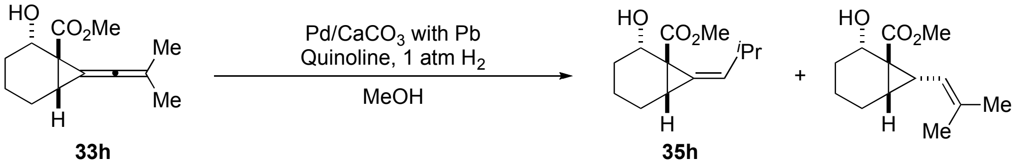


(Z)-Methyl 2-(tert-butyldimethylsilyloxy)-7-ethylidenebicyclo[4.1.0]heptane-1-carboxylate (35b). The title compound was prepared according to General Procedure **I** using methyl 2-(tert-butyldimethylsilyloxy)-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**34b**) (0.025 g, 0.081 mmol) at 0 °C for 30 minutes to yield an inseparable

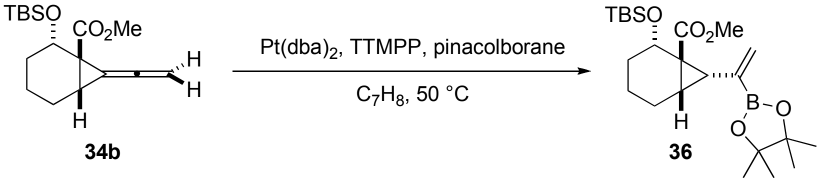
5:1 mixture of (Z)-methyl 2-(tert-butyldimethylsilyloxy)-7-ethylidenebicyclo[4.1.0]heptane-1-carboxylate (**35b**) and the corresponding vinyl cyclopropane (0.024 g, 0.077 mmol, 95% combined yield) as a clear, colorless oil after flash chromatography with 5% ethyl acetate/hexanes. Analytical data for **35b**: **IR** (thin film, cm^{-1}) 2935, 1722, 1460, 1437, 1359, 1251, 1151, 1089, 1066, 1027, 896, 834, 780, 734, 695; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.91 (qd, J = 6.5, 2.2 Hz, 1H), 4.60 (dd, J = 9.5, 5.4 Hz, 1H), 3.65 (s, 3H), 2.22-2.14 (m, 1H), 1.94-1.72 (m, 1H), 1.82 (dd, J = 6.6, 2.3 Hz, 3H), 1.60-1.40 (m, 3H), 1.20-0.95 (m, 2H) 0.85 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8, 129.6, 114.6, 68.1, 51.6, 32.5, 30.7, 26.9, 25.8, 23.0, 20.9, 17.9, 17.1, –4.6, –4.7; TLC (10% EtOAc/hexanes) R_f 0.58; **LRMS** (ESI) Calcd. for $C_{17}H_{30}O_3Si$+Na 333.2, Found 333.2.



(Z)-Methyl 2-hydroxy-7-propylidenebicyclo[4.1.0]heptane-1-carboxylate (35g). The title compound was prepared according to General Procedure **I** using methyl 2-hydroxy-7-(prop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (**33g**) (0.050 g, 0.24 mmol) at 0 °C for 30 minutes. Because the product coelutes with quinoline, as acid-base extraction was used to remove it as follows. After the initial solvents were removed under vacuum, the residue was taken up in diethyl ether (10 mL). This was washed with aqueous hydrochloric acid (1M, 3 x 3 mL), dried with magnesium sulfate, and the solvents were removed under vacuum. The residue was then purified by flash chromatography, eluting with 20% ethyl acetate/hexanes to yield (Z)-methyl 2-hydroxy-7-propylidenebicyclo[4.1.0]heptane-1-carboxylate (**35g**) (0.039 g, 0.19 mmol, 77%) as a clear, colorless oil. Analytical data for **35g**: **IR** (thin film, cm^{-1}) 2935, 2866,1714, 1699, 1460, 1422, 1274, 1244, 1189, 1128, 1066, 842; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.88 (td, J = 7.1, 2.1 Hz, 1H), 4.47 (dd, J = 8.5, 5.7 Hz, 1H), 3.67 (s, 3H), 2.84 (br s, 1H), 2.38 (dt, J = 8.2, 1.5 Hz, 1H), 2.20 (q, J = 7.4 Hz, 1H), 2.18 (q, J = 7.4 Hz, 1H), 1.93-1.82 (m, 1H), 1.72-1.62 (m, 1H), 1.60-1.45 (m, 2H), 1.28-1.05 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 174.5, 128.2, 121.3, 67.6, 52.0, 32.7, 28.3, 25.2, 25.1, 22.8, 20.7, 13.8; TLC (30% EtOAc/hexanes) R$_f$ 0.46; **LRMS** (ESI) Calcd. for $C_{12}H_{18}O_3$+Na 233.1, Found 233.1.

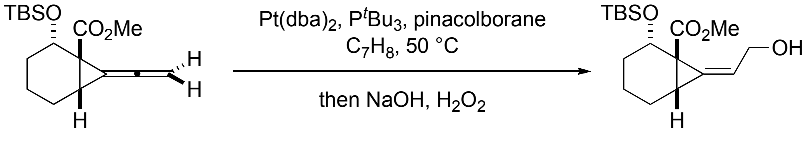


(Z)-Methyl 2-hydroxy-7-(2-methylpropylidene)bicyclo[4.1.0]heptane-1-carboxylate (35h). The title compound was prepared according to General Procedure **I** using methyl 2-hydroxy-7-(2-methylprop-1-enylidene)bicyclo[4.1.0]heptane-1-carboxylate (**33h**) (0.020 g, 0.090 mmol) at rt for 20 minutes to yield (Z)-methyl 2-hydroxy-7-(2-methylpropylidene)bicyclo[4.1.0]heptane-1-carboxylate (**35h**) (0.018 g, 0.078 mmol, 87%) as a clear, colorless oil after flash chromatography with 10% ethyl acetate/hexanes. Analytical data for **35h**: **IR** (thin film, cm^{-1}) 2958, 2866, 1707, 1464, 1437, 1290, 1189, 1143, 1050; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.72 (dd, J = 8.8, 2.0 Hz, 1H), 4.50-4.40 (m, 1H), 3.66 (s, 3H), 2.87 (d, J = 3.0, 1H), 2.58-2.45 (m, 1H), 2.34 (d, J = 8.1 Hz, 1H), 1.94-1.80 (m, 1H), 1.72-1.60 (m, 1H), 1.59-1.40 (m, 2H), 1.27-1.45 (m, 2H), 1.01 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.5, 126.5, 126.4, 67.5, 51.9, 32.8, 31.4, 28.3, 24.7, 22.7, 22.5, 22.4, 20.7; TLC (30% EtOAc/hexanes) R_f 0.57; **LRMS** (ESI) Calcd. for $C_{13}H_{20}O_3$+K 263.1, Found 263.1.



Methyl 2-(tert-butyldimethylsilyloxy)-7-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)bicyclo[4.1.0]heptane-1-carboxylate (36). To a flame-dried vial equipped with a mangetic stir bar was added methyl 2-(tert-butyldimethylsilyloxy)-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**34b**) (0.100 g, 0.32 mmol), platinum bisdibenzylideneacetone[62] (0.0106 g, 0.016 mmol), tris(trimethoxyphenyl)phosphine (0.017 g, 0.032 mmol) and anhydrous toluene (2.0 mL). Pinacolborane (0.061 g, 0.48 mmol) was then added, the vial was sealed with a rubber septum, and the vial was then heated to 50 °C. After stirring at this temperature for 2.5 hours, the solvents were removed under vacuum. The residue was directly purified by flash column chromatography, eluting with 7.5%→10% ethyl acetate/hexanes to yield the title compound (0.083 g, 0.19 mmol, 60% yield) as a clear oil that solidifies to a colorless, waxy solid upon standing at –30 °C. Analytical data for **36**: **IR** (thin film, cm^{-1}) 2935, 2858, 1722, 1599, 1459, 1437, 1383, 1313, 1251, 1143, 1097, 1027, 834; **^{1}H NMR** (400

MHz, C_6D_6) δ 6.26 (dd, J = 3.7, 1.0 Hz, 1H), 6.01 (d, J = 3.3 Hz, 1H), 4.89 (t, J = 4.8 Hz, 1H), 3.34 (s, 3H), 2.83-2.77 (m, 1H), 2.53 (d, J = 8.0 Hz, 1H), 1.70-1.58 (m, 2H), 1.3-0.85 (m, 4H), 1.18 (s, 6H), 1.17 (s, 6H), 1.02 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 173.9, 128.4, 115.6, 82.9, 68.5, 51.6, 32.7, 30.4, 27.1, 26.0, 24.9, 24.7, 23.0, 21.3, 18.0, –4.6, –4.6; TLC (7.5% EtOAc/hexanes) R_f 0.23; **LRMS** (ESI) Calcd. for $C_{23}H_{41}BO_5Si$+K 375.1, Found 375.1.



34b **38**

Methyl 2-(tert-butyldimethylsilyloxy)-7-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)bicyclo[4.1.0]heptane-1-carboxylate (38). To a flame-dried vial equipped with a mangetic stir bar was added methyl 2-(tert-butyldimethylsilyloxy)-7-vinylidenebicyclo[4.1.0]heptane-1-carboxylate (**34b**) (0.028 g, 0.091 mmol), platinum bisdibenzylideneacetone[62] (0.0030 g, 0.005 mmol), tri-*tert*-butylphosphine (10% wt in hexanes, 0.018 g, 0.009 mmol) and anhydrous toluene (2.0 mL). Pinacolborane (0.017 g, 0.136 mmol) was then added, the vial was sealed with a rubber septum, and the vial was then heated to 50 °C. After stirring at this temperature for 1.0 hours, the reaction was cooled to 0 °C and diethyl ether (5.0 mL) and deionized water (2.0 mL) was added. Then, 30% aqueous hydrogen peroxide solution (1.0 mL) was added, followed by 50% aqueous sodium hydroxide solution (1.0 mL). The reaction was allowed to warm to room temperature and an additional portion of 30% hydrogen peroxide (1.0 mL) was added every 30 minutes until the reaction was complete by TLC (60 minutes). The reaction was diluted with saturated aqueous sodium chloride solution (5 mL) and extracted with diethyl ether (3 x 10 mL). The extracts were washed with saturated aqueous sodium chloride (1 x 5 mL) and dried with magnesium sulfate. The residue was purified by sequential flash column chromatography, eluting first with 0.5%→3.0% MeOH/CH_2Cl_2 then with 15% ethyl acetate/hexanes to yield the title compound (0.018 g, 0.055 mmol, 61% yield) as a clear oil. Analytical data for **38**: **IR** (thin film, cm^{-1}) 2935, 2858, 1722, 1460, 1442, 1359, 1267, 1189, 1159, 1058, 958, 888, 834, 780, 672; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.17 (br q, J = 3.1 Hz, 1H), 4.66 (dd, J = 10.4, 5.7 Hz, 1H), 4.30-4.11 (m, 3H), 3.67 (s, 3H), 2.28 (dt, J = 8.9, 2.4 Hz, 1H), 2.00-1.87 (m, 1H), 1.65 (dt, J = 12.4, 10.1 Hz, 1H), 1.57-1.43 (m, 2H), 1.27-1.10 (m, 1H), 1.10-0.97 (m, 1H), 0.89 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0, 127.7, 119.5, 68.9, 61.4, 52.0, 32.0, 30.4, 25.8, 25.0, 22.8, 21.2, 18.1, –4.5, –5.0; TLC (20% EtOAc/hexanes) R_f 0.27; **LRMS** (ESI) Calcd. for $C_{17}H_{30}O_4Si$+Na 349.2, Found 349.2.

2.6 References

(1) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846-3852.

(2) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736-738.

(3) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

(4) Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845-848.

(5) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, 3007-3011.

(6) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490-493.

(7) Ichikawa, J.; Lapointe, G.; Iwai, Y. *Chem. Commun.* **2007**, 2698-2700.

(8) Doan, H. D.; Gallon, J.; Piou, A.; Vatele, J. M. *Synlett* **2007**, 983-985.

(9) Bogen, S.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **1997**, *119*, 5037-5038.

(10) Inokuchi, T.; Matsumoto, S.; Tsuji, M.; Torii, S. *J. Org. Chem.* **1992**, *57*, 5023-5027.

(11) Berg, T. C.; Gundersen, L. L.; Eriksen, A. B.; Malterud, K. E. *Eur. J. Org. Chem.* **2005**, 4988-4994.

(12) Breen, T. L.; Stephan, D. W. *J. Am. Chem. Soc.* **1995**, *117*, 11914-11921.

(13) Reisch, J.; Zappel, J.; Henkel, G.; Ekizgucer, N. *Mon. Chem.* **1993**, *124*, 1169-1175.

(14) Matsoyan, S. G.; Chukhadzhyan, G. A.; Vartanyan, S. A. *Izvest. Akad. Nauk Armyan. S.S.R., Khim. Nauki* **1959**, *12*, 187-193.

(15) Colonge, J.; Falcotet, R.; Gaumont, R. *Bull. Soc. Chim. Fr.* **1958**, 211-218.

(16) Hekkert, G. L.; Drenth, W. *Rec. Trav. Chim.* **1961**, *80*, 1285-1304.

(17) Strozier, R. W.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 1340-1343.

(18) Eisenstein, O.; Procter, G.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2538-2541.

(19) Wallis, J. D.; Dunitz, J. D. *J. Chem. Soc., Chem. Commun.* **1984**, 671-672.

(20) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014-16015.

(21) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057-1059.

(22) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642-8650.

(23) The initial studies described in this section were all performed by Patrick Pohlhaus.

(24) Pohlhaus, P. D. Ph.D. Thesis, University of North Carolina at Chapel Hill, Chapel Hill, NC, 2006.

(25) Li, J. J. In *Name Reactions : A Collection of Detailed Reaction Mechanisms*; 3rd expanded ed.; Springer: Berlin ; New York, 2006, p 157-159.

(26) Bleiholder, R. F.; Shechter, H. *J. Am. Chem. Soc.* **1964**, *86*, 5032-5033.

(27) Hartzler, H. D. *J. Am. Chem. Soc.* **1961**, *83*, 4990-4996.

(28) Isagawa, K.; Mizuno, K.; Sugita, H.; Otsuji, Y. *J. Chem. Soc., Perkin Trans. 2* **1991**, 2283-2285.

(29) Pasto, D. J.; Borchard, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 6937-6943.

(30) Pasto, D. J.; Borchardt, J. K.; Fehlner, T. P.; Baney, H. F.; Schwartz, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 526-529.

(31) Sasaki, T.; Eguchi, S.; Ogawa, T. *J. Am. Chem. Soc.* **1975**, *97*, 4413-4414.

(32) Mizuno, K.; Nire, K.; Sugita, H.; Maeda, H. *Tetrahedron Lett.* **2001**, *42*, 2689-2692.

(33) Mizuno, K.; Sugita, H.; Kamada, T.; Otsuji, Y. *Chem. Lett.* **1994**, 449-452.

(34) Mizuno, K.; Maeda, H.; Sugita, H.; Nishioka, S.; Hirai, T.; Sugimoto, A. *Org. Lett.* **2001**, *3*, 581-584.

(35) Mizuno, K.; Nire, K.; Sugita, H.; Otsuji, Y. *Tetrahedron Lett.* **1993**, *34*, 6563-6566.

(36) Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.* **2001**, *42*, 3363-3366.

(37) Pasto, D. J.; Miles, M. F.; Chou, S. K. *J. Org. Chem.* **1977**, *42*, 3098-3101.

(38) Xu, G. C.; Ma, M.; Liu, L. P.; Shi, M. *Synlett* **2005**, 1869-1872.

(39) Campbell, M. J.; Pohlhaus, P. D.; Min, G.; Ohmatsu, K.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 9180-9181.

(40) Wang, C.; Gu, X.; Yu, M. S.; Curran, D. P. *Tetrahedron* **1998**, *54*, 8355-8370.

(41) Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129-8133.

(42) Fleming, F. F.; Huang, A.; Sharief, V. A.; Y., P. *J. Org. Chem.* **1997**, *62*, 3036-3037.

(43) Wright, J. L.; Caprathe, B. W.; Downing, D. M.; Glase, S. A.; Heffner, T. G.; Jaen, J. C.; Johnson, S. J.; Kesten, S. R.; Mackenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D.; Wustrow, D. J. *J. Med. Chem.* **1994**, *37*, 3523-3533.

(44) Kim, S.; Park, J. H. *Synlett* **1995**, 163-164.

(45) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528.

(46) X-ray crystallography was performed by Dr. Peter White.

(47) CCDC 671491 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(48) Gomez, C.; Huerta, F. F.; Pastor, I. M.; Yus, M. *Tetrahedron* **1997**, *53*, 17201-17210.

(49) Trost, B. M.; Li, C.-J. *Tetrahedron Lett.* **1993**, *34*, 2271-2274.

(50) Shi, M.; Ma, M.; Zhu, Z.-B.; Wei, L. *Synlett* **2006**, 1943-1947.

(51) Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360-1362.

(52) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841-4844.

(53) Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488-2501.

(54) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507-7507.

(55) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624-13625.

(56) Yamamoto, Y.; Fujikawa, R.; Yamada, A.; Miyaura, N. *Chem. Lett.* **1999**, 1069-1070.

(57) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58*, 5130-5134.

(58) Cope, A. C.; Hofmann, C. M.; Wyckoff, C.; Hardenbergh, E. *J. Am. Chem. Soc.* **1941**, *63*, 3452-3456.

(59) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549-2553.

(60) Shepard, M. S.; Carreira, E. M. *Tetrahedron* **1997**, *53*, 16253-16276.

(61) Deslongchamps, P.; Lamothe, S.; Lin, H.-S. *Can. J. Chem.* **1984**, *62*, 2395-2398.

(62) Moseley, K.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1974**, 169-175.

CHAPTER THREE

TOTAL SYNTHESIS OF (+)-POLYANTHELLIN A

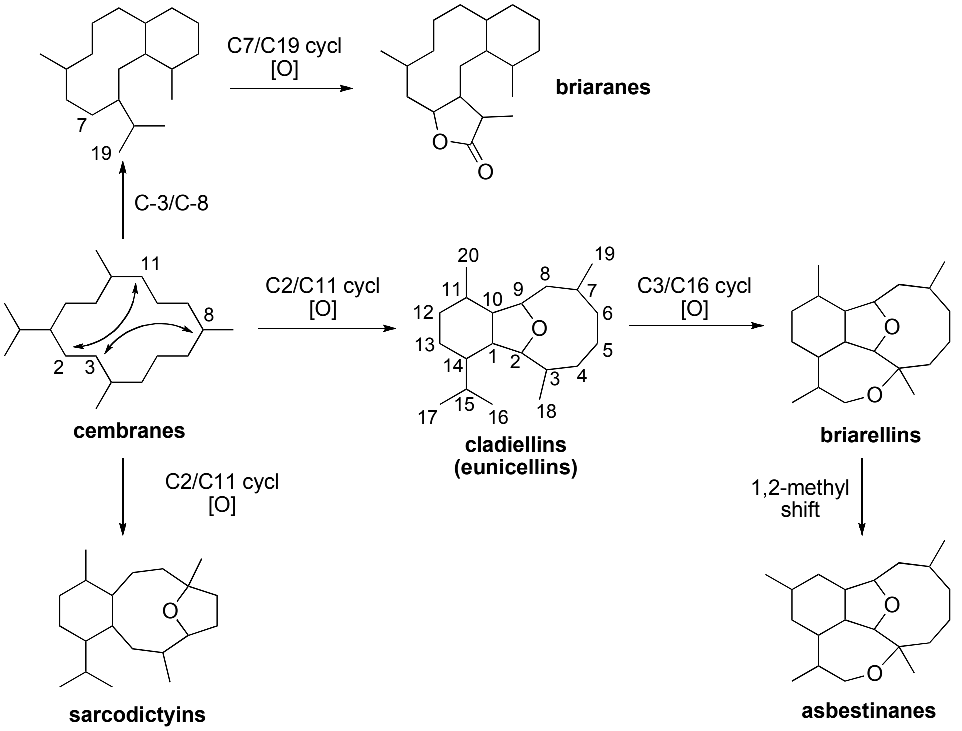
3.1 Introduction

3.1.2 Biogenetic Proposal and Properties of Cladiellins

Gorgonian octocorals (order Gorgonacea, phylum Cnidaria) produce novel metabolites in diverse classes such as sterols, carotenoids, fatty acids, biopolymers, and diterpenoids. The five families of diterpenoids found in the octocorals have attracted considerable attention from both the natural product and synthetic chemistry communities. These compounds interest synthetic chemists in part because of their unusual structural topology, but the activities of certain members, which include antitumor activity, anti-inflammatory activity, and cell division inhibition, provide medical relevance. These compounds also exhibit molluscicidal activity, ichthyotoxicity, and are lethal to brine shrimp and starfish eggs, supporting the hypothesis that they are present in the octocorals to discourage predation.[1-3]

It has been proposed that the five families of diterpenoids are biogenetically derived from cembranes via various oxidative cyclizations (Scheme 3-1).[4] Briaranes are the only class produced from an initial C3/C8 cyclization, with a subsequent oxidative C7/C19 cyclization to form a characteristic γ-butyrolactone. The other four classes are formed from a C2/C11 cyclization. Of these, the sarcodictyins are structurally unique, undergoing a distal oxidative cyclization, while the cladiellins and derivatives oxidatively cyclize to form a fused [6,5]-hydroisobenzofuran core. Briaranes are further functionalized with an oxepane linkage between C16 and C3. Asbestinanes are thought to be formed from the briarellin skeleton by a suprafacial 1,2-methyl shift and are furthest removed from the cembranes, according to the biogenetic proposal.

Scheme 3-1. Biogenetic Proposal for the Cyclized Cembranoids

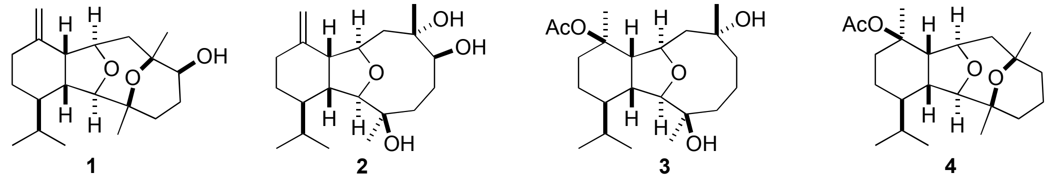

C7/C19 cycl
[O]
briaranes
7
19
C-3/C-8
11
8
2
3
cembranes
C2/C11 cycl
[O]
20
19
8
11
10
9
7
12
6
13
1
2
5
14
3
4
15
17
16
18
cladiellins
(eunicellins)
C3/C16 cycl
[O]
briarellins
1,2-methyl
shift
C2/C11 cycl
[O]
sarcodictyins
asbestinanes

Eunicellin, of the cladiellin family, was the first C2/C11-cyclized cembranoid to be discovered and structurally assigned.[5] This family still contains the largest percentage of C2-C11-cyclized cembranoids known. Their carbon skeletons are almost universally oxidized at, but not limited to, C2, C3, C6, C7, C9, and C11. Total synthesis research groups have targeted all five families, and synthetic endeavors toward the cladiellins have proven particularly fruitful; over ten have succumbed to total synthesis. Targets selected often exhibit biological activity of therapeutic interest; thus, the total syntheses of the anti-tumor agents 11-acetoxy-4-deoxyasbestinin D (asbestinane),[6] eleutherobin (sarcodictyin),[7] vigulariol,[8,9] and schlerophytin A[10,11] as well as the anti-malarial agent polyanthellin A[12] have been completed. To our knowledge, polyanthellin A and its deacetylated derivative are the only cladiellins to have been isolated from different species in both antipodes.[13,14] The other cladiellins exhibit the same sense of absolute stereochemistry. Although synthetic studies toward cladiellins, briarellins, and asbestinanes have been exhaustively reviewed,[15] an overview of syntheses pertinent to our target, polyanthellin A, will be discussed (*vide infra*).

3.1.3 Syntheses of Cladiellins Containing Two Oxygen Bridges

Schlerophytin A was initially formulated as **1**,[16,17] containing two ether bridges (Figure 3-1). Because this same motif is present in polyanthellin A (**4**), the synthetic studies of schlerophytin A are of direct relevance and will be presented alongside the sole total synthesis of polyanthellin A.[12] In an unusual twist, polyanthellin A (**4**) was incorrectly proposed by Bowden as **3** which contains two tertiary alcohols in the oxonane ring, similar to the triol ultimately determined to exist in sclerophytin A (**2)** (Figure 3-1).[13] The actual structure of **4** was successfully revised by spectroscopic analysis,[14] while that of **2** was determined by independent total syntheses by the Overman and Paquette groups.[10,18]

Figure 3-1. Initially Proposed and Actual Structures Sclerophytin A and Polyanthellin A



1
proposed structure of
sclerophytin A

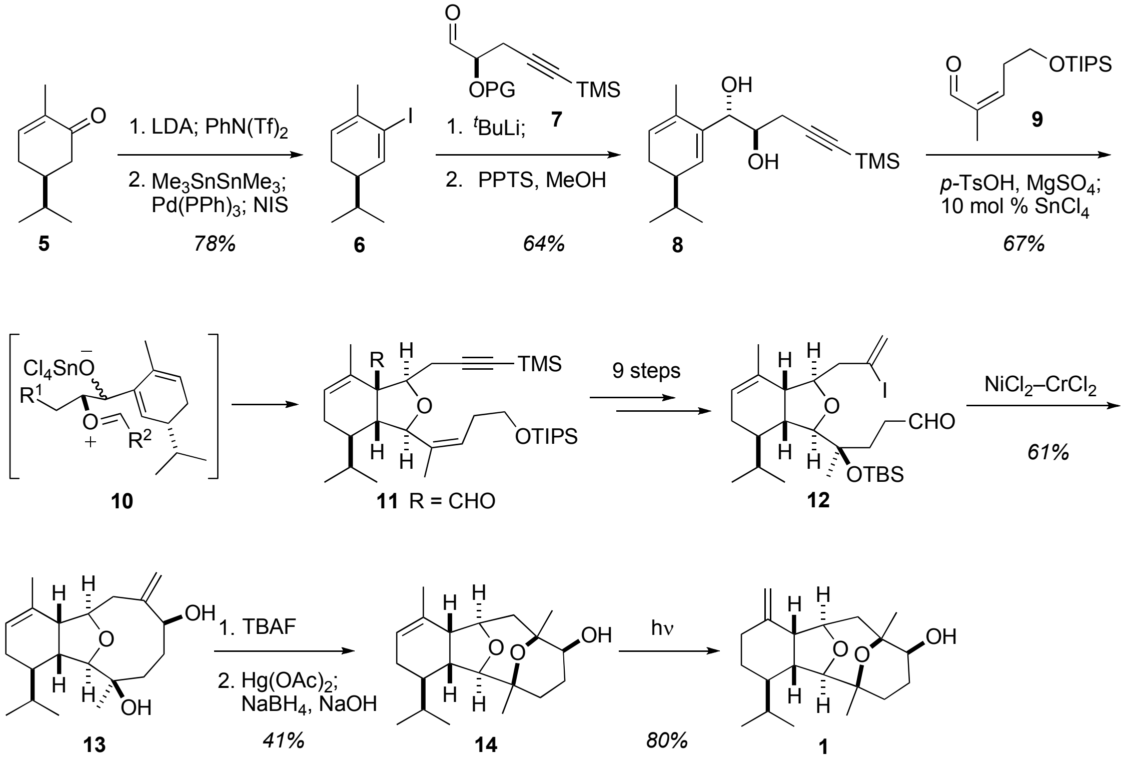
2
actual structure of
sclerophytin A

3
proposed structure of
polyanthellin A

4
actual structure of
polyanthellin A

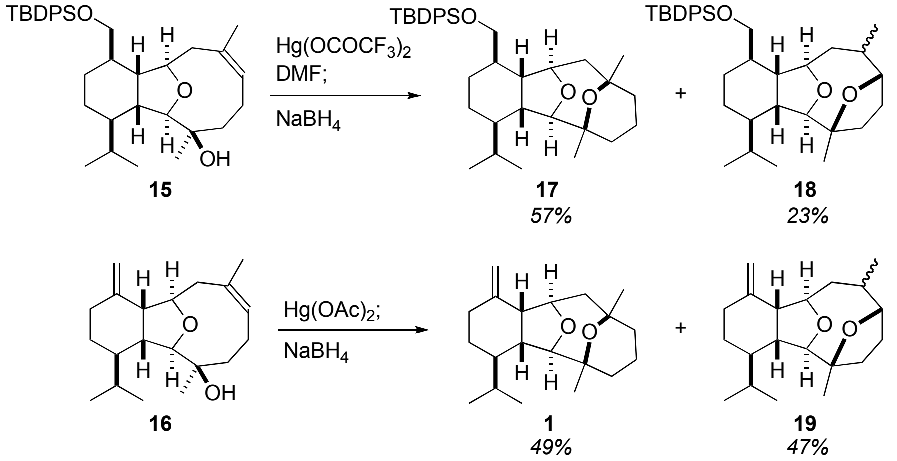
The Overman laboratory was among the first to report the total synthesis of a cladiellin with the completion of (–)-7-deacetoxyalcyonin,[19] using a Prins-pinacol condensation-rearrangement. In an effort to extend this methodology to other members of the cladiellin family, they next targeted the proposed structure of sclerophytin A.[10] (*S*)-Dihydrocarvone (**5**) was converted to vinyl iodide **6** through an intermediate vinyl stannane (Scheme 3-2). Successive treatment with *t*-BuLi and aldehyde **7** provided the *anti*-diol **8** after acid-catalyzed acetal removal. Prins-pinacol condensation-rearrangement with enal **9** proceeded smoothly through the favored chair transition state **10** to provide the hydroisobenzofuran core containing the requisite stereochemistry at all five stereocenters. A series of functional group interconversions installed a vinyl iodide and aldehyde necessary for the second key step, an exquisitely diastereoselective Nozaki–Hiyama–Kishi coupling. Afterwards, an intramolecular oxymercuration with $Hg(OAc)_2$ provided the tetrahydropyran **14**, the olefin of which was photochemically isomerized to furnish the proposed structure of sclerophytin A. Impressively, this work provided the most efficient synthesis of the cladiellin skeleton for nearly a decade, and established oxymercuration as the method of choice for future syntheses to install the tetrahydropyran.

Scheme 3-2. Overman Synthesis of the Proposed Structure of Sclerophytin A (**1**)


1. LDA; PhN(Tf)2
2. Me3SnSnMe3; Pd(PPh)3; NIS
78%
OPG
TMS
7
1. tBuLi;
2. PPTS, MeOH
64%
OH
OH
TMS
OTIPS
9
p-TsOH, MgSO4; 10 mol % SnCl4
67%
Cl4SnO
R1
R2
R
H
TMS
O
OTIPS
11 R = CHO
9 steps
I
CHO
OTBS
NiCl2–CrCl2
61%
OH
1. TBAF
2. Hg(OAc)2; NaBH4, NaOH
41%
hν
80%
5
6
8
10
12
13
14
1

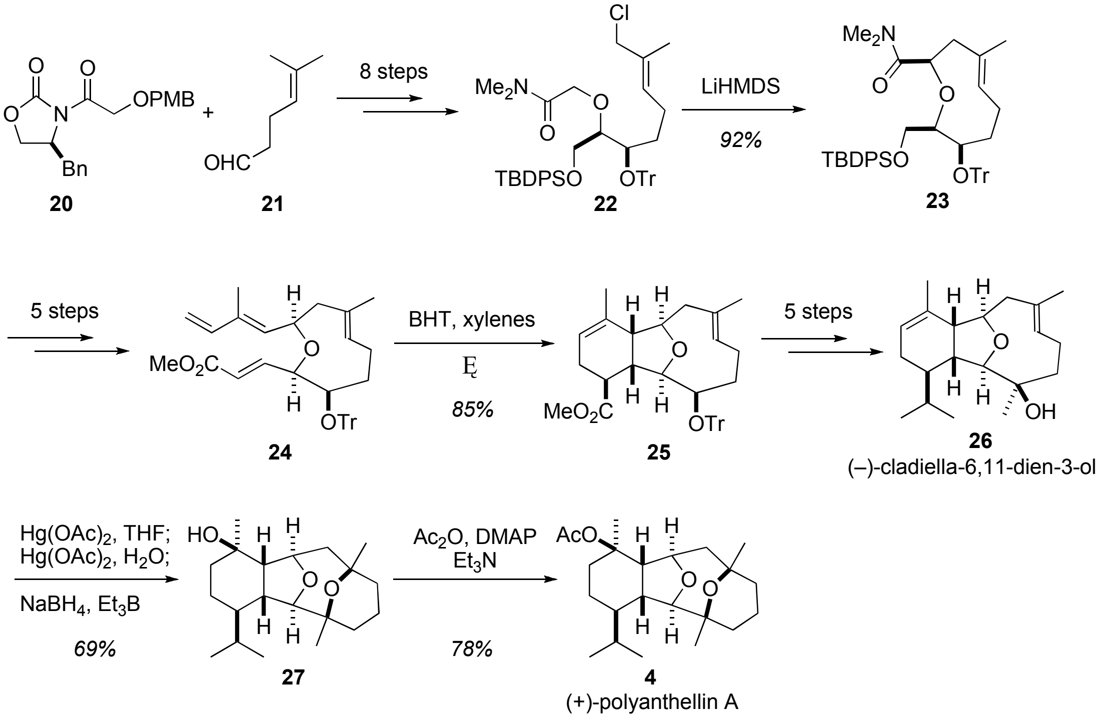
Concurrently with Overman, Paquette also synthesized **2**,[18] ultimately using an oxymercuration/oxidation sequence to provide the hydroxytetrahydropyran moiety. Studies employing a reductive workup found that the use of trisubstituted olefins (**15** and **16**) instead of a 1,1-disubstituted olefin provided increased efficiency of cyclization (Scheme 3-3); however, selectivity was low as the kinetic tetrahydrofuran products **18** and **19** were competitively formed.

Scheme 3-3. Paquette's Reductive Oxymercurations



Using the intramolecular amide alkylation chemistry developed in their laboratory, Kim and coworkers were able to synthesize the first (*E*)-olefin containing cladiellin.[12] This geometry is common in the isolation literature, but was not previously targeted synthetically. The utility of this olefin geometry was exhibited by readily converting **26** into several other cladiellins, which included (+)-polyanthellin A – its only total synthesis. The key alkylation substrate **22** was prepared in eight steps from oxazolidinone **20** and γ,δ-unsaturated aldehyde **21** (Scheme 3-4). Five steps were required to provide the Diels-Alder substrate **24**, which cyclized to form the cladiellin skeleton in 85% yield. Another short sequence converted methyl ester **25** into dienol **26**. A tandem intramolecular reductive oxymercuration/hydroxymercuration reaction efficiently produced the second ether bridge and the tertiary alcohol at C11 to form **27**. The synthesis of (+)-polyanthellin A (**4**) was completed by acetylation with Ac$_2$O/DMAP.

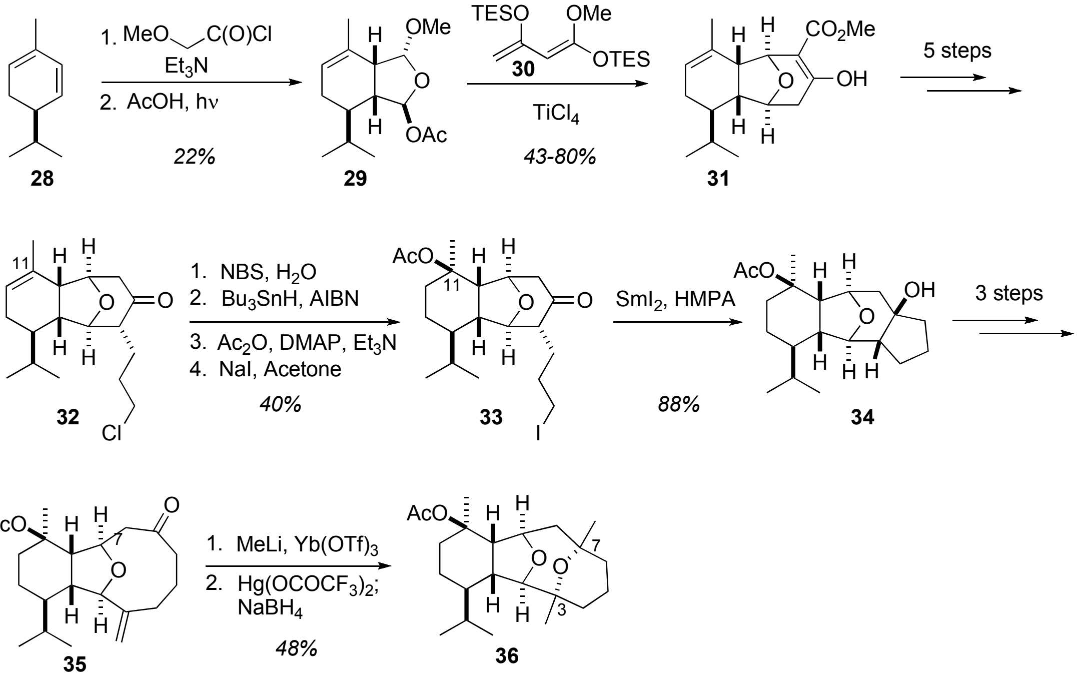
Scheme 3-4. Kim's Synthesis of (+)-Polyanthellin A (**4**)



OPMB
Bn
20
OHC
21
8 steps
Cl
Me2N
TBDPSO
OTr
22
LiHMDS
92%
Me2N
TBDPSO
OTr
23
5 steps
MeO2C
OTr
24
BHT, xylenes
85%
MeO2C
OTr
25
5 steps
OH
26
(–)-cladiella-6,11-dien-3-ol
Hg(OAc)2, THF;
Hg(OAc)2, H2O;
NaBH4, Et3B
69%
HO
27
Ac2O, DMAP
Et3N
78%
AcO
4
(+)-polyanthellin A

The Molander laboratory attempted to prepare polyanthellin A using a [4+3] annulation strategy previously developed and employed to synthesize (–)-7-deacetoxyalcyonin acetate.[20] The three step sequence to prepare keto ester **31** was low yielding, but quickly established the five stereocenters in the hydroisobenzofuran core. Bis(acetal) **29** was formed from a ketene [2+2]-cycloaddition with α-phellandrene (**28**), followed by a photochemical rearrangement in AcOH. The formal [4+3]-cycloaddition between bis(siloxy)diene **30** and **29** proceeded in variable yield to keto ester **31**. Alkylation and decarboalkoxylation over five steps produced the chloroketone **32**. The C11 tertiary acetoxy group was installed in three steps through the bromohydrin, and the Finkelstein reaction then furnished the iodide **33** needed to perform a samarium diiodide mediated reductive cyclization. This afforded the tetracycle **34** in 88% yield, which was then transformed into the ketone **35** over three steps. Unfortunately, methyllithium addition to the ketone afforded the undesired stereochemistry at C7, which after reductive oxymercuration with $Hg(OCOCF_3)_2/NaBH_4$ resulted in the 3,7-diastereomer of polyanthellin A (**36**).

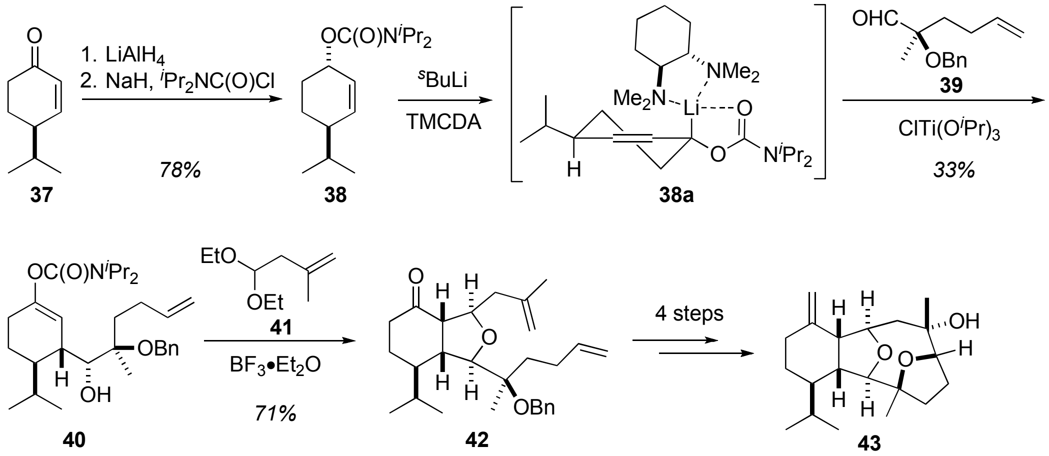
Scheme 3-5. Synthesis of 3,7-Diastereomer of Polyanthellin A (**36**)



1. MeO⁀C(O)Cl Et3N
2. AcOH, hν
22%
28
29
30
TESO
OMe
OTES
TiCl4
43-80%
31
CO2Me
OH
5 steps
32
11
Cl
1. NBS, H2O
2. Bu3SnH, AIBN
3. Ac2O, DMAP, Et3N
4. NaI, Acetone
40%
33
AcO
I
SmI2, HMPA
88%
34
OH
3 steps
35
1. MeLi, Yb(OTf)3
2. Hg(OCOCF3)2; NaBH4
48%
36
7
3

An efficient approach to the cladiellin core was recently reported by Hoppe and coworkers.[9] Though vigulariol was targeted, their endeavors will be summarized here because of the conceptual similarities to our proposed synthesis. The enone **37**, which was isolated from eucalyptus essential oil, was diastereoselectively reduced with $LiAlH_4$ and converted to the *N,N*-diisopropyl carbamate **38**. A homoaldol reaction was conducted by deprotonation with *s*-BuLi/TMCDA and sequential treatment with ClTi(O*i*-Pr)$_3$ and enantioenriched aldehyde **39** to produce the enol carbamate **40**. The synthesis of the fused bicycle **42** was completed by nucleophilic trapping of an oxocarbenion ion formed *in situ* from the diethylacetal **41** and **40**. Only four further transformations were required to synthesize (+)-vigulariol (**43**). This currently represents the shortest synthesis of any cladiellin, requiring only 11 steps from methallylalcohol.

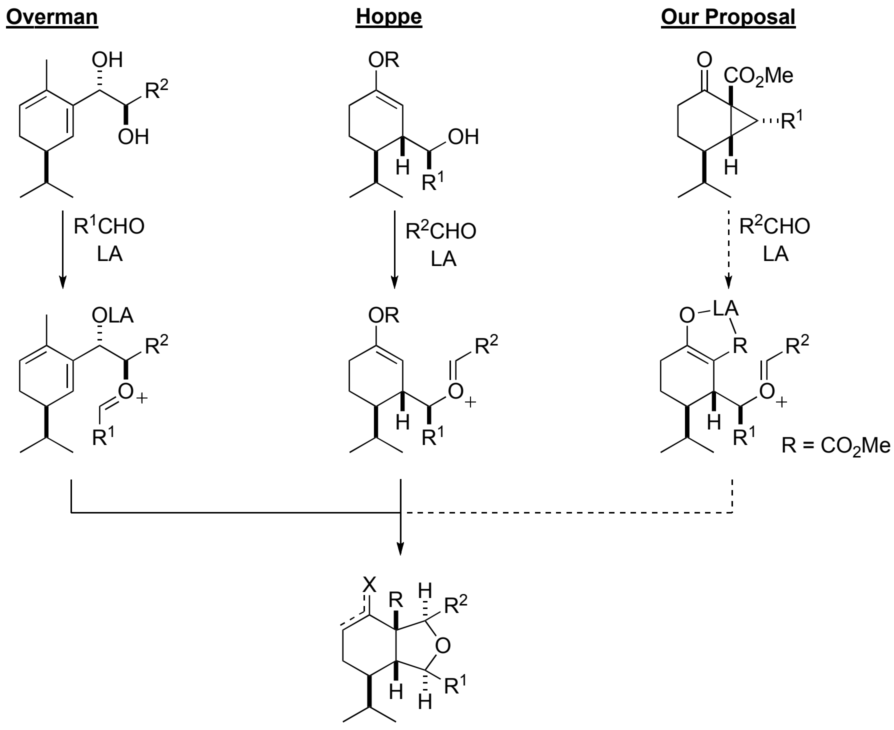
Scheme 3-6. Hoppe's Synthesis of (+)-Vigulariol (**43**)



37
1. LiAlH4
2. NaH, iPr2NC(O)Cl
78%
OC(O)NiPr2
38
sBuLi
TMCDA
NMe2
Me2N
Li
O
O
NiPr2
H
38a
OHC
OBn
39
ClTi(OiPr)3
33%
OC(O)NiPr2
OBn
H
OH
40
EtO
OEt
41
BF3•Et2O
71%
O
H
H
O
H
H
OBn
42
4 steps
H
H
OH
H
O
O
H
H
43

The synthetic strategies devised to prepare the cladiellin skeleton can invariably be sorted into two camps: those that initially target the hydroisobenzofuran, and those that first form the oxonane. The structural variety found throughout the 2,11-cyclized cembranoids has ensured that neither strategy has become dominant. However, the syntheses by Overman and Hoppe are noteworthy for their convergence, and both build the hydroisobenzofuran first and subsequently install the oxonane. They similarly distill into three modular components (two functionally rich aldehydes and a cyclohexene core), and use a Lewis acid-catalyzed cyclization onto an *in situ* generated oxocarbenium ion. As described in chapter 2, we propose to build the core by using a [3+2]-cycloaddition between a donor-acceptor cyclopropane and an aldehyde. Although the oxocarbenium is generated by a nucleophilic substitution instead of a condensation, the intermediate is reminiscent of that found in Hoppe's synthesis (Scheme 3-7). In this chapter, we will detail the synthesis of (+)-polyanthellin A using this approach.

Scheme 3-7. Approaches to the Cladiellin Core using Oxocarbenium Intermediates



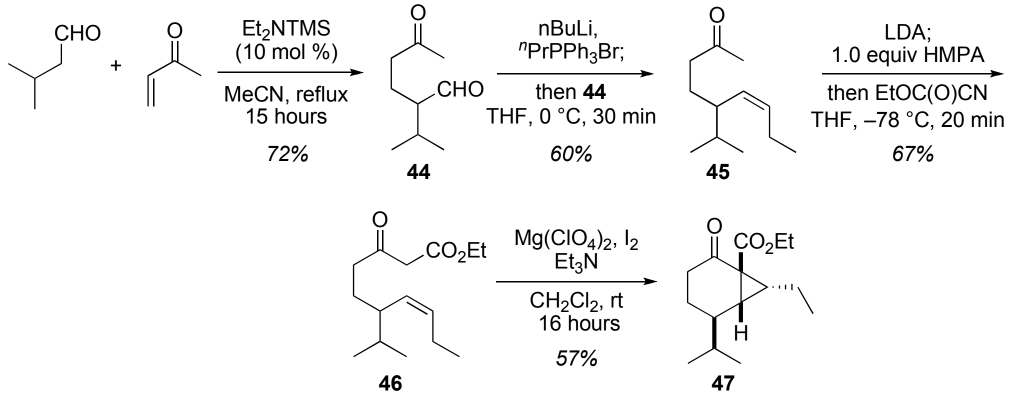
Overman
Hoppe
Our Proposal
OH
R^2
OH
OR
OH
H
R^1
O
CO_2Me
R^1
H
R^1CHO
LA
R^2CHO
LA
R^2CHO
LA
OLA
R^2
O+
R^1
OR
R^2
O+
H
R^1
O–LA
R
R^2
O+
H
R^1
R = CO_2Me
X
R
H
R^2
O
H
H
R^1

3.2 Results and Discussion

3.2.1 Synthesis of Model Systems

Before devising our retrosynthesis of polyanthellin A, we prepared two model bicyclic cyclopropanes that would allow us to explore the scope of the linchpin step – the [3+2]-cycloaddition of a donor-acceptor cyclopropane with an aldehyde.[21-23] The ethyl cyclopropane **47** was synthesized in four steps, beginning with an Et_2NTMS-catalyzed conjugate addition of isovaleraldehyde to MVK to directly furnish keto aldehyde **44** (Scheme 3-8).[24] A chemoselective Wittig reaction provided (*Z*)-alkene **45**, which was converted to keto ester **46** with Mander's reagent.[25] Cyclopropane **47** was formed using a protocol developed by Yang[26] that preserves the olefin geometry through the reaction, placing the ethyl group on the concave face of the bicycle. Unfortunately, the relative stereochemistry of the product could not be unambiguously confirmed with NOESY experiments.

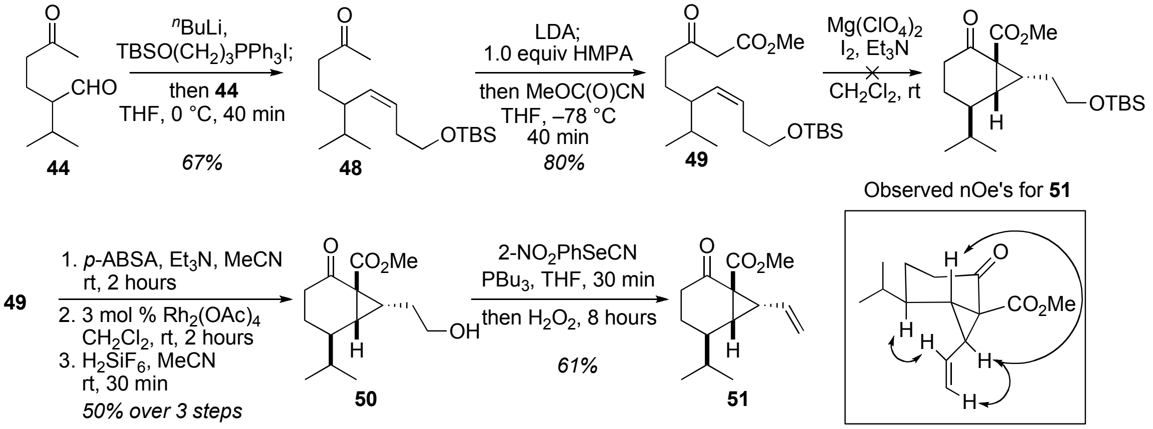
Scheme 3-8. Synthesis of Ethyl Cyclopropane **47**



CHO
O
+
Et$_2$NTMS
(10 mol %)
MeCN, reflux
15 hours
72%
O
CHO
44
nBuLi,
^{n}PrPPh$_3$Br;
then 44
THF, 0 °C, 30 min
60%
O
45
LDA;
1.0 equiv HMPA
then EtOC(O)CN
THF, –78 °C, 20 min
67%
O
CO$_2$Et
46
Mg(ClO$_4$)$_2$, I$_2$
Et$_3$N
CH$_2$Cl$_2$, rt
16 hours
57%
O
CO$_2$Et
H
47

The vinyl cyclopropane **51** was prepared using a silyl ether as a protected olefin. This conservative approach was taken to avoid potential complications with a conjugated diene during cyclopropanation. Additionally, a methyl ester was chosen in preference to the ethyl ester to simplify the spectrum for eventual NOESY experiments. After successful Wittig olefination and carboalkoxylation, the Yang cyclopropanation[26] of **49** was found to be ineffective, presumably a result of steric or electronic deactivation by the -OTBS group (Scheme 3-9). Instead, the cyclopropane was installed by conversion to the diazo compound and Rh-catalyzed cyclopropanation. TBS removal with H_2SiF_6 afforded alcohol **50** in 50% yield over three steps. Grieco selenoxide elimination[27] provided the vinyl cyclopropane **51**. NOESY experiments confirmed the relative stereochemistry.

Scheme 3-9. Synthesis of Vinyl Cyclopropane **51**



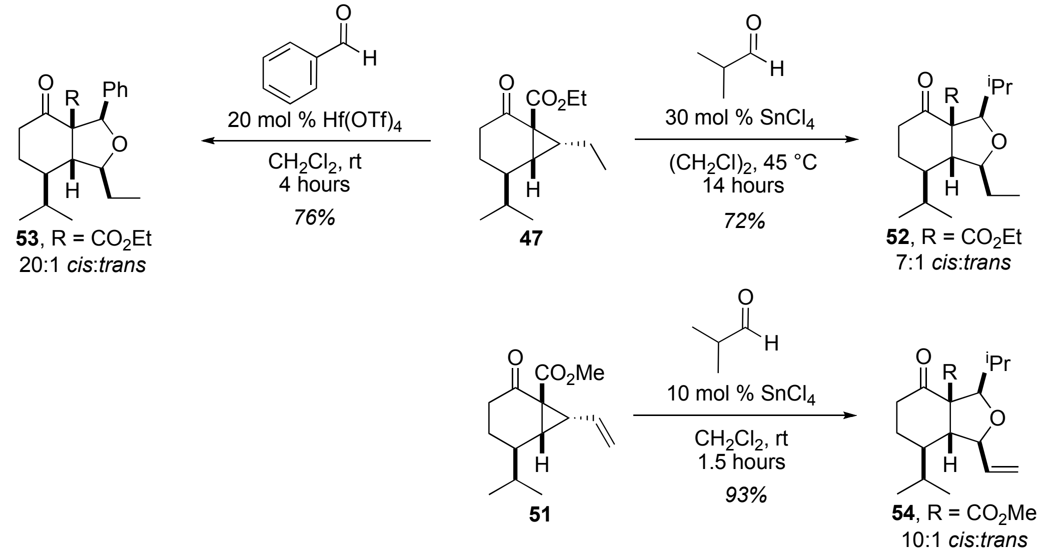
44
ⁿBuLi, TBSO(CH2)3PPh3I; then 44
THF, 0 °C, 40 min
67%
CHO
48
OTBS
LDA; 1.0 equiv HMPA
then MeOC(O)CN
THF, –78 °C
40 min
80%
49
CO2Me
Mg(ClO4)2
I2, Et3N
CH2Cl2, rt
H
OTBS
49
1. p-ABSA, Et3N, MeCN rt, 2 hours
2. 3 mol % Rh2(OAc)4 CH2Cl2, rt, 2 hours
3. H2SiF6, MeCN rt, 30 min
50% over 3 steps
50
OH
2-NO2PhSeCN
PBu3, THF, 30 min
then H2O2, 8 hours
61%
51
Observed nOe's for 51
CO2Me
H

3.2.2 Cycloadditions with Model Systems

Using the standard conditions developed in our laboratory for the [3+2]-cycloaddition, several cyclopropane-aldehyde combinations were found effective: alkyl-aryl, alkyl-alkyl, and vinyl-alkyl. The rate, diastereoselectivity, and efficiency of the cycloadditions were all consistent with expectations founded from our experience with simpler systems; vinyl cyclopropanes are more active than their alkyl counterparts, and aryl aldehydes give higher dr's than alkyl aldehydes (Scheme 3-10). The lowest yielding cycloaddition was the reaction of ethyl cyclopropane **47** with isobutyraldehyde requiring 30 mol % $SnCl_4$ at 45 °C for 14 hours to give only a 71% yield of **52** with 7:1 dr. Benzaldehyde reacted at room temperature with 20 mol % $Hf(OTf)_4$, still reasonably forcing conditions, to give 74% of the cycloadduct **53** in 20:1 dr. Cycloaddition of the activated vinyl cyclopropane (**51**) with isobutyraldehyde was most facile and provided **54** in 93% yield with a moderate 10:1 dr.

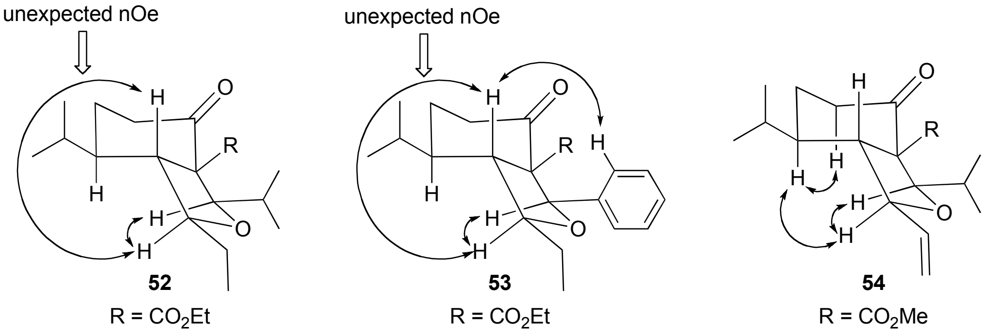
Complications arose during NOESY experiments with cycloadducts **52** and **53**. Key interactions could not be located due to overlapping signals in the alkyl region of the spectra. Furthermore, an unexpected nOe was observed for these two adducts between hydrogen atoms we projected to be oriented on opposite sides of the molecules (Figure 3-1). We felt these signals were likely artifacts due to zero-quantum effects for two reasons: (1) these hydrogen atoms would be anti-periplanar to one another in the desired diastereomer and couple strongly, and (2) other nOe's observed in **53** were consistent with the structure drawn. Although experimental parameters can be modified to reduce artifacts due to zero-quantum effects in NOESY spectra,[28-30] we sought to unambiguously determine the structure of **52** using X-ray analysis (*vide infra*). NOESY experiments were able to confirm the structure of **54.**

Scheme 3-10. Cycloadditions with Model Systems



20 mol % Hf(OTf)$_4$
CH$_2$Cl$_2$, rt
4 hours
76%
30 mol % SnCl$_4$
(CH$_2$Cl)$_2$, 45 °C
14 hours
72%
10 mol % SnCl$_4$
CH$_2$Cl$_2$, rt
1.5 hours
93%
53, R = CO$_2$Et
20:1 *cis*:*trans*
47
52, R = CO$_2$Et
7:1 *cis*:*trans*
51
54, R = CO$_2$Me
10:1 *cis*:*trans*

Figure 3-2. Diagnostic nOe Enhancements for Cycloadducts **52**, **53**, and **54**

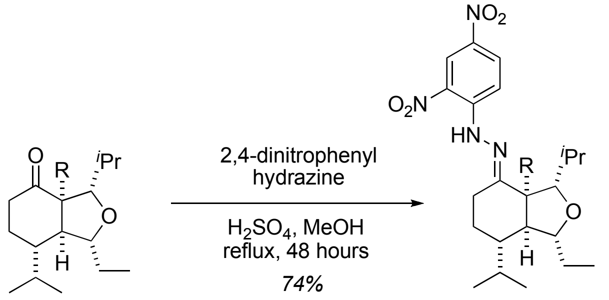

unexpected nOe
unexpected nOe
H
O
R
H
H
H
O
H
O
R
H
H
H
H
O
H
O
R
H
H
H
H
O

52
R = CO_2Et

53
R = CO_2Et

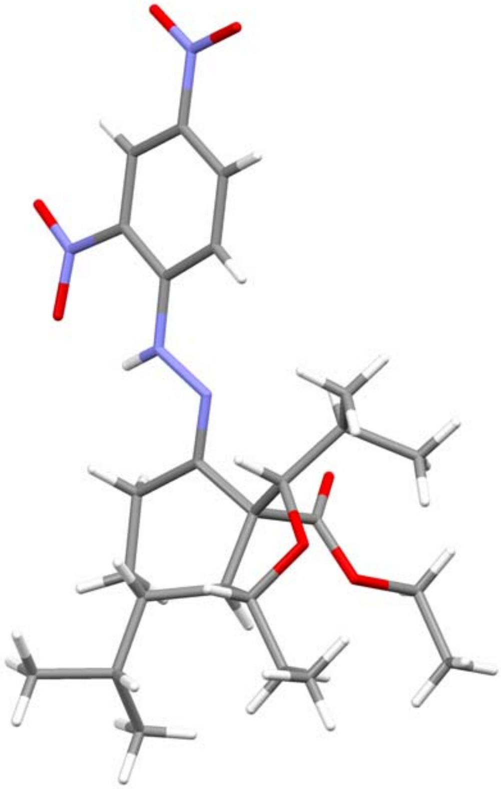
54
R = CO_2Me

The crystalline 2,4-dinitrophenylhydrazone of **55** was prepared in good yield as a single diastereomer (eq 1). X-ray quality crystals were obtained by slow evaporation of an ethanolic solution of **55**. Gratifyingly, the structure was solved to confirm our stereochemical assignment (Figure 3-3).[31]


O
R
iPr
O
H
2,4-dinitrophenyl hydrazine
H2SO4, MeOH
reflux, 48 hours
74%
NO2
O2N
HN
N
R
iPr
O
H

52, R = CO_2Et **55**, R = CO_2Et (1)

Figure 3-3. X-Ray Crystal Structure of **55**

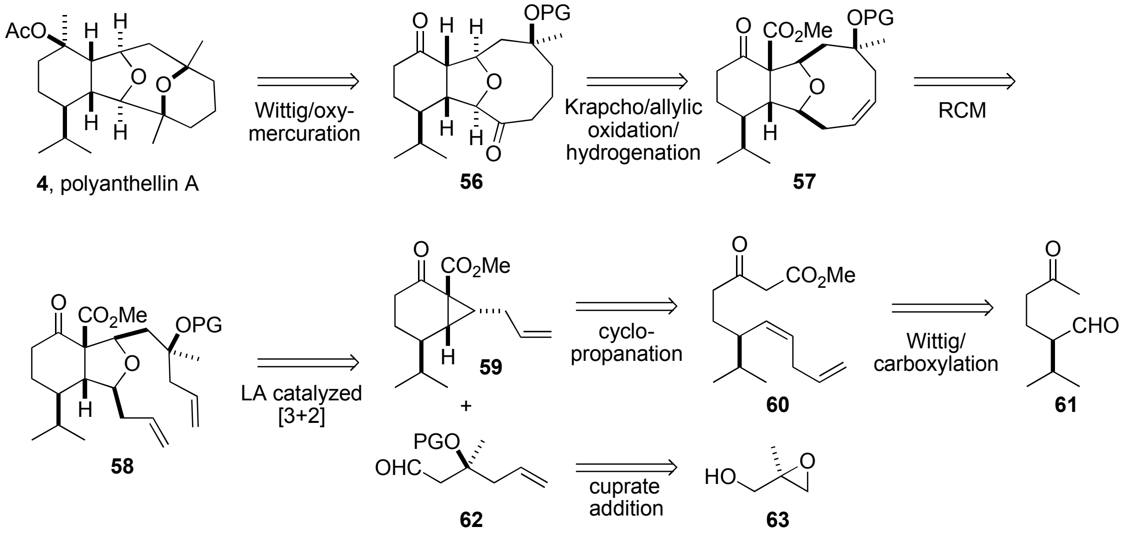


3.2.3 Retrosynthetic Analysis of (+)-Polyanthellin A

To begin our retrosynthetic analysis of polyanthellin A (**4**), we reasoned a double methylene Wittig and subsequent oxymercurations of protected hydroxy dione **56** would afford **4**, in close analogy with Kim's synthesis (Scheme 3-11). This dione would arise from allylic oxidation, Krapcho decarboalkoxylation, and hydrogenation of oxonene **57**, itself prepared by a RCM of cycloadduct **58**. Our studies with model systems suggested a challenging allyl cyclopropane-alkyl aldehyde cycloaddition would be feasible, with the requisite cyclopropane **59** available using the methods employed with the model systems.

A suitably protected hydroxy aldehyde (**62**) would be formed by a vinyl cuprate epoxide opening of enantiopure epoxide **63** and subsequent functional group manipulations.

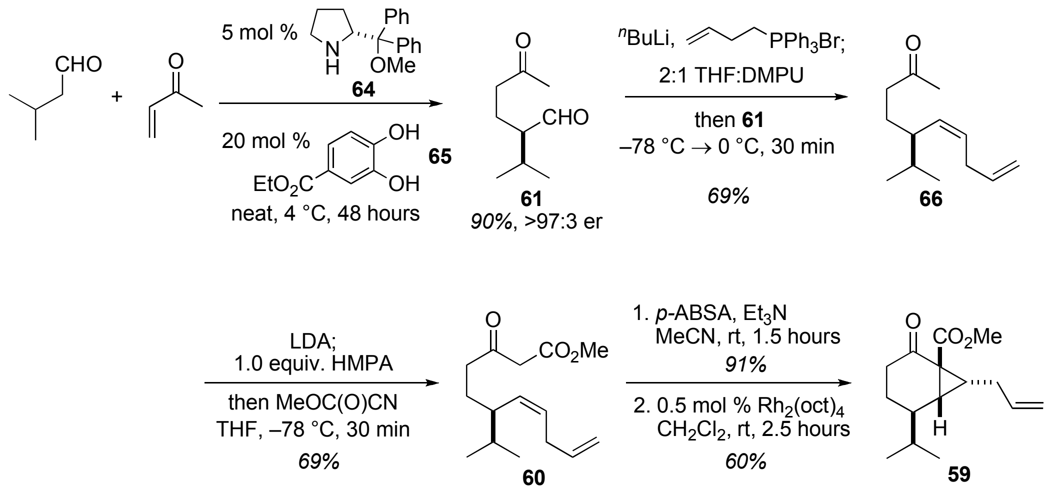
Scheme 3-11. Retrosynthetic Analysis of Polyanthellin A (**4**)


Wittig/oxy-mercuration
Krapcho/allylic oxidation/ hydrogenation
RCM
LA catalyzed [3+2]
cyclo-propanation
Wittig/ carboxylation
cuprate addition
4, polyanthellin A
56
57
58
59
60
61
62
63

3.2.4 Synthesis of the Allyl Cyclopropane

The synthesis of allyl cyclopropane **59** began with an enantioselective organocatalyzed conjugate addition of isovaleraldehyde to MVK developed by Gellman (Scheme 3-12).[32] In the initial communication, the authors reported a 65% yield of **61** using D-diphenylprolinol methyl ether (**64**) after 36 hours. Following this procedure, we observed only trace product. Gellman and coworkers found the addition of a cocatalyst, catechol **65**, increased the rate with challenging substrates, but that it was not necessary for **61**. We found the use of this additive was essential, and obtained the keto aldehyde **61** in 90% yield after 48 hours. Chiral GLC analysis of the corresponding acid quantified the er as >97:3, lower than the 99:1 er reported. Wittig olefination in THF provided the skipped diene **66** in 59% yield. Changing the counterion to Na$^+$ or K$^+$ reduced the yield, but the addition of a cosolvent was beneficial. A 2:1 THF:HMPA mixture was found to be optimal (80%), though we chose to use DMPU as a safer, but less effective alternative (69%). Keto ester **60** was prepared with Mander's reagent.[25] Yang's cyclopropanation conditions[26] ($Mg(ClO)_4$, $I_{2,}$ Et_3N) failed in the presence of the terminal olefin, so the use of metal carbenoids were investigated. After diazo formation with *p*-ABSA, experiments revealed $Rh_2(oct)_4$ in CH_2Cl_2 to be optimal, providing **59** in 60% yield.

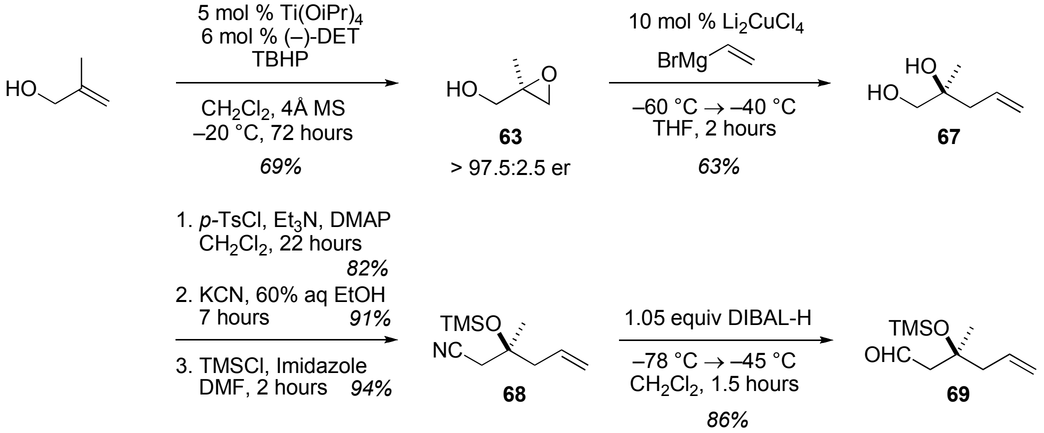
Scheme 3-12. Synthesis of Allyl Cyclopropane **59**


CHO
+
O
5 mol %
Ph
Ph
N
H
OMe
64
20 mol %
OH
65
EtO2C
OH
neat, 4 °C, 48 hours
O
CHO
61
90%, >97:3 er
nBuLi,
PPh3Br;
2:1 THF:DMPU
then 61
−78 °C → 0 °C, 30 min
69%
O
66
LDA;
1.0 equiv. HMPA
then MeOC(O)CN
THF, −78 °C, 30 min
69%
O
CO2Me
60
1. p-ABSA, Et3N
MeCN, rt, 1.5 hours
91%
2. 0.5 mol % Rh2(oct)4
CH2Cl2, rt, 2.5 hours
60%
O
CO2Me
H
59

3.2.5 Synthesis of the Aldehyde Coupling Partner

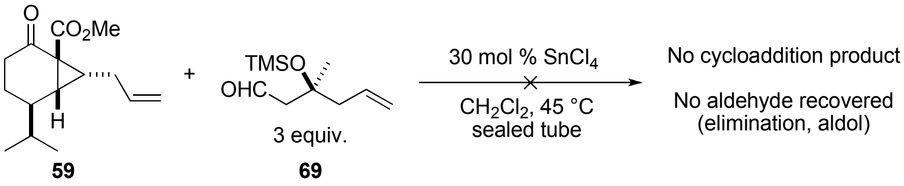
Hexenal **69** was prepared uneventfully from methallyl alcohol in six steps (Scheme 3-13). Sharpless asymmetric epoxidation[33,34] provided the known epoxy alcohol **63** (er > 97.5:2.5) [35,36], which was opened with a vinyl cuprate to give diol **67**.[37] The primary alcohol was selectively converted to the nitrile by activation as a sulfonate and S_N2 displacement with cyanide. The tertiary alcohol was protected to afford the TMS ether **68**. The requisite aldehyde, **69**, was prepared in 86% yield by DIBAL-H reduction and SiO_2-promoted hydrolysis of the intermediate imine.

Scheme 3-13. Synthesis of Hexenal **69**


5 mol % Ti(OiPr)4
6 mol % (–)-DET
TBHP
CH2Cl2, 4Å MS
–20 °C, 72 hours
69%
63
> 97.5:2.5 er
10 mol % Li2CuCl4
BrMg
–60 °C → –40 °C
THF, 2 hours
63%
67
1. p-TsCl, Et3N, DMAP
CH2Cl2, 22 hours
82%
2. KCN, 60% aq EtOH
7 hours 91%
3. TMSCl, Imidazole
DMF, 2 hours 94%
68
1.05 equiv DIBAL-H
–78 °C → –45 °C
CH2Cl2, 1.5 hours
86%
69

3.2.6 [3+2]-Cycloaddition Optimization

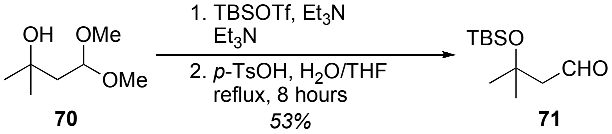
With the cyclopropane **59** and aldehyde **69** in hand, we attempted the [3+2]-cycloaddition using the conditions that were effective during our model studies - 30 mol % $SnCl_4$ at 45 ºC. Although cognizant that **69** could be prone to elimination in the presence of a Lewis acid, we were disappointed that this was indeed a serious complication. After reaction, no cycloadduct was detected by ^{1}H NMR, and the aldehyde had completely decomposed. Realizing that extensive optimization studies would be required, we decided to examine a model system, both to preserve our more precious material and ease analysis.


CO2Me
H
59
+
3 equiv.
69
30 mol % SnCl4
CH2Cl2, 45 °C
sealed tube
No cycloaddition product
No aldehyde recovered
(elimination, aldol)

(2)

Model aldehyde **71** was synthesized from commercially available 4,4-dimethoxy-2-methyl-2-butanol (**70**) in two steps (Scheme 3-14). The alcohol was protected as the TBS ether with TBSOTf, and the acetal removed with *p*-TsOH in H_2O/THF. The TBS ether was selected, because we hypothesized its large size would prevent coordination of the ether oxygen to a Lewis acid, preventing elimination.

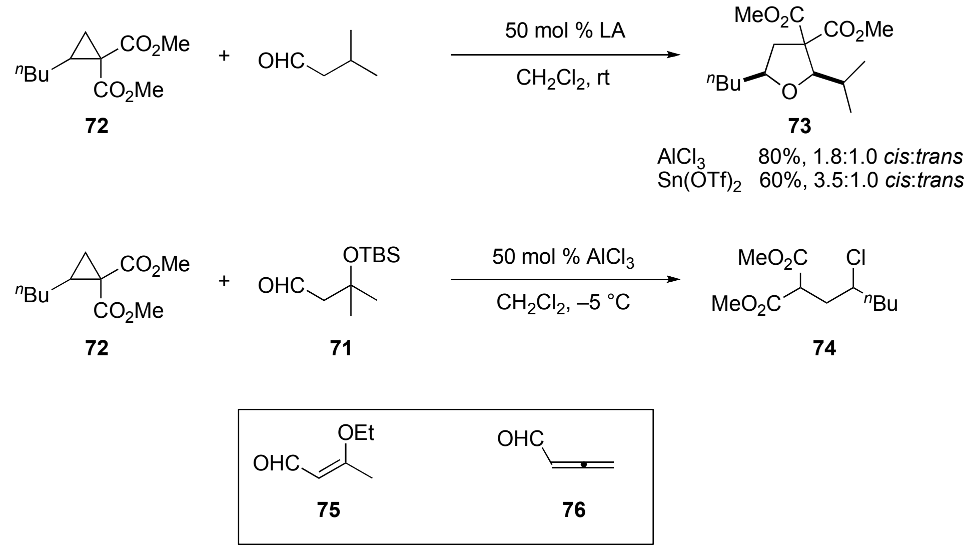
Scheme 3-14. Synthesis of Model Aldehyde **71**



Before using aldehyde **71**, a screen of Lewis acids was conducted with *n*-butyl cyclopropane **72** and isovaleraldehyde (Scheme 3-15). In previous studies, our laboratory had never extensively evaluated Lewis acids for use with alkyl cyclopropanes and alkyl aldehydes. Ten Lewis acids (50 mol %) that were effective to varying degrees with aryl-aryl cycloadditions were screened, but only $AlCl_3$ and $Sn(OTf)_2$ produced more than trace quantities of cycloadduct **73** (entire screen not shown). These two Lewis acids were chosen for further study with the model aldehyde **71**. We found **71** was completely decomposed by $Sn(OTf)_2$, but was only partially degraded by $AlCl_3$. Although the aldehyde survived, only the chloride **74** was isolated from the attempted cycloaddition reaction; apparently, ring-opening by the hindered aldehyde is not able to compete with chloride ions present in solution.

At this time, we explored the use of less functionalized aldehydes that could be converted into ketones after cycloaddition. Several asymmetric ketone allylations[38-40] are known that could ultimately be used to prepare the desired homoallyl alcohol; however, preliminary experiments with **75**[41] and **76**[42] were not encouraging. Because a route that uses these aldehydes is inherently less efficient but would still require optimization, we returned to TBS-protected hydroxyaldehyde **71**.

Scheme 3-15. Initial Results from Model Cycloadditions



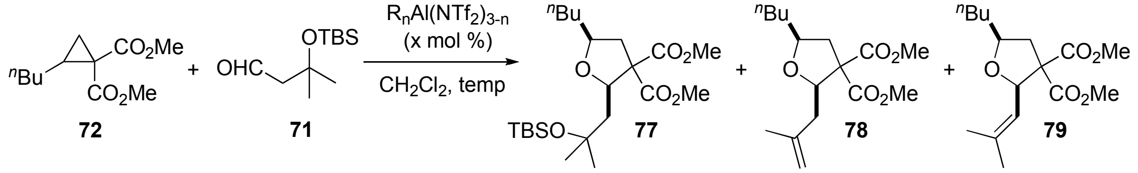
CO2Me
nBu
CO2Me
72
+
OHC
50 mol % LA
CH2Cl2, rt
MeO2C
CO2Me
nBu
O
73
AlCl3 80%, 1.8:1.0 cis:trans
Sn(OTf)2 60%, 3.5:1.0 cis:trans
CO2Me
nBu
CO2Me
72
+
OHC
OTBS
71
50 mol % AlCl3
CH2Cl2, –5 °C
MeO2C
Cl
MeO2C
nBu
74
OEt
OHC
75
OHC
76

Because we observed competitive chloride addition to **72**, we hypothesized that excluding such nucleophilic anions would permit successful cycloaddition. In this light, a series of aluminum bistriflimides were examined as potential catalysts (Table 3-1). These complexes were prepared and used *in situ* after protonolysis of $AlMe_3$ with $HNTf_2$. $Al(NTf_2)_3$ was too active and completely decomposed **71**, even at –70 ºC. Reducing the Lewis acidity by replacing one bistriflimide with a methyl group resulted in a low yield of cycloadduct **79**, but completely eliminated the -OTBS group in cycloadduct and aldehyde. The first promising result was found by changing to Me_2AlNTf_2. This catalyst still promoted elimination in both the aldehyde and cycloadduct, but the desired adduct **77** made up 50% of the product mixture at 0 ºC. This was increased to 66% at –20 ºC, but further reduction to –35 ºC shut down the cycloaddition and instead catalyzed the trimerization of **71** to **80**.

Yamamoto has reported the use of a bisphenoxy aluminum bistriflimide for ketene cycloadditions.[43] Using this precedent, we prepared several alkoxy- and phenoxy aluminum bistriflimide complexes. Although Yamamoto prepared the catalyst from $AlMe_3$ and 2,6-diphenylphenol without isolation of the $(ArO)_2AlMe$ complex prior to protonolysis with $HNTf_2$, we found that only catalysts directly prepared from isolated and recrystallized $(RO)_nAlMe_{3-n}$ complexes were effective. The best catalysts were the hindered $MABRNTf_2$ and $MADNTf_2$ complexes; both curtailed -OTBS elimination in the aldehyde **71** and cycloadduct **77**. $MABRNTf_2$ gave the best dr at 8.1:1, but 25% $MADNTf_2$ was used for further studies because of superior reaction efficiency.

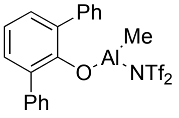
The optimized conditions were not able to effect the cycloaddition of **59** and **71**, affording only trace product after 10 hours at room temperature (Scheme 3-16). We surmised that bicyclic cyclopropane **59** is less sterically accessible than *n*-butyl cyclopropane **72**, and hoped a reduction in the size of the protecting group would provide a solution. Because we had already prepared aldehyde **69** with an -OTMS group, we delved directly into the cycloaddition of **59** and **69**. Gratifyingly, the cycloadduct **82** was formed, but in a modest 35-40% yield in 10-11:1:1 dr. None of the diastereomers were separable. $MABNTf_2$, which contained a bulky triethylmethyl substituent, was prepared but did not increase the efficiency of the reaction.

Table 3-1. Screen of Aluminum Bistriflimides



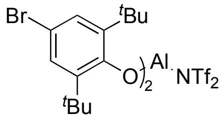
^{n}Bu
CO$_2$Me
CO$_2$Me
72
+
OHC
OTBS
71
R$_n$Al(NTf$_2$)$_{3-n}$
(x mol %)
CH$_2$Cl$_2$, temp
^{n}Bu
O
CO$_2$Me
CO$_2$Me
TBSO
77
+
^{n}Bu
O
CO$_2$Me
CO$_2$Me
78
+
^{n}Bu
O
CO$_2$Me
CO$_2$Me
79

Entry	Lewis Acid[a]	mol	Temp (°C)	Total Yield[b] (%)	**77**:**78**:**79**[c]	**77**(*cis*:*trans*)[c]
1	Al(NTf$_2$)$_3$	50	–70	0	NA	NA
2	MeAl(NTf$_2$)$_2$	50	0	28	0:0:1	NA
3		50	–20	<5	0:0:1	NA
4		50	–35	0 (0% conv. **72**)	NA	NA
5	Me$_2$NTf$_2$	50	0	63	2:1:1	5.5:1
6		50	–20	72	4:1:1	5.5:1
7		50	–35	**80** (0% conv. **72**)	NA	NA
8	^{t}BuOAlMeNTf$_2$	25	rt	78	1.3:1:0.3	6.8:1
9	DPPAlMeNTf$_2$	25	rt	39	32:1:0	5.3:1
10	MABRNTf$_2$	25	rt	55	1:0:0	8.1:1
11	MADNTf$_2$	25	rt	71	85:1:0	6.1:1
12		10	rt	58	1:0:0	6.3:1



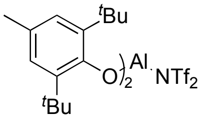
Ph
Me
O
Al
NTf$_2$
Ph

DPPAlMeNTf$_2$



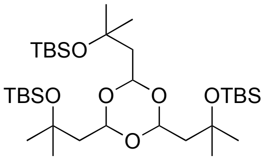
Br
^{t}Bu
O
2
Al
NTf$_2$
^{t}Bu

MABRNTf$_2$



^{t}Bu
O
2
Al
NTf$_2$
^{t}Bu

MADNTf$_2$

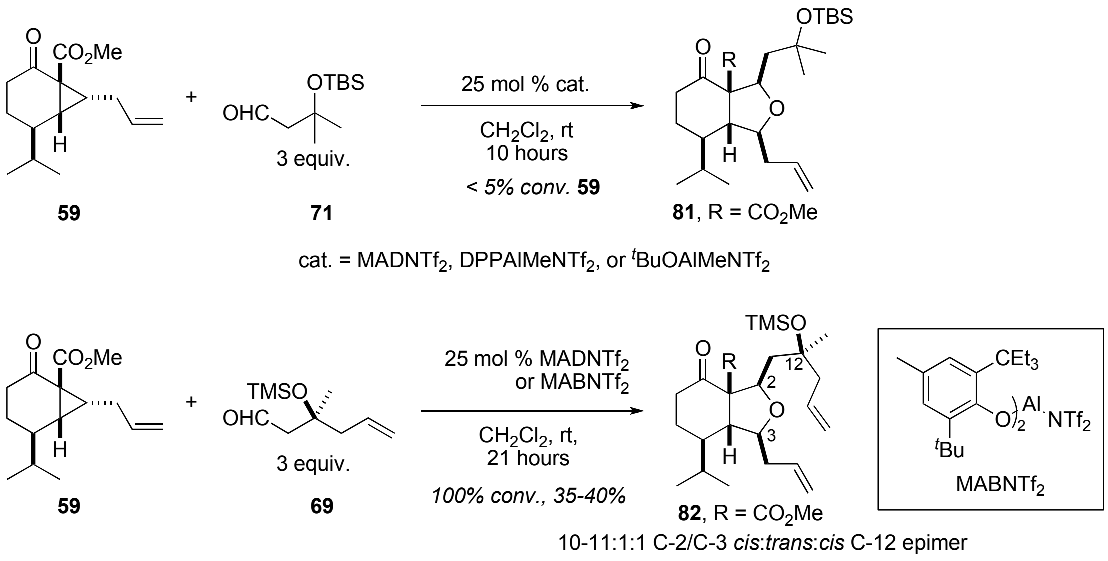


TBSO
TBSO
O
O
OTBS
O

80

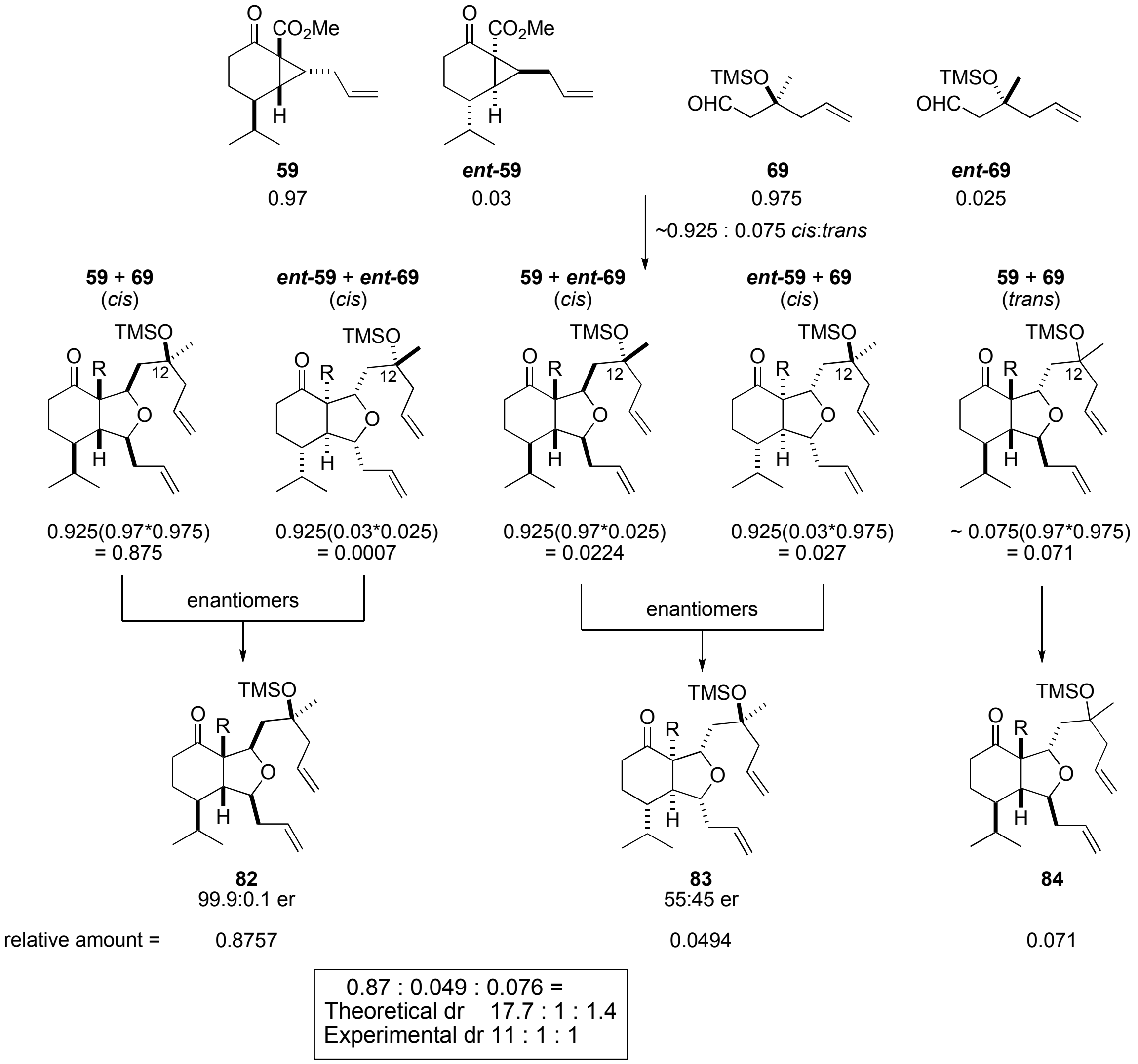
All reactions were conducted with 3 equivalents of **71** until complete conversion of **72**, unless otherwise noted. The reaction times varied between 1.5 and 18 hours. [a]The aluminum bistriflimides were generated and used *in situ* by protonolysis of either AlMe$_3$ or recrystallized (RO)$_n$AlMe$_{3-n}$ complexes with HNTf$_2$. [b]Determined by ^{1}H NMR spectroscopy by integration relative to an internal standard. [c]Determined by ^{1}H NMR spectroscopy.

Scheme 3-16. Cycloaddition with **59** using Optimized Conditions


O
CO₂Me
H
+
OTBS
OHC
3 equiv.
25 mol % cat.
CH₂Cl₂, rt
10 hours
< 5% conv. 59
OTBS
O
R
O
H
59
71
81, R = CO₂Me
cat. = MADNTf₂, DPPAlMeNTf₂, or ᵗBuOAlMeNTf₂
O
CO₂Me
H
+
TMSO
OHC
3 equiv.
25 mol % MADNTf₂
or MABNTf₂
CH₂Cl₂, rt,
21 hours
100% conv., 35-40%
TMSO
O
R
12
2
O
3
H
59
69
82, R = CO₂Me
10-11:1:1 C-2/C-3 cis:trans:cis C-12 epimer
CEt₃
Al
O)₂
NTf₂
ᵗBu
MABNTf₂

The formation of a third diastereomer is rationalized by the combination of **59** and **69** with ***ent*-69** and ***ent*-59**, respectively (Scheme 3-17). Using the measured er's for both **59** and **69**, simple calculations predict a 17.7:1:1.4 dr which is close to the measured 11:1:1 dr. This prediction assumes the rate of the cycloaddition of ***ent*-59** with **69** is identical to that of **59** and **69**. These reactions proceed through diastereomeric transition states, and thus this assumption is false, likely accounting for the difference between the theoretical and experimental values. The production of the additional diastereomer causes the er of **82** to be upgraded to 99.9:0.1 at the expense of chemical yield.

Scheme 3-17. Rationalization of Additional Diastereomer



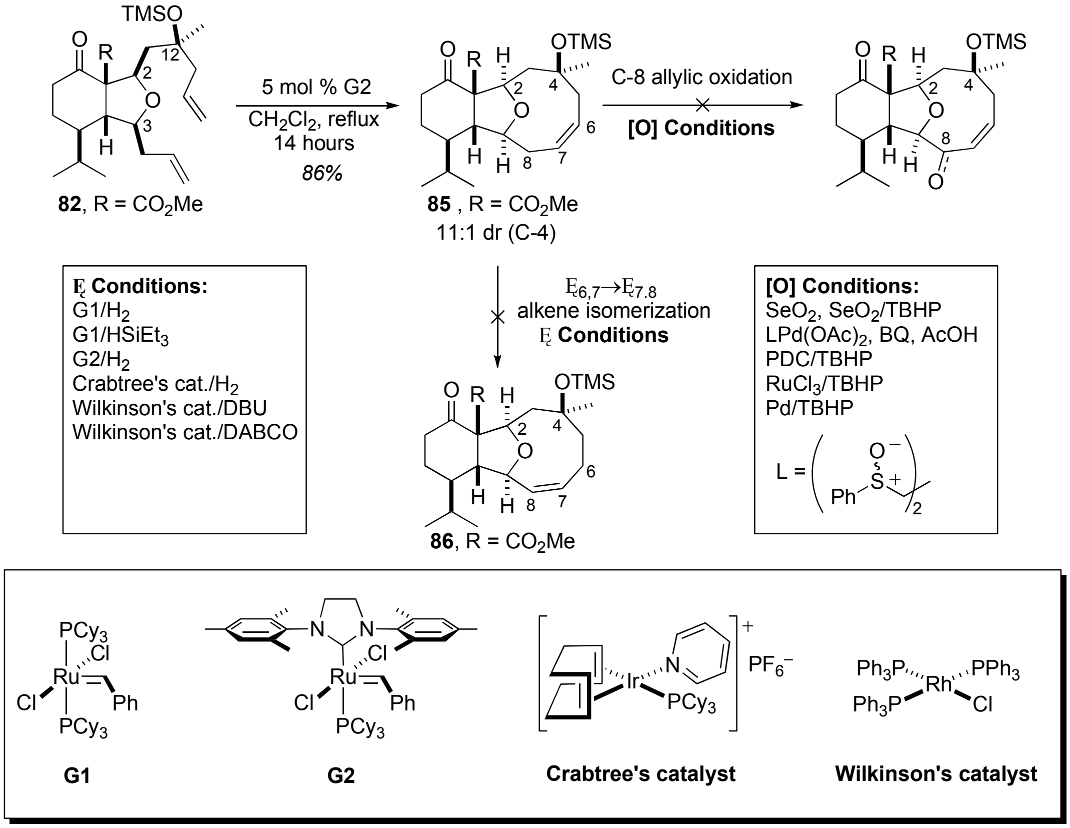
CO2Me
H
59
0.97
ent-59
0.03
TMSO
OHC
69
0.975
ent-69
0.025
~0.925 : 0.075 cis:trans
59 + 69 (cis)
ent-59 + ent-69 (cis)
59 + ent-69 (cis)
ent-59 + 69 (cis)
59 + 69 (trans)
R
12
0.925(0.97*0.975) = 0.875
0.925(0.03*0.025) = 0.0007
0.925(0.97*0.025) = 0.0224
0.925(0.03*0.975) = 0.027
~ 0.075(0.97*0.975) = 0.071
enantiomers
enantiomers
82
99.9:0.1 er
83
55:45 er
84
relative amount =
0.8757
0.0494
0.071
0.87 : 0.049 : 0.076 =
Theoretical dr 17.7 : 1 : 1.4
Experimental dr 11 : 1 : 1

3.2.7 Failed Allylic Oxidation and Alkene Isomerization

Instead of optimizing the cycloaddition further, cycloadduct **82** was advanced to determine if the remainder of the synthesis would be feasible. RCM with 5 mol % of Grubbs' 2nd generation catalyst was efficient under standard conditions to provide the oxonene **85** (Scheme 3-18). The minor *trans* diastereomer cannot cyclize due to conformational constraints and was easily separated at this stage.

Allylic oxidation of **85** proved more challenging. A variety of conditions were ineffective, including both SeO_2 and transition metal catalyzed oxidations (Scheme 3-18).[44-47] Oxidation of either the cycloadduct **82** or allyl cyclopropane **59** was also unsuccessful, forcing a change of strategy. It was hoped that alkene isomerization to alkenyl substituted THF **86** would permit direct olefin oxidation, either through hydroboration or epoxidation. Several protocols have been developed that convert RCM catalysts into isomerization catalysts by the addition of diluted H_2 or Et_3SiH after metathesis is complete.[48-50] However, with the exception of TMS deprotection, **82** was completely inert to these conditions and others using Crabtree's or Wilkinson's catalysts. We did not attempt these reactions with alternative protecting groups or after conducting the Krapcho decarboalkoxylation, primarily because we surmised oxonene **86** could be readily synthesized from vinyl cyclopropane **89**. Hopefully, the efficiency of the cycloaddition would also benefit by using this more active cyclopropane.

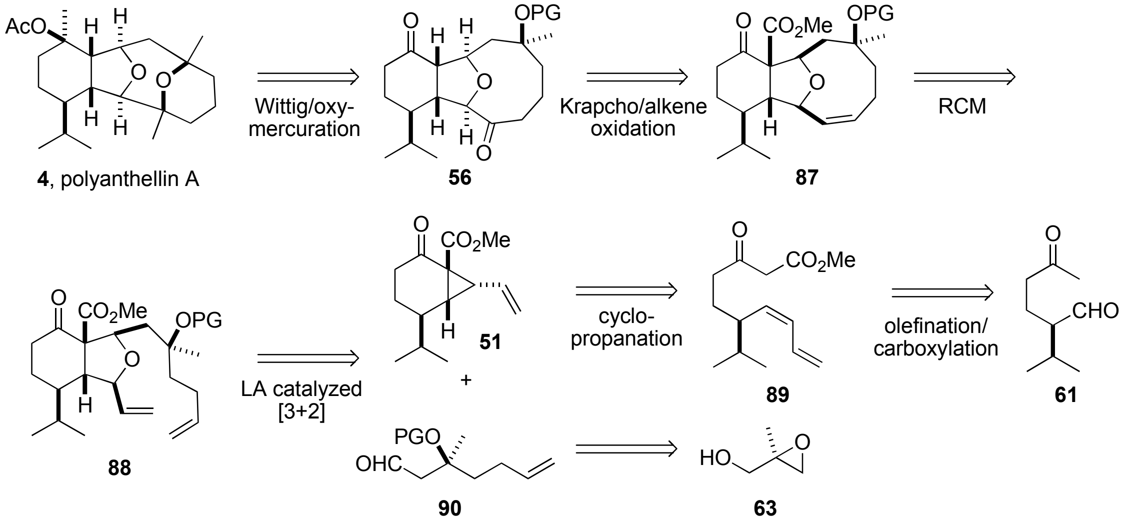
Scheme 3-18. Olefin Metathesis and Unsuccessful Oxidation or Isomerization


TMSO
12
2
3
82, R = CO2Me
5 mol % G2
CH2Cl2, reflux
14 hours
86%
OTMS
4
6
7
8
85 , R = CO2Me
11:1 dr (C-4)
C-8 allylic oxidation
[O] Conditions
E Conditions:
G1/H2
G1/HSiEt3
G2/H2
Crabtree's cat./H2
Wilkinson's cat./DBU
Wilkinson's cat./DABCO
E6,7→E7,8
alkene isomerization
E Conditions
86, R = CO2Me
[O] Conditions:
SeO2, SeO2/TBHP
LPd(OAc)2, BQ, AcOH
PDC/TBHP
RuCl3/TBHP
Pd/TBHP
L =
G1
G2
Crabtree's catalyst
Wilkinson's catalyst

3.2.8 Revised Retrosynthetic Analysis of (+)-Polyanthellin A

The revised retrosynthesis with vinyl cyclopropane **51** is similar to that discussed with allyl cyclopropane **59** (*vide supra*). The major changes are removal of a methylene spacer in the cyclopropane and the addition of a methylene group in the aldehyde (Scheme 3-19). The transposition of the olefin in the oxonene **87** requires a direct olefin oxidation instead of an allylic oxidation.

Scheme 3-19. Retrosynthetic Analysis with Vinyl Cyclopropane **51**

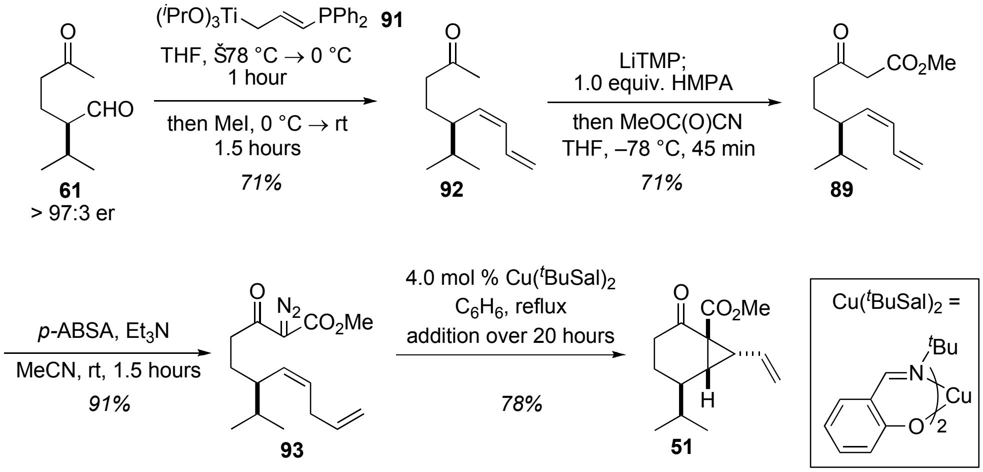


4, polyanthellin A
Wittig/oxy-mercuration
56
Krapcho/alkene oxidation
87
RCM
88
LA catalyzed [3+2]
51
+
90
cyclo-propanation
89
olefination/ carboxylation
61
63

3.2.9 Revised Synthesis of the Vinyl Cyclopropane

A racemic synthesis of **51** had already been accomplished during our model studies; however, we wished to pursue a more efficient synthesis that avoided protecting groups. From keto aldehyde **61**, the (*Z*)-diene was installed using Yamamoto's protocol.[51] Allyldiphenyl phosphine (not shown) was deprotonated with *t*-BuLi and transmetalated to titanium with $Ti(O^iPr)_4$ to give **91**. Reaction of **91** with **61** forms an intermediate *anti*-phosphine alkoxide that undergoes a *syn*-elimination after treatment with MeI to yield **92** in 71% yield (Scheme 3-20). Deprotonation with LiTMP and treatment with Mander's reagent gave the keto ester **89**. LiTMP was more effective than either LDA or LiHMDS. Diazo formation with *p*-ABSA proceeded cleanly, but various Rh complexes provided poor yields of the desired vinyl cyclopropane **51** (< 39%). Experimentation revealed that $Cu(^tBuSal)_2$ provides better selectivity for cyclopropanation over C–H insertion and a 78% yield.[52]

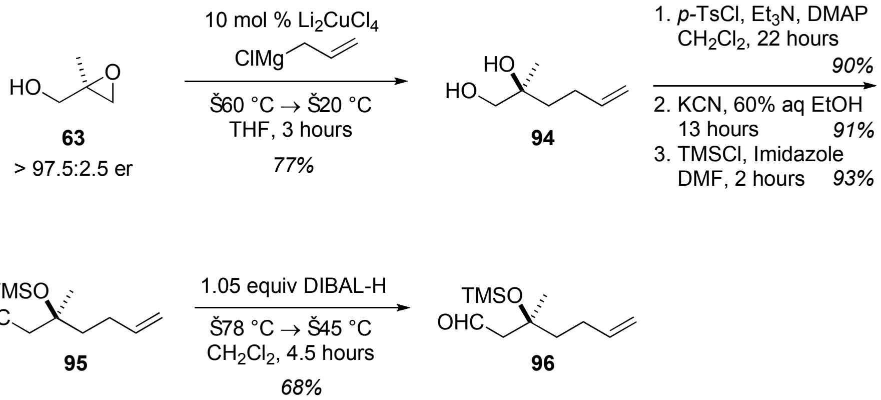
Scheme 3-20. Revised Synthesis of Vinyl Cyclopropane **51**



(^{i}PrO)$_3$Ti PPh$_2$ 91
THF, Š78 °C → 0 °C
1 hour
then MeI, 0 °C → rt
1.5 hours
71%
61
> 97:3 er
92
LiTMP;
1.0 equiv. HMPA
then MeOC(O)CN
THF, –78 °C, 45 min
71%
89
CO$_2$Me
p-ABSA, Et$_3$N
MeCN, rt, 1.5 hours
91%
93
N$_2$
4.0 mol % Cu(^{t}BuSal)$_2$
C$_6$H$_6$, reflux
addition over 20 hours
78%
51
Cu(^{t}BuSal)$_2$ =
^{t}Bu
Cu
2

Heptenal **96** was synthesized by an analogous sequence to **69**, with an allyl rather than vinyl cuprate used to prepare the diol **94**[37] (Scheme 3-21). Sulfonylation, cyanide substitution, TMS-protection, and DIBAL-H reduction all proceeded uneventfully to produce aldehyde **96**.

Scheme 3-21. Synthesis of Heptenal **96**

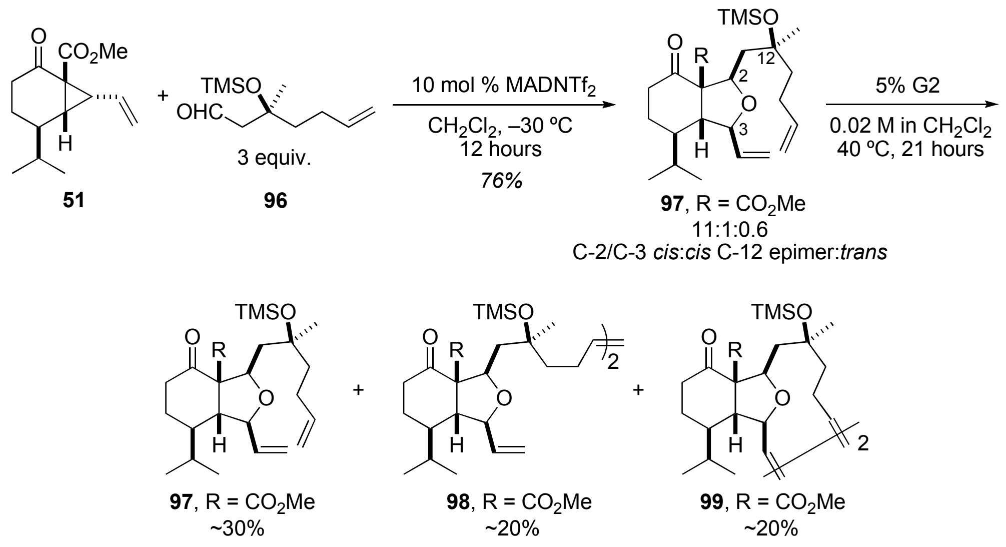


63
> 97.5:2.5 er
10 mol % Li$_2$CuCl$_4$
ClMg
Š60 °C → Š20 °C
THF, 3 hours
77%
94
1. p-TsCl, Et$_3$N, DMAP
CH$_2$Cl$_2$, 22 hours
90%
2. KCN, 60% aq EtOH
13 hours 91%
3. TMSCl, Imidazole
DMF, 2 hours 93%
95
1.05 equiv DIBAL-H
Š78 °C → Š45 °C
CH$_2$Cl$_2$, 4.5 hours
68%
96

3.2.10 Cycloaddition and Olefin Metathesis of the Vinyl Cycloadduct

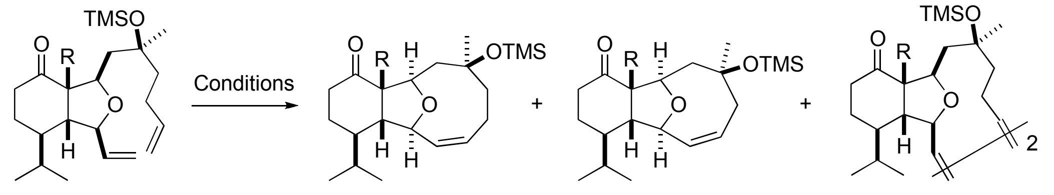
As expected, the cycloaddition of vinyl cyclopropane **51** with **96** was higher yielding (76% vs. 41%), more diastereoselective (18:1 *cis*:*trans*), and occurred under more mild conditions (10% MADNTf$_2$ at –30 ºC) than the allyl cyclopropane **59** (Scheme 3-22). However, the olefin metathesis of cycloadduct **97** failed completely under the conditions that were previously successful with adduct **82**. Dimerization and macrocyclic dimerization to afford **98** and **99** were the only identifiable products of metathesis, with an appreciable amount of starting material recovered.

Scheme 3-22. Cycloaddition of Vinyl Cyclopropane **51** and Failed Olefin Metathesis


O
CO2Me
H
51
TMSO
OHC
3 equiv.
96
10 mol % MADNTf2
CH2Cl2, –30 ºC
12 hours
76%
TMSO
O
R
12
2
O
3
H
97, R = CO2Me
11:1:0.6
C-2/C-3 cis:cis C-12 epimer:trans
5% G2
0.02 M in CH2Cl2
40 ºC, 21 hours
97, R = CO2Me
~30%
98, R = CO2Me
~20%
2
99, R = CO2Me
~20%

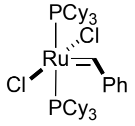
After a brief survey of solvents, it was apparent CH$_2$Cl$_2$ was optimal under high dilution (Table 3-2, entries 1-9). Concentrated solutions and aromatic solvents facilitated both dimerization and olefin isomerization, the latter resulting in the ring contracted eight-membered oxonene **101**. The use of G1 only returned starting material and uncyclized dimer **98** (entry 10). We found G2 and H-G2 were effective catalysts at elevated temperatures (60-80 ºC) in sealed tubes, with H-G2 being slightly more efficient (compare entries 13 and 14). Unfortunately, high catalyst loadings and long reactions (16-24 hours) were required to force the reactions to completion.

Table 3-2. Optimization of the Ring Closing Metathesis of **97**

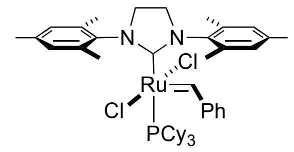


97, R = CO_2Me **100** **101** **99**

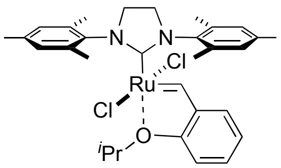
Entry	Catalyst (mol %)	Temp (°C)	Solvent	Time (hours)	[**97**] (M)	Yield (%)[b]			
						97	**100**	**101**	**99**
1	G2, 10%	90	C_7H_8	3	0.011	0	0	27	34
2	G2, 10%	75	C_6H_6	2	0.0055	14	17	tr.	29
3	G2, 10%, from **98**	75	C_6H_6	2	0.0055	12	18	tr.	39
4	G2, 10%	40	CH_2Cl_2	14	0.055	tr.	0	35	31
5	G2, 10%	40	CH_2Cl_2	15	0.011	47	0	tr.	15
6	G2, 10%	40	CH_2Cl_2	15	0.0011	61	28	0	0
7	G2, 10%	80	$PhCF_3$	3	0.0011	20	40	0	11
8	G2, 10%	80	C_6H_6	3	0.0011	tr.	11	27	20
9	G2, 10%	40	C_6H_6	14	0.0011	15	7	20	20
10	G1, 10%	40	CH_2Cl_2	15	0.011	48	0	0	tr.
11	H-G2, 10%	40	CH_2Cl_2	15	0.011	58	0	7	0
12	G2, 10%	80	CH_2Cl_2	3	0.0011	12	55	0	tr.
13	G2, 10%	60	CH_2Cl_2	14	0.0011	32	40	0	4
14	H-G2, 10%	60	CH_2Cl_2	14	0.0011	46	34	0	4
15	H-G2, 10%	80	CH_2Cl_2	5	0.0011	40	39	0	4
16	H-G2, 20%	80	CH_2Cl_2	3	0.0011	45	41	0	3
17	H-G2, 20%	80	CH_2Cl_2	3	0.0015	47	32	0	3
18	H-G2, 20%	80	CH_2Cl_2	3	0.0022	30	37	0	5
19	H-G2, 20%	80	CH_2Cl_2	3	0.0044	12	38	0	8
20	H-G2, 20%	80	CH_2Cl_2	24	0.0015	0	64	0	4
21	H-G2, 20%	80	$(CH_2Cl)_2$	15	0.0022	tr.	39	11	8



G1



G2

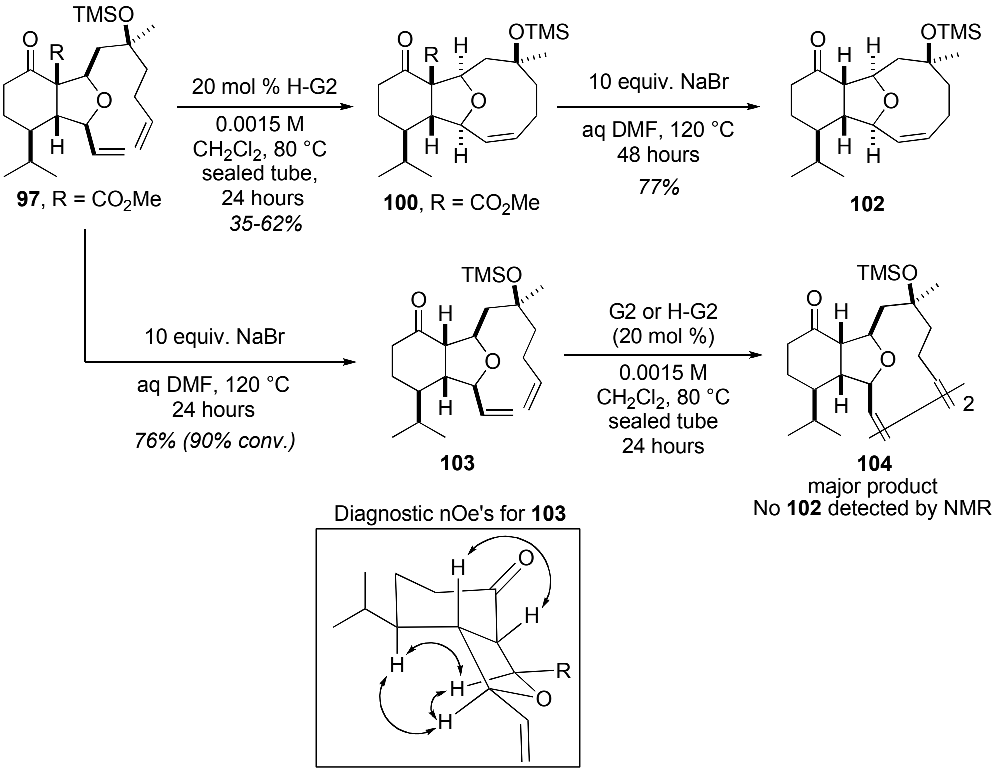


H-G2

[a] All reactions were conducted with 0.011 mmol **97** in a sealed tube at the indicated temperature unless otherwise noted. [b] Determined by ^{1}H NMR by integration relative to an internal standard.

The optimization studies of the metathesis were conducted with 5 mg of **97** (0.011 mmol). Unfortunately, the metathesis is not reproducible upon scale up, even to 20 mg, and variable yields (35-62%) are obtained (Scheme 3-23). Krapcho decarboalkoxylation with NaBr in aq. DMF at 120 ºC provided **102** in 77% yield. A variety of salts were capable of promoting the reaction, but NaBr had the advantage of leaving the TMS ether intact. Higher temperatures and the use of DMSO led to unidentified byproduct formation. By reversing the order of the metathesis and decarboalkoxylation steps, only the macrocyclic dimer **104** was produced using the previous optimized conditions – the ester is essential for a successful RCM.

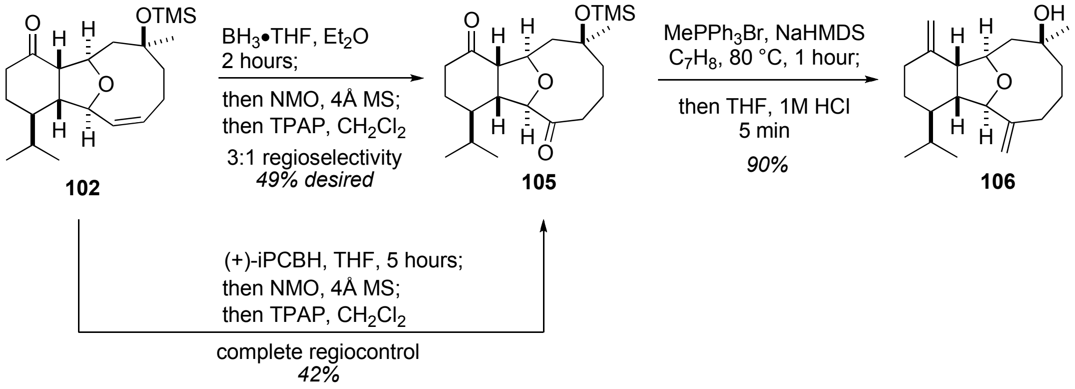
Scheme 3-23. Ring-Closing Olefin Metathesis and Krapcho Decarboalkoxylation


TMSO
O
R
H
97, R = CO2Me
20 mol % H-G2
0.0015 M
CH2Cl2, 80 °C
sealed tube,
24 hours
35-62%
OTMS
100, R = CO2Me
10 equiv. NaBr
aq DMF, 120 °C
48 hours
77%
102
10 equiv. NaBr
aq DMF, 120 °C
24 hours
76% (90% conv.)
103
G2 or H-G2
(20 mol %)
0.0015 M
CH2Cl2, 80 °C
sealed tube
24 hours
2
104
major product
No 102 detected by NMR
Diagnostic nOe's for 103
R

3.2.11 Completion of (+)-Polyanthellin A

With the olefin **102** in hand, we attempted a hydroboration with BH_3•THF followed by an oxidative workup (Scheme 3-24).[53] The ketone is also reduced during the hydroboration, but is restored in the presence of TPAP and NMO. Fortunately, the reaction was modestly selective for the desired regioisomer; the dione **105** was produced in 49% yield. The use of (+)-diisopinocampheylborane[54] gave complete regioselectivity, but a reduced overall yield of 42%. The dione was converted to the dienol **106** in excellent yield via a double methylene Wittig and treatment with aqueous HCl in THF.

Scheme 3-24. Synthesis of Dienol **106**


OTMS
102
BH3•THF, Et2O
2 hours;
then NMO, 4Å MS;
then TPAP, CH2Cl2
3:1 regioselectivity
49% desired
OTMS
105
MePPh3Br, NaHMDS
C7H8, 80 °C, 1 hour;
then THF, 1M HCl
5 min
90%
OH
106
(+)-iPCBH, THF, 5 hours;
then NMO, 4Å MS;
then TPAP, CH2Cl2
complete regiocontrol
42%

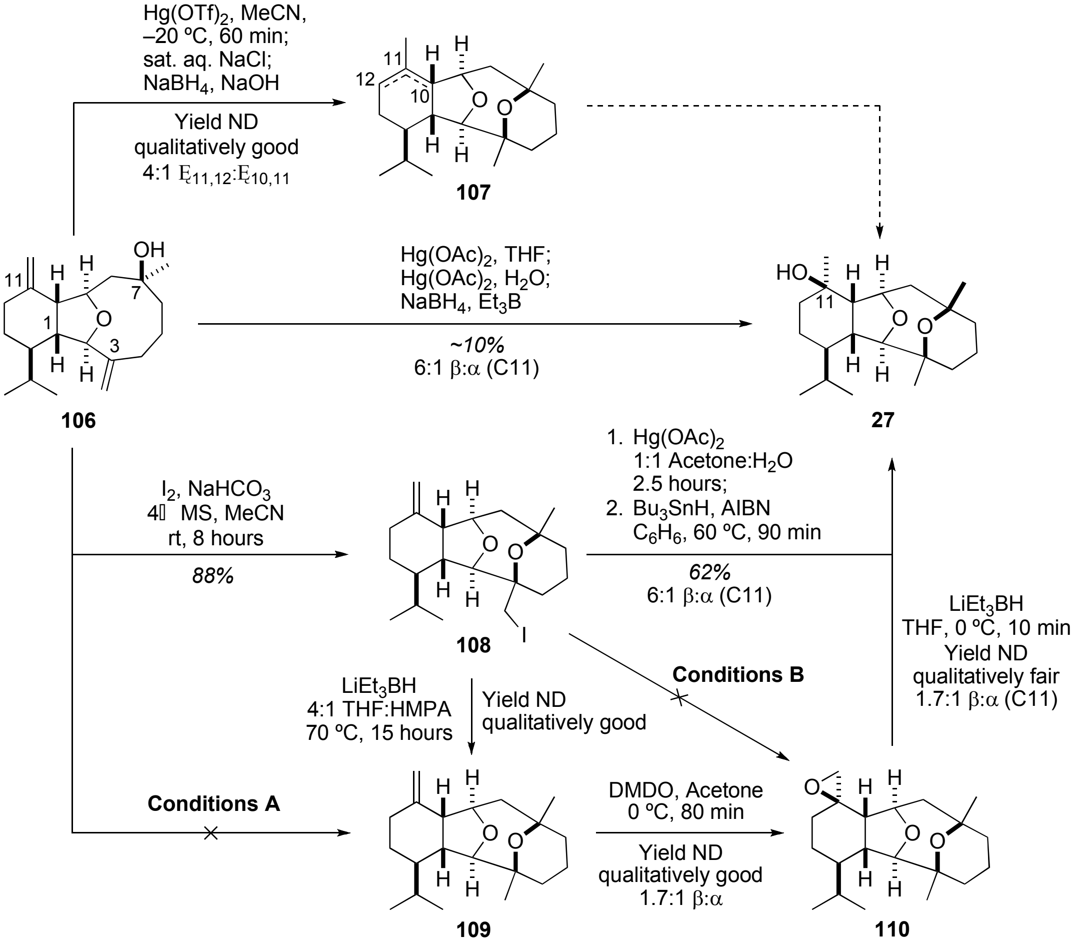
Our attempts to perform an intramolecular etherification and olefin oxidation are summarized in Scheme 3-25. First, we sought to emulate the one-pot method developed by Kim via tandem intra- and intermolecular oxymercurations and reduction. Unfortunately, this sequence provided only ~10% of **27** in a 6:1 mixture of inseparable diastereomers at C11. Mercury salts other than $Hg(OAc)_2$ such as $Hg(OCOCF_3)_2$ and $Hg(OTf)_2$ must be used under anhydrous conditions, because water promotes β-alkoxyelimination of the newly formed ether. Therefore, the intermolecular addition of H_2O cannot be conducted in tandem, and at least two steps are required if these more powerful π-acids are to be used. $Hg(OCOCF_3)_2$ led only to decomposition, but $Hg(OTf)_2$[55,56] was effective at promoting the cyclization. The triflic acid released caused the isomerization of the distal alkene to both the tri- and tetrasubstituted olefin (**107**) in a

4:1 ratio. The use of $Hg(OTf)_2{\bullet}PhNEt_2$ was unsuccessful (not shown), but other bases have not yet been evaluated.

$BF_3{\bullet}Et_2O$[57] and $Bi(OTf)_3$[58] have both been used as hydroalkoxylation catalysts; however, their use only led to elimination and decomposition of **106**. Iodoetherification of **106** with $I_2/NaHCO_3$ in MeCN resulted in 88% of the iodide **108**. We envisioned a variety of oxidations could functionalize the remaining olefin, including epoxidation or halohydrin formation (Scheme 3-25, Conditions B). The former only resulted in decomposition, while NBS gave several major products, with the bromohydrins formed unselectively. To enable epoxidations, the neopentyl iodide was reduced under forcing conditions[59] ($LiEt_3BH$, 4:1 THF:HMPA, 70 ºC) to cleanly afford alkene **107**. Epoxidation with DMDO[60] provided a 1.7:1.0 mixture of epoxides as the sole products, which after reduction with $LiEt_3BH$ gave **27** with complete preservation of dr. The best route thus far is iodoetherification followed by oxymercuration and global Bu_3SnH reduction. The dr of **27** was increased to 10:1 by repetitive flash chromatography. The ^1H and ^{13}C NMR spectra were identical to that of deacetylpolyanthellin A (**27**).

Future efforts will focus in two areas: (1) obtain complete diastereoselectivity during the C11 oxidation, or (2) intersect an intermediate after C11 oxdiation that can be purified via chromatography. The first may be achieved from the trisubstituted olefin **$\Delta_{11,12}$-107**, as this compound is reported to give complete diastereocontrol for the β-alcohol with $Hg(OAc)_2$ and $NaBH_4/Et_3B$.[12] Although the epoxides **110** were directly reduced in order to confirm the stereochemical assignments, they are chromatographically separable. Alternative epoxidation catalysts/reagents will also be explored to increase the selectivity.

Scheme 3-25. Attempts to Synthesize (+)-Deacetylpolyanthellin A (**27**)

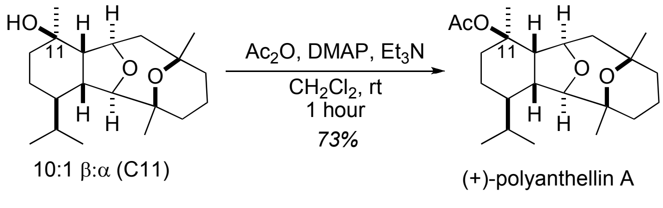


$Hg(OTf)_2$, MeCN,
–20 °C, 60 min;
sat. aq. NaCl;
$NaBH_4$, NaOH
Yield ND
qualitatively good
4:1 $\Delta_{11,12}$:$\Delta_{10,11}$
11
12
10
H
H
O
O
107
OH
7
1
3
106
$Hg(OAc)_2$, THF;
$Hg(OAc)_2$, H_2O;
$NaBH_4$, Et_3B
~10%
6:1 β:α (C11)
HO
11
27
I_2, $NaHCO_3$
4Å MS, MeCN
rt, 8 hours
88%
108
I
1. $Hg(OAc)_2$
1:1 Acetone:H_2O
2.5 hours;
2. Bu_3SnH, AIBN
C_6H_6, 60 °C, 90 min
62%
6:1 β:α (C11)
$LiEt_3BH$
THF, 0 °C, 10 min
Yield ND
qualitatively fair
1.7:1 β:α (C11)
Conditions B
$LiEt_3BH$
4:1 THF:HMPA
70 °C, 15 hours
Yield ND
qualitatively good
Conditions A
109
DMDO, Acetone
0 °C, 80 min
Yield ND
qualitatively good
1.7:1 β:α
110

Conditions A	Result	Conditions B	Result
BF_3•Et_2O, Et_2O, 0 °C	elimination	*m*-CPBA, CH_2Cl_2	decomposition
$Bi(OTf)_3$, C_6H_6, 60 °C	decomposition	DMDO, Acetone or C_7H_8 or THF	decomposition
$Hg(OCOCF_3)_2$, MeCN, –20 °C; $NaBH_4$, NaOH	decomposition	NBS, H_2O/THF (to bromohydrin)	unselective
		MeI, DMDO (to iodohydrin)	decomposition

To complete the synthesis, **27** was acetylated with Ac_2O/DMAP to afford (+)-polyanthellin A (**4**) as a single diastereomer in 73% yield. The ^{1}H and ^{13}C NMR spectra as well as the optical rotation are identical to that reported in the literature. Prof. Kim provided a synthetic sample for direct comparison (Figure 3-4).

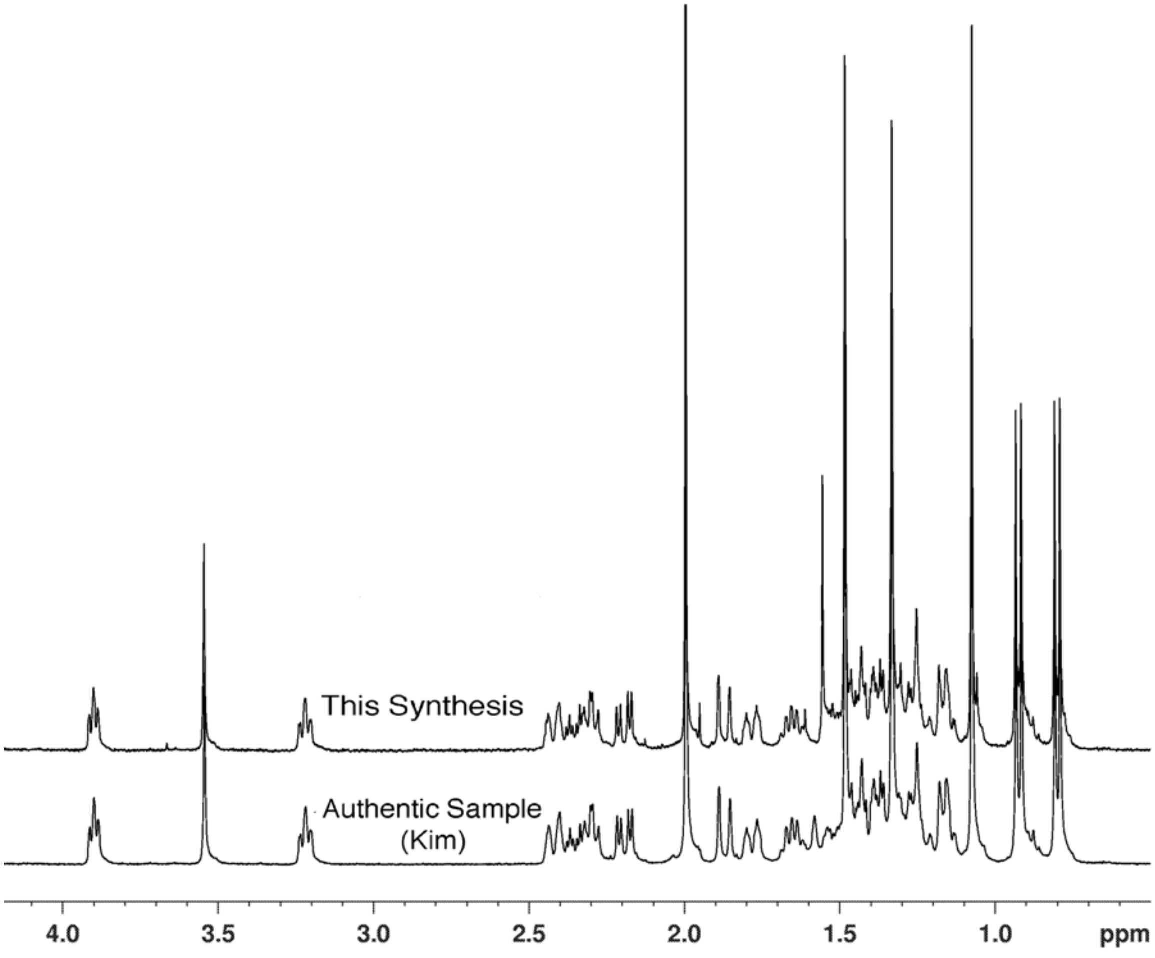
Scheme 3-26. Completion of the Synthesis of (+)-Polyanthellin A (**4**)


HO
11
Ac$_2$O, DMAP, Et$_3$N
CH$_2$Cl$_2$, rt
1 hour
73%
10:1 β:α (C11)
AcO
(+)-polyanthellin A

27

4

Figure 3-4. Comparison of ^{1}H NMR Spectra (400 MHz) of **4**

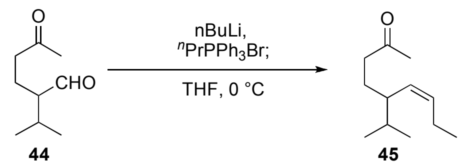


3.3 Conclusion

In summary, (+)-polyanthellin A was synthesized in 15 linear steps from methallyl alcohol in 2% overall yield, in an average yield of 77% per step. We have demonstrated the utility of a [3+2]-cycloaddition between cyclopropanes and aldehydes in the context of a complex setting. The use of the hindered catalyst, MADNTf$_2$, was essential to ensure a successful cyclization, and has extended the scope of the cycloaddition to include sensitive protected β-hydroxyaldehydes. The aim of future work is to improve two key steps, the olefin metathesis and hydroboration/oxidation, and to find route from dienol **106** to deacetylpolyanthellin A from which diastereomerically pure material can be obtained.

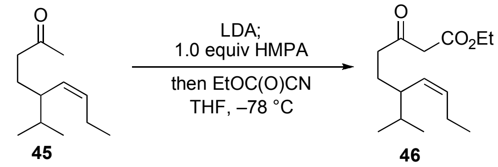
3.4 Experimental

Materials and Methods: General. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or a Bruker AMX 300 (^{1}H NMR at 400 MHz or 300MHz and ^{13}C NMR at 100 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: CDCl$_3$ at 7.26 ppm; ^{13}C NMR: CDCl$_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, br t = broad triplet, q = quartet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. GLC analysis was performed on an Agilent 6890N Network GC System equipped with a Chiradex B-DM column (30 m x 0.250 mm, pressure = 80 kPa, flow = 0.6 mL/min, detector = FID, 250ºC) or a J&W DB-1701 column (30 m x .249 mm) with helium gas as carrier. Mass spectra were obtained using a Micromass Quattro II (triple quad) instrument with nanoelectrospray ionization. Analytical thin layer chromatography (TLC) was performed on Whatman 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate solution, or aqueous ceric ammonium molybdate solution followed by heating. Purification of the reaction products was carried out either by acid/base extractive work-up or flash chromatography using Silia-P flash silica gel (40-63 μm) purchased from Silicycle. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are reported for a specific experiment and as a result may differ slightly from those found in the schemes, which are averages of at least two experiments. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use.[61] Hexanes were dried by distillation from sodium metal immediately prior to use. Hexamethylphosphoramine, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, and triethylamine were freshly distilled from calcium hydride. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

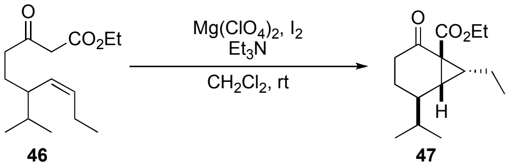


44 **45**

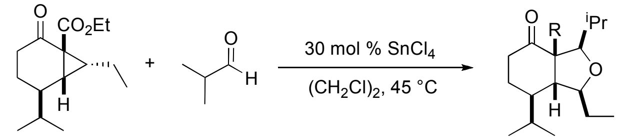
(Z)-5-isopropylnon-6-en-2-one (45). A flame-dried vial equipped with a magnetic stir bar was charged with *n*-propylphosphonium bromide (0.142 g, 0.37 mmol, 1.15 equiv) and anhydrous tetrahydrofuran (2.0 mL). *n*-Butyllithium (1.5 M in hexanes, 0.235 mL, 0.35 mmol, 1.10 equiv) was added and the solution was stirred at room temperature for 30 min before being cooled to 0 ºC. 2-Isopropyl-5-oxohexanal[24] (**44**) (0.053 mL, 0.050 g, 0.32 mmol, 1.0 equiv) was added at once via syringe the reaction was stirred at 0 ºC for 30 min. The reaction was quenched with saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (2 x 5 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 x 5 mL), and dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 10% ethyl acetate/hexanes to give (*Z*)-5-isopropylnon-6-en-2-one (0.035 g, 0.19 mmol, 60% yield) as a pale yellow oil. Analytical data for **45**: **IR** (thin film, cm^{-1}) 2959, 1718, 1594, 1464, 1365, 1302, 1167, 919, 734; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.41 (dt, *J* = 11.0, 7.3 Hz, 1H), 4.96 (t, *J* = 10.7 Hz, 1H), 2.36 (ddd, *J* = 17.1, 9.3, 5.3 Hz, 1H), 2.26 (ddd, *J* =17.2, 9.1, 6.7 Hz, 1H), 2.06 (s, 3H), 2.10-1.87 (m, 3H), 1.73 (dddd, *J* = 13.2, 9.7, 6.6, 3.6 Hz, 1H), 1.49 (oct, *J* = 6.6 Hz, 1H), 1.31 (dddd, *J* = 13.6, 1-.6, 9.3, 5.4 Hz, 1H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.9, 133.0, 130.9, 42.7, 41.8, 32.3, 29.7, 26.6, 20.9, 20.5, 19.0, 14.2; TLC (15% EtOAc/hexanes) R_f 0.34; **LRMS** (ESI) Calcd. for $(C_{12}H_{22}O)_2$+Na 387.3, Found 387.3.



(*Z*)-Ethyl 6-isopropyl-3-oxodec-7-enoate (46). A flame-dried vial equipped with a magnetic stir bar was charged with diisopropylamine (0.046 mL, 0.035 g, 0.34 mmol, 1.25 equiv) and anhydrous tetrahydrofuran (200 μL). The solution was cooled to 0 ºC and *n*-butyllithium (1.5 M in hexanes, 0.220 mL, 0.33 mmol, 1.2 equiv) was added and the solution was stirred at 0 ºC for 20 min before being cooled to –78 ºC. A solution of (*Z*)-5-isopropylnon-6-en-2-one (**45**) (0.050 g, 0.27 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (250 μL) was added dropwise via cannula over 5 min. The solution was stirred at –78 ºC for 1 h. Hexamethylphosphoramide (0.047 mL, 0.048 g, 0.27 mmol, 1.0 equiv) was added and the solution was stirred at –78 ºC for 3 min. Ethyl cyanoformate (0.033 mL, 0.033 g, 0.33 mmol, 1.2 equiv) was added and the solution was stirred at –78 ºC for 20 min before being quenched with water (3 mL). The mixture was extracted with diethyl ether (3 x 3 mL). The combined organic extracts were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 10% ethyl acetate/hexanes to give (*Z*)-ethyl 6-isopropyl-3-oxodeca-7-enoate (**46**) (0.046 g, 0.18 mmol, 67% yield) as a pale yellow oil. Analytical data for **46**: **IR** (thin film, cm^{-1}) 2960, 1745, 1718, 1649, 1465, 1367, 1308, 1234, 1155, 1035, 796, 739; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.06 (s, enol 1H), 5.43 (dt, *J* = 11.0, 7.3 Hz, 1H), 4.96 (t, *J* = 10.7 Hz, 1H), 4.91 (s, enol 1H), 4.25-4.05 (m, 2H), 3.36 (s, 2H), 2.48 (ddd, *J* = 17.6, 9.4, 5.3 Hz, 1H), 2.37 (ddd, *J* = 17.6, 9.2, 6.6 Hz, 1H), 2.06 (tdd, *J* = 10.3, 5.9, 3.8 Hz, 1H), 2.01-1.89 (m, 2H), 1.76 (dddd, *J* = 13.2, 9.6, 6.6, 3.6 Hz, 1H), 1.49 (oct, *J* = 6.6 Hz, 1H), 1.35 (dddd, *J* = 13.5, 10.6, 9.4, 5.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.9, 167.1, 133.3, 130.7, 61.1, 49.3, 42.6, 41.2, 32.3, 26.3, 20.9, 20.5, 19.0, 14.2, 14.0; TLC (15% EtOAc/hexanes) R_f 0.31; **LRMS** (ESI) Calcd. for $(C_{15}H_{26}O_3)_2$+Na 531.2, Found 531.2.



Ethyl 7-ethyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (47). The procedure developed by Yang was followed.[26] A flame-dried vial equipped with a magnetic stir bar was charged with (*Z*)-ethyl 6-isopropyl-3-oxodec-7-enoate (**46**) (0.089 g, 0.35 mmol, 1.0 equiv), magnesium perchlorate (0.156 g, 0.70 mmol, 2.0 equiv), and anhydrous dichloromethane (8.0 mL). Iodine (0.356 g, 1.40 mmol, 4.0 equiv) and triethylamine (0.122 mL, 0.089 g, 0.88 mmol, 2.5 equiv) were added sequentially. The solution was stirred at room temperature for 16 h. The reaction was diluted with dichloromethane (30 mL), washed with saturated aqueous sodium thiosulfate (2 x 15 mL), and dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 5% ethyl acetate/hexanes to give ethyl 7-ethyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**47**) (0.050 g, 0.20 mmol, 57% yield) as a pale yellow oil. Analytical data for **47**: **IR** (thin film, cm^{-1}) 2963, 1714, 1465, 1367, 1249, 1205, 1103, 1056, 1015, 854, 812, 731; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.14 (q, *J* = 7.1 Hz, 2H), 2.61-2.50 (m, 1H), 1.98 (td, *J* = 8.9, 6.8 Hz, 1H), 1.94-1.80 (m, 2H), 1.80-1.68 (m, 2H), 1.68-1.53 (m, 1H), 1.39 (sept, *J* = 7.1 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.22-1.08 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.7, 171.1, 61.3, 40.1, 37.5, 35.5, 35.2, 34.2, 33.0, 27.9, 20.4, 20.0, 18.6, 14.1, 12.6; TLC (10% EtOAc/hexanes) R_f 0.10; **LRMS** (ESI) Calcd. for $C_{15}H_{24}O_3$+Na 275.2, Found 275.2.

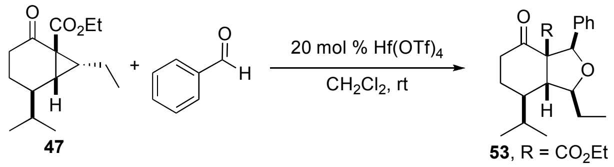


47

52, R = CO_2Et

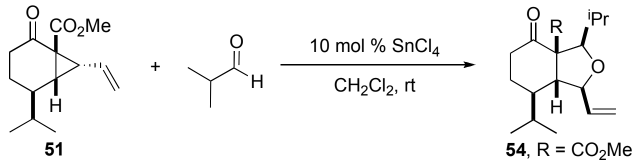
Ethyl 1-ethyl-3,7-diisopropyl-4-oxooctahydroisobenzofuran-3a-carboxylate (52). A flame-dried vial equipped with a magnetic stir bar was charged with ethyl 7-ethyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**47**) (0.045 g, 0.18 mmol, 1.0 equiv) and isobutyraldehyde (0.048 mL, 0.038 g, 0.53 mmol, 3.0 equiv). A solution of tin tetrachloride (0.006 mL, 0.014 g, 0.054 mmol, 0.30 equiv) in anhydrous 1,2-dichloroethane (0.50 mL) was added and the reaction was stirred at 45 ºC for 14 h. The solution was eluted through a 1" silica plug with diethyl ether and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 5-7.5% ethyl acetate/hexanes to give ethyl 1-ethyl-3,7-diisopropyl-4-oxooctahydroisobenzofuran-3a-carboxylate (**52**) (0.050 g, 0.20 mmol, 57% yield) as a pale yellow oil and as a 7:1 mixture of inseparable diastereomers. Analytical data for **52**: **IR** (thin film, cm^{-1}) 2962, 2876, 1715, 1465, 1389, 1368, 1216, 1111, 1034, 885; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 4.29-4.10 (m, 3H), 3.21-3.12 (m, 1H), 2.76 (dd, *J* = 9.3, 7.9 Hz, 1H), 2.68 (ddd, *J* = 17.7, 5.6, 4.6 Hz, 1H), 2.19 (ddd, *J*

= 17.6, 10.7, 6.2 Hz, 1H), 1.9-1.66 (m, 4H), 1.66-1.42 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.20-1.10 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 207.5, 170.6, 84.9, 83.7, 67.0, 61.6, 54.0, 41.7, 37.7, 29.9, 28.9, 26.6, 21.6, 21.1, 19.9, 19.5, 16.7, 13.9, 10.2; TLC (10% EtOAc/hexanes) R_f 0.28; **LRMS** (ESI) Calcd. for $C_{19}H_{32}O_4$+Na 347.2, Found 347.2.



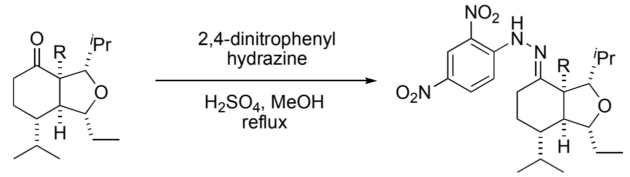
Ethyl 1-ethyl-7-isopropyl-4-oxo-3-phenyloctahydroisobenzofuran-3a-carboxylate (53). A flame-dried vial equipped with a magnetic stir bar was charged with ethyl 7-ethyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**47**) (0.012 g, 0.048 mmol, 1.0 equiv) and benzaldehyde (0.014 mL, 0.015 g, 0.140 mmol, 3.0 equiv). A solution of hafnium triflouromethanesulfonate (0.007 g, 0.009 mmol, 0.20 equiv) in anhydrous dichloromethane (0.10 mL) was added and the reaction was stirred at room temperature for 4 h. The solution was eluted through a 1" silica plug with diethyl ether and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 7.5% ethyl acetate/hexanes to give ethyl 1-ethyl-7-isopropyl-4-oxo-3-phenyloctahydroisobenzofuran-3a-carboxylate (**53**) (0.013 g, 0.036 mmol, 76% yield) as a pale yellow oil and as a 20:1 mixture of inseparable diastereomers. Analytical data for **53**: **IR** (thin film, cm^{-1}) 2961, 1714, 1464, 1368, 1230, 1212, 1111, 1048, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) major diastereomer: δ 7.44-7.38 (m, 2H), 7.29-7.23 (m, 2H), 7.23-7.17 (m, 1H), 5.71 (s, 1H), 3.62-3.47 (m, 2H), 3.62-3.39

(m, 1H), 3.03 (dd, *J* = 9.8, 8.4 Hz, 1H), 2.66 (ddd, *J* = 17.8, 6.5, 3.8 Hz, 1H), 2.27 (ddd, *J* = 17.8, 10.8, 6.6 Hz, 1H), 1.97-1.81 (m, 2H), 1.78-1.64 (m, 2H), 1.64-1.52 (m, 1H), 1.26-1.16 (m, 1H), 1.12 (t, *J* = 7.4 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 206.9, 169.1, 138.8, 127.6, 127.6, 127.2, 84.6, 81.0, 70.5, 61.5, 52.0, 42.0, 37.7, 28.9, 26.5, 21.7, 21.1, 16.6, 13.4, 10.0; TLC (15% EtOAc/hexanes) R_f 0.44; **LRMS** (ESI) Calcd. for $C_{22}H_{30}O_4$+Na 381.2, Found 381.2.



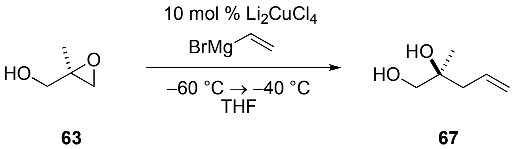
Methyl 3,7-diisopropyl-4-oxo-1-vinyloctahydroisobenzofuran-3a-carboxylate (54). A flame-dried vial equipped with a magnetic stir bar was charged with methyl 7-vinyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**51**) (0.010 g, 0.042 mmol, 1.0 equiv) and isobutyraldehyde (0.012 mL, 0.009 g, 0.126 mmol, 3.0 equiv). A solution of tin tetrachloride (0.0005 mL, 0.001 g, 0.004 mmol, 0.10 equiv) in anhydrous dichloromethane (0.150 μL) was added and the reaction was stirred at 45 ºC for 1.5 h. The solution was eluted through a 1" silica plug with diethyl ether and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 15% ethyl acetate/hexanes to give methyl 3,7-diisopropyl-4-oxo-1-vinyloctahydroisobenzofuran-3a-carboxylate (**54**) (0.012 g, 0.039 mmol, 93% yield) as a pale yellow oil and as a 10:1 mixture of inseparable diastereomers. Analytical data for **54**: **IR** (thin film, cm^{-1}) 2959, 1716, 1466, 1433, 1390. 1229, 1081, 930; **^{1}H NMR** (400

MHz, $CDCl_3$) major diastereomer: δ 5.85 (ddd, *J* = 17.3, 10.2, 7.8 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 4.23 (d, *J* = 7.9 Hz, 1H), 3.73 (s, 3H), 3.63 (dd, *J* = 9.5, 8.2 Hz, 1H), 2.87 (dd, *J* = 9.7, 8.1 Hz, 1H), 2.70 (ddd, *J* = 17.6, 6.1, 4.4 Hz, 1H), 2.22 (J = 17.6, 11.2, 6.6 Hz, 1H), 1.92-1.67 (m, 3H), 1.66-1.49 (m, 1H), 1.24-1.13 (m, 1H), 0.99 (d, *J* = 6.53, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.9, 170.9, 137.0, 118.7, 85.5, 84.9, 66.8, 55.0, 52.5, 41.6, 37.9, 30.0, 28.6, 21.4, 21.3, 19.9, 19.3, 16.7; TLC (25% EtOAc/hexanes) R_f 0.55; **LRMS** (ESI) Calcd. for $C_{18}H_{28}O_4$+Na 331.1, Found 331.1.

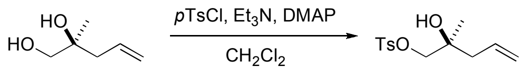


52, R = CO_2Et **55**, R = CO_2Et

(*E*)-ethyl 4-(2-(2,4-dinitrophenyl)hydrazono)-1-ethyl-3,7-diisopropyloctahydro-isobenzofuran-3a-carboxylate (55). A vial equipped with a magnetic stir bar was charged with ethyl 1-ethyl-3,7-diisopropyl-4-oxooctahydroisobenzofuran-3a-carboxylate (**52**) (0.032 g, 0.099 mmol, 1.0 equiv), 2,4-dinitrophenylhydrazine (70% ca. 30% water) (0.140 g, 0.49 mmol, 5.0 equiv), sulfuric acid (0.024 g, 0.25 mmol, 2.5 equiv), and methanol (2.0 mL). The solution was heated to 60 ºC for 48 h, and then diluted with diethyl ether (25 mL). The organic layer was washed with aqueous sodium bicarbonate (1 x 20 mL). This washing was back extracted with diethyl ether (1 x 20 mL). The combined organic extracts were washed with hydrochloric acid (1 M, 1 x 10 mL), saturated aqueous sodium chloride (1 x 10 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure. The residue was eluted through a 1" silica plug with dichloromethane to remove unreacted hydrazine and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 7.5% ethyl acetate/hexanes to give (Z)-ethyl 4-(2-(2,4-dinitrophenyl)hydrazono)-1-ethyl-3,7-diisopropyloctahydroisobenzofuran-3a-carboxylate (**55**) (0.037 g, 0.073 mmol, 74% yield) as an orange solid. X-ray quality crystals were obtained by slow evaporation of a sample dissolved in absolute ethanol. Analytical data for **55**: **IR** (thin film, cm^{-1}) 3320, 3106, 2961, 1730, 1621, 1519, 1336, 1219, 1136, 1031, 922, 833, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.14 (d, *J* = 2.2 Hz, 1H), 8.35 (dd, *J* = 9.4, 2.2 Hz, 1H), 7.95 (d, *J* = 9.5 Hz, 1H), 4.58 (d, *J* = 8.5 Hz, 1H), 4.31-4.10 (m, 2H), 3.20 (td, *J* = 8.9, 2.3 Hz, 1H), 2.78-2.64 (m, 2H), 2.39 (ddd, *J* = 17.6, 12.1, 6.2 Hz, 1H), 1.94 (hex, *J* = 6.5 Hz, 1H), 1.89-1.69 (m, 3H), 1.55 (oct, *J* = 7.2 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 158.0, 145.2, 138.3, 130.1, 129.7, 123.4, 116.6, 86.0, 84.5, 62.5, 61.7, 53.7, 42.2, 30.1, 29.6, 27.0, 26.6, 21.6, 20.5, 19.9, 16.1, 14.0, 10.2; TLC (15% EtOAc/hexanes) R_f 0.45; **LRMS** (ESI) Calcd. for $C_{25}H_{36}N_4O_7$+H 505.3, Found 505.3.

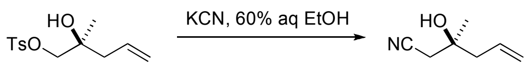


(*S*)-2-Methylpent-4-ene-1,2-diol (67). A flame-dried round-bottomed flask equipped with a magnetic stir bar and a Teflon-coated thermocouple was charged with anhydrous copper(II) chloride (0.214 g, 1.6 mmol, 0.1 equiv) and anhydrous lithium chloride (0.135 g, 3.2 mmol, 0.2 equiv). The flask was purged and backfilled with nitrogen three times. Anhydrous tetrahydrofuran (50 mL) was added, and the solids dissolved leaving a bright orange solution. The solution was cooled to –60 ºC, then (*R*)-2-methylglycidol[35] (**63**) (1.38 g, 15.6 mmol, 1.0 equiv) was added. A solution of vinylmagnesium bromide (0.7 M in tetrahydrofuran, 51.2 mL, 36.0 mmol, 2.3 equiv) was added slowly over 40 min, keeping the internal temperature at –60 ºC. The reaction was stirred at –65 ºC for 50 min at which point the reaction was judged compete by TLC analysis. The reaction was slowly allowed to warm to –20 ºC over 60 min and quenched with the addition of aqueous hydrochloric acid (6 M, 7 mL) and saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with aqueous ammonium hydroxide (3 M, 3 x 10 mL). These washings were back extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 80-100% diethyl ether/pentane to give (*S*)-2-methylpent-4-ene-1,2-diol (**67**) (1.14 g, 9.9 mmol, 63% yield) as an orange oil. Analytical data for **67**: $[\alpha]_D^{27.1}$ = –7.8 (*c* = 0.53, $CHCl_3$); **IR** (thin film, cm^{-1}) 3378, 2977, 2932, 1641, 1378, 1129, 1045, 915, 783; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 15.8, 11.2, 7.5 Hz, 1H), 5.08 (d, *J* = 11.2 Hz, 1H), 5.08 (d, *J* = 16.0 Hz, 1H), 3.42 (d, *J* = 11.2 Hz, 1H), 3.36 (d, *J* = 11.2 Hz, 1H), 3.27 (br s, 2H), 2.30–2.15 (m, 2H), 1.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 133.4, 118.5, 72.6, 69.2, 43.1, 23.1; TLC (80% EtOAc/hexanes) R_f 0.54; **LRMS** (ESI) Calcd. for $C_6H_{12}O_2$+Na 139.1, Found 139.1.



67 **S1**

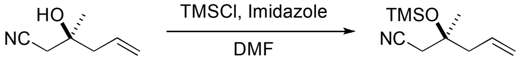
(*S*)-2-Hydroxy-2-methylpent-4-enyl 4-methylbenzenesulfonate (S1). A flame-dried vial equipped with a magnetic stir bar was charged with *p*-toluenesulfonyl chloride (2.08 g, 10.9 mmol, 1.1 equiv), triethylamine (1.65 mL, 1.20 g, 11.9 mmol, 1.2 equiv), 4-(dimethylamino)pyridine (0.121 g, 1.0 mmol, 0.1 equiv), and anhydrous methylene chloride (8.0 mL). (*S*)-2-methylpent-4-ene-1,2-diol (**67**) (1.14 g, 9.9 mmol, 1.0 equiv) was added at once and solution was stirred at room temperature for 22 h. The reaction was diluted with diethyl ether (20 mL) and filtered through a cotton plug and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 25-30% ethyl acetate/hexanes to give (*S*)-2-hydroxy-2-methylpent-4-enyl 4-methylbenzenesulfonate (**S1**) (2.18 g, 8.1 mmol, 82% yield) as a thick yellow oil. Analytical data for **S1**: $[\alpha]_D^{27.2} = -2.1$ ($c = 0.52$, $CHCl_3$); **IR** (thin film, cm^{-1}) 3525, 2979, 1642, 1599, 1455, 1360, 1176, 985, 840; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 5.67 (ddt, $J = 16.8, 10.3, 7.5$ Hz, 1H), 5.01 (d, $J = 10.2$ Hz, 1H), 4.99 (d, $J = 17.0$ Hz, 1H), 3.77 (s, 2H), 2.56 (br s, 1H), 2.37 (s, 3H), 2.25–2.11 (m, 2H), 1.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.8, 132.2, 132.1, 129.7, 127.6, 119.0, 75.3, 70.5, 42.6, 23.2, 21.3; TLC (25% EtOAc/hexanes) R_f 0.15; **LRMS** (ESI) Calcd. for $C_{13}H_{18}O_4S$+Na 293.1, Found 293.1.



S1

S2

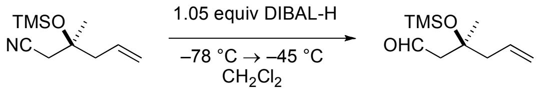
(*S*)-3-Hydroxy-3-methylhex-5-enenitrile (S2). A 50 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*S*)-2-hydroxy-2-methylpent-4-enyl 4-methylbenzenesulfonate (**S1**) (1.73 g, 6.4 mmol, 1.0 equiv) and 60% aqueous ethanol (11.6 mL, from ethanol (7.0 mL) and water (4.6 mL)). Potassium cyanide (1.25 g, 19.3 mmol, 3.0 equiv) was added and the mixture was stirred for 7 h. The ethanol was removed under reduced pressure. The residue was taken up in saturated aqueous sodium chloride (5 mL), and extracted with diethyl ether (4 x 15 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 x 5 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 60% diethyl ether/pentane to give (*S*)-3-hydroxy-3-methylhex-5-enenitrile (**S2**) (0.731 g, 5.8 mmol, 91% yield) as a clear colorless oil. Analytical data for **S2**: $[\alpha]_D^{27.0}$ = +4.9 (*c* = 0.50, $CHCl_3$); **IR** (thin film, cm^{-1}) 3437, 2980, 2934, 2253, 1642, 1417, 1383, 1121, 1001, 926, 738; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.0, 10.2, 7.5 Hz, 1H), 5.25 (dq, *J* = 10.2, 0.9 Hz, 1H), 5.23 (ddt, *J* = 17.3, 1.8, 1.3 Hz, 1H), 2.54 (d, *J* = 16.5 Hz, 1H), 2.49 (d, *J* = 16.6 Hz, 1H), 2.44–2.33 (m, 2H), 1.87 (s, 1H), 1.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.0, 120.0, 117.5, 70.4, 45.6, 30.4, 26.5; TLC (20% EtOAc/hexanes) R_f 0.14; **LRMS** (ESI) Calcd. for $C_7H_{11}NO$+H 126.1, Found 126.1.



S2

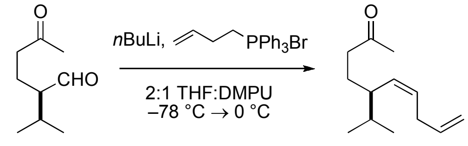
68

(*S*)-3-Methyl-3-(trimethylsilyloxy)hex-5-enenitrile (68). A vial equipped with a magnetic stir bar was charged with (*S*)-3-hydroxy-3-methylhex-5-enenitrile (**S2**) (0.400 g, 3.2 mmol, 1.0 equiv), imidazole (0.435 g, 6.4 mmol, 2.0 equiv), and reagent grade *N,N*-dimethylformamide (5.0 mL). The solution was cooled to 0 ºC and trimethylsilyl chloride (0.61 mL, 0.52 g, 4.8 mmol, 1.5 equiv) was added. The solution was stirred at room temperature for 2 h, after which time the reaction was diluted with water (15 mL) and extracted with diethyl ether (2 x 15 mL). The combined organic extracts were washed with 10% aqueous sodium chloride (2 x 10 mL), saturated aqueous sodium chloride (1 x 10 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 10% diethyl ether/pentane to give (*S*)-3-methyl-3-(trimethylsilyloxy)hex-5-enenitrile (**68**) (0.600 g, 3.0 mmol, 94% yield) as a pale yellow oil. Analytical data for **68**: $[\alpha]_D^{25.4}$ = +21.0 (*c* = 0.59, $CHCl_3$); **IR** (thin film, cm^{-1}) 3080, 2961, 2251, 1642, 1418, 1380, 1253, 1173, 1135, 1086, 1020, 921, 843, 756; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 9.6, 7.3 Hz, 1H), 5.20–5.10 (m, 2H), 2.47 (d, *J* = 16.3 Hz, 1H), 2.41 (d, *J* = 16.6 Hz, 1H), 2.44–2.28 (m, 2H), 1.40 (s, 3H), 0.16 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.9, 119.1, 117.7, 73.6, 46.8, 31.3, 27.1, 2.2; TLC (15% EtOAc/hexanes) R_f 0.38; **LRMS** (ESI) Calcd. for $C_{10}H_{19}NOSi$+Na 220.1, Found 220.1.



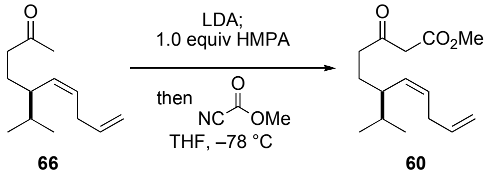
68 **69**

(*S*)-3-Methyl-3-(trimethylsilyloxy)hex-5-enal (69). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*S*)-3-methyl-3-(trimethylsilyloxy)hex-5-enenitrile (**68**) (2.97 g, 15.0 mmol, 1.0 equiv) and anhydrous dichloromethane (60 mL). The solution was cooled to –78 ºC and neat diisobutylaluminum hydride (2.82 mL, 2.25 g, 15.8 mmol, 1.05 equiv) was added dropwise over 5 min. The solution was stirred at –78 ºC for 60 min, after which the reaction was warmed to –45 ºC over 30 mintues. Ethyl acetate (5 mL) was added to quench the reaction. A slurry of silica (25 g) and diethyl ether (75 mL) was added, and the resulting suspension was stirred at 0 ºC for 30 min. The mixture was filtered through a plug of silica, eluting with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 15% diethyl ether/pentane to give (*S*)-3-methyl-3-(trimethylsilyloxy)hex-5-enal (**69**) (2.58 g, 12.9 mmol, 86% yield) as a pale yellow oil. Analytical data for **69**: $[\alpha]_D^{27.4} = +18.6$ ($c = 0.49$, $CHCl_3$); **IR** (thin film, cm^{-1}) 3078, 2960, 2739, 1723, 1378, 1253, 1137, 1049, 841, 754; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (t, *J* = 3.0 Hz, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 7.4 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.0, 1H), 5.07 (ddt, *J* = 17.1, 1.8, 1.3 Hz, 1H), 2.52 (dd, *J* = 14.8, 2.8 Hz, 1H), 2.37 (dd, *J* = 14.8, 3.1 Hz, 1H), 2.42–2.27 (m, 2H), 1.35 (s, 3H), 0.14 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.5, 133.5, 118.4, 74.6, 54.5, 47.9, 27.9, 2.3; TLC (15% EtOAc/hexanes) R_f 0.42; **LRMS** (ESI) Calcd. for $C_{10}H_{20}O_2Si$+Na 223.1, Found 223.1.

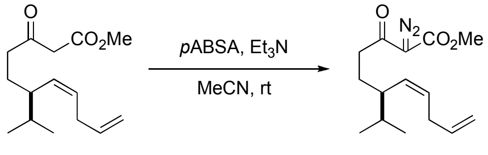


61 **66**

(*R*,*Z*)-5-Isopropyldeca-6,9-dien-2-one (66). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with but-3-enyltriphenylphosphonium bromide[62] (3.50 g, 8.8 mmol, 1.1 equiv), anhydrous 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (21 mL), and anhydrous tetrahydrofuran (42 mL). *n*-Butyllithium (1.5 M in hexanes, 5.6 mL, 8.4 mmol, 1.05 equiv) was added and the solution was stirred at room temperature for 20 min before being cooled to –78 ºC. (*R*)-2-Isopropyl-5-oxohexanal (**61**) (1.30 mL, 1.25 g, 8.0 mmol, 1.0 equiv) was added at once via syringe the reaction was stirred at 0 ºC for 30 min. Water (30 mL) was added to quench the reaction. The mixture was extracted with diethyl ether (2 x 20 mL). The combined organic extracts were washed with water (1 x 10 mL), saturated aqueous sodium chloride (1 x 5 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 7.5% diethyl ether/pentane to give (*R*,*Z*)-5-isopropyldeca-6,9-dien-2-one (**66**) (1.07 g, 5.5 mmol, 69% yield) as a pale yellow oil. Analytical data for **66**: $[\alpha]_D^{25.4}$ = –17.4 (*c* = 1.20, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2957, 2873, 1718, 1637, 1468, 1413, 1365, 1164. 993, 910, 733; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H), 5.51 (dt, *J* = 11.0, 7.5 Hz, 1H), 5.14 (tt, *J* = 10.8, 1.3 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.98 (ddt, *J* = 10.1, 1.6, 1.5 Hz, 1H), 2.80–2.72 (m, 2H), 2.41 (ddd, *J* = 17.3, 9.4, 5.3 Hz, 1H), 2.30 (ddd, *J* = 17.3, 9.1, 6.7 Hz, 1H), 2.15–2.05 (m, 1H), 2.10 (s, 3H), 1.78 (dtd, *J* = 16.6, 6.6, 3.6 Hz, 1H), 1.56 (oct, *J* = 6.6 Hz, 1H), 1.37 (dddd, *J* = 13.7, 10.7, 9.2, 5.4 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 208.5, 136.8, 132.5, 128.1, 114.4, 42.5, 41.6, 32.1, 31.8, 29.6, 26.3, 20.3, 18.9; TLC (10% Et_2O/pentane) R_f 0.38; **LRMS** (ESI) Calcd. for $C_{13}H_{22}O$+Na 217.2, Found 217.2.



(*R*,*Z*)-Methyl 6-isopropyl-3-oxoundeca-7,10-dienoate (60). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with diisopropylamine (1.81 mL, 1.30 g, 12.9 mmol, 1.25 equiv) and anhydrous tetrahydrofuran (24 mL). The solution was cooled to 0 ºC and *n*-butyllithium (1.45 M in hexanes, 8.5 mL, 12.4 mmol, 1.2 equiv) was added and the solution was stirred at 0 ºC for 30 min before being cooled to –78 ºC. A solution of (*R*,*Z*)-5-isopropyldeca-6,9-dien-2-one (**66**) (1.30 mL, 1.25 g, 8.0 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (10 mL) was added dropwise via cannula over 30 min. The solution was stirred at –78 ºC for 1.5 h. Hexamethylphosphoramide (1.79 mL, 1.85 g, 10.3 mmol, 1.0 equiv) was added and the solution was stirred at –78 ºC for 25 min. Methyl cyanoformate (0.99 mL, 1.05 g, 12.4 mmol, 1.2 equiv) was added and the solution was stirred at –78 ºC for 30 min before being quenched with saturated aqueous ammonium chloride (50 mL). The mixture was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 x 50 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 10% ethyl acetate/hexanes to give (*R*,*Z*)-methyl 6-isopropyl-3-oxoundeca-7,10-dienoate (**60**) (1.79 g, 7.1 mmol, 69% yield) as a pale yellow oil. Analytical data for **60**: $[\alpha]_D^{26.0} = -19.9$ (c = 1.15, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2957, 2873, 1751, 1718, 1637, 1438, 1273, 995, 911, 741; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.02 (s, enol 1H), 5.80 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.52 (dt, *J* = 10.9, 7.3 Hz, 1H), 5.13 (dt, *J* = 10.8, 1.5 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.98 (dtd, *J* = 10.1, 1.7, 1.5 Hz, 1H), 3.73 (s, 3H), 3.42 (s, 2H), 2.82–2.69 (m, 2H), 2.51 (ddd, *J* = 17.7, 9.1, 5.2 Hz, 1H), 2.41 (ddd, *J* = 17.8, 9.0, 6.6 Hz, 1H), 2.11 (tdd, *J* = 10.5, 5.8, 4.3 Hz, 1H), 1.81 (dddd, *J* = 13.4, 9.5, 6.7, 3.6 Hz, 1H), 1.55 (oct, *J* = 6.7 Hz, 1H), 1.39 (dddd, *J* = 14.2, 10.7, 9.1, 5.3 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.7, 167.5, 136.9, 132.5, 128.5, 114.7, 52.1, 49.0, 42.6, 41.2, 32.3, 31.9, 26.1, 20.5, 19.1; TLC (10% EtOAc/hexanes) R_f 0.19; **LRMS** (ESI) Calcd. for $C_{15}H_{24}O_3$+Na 275.2, Found 275.2.

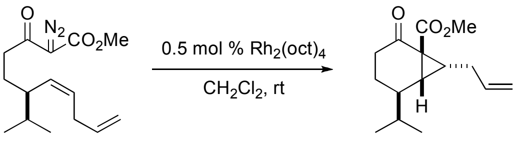


60

S3

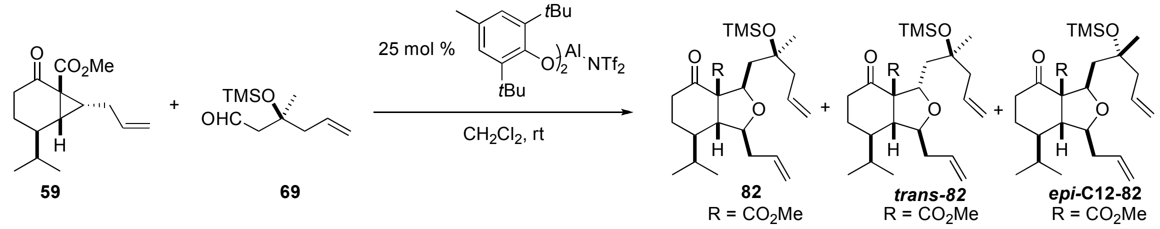
(*R*,*Z*)-Methyl 2-diazo-6-isopropyl-3-oxoundeca-7,10-dienoate (S3). A flame-dried 500 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*R*,*Z*)-methyl 6-isopropyl-3-oxoundeca-7,10-dienoate (**60**) (5.35 g, 21.2 mmol, 1.0 equiv) and reagent grade acetonitrile (70 mL). Triethylamine (8.8 mL, 6.44 g, 64 mmol, 3.0 equiv) was added followed by *p*-acetamidobenzenesulfonyl azide (5.50 g, 22.9 mmol, 1.08

equiv). The solution was stirred at room temperature for 1.5 h, after which the solvent was removed under reduced pressure. The residue was taken up in diethyl ether (150 mL) and filtered through Celite®. The filtrate was washed with aqueous hydrochloric acid (1 M, 1 x 30 mL), saturated aqueous sodium chloride (1 x 25 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 7.5% ethyl acetate/hexanes to give (*R*,*Z*)-methyl 2-diazo-6-isopropyl-3-oxoundeca-7,10-dienoate (**S3**) (5.40 g, 19.3 mmol, 91% yield) as a bright yellow oil. Analytical data for **S3**: $[\alpha]_D^{25.1}$ = –20.3 (*c* = 1.35, CH_2Cl_2); **IR** (thin film, cm^{-1}) 2957, 2134, 1725, 1655, 1437, 1308, 1212, 1131, 999, 911, 743; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.1, 10.1, 6.2 Hz, 1H), 5.52 (dt, *J* = 10.9, 7.5 Hz, 1H), 5.18 (tt, *J* = 10.8, 1.4 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.96 (ddt, *J* = 10.1, 1.6, 1.4 Hz, 1H), 3.82 (s, 3H), 2.87–2.67 (m, 2H), 2.19 (tdd, *J* = 10.5, 5.6, 3.9 Hz, 1H), 1.83 (dddd, *J* = 13.3, 9.5, 6.6, 3.8 Hz, 1H), 1.58 (oct, *J* = 6.7 Hz, 1H), 1.46 (dddd, *J* = 13.5, 10.4, 9.2, 5.6 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.9, 161.7, 137.0, 132.6, 128.4, 114.6, 75.6, 52.0, 42.8, 38.5, 32.2, 31.9, 27.1, 20.5, 19.0; TLC (7.5% EtOAc/hexanes) R_f 0.28; **LRMS** (ESI) Calcd. for $C_{15}H_{22}N_2O_3$+Na 301.2, Found 301.2.

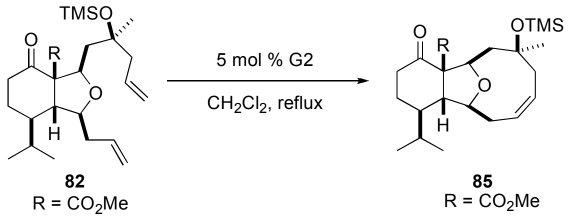


S3 **59**

(1*S*,5*R*,6*S*,7*R*)-Methyl 7-allyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (59). A flame-dried 2 L round-bottomed flask equipped with a magnetic stir bar was charged with (*R*,*Z*)-methyl 2-diazo-6-isopropyl-3-oxoundeca-7,10-dienoate (**S3**) (5.35 g, 19.2 mmol, 1.0 equiv) and anhydrous dichloromethane (1.2 L). Rhodium(II) octanoate dimer (0.075 g, 0.10 mmol, 0.005 equiv) was added, and the solution was stirred at room temperature for 2.5 h, after which the solvent was removed under reduced pressure. Is this two columns? Please clarify. The residue was purified by flash chromatography, eluting with a linear gradient of 0-2% MeOH/CH_2Cl_2, A second purification was performed, eluting with a linear gradient of 10-15% ethyl acetate/hexanes to give (1*S*,5*R*,6*S*,7*R*)-methyl 7-allyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**59**) (2.89 g, 11.5 mmol, 60% yield) as a pale yellow oil. Analytical data for **59**: $[\alpha]_D^{25.0} = -174.5$ ($c = 0.45$, $CHCl_3$); **IR** (thin film, cm^{-1}) 2957, 2875, 1724, 1709, 1437, 1262, 1227, 1118, 1054, 998, 917, 760; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.11 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.06 (dd, *J* = 10.3, 1.3 Hz, 1H), 3.71 (s, 3H), 2.60 (ddd, *J* = 19.3, 2.0, 4.8 Hz, 1H), 2.24–2.09 (m, 2H), 1.99–1.80 (m, 4H), 1.75 (oct, *J* = 6.8 Hz, 1H), 1.63 (qd, *J* = 12.5, 5.4 Hz, 1H), 1.17 (tdd, *J* = 9.3, 6.7, 3.1 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.1, 171.1, 134.5, 116.0, 52.2, 39.8, 37.2, 34.8, 34.3, 32.7, 31.1, 28.9, 27.5, 20.1, 19.8; TLC (15% EtOAc/hexanes) R_f 0.25; **LRMS** (ESI) Calcd. for $C_{15}H_{22}O_3$+Na 273.1, Found 273.1.

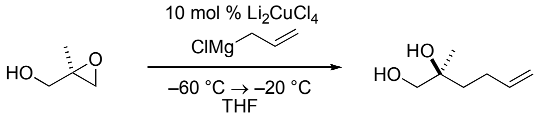


(1*S*,3*R*,3a*R*,7*R*,7a*R*)-methyl 1-allyl-7-isopropyl-3-((S)-2-methyl-2-(trimethylsilyloxy) pent-4-enyl)-4-oxooctahydroisobenzofuran-3a-carboxylate (82). A flame-dried vial equipped with a magnetic stir bar was charged with bis(2,6-di-*tert*-butyl-4-methylphenoxy)(methyl)aluminum (0.055 g, 0.115 mmol, 0.3 equiv) and anhydrous methylene chloride (0.80 mL). Trifluoromethanesulfonimide (0.027 g, 0.096 mmol, 0.25 equiv) was added, and the solution was stirred at room temperature for 5 min. Then, a solution of (1*S*,5*R*,6*S*,7*R*)-methyl 7-allyl-5-isopropyl-2-oxobicyclo[4.1.0]heptane-1-carboxylate (**59**) (0.096 g, 0.38 mmol, 1.0 equiv) and (*S*)-3-methyl-3-(trimethylsilyloxy)hex-5-enal (**69**) (0.230 g, 1.15 mmol, 3.0 equiv) in anhydrous dichloromethane (2.00 mL) was added. The solution was stirred at room temperature for 20 h, after which the reaction was eluted through a silica plug with 5% MeOH/CH_2Cl_2. The solvents were removed under reduced pressure, and the residue was purified three times by flash chromatography eluting with a linear gradient of 3-5% ethyl acetate/hexanes to give (1*S*,3*R*,3a*R*,7*R*,7a*R*)-methyl 1-allyl-7-isopropyl-3-((S)-2-methyl-2-(trimethylsilyloxy)pent-4-enyl)-4-oxooctahydroisobenzofuran-3a-carboxylate (**82**) (0.065 g, 0.14 mmol, 38% yield) as a pale yellow oil in an inseparable 11:1:1 mixture of **82**:*trans*-**82**:*epi*-C12-**82**. Analytical data for **82**: $[\alpha]_D^{26.0}$ = +22.8 (*c* = 0.50, $CHCl_3$); **IR** (thin film, cm^{-1}) 2958, 1718, 1434, 1249, 1224, 1044, 913, 841, 754; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.97–5.78 (m, 2H), 5.12–4.96 (m, 4H), 4.41 (dd, *J* = 8.1, 3.3 Hz, 1H), 3.71 (s, 3H), 3.46 (td, *J* = 7.9, 3.4 Hz, 1H), 2.72 (t, *J* = 9.2 Hz, 1H), 2.62 (ddd, *J* = 17.7, 6.7, 3.8 Hz, 1H), 2.48–2.39 (m, 1H), 2.36–2.17 (m, 4H), 1.89–1.73 (m, 2H), 1.73–1.48 (m, 3H), 1.29 (s, 3H), 1.26–1.16 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.9, 170.9, 135.3, 134.9, 117.0, 116.6, 83.2, 77.5, 75.3, 67.7, 52.5, 52.2, 48.7, 43.3, 42.9, 38.8, 37.6, 28.1, 27.1, 21.6, 21.3, 16.1, 2.6; TLC (10% EtOAc/hexanes) R_f 0.27; **LRMS** (ESI) Calcd. for $C_{25}H_{42}O_5Si$+Na 473.3, Found 473.3.



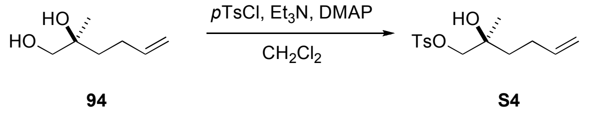
Keto ester 85. A flame-dried vial equipped with a magnetic stir bar was charged with (1*S*,3*R*,3a*R*,7*R*,7a*R*)-methyl 1-allyl-7-isopropyl-3-((S)-2-methyl-2-(trimethylsilyloxy) pent-4-enyl)-4-oxooctahydroisobenzofuran-3a-carboxylate (**82**) (0.0100 g, 0.022 mmol, 1.0 equiv) and anhydrous dichloromethane (2.0 mL). Grubbs 2nd generation catalyst (0.0009 g, 0.0011 mmol, 0.05 equiv) was added and the vial was sealed with a Teflon screw cap. The solution was stirred at 40 ºC for 14 hour, after which time the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 5% ethyl acetate/hexanes to give ketoester **85** (0.0080 g, 0.019 mmol, 86% yield) as a pale orange oil in an inseparable 11:1 mixture of diastereomers (C12). Analytical data for **85**: $[\alpha]_D^{27.0}$ = +68.1 (*c* = 0.86, $CHCl_3$); mp 97-100 ºC; **IR** (thin film, cm^{-1}) 2959, 1723, 1439, 1249, 1132, 1035, 840, 759; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.91 (tdd, *J* = 11.3, 5.1, 1.7 Hz, 1H), 5.72 (ddd, *J* = 11.0, 8.3, 6.8 Hz, 1H), 4.84 (dd, *J* = 12.7, 4.7 Hz, 1H), 3.80 (dt, *J* = 9.5, 2.9 Hz, 1H), 3.69 (s, 3H), 3.28 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.80 (d, *J* = 12.1 Hz, 1H), 2.68–2.57 (m, 1H), 2.51 (ddd, *J* = 16.9, 6.8, 5.4 Hz, 1H), 2.24 (ddd, *J* = 16.7, 9.0, 5.6 Hz, 1H), 2.11–1.97 (m, 2H), 1.89–

1.72 (m, 4H), 1.36 (s, 3H), 1.21 (qd, *J* = 8.0, 4.1 Hz, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.98–0.92 (m, 1H), 0.07 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.5, 168.2, 134.2, 125.1, 85.5, 76.8, 75.4, 68.6, 52.8, 45.6, 43.0, 42.8, 41.7, 37.3, 30.1, 29.6, 27.4, 23.3, 21.7, 19.3, 2.7; TLC (10% EtOAc/hexanes) R_f 0.12; **LRMS** (ESI) Calcd. for $C_{23}H_{38}O_5Si$+Na 445.2, Found 445.2.

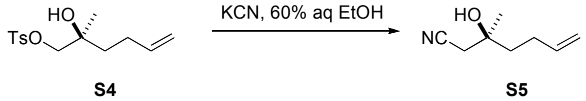


63 **94**

(*S*)-2-Methylhex-5-ene-1,2-diol (94). A flame-dried round-bottomed flask equipped with a magnetic stir bar and a Teflon-coated thermocouple was charged with anhydrous copper(II) chloride (0.505 g, 3.75 mmol, 0.1 equiv) and anhydrous lithium chloride (0.320 g, 7.50 mmol, 0.2 equiv). The flask was purged and backfilled with nitrogen three times. Anhydrous tetrahydrofuran (100 mL) was added, and the solids dissolved leaving a bright orange solution. The solution was cooled to –60 ºC, then (*R*)-2-methylglycidol[35] (**63**) (1.38 g, 15.6 mmol, 1.0 equiv) was added. A solution of allylmagnesium chloride (1.25 M in tetrahydrofuran, 69.0 mL, 86.1 mmol, 2.3 equiv) was added slowly over 30 min, keeping the internal temperature at –60 ºC. The reaction was stirred at –60 ºC for 60 min at which point the reaction was judged compete by TLC analysis. The reaction was slowly allowed to warm to –20 ºC over 60 min and quenched with the addition of saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were washed with aqueous sodium chloride (1 x 10 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure to give (*S*)-2-methylhex-5-ene-1,2-diol (**94**) (3.75 g, 28.8 mmol, 77%) as a pale yellow oil. The spectral data was consistent with that reported in literature for *ent*-**94**.[9]

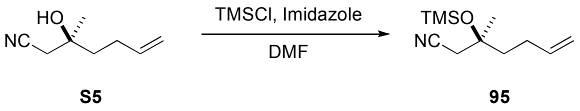


(*S*)-2-Hydroxy-2-methylhex-5-enyl 4-methylbenzenesulfonate (S4). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with *p*-toluenesulfonyl chloride (6.60 g, 34.6 mmol, 1.2 equiv), triethylamine (5.00 mL, 3.64 g, 36.0 mmol, 1.25 equiv), 4-(dimethylamino)pyridine (0.35 g, 2.9 mmol, 0.1 equiv), and anhydrous methylene chloride (50 mL). (*S*)-2-methylhex-5-ene-1,2-diol (**94**) (3.75 g, 28.8 mmol, 1.0 equiv) was added at once and solution was stirred at room temperature for 22 h. The reaction was washed with aqueous hydrochloric acid (1M, 1 x 20 mL), saturated aqueous sodium bicarbonate (1 x 20 mL), saturated aqueous sodium chloride (1 x 10 mL), and dried over sodium sulfate. The residue was purified by flash chromatography eluting with a linear gradient of 10-50% ethyl acetate/hexanes to give (*S*)-2-hydroxy-2-methylhex-5-enyl 4-methylbenzenesulfonate (**S4**) (7.40 g, 26.0 mmol, 90% yield) as a thick yellow oil. Analytical data for **S4**: $[\alpha]_D^{27.0}$ = +0.1 (*c* = 0.52, $CHCl_3$); **IR** (thin film, cm^{-1}) 3532, 2978, 1642, 1598, 1454, 1360, 1175, 1097, 985, 845, 668; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 5.75 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1H), 4.98 (dq, *J* = 17.2, 1.5 Hz, 1H), 4.93 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.83 (s, 2H), 2.44 (s, 3H), 2.11–1.96 (m, 3H), 1.63–1.47 (m, 2H), 1.16 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 145.0, 138.0, 132.6, 129.9, 127.9, 114.8, 76.0, 71.2, 37.3, 27.6, 23.4, 21.6; TLC (20% EtOAc/hexanes) R_f 0.13; **LRMS** (ESI) Calcd. for $C_{14}H_{20}O_4S$+Na 307.1, Found 307.1.

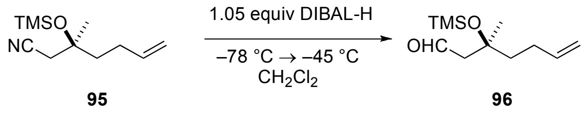


(*S*)-3-Hydroxy-3-methylhept-6-enenitrile (S5). A 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*S*)-2-hydroxy-2-methylhex-5-enyl 4-methylbenzenesulfonate (**S4**) (7.30 g, 25.7 mmol, 1.0 equiv) and 60% aqueous ethanol (41 mL, from ethanol (25 mL) and water (16 mL)). Potassium cyanide (5.0 g, 77.0 mmol, 3.0 equiv) was added and the mixture was stirred for 13 h. The ethanol was removed under reduced pressure. The residue was taken up in saturated aqueous sodium chloride (25 mL), and extracted with diethyl ether (4 x 60 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 x 10 mL), dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 10-30% ethyl acetate/hexanes to give (*S*)-3-hydroxy-3-methylhept-6-enenitrile (**S5**) (3.26 g, 23.4 mmol, 91% yield) as a clear colorless oil. Analytical data for **S5**: $[\alpha]_D^{27.5}$ = +3.0 (*c* = 0.55, $CHCl_3$); **IR** (thin film, cm^{-1}) 3444, 2978, 2937, 2253, 1642, 1416, 1382, 1120, 916, 735; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.97 (ddt, *J* = 10.2, 1.6, 1.3 Hz, 1H), 2.58–2.44 (m, 2H), 2.49 (br s, 1H), 2.21–2.06 (m, 2H), 1.77–1.59 (m, 2H), 1.34 (s, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ

137.6, 117.6, 115.2, 70.9, 40.2, 31.2, 28.0, 26.5; TLC (30% EtOAc/hexanes) R$_f$ 0.34; **LRMS** (ESI) Calcd. for $C_8H_{13}NO$+Na 162.1, Found 162.1.

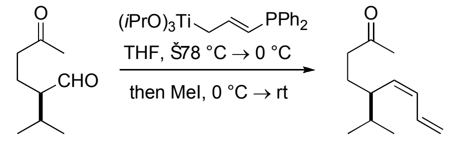


(*S*)-3-Methyl-3-(trimethylsilyloxy)hept-6-enenitrile (95). A 200 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*S*)-3-hydroxy-3-methylhept-6-enenitrile (**S5**) (3.17 g, 22.8 mmol, 1.0 equiv), imidazole (3.10 g, 45.6 mmol, 2.0 equiv), and reagent grade *N,N*-dimethylformamide (50 mL). The solution was cooled to 0 ºC and trimethylsilyl chloride (4.35 mL, 3.72 g, 34.2 mmol, 1.5 equiv) was added. The solution was stirred at room temperature for 2 h, after which the reaction was diluted with water (150 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic solutions were washed with 10% aqueous sodium chloride (3 x 25 mL), saturated aqueous sodium chloride (1 x 20 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with a linear gradient of 5-10% ethyl acetate/hexanes to give (*S*)-3-methyl-3-(trimethylsilyloxy)hept-6-enenitrile (**95**) (4.50 g, 21.3 mmol, 93% yield) as a pale yellow oil. Analytical data for **95**: $[\alpha]_D^{26.7}$ = +4.8 (*c* = 0.52, $CHCl_3$); **IR** (thin film, cm^{-1}) 2957, 2251, 1643, 1455, 1381, 1252, 1126, 1083, 1022, 842, 755; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.4 Hz, 1H), 2.50 (d, *J* = 16.4 Hz, 1H), 2.44 (d, *J* = 16.4 Hz, 1H), 2.18–2.02 (m, 2H), 1.78–1.58 (m, 2H), 1.39 (s, 3H), 0.14 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.8, 117.7, 114.9, 73.7, 41.3, 31.7, 28.2, 27.3, 2.3; TLC (15% EtOAc/hexanes) R_f 0.42; **LRMS** (ESI) Calcd. for $C_{11}H_{21}NOSi$+Na 234.1, Found 234.2.



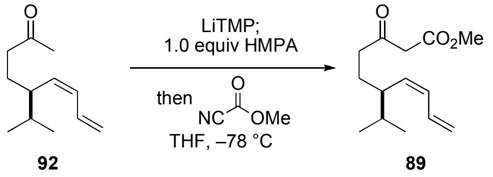
(*S*)-3-Methyl-3-(trimethylsilyloxy)hept-6-enal (96). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*S*)-3-methyl-3-(trimethylsilyloxy)hept-6-enenitrile (**95**) (4.40 g, 20.8 mmol, 1.0 equiv) and anhydrous dichloromethane (80 mL). The solution was cooled to –78 ºC and neat diisobutylaluminum hydride (3.90 mL, 3.11 g, 21.9 mmol, 1.05 equiv) was added dropwise over 5 min. The solution was stirred at –78 ºC for 4 h, after which the reaction was warmed to –45 ºC over 30 mintues. Ethyl acetate (5 mL) was added to quench the reaction. A slurry of silica (30 g) and diethyl ether (75 mL) was added, and the resulting suspension was stirred at 0 ºC for 30 min. The mixture was filtered through a plug of silica, eluting with diethyl ether. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 10% ethyl acetate/hexanes to give (*S*)-3-methyl-3-(trimethylsilyloxy)hept-6-enal (**96**) (3.04 g, 14.2 mmol, 68% yield) as a pale yellow oil. Analytical data for **96**: $[\alpha]_D^{26.0} = +14.2$ ($c = 0.60$, $CHCl_3$); **IR** (thin film, cm^{-1}) 2958, 2855, 2738, 1723, 1378, 1252, 1049, 841, 754; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (t, *J* = 3.0 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.4 Hz, 1H), 2.53 (dd, *J* = 14.7, 2.9 Hz, 1H), 2.40 (dd, *J* = 14.6, 3.1 Hz, 1H), 2.19–2.02 (m, 2H), 1.70–1.61 (m, 2H), 1.36 (s, 3H), 0.14

(s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 203.0, 138.2, 114.5, 74.8, 54.9, 42.5, 28.4, 28.2, 2.4; TLC (15% EtOAc/hexanes) R_f 0.48; **LRMS** (ESI) Calcd. for $C_{11}H_{22}O_2Si$+Na 237.1, Found 237.2.

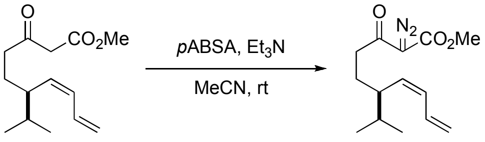


61 **92**

(*R*,*Z*)-5-Isopropylnona-6,8-dien-2-one (92). A flame-dried 200 mL round-bottomed flask equipped with a magnetic stir bar was charged with allyldiphenylphosphine (3.75 g, 16.6 mmol, 1.05 equiv) and anhydrous tetrahydrofuran (50 mL). The reaction was cooled to –78 ºC, and *t*-butyllithium (1.8 M in pentane, 9.2 mL, 16.6 mmol, 1.05 equiv) was added quickly with stirring. The solution was stirred at –78 ºC for 20 min, warmed to 0 ºC for 30 min, and then cooled back to –78 ºC. Titanium(IV) isopropoxide (4.9 mL, 4.72 g, 16.6 mmol, 1.05 equiv) was added dropwise over five min. Then the reaction was stirred at –78 ºC for 40 min. The solution was then transferred via cannula over twelve min to a flame-dried 250 mL round-bottomed flask containing (*R*)-2-isopropyl-5-oxohexanal (**61**) (2.45 g, 15.7 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (50 mL) at –78 ºC. The reaction was stirred at 0 ºC for 1 h. Iodomethane (1.03 mL, 2.36 g, 16.6 mmol, 1.05 equiv) was added, and the reaction was stirred at room temperature for 1.5 h. The reaction was poured onto aqueous hydrochloric acid (1 M, 100 mL), and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 x 50 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 5% diethyl ether/petroleum ether to give (*R*,*Z*)-5-isopropylnona-6,8-dien-2-one (**92**) (2.01 g, 11.1 mmol, 71% yield) as a pale yellow oil. Analytical data for **92**: $[\alpha]_D^{25.8}$ = –11.9 (*c* = 0.52, $CHCl_3$); **IR** (thin film, cm^{-1}) 2958, 1718, 1592, 1366, 1169, 1001, 904, 796, 734; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.54 (dt, *J* = 16.9, 11.0 Hz, 1H), 6.13 (t, *J* = 11.0 Hz, 1H), 5.20 (d, *J* = 16.8 Hz, 1H), 5.15 (t, *J* = 11.2 Hz, 1H), 5.09 (d, *J* = 10.1 Hz, 1H), 2.44–2.21 (m, 3H), 2.10 (s, 3H), 1.83 (dddd, *J* = 13.4, 8.8, 7.0, 3.5 Hz, 1H), 1.59 (oct, *J* = 6.8 Hz, 1H), 1.39 (dddd, *J* = 13.5, 10.8, 8.6, 5.9 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ 208.6, 134.5, 132.3, 130.8, 117.2, 43.1, 41.4, 32.3, 29.8, 26.3, 20.4, 19.0; TLC (10% EtOAc/hexanes) R_f 0.30; **LRMS** (ESI) Calcd. for $C_{12}H_{20}O$+Na 203.1, Found 203.1.

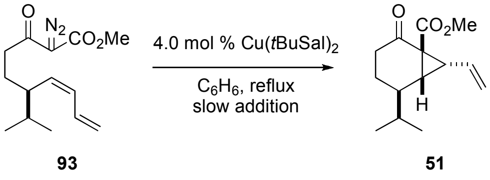


(*R*,*Z*)-Methyl 6-isopropyl-3-oxodeca-7,9-dienoate (89). A flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with 2,2,6,6-tetramethylpiperidine (1.01 mL, 0.84 g, 5.9 mmol, 1.3 equiv) and anhydrous tetrahydrofuran (18 mL). The solution was cooled to 0 ºC and *n*-butyllithium (1.5 M in hexanes, 3.65 mL, 5.5 mmol, 1.2 equiv) was added and the solution was stirred at 0 ºC for 10 min before being cooled to –78 ºC. A solution of (*R*,*Z*)-5-isopropylnona-6,8-dien-2-one (**92**) (0.823 g, 4.57 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (20 mL) was added dropwise via cannula over 30 min. The solution was stirred at –78 ºC for 1 hour. Hexamethylphosphoramide (0.80 mL, 0.82 g, 4.6 mmol, 1.0 equiv) was added and the solution was stirred at –78 ºC for 5 min. Methyl cyanoformate (0.44 mL, 0.47 g, 5.5 mmol, 1.2 equiv) was added and the solution was stirred at –78 ºC for 45 min before being quenched with saturated aqueous ammonium chloride (10 mL). The mixture was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (1 x 10 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with a linear gradient of 7.5-10% ethyl acetate/hexanes to give (*R*,*Z*)-methyl 6-isopropyl-3-oxodeca-7,9-dienoate (**89**) (0.775 g, 3.25 mmol, 71% yield) as a pale yellow oil. Analytical data for **89**: $[\alpha]_D^{26.4}$ = –11.3 (*c* = 0.50, $CHCl_3$); **IR** (thin film, cm^{-1}) 2957, 2873, 1750, 1717, 1629, 1438, 1320, 1242, 1162, 906, 797, 735; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.01 (s, enol 1H), 6.53 (dt, 17.6, 11.6 Hz, 1H), 6.13 (td, *J* = 11.0, 0.7 Hz, 1H), 5.21 (ddd, *J* = 17.3, 1.3, 0.6 Hz, 1H), 5.14 (d, 11.2 Hz, 1H), 5.10 (d, 10.0 Hz, 1H), 3.72 (s, 3H), 3.41 (s, 2H), 2.49 (ddd, *J* = 17.9, 8.6, 5.6 Hz, 1H), 2.42 (ddd, *J* = 17.8, 8.0, 7.0 Hz, 1H), 2.29 (tdd, *J* = 11.0, 5.7, 3.4 Hz, 1H), 1.87 (dddd, *J* = 13.6, 8.8, 7.0, 3.6 Hz, 1H), 1.58 (oct, 6.7 Hz, 1H), 1.42 (dddd, *J* = 13.8, 11.0, 8.4, 5.8 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.84 (d, 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.6, 167.4, 134.4, 132.3, 131.0, 117.5, 52.1, 49.0, 43.1, 41.0, 32.3, 26.1, 20.4, 19.0; TLC (10% EtOAc/hexanes) R_f 0.18; **LRMS** (ESI) Calcd. for $C_{14}H_{22}O_3$+Na 261.1, Found 261.1.

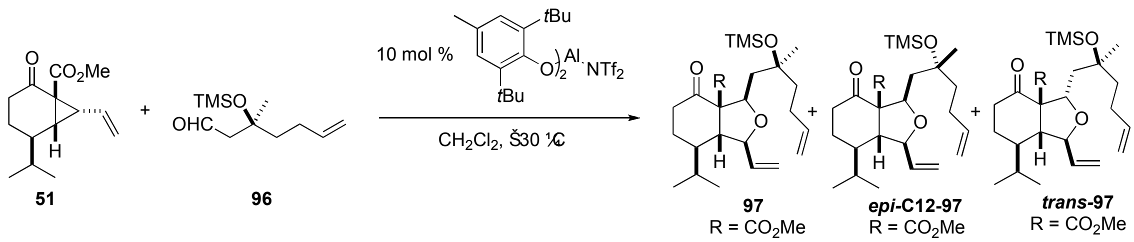


89 **93**

(*R*,*Z*)-Methyl 2-diazo-6-isopropyl-3-oxodeca-7,9-dienoate (93). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar was charged with (*R*,*Z*)-methyl 6-isopropyl-3-oxodeca-7,9-dienoate (**89**) (0.800 g, 3.36 mmol, 1.0 equiv) and reagent grade acetonitrile (20 mL). Triethylamine (1.40 mL, 1.02 g, 10.1 mmol, 3.0 equiv) was added followed by *p*-acetamidobenzenesulfonyl azide (0.850 g, 3.52 mmol, 1.05 equiv). The solution was stirred at room temperature for 1.5 h, after which the solvent was removed under reduced pressure. The residue was taken up in diethyl ether (30 mL) and filtered through Celite®. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 10% ethyl acetate/hexanes to give (*R*,*Z*)-methyl 2-diazo-6-isopropyl-3-oxodeca-7,9-dienoate (**93**) (0.812 g, 3.06 mmol, 91% yield) as a bright yellow oil. Analytical data for **93**: $[\alpha]_D^{27.3}$ = –25.3 (*c* = 0.53, $CHCl_3$); **IR** (thin film, cm^{-1}) 2957, 2135, 1725, 1657, 1437, 1309, 1212, 1120, 1000, 904, 744; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.54 (dtd, *J* = 16.9, 11.0, 0.9 Hz, 1H), 6.13 (t, *J* = 11.0 Hz, 1H), 5.20 (t, *J* = 10.8 Hz, 1H), 5.18 (dd, *J* = 16.7, 2.0 Hz, 1H), 5.07 (d, 10.1 Hz, 1H), 3.81 (s, 3H), 2.85–2.69 (m, 2H), 2.37 (tdd, *J* = 10.2, 5.8, 4.0 Hz, 1H), 1.87 (dddd, *J* = 13.1, 8.8, 7.1, 3.8 Hz, 1H), 1.61 (oct, *J* = 6.7 Hz, 1H), 1.50 (dddd, *J* = 13.6, 10.5, 8.2, 6.5 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.8, 161.6, 134.5, 132.5, 130.9, 117.1, 75.7, 52.0, 43.3, 38.2, 32.3, 27.3, 20.5, 19.0; TLC (15% EtOAc/hexanes) R_f 0.39; **LRMS** (ESI) Calcd. for $C_{14}H_{20}N_2O_3$+Na 287.1, Found 287.1.

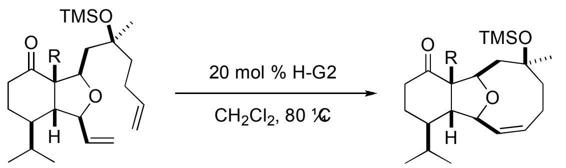


(1*S*,5*R*,6*S*,7*R*)-Methyl 5-isopropyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate (51). A flame-dried 250 mL round-bottomed flask equipped with a magnetic stir bar and reflux condenser was charged with copper(II) bis(*t*-butyl-salicylimine)[52] (0.025 g, 0.060 mmol, 0.04 equiv) and anhydrous benzene (20 mL). After the solution was brought to reflux, a solution of (*R*,*Z*)-methyl 2-diazo-6-isopropyl-3-oxodeca-7,9-dienoate (**93**) (0.400 g, 1.51 mmol, 1.0 equiv) in anhydrous benzene (20 mL) was added over 20 h via syringe pump. The solution was refluxed for 30 min further, after which time the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 10-15% ethyl acetate/hexanes to give (1*S*,5*R*,6*S*,7*R*)-methyl 5-isopropyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate (**51**) (0.280 g, 1.18 mmol, 78% yield) as a pale yellow oil. Analytical data for **51**: $[\alpha]_D^{26.4}$ = –202.0 (*c* = 0.60, CHCl$_3$); **IR** (thin film, cm^{-1}) 2957, 1727, 1708, 1436, 1255, 1215, 1053, 762; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.46–5.24 (m, 3H), 3.73 (s, 3H), 2.82–2.75 (m, 1H), 2.59 (ddd, *J* = 19.0, 4.7, 2.5 Hz, 1H), 2.01–1.90 (m, 2H), 1.86 (ddt, *J* = 13.0, 5.5, 2.9 Hz, 1H), 1.76 (oct, *J* = 6.8 Hz, 1H), 1.66 (qd, *J* = 13.1, 4.6 Hz, 1H), 1.33 (dddd, *J* = 12.6, 6.8, 6.0, 3.1 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 203.7, 170.8, 130.1, 121.1, 52.6, 39.9, 37.8, 36.7, 36.0, 35.7, 32.8, 27.4, 20.1, 19.7; TLC (20% EtOAc/hexanes) R_f 0.24; **LRMS** (ESI) Calcd. for $C_{14}H_{20}O_3$+Na 259.1, Found 259.1.



(1*S*,3*R*,3a*R*,7*R*,7a*R*)-Methyl 7-isopropyl-3-((S)-2-methyl-2-(trimethylsilyloxy)hex-5-enyl)-4-oxo-1-vinyloctahydroisobenzofuran-3a-carboxylate (97). A flame-dried vial equipped with a magnetic stir bar was charged with bis(2,6-di-*tert*-butyl-4-methylphenoxy)(methyl)aluminum (0.082 g, 0.17 mmol, 0.15 equiv) and anhydrous methylene chloride (4.0 mL). Trifluoromethanesulfonimide (0.035 g, 0.11 mmol, 0.10 equiv) was added, and the solution was stirred at room temperature for 10 min. A flame-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with (1*S*,5*R*,6*S*,7*R*)-methyl 5-isopropyl-2-oxo-7-vinylbicyclo[4.1.0]heptane-1-carboxylate (**51**) (0.270 g, 0.38 mmol, 1.0 equiv), (*S*)-3-methyl-3-(trimethylsilyloxy)hept-6-enal (**96**) (0.735 g, 3.43 mmol, 3.0 equiv), and anhydrous dichloromethane (12.0 mL) and cooled to –78 ºC. The catalyst solution was added and the reaction was stirred at –30 ºC for 14 h. The solution was washed with saturated aqueous sodium bicarbonate (1 x 10 mL), dried with sodium sulfate, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 2.5-5% ethyl acetate/hexanes to give (1*S*,3*R*,3a*R*,7*R*,7a*R*)-methyl 7-isopropyl-3-((S)-2-methyl-2-(trimethylsilyloxy)hex-5-enyl)-4-oxo-1-vinyloctahydroisobenzofuran-3a-carboxylate (**97**) (0.388 g, 0.86 mmol, 76% yield) as a pale yellow oil in an inseparable 11:1:0.6 mixture of **97**:*epi*-C12-**97**:*trans-**97*** and to give (*S*)-3-methyl-3-(trimethylsilyloxy)hept-6-enal (**96**) (0.391 g, 1.82 mmol, 71%) Analytical data for **97**: $[\alpha]_D^{24.9}$ = +29.7 (*c* = 1.02, $CHCl_3$); **IR**

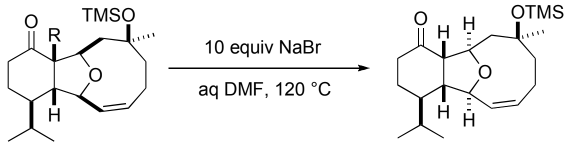
(thin film, cm^{-1}) 2958, 1717, 1463, 1434, 1250, 1042, 840, 755; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.92–5.73 (m, 2H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 4.97 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.48 (dd, *J* = 9.3, 2.0 Hz, 1H), 3.79–3.60 (m, 1H), 3.72 (s, 3H), 2.80 (t, *J* = 9.1 Hz, 1H), 2.63 (ddd, *J* = 17.8, 6.6, 3.4 Hz, 1H), 2.22 (ddd, *J* = 17.8, 10.9, 6.9 Hz, 1H), 2.16–2.00 (m, 2H), 1.87 (sextd, *J* = 6.7, 3.8 Hz, 1H), 1.75 (ddd, *J* = 13.9, 10.5, 3.5 Hz, 1H), 1.71–1.45 (m, 5H), 1.29 (s, 3H), 1.27–1.16 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 6.82 (d, *J* = 0.81 Hz, 3H), 0.08 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 206.8, 170.8, 139.5, 137.4, 117.8, 113.7, 85.3, 77.7, 75.5, 67.6, 53.7, 52.5, 43.4, 42.8, 42.5, 37.7, 28.4, 27.8, 27.5, 21.5, 21.2, 15.9, 2.6; TLC (20% EtOAc/hexanes) R_f 0.42; **LRMS** (ESI) Calcd. for $C_{25}H_{42}O_5Si$+Na 473.3, Found 473.3.



97
R = CO_2Me

100
R = CO_2Me

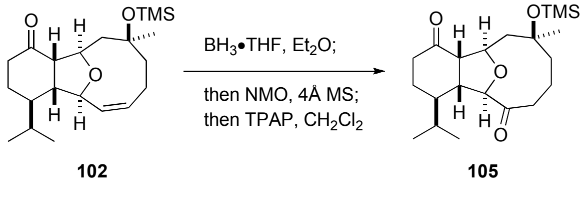
Keto ester 100. A flame-dried 500 mL Schlenk round-bottomed flask equipped with a magnetic stir bar was charged with (1*S*,3*R*,3a*R*,7*R*,7a*R*)-methyl 7-isopropyl-3-((S)-2-methyl-2-(trimethylsilyloxy)hex-5-enyl)-4-oxo-1-vinyloctahydroisobenzofuran-3a-carboxylate (**97**) (0.044 g, 0.098 mmol, 1.0 equiv) and anhydrous dichloromethane (65.0 mL). Hoveyda-Grubbs 2nd generation catalyst (0.012 g, 0.020 mmol, 0.20 equiv) was added and the flask was sealed. The solution was stirred at 80 ºC for 18 h, after which time the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with a linear gradient of 5-10% ethyl acetate/hexanes to give ketoester **100** (0.026 g, 0.061 mmol, 62% yield) as a clear, colorless oil and as a 10:1 mixture of inseparable diastereomers. Analytical data for **100**: $[\alpha]_D^{26.9} = +98.9$ (c = 1.90, CHCl$_3$); **IR** (thin film, cm^{-1}) 2956, 1723, 1464, 1375, 1249, 1107, 1046, 925, 840, 754; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 5.51–5.30 (m, 2H), 5.14 (dd, J = 13.1, 2.8 Hz, 1H), 4.36 (br d, J = 5.6 Hz, 1H), 3.71 (s, 3H), 3.38 (dd, J = 8.8, 6.0 Hz, 1H), 2.84 (td, J = 11.2, 8.8 Hz, 1H), 2.53 (ddd, J = 17.5, 6.4, 3.8 Hz, 1H), 2.34–2.21 (m, 2H), 1.98–1.84 (m, 2H), 1.84–1.58 (m, 3H), 1.51 (t, J = 11.7 Hz, 1H), 1.43 (s, 3H), 1.28–1.18 (m, 1H), 1.13 (dd, J = 14.3, 2.8 Hz, 1H), 1.01 (d, 6.8 Hz, 3H), 0.94 (d, 6.8 Hz, 3H), 0.06 (s, 9H); **^{13}C NMR** (100 MHz, CDCl$_3$) δ 204.2, 168.8, 131.7, 129.3, 85.1, 78.3, 78.0, 68.7, 53.2, 53.0, 45.9, 43.6, 42.9, 37.5, 29.0, 26.3, 22.9, 21.6, 20.8, 16.6, 2.8; TLC (15% EtOAc/hexanes) R$_f$ 0.28; **LRMS** (ESI) Calcd. for $C_{23}H_{38}O_5Si$+Na 445.2, Found 445.2.



100
R = CO$_2$Me

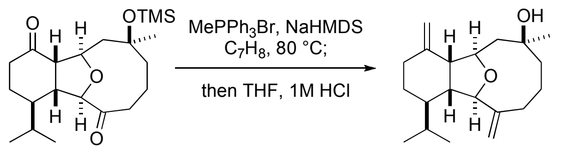
102

Ketone 102. A 20 mL vial equipped with a magnetic stir bar was charged with ketoester **100** (0.075 g, 0.18 mmol, 1.0 equiv), sodium bromide (0.183 g, 1.80 mmol, 10 equiv), reagent grade *N,N*-dimethylformamide (10 mL), and water (0.5 mL). The vial was flushed with nitrogen for five min before a Teflon-lined screw cap was affixed. The vial was heated to 120 ºC for 42 h, after which the reaction was cooled to room temperature. The solution was diluted with water (15 mL), and extracted with diethyl ether (4 x 8 mL). The combined organic extracts were washed with 10% aqueous sodium chloride (2 x 5 mL), saturated aqueous sodium chloride (1 x 5 mL), dried with magnesium sulfate, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with a linear gradient of 5-7.5% ethyl acetate/hexanes to give ketone **102** (0.049 g, 0.14 mmol, 76% yield) as a pale yellow oil and as a 10:1 mixture of inseparable diastereomers. Analytical data for **102**: $[\alpha]_D^{26.7} = +9.1$ (c = 0.75, $CHCl_3$); **IR** (thin film, cm^{-1}) 2958, 2360, 1710, 1463, 1249, 1118, 1045, 839, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.51 (dddd, J = 11.5, 9.8, 6.6, 2.5 Hz, 1H), 5.31 (d, J = 11.6 Hz, 1H), 4.58 (br s, 1H), 4.48 (dt, J = 12.0, 4.4 Hz, 1H). 2.93 (dt, J = 12.4, 11.1 Hz, 1H), 2.62 (dd, J = 8.6, 4.1 Hz, 1H), 2.48 (td, J = 9.9, 2.7 Hz, 1H), 2.41 (dt, J = 16.4, 4.2 Hz, 1H), 2.30 (ddd, J = 22.0, 11.5, 5.6 Hz, 1H), 2.22 (dd, J = 14.4, 12.1 Hz, 1H), 1.99–1.78 (m, 4H), 1.73 (dd, J = 14.4, 4.3 Hz, 1H), 1.53 (t, J = 11.5 Hz ,1H), 1.58–1.45 (m, 1H), 1.44 (s, 3H), 1.42–1.32 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.09 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.8, 132.4, 131.7, 82.5, 77.9, 77.6, 57.2, 51.5, 49.7, 43.3, 43.2, 38.2, 29.0, 26.0, 23.8, 22.5, 21.7, 16.4, 2.9; TLC (20% EtOAc/hexanes) R_f 0.44; **LRMS** (ESI) Calcd. for $C_{21}H_{36}O_3Si$+Na 387.2, Found 387.2.



Dione 105. A flame-dried vial equipped with a magnetic stir bar was charged with ketone **102** (0.085 g, 0.23 mmol, 1.0 equiv) and anhydrous diethyl ether (3.0 mL). A solution of borane (1.0 M in tetrahydrofuran, 0.17 mL, 0.17 mmol, 0.7 equiv) was added.

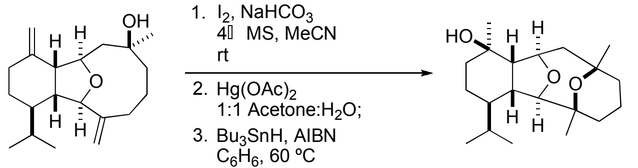
The solution was stirred at room temperature for 3 h, after which the solution solidifies into a gel. The diethyl ether is removed with a stream of nitrogen, after which anhydrous dichloromethane (3.0 mL) and powdered 4Å molecular sieves (0.40 g) were added. *N*-Methylmorpholine oxide (0.141 g, 1.20 mmol, 5.0 equiv) was added, which quickly dissolved the gel to form a cloudy solution. After stirring for 1 hour, tetrapropylammonium perruthenate (0.006 g, 0.017 mmol, 0.07 equiv) was added. The dark mixture was stirred for 2 h at room temperature. The reaction was diluted with diethyl ether (15 mL) and filtered through Celite®. The filtrate was washed with water (1 x 10 mL), saturated aqueous sodium chloride (1 x 10 mL), and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with a linear gradient of 10-15% ethyl acetate/hexanes to give dione **105** (0.043 g, 0.11 mmol, 49% yield) as a pale yellow solid and as a 10:1 mixture of inseparable diastereomers. Analytical data for **105**: $[\alpha]_D^{26.8} = -16.8$ (c = 0.49, $CHCl_3$); **IR** (thin film, cm^{-1}) 2957, 1711, 1463, 1375, 1249, 1147, 1022, 838, 753; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.78 (d, *J* = 12.8 Hz, 1H), 3.88 (d, *J* = 3.7 Hz, 1H), 3.37 (td, *J* = 10.4, 3.7 Hz, 1H), 2.70 (ddd, *J* = 12.2, 10.2, 2.3 Hz, 1H), 2.56 (d, *J* = 10.5 Hz, 1H), 2.47 (ddd, *J* = 18.2, 6.4, 3.2 Hz, 1H), 2.35–2.28 (m, 1H), 2.24 (ddd, *J* = 18.2, 10.9, 6.9 Hz, 1H), 2.00 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.91–1.58 (m, 6H), 1.47 (dd, *J* = 14.7, 13.3 Hz, 1H), 1.36 (s, 3H), 1.23–1.08 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (s, *J* = 6.9 Hz, 3H), 0.04 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 215.9, 210.3, 88.3, 76.5, 74.9, 56.8, 45.4, 43.4, 42.6, 41.9, 41.7, 38.2, 29.3, 28.7, 21.4, 21.4, 20.7, 16.4, 2.6; TLC (15% EtOAc/hexanes) R_f 0.22; **LRMS** (ESI) Calcd. for $C_{21}H_{36}O_4Si$+Na 403.2, Found 403.2.



105 **106**

Dienol 106. A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with triphenylphosphonium bromide (0.242 g, 0.68 mmol, 6.0 equiv) and anhydrous toluene (4.0 mL). A solution of sodium hexamethyldisilazane (0.5 M in tetrahydrofuran, 1.02 mL, 0.56 mmol, 5.0 equiv) was added. The tube was sealed and the mixture was stirred at 80 ºC for 30 min to give a bright orange solution of the ylide, after which the solution was cooled to room temperature. A solution of dione **105** (0.042 g, 0.11 mmol, 1.0 equiv) in anhydrous toluene (4.0 mL) was added. The reaction was heated to 90 ºC for 40 min and cooled to room temperature. Several drops of water were added and the solvents were removed. Tetrahydrofuran (5.0 mL) and aqueous hydrochloric acid (1M, 1.0 mL) were added and the solution was stirred for 5 min. The reaction was diluted with saturated aqueous sodium bicarbonate (4 mL) and extracted with diethyl ether (2 x 10 mL). The combined organic fractions were washed with saturated aqueous sodium chloride (1 x 5 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with a linear gradient of 10-20% ethyl acetate/hexanes to give diene **106** (0.0303 g, 0.10 mmol, 90% yield) as a white foam and as a 10:1 mixture of inseparable diastereomers. Analytical data for **106**: $[\alpha]_D^{24.0}$ = +39.5 (*c* = 0.62, $CHCl_3$); **IR** (thin film, cm^{-1}) 3399, 3073, 2957, 1645, 1463, 1369, 1108, 1071, 891; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.96 (br s, 1H), 4.87 (br s, 1H), 4.68 (br s, 1H), 4.63 (br s, 1H), 4.18 (s, 1H), 3.77 (ddd, *J* = 11.8, 6.1, 3.6 Hz, 1H), 2.78 (t, *J* = 6.7 Hz, 1H), 2.51 (dd, *J* = 12.4, 7.6 Hz, 1H), 2.40 (dd, *J* =

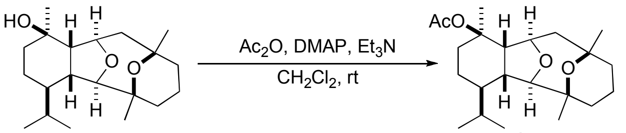
10.9, 7.3 Hz, 1H), 2.29 (dt, *J* = 13.6, 2.9 Hz, 1H), 2.18 (dd, *J* = 14.6, 8.5 Hz, 1H), 2.11–1.83 (m, 4H), 1.83–1.65 (m, 3H), 1.59–1.43 (m, 2H), 1.39–1.29 (m, 1H), 1.26 (s, 3H), 1.24 (s, 1H), 1.02 (qd, *J* = 12.9, 3.0 Hz, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.2, 147.9, 110.5, 109.2, 85.3, 79.8, 72.6, 53.2, 46.8, 44.3, 43.1, 43.0, 37.6, 31.7, 29.5, 28.5, 25.4, 25.2, 21.8, 16.3; TLC (30% EtOAc/hexanes) R_f 0.35; **LRMS** (ESI) Calcd. for $C_{20}H_{32}O_2$+Na 327.23, Found 327.23.



106

27

(+)-Deacetylpolyanthellin A (27). A flame-dried vial equipped with a magnetic stir bar was charged with **106** (0.011 g, 0.036 mmol, 1.0 equiv), powdered 4Å molecular sieves (0.200 g), sodium bicarbonate (0.060 g, 0.72 mmol, 20 equiv), and anhydrous acetonitrile (2.0 mL). The mixture was cooled to 0 ºC, and iodine (0.018 g, 0.072 mmol, 2.0 equiv) was added at once. The mixture was left to stand in the refrigerator (~4 ºC) for 8 h. The reaction was diluted with saturated aqueous sodium bicarbonate (2 mL) and extracted with hexanes (3 x 3 mL). The combined organic fractions were washed with saturated aqueous sodium chloride (1 x 2 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 2.5% ethyl acetate/hexanes to give a mixture of products from decomposition on the silica. The residue was added to a vial equipped with a magnetic stir bar in acetone (1.0 mL) and deionized water (1.0 mL). Mercuric acetate (0.023 g, 0.072 mmol, 2.0 equiv) was added, and the mixture was stirred at room temperature for 2.5 h. Saturated aqueous sodium chloride (1.0 mL) was added the the mixture was stirred for 30 min. Then, the mixture was extracted with hexanes (3 x 4 mL) and dried with sodium sulfate. This was filtered and evaporated to give a white solid. This solid was dissolved in anhydrous benzene (1.0 mL) after which tri-*n*-butyltin hydride (0.042 g, 0.144 mmol, 4.0 equiv) and azobisisobutyronitrile (0.0018 g, 0.011 mmol, 0.3 equiv) were added. The vial was purged with nitrogen, sealed with a Teflon screw cap, and heated to 60 ºC for 90 min. The solvents were removed under reduced pressure and the residue purified by flash chromatography eluting with 10% potassium fluoride/silica, eluting with a linear gradient of 15-20% ethyl acetate/hexanes to give **27** (0.0065 g, 0.020 mmol, 56% yield) as a clear film as a 6:1 mixture of diastereomers. This material was repeatedly purified via flash chromatography (silica), collecting only the first fractions, to give **27** (0.0034 g) as a 10:1 mixture of diastereomers. Analytical data for **27**: **IR** (thin film, cm^{-1}) 3441, 2959, 2926, 1737, 1460, 1371, 1077, 1055, 956, 813; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.90-3.85 (m, 1H), 3.58 (s, 1H), 2.86 (td, *J* = 6.8, 1.7 Hz, 1H), 2.42-2.28 (m, 1H), 2.32 (dd, *J* = 11.1, 7.2 Hz, 1H), 2.18 (dd, *J* = 14.2, 5.0 Hz, 1H), 1.85 (d, *J* = 13.5 Hz, 1H), 1.82-1.74 (m, 1H), 1.68 (quint of d, *J* = 6.9, 2.1 Hz, 1H), 1.57-1.32 (m, 8H), 1.30 (s, 3H), 1.30-1.23 (m, 1H), 1.19 (s, 3H), 1.17-1.08 (m, 1H), 1.06 (s, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 93.3, 78.5, 75.5, 74.2, 70.3, 53.9, 47.7, 42.3, 41.8, 39.7, 36.6, 35.8, 33.8, 29.7, 29.6, 27.5, 21.8, 18.2, 17.5, 15.9; TLC (20% EtOAc/hexanes) R_f 0.16; **LRMS** (ESI) Calcd. for $C_{20}H_{34}O_3$+Na 345.23, Found 345.23.



27

4
(+)-polyanthellin A

(+)-Polyanthellin A (4). A flame-dried vial equipped with a magnetic stir bar was charged with **27** (0.0034 g, 0.0105 mmol, 1.0 equiv), triethylamine (0.073 mL, 0.053 g, 0.525 mmol, 50 equiv), 4-dimethylaminopyridine (0.0016 g, 0.013 mmol, 1.25 equiv), and anhydrous dichloromethane (2.0 mL). Acetic anhydride (0.040 mL, 0.043 g, 0.42 mmol, 40 equiv) was added at once, and the solution was stirred at room temperature. The reaction was diluted with saturated aqueous sodium bicarbonate (2 mL) and extracted with diethyl ether (3 x 3 mL). The combined organic fractions were washed with saturated aqueous sodium chloride (1 x 2 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified twice by flash chromatography eluting with a linear gradient of 5-7.5% ethyl acetate/hexanes to give **4** (0.0028 g, 0.0077 mmol, 73% yield) as a clear film as a single diastereomer. The spectral characteristics of the synthetic (+)-polyanthellin A (**4**) are in agreement with the natural product. Analytical data for **4**: $[\alpha]_D^{25.0}$ = +9.9 (c = 0.085, CHCl$_3$), lit.[12] $[\alpha]_D^{20.0}$ = +10.5 (c = 0.31, CHCl$_3$), lit.[13] $[\alpha]_D$ = +8.9 (c = 0.22, CHCl$_3$), lit.[14] ***ent*-4** $[\alpha]_D^{20.0}$ = –9.9 (c = 1.0, CHCl$_3$); **IR** (thin film, cm^{-1}) 2928, 2872, 1732, 1462, 1367, 1254, 1185, 1151, 1114, 1077, 1055, 1014, 991, 833, 800, 735; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 3.90 (td, J = 5.7, 1.1 Hz, 1H), 3.54 (s, 1H), 3.22 (td, J = 7.1, 2.2 Hz, 1H), 2.46-2.38 (m, 1H), 2.36 (dt, J = 13.1, 4.2 Hz, 1H), 2.33-2.26 (m, 1H), 2.19 (dd, J = 14.3, 4.9 Hz, 1H), 2.00 (s, 3H), 1.87 (dd, J = 14.1, 1.1 Hz, 1H), 1.82-1.74 (m, 1H), 1.70-1.60 (m, 1H), 1.55-1.22 (m, 6H), 1.48 (s, 3H), 1.33 (s, 3H), 1.22-1.12 (m, 2H), 1.08 (s, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.80

(d, *J* =6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.3, 93.8, 83.2, 77.4, 75.5, 74.3, 51.0, 47.5, 42.3, 41.7, 39.7, 36.2, 35.6, 29.7, 29.6, 27.5, 24.1, 22.5, 21.7, 18.2, 17.5, 15.6; TLC (25% EtOAc/hexanes) R_f 0.57; **HRMS** (ESI) Calcd. for $C_{22}H_{36}O_4$+Cs 497.1668, Found 497.1681.

3.5 References

(1) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531-556.

(2) Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571-4618.

(3) Sung, P. J.; Chen, M. C. *Heterocycles* **2002**, *57*, 1705-1715.

(4) Stierle, D. B.; Carte, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088-5092.

(5) Kennard, O.; Watson, D. G.; di Sanseverino, L. R.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron Lett.* **1968**, *9*, 2879-2884.

(6) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200-17201.

(7) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674-8680.

(8) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 437-440.

(9) Becker, J.; Bergander, K.; Fröhlich, R.; Hoppe, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 1654-1657.

(10) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683-2686.

(11) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135-137.

(12) Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 15851-15855.

(13) Bowden, B. F.; Coll, J. C.; Vasilescu, I. M. *Aust. J. Chem.* **1989**, *42*, 1705-1726.

(14) Ospina, C. A.; Rodriguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357-363.

(15) Ellis, J. M.; Crimmins, M. T. *Chem. Rev.* **2008**, *108*, 5278-5298.

(16) Alam, M. J.; Sharma, P.; Zektzer, A. S.; Martin, G. E.; Ji, X.; van der Helm, D. J. *J. Org. Chem.* **1989**, *54*, 1896-1900.

(17) Sharma, P.; Alam, M. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537-2540.

(18) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875-1878.

(19) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391-10392.

(20) Molander, G. A.; Czako, B.; St. Jean, D. J. *J. Org. Chem* **2006**, *71*, 1172-1180.

(21) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057-1059.

(22) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014-16015.

(23) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642-8650.

(24) Hagiwara, H.; Ono, H.; Hoshi, T. *Org. Synth.* **2003**, *80*, 195-199.

(25) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425-5428.

(26) Yang, D.; Gao, Q.; Lee, C.-S.; Cheung, K.-K. *Org. Lett.* **2002**, *4*, 3271-3274.

(27) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem* **1976**, *41*, 1485-1486.

(28) Hore, P. J.; Grainger, D. S.; Wimperis, S.; Daniell, G. J. *J. Magn. Reson.* **1990**, *89*, 415-422.

(29) Wang, K.-Y.; Borer, P. N.; Levy, G. C.; Pelczer, I. *J. Magn. Reson.* **1992**, *96*, 165-170.

(30) Wang, H.; Glick, G. D.; Zuiderweg, E. R. P. *J. Magn. Reson., Ser. A* **1993**, *102*, 116-121.

(31) X-ray crystallography was performed by Dr. Peter White.

(32) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253-4256.

(33) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem* **1989**, *54*, 1295-1304.

(34) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem* **1986**, *51*, 1922-1925.

(35) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem* **1995**, *60*, 790-791.

(36) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5985-5990.

(37) M. E. Kuehne, W. G. B., I. Markó, Y. Qin, K. L. LeBoulluec, D. A. Frasier, F. Xu, T. Mulamba, C. L. Ensinger, L. S. Borman, A. E.Huot, C. Exon, F. T. Bizzarro, J. B. Cheung, S. L. Bane, *Org. Biomol. Chem.* **2003**, *1*, 2120-2136.

(38) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572-11573.

(39) Casolari, S.; D'Addari, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061-1063.

(40) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701-2704.

(41) Moller, R.; Engel, N.; Stelich, W. *Synthesis* **1978**, 620-622.

(42) Qiao, C.; Jeon, H.-B.; Sayre, L. M. *J. Am. Chem. Soc.* **2004**, *126*, 8038-8045.

(43) Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127-3129.

(44) Covell, D. J.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448-6451.

(45) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727-2730.

(46) Fousteris, M. A.; Koutsourea, A. I.; Nikolaropoulos, S. S.; Riahi, A.; Muzart, J. *J. Mol. Catal. A: Chem.* **2006**, *250*, 70-74.

(47) Choi, H.; Doyle, M. P. *Org. Lett.* **2007**, *9*, 5349-5352.

(48) Schmidt, B. *J. Org. Chem* **2004**, *69*, 7672-7687.

(49) Corey, E. J.; Suggs, J. W. *J. Org. Chem* **1973**, *38*, 3224-3224.

(50) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127-130.

(51) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723-730.

(52) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559-3562.

(53) Yates, M. H. *Tetrahedron Lett.* **1997**, *38*, 2813-2816.

(54) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem* **1982**, *47*, 5065-5069.

(55) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806-813.

(56) Imagawa, H.; Shigaraki, T.; Suzuki, T.; Takao, H.; Yamada, H.; Sugihara, T.; Nishizawa, M. *Chem. Pharm. Bull.* **1998**, *46*, 1341-1342.

(57) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1980**, *21*, 4055-4056.

(58) Kelly, B. D.; Allen, J. M.; Tundel, R. E.; Lambert, T. H. *Org. Lett.* **2009**, *11*, 1381-1383.

(59) Schuster, C.; Broeker, J.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2631-2647.

(60) Murray, R. W.; Singh, M. *Org. Synth.* **1998**, *74*, 91-100.

(61) Alaimo, P. J.; W., P. D.; Arnold, J.; Bergman, R. G. *J. Chem. Educ.* **2001**, *78*, 64-67.

(62) Mahler, G.; Serra, G.; Manta, E. *Synth. Commun.* **2005**, *35*, 1481-1492.