The Dissertation Committee for Jeffrey Scott Thomas Gorman Certifies that this is the approved version of the following dissertation:

Transition Metal-Mediated Cyclizations and Synthesis of Annonaceous Acetogenin Analogs

Committee:

Brian L. Pagenkopf, Supervisor

Alan H. Cowley

Brent L. Iverson

Christopher W. Bielawski

Sean M. Kerwin

Transition Metal-Mediated Cyclizations
and
Synthesis of Annonaceous Acetogenin Analogs

by

Jeffrey Scott Thomas Gorman, B.S.

Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August, 2006

Dedication

To my wonderful family for all the love, support and understanding.

Acknowledgements

I am very thankful to Dr. Brian L. Pagenkopf for his patient guidance and support over the years and for giving me encouragement and advice when I truly needed it.

I am thankful to all of my labmates in the Pagenkopf group who have helped make the graduate experience more pleasant and put up with most of my attempts at singing and humor. I thank Dr. Ming Yu (my "brother") and Dr. Brandon Young for showing me the ropes at the beginning. I owe so much gratitude to Dr. Julie Le, Dr. Darren Engers, and particularly A.J. Boydston for the always thought-provoking, sometimes silly discussions on chemistry and life and for keeping me grounded. I thank Hongda Zhao for all of his hard work and spectacular contributions to the acetogenins project and a great experience working together. Additionally, I thank Scott Iacono for his contributions to the zirconocycle oxidation project.

I also want to thank Dr.Vince Lynch for solving an X-Ray structure when I thought I didn't need it and Dr. Steve Sorrey for his excellent NMR work.

Transition Metal-Mediated Cyclizations
and
Synthesis of Annonaceous Acetogenin Analogs

Publication No._____

Jeffrey Scott Thomas Gorman, Ph.D

The University of Texas at Austin, 2006

Supervisor: Brian L. Pagenkopf

A new protocol for functionalization of zirconocyclopentenes formed by Negishi bicyclization of 1,7- and 1,6-enynes is described. Regioselective transfer of the alkyl ligand to select boron electrophiles followed by oxidation provides 1-alkylidene-2-hydroxymethylcycloalkanes in yields comparable to protonation of the zirconocycles.

The scope and limitations of Mukaiyama's cobalt-mediated oxidative cyclization of 4-alkene-1-ols are detailed with a focus on the effects of substitution patterns on efficiency and stereochemistry. Additionally, improvements in the ligand and cobalt complex syntheses are discussed.

Additionally, modular syntheses of two Annonaceous acetogenin analogs are described. The flexible approach allows for rapid synthesis of analogs through late stage diversification, allowing the elucidation of structure activity relationships (SARs).

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ac	Acetate
9-BBN	9-Borabicyclo[3,3,1]nonane
BHT	Butylated hydroxy toluene/2,5-Di-*tert*-butyl-4-methylphenol
Bn	Benzyl
n-Bu	*normal*-Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
CAM	Ceric ammonium molybdate
m-CPBA	*meta*-Chloroperoxybenzoic acid
Cp	Cyclopentadienyl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
ED_{50}	Effective dosage
Et	Ethyl
FID	Flame ionization detector
FT-IR	Fourier transform-infrared
GC	Gas Chromatography
GOESY	Gradient Overhauser effect spectroscopy
HRMS	High resolution mass spectrometry
c-Hex	Cyclohexyl
n-Hex	*normal*-Hexyl
Me	Methyl

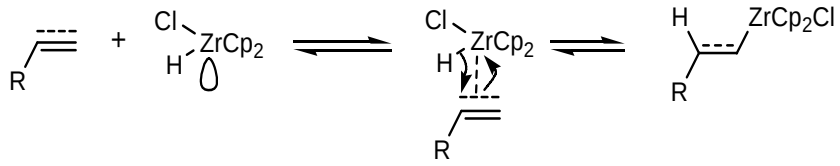
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
NIS	N-Iodosuccinimide
NMO	N-methylmorpholine N-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
ORTEP	Oak Ridge Thermal-Ellipsoid Plot
[O]	Oxidation
PCC	Pyridinium chlorochromate
Ph	Phenyl
i-Pr	*iso*-Propyl
n-Pr	*normal*-Propyl
R_f	Retention time
TBS	*tert*-Buyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl piperidine N-oxide
Tf	Triflate or Trifluoromethylsulfonyl
THF	Tetrahydofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	Tosyl
Δ	Heat

Chapter 1: Selective Oxidation of Zirconocyclopentenes Via Organoboranes

1.1 INTRODUCTION

While Wilkinson's 1953 report of zirconocene dibromide was among the earliest examples of metallocene complexes,[1] application of zirconocene complexes to organic chemistry matured slowly until the 1970s.[2] Preferential disubstitution and facile β-hydride elimination greatly limited metathesis approaches employing organolithiums and Grignard reagents.[2] A breakthrough in this research area was Wailes' discovery of chlorozirconocene hydride ($HZrClCp_2$) and its hydrozirconation reactions with alkenes and alkynes.[3] Schwartz later studied these reactions more extensively, determining the scope and limitations and examining applications to organic synthesis.[4] This first, general route to organozirconocene compounds has provided valuable information regarding their reactivity.

Scheme 1.1 Hydrozirconation of alkenes and alkynes

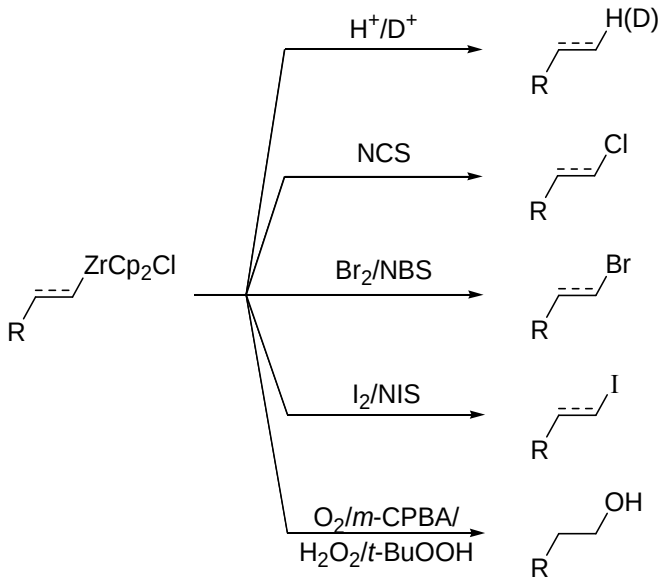


1.1.1 Reactivity of hydrozirconation products

Having examined the scope of the hydrozirconation reaction, Schwartz's group began to explore reactions of the resulting alkyl and alkenylzirconocenes. They found

that these monoorganylzirconocenes react readily with electrophilic halogenating agents such as Br_2, I_2, NBS and NCS to provide alkyl halides and haloalkenes (Scheme 1.2).[4] Similarly, oxidation of alkylzirconocenes with O_2 or electrophilic oxidizing reagents such as *t*-BuOOH, *m*-CPBA or H_2O_2 provides the corresponding alcohols.[4,5] However, similar attempts to oxidize alkenylzirconocenes to aldehydes or ketones have proven less successful.[2]

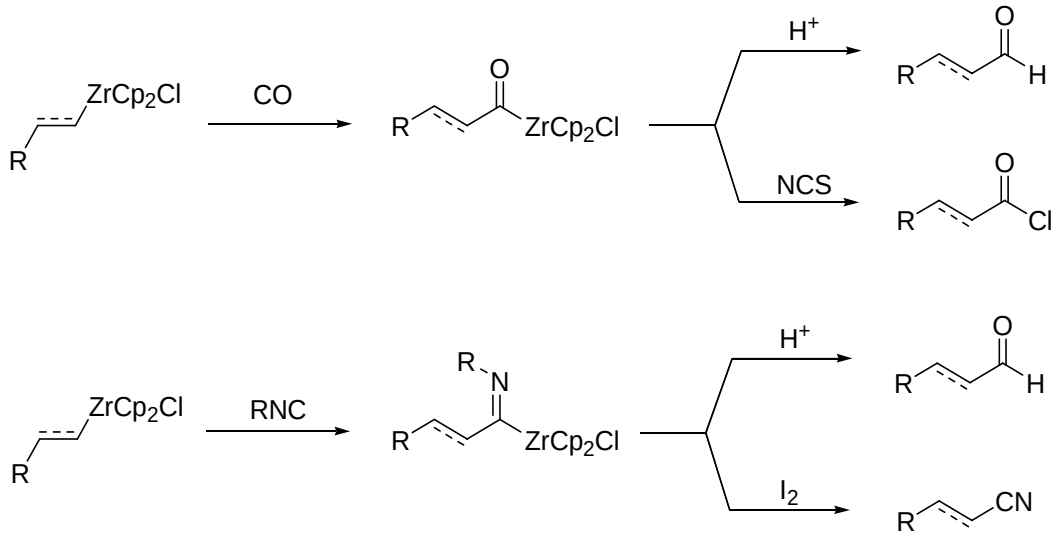
Scheme 1.2 General reactions of hydrozirconation products



Another significant contribution to organozirconium chemistry was the discovery that carbon monoxide inserts into the C-Zr bond of most alkyl and alkenylzirconocenes to provide acylzirconium compounds (Scheme 1.3).[6] Subsequent treatment of these intermediates with protic acid provides the corresponding aldehydes or with electrophilic halogenating reagents provides acid halides, carboxylic acids or esters depending on workup conditions. Similar insertion reactions have been reported with isonitriles to

provide iminoacylzirconium intermediates,[7] which can either be treated with halogenating reagents to provide nitriles[8] or hydrolyzed to give aldehydes.[9]

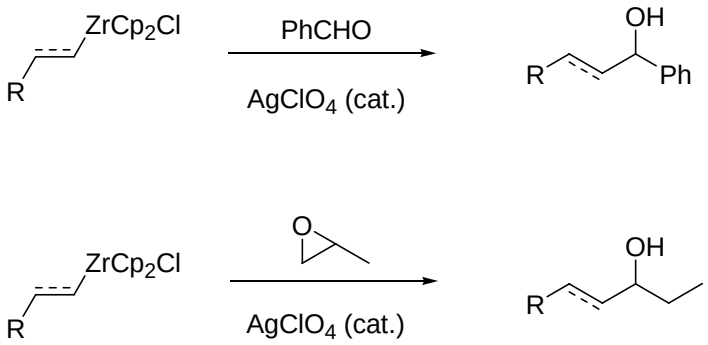
Scheme 1.3 Insertion reactions of alkyl and alkenylzirconocoenes



Despite these advances, the organozirconocenes formed by hydrozirconation are relatively unreactive toward many common organic electrophiles, likely due to the crowded Zr coordination sphere.[2] Specifically, many of the C-C bond forming reactions integral to organic synthesis such as aldehyde additions, additions to α,β-unsaturated ketones,[10] epoxide opening and S_N2 reactions with alkyl halides are largely unavailable with hydrozirconation products.[2] One solution to this problem has been the use of Ag(I) salts such as $AgAsF_6$ to increase the Lewis acidity and reduce the steric environment of the metal by halogen abstraction.[11] This has allowed for successful addition to aldehydes and an interesting isomerization/addition reaction with epoxides (Scheme 1.4). A second, more general approach to the problem of low reactivity is transmetallation. By transfer of

the alkyl or alkenyl group to another metal, the utility of organozirconocenes has been expanded immensely.

Scheme 1.4 Reactions of cationic zirconocene complexes with aldehydes and epoxides



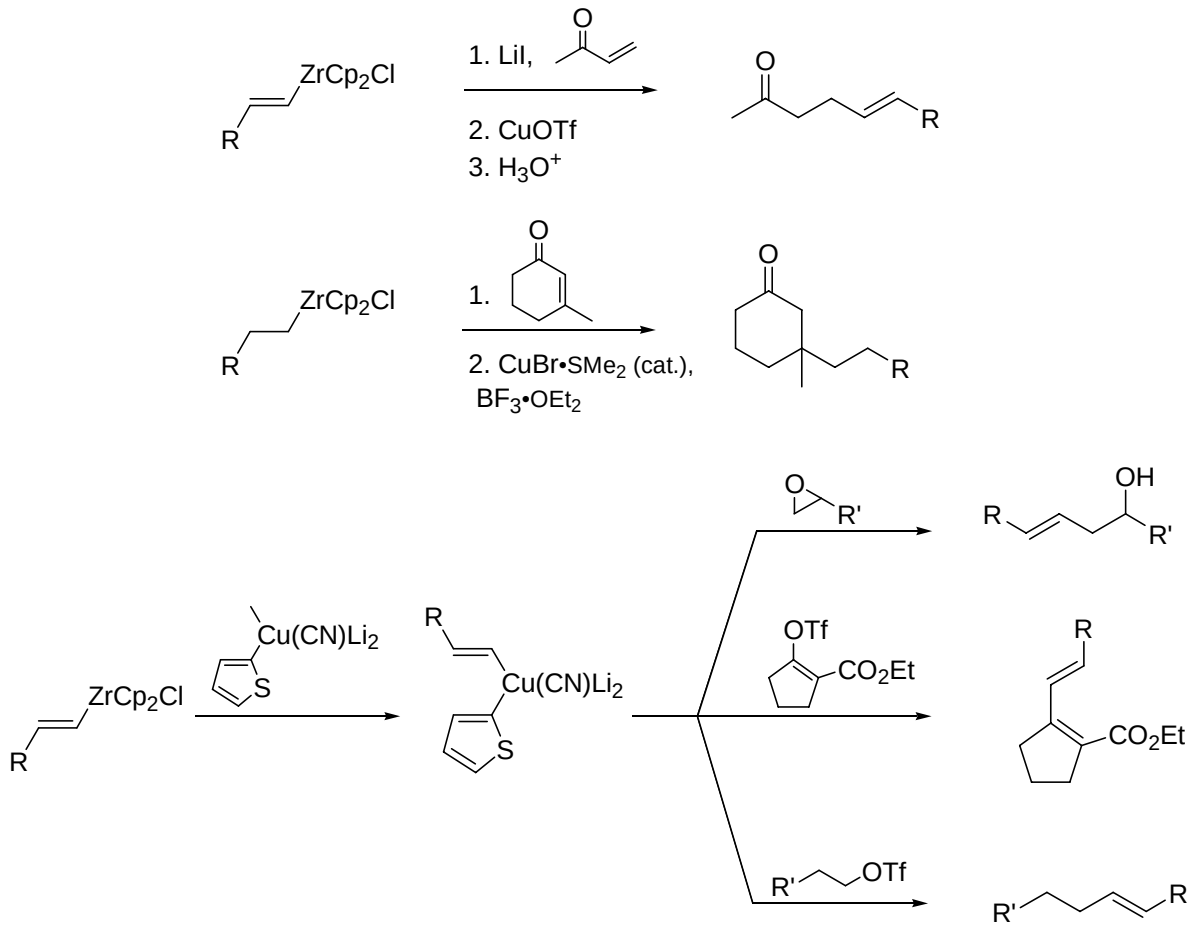
1.1.2 Transmetallation of hydrozirconation products

For transmetallation to be favorable, a difference in electronegativity between the two metals is necessary, which is strongly influenced by the electron donating or electron withdrawing nature of each. Examples of transmetallations of organozirconocenes to various transition and main group metals have been reported including Cu, Pd, Ni, Sn, Hg, B, Al and Si.[2,12a] By using this strategy, the chemistry of relatively unreactive organozirconocenes has been joined with the wealth of reactions available to other metals.

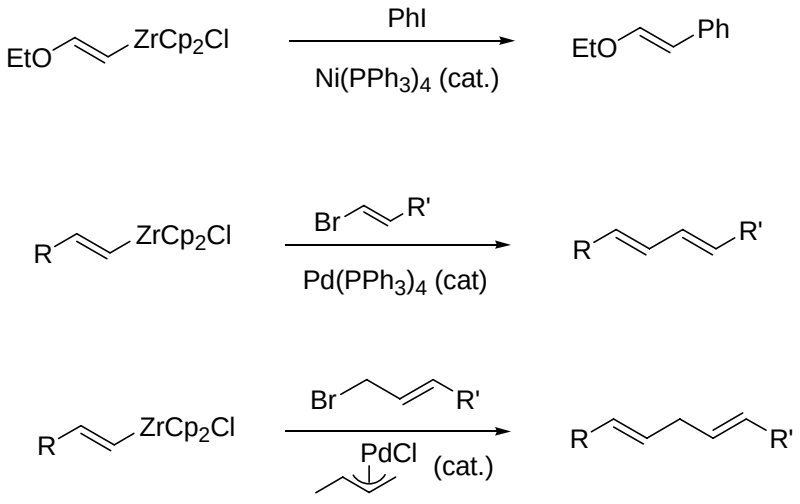
Examples of this approach include the transfer of organic ligands from Zr to Cu, accessing additions to α,β-unsaturated ketones[12] and epoxides[13] as well as substitution reactions with alkyl triflates,[13] allylic and benzylic halides and phosphates,[14] and vinyl halides and sulfonates (Scheme 1.5).[13] Transmetallation of alkenylzirconocenes to Ni and

Pd has also been applied to allylic substitution reactions and cross-couplings with vinyl halide (Scheme 1.6)[12d,15] Transmetallation of hydrozirconation products to Zn has provided organozinc intermediates useful in additions to aldehydes[16] and as secondary transfer agents to other metals (Scheme 1.7).[17] Additionally, transfer of hydrozirconation products to B has provided a solution to the problematic oxidation of alkenylzirconocenes.[18]

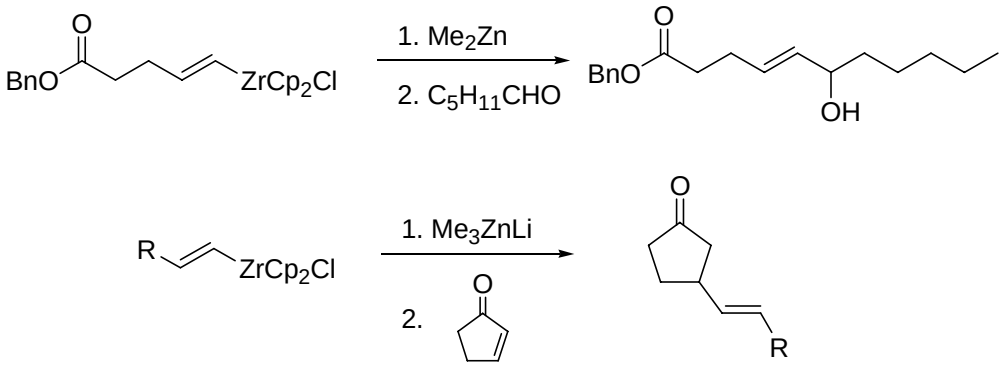
Scheme 1.5 Applications of transmetallation from Zr to Cu



Scheme 1.6 Examples of transmetallation from Zr to Ni and Pd



Scheme 1.7 Transmetallations from Zr to Zn

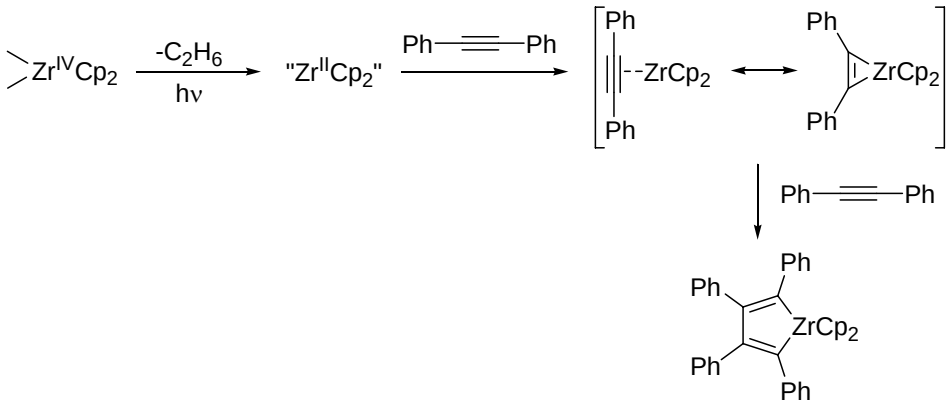


1.2 ZIRCONOCYCLES

1.2.1 Methods of Formation

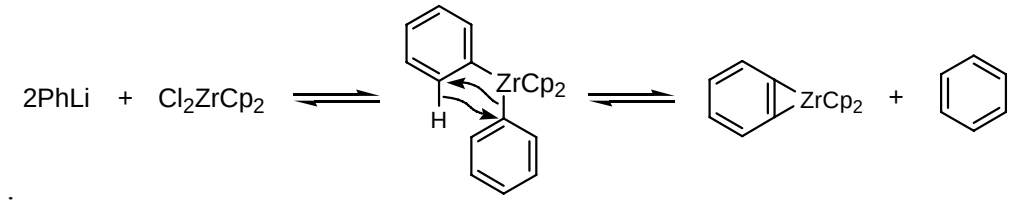
Rausch reported an early example of zirconocyle formation that provided insight into this chemistry by photolysis of dimethylzirconocene in the presence of diphenylacetylene (Scheme 1.8).[19] Homolytic cleavage of the methyl groups provided a transient Zr(II) complex, which formed a π-complex with the alkyne. Since Zr(II) has a lone pair of electrons available for back bonding, this π-complex could also be viewed as a Zr(IV) zirconocyclopropene. This intermediate underwent further ring expansion with an additional equivalent of the alkyne to produce a zirconocyclopentadiene. Related approaches to zirconocycles involving reduction of zirconocene(IV) dichloride to zirconocene(II) with Na/Hg or $Mg/HgCl_2$ in the presence of π-systems have also been reported.[20] However, more recent methods based on thermal decomposition of diorganozirconocenes currently offer the most general and reliable route to zirconocycles.

Scheme 1.8 Rausch's synthesis of a zirconocylopentadiene



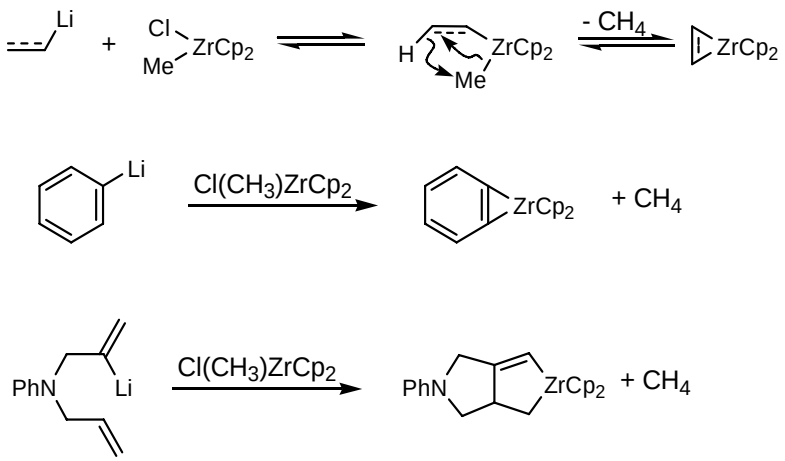
Erker observed that when diphenylzirconocene was thermolyzed in hydrocarbon solvents, benzene and a benzyne π-complex of zirconocene (or zirconocyclopropene) were formed (Scheme 1.9).[21] He studied the mechanism of this reaction and found that a β-H of one phenyl was abstracted by the Zr-C bond of the second phenyl group.[22] The resulting, highly strained complexes reacted readily with other π-systems including alkenes, alkynes, aldehydes and imines to give 5-membered zirconocycles. An elegant and practical modification to Erker's method, which effectively wasted one of the organic groups, was introduced by Buchwald.[23] Formation of mixed diorganozirconocenes by reactions of alkyl, alkenyl and aryllithiums with methylzirconocene chloride allowed the methyl group to serve as the sacrificial ligand (Scheme 1.10). These approaches to π-complexes of zirconocene have proven very useful when the "free" π-system is unstable (benzynes) or incompatible with other methods (terminal alkynes).

Scheme 1.9 Erker's approach to benzyne adducts of zirconocene



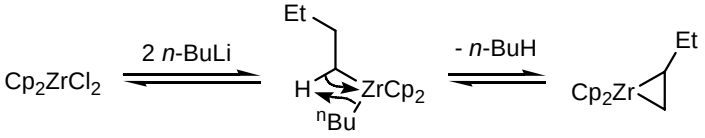
.

Scheme 1.10 Buchwald's modification of Erker's method



A complementary method for the preparation of zirconocycles from stable π-systems was described in the 1980's by Negishi and coworkers.[24] They found that dibutylzirconocene, produced from the metathesis reaction between *n*-BuLi and zirconocene dichloride, decomposes cleanly at relatively low temperatures (0 °C to rt) to provide a zirconocyclopropane (Scheme 1.11). This reagent may be used as a precursor to other zirconocycles including zirconocyclopentanes, zirconocyclopentenes, zirconocyclopentadienes by ring-expansion and ring-contraction in the presence of alkenes, alkynes, aldehydes or nitriles.

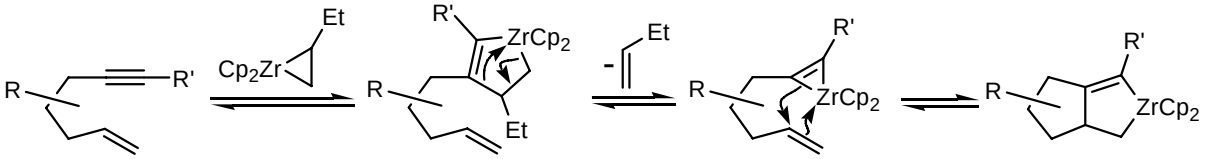
Scheme 1.11 Negishi's zirconocyclopropane



Negishi also reported a useful application of this method in the bicyclization of 1,6- and 1,7-dienes, diynes and enynes.[25] In the case of enyne bicyclization, the initial zirconocyclopropane reacts with the alkyne to form a zirconocyclopentene (Scheme

1.12). This intermediate undergoes ring-contraction, producing a zirconocyclopropene that can react intramolecularly with the pendant alkene to form a bicyclozirconocyclopentene. Similarly, treatment of with dienes and diynes has been used in the formation of bicyclic zirconocyclopentanes and zirconocyclopentadienes, respectively.

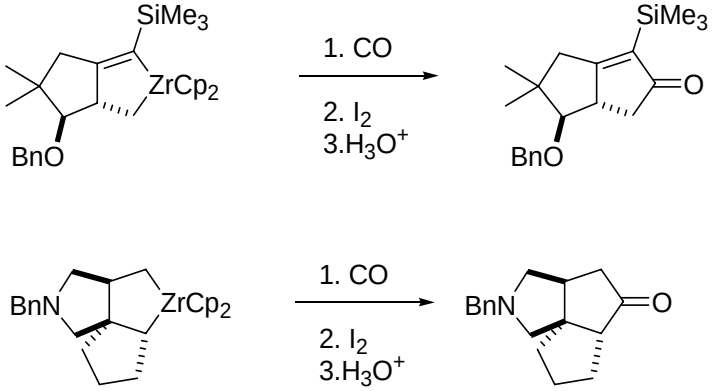
Scheme 1.12 Formation of bicyclozirconocyclopentenes by Negishi's method



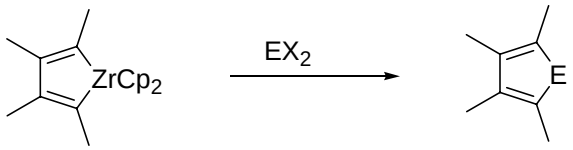
1.2.2 Reactions of zirconocycles

The reactivity of zirconocycles largely follows that of hydrozirconation products, but notable distinctions exist mainly due to the presence of the second C-Zr bond. For example, reaction of zirconocyclopentanes[26] and zirconocylopentenes[25] with carbon monoxide initially gives the expected acylzirconium intermediates. However, the additional C-Zr undergoes facile insertion as well, providing cyclopentanones or cyclopentenones, respectively (Scheme 1.13). Similarly, Fagan and Nugent showed that both C-Zr bonds of zirconocylopentadienes transfer to main group electrophiles to form the corresponding heterocycles (Scheme 1.14).[27]

Scheme 1.13 Carbon monoxide insertion into zirconocylopentenes and zirconocyclopentanes



Scheme 1.14 Fagan and Nugent's synthesis of main group heterocycles

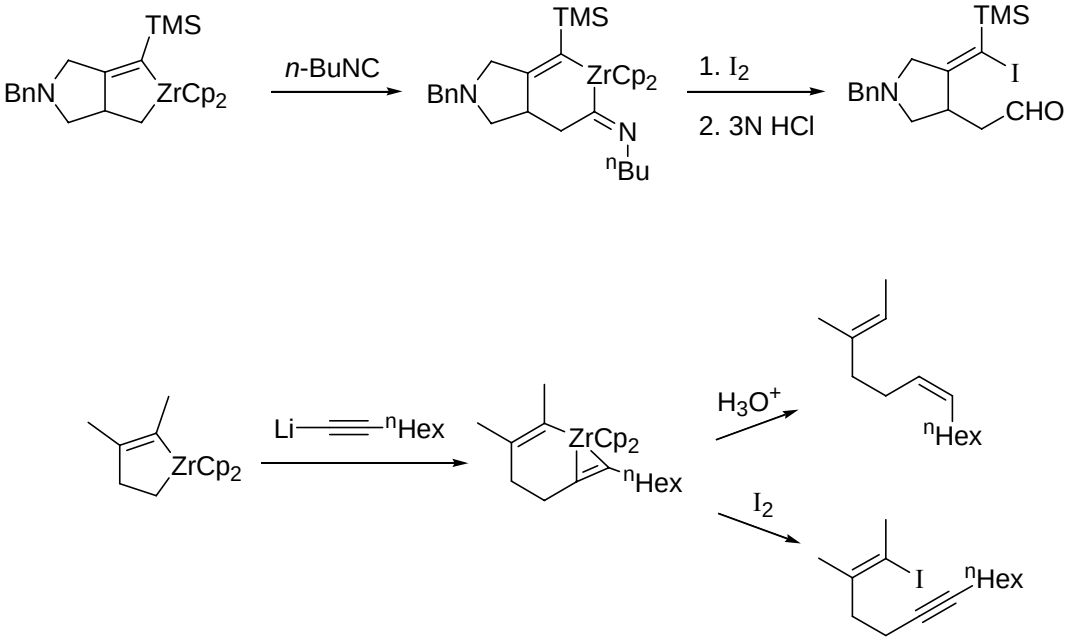


E = PhP, PhAs, PhSb, PhBi
PhB, $SiBr_4$, $GeCl_2$

1.2.2.1 Zirconocyclopentenes

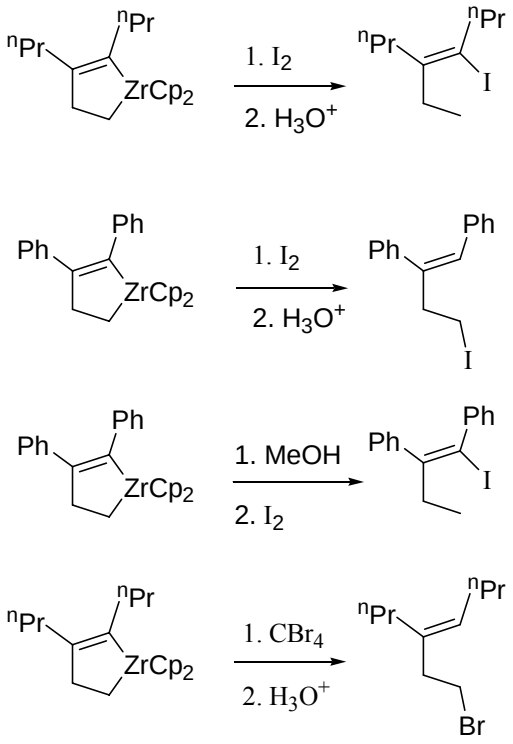
Containing both a C_{sp^3}-Zr and a C_{sp^2}-Zr bond, zirconocyclopentenes elicit a question of regioselectivity. One of the earliest examples of a regioselective reaction of these complexes was reported by Negishi in the migratory insertion of isonitriles, which occurs regioselectively at the C_{sp^3}-Zr bond.[9] In contrast to reactions with carbon dioxide, a second migratory insertion occurs less readily for isonitriles, making the acyliminium species a viable synthetic intermediate (Scheme 1.15). Similar regioselectivity has been observed for migratory insertion of acetylides[28] and allenyl carbenoids.[29]

Scheme 1.15 Regioselective migratory insertion reactions of zirconocyclopentenes



Negishi also found that the reactivity of zirconocyclopentenes is somewhat enhanced relative to hydrozirconation products as reactions with aldehydes proceed efficiently and regioselectively at the alkyl zirconium bond.[30] Monoprotonation of zirconocylcopentenes is also selective for the C_{sp3}-Zr bond, producing an alkenylzirconium species available for further transformation.[31] Additionally, Takahashi and coworkers investigated the regioselective halogenation of zirconocyclopentenes, providing convenient reagent-controlled methods for formation of either the vinyl halide or the homoallylic halide (Scheme 1.16).[31,32] Notably, the regioselectivity of iodination using I_2 was highly dependent on the substitution of the alkyne used for zirconocycle formation as aryl alkynes provided the vinyl iodide while alkyl-substituted gave the homoallylic iodide.

Scheme 1.16 Takahashi's regioselective halogenations of zirconocyclopentenes

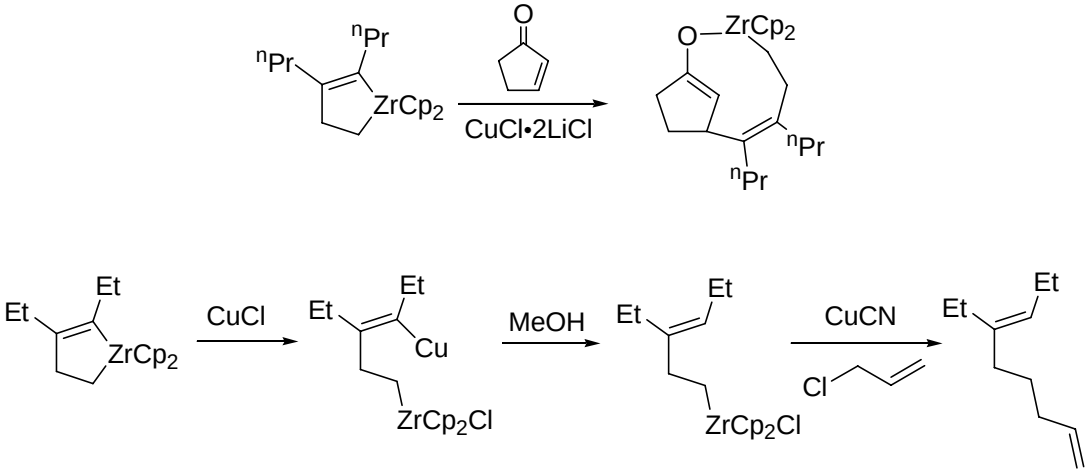


1.2.2.2 Transmetallation of zirconocyclopentenes

As with hydrozirconation products, transmetallation has expanded the reactions available to zirconocyclopentenes, but with much fewer examples reported in the literature. Lipshutz observed that zirconocyclopentenes react selectively with copper halides at the C_{sp^2}-Zr bond to produce alkenylcopper species (Scheme 1.17). The resulting mixed-dimetallated species have been used successfully in conjugate additions to α,β-unsaturated ketones and substitutions of allylic halides.[33] Takahashi later developed a complementary modification, using selective protonation of the C-Cu bond

followed by transmetallation of the remaining C_{sp^3}-Zr bond to Cu and reaction with allyl chloride, effecting substitution at the C_{sp^3} site.[34]

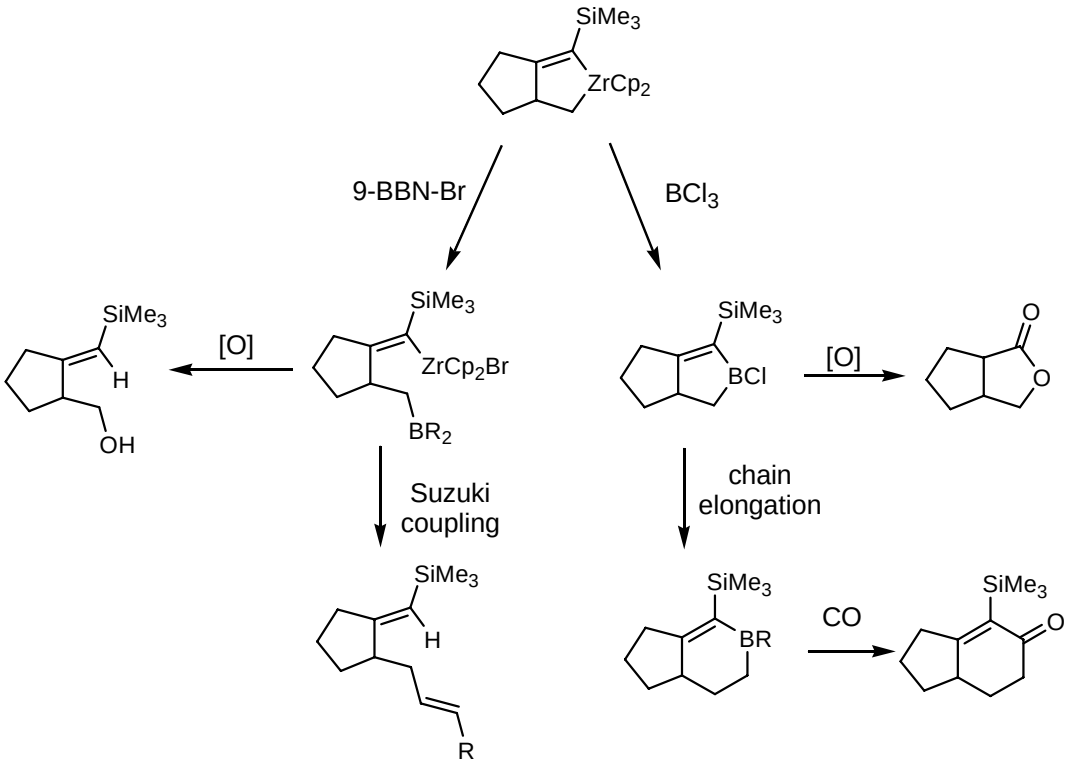
Scheme 1.17 Regioselective transmetallations of zirconocyclopentenes to Cu



1.3 OBJECTIVE OF THE CURRENT STUDY

Our interest in this arena has focused on further increasing the synthetic utility of zirconocyclopentenes through transmetallation to boron. Inspired by Cole's and Nugent's transmetallation of other zirconocycles to boron and the regioselective reactions of zirconocylopentenes, we hoped to bridge the chemistry of bicyclization reactions of 1,6 and 1,7-enynes with the rich chemistry of organoboranes. It was envisioned that transfer of one or both C-Zr bonds to boron followed by oxidation, homologation,[35] carbonylation[36] or Suzuki coupling[37] would enhance the usefulness of these zirconocycles (Scheme 1.18). In the current study the regioselectivity and efficiency of transmetallation to boron electrophiles followed by oxidation of the C-B bond was investigated as a proof of concept.

Scheme 1.18 Potential applications of zirconocyclopentene transfer to boron



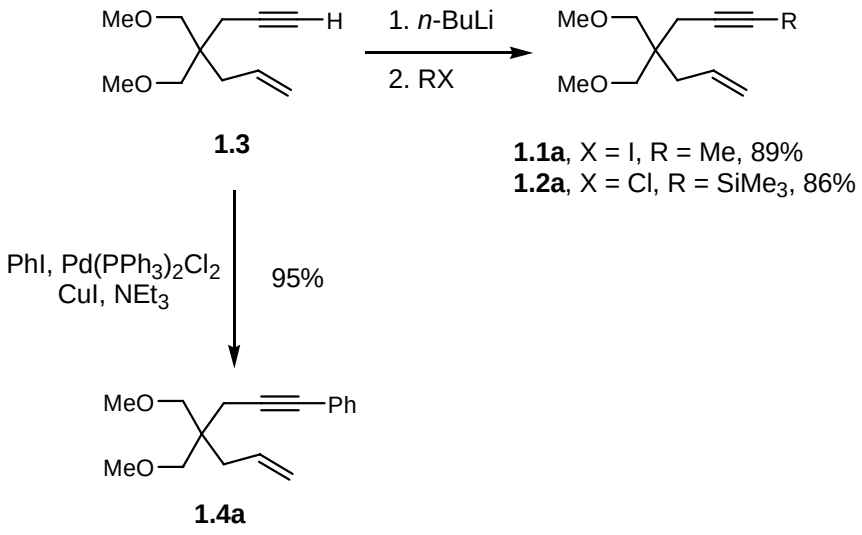
1.4 RESULTS AND DISCUSSION

1.4.1 Substrate preparation

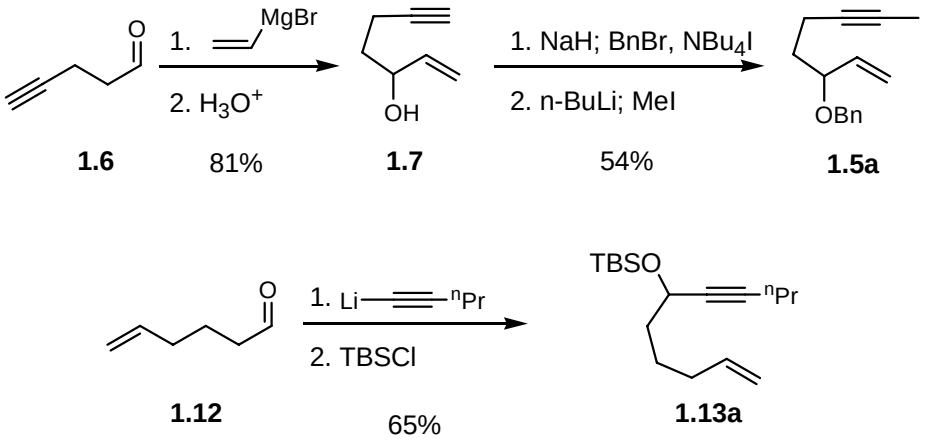
A representative set of enynes was prepared to examine the scope and limitations of the boron-mediated oxidation of zirconocyclopentenes. Malonate-derived enynes **1.1a** and **1.2a** were prepared by deprotonation of terminal alkyne **1.3**[38] with *n*-BuLi and treatment of the resulting acetylide with MeI and Me_3SiCl, respectively (Scheme 1.19). Phenyl-substituted alkyne **1.4a** was prepared from **1.3** and iodobenzene using standard Sonogashira conditions.[39] Enyne **1.5a** was prepared by addition of vinylmagnesium bromide to 4-pentynal followed by benzylation of the resulting alcohol and methylation

of the terminal alkyne with *n*-BuLi/MeI (Scheme 1.20). Enynes **1.8a**, **1.9a** and **1.10a** were prepared by addition of the corresponding lithium acetylides to aldehyde **1.11** followed by treatment of the resulting alkoxide with TBSCl (Scheme 1.21).[40] A similar reaction using 5-hexenal provided 1,7-enyne **1.13a** (Scheme 1.20). Treatment of TMS-substituted alkyne **1.8a** with catalytic NaOH in MeOH provided terminal alkyne **1.14**, which was treated with *n*-BuLi followed by MeI to provide enyne **1.15a** (Scheme 1.21).

Scheme 1.19 Preparation of enynes **1.1a , 1.2a, 1.4a**



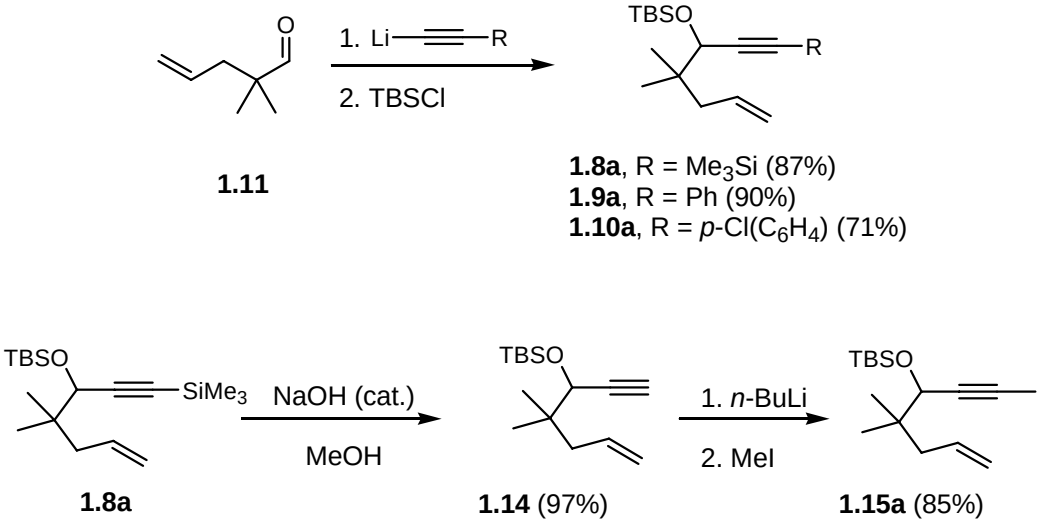
Scheme 1.20 Synthesis of enynes **1.5a** and **1.13a**



1.6 81% **1.7** 54% **1.5a**

1.12 65% **1.13a**

Scheme 1.21 Synthesis of enyne substrates **1.8a**, **1.9a**, **1.10a** and **1.15a**



1.11

1.8a, R = Me_3Si (87%)
1.9a, R = Ph (90%)
1.10a, R = *p*-Cl(C_6H_4) (71%)

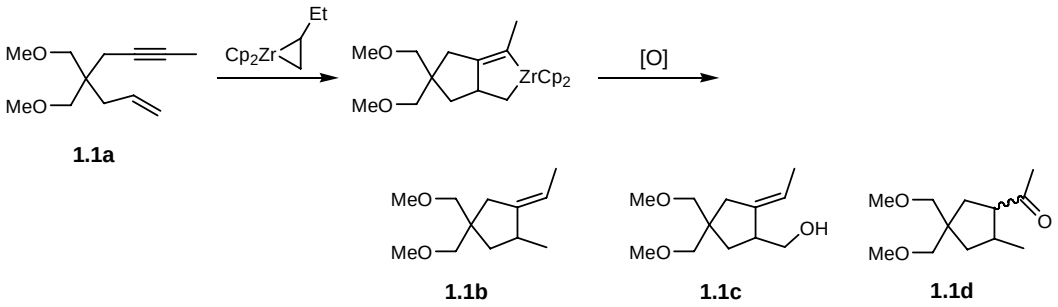
1.8a **1.14** (97%) **1.15a** (85%)

1.4.2 Control experiments

The zirconocyclopentene derived from enyne **1.1a** was chosen as a model for a series of control experiments examining the possibility of direct oxidation. All attempts

to oxidize this organozirconocene with reagents such as NMO, TEMPO, benzoyl peroxide were met with low yields and modest regioselectivities (Table 1.1).[41] The major product in most cases was the cycloreduction product resulting from protonation either under reaction conditions or upon workup. While formation of this product with protic oxidants (entries 5-8) was unsurprising, aprotic oxidants offered little or no improvement (entries 1-4) and reaction of the zirconocyclopentene with O_2 caused decomposition.

Table 1.1 Control oxidations of the zirconocycle from enyne **1.1a**



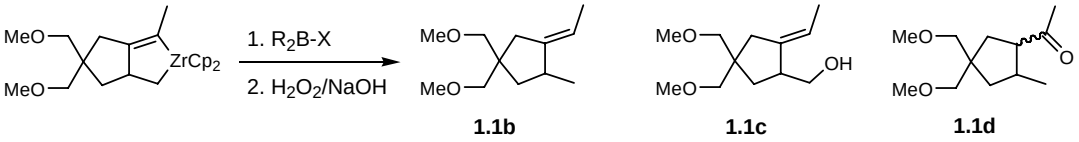
1.1a **1.1b** **1.1c** **1.1d**

Entry	Oxidant	1.1b	1.1c	1.1d
1	NMO	72	21	7
2	TEMPO	95	5	0
3	BzO_2	87	3	10
4	Me_3NO	63	13	24
5	H_2O_2, NaOH	96	4	0
6	$NaBO_3$	96	4	0
7	*t*-BuOOH	81	19	0
8	*m*-CPBA	80	20	0

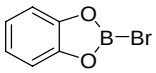
With only moderate yields and selectivity for these oxidations, transmetallation of the zirconocyclopentene formed from enyne **1.1a** to boron was examined. The zirconocycle was treated with a variety of electrophilic boron reagents followed by a

standard oxidative workup with $NaOH/H_2O_2$ (Table 1.2).[41] Transmetallation with BCl_3 produced a complex mixture of demethylation and oxidation products, indicating a need to modulate the Lewis acidity of the boron reagent. Treatment of the zirconocycle with BBr_3 produced cycloreduced product **1.1b**, exclusively, while transmetallation with catechol-BBr, 9-BBN-Cl and (-)-Ipc_2BCl provided minor amounts of oxidation product of alcohol **1.1c**. These results suggest that the counter ion and steric requirements of the boron reagent have significant impact on transmetallation. Still, the high regioselectivity observed for the minor oxidation product (**1.1c**) was encouraging. The efficiency of the process was improved significantly without loss of regioselectivity by using Bu_2BOTf. Further improvement was observed in the transmetallation with $(^cHex)_2BCl$, providing alcohol **1.1c** in a useful yield of 75%.

Table 1.2 Screening of boron electrophiles for transmetallation



1.1b **1.1c** **1.1d**

Entry	R_2B-X	1.1b	1.1c	1.1d
1	BCl_3	11	5	0
2	BBr_3	75	0	0
3		62	25	0
4	9-BBN-Cl	79	11	0
5	(-)-Ipc-BCl	59	24	0
6	Bu_2BOTf	8	57	0
7	$(^cHex)_2BCl$	8	75	0

1.4.3 Scope and limitations

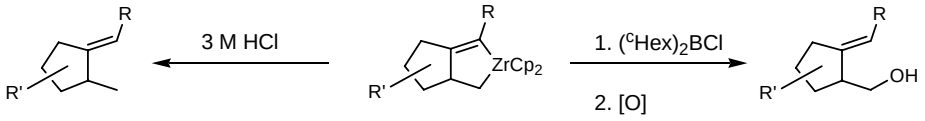
The results of the boron-mediated regioselective oxidation of zirconocyclopentenes from the enynes synthesized above are summarized in Table 1.3. In particular, 1,6-enynes for zirconocycle formation due to favorable kinetics in the formation of a 5-membered rings and geminal substitution along the tether further enhances the rate and efficiency of cyclization due to the Thorpe-Ingold effect.[42] While enynes without geminal substitution and 1,7-enynes still undergo the cyclization, a control experiment was deemed necessary to distinguish between the efficiency of zirconocycle formation versus the efficiency of the transmetallation/oxidation protocol. Accordingly, each zirconocycle intermediate was also protonated in a separate experiment to provide the corresponding cycloreduced product for comparison.

Initially, yields for the transmetallation/oxidation reactions varied greatly which was attributed to decomposition of the $(^{c}Hex)_2BCl$, likely through disproportionation, over time. As a remedy to this, the reagent was prepared fresh from dry box-stored $(^{c}Hex)_2BH$ before each experiment. After instituting this practice, isolated yields for the transmetallation/oxidation protocol were generally close to yields for protonation. The reaction conditions were found compatible with various 1,6- and 1,7-enynes with alkyl- and aryl-substituted alkynes with no variation in regioselectivity. Significantly, the transmetallation/oxidation reaction conditions tolerated common alcohol protecting groups such as methyl, TBS and benzyl ethers.

Enyne **1.5a** gave a markedly lower yield of the oxidation product (38%) with a significant amount of cycloreduced product **1.5b** (52%). The yield of the desired alcohol

was improved somewhat by extending the transmetallation reaction time from 3 h to 28 h (64%). The lower efficiency of transmetallation for this substrate is likely due to the electron-withdrawing nature and increased steric demand of the allylic benzyl ether, making the C_{sp^3}-Zr bond of the zirconocycle less nucleophilic.

Table 1.3 Transmetallation/oxidation of enyne substrates using $(^cHex)_2BCl$



b **c**

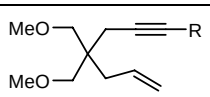
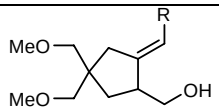
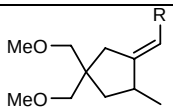
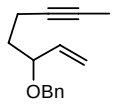
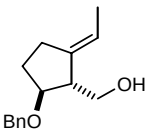
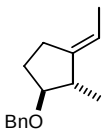
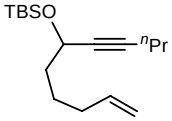
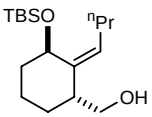
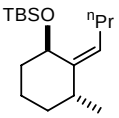
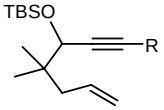
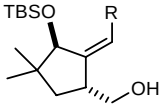
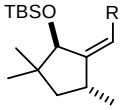
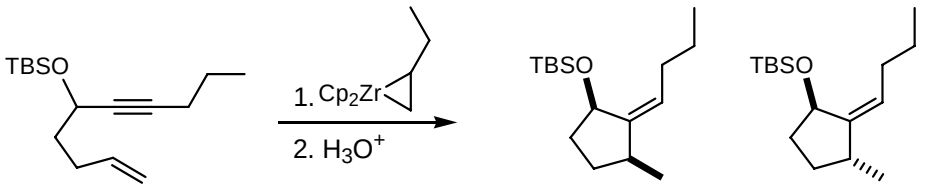
Compound #	Enyne	Transmetallation/ Oxidation	Protonation
			
1.1	R = Me	75%	84%
1.4	R = Ph	83%	89%
1.2	R = $SiMe_3$	64%	95%
1.5		 64%	 82%
1.13		 49%	 56%

Table 1.4 Transmetallation/oxidation of enyne substrates using (^{c}Hex)$_2$BCl (cont'd)

Compound #	Enyne	Transmetallation/ Oxidation	Protonation
			
1.15	R = Me	76%	83%
1.9	R = Ph	70%	74%
1.10	R = *p*-Cl(C_6H_4)	60%	61%
1.8	R = $SiMe_3$	51%	86%

Where applicable, relative stereochemistry was conserved between protonolysis and oxidation products, and followed previously observed trends[43] for enynes **1.13a** and **1.5a**. However, substrates **1.8a**, **1.9a**, **1.10a** gave exclusively *trans*-isomers for both protonation and oxidation by GOESY NMR experiments, while enyne **1.15a** gave a mixture of *trans* and *cis* (dr 1.6:1), contrary to RajanBabu's report of *cis*-selectivity for a similar propargyl-substituted enyne (Scheme 1.22).[44]

Scheme 1.22 *Cis*-selective cyclization reported by RajanBabu



Substrates with silyl-substituted alkynes were of particular interest because of the synthetic utility of the vinyl silanes produced by the reaction.[45] Indeed, the reactivity of the vinyl silanes produced made these enynes somewhat fickle substrates for both the

oxidation and protonation experiments. Specifically, malonate-derived enyne **1.2a** provided *E*/*Z* mixtures of products for both protonolysis (3 M HCl) and the transmetallation oxidation procedures. As the zirconocycle intermediate templates a specific olefin geometry, it was reasoned that isomerization was likely occurring after cleavage of the zirconocyle by acid or transmetallation. For protonation, it was found that simply substituting H_2SO_4 for HCl prevented isomerization and provided the cycloreduced product in excellent yield (95%). Since a major difference between these two acids is the lower basicity of the sulfate ion, the oxidative workup for the corresponding transmetallation was adjusted by using the less basic, preformed NaOOH rather than sequential addition of NaOH and H_2O_2. Gratifyingly, this small modification provided the desired product **1.2ac** as a single double bond isomer, albeit in a lower 64% yield.

When this modified oxidative workup was extended to substrate **1.8a**, the product was also obtained as the expected *Z*-isomer, but was apparently accompanied by the corresponding TBS-deprotected diol (31%). However, a single crystal of this diol suitable for X-ray crystallography was isolated, surprisingly revealing the *E*-olefin isomer **1.8g** (Figure 1.1). Notably, attempts to desilylate the TBS-protected *Z*-isomer for comparison revealed that it was quite resistant to common methods including *n*-Bu_4F, 1 M HCl and *i*-Bu_2AlH, requiring HF•pyridine, which provided *Z*-diol **1.8f** along with protonolysis of the vinyl silane.

Surprisingly, the formation of *E*-diol **1.8g** was found to be dependent on the amount of $(Chx)_2BCl$ used during transmetallation (Figure 1.1). It was expected that an increase in the amount of the Lewis acidic chloroborane would cause more deprotection,

but the opposite was observed as a change from 1.5 to 2.3 eq of $(Chx)_2BCl$ shut down the deprotection entirely, providing an *E*/*Z* mixture of TBS ethers. The large steric demand of the *Z*-isomers formed during the reaction, with a TMS group adjacent to a TBS ether, and the ability of the silyl group to stabilize β-carbocations likely makes this substrate particularly susceptible to *E*/*Z* isomerization during the Lewis acidic conditions of transmetallation. A possible explanation for the selective deprotection of the *E*-isomer is that the intermediate chlorozirconocene participates in intramolecular cleavage of the silyl ether, which is unavailable for the *Z*-isomer (Scheme 1.23).

Figure 1.1 ORTEP representation of diol **1.8g**

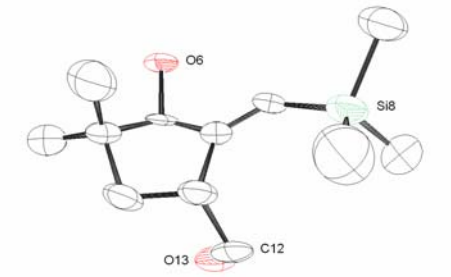
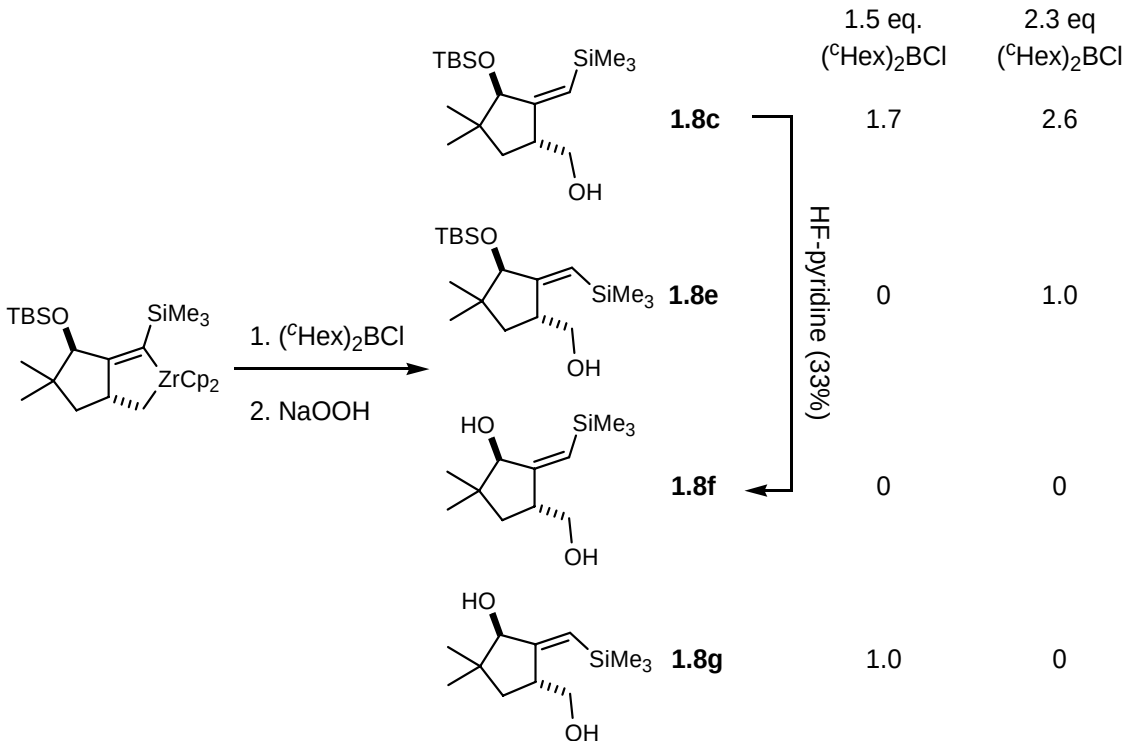
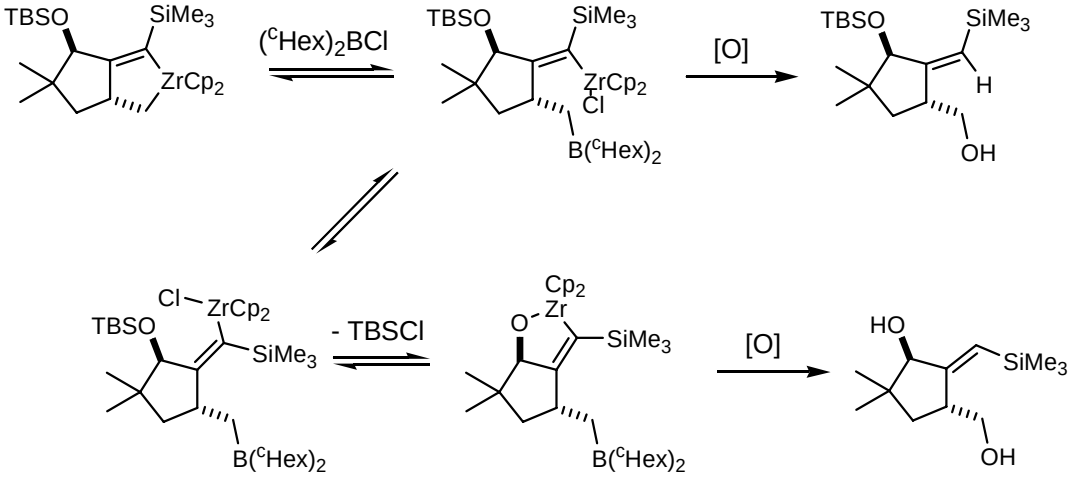


Figure 1.2 Isomerization vs. TBS-deprotection of the zirconocycle from enyne **1.8a**

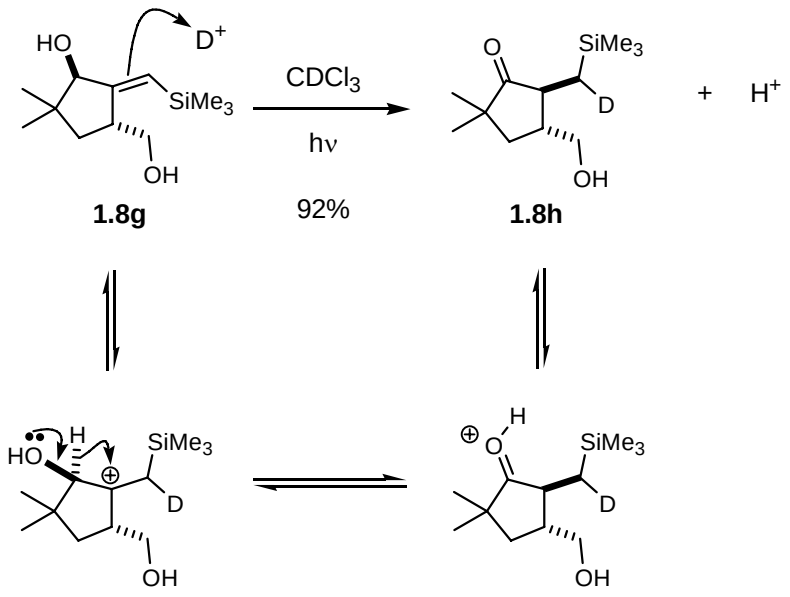


Scheme 1.23 Proposed rationale for selective deprotection of the *E*-isomer



Another interesting observation from the oxidization of the zirconocycle derived from enyne **1.8a** was a further reaction of *E*-alkene diol **1.8f**. Simply allowing an NMR sample in $CDCl_3$ to stand, unprotected from light, caused isomerization to a single diastereomer of ketone **1.8h**. It is well known that exposure of chloroform to light produces acid and that vinyl silanes react with acid to form β-carbocations. Diol **1.8g** is particularly susceptible to protonation as the resultant carbocation is not only stabilized by silicon but is also tertiary. As such, the proposed mechanism for this reaction involves generation of the stabilized carbocation followed by a 1,2-Meerwein-Wagner hydride shift analogous to a pinacol rearrangement. Deprotonation of the resulting intermediate regenerated the acid catalyst and provided ketone **1.8h** in high yield. There was no appreciable deuterium incorporation in this product, which can be attributed to this secondary source of acid.

Scheme 1.24 Acid-catalyzed isomerization of allylic silyl alkene **1.8g** to ketone **1.8h**



1.5 CONCLUSION

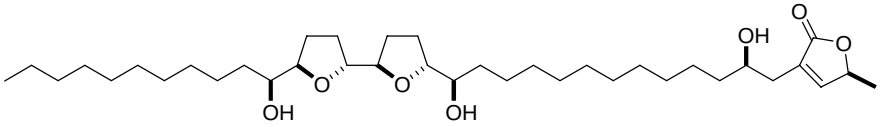
In this study, ligand transfer of zirconocylcopentenes to boron followed by oxidation of the resulting organoboranes has been investigated. Conversion was strongly dependent on the boron reagent used with (^{c}Hex)$_2$BCl giving the best results of the reagents screened and providing yields close to protonolysis of the zirconocycle. The process takes place regioselectively at the C_{sp3}-Zr bond regardless of alkyne substitution and relative stereochemistry is conserved between protonation and oxidation products. The method produces 5- and 6-membered rings with a hydroxymethyl substituent available for further elaboration and constitutes a proof of concept for connecting the chemistry of relatively unreactive zirconocyclopentenes with that of organoboranes.[46]

Chapter 2: Cobalt-Mediated Oxidation of 4-Alkenols

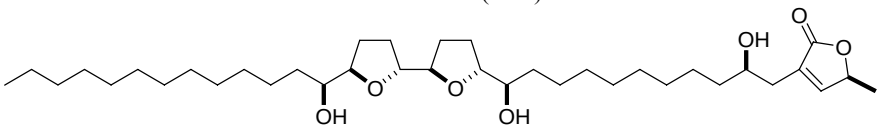
2.1 INTRODUCTION

Tetrahydrofurans are found in a variety of natural products including Annonaceous acetogenins,[47] polyether antibiotics[48] and C-glycosides,[49] inspiring numerous approaches to this heterocycle.[50] Our interests in this area have focused on the acetogenins bullatacin (**2.16**) and squamotacin (**2.17**), which despite very similar structures (Figure 2.1) exhibit remarkable differences in cytotoxicity toward lung, renal and colon cancer cell lines (Table 2.1).[51,52] Recent studies in this laboratory have focused on the effect of chain length between the bis-THF and butenolide subunits on biological activity, requiring a modular synthetic approach to analogs. Monoprotected bis-THF diol **2.18** was chosen as a key precursor, allowing systematic introduction of different tether lengths (Scheme 2.1).

Figure 2.1 Annonaceous acetogenins bullatacin and squamotacin



Bullatacin (**2.16**)

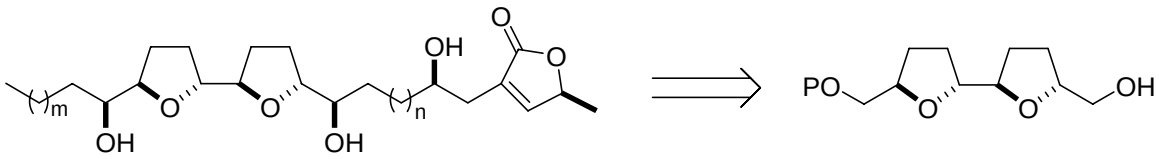


Squamotacin (**2.17**)

Table 2.1 Cytotoxicity profiles of acetogenins **2.16** and **2.17** for lung, colon and renal cancer cell lines[51]

	Cytotoxicity (ED_{50}, µg/mL)		
	A-549 (lung)	**HT-29 (colon)**	**A-498 (renal)**
Bullatacin	2.44×10^{-6}	>1	6.96×10^{-1}
Squamotacin	2.77×10^{-2}	1.0×10^{-3}	>1

Scheme 2.1 Monoprotected bis-THF diol **2.18** as a precursor to *Annonaceous* acetogenin analogs

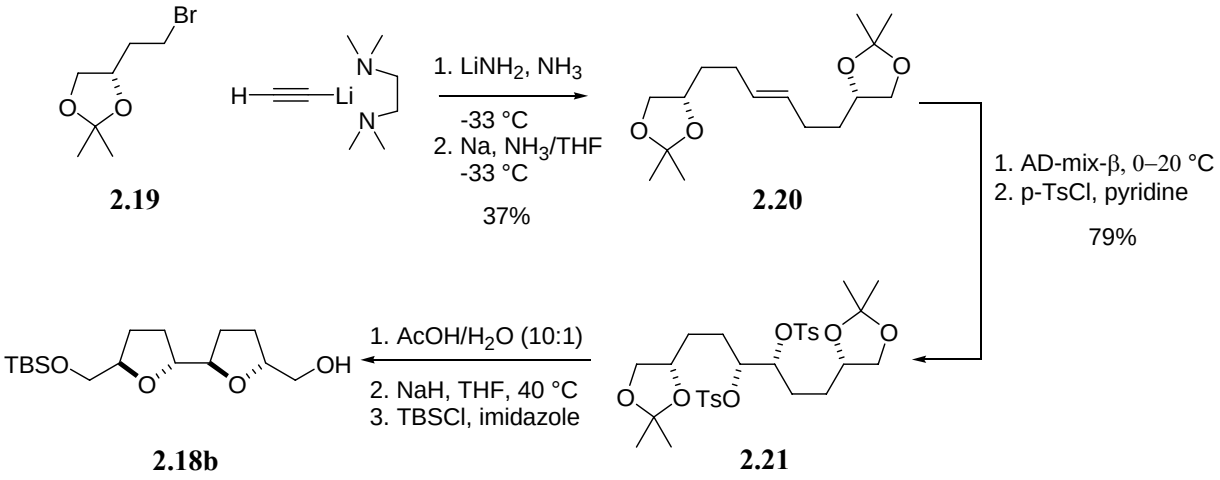


2.18

2.2 PREVIOUS APPROACHES TO THE MONOPROTECTED BIS-THF

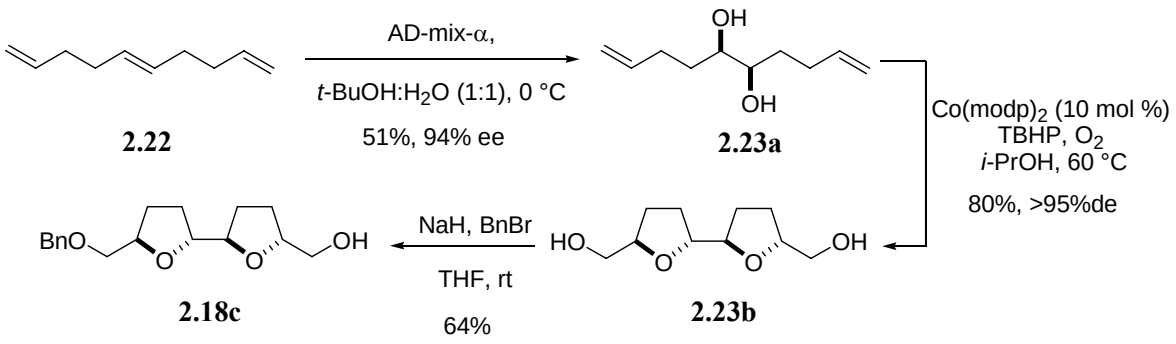
Monoprotected bis-THF diol **2.18** has been used in previous syntheses of acetogenins and has been prepared in two distinct ways. Koert's route to **2.18b** (P = TBS) began with double alkylation of bromide **2.19** with acetylene followed by dissolving metals reduction of the internal alkyne to give *trans* alkene **2.20** (Scheme 2.2).[53a] Sharpless asymmetric dihydroxylation[54] and tosylation of the resulting diol provided bis-tosylate **2.21**. Finally, hydrolysis of the acetonides followed by dual cyclization under basic conditions and monoprotection of the diol provided **2.18b.**[53b]

Scheme 2.2 Koert's approach to the bis-THF core of acetogenins



Wang and Shi described a more direct and efficient, three-step preparation of bis-THF **2.18c** (P = Bn) starting from *trans*-triene **2.22** (Scheme 2.3).[55a,55b] Sharpless asymmetric dihydroxylation of the internal double bond provided diol **2.23a**, which was transformed to bis-THF diol **2.23b** using Mukaiyama's cobalt-mediated oxidative cyclization of bishomoallylic alcohols.[56] Selective protection of one of the primary hydroxyls as a benzyl ether provided **2.18c**. This attractive route to the bis-THF core inspired our current interest in the Mukaiyama oxidative cyclization of bis-homoallylic alcohols.

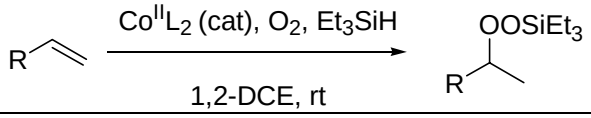
Scheme 2.3 Wang and Shi's approach to the bis-THF core



2.3 ORIGIN OF THE COBALT OXIDATION OF BIS-HOMOALLYLIC ALCOHOLS

In 1989, Mukaiyama described the aerobic peroxygenation of alkenes using triethylsilane and catalytic amounts of bis(1,3-diketonato)cobalt(II) complexes, providing triethylsilyl peroxides with Markovnikov regiochemistry (Table 2.1).[57a-57c] Modifying the conditions by employing *i*-PrOH as solvent/reductant provided hydration products under neutral conditions along with minor amounts of the corresponding ketones and alkanes (Table 2.3).[58] Interestingly, when bis-homoallylic alcohols were subjected to similar conditions, a mixture of *trans*-methyltetrahydrofurans and *trans*-hydroxymethyltetrahydrofurans was obtained. Optimization of conditions and catalyst screening effected a more selective reaction, providing exclusively the latter oxidative cyclization products, extremely useful synthetic intermediates.

Table 2.2 Mukaiyama's aerobic peroxidation of alkenes



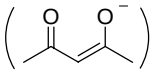
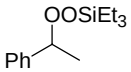
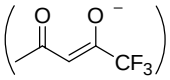
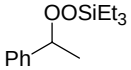
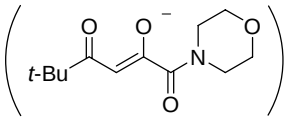
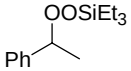
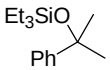
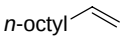
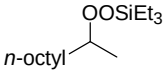
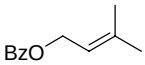
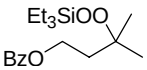
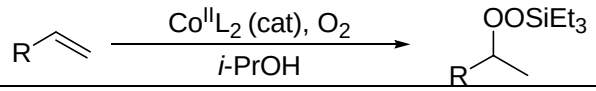
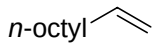
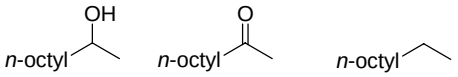
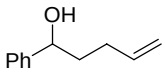
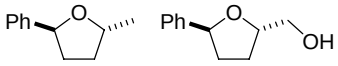
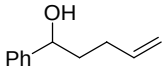
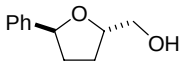
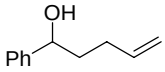
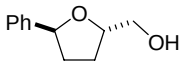
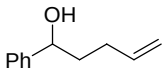
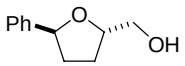
Alkene	L	Product	Yield (%)
	acac 		30
	tfa 		73
	modp 		96
	modp		95
	modp		80
	modp		99

Table 2.3 Cobalt-catalyzed hydration of alkenes and cyclization of bis-homoallylic alcohols



Alkene	Conditions	L	Products (yield/%)
	75 °C	tfa	 (81%) (9%) (4%)
	75 °C 4Å MS	tfa	 (24%) (21%)
	50 °C 4Å MS	tfa	 (55%)
	50 °C 4Å MS	modp	 (64%)
	50 °C 4Å MS 1.0 eq *t*-BuOOH	modp	 (73%)

2.4 OBJECTIVES OF THE CURRENT RESEARCH

The reported high *trans*-selectivity (>95% dr) and relatively low catalyst loadings (20 mol %) for Mukayama's protocol offer a promising complement to $VO(acac)_2$/*t*-BuOOH and Re_2O_7 oxidations. Vanadium oxidations generally give good ratios of the

cis-THF isomer (~80-90% dr) and *anti*-specific formation of the two new C-O bonds due to a directed epoxidation/epoxide-opening mechanism.[50a,59] However, *cis*/*trans* selectivity falls lower for unsubstituted alkenes. The Kennedy oxidation provides excellent *trans*-selectivities and *syn*-stereospecific formation of the C-O bonds, but typically requires at least 50 mol % Re for best results.[50a,60]

Despite the great potential of the Mukaiyma oxidation, Wang and Shi's syntheses were the only reported applications when the current research began, a decade after Mukaiyama's initial discovery. While two additional examples have since been described by Evans[61] and Takahashi[62] in separate syntheses of the acetogenin mucocin, one group of researchers has cited difficulty in reproducing Mukayama's yields.[63] Indeed, early attempts to recreate Mukaiyama's results in this laboratory were similarly disappointing.

As such, one goal of the current research was to determine the cause of these lower yields and improve the reliability of the method. Additionally, we were interested in substrate control of diastereoselectivity in these oxidations. The alkenols tested by Mukaiyama were exclusively α-substituted, providing the corresponding 2,5-disubstituted THFs. Therefore, a secondary objective of this work was to explore the scope of this reaction by determining the stereochemical outcomes and reaction efficiencies for other substitution patterns.

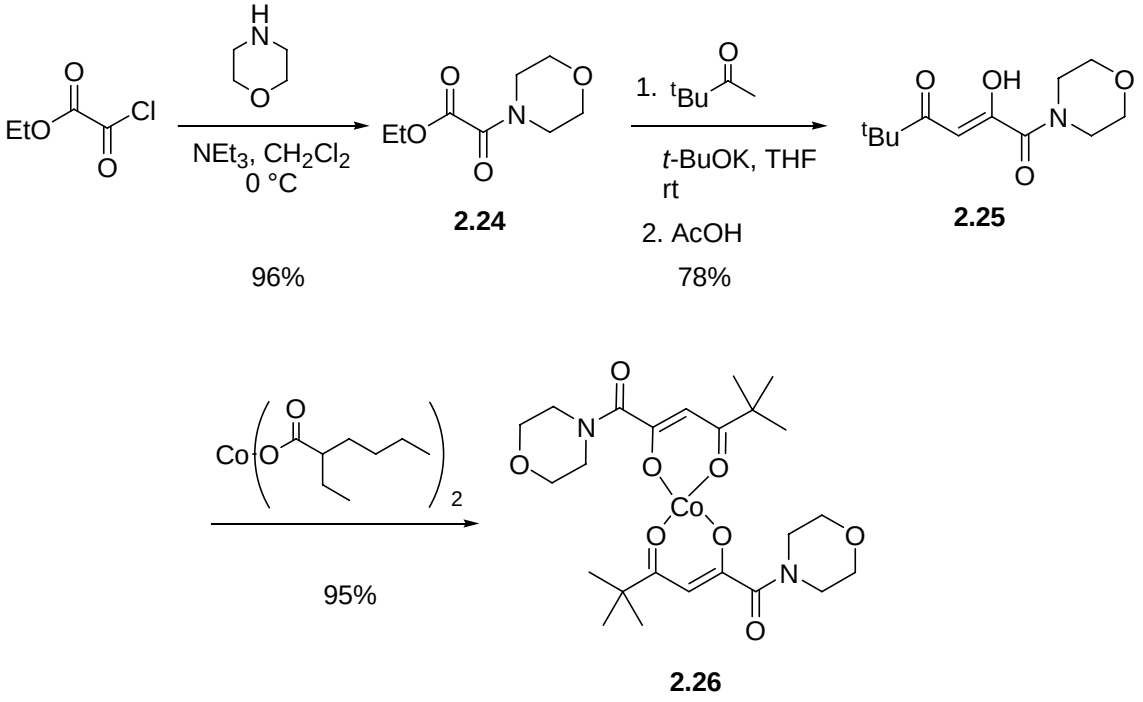
2.5 RESULTS AND DISCUSSION

2.5.1 Ligand and catalyst preparation

The modp ligand and cobalt catalyst used for the cobalt catalyzed oxidation were prepared by modification of the original procedure (Scheme 2.4).[64] Ethylmorpholine glyoxylate (**2.24)** was prepared in 96% yield by reaction of ethyloxalyl chloride with morpholine and NEt_3. The reported 36% yield for KO^tBu promoted condensation of **2.24**

with pinacolone was improved to 78% by changing the reaction conditions from toluene at reflux to THF at rt and using AcOH instead of HCl for protonation. Additionally, Mukaiyama reported complexation of the ligand with $CoCl_2$ under basic conditions. A previous researcher in this laboratory found that the $Co^{II}(modp)_2$ produced by this method gave low yields in the oxidation of bis-homoallylic alcohols. Suspecting competitive hydrolysis of the activated amide, the complexation procedure was altered by treating the ligand with Co^{II}(2-ethylhexanoate) under neutral conditions to produce $Co^{II}(modp)_2$ (**2.26)** in 95% yield. The $Co^{II}(modp)_2$ prepared in this way consistently gave yields for the oxidation comparable to those reported by Mukayama.

Scheme 2.4 Synthesis of the modp ligand and its cobalt complex

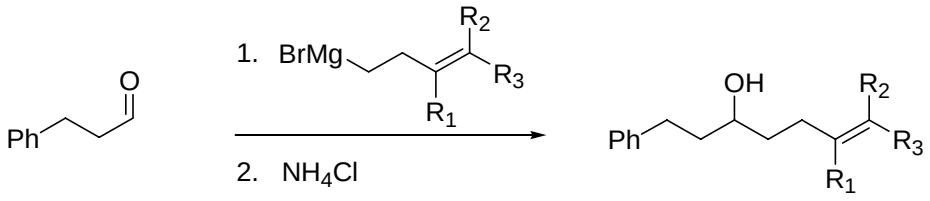


2.5.2 Substrate preparation

A series of bis-homoallylic alcohols were prepared to determine the scope of the cobalt-mediated oxidation and the effect of substitution on diastereoselectivity. Substrates

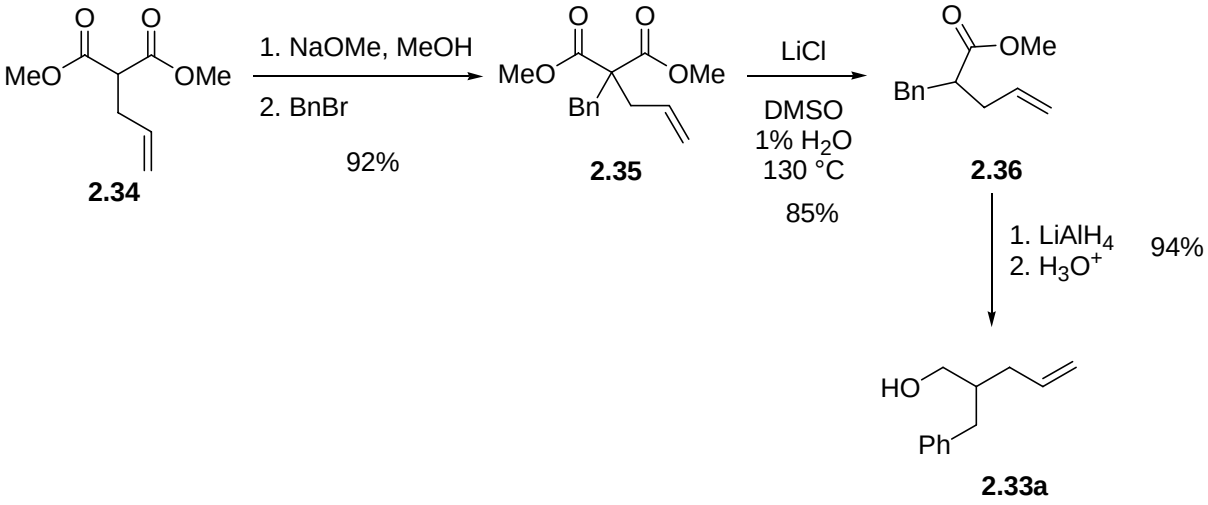
2.27a-2.31a, exhibiting various alkene substitution patterns, were prepared by treatment of hydrocinnamaldehyde with the corresponding Grignard reagents (Scheme 2.5). 2-Substituted alcohol **2.33a** was prepared by benzylation of allyl dimethylmalonate, Krapcho decarboxylation and $LiAlH_4$ reduction of the resulting methyl ester (Scheme 2.6). 3-Substituted alcohol **2.37a** was prepared by $NaBH_4$ reduction of the corresponding aldehyde, which was obtained by Claisen rearrangement/decarboxylation of the *trans*-cinnamyl alcohol adduct of (*E*)-(carboxyvinyl)trimethylammonium betaine **2.39** (Scheme 2.7).[65]

Scheme 2.5 Synthesis of substrates **2.27a-2.31a** from hydrocinnamaldehyde



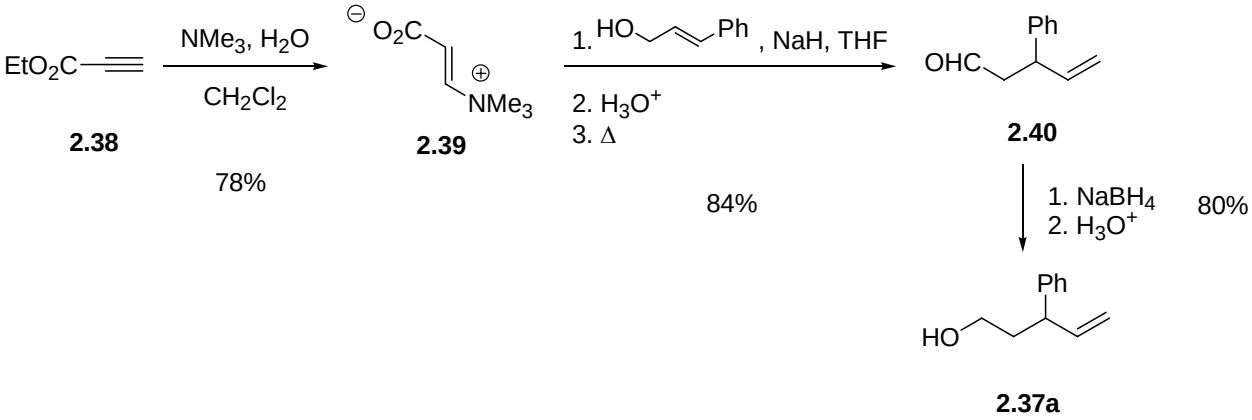
2.27a, $R_1=R_2=R_3=H$ (65%)
2.28a, $R_1=Me$, $R_2=R_3=H$ (61%)
2.29a, $R_1=R_2=H$, $R_3=Et$ (54%)
2.30a, $R_1=R_3=H$, $R_2=Et$ (50%)
2.31a, $R_1=H$, $R_2=R_3=Me$ (42%)

Scheme 2.6 Synthesis of 2-substituted alkenol **2.33a**



2.34 **2.35** **2.36** **2.33a**

Scheme 2.7 Synthesis of 3-substituted alkenol **2.37a**

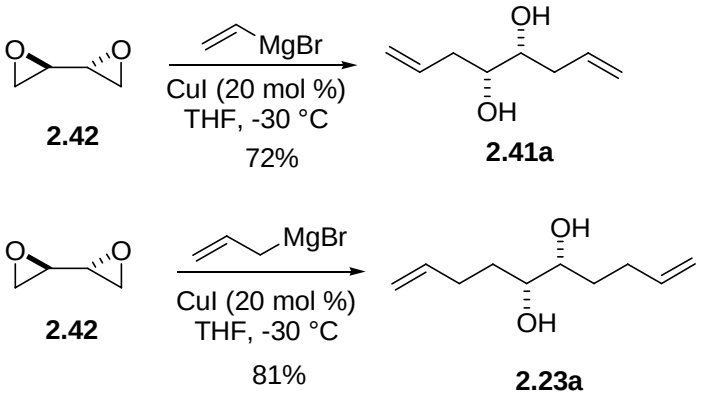


2.38 **2.39** **2.40** **2.37a**

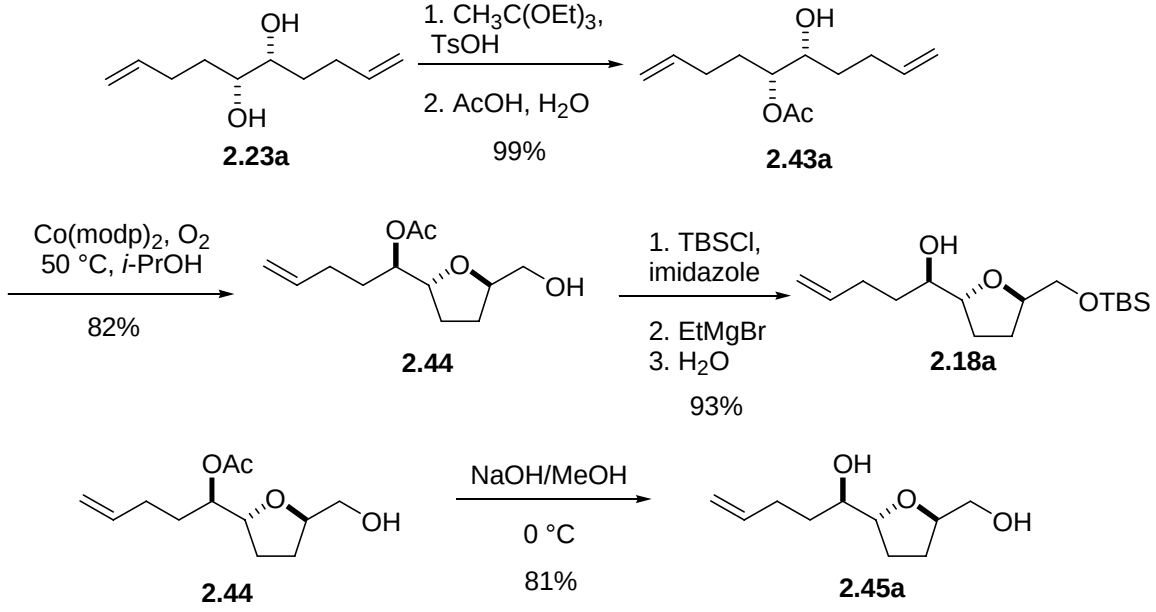
Diols **2.23a** and **2.41a** were prepared by Cu(I)-catalyzed addition of allyl- and vinylmagnesium bromide to epoxide **2.42**[66] (Scheme 2.8). Monoacetate **2.43a** was obtained from **2.23a** by condensation with triethylorthoacetate followed by hydrolysis of the resulting orthoester with AcOH/H_2O (Scheme 2.9). Mono-THF **2.18a** was prepared by cobalt-mediated oxidation of **2.43a** followed by TBS ether protection of the resulting

alcohol and deprotection of the acetate with EtMgBr. Similarly, **2.45a** was furnished by acetate deprotection (NaOH/MeOH) of the cobalt oxidation product of **2.43a**. Finally, diol **2.46a** was prepared in several steps from triflate **2.47**.[67] Monoallylation and hydrolysis of the acetonide gave diol tosylate **2.48**, which after treatment with K_2CO_3/MeOH and TBS protection of the remaining alcohol, afforded epoxide **2.49**. Copper-catalyzed addition of phenethylmagnesiumbromide followed by NBu_4F deprotection of the TBS ether provided diol **2.46a**.

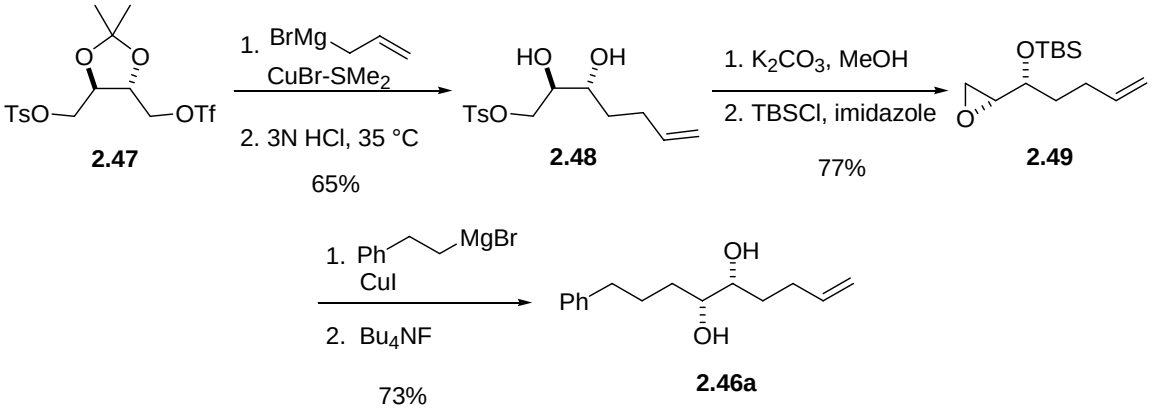
Scheme 2.8 Synthesis of diene diols **2.23a** and **2.41a**, a fused-THF precursor



Scheme 2.9 Synthesis of **2.43a**, **2.18a** and **2.45a**



Scheme 2.10 Synthesis of diol **2.46a**



2.5.3 Evaluation of oxidation conditions

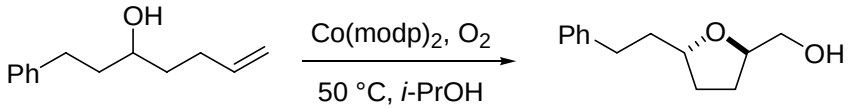
The reaction conditions described by Mukaiyama included the use of molecular sieves one equivalent of *t*-BuOOH relative to the substrate and 20 mol % of the

$Co(modp)_2$ catalyst. Indeed, no experiments without molecular sieves or with lower catalyst loadings were reported. The use of the *t*-BuOOH was ascribed to decreasing the induction period of the reaction by accelerating oxidation of Co^{II} to Co^{III}. While this process and the subsequent oxidative cyclization of the substrate take place under the O_2 atmosphere of the reaction, Mukaiyama observed slightly lower yields without the use of *t*-BuOOH. As our intended use of this method in the synthesis of acetogenins and analogs was prior to diversification, we required large scale oxidations and hoped to streamline this method by reducing or eliminating potentially unnecessary components.

Mukaiyama's optimized conditions were reproduced using alkenol **2.27a** as a model providing **2.27b** in 81% yield (Table 2.4, entry 1). Visually, molecular sieves appeared to accelerate the conversion of Co^{II} to Co^{III} as the reaction mixture changed colors from pink to green in seconds rather than hours without sieves. However, the yield of the reaction was unaffected by the exclusion of molecular sieves or lowering the catalyst loading to 5 mol % (entries 2 and 3). Further decreases in catalyst loading led to incomplete conversion, likely due to decomposition of the catalyst over time (entry 4).

As reported, the yield decreased when no or a substoichiometric amount of *t*-BuOOH was added to the reaction mixture (entries 5 and 6). It was thought that if the role of the *t*-BuOOH was simply to accelerate oxidation of the cobalt complex, preactivation of the complex might be as effective and reduce the amount required. Oxidation of the $Co^{II}(modp)_2$ using *t*-BuOOH or H_2O_2 was found to be very rapid in CH_2Cl_2, providing a green complex isolable by flash chromatography. However, these preactivated catalysts gave slightly lower yields in the oxidation (entry 7).

Table 2.4 Evaluation of reaction conditions



2.27a **2.27b**

Entry	Catalyst Loading	Additives	Catalyst Activation	Yield
1	20 mol %	4 Å MS 1 eq *t*-BuOOH	in situ	81%
2	10 mol %	1 eq *t*-BuOOH	in situ	82%
3	5 mol %	1 eq *t*-BuOOH	in situ	80%
4	2.5 mol %	1 eq *t*-BuOOH	in situ	58%*
5	10 mol %	none	n/a	58%
6	10 mol %	0.2 eq *t*-BuOOH	in situ	72%
7	10 mol %	none	preactivated with *t*-BuOOH	68%

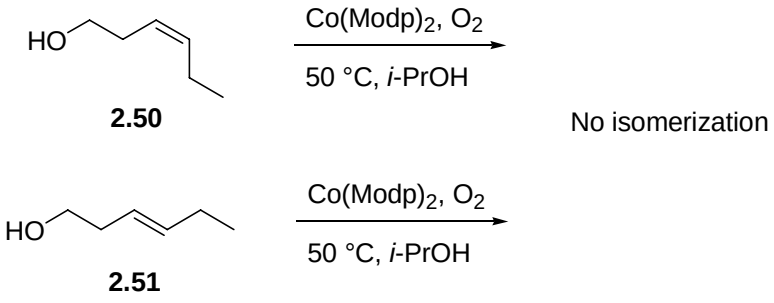
* GC conversion

2.5.4 Scope and limitations

The results of the cobalt-mediate oxidations of the substrates prepared above are summarized in Table 2.5 and Table 2.6. In agreement with Mukaiyama's findings, cobalt-mediated oxidation of bishomoallylic alcohol **2.27a** provided the *trans*-2,5-substituted THF exclusively in 82% yield. Similarly, oxidation of 4-methylsubstituted **2.28a** proceeded in 75% yield, affording a single diastereomer with the methyl and ring methine hydrogen *trans* to one another. Notably, attempts to oxidize 5,5-disubstituted substrate **2.31a** were unsuccessful even at elevated temperatures, providing only recovered starting material.

The oxidation of *cis*- and *trans*-alkenes **2.30a** and **2.29a** provided nearly identical mixtures of two diastereomers with little selectivity (71%, 1.2:1 dr; 53%,1.3:1 dr, respectively). Homoallylic *cis*- and *trans*- alkenes **2.50** and **2.51** were subjected to the reaction conditions as a control to determine if equilibration between the olefin isomers was occurring, and each alkene was recovered without any change. The ^{1}H and ^{13}C NMR spectra of these products matched those obtained from Swern oxidation/EtMgBr addition for alcohol **2.27b**, indicating *trans*-THF rings were formed in both cases and that the stereocenter adjacent to the THF ring was epimeric. The relative stereochemistry between this stereocenter and the proximal ring stereocenter was determined for each diastereomer by characteristic ^{1}H NMR chemical shifts.[68] The scrambling of stereochemistry and nearly identical product distributions for the *cis*- and *trans*-alkenes preclude an epoxide-forming/epoxide-opening process as in the case of vanadium oxidations and the cycloaddition mechanism proposed for the related Kennedy oxidation. A reasonable mechanistic explanation for this stereoselectivity is the formation of a stereochemically labile C-Co bond or radical at the position alpha to the ring followed by reaction with O_2.

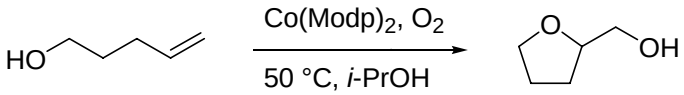
Scheme 2.11 *Cis*/*trans* isomerization control experiment



The effects of substitution at the allylic and homoallylic positions on reaction efficiency and diastereoselectivity were examined similarly. Oxidation of 2-substituted alcohol **2.33a**, proceeded in high yield but moderate diastereoselectivity, providing a mixture of *cis*- and *trans*-THF products (83%, 1.7:1 dr). In contrast, 3-substituted **2.37a**

afforded *trans*-THF **2.37b** with a small amount of the *cis*-isomer (75%, 8:1 dr). Relative stereochemistry for both entries was determined by comparison of ^{1}H and ^{13}C NMR spectra to a literature reference in a similar study of diastereoselectivity of vanadium oxidations.[69]

Table 2.5 Summary of oxidation results



a **b**

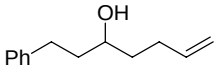
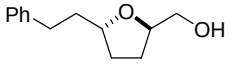
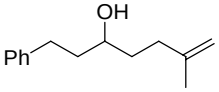
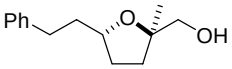
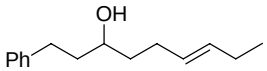
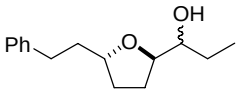
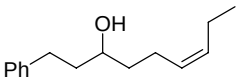
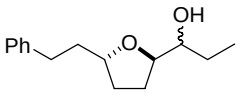
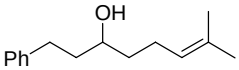
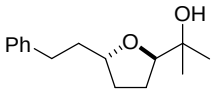
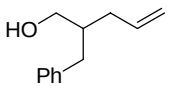
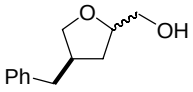
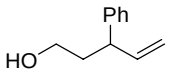
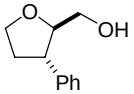
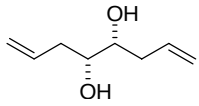
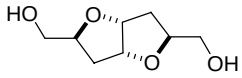
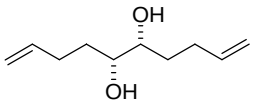
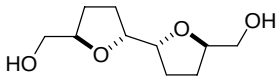
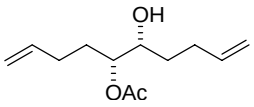
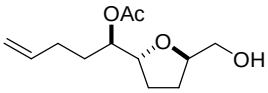
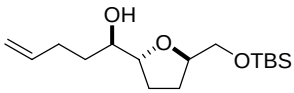
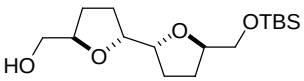
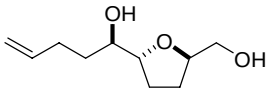
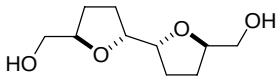
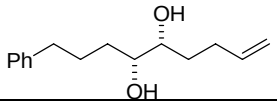
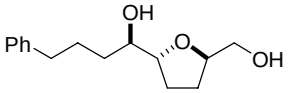
Entry	Alcohol	Oxidation Product	Yield
2.27			82%
2.28			75%
2.29			53% (1.3:1 *syn*:*anti*)
2.30			71% (1.2:1 *syn*:*anti*)
2.31			0%
2.33			83% 1.7:1 *cis*/*trans*
2.37			75% 8:1 *trans*/*cis*

Table 2.6 Summary of oxidation results (cont'd)

Entry	Alcohol	Oxidation Product	Yield
2.41			50%
2.23			45%
2.43			82%
2.18			79%
2.45			77%
2.46			74%

As mentioned previously, the bis-oxidation of diol **2.23a** has been of considerable interest in this laboratory as a key reaction in a synthetic effort toward Annonaceous acetogenins and analogues. While this oxidation was reported previously,[55] efforts to reproduce these results have consistently given significantly lower yields (78% vs 35%); undesirable at such an early stage of a multi-step synthesis and prior to diversification in the analog syntheses. Screening of reaction conditions including concentration (0.01M-1M), temperature (40 °C-60 °C), catalyst loading (2.5%-20%) and the use of additives (4 Å sieves, H_2O, ^tBuOOH, BHT) have yielded modest improvement to 45%. Interestingly, despite Mukaiyama's consistent use of sieves, addition of 1% (v/v) H_2O was found beneficial, accounting for the majority of this improvement. However, larger quantities slowed the rate of reaction without further increase in yield. A slightly longer but more

efficient, stepwise strategy involving oxidations of **2.43a** and **2.18a**, both excellent oxidation substrates, has been developed as an alternative.

Substrates **2.45a** and **2.46a** were prepared with the aim of gaining further insight into the cause of the low yields for the oxidation of **2.23a** and aiding in optimization efforts. Diol **2.46a** was chosen as a model for the first oxidative cyclization, to determine if 1,2-diols might simply be sensitive to the oxidation conditions. However, the resulting *trans*-THF diol **2.46b** was produced in 74% yield. Similarly, mono-THF diol **2.45a** the presumed intermediate in the oxidation of **2.23a**, was subjected to the oxidation conditions and produced bis-THF **2.45b** in 77% yield, indicating that the intermediate and the bis-THF product are stable under the reaction and workup conditions. For additional comparison, diol **2.41a** was subjected to similar oxidation conditions providing the fused bicyclic bis-THF **2.41b** as a single diastereomer in 50% yield. The similarity of this yield to that for **2.23a** provides support for the explanation that low yields in these bis-oxidations are simply artifacts of combined yields over two reactions.

2.6 CONCLUSION

The stereoselectivity and efficiency of the cobalt-mediated oxidative cyclization of bis-homoallylic alcohols has been studied. Additionally, the synthesis of the $Co(modp)_2$ complex used for this process has been optimized, providing a reliable catalyst from batch to batch. Oxidation of a 4-methylsubstituted alkenol proceeds with very high stereoselection, affording a THF product with the ring methine hydrogen and the methyl group in a *trans* relationship, while a 5,5-dimethylsubstituted alkenol failed to cyclize. *Cis*- and *trans*-bishomoallylic alcohols exhibit high selectivity for the *trans*-THF, but poor and nearly identical *syn*/*anti* selectivity. The oxidation of 2- and 3-substituted

alkenols occurs with moderate to good stereoselectivity with preference for *cis*- and *trans*-THF rings, respectively.

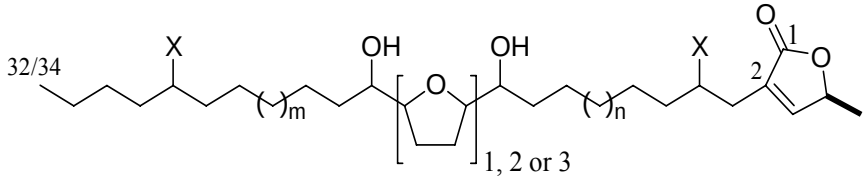
Investigation into the low yield of a bis-oxidation relevant to acetogenin synthesis has demonstrated that 1,2-diols and THF-substituted alkenols behave typically in the oxidation and that the low yield of these bis-oxidations is likely due to the combined yield of the two reactions.

Chapter 3: Annonaceous Acetogenins

3.1 INTRODUCTION

Acetogenins from the *Annonaceae* family of plants (e.g. apple custard, soy sop) constitute a large class of natural products, many of which exhibit potent biological effects including antitumoral, antimalarial and pesticidal acitivties.[47] Currently, over 400 compounds have been reported in this class since uvaricin was first isolated in 1982. Acetogenins are believed to originate from C32/C34 fatty acids that combine with a 2-propanol group to form a γ-lactone and typically contain one or more THF, THP or epoxide rings and hydroxyl groups in various postitional and stereochemical arrangements along the chain (Figure 3.1). In particular, the extremely high cytotoxicity of certain acetogenins toward various tumor cell lines, including multi-drug resistant (MDR) cancer cells has inspired investigations into the mode of action[70] for acetogenins as well as structure-activity relationship (SAR) studies[71] and numerous partial and total synthetic efforts.[72]

Figure 3.1 Representative structure of selected Annonaceous acetogenins



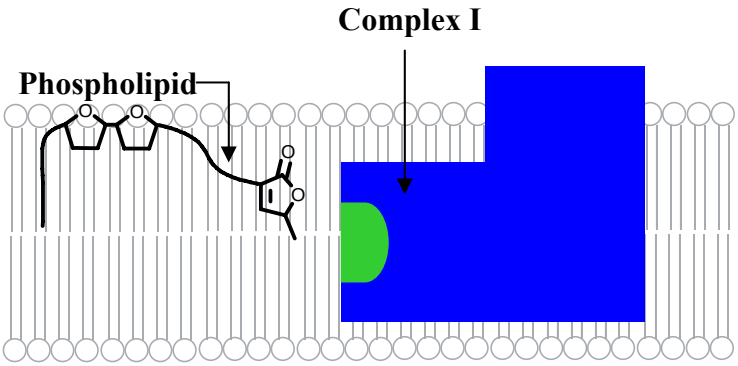
X = H, OH

3.2 PROPOSED MODES OF ACTION

3.2.1 Mitochondrial complex I inhibition

The primary source of biological activity for the acetogenins involves interaction with membrane bound mitochondrial complex I (NADH:ubiquinone oxidoreductase).[70] It is believed that these compounds interfere with the terminal electron transfer step between an Fe-S cluster and ubiquinone.[73] As a result, the cross-membrane proton gradient created by complex I during NADH reduction of ubiquinone and the electron transfer necessary for respirative reduction of O_2 to H_2O are inhibited, significantly reducing ATP levels. The exact nature of the interaction with complex I and the location of the binding site have yet to be determined, but a current model is depicted below (Figure 3.2). McLaughlin has proposed that the hydrophilic central region of acetogenins acts as an anchor to the glycerol backbone of phosphatidylcholine at the surface of the membrane, allowing the alkyl-tethered lactone ring to diffuse into the membrane interior and interact with the binding site of the enzyme.[74]

Figure 3.2 McLaughlin's model for acetogenin inhibition of mitochondrial complex I



Ultimately, complex I inhibition starves the cell of ATP, inhibiting cell growth and disturbing cell timing, inducing apoptosis. Significantly, this ATP depletion has been linked to the efficacy of acetogenins against MDR cancer cell lines.[71c,75] The resistance developed by these cells typically results from increased expression of a glycoprotein which forms a channel in the cell membrane that actively exports antitumor agents.[76] As additional ATP is required for this extrusion process, the ATP starvation induced by acetogenins makes these cells especially susceptible (~ 5 x non-MDR). For example, bullatacin was shown to be cytotoxic to MDR human mammary adenocarcinoma cells, while cytostatic to the parent non-MDR cell line.[75]

3.2.2 Inhibition of ubiquinone-linked NADH oxidase

A distinct, but closely related mode of action is the inhibition of membrane-bound NADH oxidase activity required for substrate-level phosphorylation.[70c] This secondary mechanism is believed to impart additional selectivity for cancerous cells over normal cells and differential selectivity between cancer cell lines. Cancerous cells generally express these oxidases throughout their plasma membranes to accommodate the high energy demand, while normal cells generally contain much fewer.

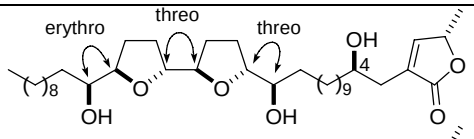
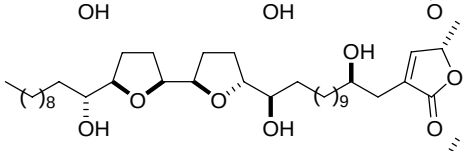
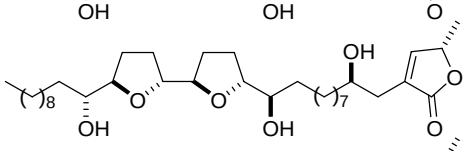
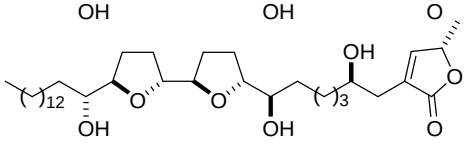
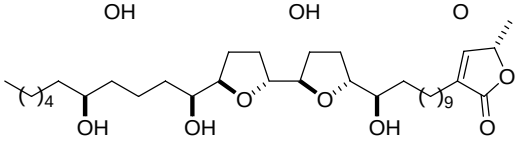
3.3 STRUCTURE ACTIVITY RELATIONSHIPS

3.3.1 Inhibition studies

Several papers outlining the critical elements for strong inhibition of complex I have been reported using various acetogenins. An early report by Alfonso concluded that acetogenins containing adjacent bis-THFs are more potent inhibitors of complex I than non-adjacent bis-THF compounds, which are more active than mono-THF substrates.[71j]

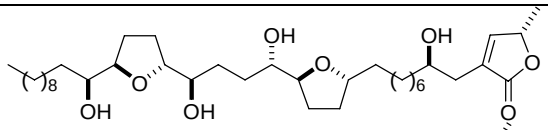
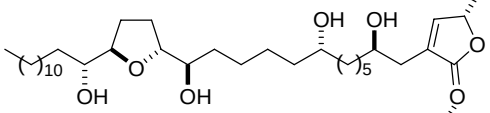
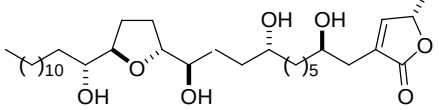
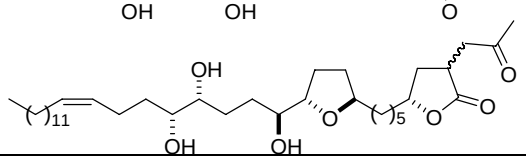
Additionally, the authors indicated that the presence of a hydroxyl at C-4 and the stereochemical configurations of the bis-THF and the flanking hydroxyl groups were significant. Specifically, compounds having *erythro*/*trans*/*threo*/*trans*/*threo* stereochemistry (e.g. bullatacin) provided the highest activities. However, Miyoshi and coworkers have downplayed the importance of each of these structural features, with acetogenins having various stereochemical arrangements, non-adjacent bis-THF or mono THF rings, and examples lacking a hydroxyl at C-4 providing similar inhibition levels (Table 3.1).[71g,71k,71m] Additionally, these researchers found that the α,β-unsaturated lactone present in most acetogenins was not critical for inhibition as gigantetroninone, containing an isomeric keto-lactone, provided a result comparable to bullatacin.

Table 3.1 Acetogenin SAR study of NADH oxidase inhibition

Acetogenin	Structure	IC_{50} (nM)
Bullatacin		1.2
Trilobacin		1.4
Parviflorin		1.9
Longimicin C		14
Squamocin B		1.8

The IC_{50} value is the molar concentration required to decrease the NADH oxidase activity of bovine heart submitochondrial particles by half

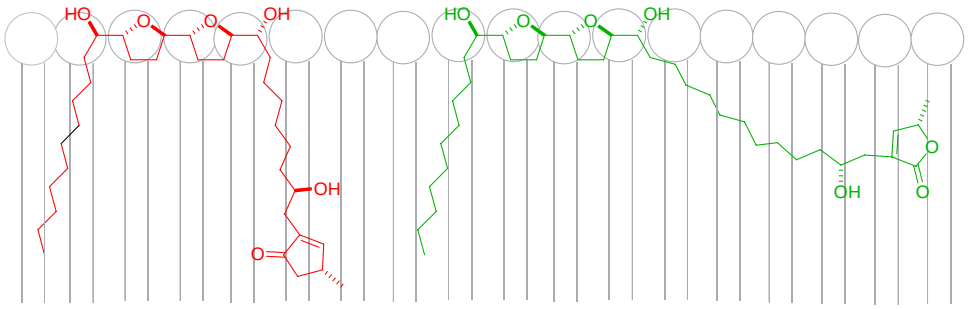
Table 3.2 Acetogenin SAR study of NADH oxidase inhibition (cont'd)

Acetogenin	Structure	IC_{50} (nM)
Bullatalicin		1.6
Annonacin		3.8
Goniothalamicin		21
Giganantetroneninone		2.9

The IC_{50} value is the molar concentration required to decrease the NADH oxidase activity of bovine heart submitochondrial particles by half

One structural feature that has shown a definitive impact on inhibition is the length of the alkyl spacer between the central THF region and the γ-lactone.[71c,71g,71k,71m] The difference in activity between parviflorin and longimicin C and between annonacin and goniothalamicin, which differ only in tether length, illustrate this effect. That is, a small decrease in spacer length results in a marked decrease in potency. This could be attributed to preventing the active lactone moiety from penetrating deep enough into the membrane to reach the active site of complex I. However, McLaughlin has investigated the membrane conformations of a set of aceteogenins possessing tether lengths of 13, 11, and 9 carbons by ^{1}H NMR NOE's and DSC, elucidating a more subtle effect.[74] The 9-carbon tether actually caused the tether to point downward, with the lactone residing around the midplane of the bilayer while the 13- and 11-carbon chains allowed the lactone to diffuse laterally through the midchain area of the upper layer.

Figure 3.3 Tether length-dependent membrane conformations of acetogenins

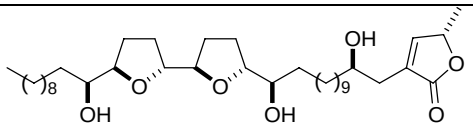
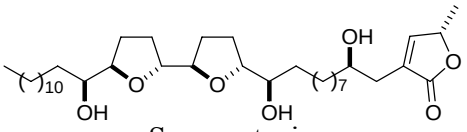


3.3.2 Cytotoxicity Studies

Although complex I inhibition is believed to be the primary mode of action and many acetogenins are potent inhibitors, cytotoxicity against tumor cell lines varies widely, and it has been difficult to reliably correlate inhibition levels with cytotoxicity. Of course, assays using intact cells are more complicated than the inhibition studies which use submitochondrial particles. Additional factors such as membrane transport, intracellular transport and metabolic inactivation require consideration in cytotoxicity studies and the picture is further muddled by cell line specificity.[71m] Consequently, attempts to formulate SARs from these cytotoxicity profiles is far more challenging.

Interestingly, the role of the chain length between the THF core and the butenolide on inhibition does correlate well to anti-tumor activity. Squamotacin only differs from bullatacin in that the bis-THF core is shifted two carbons closer to the butenolide. While McLaughlin's conformational studies might suggest that an 11-carbon tether is sufficiently long to allow lateral diffusion, squamotacin showed remarkably different activity than bullatacin (Table 3.3).[51]

Table 3.3 Cytotoxicity dependence on tether length

	ED_{50} (μg/mL)		
	A-549	MCF-7	HT-29
 Bullatacin	2.44×10^{-6}	6.96×10^{-1}	>1
 Squamotacin	2.77×10^{-2}	>1	1.0×10^{-3}

A-549 = human lung carcinoma; MCF-7 = human mammary adenocarcinoma; HT-29 = human colon adenocarcinoma

3.4 OBJECTIVE OF THE CURRENT WORK

The long term objective of the current research is to help clarify the SAR picture for the cytotoxicity of acetogenins. Despite the many acetogenins that have been isolated, defining trends from biological assays of natural products is limited by lack of control over nature's variation. Synthesis should allow more systematic evaluation of the features necessary for activity by limiting the variables between structures and filling in gaps of compounds unavailable from nature. Intrigued by the disparity in activity between bullatacin and squamotacin, we decided to further explore the effect of tether length between the bis-THF core and the butenolide further by synthesizing analogs with longer and shorter tethers, respectively. As such, the goal of the current research was implementation of a concise, modular synthesis of unnatural acetogenins recently developed in our laboratory.[77]

3.5 PREVIOUSLY REPORTED SYNTHESES OF BULLATACIN

Largely due to their exciting biological effects, a large number of synthetic efforts towards acetogenins have been reported and comprehensive reviews are available. With our research efforts focused on preparing analogs of bullatacin and squamotacin, an overview of previous syntheses of these acetogenins will be presented here.

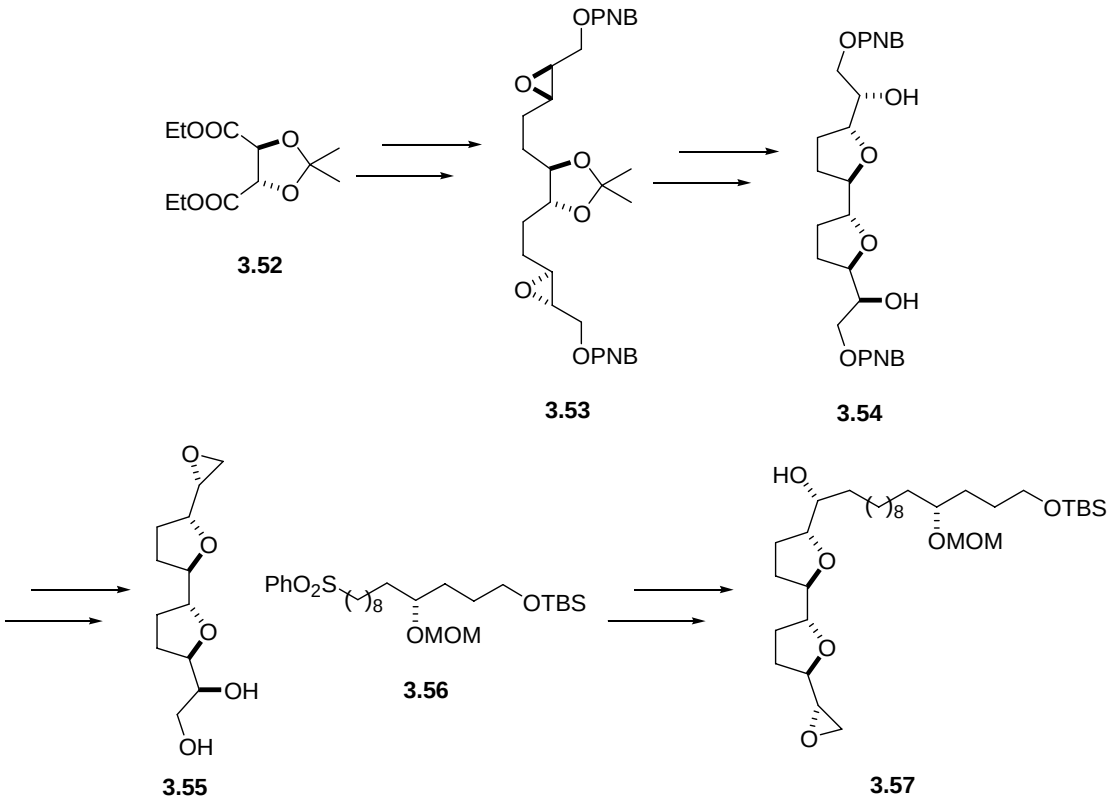
3.5.1 Sasaki's synthesis of bullatacin

The first total synthesis of bullatacin was reported by Sasaki, beginning with acetonide-protected *D*-diethyl tartrate **3.52**.[78] Wadsworth-Emmons homologations and appropriate reductions set up a double Sharpless asymmetric epoxidation,[79] which provided bis-epoxide **3.53** after PNB protection. Subsequent Lewis acid-catalyzed ketal cleavage and intramolecular epoxide-opening provided bis-THF **3.54**. Mono-mesylation and basic hydrolysis of the PNB esters afforded epoxy diol **3.55**, which was treated with an α-sulfonylanion to introduce the chain that ultimately would contain the butenolide. After desulfonation and selective tosylation of the primary hydroxyl, epoxide **3.57** was produced under basic conditions. Copper-catalyzed addition of the appropriate Grignard followed by MOM protection produced advanced intermediate **3.58**. Following TBS deprotection and methyl ester formation, a crossed aldol reaction with an aldehyde derived from (*S*)-(-)-methyl lactate furnished the butenolide subunit. Deprotection of the MOM ethers provided bullatacin.

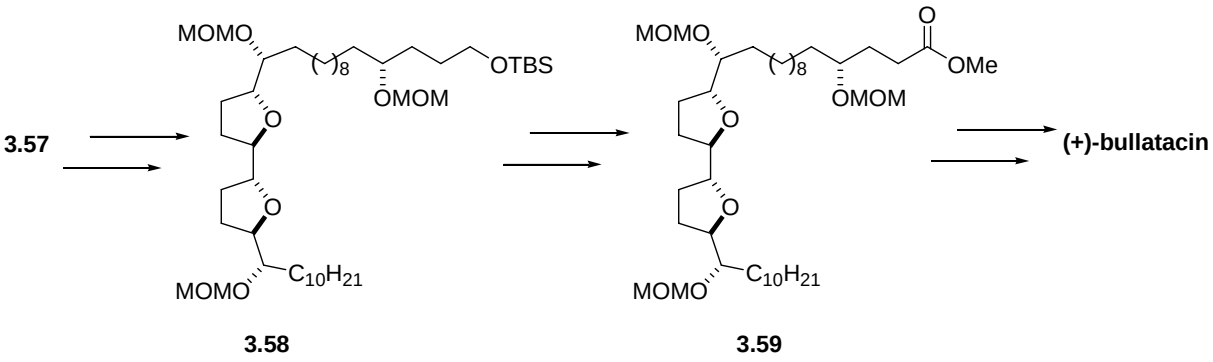
One advantage of Sasaki's approach was its use of tartaric acid, a highly enantioenriched starting material, to set the stereochemistry of the core bis-THF. The most common alternative, Sharpless asymmetric dihydroxylation, can provide high enantiomeric excesses (~95%),[54] but even a small contamination in optical purity might further complicate cytotoxicity assays. Sasaki's synthesis also took great advantage of the

C-2 symmetry of the tartrate derivatives, allowing for bidirectional synthesis. However, from the perspective of making analogs with varying tether lengths, a drawback of this route was the formation of the butenolide after the alkyl spacer was introduced. A more modular approach, where the spacer and butenolide could be introduced separately would be more desirable for our purposes.

Scheme 3.1 Sasaki's approach to bullatacin



Scheme 3.2 Sasaki's approach to bullatacin (cont'd)

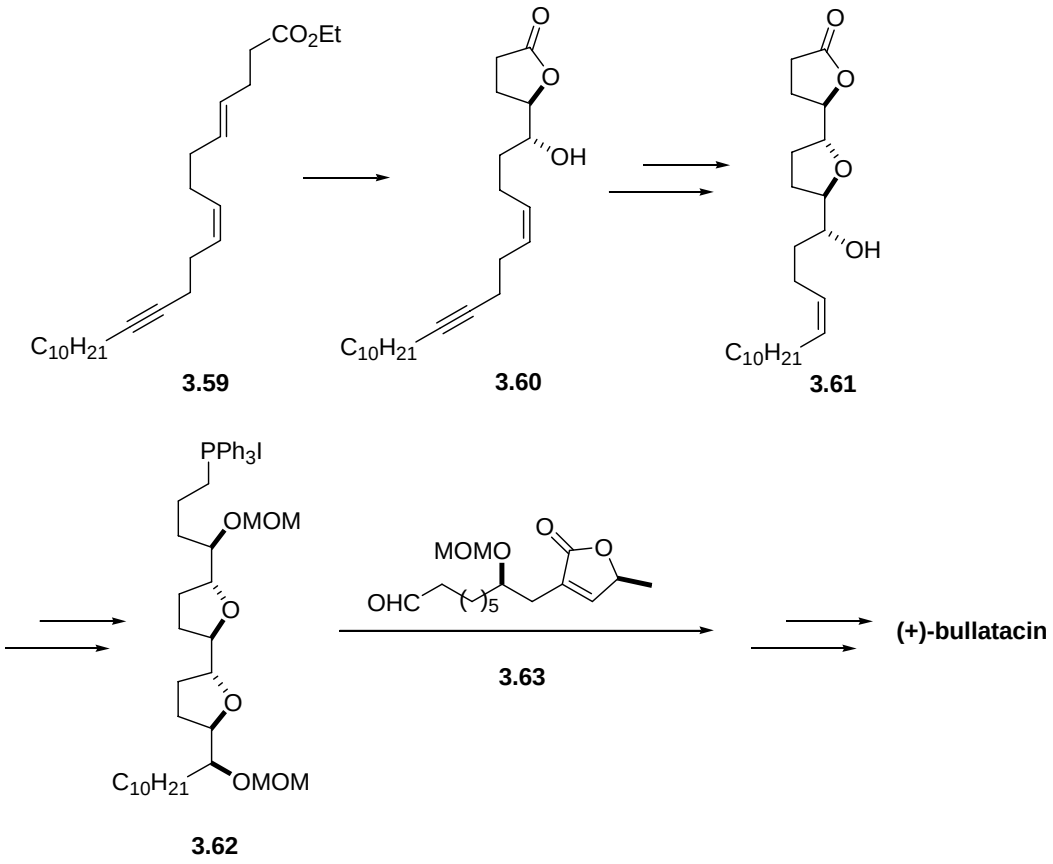


3.5.2 Keinan's synthesis of bullatacin and squamotacin

Keinan's described a "naked" carbon skeleton strategy for the synthesis of bullatacin, where all of the oxygenated stereocenters were generated by appropriate oxidation at sites of unsaturation.[80] Selective Sharpless asymmetric dihydroxylation of the *trans*-alkene of dienyne **3.59** provided lactone **3.60**. The THF rings were then formed stepwise by Re_2O_7 oxidation of the corresponding *cis*-bishomoallylic alcohols. Tranformation of the lactone into a Wittig salt and condensation with aldehyde **3.63** assembled the bullatacin skeleton. Reduction of the resulting alkene and deprotection of the MOM ethers provided bullatacin. A nearly identical approach was used by Keinan in the synthesis of squamotacin.[81]

While Keinan's route is elegantly simple, the nature of this "naked" carbon skeleton strategy makes divergence difficult. That is, the majority of the steps take place after the carbon skeleton, the feature we wish to vary, has been assembled. Also, as mentioned in the previous section, the route is limited by the level of enantiopurity attainable using the asymmetric dihydroxylation method.

Scheme 3.3 Keinan's synthesis of bullatacin



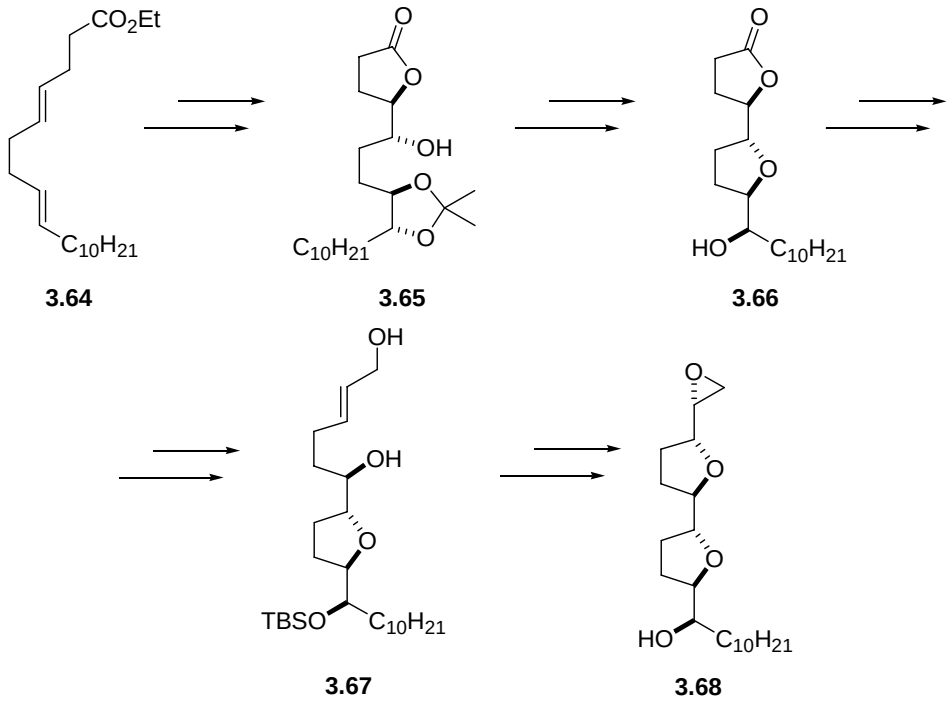
3.5.3 Hoye's synthesis of bullatacin

Hoye employed a similar approach to Keinan's, beginning with Sharpless dihydroxylation of diene **3.64** followed by acetonide formation to give **3.65**.[82] Tosylation followed by basic cleavage of the lactone provided an intermediate epoxide, which underwent cyclization upon hydrolysis of the acetonide to give THF lactone **3.66**. Reduction of the lactone and Wittig olefination of the lactol provided allylic alcohol **3.67** which was subjected to Sharpless epoxidation**.** The resulting epoxide underwent cyclization to form the second THF ring under the reaction conditions and the resulting

diol was converted to epoxide **3.68** in a three step process. Mitsunobu inversion[83] of the alcohol followed by addition of the lithium anion of TMS-acetelyne and desilylation of the alkyne provided alkyne **3.69**. Pd-catalyzed cross coupling with vinyl iodide **3.70** followed by selective reduction of the resulting enyne with Wilkinson's catalyst and silyl deprotection produced bullatacin.

As the approaches are strategically similar, the advantages and disadvantages of Keinan's synthesis apply here. While an effective synthesis of bullatacin, the use of asymmetric dihydroxylation to set the core stereochemistry and the lack of flexibility make it undesirable for our purposes.

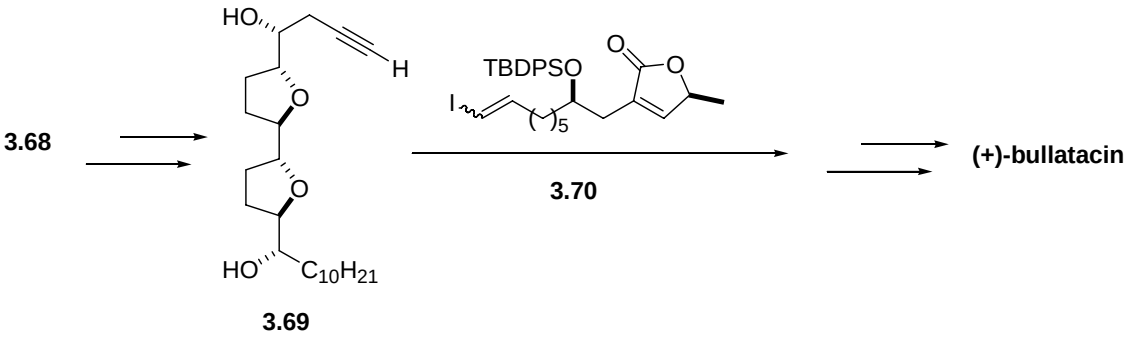
Scheme 3.4 Hoye's synthesis of bullatacin



3.64 **3.65** **3.66**

3.67 **3.68**

Scheme 3.5 Hoye's synthesis of bullatacin (cont'd)

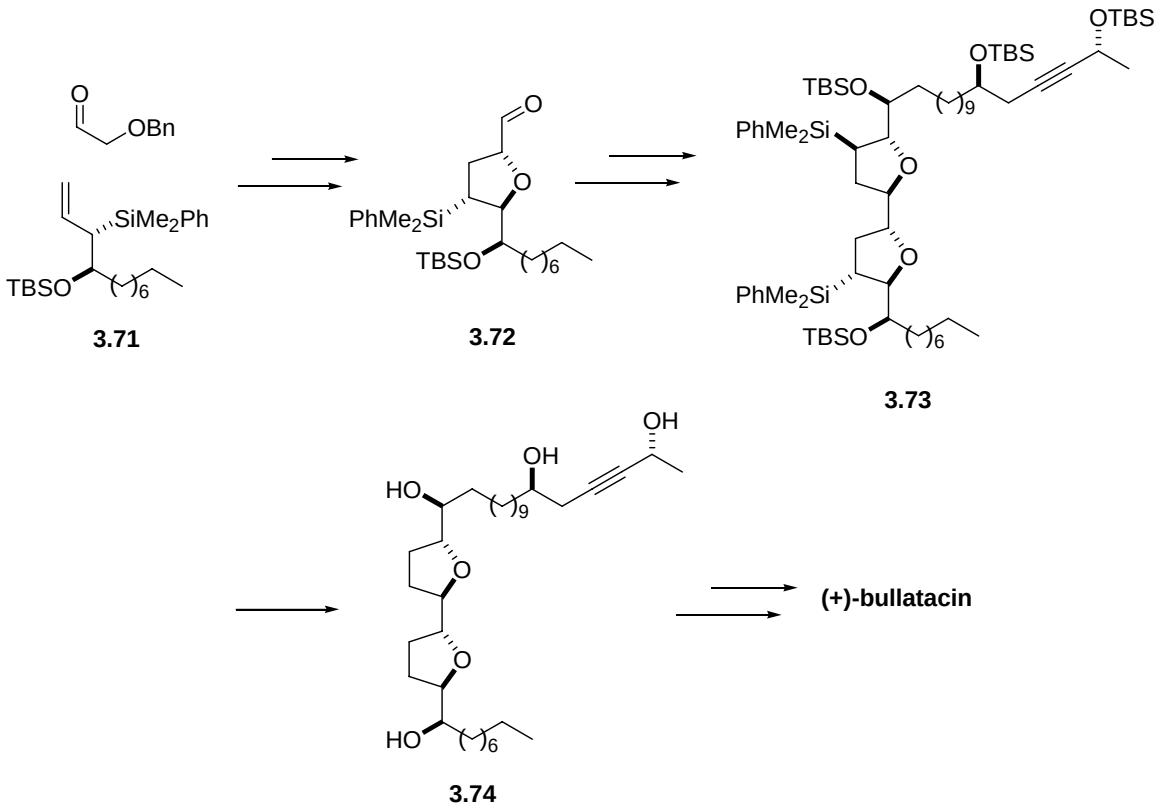


3.5.4 Roush's synthesis of bullatacin

Roush recently reported a synthesis of bullatacin utilizing [3+2] annulations of aldehydes with chiral allylsilanes.[84,85] Cyclization of benzyloxyacetaldehyde with allylsilane **3.71**, followed by removal of the benzyl group and oxidation provded aldehyde **3.72**. A second [3+2] annulation formed the second THF ring and assembled the bullatacin skeleton. One-pot protiodesilylation of the C-Si bonds and cleavage of the TBS ethers provided **3.74**, which was transformed into bullatacin in a 4-step sequence.

Roush's synthesis of bullatacin was very direct but too linear for our purpose. Formation of the butenolide at the end of the synthesis would add these steps to each analog synthesis and each analog would require a separate multi-step synthesis of the chiral allylsilane.

Scheme 3.6 Roush's synthesis of bullatacin (cont'd)



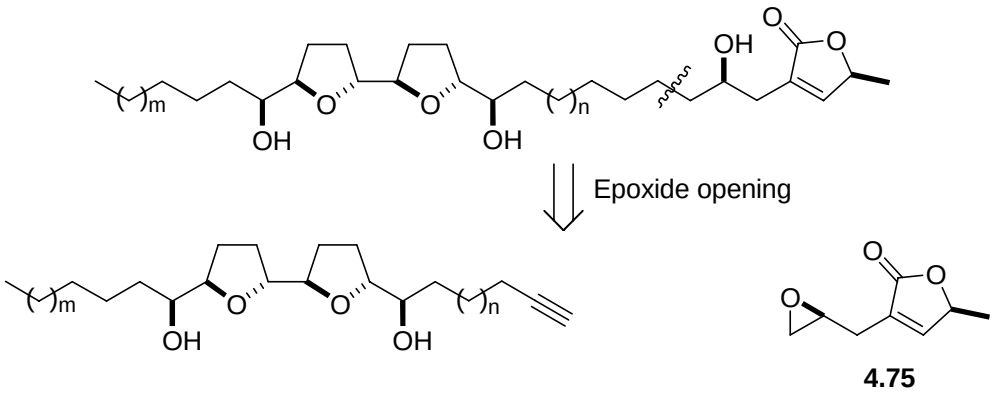
Chapter 4: Synthesis of Acetogenin Analogs

4.1 RETROSYNTHETIC ANALYSIS

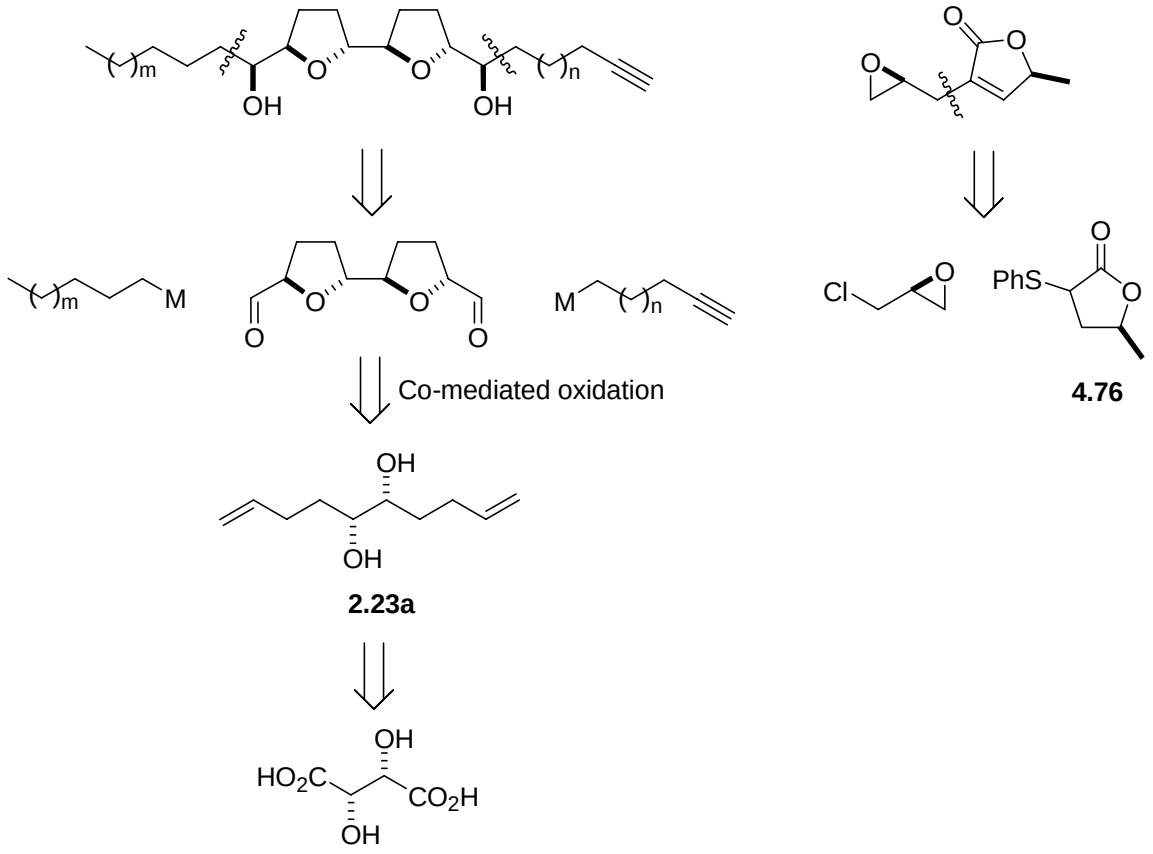
With a modular synthesis of bullatacin and squamotacin analogs in mind, our retrosynthetic analysis divided the basic structure into four subunits: the alkyl chain, the bis-THF core, the alkyl tether and the butenolide. We envisioned using aldehyde additions to connect the alkyl groups to the bis-THF and acetylide addition to epoxy butenolide **4.75** to complete the acetogenin skeleton (Scheme 4.1 and Scheme 4.2). A major benefit of this approach is that the components we wished to vary, the alkyl chain and the tether, could either be purchased or are readily available.

As described in Chapter 2, a suitably protected bis-THF diol could be attained using Mukaiyama's oxidative cyclization of diol **2.23a**. In contrast to Wang and Shi's use of asymmetric dihydroxylation, we chose to prepare this diol by allylation of bis-epoxide **2.42**, conveniently available from (D)-tartaric acid.[66] Finally, previous research in this laboratory[77] has offered convenient access to epoxy butenolide **4.75** by selective alkylation of epichlorohydrin with White's lactone **4.76**.[86]

Scheme 4.1 Retrosynthetic analysis



Scheme 4.2 Retrosynthetic analysis (cont'd)

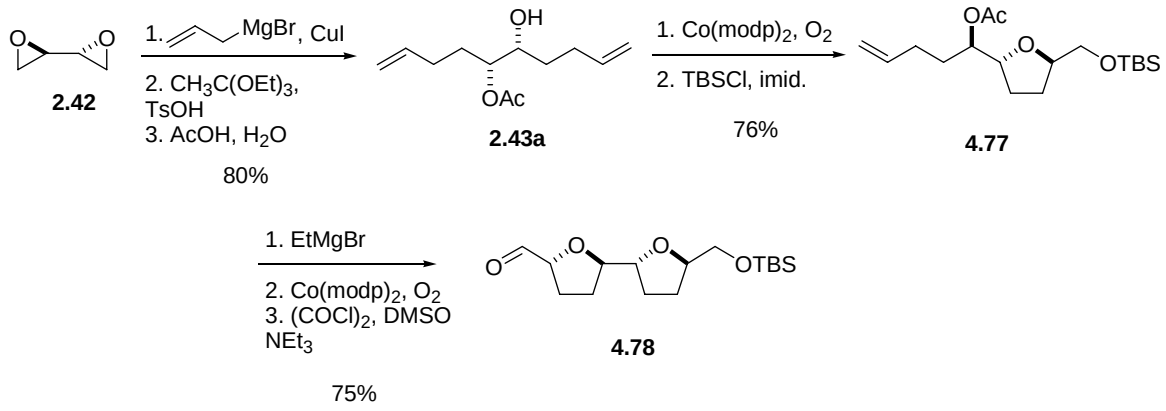


4.2 SYNTHESIS OF THE BIS-THF CORE

Although individual steps of the bis-THF synthesis were described in Chapter 2, a brief overview is presented here (Scheme 4.3). Copper-catalyzed Grignard allylation of bis-epoxide **2.42** provided diol **2.23** in 81% yield. The diol was treated with triethylorthoacetate and acidic hydrolysis of the resulting orthoester gave a 99% yield of monoacetate **2.43a**. Cobalt-mediated oxidation of **2.43a** provided mono-THF **2.43b**, which was protected as a TBS ether to give **4.77** in 76% yield over two steps. Deprotection of the acetate with EtMgBr and cobalt-mediated oxidative cyclization

afforded monoprotected bis-THF diol **2.18b** in 78% yield. Swern oxidation provided a 96% yield of aldehyde **4.78**, which was used to introduce the first alkyl side chain.

Scheme 4.3 Synthesis of the bis-THF core

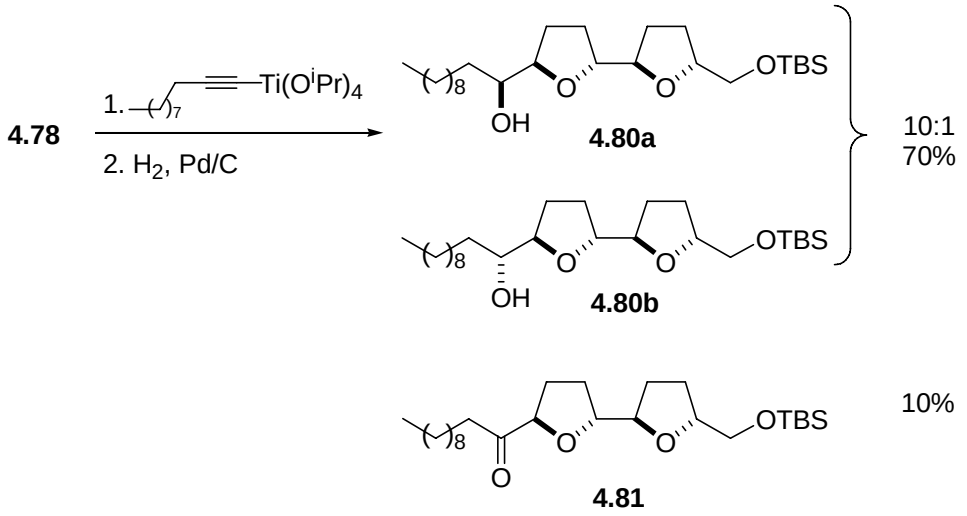


4.3 INTRODUCTION OF THE ALKYL CHAIN

Stereoselective addition to α-chiral aldehydes has been the focus of intense study by several groups and successful approaches using chelation control or the Felkhin-Anh model have been developed. However, stereoselective addition to α-THF aldehydes has historically been difficult.[87] A common remedy for this issue has been to perform an unselective addition, oxidize and reduce the ketone with L-Selectride™ to provide the *threo* isomer.[88] While the *erythro* isomer can be obtained by subsequent Mitsunobu inversion followed by hydrolysis of the ester, this process comprises 5 synthetic steps and detracts from overall efficiency. Bullatacin and squamotacin require *erythro* sterechemistry at the hydroxyl joined to the terminal alkyl chain, and the initial synthesis of the natural products in this laboratory utilized this indirect and somewhat inefficient route. The goal of preparing multiple analogs prompted efforts in our laboratory to achieve a more direct addition.

Another researcher in our laboratory screened several chelation-controlled and reagent-controlled additions of alkyl metals to bis-THF aldehyde **4.78**, which consistently gave low to moderate levels of selectivity.[77] He discovered that acetylides generally gave better selectivities than aliphatic organometallics. In particular, Ti-acetylides, generated from the corresponding lithium acetylide and $ClTi(O^iPr)_3$, gave excellent stereoselectivity for the desired *erythro* isomer. Treatment of aldehyde **4.78** with the Ti-acetylide of 1-decyne provided **4.79** as an inseparable mixture of isomers in 82% yield (*erythro*/*threo*: 10:1; Scheme 4.4). Hydrogenation provided a separable mixture of *erythro*/*threo* isomers **4.80a** and **4.80b** in 85% yield, along with 10% of the reductive isomerization product, ketone **4.81**.

Scheme 4.4 Stereoselective, direct formation of the *erythro* isomer



4.4 THE TETHER

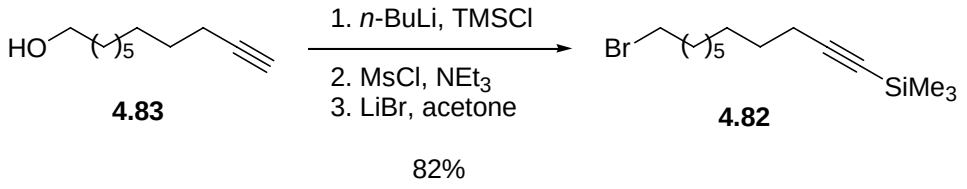
4.4.1 Synthesis of the tether

For bullatacin and squamotacin, the hydroxyl on the tether side of the THF core is *threo* relative to the adjacent THF stereocenter, so we chose to use the non-selective addition/oxidation/L-Selectride™ reduction protocol to achieve the correct

stereochemistry. For this, we required a tether precursor with a halogen for Grignard formation and addition to a THF aldehyde at one end, and a suitably protected (TMS) alkyne at the other terminus for addition to the epoxy butenolide. Many such compounds have been reported in the literature and are most easily prepared by conversion of the corresponding alcohols to the halides.[89] The alcohols are available by persilylation of the appropriate ω-hydroxyalkynes followed by acidic hydrolysis of the TMS ether. A few of these ω-hydroxyalkynes are commercially available while others can be prepared by zipper isomerization of commercially available internal alkynes.

The synthesis of tether precursor **4.82** illustrates this approach (Scheme 4.5). Silylation of 1-hydroxy-10-undecyne (**4.83**) with an excess of *n*-BuLi and TMSCl followed by hydrolysis of the TMS ether provided a 90% yield of the hydroxy TMS-alkyne. Mesylation of the alcohol and substitution with LiBr provided **4.82** in 91% yield over two steps.

Scheme 4.5 Synthesis of tether precursor **4.82**

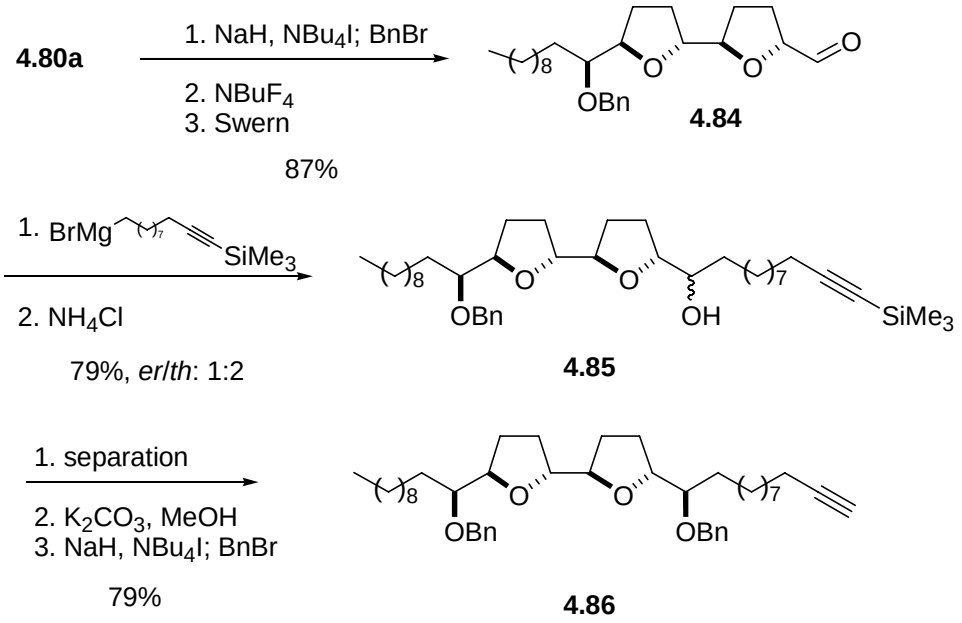


4.4.2 Incorporation of the tether

Prior to addition of the tether, the free alcohol of **4.79a** was protected as a benzyl ether and the TBS ether was converted to aldehyde **4.84** by NBu_4F deprotection and Swern oxidation in 87% yield over three steps (Scheme 4.6). Subsequent addition of the

Grignard reagent formed from **4.82** provided a separable mixture of *erythro*/*threo* diastereomers **4.85a** and **4.85b** in 79% yield (*erythro*/*threo*: 1:2). The desired *threo isomer* **4.85b** was isolated and used for the remainder of the synthesis. Desilylation of the TMS-alkyne using K_2CO_3/MeOH followed by benzylation of the alcohol afforded a 79% yield of terminal alkyne **4.86**, which could be used in the addition to epoxy butenolide **4.75**.

Scheme 4.6 Incorporation of the tether

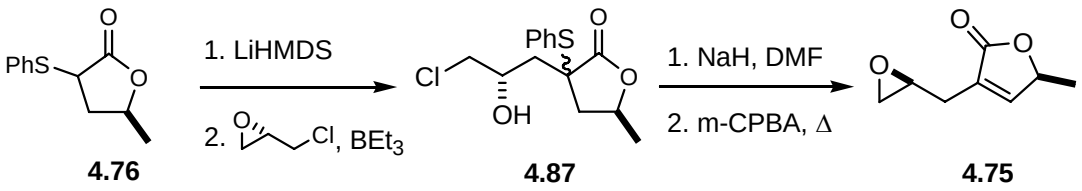


4.5 SYNTHESIS OF THE EPOXY BUTENOLIDE

As previously mentioned, another researcher in our laboratory prepared epoxy butenolide **4.75** in three steps from White's lactone **4.76** (Scheme 4.7).[77] Chemoselective alkylation of the lithium enolate of **4.76** with *R*-epichlorohydrin in the presence of BEt_3

provided chlorohydrin **4.87** in 86% yield. Cyclization to the epoxide with NaH and oxidative elimination furnished the epoxy lactone **4.75** in 70% yield over two steps.

Scheme 4.7 Synthesis of epoxy butenolide **4.75**

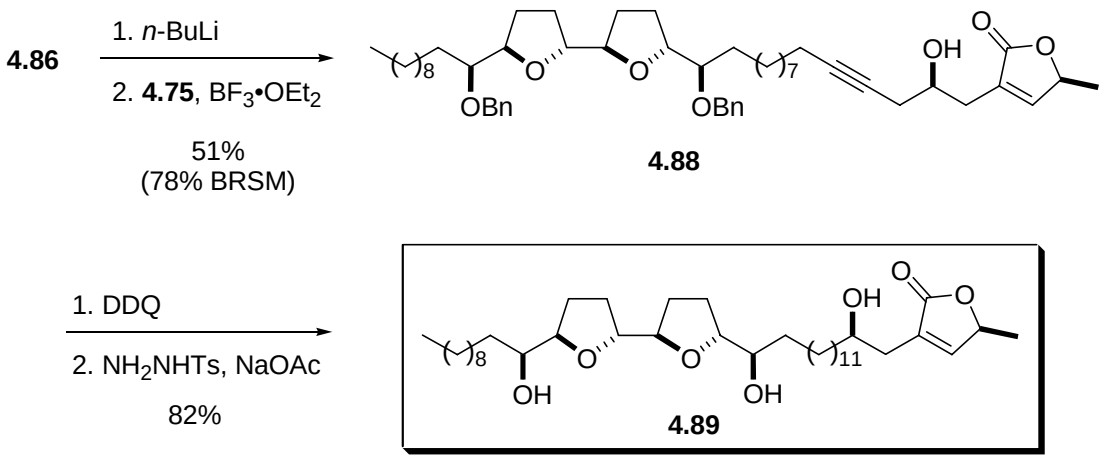


4.76 **4.87** **4.75**

4.6 FINAL ASSEMBLY OF THE TETHER-ELONGATED BULLATACIN ANALOG

With terminal alkyne **4.86** and epoxy butenolide **4.75** in hand, the acetogenin skeleton was nearly complete. Addition of the lithium acetylide of **4.86** to **4.75** in the presence of BF_3•OEt_2 was found to be extremely moisture sensitive at the small scales used, consistently returning unreacted starting material. Predrying THF solutions of the alkyne and the epoxide with activated 4Å MS proved insufficient to remedy this issue. However, extended drying of the startin materials in vacuo allowed addition to take place, affording advanced intermediate **4.88** in 51% yield (78% BRSM; Scheme 4.8). Deprotection of the benzyl ethers with DDQ[90] and diimide reduction of the internal alkyne provided the tether-elongated analog of bullatacin **4.89** in 82% over two steps**.**

Scheme 4.8 Completion of acetogenin analog **4.89**



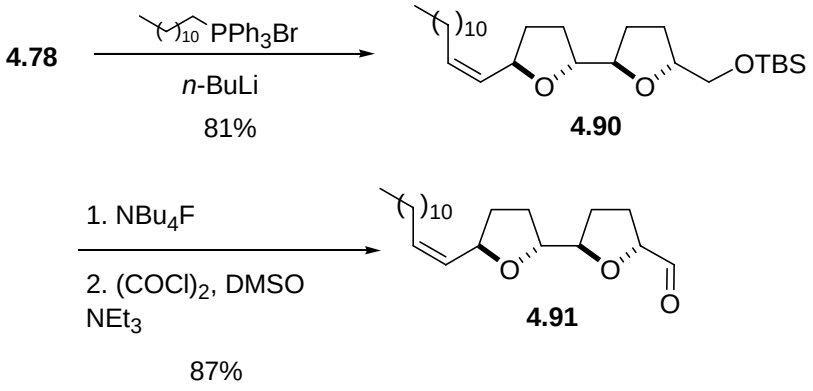
4.7 22-DEOXY ANALOG OF SQUAMOTACIN

Prior to the innovation of the Ti-acetylide addition, an alternative solution to the problematic *erythro* stereochemistry of the hydroxyl on the terminal alkyl chain side of the THF was explored. We envisioned that a set of deoxy analogs lacking this stereocenter, while potentially compromising activity, might still provide insight into the effect of the tether length. As many of the reactions used in the synthesis of the tether-elongated analog of bullatacin overlaps, a brief summary of the synthesis of a 22-deoxysquamotacin is presented here.

4.7.1 Introduction of the terminal alkyl chain

The terminal alkyl chain of the deoxy analog was introduced by Wittig olefination of aldehyde **4.78**,[91] providing alkene **4.90** in 81% yield (*Z*/*E*: >20:1), which could be reduced along with the alkyne at the end of the synthesis (Scheme 4.9). Deprotection of the TBS ether with NBu_4F and oxidation under Swern conditions provided aldehyde **4.91** in 87% yield.

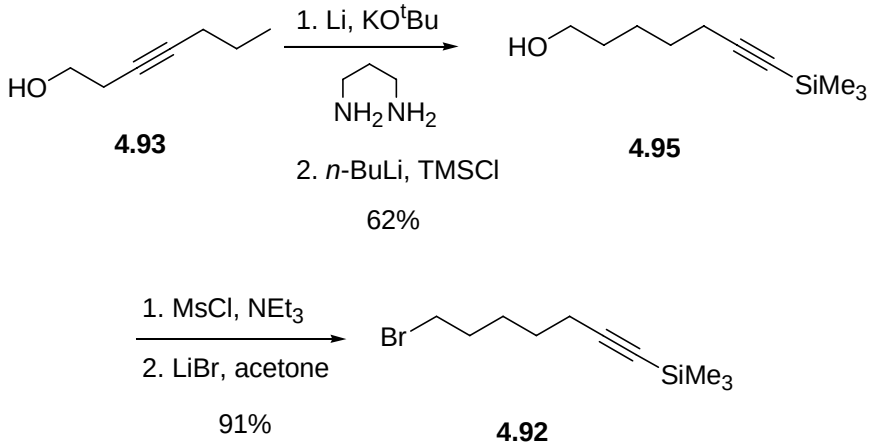
Scheme 4.9 Formation of the deoxy analog precursor by Wittig olefination



4.7.2 Synthesis of the tether precursor

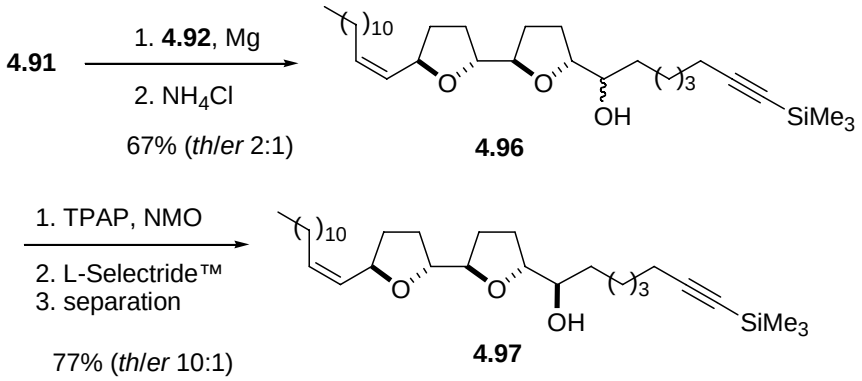
The synthesis of tether precursor **4.92** began with zipper isomerization of 1-hydroxy-3-heptyne to give terminal alkyne **4.94** in 69% yield (Scheme 4.10). Persilylation of **4.94** with *n*-BuLi and TMSCl and hydrolysis of the TMS ether provided a 90% yield of TMS alkyne **4.95**. Conversion of the alcohol to the mesylate and displacement with LiBr provide bromo alkyne **4.92** in 91% yield.

Scheme 4.10 Synthesis of tether precursor **4.92**



Addition of the Grignard reagent formed from **4.92** to aldehyde **4.91** provided a separable mixture of diastereomers **4.96a** and **4.96b** in 67% overall yield (*threo*:*erythro* 2:1, Scheme 4.11). TPAP oxidation of the mixture and L-Selectride™ reduction of the ketone gave a 77% yield of **4.96a** and **4.96b** (*threo*:*erythro* 10:1). The desired *threo* isomer **4.96a** was isolated at this stage and used in the remainder of the synthesis.

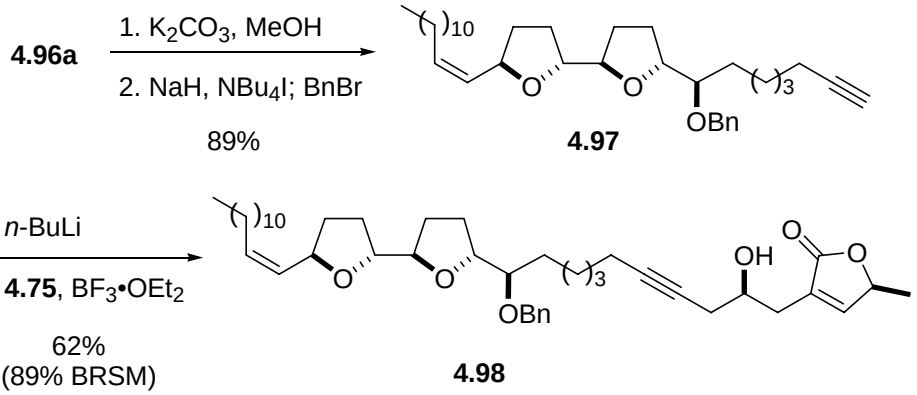
Scheme 4.11 Incorporation of the tether



4.7.3 Completion of 22-deoxysquamotacin

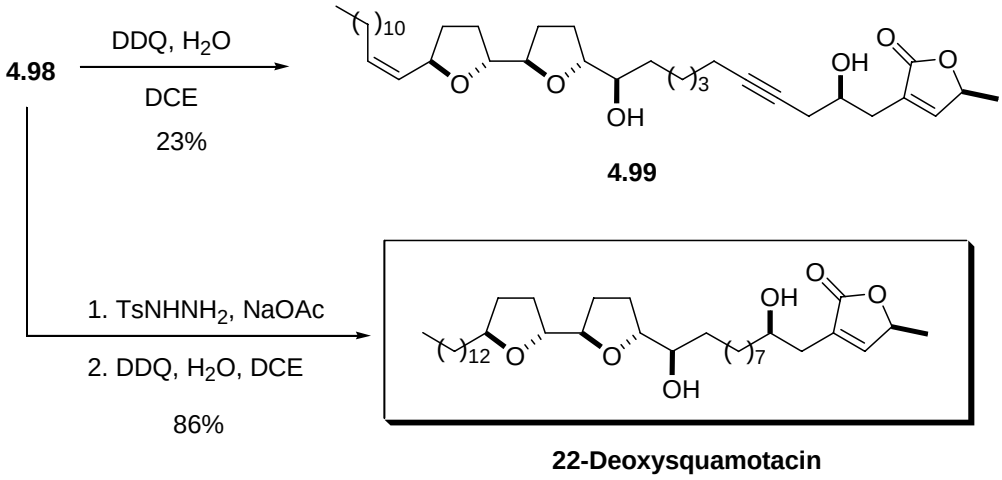
Desilylation of alkyne **4.96a** using K_2CO_3/MeOH followed by benzylation of the alcohol gave terminal alkyne **4.97** in 89% yield over two steps (Scheme 4.12). The lithium acetylide of **4.97** was then added to epoxy butenolide **4.75** in the presence of BF_3•OEt_2, providing **4.98** in 62% yield (89% BRSM).

Scheme 4.12 Addition of alkyne **4.97** to the epoxy butenolide



Attempted DDQ deprotection of the benzyl ether of **4.98** produced a meager 23% yield of the desired product **4.99**, presumably caused by competive oxidation of the allylic ether of the terminal alkyl chain (Scheme 4.13). As a solution to this, the diimide reduction was performed prior to debenzylation, providing **22-deoxysquamotacin** in 86% yield over two steps.

Scheme 4.13 Solution to the low yield of DDQ debenzylation of **4.98**



4.8 CONCLUSION

The synthesis of bullatacin analogs recently developed in our laboratory has been successfully applied to two new derivatives, C-14 tether **4.89** and 22-deoxysquamotacin. As our objective was to study the effects of tether length on biological activity, these and additional bullatacin analogs with tether lengths of 10, 11 and 12 carbons have been prepared by another researcher in our laboratory[77] and submitted to NIH for testing. Additionally, synthetic bullatacin (C-13) and squamotacin (C-9) have been prepared and submitted for side-by-side comparison.[77]

CHAPTER 5: EXPERIMENTAL PROCEDURES

5.1 GENERAL PROCEDURES

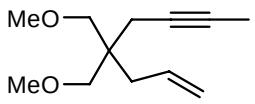
All reactions were run under an atmosphere of nitrogen or argon unless specified otherwise. Flasks were oven or flame-dried and allowed to cool in a desiccator prior to use. A solution of anhydrous *tert*-butylhydroperoxide (TBHP) in isooctane was prepared according to the previously described procedure Solvents and reagents were purified by standard methods.[92] Thin-layer chromatography (TLC) was performed on EM 250 Kieselgel 60 F254 silica gel plates. The plates were visualized by staining with I_2 on silica, CAM,[79] or potassium permanganate. GC analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with an Econocap column (Altech, 15 m x 0.53 μm) and FID detector.

The ^{1}H and ^{13}C NMR data was obtained on a Varian Unity Plus 300 or a Varian INOVA 400 or 500 spectrometer. For ^{1}H NMR, chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and are, in all cases, referenced to the residual proton resonance peaks: δ 7.24 for $CHCl_3$. The ^{13}C NMR chemical shifts were reported in ppm relative to the center peak of the solvent multiplet: δ 77.0 (t) for $CDCl_3$. ^{13}C NMR spectra were routinely run with broadband ^{1}H decoupling. NOE differences were determined using a double pulsed field gradient spin echo sequence (mixing time = 800 msec) and values are reported adjacent to the enhanced hydrogen(s). Infrared spectra were obtained on a Nicolet AVATAR 360 FTIR. HRMS (CI) were made with a VG

analytical ZAB2-E instrument. Where appropriate, descriptions of signals include broad (br), apparent (app) and multiplet (m).

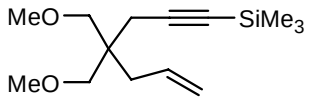
Compounds **1.3,**[38] **1.7,**[93] **1.8a,**[40] **1.9a,**[94] **1.15a,**[40] **2.29a**,[95] **2.33a**,[96] **2.37a**,[97] **2.42,**[66] **2.47,**[67] **4.82**[98] and **4.92**[89] have been prepared previously.

5.2 ENYNE SUBSTRATE PREPARATION



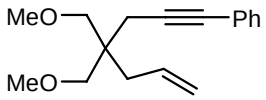
1.1a

4,4-Bis(methoxymethyl)oct-1-en-6-yne (1.1a). To a 0 °C THF (30 mL) solution of **1.3** (5.4 g, 30 mmol) was added *n*-BuLi (13 mL, 2.53 M, 33 mmol) dropwise. After 30 min, MeI (2.3 mL, 36 mmol) was added dropwise to the solution, the reaction mixture was stirred an additional 1 h, and then allowed to warm to rt. After stirring 10 h at rt, a solution of NH_4Cl (20 mL, sat'd) was added and the layers were separated. The aqueous phase was extracted with ether and the combined layers were washed with $Na_2S_2O_3$ (20 mL, 10%) brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting liquid was purified by vacuum distillation (62-65 °C, 0.3 mm Hg) to give the title compound as a clear colorless oil (5.2 g, 27 mmol, 89%): R_f 0.33 (5% EtOAc/hexanes); IR (thin film) ν 3075, 1639, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, J = 9.9, 17.4, 7.5 Hz, 1H), 5.10-5.01 (m, 2H), 3.30 (s, 6H), 3.22 (d, J = 13.0 Hz, 2H), 3.19 (d, J = 13.0 Hz, 2H), 2.14-2.08 (m, 4H), 1.77 (t, J = 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 117.7, 77.2, 75.5, 74.4, 59.2, 41.8, 36.2, 22.2, 3.5; HRMS *m/z* 197.1542 (calc'd for $C_{12}H_{21}O_2$ $[M+H]^+$, 197.1542).



1.2a

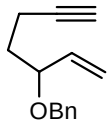
4,4-Bis(methoxymethyl)-7-trimethylsilylhept-1-en-6-yne (1.2a). To a 0 °C THF (30 mL) solution of **1.3** (5.4 g, 30 mmol) was added *n*-BuLi (13 mL, 2.53 M, 33 mmol) dropwise. After 30 min, Me_3SiCl (4.5 mL, 36 mmol) was added dropwise to the canary yellow solution, the reaction mixture was stirred an additional h, and then allowed to warm to rt. After stirring 10 h at rt, a solution of NH_4Cl (20 mL, sat'd) was added and the layers were separated. The aqueous phase was extracted with EtOAc and the combined layers were washed with brine (50 mL), dried ($MgSO_4$), filtered (Celite), and concentrated in vacuo. The resulting liquid was purified by vacuum distillation (80-83 °C, 0.25 mm Hg) to give the title compound as a clear colorless oil (6.48 g, 26 mmol, 86%): R_f 0.35 (2.5% EtOAc/hexanes); IR (thin film) ν 3076, 2174, 1653, 1250, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, J = 9.9, 17.10, 7.5 Hz, 1H), 5.10-5.01 (m, 2H), 3.30 (s, 6H), 3.22 (d, J = 12.3 Hz, 2H), 3.20 (d, J = 12.3 Hz), 2.18 (s, 2H), 2.13 (d, J = 7.5 Hz), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 118.0, 104.2, 86.6, 74.3, 59.3, 41.9, 36.2, 23.3, 0.1; HRMS *m/z* 255.1783 (calc'd for $C_{14}H_{27}O_2Si$ $[M+H]^+$, 255.1780).



1.4a

4,4-Bis(methoxymethyl)-7-phenylhept-1-en-6-yne (1.4a). $Pd(PPh_3)_2Cl_2$ (0.51 g, 0.73 mmol) and CuI (0.28 g, 1.5 mmol) were added to degassed NEt_3 (24 mL, 173 mmol) at rt.

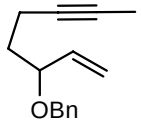
To the resulting mixture was added **1.3** (4.37 g, 24 mmol). After 30 min, THF (20 mL) was added and the reaction mixture was stirred for 3 h. The reaction mixture was concentrated, and the solid residue was extracted with Et_2O and the extracts were filtered through a SiO_2 plug using Et_2O for elution. Concentration and purification of the resulting liquid by flash chromatography on SiO_2 0.25% EtOAc/hexanes) provided the title compound as a light yellow liquid (5.88 g, 23 mmol, 95%): R_f 0.32 (2.5% EtOAc/hexanes); IR (thin film) ν 3074, 1110, 756, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.38 (m, 2H), 7.32-7.25 (m, 3H), 5.85 (ddt, J = 7.5, 9.9, 17.1 Hz, 1H), 5.17-5.08 (m, 2H), 3.36 (s, 6H), 3.33 (d, J = 13.0 Hz, 2H), 3.31 (d, J = 13.0 Hz, 2H), 2.42 (s, 2H), 2.24 (d, J = 7.52 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 133.9, 131.5, 128.2, 127.5, 124.0, 118.1, 87.0, 82.5, 74.5, 59.3, 42.2, 36.4, 22.9; HRMS *m/z* 259.1699 (calc'd for $C_{17}H_{23}O_2$ $[M+H]^+$, 259.1698).



1.100

3-Benzyloxyhept-1-en-6-yne (1.100). To a suspension of NaH (0.31 g, 94%, 12 mmol) in DMF (11 mL) at 0 °C, was added **1.7** (1.20 g, 11 mmol) dropwise. After 10 min benzyl bromide (1.45 mL, 12 mmol) was added dropwise, the reaction mixture was stirred for 1 h, and poured into a solution of NH_4Cl (25 ml, sat'd). The resulting mixture was extracted with hexanes and the combined organic layers were washed with water (2 x 20 mL) and Na_2SO_3 (20 mL, 10%), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash chromatography on SiO_2 (elution gradient: hexanes to

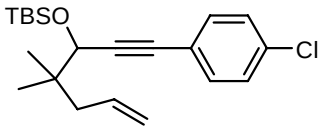
2.5% EtOAc/hexanes) provided the title compound as a clear, colorless liquid (1.39 g, 7.0 mmol, 63%): R_f 0.36 (2.5% EtOAc/hexanes); IR (thin film) ν 3300, 3069, 3031, 1072 739, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.27 (m, 5H), 5.78 (ddd, J = 7.4, 10.3, 17.4 Hz, 1H), 5.35-5.31 (m, 1H), 5.30-5.27 (m, 1H), 4.64 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 11.7 Hz, 1H), 3.95 (ddd, J = 5.4, 7.4, 7.7 Hz, 1H), 2.44-2.25 (m, 2H), 1.96 (t, J = 2.8 Hz, 1H), 1.95-1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.2, 128.3, 127.7, 127.5, 117.6, 84.0, 79.0, 70.3, 68.4, 34.2, 14.6; HRMS *m/z* 201.1272 (calc'd for $C_{14}H_{17}O$ $[M+H]^+$, 201.1279).



1.5a

3-Benzyloxyoct-1-en-6-yne (1.5a). To a THF (10 mL) solution of benzyl ether **1.100** (1.34 g, 6.7 mmol) cooled to 0 °C was added *n*-BuLi (3.1 mL, 2.56 M, 8.0 mmol) dropwise. After 30 min, MeI (0.63 mL, 10 mmol) was added and the reaction mixture was stirred an additional 1 h and then poured into a stirred solution of NH_4Cl (30 ml, sat'd). The layers were separated and the aqueous phase was extracted with EtOAc. The combined extracts were washed with Na_2SO_3 (20 mL, 10%) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting oil was purified by flash chromatography on SiO_2 (elution gradient: hexanes to 2.5% EtOAc/hexanes) provided the title compound as a clear, colorless liquid (1.22 g, 5.7 mmol, 85%): R_f 0.39 (2.5% EtOAc/hexanes); IR (thin film) ν 3031, 1070, 736, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.21 (m, 5H), 5.78-5.65 (m, 1H), 5.28-5.18 (m, 2H), 4.57 (dd, J = 2.1, 12.0 Hz,

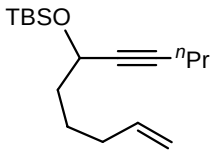
1H), 4.35 (dd, J = 1.7, 12.0 Hz, 1H), 3.87 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 2.30-2.13 (m, 2H), 1.85-1.58 (m, 2H), 1.74 (t, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.4, 128.3, 127.7, 127.4, 117.4, 79.1, 78.6, 45.7, 40.2, 13.7, 14.9, 3.4; HRMS *m/z* 215.1430 (calc'd for $C_{15}H_{19}O$ $[M+H]^+$, 215.1436).



1.10a

5-*tert*-Butyldimethylsiloxy-7-(4-chlorophenyl)-4,4-dimethylhept-1-en-6-yne (1.10a). A THF (20 mL) solution of *p*-chlorophenylacetylene (2.06 g, 15 mmol) was cooled to 0 °C and *n*-BuLi (5.9 mL, 2.71 M, 16 mmol) was added dropwise. The acetylide solution was added dropwise to a 0 °C THF (15 mL) solution of aldehyde **1.11** (2.04 g, 18 mmol) via cannula. After 1 h the ice bath was removed and the reaction mixture was stirred 2 h at rt. Following cannular addition of a solution of TBSCl in THF (10 mL), the reaction mixture was heated at reflux for 11 h. Afer cooling to rt, NH_4Cl (20 mL, sat'd) was added and the mixture was stirred for 5 min. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated. Vacuum distillation (162-165 0 °C, 0.25 mm Hg) of the liquid provided the title compound as a clear, colorless liquid (3.89 g, 11 mmol, 71%): R_f 0.65 (hexanes); IR (thin film) ν 3076, 1640, 1257, 1091, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 4H), 5.88 (dddd, J = 7.4, 7.4, 9.22, 17.9 Hz, 1H), 5.13-5.04 (m, 2H), 4.26 (s, 1H), 2.27-2.12 (m, 2H), 1.01 (s, 3H), 1.00 (s,

3H), 0.97 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 134.0, 132.6, 128.6, 121.8, 117.3, 90.9, 84.4, 70.9, 42.7, 39.5, 25.8, 22.8, 22.7, 18.2, -4.2, -5.2; HRMS *m/z* 363.1913 (calc'd for $C_{21}H_{32}OSiCl$ $[M+H]^+$, 363.1911).

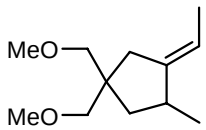


1.13a

***6-tert*-Butyldimethylsiloxyundec-1-en-7-yne (1.13a).** A solution of 1-hexen-6-al in CH_2Cl_2 (200 mL) and Et_2O (200 mL) was prepared by PCC oxidation of 1-hexen-6-ol (3.6 mL, 30 mmol).[99] To a 0 °C solution of 1-pentyne in Et_2O (50 mL) was added *n*-BuLi (16 mL, 2.71 M, 43 mmol) dropwise. The resulting acetylide solution was added by cannula to the solution of 1-hexen-6-al at -78 °C. After 2 h the cooling bath was removed and the reaction mixture was stirred for 10 h at rt. A solution of NH_4Cl (60 mL, sat'd) was added and the layers were separated. The aqueous phase was extracted with Et_2O, and the combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The resulting residue (1.67 g, 10 mmol) was taken up in DMF (2 mL) and added to a slurry of imidazole (1.89 g, 28 mmol) and TBSCl (1.84 g, 11 mmol) at rt. After 6 h the reaction mixture was poured into a stirred solution of $NaHCO_3$ (30 mL, sat'd). The mixture was extracted with hexanes and the combined extracts were washed with water, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 (elution gradient: hexanes to 1% EtOAc/hexanes) to give the title compound as a colorless liquid (2.8 g, 11 mmol, 35%):

R_f 0.26 (hexanes); IR (thin film) ν 3078, 1641, 1253, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dddd, J = 6.7, 6.7, 10.3, 16.9 Hz, 1 H), 5.08-4.94 (m, 2H), 4.36 (ddd, J = 2.1, 2.1, 6.4, 6.4 Hz, 1H), 2.19 (app dt, J = 2.1, 6.9 Hz, 2H), 2.09 (app q, J = 6.9 Hz, 2H), 1.72-1.61 (m, 2H), 1.60-1.47 (m, 4H), 0.99 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 114.4, 84.3, 82.0, 63.0, 38.4, 33.4, 25.8, 24.6, 22.1, 20.7, 18.3, 13.5, -4.5, -5.0; HRMS *m/z* 281.2294 (calc'd for $C_{17}H_{33}OSi$ $[M+H]^+$, 281.3001).

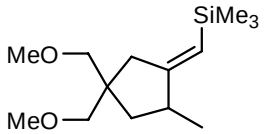
5.3 ZIRCONOCYLOPENTENE PROTONATION CONTROL EXPERIMENTS



1.1b

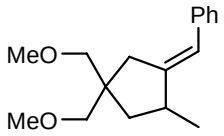
3*E*-Ethylidene-1,1-bis(methoxymethyl)-4-methylcyclopentane (1.1b). To a solution of Cp_2ZrCl_2 (98 mg, 0.34 mmol) in THF (3 mL) cooled to -78 °C, was added *n*-BuLi (0.26 mL, 2.56 M, 0.68 mmol) and the dry ice bath was removed. The reaction mixture was allowed to warm until homogenous (~0 °C), at which point the mixture was cooled to -78 °C. A solution of enyne **1.1a** (63 mg, 0.32 mmol) in THF (1.5 mL) was added via cannula, and the dry ice bath was replaced with an ice bath. After 1h the ice bath was removed and the reaction mixture was allowed to warm to rt. After 12 h, HCl (0.5 mL, 3 M, 1.5 mmol) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous phase was extracted with hexanes. The combined extracts were washed with $NaHCO_3$ (sat'd) and brine, dried ($MgSO_4$), filtered and concentrated.

Purification by flash chromatography on SiO_2 (hexanes to 2.5% EtOAc/hexanes) provided the title compound as a colorless oil (53 mg, 0.27 mmol, 84%): R_f 0.23 (2.5% EtOAc/hexanes); IR (thin film) ν 3035, 1198, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18-5.08 (m, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 3.25 (d, J = 8.7 Hz, 1H), 3.20 (d, J = 8.7 Hz, 1H), 3.19 (s, 2H), 2.53-2.38 (m, 1H), 2.12 (s, 2H), 1.82 (dd, J = 7.7, 12.8 Hz, 1H), 1.57-1.51 (m, 3H), 1.04-0.94 (m, 1 H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 114.0, 77.8, 75.4, 59.3, 45.5, 40.6, 36.4, 35.7, 31.6, 18.6, 14.4; HRMS *m/z* 199.1700 (calc'd for $C_{12}H_{23}O_2$ $[M+H]^+$, 199.1698).



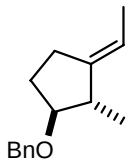
1.2b

1,1-Bis(methoxymethyl)-4-methyl-3*E*-trimethylsilylvinylidenecyclopentane (1.2b). The title compound was prepared from enyne **1.2a** (247 mg, 0.97 mmol) according to the procedure described for **1.1b** except that H_2SO_4 (1.3 mL, 10%) was used for protonation of the zirconocycle (colorless liquid, 236 mg, 0.92 mmol, 95%): R_f 0.33 (5% EtOAc/hexanes); IR (thin film) ν 1637, 1248, 1110, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.21 (ddd, J = 2.3, 2.3, 2.3 Hz, 1H), 3.31 (s, 3H), 3.31 (s, 3H), 3.22 (d, J = 11.0 Hz, 2H), 3.19 (d, J = 11.0 Hz, 2H), 2.54-2.40 (m, 1H), 2.24 (app s, 2H), 1.84 (dd, J = 8.5, 13.1 Hz, 1H), 1.02 (d, J = 6.7 Hz, 3H), 1.01 (dd, J = 10.8, 12.8 Hz, 1 H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 117.3, 77.4, 75.6, 59.3, 59.2, 45.6, 39.6, 39.2, 39.0, 18.7, -0.2; HRMS *m/z* 255.1772 (calc'd for $C_{14}H_{28}O_2Si$ $[M]^+$, 255.1780).



1.4b

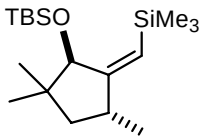
3*E*-Benzylidene-1,1-bis(methoxymethyl)-4-methylcyclopentane (1.4b). The title compound was prepared from enyne **1.4a** (129 mg, 0.50 mmol) according to the procedure described for **1.1b** (light yellow oil, 116 mg, 0.45 mmol, 89%): R_f 0.35 (2.5% EtOAc/hexanes); IR (thin film) ν 3022, 1198, 1107, 747, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 4H), 7.21-7.14 (m, 1H), 6.22 (ddd, J = 2.4, 2.4, 2.4 Hz, 1H), 3.34 (s, 6H), 3.31 (d, J = 8.6 Hz, 1H), 3.28 (d, J = 8.6 Hz, 1H), 3.27 (s, 2H), 2.84-2.71 (m 1H), 2.58 (d, J = 17.4 Hz, 1H), 2.52 (dd, J = 2.4, 17.4 Hz, 1H), 1.93 (dd, J = 7.9, 12.7 Hz, 1H) 1.21 (d, J = 6.5 Hz, 3H), 1.14 (dd, J =11.3, 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 138.4, 128.2, 128.1, 125.7, 120.7, 77.5, 75.4, 59.2, 59.2, 46.5, 39.5, 38.4, 37.8, 18.9; HRMS *m/z* 260.1768 (calc'd for $C_{17}H_{24}O_2$ $[M]^+$, 260.1776).



1.5b

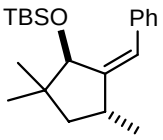
***trans*-1-Benzyloxy-3*E*-ethylidene-2-methylcyclopentane (1.5b).** The title compound was prepared from enyne **1.5a** (107 mg, 0.50 mmol) according to the procedure described for **1.1b** (colorless liquid, 89 mg, 0.41 mmol, 82%): R_f 0.44 (5% EtOAc/hexanes); IR (thin film) ν 3064, 3031, 1105, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 5.31-5.23 (m, 1H), 4.63 (d, J = 2..0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H) 3.45 (q, J = 6.6 Hz, 1H), 2.56-2.36 (m, 2H), 2.28-2.13 (m, 1H), 2.09-1.99 (m, 1H), 1.73-1.60 (m,

1H), 1.60 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 138.9, 128.3, 127.4, 115.0, 86.1, 71.1, 44.6, 29.1, 25.5, 17.1, 14.0; HRMS *m/z* 217.1589 (calc'd for $C_{15}H_{21}O$ $[M+H]^+$, 217.1592).



1.8b

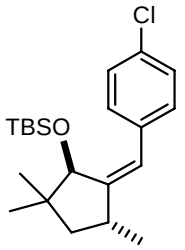
***trans*-1-*tert*-Butyldimethylsiloxy-3,5,5-trimethyl-2*Z*-trimethylsilylvinylidenecyclopentane (1.8b).** The title compound was prepared from enyne **1.8a** (162 mg, 0.50 mmol) according to the procedure described for **1.1b** (colorless liquid, 141 mg, 0.45 mmol, 91%): R_f 0.87 (hexanes); IR (thin film) ν 1636, 1249, 1079 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, J = 2.4 Hz, 1H), 3.90 (s, 1H), 2.86-2.75 (m, 1H), 1.99 (dd, J = 11.8, 11.8 Hz, 1H), 1.02 (s, 3H), 1.00 (s, 3H), 0.85 (s, 9H), 0.72 (s, 3H), 0.11 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 118.7, 82.6, 44.7, 40.5, 35.8, 28.0, 25.8, 23.8, 19.1, 18.4, 0.6, -3.8, -4.3; HRMS *m/z* 327.2532 (calc'd for $C_{18}H_{38}OSi_2$ $[M+H]^+$, 327.2540).



1.9b

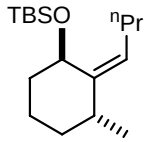
***trans*-2*Z*-Benzylidene-1-*tert*-butyldimethylsiloxy-3,5,5-trimethylcyclopentane (1.9b).** The title compound was prepared from enyne **1.9b** (164 mg, 0.50 mmol) according to the procedure described for **1.1b** (colorless liquid, 122 mg, 0.39 mmol, 74%): R_f 0.74

(hexanes); IR (thin film) ν 3024, 1252, 1068, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (m, 5H), 6.30 (d, J = 3.60 Hz, 1H), 4.48 (s, 1H), 3.02-2.91 (m, 1H), 2.15 (dd, J = 12.0, 12.0 Hz, 1H), 1.20 (d, J = 8.8 Hz, 3H), 1.10 (dd, J = 8.0, 16.0 Hz, 1H), 1.07 (s, 3H), 0.98 (s, 3H), 0.80 (s, 9H), -0.30 (s, 3H), -0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 138.8, 128.5, 128.1, 126.2, 121.9, 79.1, 45.4, 41.6, 34.5, 28.1, 25.8, 23.7, 20.0, 18.2, -4.9, -5.4; HRMS *m/z* 330.2374 (calc'd for $C_{21}H_{34}OSi$ $[M]^+$, 330.2379).



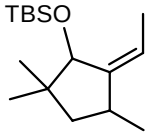
1.10b

***trans*-1-*tert*-Butyldimethylsiloxy-2*Z*-(4-chlorophenyl)vinylidene-3,5,5-trimethylcyclopentane (1.10b).** The title compound was prepared from enyne **1.10a** (360 mg, 0.99 mmol) according to the procedure described for **1.1b** (colorless liquid, 221 mg, 0.64 mmol, 65%): R_f 0.70 (hexanes); IR (thin film) ν 1254, 1073, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 7.18-7.13 (m, 2H), 6.19 (d, J = 2.7 Hz, 1H), 4.36 (s, 1H), 2.98-2.87 (m, 1H), 2.10 (dd, J = 12.0, 12.0 Hz, 1H), 1.15 (d, J = 7.2 Hz, 3H), 1.06 (dd, J = 5.1, 12.7 Hz, 1H), 1.03 (s, 3H), 0.92 (s, 3H), 0.77 (s, 9H), -0.30 (s, 3H), -0.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 137.2, 131.9, 129.7, 128.3, 120.7, 79.1, 45.2, 41.6, 34.6, 28.0, 35.7, 23.6, 19.9, 18.2, -4.8, -5.2; HRMS *m/z* 364.1980 (calc'd for $C_{21}H_{33}OSiCl$ $[M]^+$, 364.1989).



1.13b

***trans*-1-*tert*-Butyldimethylsiloxy-2*Z*-butylidene-3-methylcyclohexane (1.13b).** The title compound was prepared from enyne **1.13a** (140 mg, 0.50 mmol) according to the procedure described for **1.1b** (colorless liquid, 79 mg, 0.30 mmol, 59%): R_f 0.83 (hexanes); IR (thin film) ν 1254, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (ddd, J = 1.7, 7.2, 7.2 Hz, 1H), 4.75 (dd, J = 2.9, 2.9 Hz, 1H), 2.57-2.45 (m, 1H), 2.03 (app dq, J = 3.8, 4.8, 13.3 Hz), 1.84-1.70 (m, 2H), 1.53-1.19 (m, 5H), 0.95-0.87 (m, 6H), 0.88 (s, 9H), 0.04 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 118.8, 66.1, 37.6, 35.8, 32.1, 29.1, 25.8, 23.4, 20.4, 18.3, 18.0, 13.9, -4.7, -4.9; HRMS *m/z* 283.2449 (calc'd for $C_{17}H_{35}OSi$ $[M+H]^+$, 283.2457).



1.15b

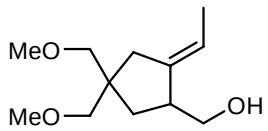
1-*tert*-Butyldimethylsiloxy-2*Z*-ethylidene-3,5,5-trimethylcyclopentane (1.15b). The title compound was prepared from enyne **1.15a** (133 mg, 0.50 mmol) according to the procedure described for **1.1b** as an inseparable mixture of *cis*/*trans* isomers (1:1.5 dr) (colorless liquid, 111 mg, 0.44 mmol, 88%):

trans: R_f 0.87 (hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (dq, J = 2.39, 6.84 Hz, 1H), 4.05 (s, 1H), 2.76-2.64 (m, 1H), 1.97 (dd, J = 10.94, 12.31 Hz, 1H), 1.71 (dd, J = 2.74, 6.84 Hz, 3H), 1.03 (d, J = 6.84 Hz, 3H), 1.00 (s, 3H), 0.95 (dd, J = 5.47, 12.31 Hz, 1H),

0.87 (s, 9H), 0.77 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 115.5, 79.5, 45.5, 41.2, 34.0, 27.8, 25.9, 23.6, 19.6, 18.3, 15.0, -4.4, -4.5; HRMS *m/z* 269.2293 (calc'd for $C_{16}H_{33}OSi$ $[M+H]^+$, 269.2301)

cis: R_f 0.87 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (ddq, J = 0.7, 1.7, 6.8 Hz, 1H), 3.94 (s, 1H), 2.52-2.39 (m, 1H), 1.70 (dd, J = 1.7, 6.8 Hz, 3H), 1.52 (dd, J = 8.2, 12.0 Hz, 1H), 1.40 (dd, J = 8.6, 12.3 Hz, 1H), 1.10 (d, J = 7.2 Hz, 3H), 1.01 (s, 3H), 0.88 (s, 9H), 0.73 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 118.8, 78.7, 44.9, 43.0, 36.1, 25.9, 25.4, 23.8, 23.4, 18.3, 15.5, -4.2, -4.6.

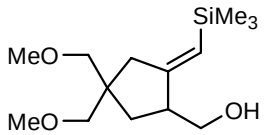
5.4 BORON-MEDIATED OXIDATION OF ZIRCONOCYCLOPENTENES



1.1c

3*E*-Ethylidene-4-hydroxymethyl-1,1-bis(methoxymethyl)cyclopentane (1.1c). To a solution of Cp_2ZrCl_2 (306 mg, 1.05 mmol) in THF (3 mL) cooled to -78 °C, was added *n*-BuLi (0.81 mL, 2.71 M, 2.20 mmol) and the dry ice bath was removed. The reaction mixture was allowed to warm until homogenous (~0 °C), at which point the mixture was cooled to - 78 °C. A solution of enyne **1.1a** (0.190 mg, 0.97 mmol) in THF (1.5 mL) was added via cannula, and the dry ice bath was replaced with an ice bath. After 1h the ice bath was removed and the reaction mixture was allowed to warm to rt. Neat $(^cHex)_2BCl$ (0.50 mL, 2.3 mmol) was added 12 h later by syringe. After 5 h the borane was oxidized

by successive treatment with aqueous NaOH (2 mL, 7.5M, 15 mmol) and H_2O_2 (2 mL, 30%) using a water bath to control the exotherm. The reaction mixture was then heated at 50 °C for 1h, allowed to cool, and the layers were separated. The aqueous layer was extracted with EtOAc and the extracts were washed with Na_2SO_3 (10%), $NaHCO_3$ (sat'd) and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: hexanes to 30% EtOAc/hexanes) provided the title compound as a colorless oil (156 mg, 0.73 mmol, 75%): R_f 0.18 (30% EtOAc/hexanes); IR (thin film) ν 3386 (br), 1198, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (dddq, J = 2.1, 2.4, 2.4, 6.8 Hz, 1H), 3.58 (d, J = 5.5 Hz, 2H), 3.32 (s, 3H), 3.30 (s, 3H), 3.30 (d, J = 8.9 Hz, 1H), 3.26 (d, J = 8.9 Hz, 1H), 3.17 (d, J = 11.1 Hz, 1H), 3.15 (d, J = 11.1 Hz, 1H), 2.72-2.61 (m, 1H), 2.23 (d, J = 16.7 Hz, 1H), 2.07 (dd, J = 2.1, 16.7 Hz, 1H), 1.81 (dd, J = 7.5, 13.0 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.36 (dd, J = 9.2, 13.0 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 116.8, 77.4, 75.3, 65.4, 59.3, 46.1, 44.6, 35.7, 34.4, 14.7; HRMS *m/z* 215.1651 (calc'd for $C_{12}H_{23}O_3$ $[M+H]^+$, 215.1647).

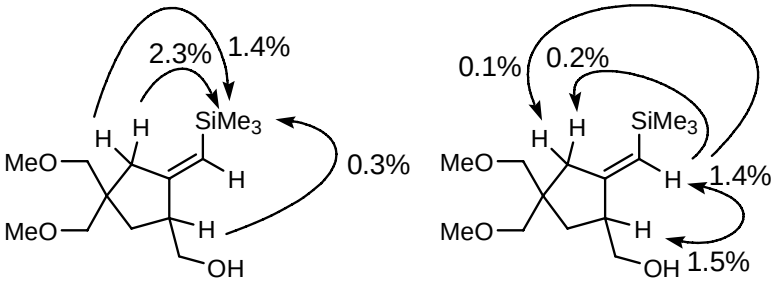


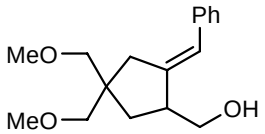
1.2c

3*E*-trimethylsilylvinylidine-4-hydroxymethyl-1,1-bis(methoxymethyl)cyclopentane (1.2c). The title compound was prepared from enyne **1.2**a (250 mg, 0.98 mmol) according to the procedure described for **1.1c** except a solution of NaOOH prepared from NaOH (2 mL, 6 M, 12 mmol) and H_2O_2 (4 mL, 30%, 35 mmol) was used for oxidation (colorless liquid, 171 mg, 0.63 mmol, 64%): R_f 0.30 (25% EtOAc/hexanes); IR (thin film) ν 3447

(br), 1653, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (ddd, J = 1.8, 2.1, 2.1 Hz, 1H), 3.68-3.58 (m, 2H), 3.35 (s, 3H), 3.33 (s, 3H), 3.30 (s, 2H), 3.20 (d, J = 12.6 Hz, 1H), 3.17 (d, J = 12.6 Hz, 1H), 2.74-2.62 (m, 1H), 2.35 (d, J = 16.4 Hz, 1H), 2.21 (dd, J =2.05, 16.4 Hz, 1H), 1.82 (dd, J = 8.7, 13.3 Hz, 1H, 1.74 (br s, 1H), 1.43 (dd, J = 8.7, 13.3 Hz, 1H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 121.0, 77.1, 75.2, 65.4, 59.2, 59.2, 47.6, 46.4, 39.2, 33.6, -0.3; HRMS *m/z* 271.1725 (calc'd for $C_{14}H_{27}O_3Si$ $[M-H]^+$, 271.1730).

GOESY:

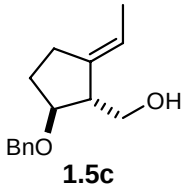




1.4c

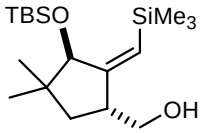
3*E*-Benzylidene-4-hydroxymethyl-1,1-bis(methoxymethyl)cyclopentane (1.4c). The title compound was prepared from enyne **1.4a** (256 mg, 0.99 mmol) according to the procedure described for **1.1c** (colorless oil, 227 mg, 0.82 mmol, 83%): R_f 0.20 (25% EtOAc/hexanes); IR (thin film) ν 3417 (br),1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 4H), 7.22-7.15 (m, 1H), 6.37 (s, 1H), 5.73 (d, J = 5.8 Hz, 2H), 3.39-3.31 (m, 2H), 3.36 (s, 3H), 3.28 (s, 3H), 3.17 (s, 2H), 2.98-2.87 (m, 1H), 2.60 (d, J = 17.1 Hz,

1H), 2.50 (d, J = 17.1 Hz, 1H), 1.99 (br s, 1H), 1.90 (dd, J = 8.6, 13.0 Hz, 1H), 1.47 (dd, J = 8.9, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 137.9, 128.4, 128.1, 126.1, 123.0, 77.1, 75.3, 65.9, 59.2, 59.2, 47.3, 46.6, 37.9, 33.3; HRMS *m/z* 277.1812 (calc'd for $C_{17}H_{25}O_3$ $[M+H]^+$, 277.1804).



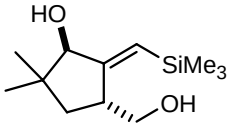
1.5c

***trans*-1-Benzyloxy-3*E*-ethylidene-2-hydroxymethylcyclopentane (1.5c).** The title compound was prepared from enyne **1.5a** (211 mg, 0.99 mmol) according to the procedure described for **1.1c** except transmetallation time was extended to 28 h (colorless oil, 147 mg, 0.63 mmol, 64%): R_f 0.37 (25% EtOAc/hexanes); IR (thin film) ν 3418 (br), 3031, 1095, 735, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 5.31 (dddq, J = 2.1, 2.3, 2.6, 6.7 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 3.87 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 3.70 (dd, J = 4.9, 10.8 Hz, 1H), 2.70-2.59 (m, 1H), 2.51-2.36 (m, 1H), 2.25-2.10 (m, 1H), 2.09-1.92 (m, 1H), 1.78-1.65 (m, 1H), 1.65-1.57 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 138.4, 128.4, 127.6, 127.6, 117.2, 82.9, 71.1, 63.8, 51.9, 29.4, 26.1, 14.3; HRMS *m/z* 233.1542 (calc'd for $C_{15}H_{21}O_2$ $[M+H]^+$, 233.1542).



1.8c

***trans*-1-*tert*-Butyldimethylsiloxy-3-hydroxymethyl-5,5-dimethyl-2*Z*-trimethylsilylvinylidenecyclopentane (1.8c).** The title compound was prepared from enyne **1.8a** (315 mg, 0.97 mmol) according to the procedure described for **1.1c** except a solution of NaOOH prepared from NaOH (2 mL, 6 M, 12 mmol) and H_2O_2 (4 mL, 30%, 35 mmol) was used for oxidation (white solid, 170 mg, 0.52 mmol, 54%): R_f 0.36 (10% EtOAc/hexanes); IR (thin film) ν 3318 (br), 1635, 1249, 1078 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 5.26 (d, J = 2.4 Hz, 1H), 3.90 (s, 1H), 3.79 (dd, J = 5.1, 10.9 Hz, 1H), 3.61 (dd, J = 6.5, 10.9 Hz, 1H), 3.02-2.91 (m, 1H), 1.92 (dd, J = 12.1, 12.1 Hz, 1H), 1.41 (br s, 1H), 1.24 (dd, J = 4.8, 12.7 Hz, 1H), 1.02 (s, 3H), 0.85 (s, 9H), 0.74 (s, 3H), 0.12 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 120.1, 82.9, 65.0, 43.8, 40.5, 39.3, 27.4, 25.8, 23.7, 18.4, 0.6, -3.8, -4.3; HRMS *m/z* 343.2459 (calc'd for $C_{18}H_{39}O_2Si_2$ $[M+H]^+$, 343.2489).

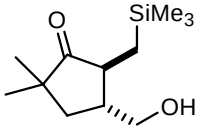


1.8g

***trans*-1-hydroxy-3-hydroxymethyl-5,5-dimethyl-2*E*-trimethylsilylvinylidenecyclopentane (1.8g).**

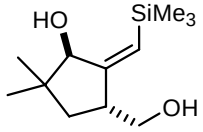
The title compound accompanied **1.8c** in the cyclization/oxidation reaction of enyne **1.8a** (white solid, 69 mg, 0.30 mmol, 31%): R_f 0.27 (30% EtOAc/hexanes); IR (thin film) ν

3276 (br), 1629, 1245, 1138 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 5.59 (dd, J = 2.2, 2.2 Hz, 1H), 3.86 (br s, 1H), 3.61 (dd, J = 4.8, 18.5 Hz, 1H), 3.58 (dd, J = 6.8, 18.5 Hz, 1H), 2.84-2.74 (m, 1H), 1.71 (dd, J = 8.9, 13.0 Hz, 1H), 1.39 (dd, J = 8.6, 13.0 Hz, 1H), 1.65-1.44 (br s, 2H), 1.10 (s, 3H), 0.68 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 120.0, 82.9, 67.1, 40.5, 40.0, 38.9, 26.4, 19.6, 0.1; HRMS *m/z* 227.1472 (calc'd for $C_{12}H_{23}O_2Si$ $[M-H]^+$, 227.1467).



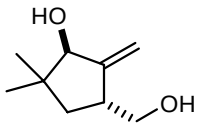
1.8h

***trans*-2-trimethylsilylmethyl-3-hydroxymethyl-5,5-dimethylcyclopentanone (1.8h).** A solution of diol **1.8g** (12 mg, 0.053 mmol) in $CDCl_3$ (0.75 mL) was allowed to stand at rt for 3 d. Concentration and flash chromatography of the residue on SiO_2 (elution gradient: 5% EtOAc/hexanes to 30 % EtOAc/hexanes) provided the title compound as a white solid (11 mg, 0.48 mmol, 91%): R_f 0.41 (30% EtOAc/hexanes); IR (thin film) ν 3458 (br), 1737, 1248 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 3.84 (dd, J = 3.3, 10.8 Hz, 1H), 3.64 (dd, J = 5.6, 10.8 Hz, 1H), 2.11-1.8 (m, 3H), 1.52 (ddd, J = 2.6, 12.8, 12.8 Hz, 1H), 1.60-1.45 (br s, 1H), 1.08 (s, 3H), 1.00 (s, 3H), 0.81 (dd, J= 7.9, 14.9 Hz, 1H), 0.69 (dd, J = 4.4, 14.9 Hz, 1H) 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 224.0, 64.7, 47.2, 44.7, 43.9, 40.1, 25.4, 25.0, 16.5, -0.7; HRMS *m/z* 228.1548 (calc'd for $C_{12}H_{24}O_2Si$ $[M]^+$, 228.1546).



1.8f

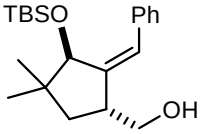
***trans*-1-hydroxy-3-hydroxymethyl-5,5-dimethyl-2*Z*-trimethylsilylvinylidinecyclopentane (1.8f).** To a solution of TBS ether **1.8c** (0.072 g, 0.21 mmol) in MeOH (4 mL) was added HF•pyridine (1.2 mL, 20%, 2.4 mmol) at rt. The reaction mixture was heated to 60 °C and after 24 h was allowed to cool to rt. Aqueous $NaHCO_3$ (15 mL, sat'd) was added and the resulting mixture was extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: 5% EtOAc/hexanes to 30% EtOAc/hexanes) provided the title compound as a white solid (16 mg, 0.070 mmol, 33%). The starting silyl ether was also recovered (14 mg, 0.041 mmol, 19%): R_f 0.44 (30% EtOAc/hexanes); IR (thin film) ν 3385 (br), 1626, 1246, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55 (dd, J = 2.4, 2.4 Hz, 1H), 4.00 (app d, J = 7.9 Hz, 1H), 3.62 (app d, J = 5.3 Hz, 1H), 2.75-2.65 (m, 1H), 1.88 (dd, J = 8.9, 13.0 Hz, 1H), 1.38 (br s, 1H), 1.35 (dd, J = 9.6, 13.0 Hz, 1H), 1.03 (s, 3H), 0.85 (s, 3H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.6, 83.1, 66.0, 44.2, 40.5, 39.2, 26.7, 20.4, 0.7; HRMS *m/z* 229.1624 (calc'd for $C_{12}H_{25}O_2Si$ $[M+H]^+$, 227.1467).



1.8i

***trans*-1-hydroxy-3-hydroxymethyl-5,5-dimethylvinylidenecyclopentane (1.8i).**

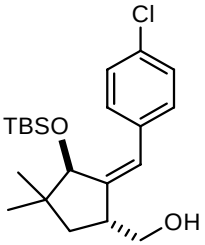
The title compound accompanied **1.8f** in the deprotection of TBS ether **1.8c** (15 mg, 0.096 mmol, 46%): R_f 0.16 (30% EtOAc/hexanes); IR (thin film) ν 3349, 1662, 1092, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (dd, J = 2.7, 2.7 Hz, 1H), 5.07 (dd, J = 2.7, 2.7 Hz, 1H), 3.94 (br s, 1H), 3.62 (dd, J = 6.2, 10.6 Hz, 1H), 3.53 (dd, J = 5.8, 10.9 Hz, 1H), 2.75-2.64 (m, 1H), 1.67 (dd, J = 8.5, 13.0 Hz, 1H), 1.52 (br s, 1H), 1.40 (br s, 1H), 1.27 (dd, J = 9.6, 13.0 Hz, 1H), 1.08 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 107.8, 82.2, 66.2, 41.2, 40.5, 38.6, 26.2, 19.5; HRMS *m/z* 155.1072 (calc'd for $C_{12}H_{25}O_2Si$ $[M+H]^+$, 155.1072).



1.9c

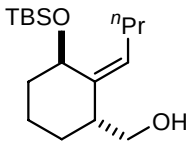
***trans*-2*Z*-Benzylidene-1-*tert*-butyldimethylsiloxy-3-hydroxymethyl-5,5-dimethylcyclopentane (1.9c).** The title compound was prepared from enyne **1.9a** (322 mg, 0.98 mmol) according to the procedure described for **1.1c** (colorless oil, 239 mg, 0.72 mmol, 74%): R_f 0.30 (15% EtOAc/hexanes); IR (thin film) ν 3436, 1255, 1067, 734, 650 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 7.26-7.18 (m, 3H), 6.43 (d, J = 2.4 Hz, 1H), 4.49 (s, 1H), 3.91 (dd, J = 5.1, 10.60 Hz, 1H), 3.72 (dd, J = 10.6, 7.2 Hz, 1H), 3.11 (m, 1H), 2.07 (dd, J = 12.0, 12.0 Hz, 1H), 1.90 (br s, 1H), 1.43 (dd, J = 4.1,

12.7 Hz, 1H), 1.09 (s, 3H), 0.99 (s, 3H), 0.79 (s, 9H), -0.33 (s, 3H), -0.35 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 138.1, 128.5, 128.1, 126.5, 122.8, 79.3, 65.8, 42.5, 41.6, 40.0, 27.4, 25.7, 23.5, 18.1, -5.0, -5.5; HRMS *m/z* 347.2398 (calc'd for $C_{21}H_{35}O_2Si$ $[M+H]^+$, 347.2406).



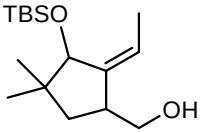
1.10c

***trans*-1-*tert*-Butyldimethylsiloxy-2*Z*-(4-chlorophenyl)vinylidene-3-hydroxymethyl-5,5-dimethylcyclopentane (1.10c).** The title compound was prepared from enyne **1.10a** (360 mg, 0.99 mmol) according to the procedure described for **1.1c** (colorless oil, 227 mg, 0.62 mmol, 63%): R_f 0.57 (25% EtOAc/hexanes); IR (thin film) ν 3329 (br), 1383, 1361, 1254, 1071 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.36 (d, J = 2.3 Hz, 1H), 4.38, (s, 1H), 3.87 (dd, J = 5.4, 10.5 Hz, 1H), 3.70 (dd, J = 6.9, 10.5 Hz, 1H), 3.14-3.02 (m, 1H), 2.04 (dd, J = 12.0, 12.0 Hz, 1H), 1.53 (br s, 1H), 1.37 (dd, J = 4.6, 13.1 Hz, 1H), 1.05 (s, 3H), 0.94 (s, 3H), 0.76 (s, 9H), -0.31 (s, 3H), -0.38 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 150.4, 136.6, 132.2, 129.8, 128.3, 121.5, 79.3, 65.8, 42.6, 41.6, 39.9, 27.4, 25.7, 23.4, 18.1, -4.9, -5.2; HRMS *m/z* 380.1948 (calc'd for $C_{21}H_{33}O_2SiCl$ $[M]^+$, 380.1938).



1.13c

***trans*-2*Z*-Butylidene-1-*tert*-butyldimethylsiloxy-3-hydroxymethylcyclohexane (1.13c).** The title compound was prepared from enyne **1.13a** (276 mg, 0.99 mmol) according to the procedure described for **1.1c** (colorless oil, 147 mg, 0.62 mmol, 62%): R_f 0.32 (10% EtOAc/hexanes); IR (thin film) ν 3316 (br), 1252, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (dddd, J = 1.0, 7.2, 7.2, 7.2 Hz, 1H), 4.73 (ddd, 2.7, 2.7, 2.7 Hz, 1H), 3.77 (dd, J = 6.5, 10.6 Hz, 1H), 3.54 (dd, J = 6.2, 10.6 Hz, 1 H), 2.66-2.56 (m, 1H), 2.03 (app dq, J = 1.0, 7.4 Hz, 2H), 1.96-1.75 (m, 3H), 1.53-1.45 (m, 1H), 1.43-1.22, (m, 4H), 1.01-0.92 (m, 1H) 0.88 (dd, J = 3.4, 3.4 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 119.3, 65.9, 64.9, 40.1, 35.9, 31.9, 29.1, 25.8, 23.3, 20.0, 18.0, 13.9, -4.6, -4.9; HRMS *m/z* 299.2406 (calc'd for $C_{17}H_{35}O_2Si$ $[M+H]^+$, 299.2406).

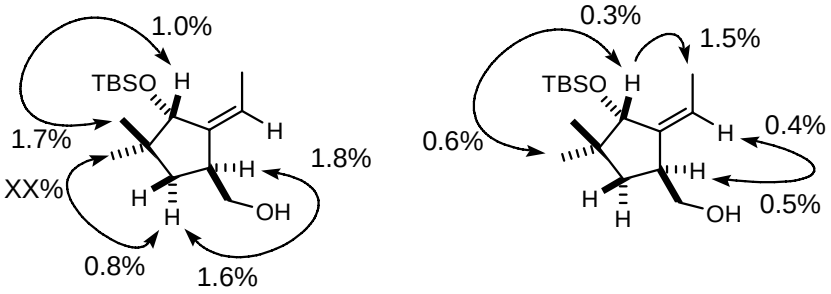


1.15c

1-*tert*-Butyldimethylsiloxy-2*Z*-ethylidine-3-hydroxymethyl-5,5-dimethylcyclopentane (1.15c). The title compound was prepared from enyne **1.15**a (262 mg, 0.98 mmol) according to the procedure described for **1.1c** as a mixture of *cis*/*trans* isomers (1:1.5 dr) (colorless oil, 213 mg, 0.79 mmol, 81%):

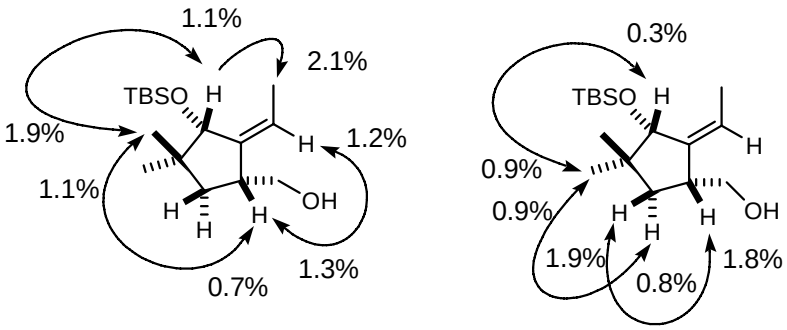
trans: R_f 0.63 (25% EtOAc/hexanes); IR (thin film) ν 3332 (br),1382, 1361, 1251, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (q, J = 6.9 Hz, 1H), 4.05 (s, 1H), 3.72 (dd, J = 5.1, 10.5 Hz, 1H), 3.55 (dd, J = 6.7, 10.5 Hz, 1H), 2.89-2.75 (m, 1H), 1.87 (dd, J = 11.0, 12.8 Hz, 1H), 1.70 (dd, J = 2.6, 6.9 Hz, 3H), 1.44 (br s, 1H), 1.24 (dd, J = 5.4, 12.8 Hz), 0.98 (s, 3H), 0.85 (s, 9H), 0.77 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 145.8, 117.0, 79.9, 65.7, 42.2, 41.2, 39.8, 27.2, 25.8, 23.3, 18.2, 14.9, -4.36, -4.44; HRMS *m/z* 285.2246(calc'd for $C_{16}H_{33}O_2Si$ $[M+H]^+$, 285.2250).

GOESY:

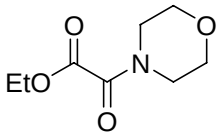


cis: R_f 0.73 (25% EtOAc/hexanes); IR (thin film) ν 3354 (br),1382, 1360, 1251, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.44 (q, J = 6.9 Hz, 1H), 3.96 (s, 1H) 3.60 (dd, J = 4.4, 9.7 Hz, 1H), 3.54-3.46 (m, 1H), 2.72-2.61 (m, 1H), 2.39 (br s, 1H), 1.73-1.63 (m, 4H), 1.45 (dd, J = 9.0, 12.8 Hz, 1H), 1.01 (s, 3H), 0.86 (s, 9H), 0.76 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 121.6, 78.3, 66.7, 44.3, 42.9, 38.0, 26.0, 25.9, 23.3, 18.2, 15.6, -4.2, -4.5; HRMS *m/z* 285.2250 (calc'd for $C_{16}H_{33}O_2Si$ $[M+H]^+$, 285.2250).

GOESY:

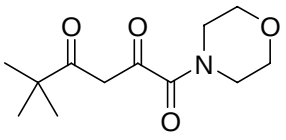


5.5 MODP LIGAND AND COBALT CATALYST SYNTHESIS



2.24

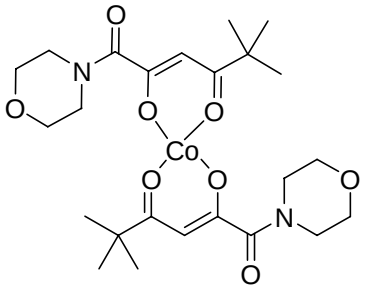
Ethylmorpholine glyoxylate (2.24). Ethyl oxalyl chloride (11.4 mL, 100 mmol, 1 eq) was added dropwise to a solution of morpholine (9.2 mL, 105 mmol, 1.05 eq) and Et_3N (14.5 mL, 105 mmol, 1.05 eq) in CH_2Cl_2 (200 mL) at 0 °C. The reaction mixture was allowed to warm to rt and after 16 h was washed with HCl (1 N), $NaHCO_3$ (sat'd) and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated, providing the title compound as an oil (18.0 g, 96%) which was used without further purification.



2.25

Morpholine 5,5-dimethyl-2,4-dioxohexanamide (2.25). A solution of *t*-BuOK (23 g, 205 mmol 2.1 eq) in THF (180 mL) was added via cannula to a solution of pinacolone (12 mL, 96 mmol, 1.0 eq) and amide **2.24** (18 g, 96 mmol, 1.0 eq) in THF (40 mL) over

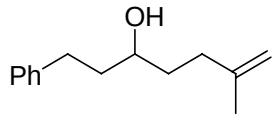
40 min at rt. After 3 h, AcOH (20 mL, 350 mmol, 3.6 eq) was added over 5 min and the resulting heterogeneous mixture was filtered and the solids were washed with CH_2Cl_2. The filtrate was washed with $NaHCO_3$ and brine, dried, filtered and concentrated. Purification of the resulting oil by flash chromatography (SiO_2, 50% EtOAc/hexanes) provided the title compound as a slightly yellow solid (18.1 g, 78%).



2.26

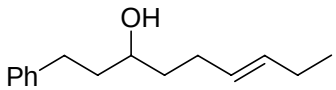
Co(modp)$_2$ (CoII(modp)2 (2.26**).** Cobalt(II) 2-ethylhexanoate (19.8 mL, 1.88 M in mineral spirits, 37 mmol, 1.0 eq) was added at rt over 10 min to a solution of ligand Error! Reference source not found. (18 g, 75 mmol, 2.0 eq) in benzene (200 mL). After 16 h hexanes was added until no additional solids precipitated and the reaction mixture was centrifuged. The supernatant layer was decanted and the solids were washed with hexanes and centrifuged an additional four times. Removal of the residual solvent under reduced pressure provided Co(modp)$_2$ as a tan solid (18.9 g, 95%).

5.6 SYNTHESIS AND COBALT-MEDIATED OXIDATION OF 4-ALKENOLS



2.28a

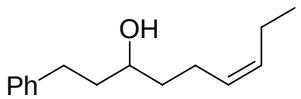
6-Methyl-1-phenylhept-6-en-3-ol (2.28a), The title compound was prepared from 2-methyl-4-bromobut-1-ene (4.6 g, 31 mmol) according to the procedure described for **2.29** except the crude product was purified by vacuum distillation (96-98 °C, 0.8 mm Hg) to give a colorless oil (1.74 g, 8.0 mmol, 61%): R_f 0.53 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.21-7.14 (m, 3H), 4.71 (app s, 1H), 4.70 (app s, 1H), 3.64 (dddd, J = 4.4, 4.4, 7.9, 7.9, 1H), 2.84-2.73 (m, 1H), 2.71-2.61 (m, 1H), 2.21-2.01 (m, 2H), 1.81-1.75 (m, 2H), 1.72 (s, 3H), 1.66-1.56 (m, 2H), 1.55 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 142.1, 128.3, 125.7, 110.1, 71.1, 39.0, 35.2, 33.9, 32.0, 22.4; HRMS *m/z* 205.1594 (calc'd for $C_{14}H_{21}O$ $[M+H]^+$, 205.1592).



2.29a

***E*-1-Phenylnon-6-en-3-ol (2.29a).** To a suspension of Mg (2.3 g, 96 mmol) in Et_2O (30 mL) was added 1,2-dibromoethane (0.50 mL, 5.8 mmol) and the resulting mixture was heated to reflux. After 30 min, a solution of *E*-1-bromohex-3-ene (6.5 g, 40 mmol) in Et_2O (10 mL) was added dropwise. After 30 min, hydrocinnamaldehyde (4.4 mL, 33 mmol) was added dropwise. After addition, the reaction mixture was allowed to cool to rt

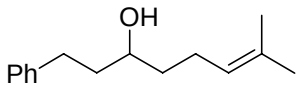
and aqueous NH_4Cl (20 mL, sat'd) was added carefully. The reaction mixture was filtered and the filtrate was washed with $NaHCO_3$ (sat'd) and brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography on SiO_2 (elution gradient: 10% EtOAc/hexanes to 30% EtOAc/hexanes), providing the title compound as a white solid (3.24 g, 15 mmol, 54%): R_f 0.46 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m 2H), 5.54 (ddd, J = 6.2, 6.2, 15.4 Hz, 1H), 5.45 (J = 1.4, 1.4, 6.2, 6.2, 15.4 Hz, 1H), 2.84 (ddd, J = 5.8, 9.6, 13.7 Hz, 1H), 2.71 (6.8, 9.2, 13.7 Hz, 1H), 2.24-2.00 (m, 5H), 1.88-1.73 (m, 2H), 1.66-1.51 (m, 2H), 1.02 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 132.9, 129.0, 128.71, 128.67, 126.1, 71.2, 39.4, 37.5, 32.3, 29.2, 25.9, 14.2; HRMS *m/z* 219.1746 (calc'd for $C_{15}H_{23}O$ $[M+H]^+$, 219.1749).



2.30a

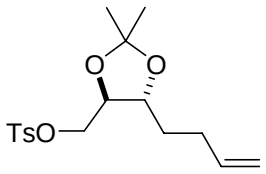
***Z*-1-Phenylnon-6-en-3-ol (2.30a).** The title compound was prepared from *Z*-1-bromohex-3-ene (5.4 g, 33 mmol) according to the procedure described for **2.29** (white solid, 3.6 g, 16 mmol, 50%): R_f 0.50 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 7.22-7.15 (m, 3H), 5.40 (ddd, J = 6.8, 6.8, 10.9 Hz, 1H), 5.33 (ddd, J = 7.2, 7.2, 10.9 Hz, 1H), 2.79 (ddd, J = 6.2, 9.9, 13.7 Hz, 1H), 2.66 (ddd, J = 6.8, 9.6, 13.7 Hz, 1H), 2.23-1.99 (m, 4H), 1.84-1.68 (m, 2H), 1.59 (br s, 1H), 1.58-1.46 (m, 2H), 0.95 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 132.3, 128.44,

128.36, 125.8, 71.1, 39.1, 37.4, 32.0, 23.4, 20.5, 14.3; HRMS *m/z* 219.1740 (calc'd for $C_{15}H_{23}O$ $[M+H]^+$, 219.1749).



2.31a

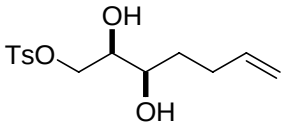
7-Methyl-1-phenyl-oct-6-en-3-ol (2.31a). The title compound was prepared from 2-methyl-5-bromopent-2-ene (6.5 g, 40 mmol) according to the procedure described for **2.29** (colorless oil, 1.7 g, 8.0 mmol, 42%): R_f 0.55 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.24 (m, 2H), 7.22-7.13 (m, 3H), 5.12 (dd, J = 7.4, 7.4 Hz, 1H), 3.63 (br s, 1H), 2.79 (ddd, J = 6.9, 9.7, 13.8 Hz, 1H), 2.65 (ddd, J = 6.9, 9.0, 13.6 Hz, 1H), 2.08 (app dddd, J = 7.9, 7.9, 15.1, 15.1 Hz, 2H), 1.80-1.70 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.56-1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 132.2, 128.40, 128.37, 125.8, 124.0, 71.2, 39.1, 37.4, 32.1, 25.7, 24.4, 17.7; HRMS *m/z* 219.1745 (calc'd for $C_{15}H_{23}O$ $[M+H]^+$, 219.1749).



2.101

(4*R*,5*S*)-4-(but-3-enyl)-5-(*p*-toluenesulfonoxymethyl-2,2-dimethyl-[1,3]dioxolane (2.101). A solution of allylmagnesium bromide (50 mL, 1.0 M, 50 mmol) was added dropwise to a suspension of CuBr•SMe_2 (1.30 g, 6.0 mmol) in Et_2O (50 mL) at 0 °C.

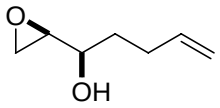
After 30 min, a solution of triflate **2.47** (13.1 g, 30 mmol) in Et_2O (200 mL) was added dropwise. After 16 h, the reaction mixture was poured, cold, into a stirred aqueous solution of NH_4Cl (200 mL, sat'd) and the resulting mixture was allowed to warm to rt. After 45 min, the layers were separated and the aqueous layer was extracted with Et_2O. The combined extracts were washed with $NaHCO_3$ (sat'd) and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the crude material by flash chromatography on SiO_2 (elution gradient: 13% Et_2O/hexanes to 35% Et_2O/hexanes provided the title compound as a colorless oil (6.59 g, 20 mmol, 67%): R_f 0.48 (50% Et_2O/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 5.84-5.66 (m, 1H), 5.65-5.66 (m 2H), 4.08 (dd, J = 4.1, 11.0 Hz, 1H), 4.03 (dd, J = 4.1, 10.8 Hz, 1H), 3.84-3.72 (m, 2H), 2.42 (s, 3H), 2.24- 1.98) (m, 2H), 1.69-1.52 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 137.4, 132.6, 129.8, 127.9, 115.1, 109.4, 78.0, 77.1, 69.0, 32.1, 29.8, 27.2, 26.6, 21.6.



2.48

(2*R*,3*R*)-*2*,3-dihydroxy-1-(*p*-toluene-4-sulfonoxy)hept-6-ene (2.48). To a rt solution of tosylate **(2.101** (6.59 g, 20 mmol) in THF (125 mL) was added aqueous HCl (125 mL, 3.0 N, 375 mmol) in one portion and the resulting mixture was heated to 35 °C. After 16 h, the reaction mixture was allowed to cool to rt and K_2CO_3 (65 g, 471 mmol) was carefully added in small portions. After gas evolution ceased, the layers were separated

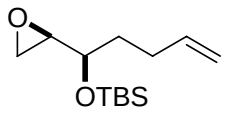
and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residual oil was purified by flash chromatography on SiO_2 (elution gradient: 25% EtOAc/hexanes to 50% EtOAc/hexanes) to provide the title compound as a colorless oil (5.82 g, 19 mmol, 97%): R_f 0.36 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 5.75 (dddd, J = 6.7, 6.7, 10.2, 16.9 Hz, 1H)< 6.02-4.89 (m, 2H), 4.07 (dd, J = 4.9, 10.5Hz, 1H), 4.02 (dd, J = 6.7, 10.5 Hz, 1H), 3.68 (ddd, J = 3.8, 3.8, 6.7 Hz, 1H), 3.57 (ddd, J = 3.8, 3.8, 8.2 Hz, 1H), 2.68, (br s, 2H) 2.41 (s, 3H), 2.24-2.19 (m, 2H), 1.66-1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 137.8, 132.3, 129.9, 127.9, 115.2, 71.4, 71.3, 70.1, 32.3, 29.6, 21.6.



2.102

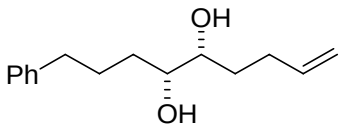
***(1'R,1R)*-1-Oxiranylpent-4-en-1-ol (2.102)**.A solution of diol tosylate **2.48** (7.9 g, 25 mmol) in MeOH (65 mL) was added dropwise at rt to a suspension of anhydrous K_2CO_3 (10.9 g, 79 mmol) in MeOH (25 mL). After 1 h, the reaction mixture was poured into a stirred aqueous solution of NH_4Cl (100 mL, sat'd). The mixture was extracted with Et_2O and the combined extracts were washed with NH_4Cl (sat'd), $NaHCO_3$ (sat'd) and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the crude material by vacuum distillation (50-52 °C, 0.2 mm Hg) provided the title compound as a colorless liquid (2.7 g, 21 mmol, 84%): R_f 0.39 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dddd, J = 6.7, 6.7, 10.0, 16.9 Hz, 1H), 5.01 (dddd, J = 1.5, 1.5, 1.5, 17.2 Hz, 1H), 4.99

(dd, J = 1.3, 10.2 Hz, 1H), 3.34 (ddd, 5.6, 5.6, 10.8 Hz, 1H), 2.95 (ddd, J = 2.8, 4.6, 7.2 Hz, 1H), 2.78 (dd, J = 4.6, 4.6 Hz, 1H), 2.67 (dd, J = 2.6, 4.9, 1H), 2.32 (br s, 1H), 2.26-2.06 (m, 2H), 1.76-1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 115.1, 71.0, 55.3, 45.1, 33.3, 29.4.



2.49

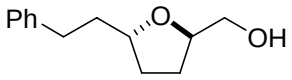
***(*1'*R*,1*R*)-1-oxiranyl-1-*tert*-butyldimethylsiloxypent-4-ene (2.49).** A mixture of TBSCl (2.85 g, 19 mmol) and imidazole (2.92 g, 43 mmol) was dissolved in DMF (5 mL) at rt. A solution of epoxy alcohol **2.102** (2.21 g, 17.2 mmol) in DMF (4 mL) was added dropwise via cannula. After 5 h, the reaction mixture was diluted with water (50 mL) and extracted with Et_2O. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the crude material by flash chromatography on SiO_2 (elution gradient: hexanes to 5% EtOAc/hexanes provide the title compound as a colorless oil (3.82 g, 16 mmol, 92%): R_f 0.28 (5% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dddd, J = 6.5, 6.5, 9.9, 16.7 Hz, 1H), 5.02 (dddd, J = 1.4, 1.4, 1.4, 17.1 Hz, 1H), 4.97 (dddd, J = 1.4, 1.4, 1.4, 10.6 Hz, 1H), 3.27 (ddd, J = 5.5, 6.8, 7.5 Hz, 1H), 2.92 (ddd, J = 2.7, 4.1, 6.8 Hz, 1H), 2.78 (dd, J = 4.1 5.1 Hz, 1H), 2.34 (dd, J = 2.7, 4.8 Hz, 1H), 2.25-2.03 (m, 2H), 1.71-1.34 (m, 2H), 0.91 (s, 9H), 0.12 (s, 3H), 0.06 (s. 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 114.8, 74.0, 55.8, 44.8, 33.9, 29.4 25.8, 18.1, -4.4, -5.0; HRMS *m/z* 243.1780 (calc'd for $C_{13}H_{27}O_2Si$ $[M+H]^+$, 243.1778).



2.46a

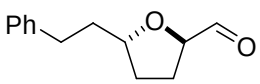
(4*R*,5*R*)-1-Phenylnon-8-ene-4,5-diol (2.46a). To a suspension of Mg (1.34 g, 56 mmol) in Et_2O (15 mL) was added 1,2-dibromoethane (0.43 mL, 5.0 mmol) at rt and the reaction mixture was heated to reflux. After 30 min, a solution of 2-bromoethylbenzene (3.84 mL, 28 mmol) in Et_2O (25 mL) was added dropwise. After 20 min and allowing the reaction mixture to cool to rt, the solution was added dropwise via cannula to a suspension of CuBr•SMe_2 (0.81 g, 3.9 mmol) at -30 °C, followed by dropwise addition of epoxide **2.49** (3.17 g, 13 mmol). After 3 h, aqueous NH_4Cl (20 mL, sat'd) was carefully added, followed by H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O. The organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was dissolved in THF (20 mL) and NBu_4F (20 mL, 1.0 M, 20 mmol) was added dropwise and the reaction mixture was allowed to warm to rt. After 12 h, H_2O (50 mL) was added and the mixture was extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: 30% EtOAc/hexanes to 50% EtOAc/hexanes) provided the title compound as a colorless oil (2.21 g, 9.5 mmol, 73%): R_f 0.37 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (m, 2H), 7.22-7.15 (m, 3H), 5.83 (dddd, J = 6.5, 6.5, 10.3, 16.8 Hz, 1H), 5.05 (dd, J = 1.0, 17.1 Hz, 1H), 4.99 (dd, J = 1.0, 10.3 Hz, 1H), 3.47-3.38 (m, 2H), 2.72-2.57 (m, 2H), 2.08 (br s, 2H), 1.90-1.76 (m, 1H), 1.76-1.64 (m, 1H), 1.63-1.43 (m, 4H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 142.1, 138.2, 128.4, 128.3, 125.8, 115.0, 74.3, 73.8, 35.8, 33.1, 29.9, 27.4; HRMS *m/z* 235.1697 (calc'd for $C_{15}H_{23}O_2$ $[M+H]^+$, 235.1697.



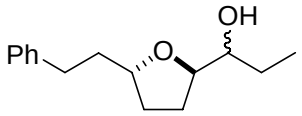
2.27b

***trans*-(5-Phenethyltetrahydrofuran-2-yl)-methanol (2.27b).** To a solution of **2.27a** (190 mg, 1.0 mmol, 1.0 eq) in *i*-PrOH (10 mL) under an atmosphere of O_2 was added $Co(Modp)_2$ (54 mg, 0.10 mmol, 0.10 eq) and *t*-BuOOH (0.28 mL, 3.57 M, 1.0 mmol, 1.0 eq) at rt. The reaction mixture was heated to 50 °C for 24 h and allowed to cool to rt. Concentration and purification of the residue by flash chromatography on SiO_2 (elution gradient: 25% EtOAc/hexanes to 30% EtOAc/hexanes) provided the title compound as a colorless liquid (170 mg, 82%): R_f 0.17 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 2H), 7.24-7.15 (m, 3H), 4.14 (dddd, J = 6.8, 10.0, 10.0, 10.0 Hz, 1H), 3.95 (dddd, J = 6.8, 6.8, 6.8, 6.8 Hz, 1H), 3.66 (app d, J = 10.4 Hz, 1H), 3.49 (dd, J = 6.0, 10.4 Hz, 1H), 2.75 (ddd, J = 5.6, 10.0, 14.0 Hz, 1H), 2.65 (ddd, J = 6.4, 9.6, 14.0 Hz, 1H), 2.09-1.85 (m, 4H), 1.81-1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 128.28, 128.26, 125.7, 78.9, 78.6, 64.9, 37.3, 32.4, 31.9, 24.4; HRMS *m/z* 205.1224 (calc'd for $C_{13}H_{17}O_2$ $[M+H]^+$, 205.1229).



2.103

***trans*-5-Phenethyltetrahydrofuran-2-carbaldehyde (2.103).** A solution of DMSO (0.40 mL, 6.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a -78 °C solution of oxalyl chloride (0.23 mL, 2.7 mmol) in CH_2Cl_2 (10 mL). After 30 min, a solution of alcohol **2.18b** (210 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture. After 45 min, Et_3N (1.3 mL, 9 mmol) was added and the reaction mixture was allowed to warm to rt. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residual oil by flash chromatography on SiO_2 (elution gradient: 30% EtOAc/hexanes to 40% EtOAc/hexanes) provided the title compound as a colorless oil (184 mg, 0.90 mmol, 89%): R_f 0.15 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, J = 2.1 Hz, 1H), 7.32-7.25 (m, 2H), 7.24-7.17 (m, 3H), 4.35 (ddd, J = 2.1, 6.8, 8.5 Hz, 1H), 4.03 (dddd, J = 5.5, 5.5, 7.9, 7.9 Hz, 1H), 2.79 (ddd, J = 5.5, 9.6, 13.7 Hz, 1H), 2.70 (ddd, J = 6.5, 9.6, 13.7 Hz, 1H), 2.25-2.16 (m, 2H), 2.08-1.91 (m, 3H), 1.87-1.77 (m, 1H), 1.63-1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 141.7, 128.4, 125.9, 82.4, 80.3, 37.0, 31.1, 27.2.

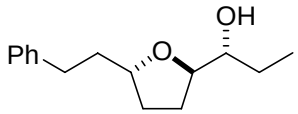


2.29b

***trans*-1-(5-Phenethyltetrahydrofuran-2-yl)-propan-1-ol (2.29b).** The title compound was prepared as a mixture of *syn*/*anti* diastereomers (dr: 1.2:1) from the corresponding *cis*-alkene (218 mg, 1.0 mmol) according to the general procedure described for **2.27b** (colorless liquid, 165 mg, 71%).

The title compound was also prepared as a mixture of *syn*/*anti* diastereomers (dr: 1.3:1) from the corresponding *trans*-alkene (218 mg, 1.0 mmol) according to the general procedure described for **2.27b** (colorless liquid, 125 mg, 53%).

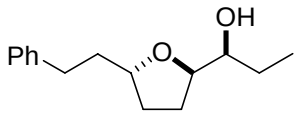
The title compound was also prepared as a mixture of *syn*/*anti* diasteromers (dr: 2:1) by dropwise addition of EtMgBr (1.0 mL, 3.0 M in Et_2O, 3.0 mmol) to a solution of aldehyde **2.103** (160 mg, 0.78 mmol) in Et_2O at 0 °C. After 1 h, aqueous NH_4Cl (5 mL, 50% sat'd) was added dropwise, the reaction mixture was allowed to warm to rt and the layers were separated. The aqueous layer was extracted with Et_2O and the combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash chromatography on SiO_2 (elution gradient: 25% EtOAc/hexanes to 30% EtOAc/hexanes), providing the title compound as a colorless liquid (172 mg, 93%):



2.29b-*syn*

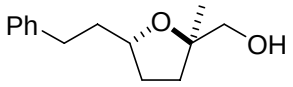
syn isomer: R_f 0.43 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H), 7.24-7.16 (m, 3H), 3.91 (dddd, J = 5.5, 5.5, 7.9, 7.4 Hz, 1H), 3.83 (ddd, J = 6.8, 6.8, 6.8 Hz, 1H), 3.32 (ddd, J = 3.8, 6.8, 7.9 Hz, 1H), 2.80-2.62 (m, 2H), 2.48 (br s, 1H), 2.08-1.86 (m, 3H), 1.84-1.72 (m, 1H), 1.69-1.35 (m, 4H), 1.01 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 128.33, 128.28, 125.7, 125.7, 81.6, 78.4, 75.4, 37.2,

32.5, 32.4, 28.3, 26.2, 10.0; HRMS *m/z* 235.1700 (calc'd for $C_{15}H_{23}O_2$ $[M+H]^+$, 235.1698).



2.29b-anti

anti isomer: R_f 0.40 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 7.22-7.15 (m, 3H), 4.02-3.91 (m, 2H), 3.73 (ddd, J = 5.1, 8.5, 2.8 Hz, 1H), 2.75 (ddd, J = 5.8, 10.3, 14.0 Hz, 1H), 2.65 (ddd, J = 6.5, 9.6, 13.7 Hz), 2.14-2.02 (m, 2H), 1.96-1.80 (m, 3H), 1.80-1.70 (m, 1H), 1.61-1.50 (m, 1H), 1.49-1.38 (m, 2H), 1.00 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 128.33, 128.30, 81.2, 79.2, 73.5, 37.6, 32.4, 32.2, 25.5, 25.0, 10.4; HRMS *m/z* 235.1698 (calc'd for $C_{15}H_{23}O_2$ $[M+H]^+$, 235.1698).

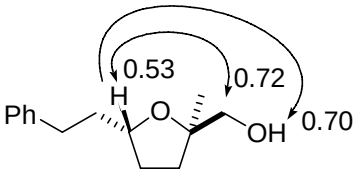


2.28b

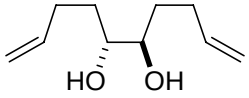
***trans*-(2-Methyl-5-phenethyltetrahydrofuran-2-yl)-methanol (2.28b).** The title compound was prepared from alkene **2.28a** (204 mg, 1.0 mmol) according to the general procedure described for **2.27b** (colorless liquid, 165 mg, 75%): R_f 0.30 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 7.25-7.17 (m, 3H), 3.96 (dddd, J = 6.6, 6.6, 6.6, 6.6 Hz, 1H), 3.46 (s, 2H), 2.82-2.62 (m, 2H), 2.23 (br s, 1H), 2.10-1.90 (m, 3H), 1.90-1.62 (m, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0,

128.3, 125.7, 82.9, 79.4, 68.5, 38.0, 33.5, 32.3, 31.8, 24.5; HRMS *m/z* 221.1544 (calc'd for $C_{14}H_{21}O_2$ $[M+H]^+$, 221.1542).

GOESY:

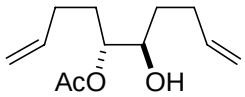


No NOE between the methyl and ring methine H



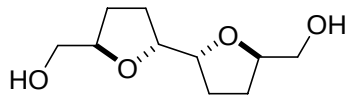
2.23a

(5*R*,6*R*)-5,6-dihydroxy-1,9-decadiene (2.23a). A suspension of CuI (3.17 g, 17.8 mmol) in THF (53 mL) was cooled to −30 °C (bromobenzene/CO_2 bath). To this suspension, allylmagnesiumbromide (175 mL, 1.0 M in Et_2O, 175 mmol) was added dropwise. After 1 h, bis-epoxide **2.42** (6.29 g, 73.1 mmol) in THF (18 mL) was added dropwise. After 1h, the cooling bath was replaced with an ice bath and aqueous NH_4Cl (sat'd, 900 mL) was slowly added. After 30 min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. Distillation under reduced pressure (82-88 °C, 0.4 mm Hg) provided the title compound as a colorless oil (10.0 g, 58.9 mmol, 81%): R_f 0.81 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93-5.80 (m. 2H). 5.12-4.99 (m, 4H), 3.49-3.40 (m, 2H), 2.32-2.05 (m, 4H), 1.65-1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 115.0, 73.8, 32.6, 29.9.



2.43a

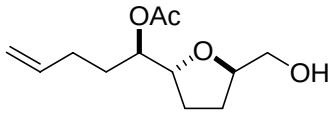
(5*R*,6*R*)-5-acetoxy-6-hydroxydeca-1,9-diene (2.43a). To a solution of diol **2.23a** (1.87 g, 11.0 mmol) in CH_2Cl_2 (22 mL) was added triethyl orthoacetate (6.0 mL, 33.0 mmol) and TsOH•H_2O (21 mg, 0.11 mmol) at rt. After 10 h, the reaction mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (15 mL) and treated with aqueous AcOH (8 mL, 80%) at rt. After 1 h, the layers were separated, the aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with $NaHCO_3$ (sat'd), H_2O, and brine. The organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography on SiO_2 (elution gradient: 14% EtOAc/hexanes to 25% EtOAc/hexanes) provided the title compound as a colorless oil (2.31 g, 11.0 mmol, 99%): R_f 0.17 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dddd, J = 6.5, 6.5, 10.3, 16.8 Hz, 2H), 5.06-4.92 (m, 4H), 4.84 (ddd, J = 3.8, 5.8, 7.5 Hz, 1H) 3.60 (ddd, J = 4.4, 4.4, 7.5 Hz, 1H), 2.27-2.09 (m, 2H), 2.09-2.01 (m, 2H), 2.07 (s, 3H), 1.80-1.65 (m, 3H), 1.57-1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 138.0, 137.5, 115.21, 115.17, 75.9, 71.8, 32.7, 29.83, 29.77, 29.6, 21.0 (calc'd for $C_{12}H_{21}O_3$ $[M+H]^+$, 213.1491).



2.23b

[(2*R*,2'*R*,5*R*,5'*R*)-5'-Hydroxymethyloctahydro-[2,2']-bifuranyl-5-yl]methanol (2.23b). The title compound was prepared from diol 2.23a (170 mg, 1.0 mmol) according to the general procedure described for **2.27b** except 1% (v/v) H_2O was added to the reaction mixture (colorless liquid, 91 mg, 45%): The ^1H and ^{13}C NMR spectra of this compound were in agreement with published values.[55a-b]

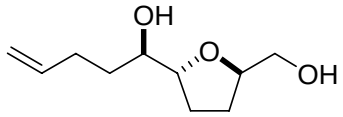
The title compound was also prepared from the corresponding mono-THF alkene **2.45a** (186 mg, 1.0 mmol) according to the general procedure described for **2.27b** (155 mg, 77%).



2.43b

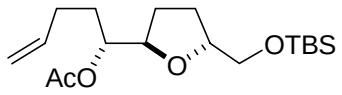
(1*R*)-1-Acetoxy-1-[(2*R*,5*R*)-5-hydroxymethyltetrahydrofuran-2-yl]-pent-4-ene (2.43b). The title compound was prepared from alkene **2.43a** (2.40 g, 11.3 mmol) according to the general procedure described for **2.27b** (colorless liquid, 2.11 g, 82%): R_f 0.20 (60% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (dddd, J = 6.4, 6.4, 10.0, 16.9 Hz, 1H), 5.02-4.87 (m, 2H), 4.86 (ddd, J = 5.4, 5.4, 8.2 Hz, 1H,), 4.10-3.94 (m 2H), 3.62 (dd, J = 3.3, 11.8 Hz, 1H) 3.44 (dd, J = 5.6, 11.8 Hz, 1H), 2.16 (br s, 1H), 2.09-1.82 (m, 4H), 2.05 (s, 3H), 1.75-1.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 137.5,

115.1, 79.7, 79.6, 74.6, 64.5, 30.1, 29.6, 28.2, 27.3, 21.1; HRMS *m/z* 229.1445 (calc'd for $C_{12}H_{21}O_4$ $[M+H]^+$, 229.1440).



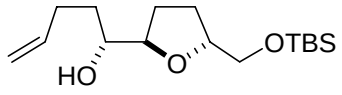
2.45a

(1*R*)-1-[(2*R*,5*R*)-5-hydroxymethyltetrahydrofuran-2-yl]-pent-4-en-1-ol (2.45a). To a solution of acetate **2.43b** (680 mg, 3.0 mmol) in MeOH (30 mL) was added NaOH (29 mg, 0.72 mmol) at 0 ºC. The reaction mixture was stirred for 2 h, diluted with water (75 mL) and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: 70% EtOAc/hexanes to EtOAc) provided the title compound as a colorless oil (452 mg, 81%): R_f 0.19 (70% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.75 (m, 1H), 4.99 (dddd, J = 1.7, 1.7, 1.7, 17.1 Hz, 1H), 4.92 (dddd, J = 1.0, 2.0, 3.1, 10.3 Hz, 1H), 4.09-4.00 (m, 1H), 3.79 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H), 3.66-3.55 (m, 1H), 3.50-3.34 (m, 2H), 3.22 (br s, 1H), 3.09 (br s, 1H), 2.30-2.18 (m, 1H), 2.17-2.04 (m 1H), 2.02-1.85 (m 2H), 1.72-1.52 (m, 2H), 1.52-1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 114.8, 82.9, 79.9, 73.4, 64.7, 32.5, 29.7, 28.5, 27.8; HRMS *m/z* 187.1342 (calc'd for $C_{10}H_{19}O_3$ $[M+H]^+$, 187.1342).



4.77

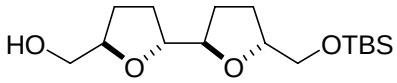
(1*R*)-1-Acetoxy-1-[(2*R*,5*R*)-5-*tert*-butyldimethylsiloxymethyltetrahydrofuran-2-yl]-pent-4-ene (4.77). To a solution of alcohol **2.43b** (5.49 g, 24.1 mmol) in DMF (30 mL) was added imidazole (4.49 g, 66.1 mmol) and TBSCl (4.49 g, 29.9 mmol) at rt. After 16 h, the reaction mixture was diluted with Et_2O and washed with H_2O and brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography on SiO_2 (elution gradient: 2.5% EtOAc/hexanes to 10% EtOAc/hexanes) provided the title compound as a colorless oil (7.7 g, 22.5 mmol, 94%): R_f 0.17 (8% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (dddd, J = 6.7, 6.7, 10.2, 16.9 Hz, 1H), 4.97 (dddd, J = 1.6, 1.6, 1.6, 16.9 Hz, 1H), 4.92 (dddd, J = 1.3, 1.3, 1.3 Hz, 1H), 4.86 (ddd, J = 5.1, 5.1, 8.5 Hz, 1H), 4.07-3.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 137.7, 115.0, 79.8, 79.6, 74.7, 65.6, 30.3, 29.6, 28.0, 27.9, 25.9, 21.1, 18.3, -5.4; HRMS *m/z* 343.2306 (calc'd for $C_{18}H_{35}O_4Si$ $[M+H]^+$, 343.2305).



2.18a

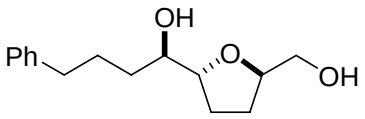
(1*R*)-1-[(2*R*,5*R*)-5-*tert*-butyldimethylsiloxymethyltetrahydrofuran-2-yl]-pent-4-en-1-ol (2.18a). To a 0 ºC solution of **4.77** (4.10 g, 12.0 mmol) in Et_2O (14 mL) was slowly added EtMgBr (13.2 mL, 2.78 M in Et_2O, 36.7 mmol). After 1 h, aqueous HCl (80 mL, 0.5 M, 40 mmol) was added dropwise. The layers were separated and the organic layer was washed with HCl (50 mL, 0.5 M) and brine, dried ($MgSO_4$), filtered and

concentrated. Purification by flash chromatography on SiO_2 (elution gradient: 5% EtOAc/hexanes to 13% EtOAc/hexanes) provided the title compound as a colorless oil (3.56 g, 11.9 mmol, 99%): R_f 0.20 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dddd, J = 6.7, 6.7, 10.2, 16.9 Hz, 1H), 5.01 (dddd, J = 1.5, 1.5, 1.5, 16.9 Hz, 1H), 4.93 (dddd, J = 1.3, 1.3, 2.3, 2.3 Hz, 1H), 4.01 (ddd, J = 4.9, 5.9, 12.3 Hz, 1H), 3.79 (ddd, J = 6.1, 6.4, 7.7 Hz, 1H), 3.60 (dd, J = 4.9, 10.8 Hz, 1H), 3.55 (dd, J = 2.8, 10.8 Hz, 1H), 3.37 (ddd, J = 5.9, 6.4, 6.4 Hz, 1H), 2.34-2.04 (m, 3H), 2.02-1.87 (m, 2H), 1.81-1.52 (m, 2H), 1.52-1.42 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 114.7, 82.6, 79.7, 73.3, 65.8, 32.8, 29.8, 28.3, 28.2, 25.9, 18.3, -5.3; HRMS *m/z* 301.2200 (calc'd for $C_{16}H_{33}O_3Si$ $[M+H]^+$, 301.2199).



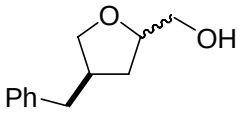
2.18a

[(2*R*,2'*R*,5*R*,5'*R*)-5'-(*tert*-Butyldimethylsilyloxymethyl)octahydro-[2,2']-bifuranyl-5-yl]-methanol (2.18b). The title compound was prepared from alkene **2.18a** (3.12g, 10.4 mmol) according to the general procedure described for **2.27b** (colorless liquid, 2.60 g, 79%): R_f 0.32 (50% EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13-4.03 (m, 2H), 3.90-3.85 (m, 2H), 3.70-3.65 (m, 2H), 3.60 (dd, *J* = 5.6, 10.0 Hz, 1H), 3.47 (dd, *J* = 4.8, 11.6 Hz, 1H), 2.23 (brs, 1H), 2.04-1.90 (m, 4H), 1.79-1.53 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.23, 82.20, 79.82, 79.80, 65.8, 64.5, 28.7, 28.39, 28.36, 27.4, 25.9, 18.3, -5.4.



2.46b

(1*R*)-1-[(2*R*,5*R*)5-Hydroxymethyltetrahydrofuran-2-yl]-4-phenyl-butan-1-ol (2.46b). The title compound was prepared from alkene **2.46a** (234 mg, 1.0 mmol) according to the general procedure described for **2.27b** (colorless liquid, 184 mg, 74%): R_f 0.21 (70% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27, (dd, J = 7.5, 7.5 Hz, 2H), 7.21-7.14 (m, 3H), 4.12-4.04 (m, 1H), 3.81 (ddd, J = 7.2, 7.2, 7.2 Hz, 1H), 3.65 (dd, J = 2.7, 12.0 Hz, 1H), 3.49 (dd, J = 6.7, 12.0 Hz, 1H), 3.44 (ddd, J = 6.5, 6.5, 6.5 Hz, 1H), 2.88 (s, 2) 2.71-2.56 (m, 2H), 2.00-1.82 (m, 3H), 1.78-1.55 (m, 3H), 1.44 (app ddd, J = 7.9, 7.9, 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; HRMS *m/z* 251.1649 (calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$, 251.1647).



2.33b

(4-Benzyltetrahydrofuran-2-yl)-methanol (2.33b). The title compound was prepared as an inseparable mixture of *cis*/*trans* diastereomers (dr: 1.7:1) from alkene **2.33a** (176 mg, 1.0 mmol) according to the general procedure described for **2.27b** (colorless liquid, 159 mg, 83%):

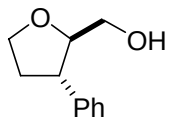
cis isomer:

R_f 0.15 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.17 (m, 2H), 7.16-7.05 (m, 3H), 4.22-3.93 (m, 1H), 3.84-3.74 (m, 1H), 3.80 (dd, J = 7.5, 7.5 Hz, 1H), 3.58-

3.43 (m, 2H), 2.77-2.49 (m, 4H), 1.96 (ddd, J = 6.5, 6.5, 12.3 Hz, 1H), 1.74 (ddd, J = 8.9, 8.9, 12.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 128.6, 128.3, 126.0, 80.2, 72.9, 64.7, 41.6, 39.0, 33.8; HRMS *m/z* 193.1227 (calc'd for $C_{12}H_{17}O_2$ $[M+H]^+$, 193.1229).

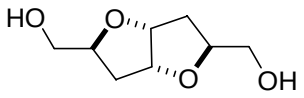
trans isomer:

R_f 0.15 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.17 (m, 2H), 7.16-7.05 (m, 3H), 4.15-4.06 (m, 1H), 3.88 (dd, J = 7.9, 7.9 Hz, 1H), 3.71 (m, 1H), 3.58-3.43 (m, 2H), 2.74-2.45 (m, 4H), 1.77 (ddd, J = 6.8, 6.8, 12.7 Hz, 1H), 1.66 (ddd, J = 7.9, 7.9, 13.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 128.6, 128.5, 126.0, 79.0, 73.1, 65.0, 40.95, 39.0, 33.2; HRMS *m/z* 193.1227 (calc'd for $C_{12}H_{17}O_2$ $[M+H]^+$, 193.1229).



2.37b

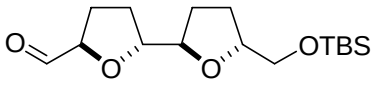
(3-Phenyltetrahydrofuran-2-yl)-methanol (2.37b). The title compound[69] was prepared from alkene **2.37a** (162 mg, 1.0 mmol) according to the general procedure described for **2.27b** (colorless liquid, 134 mg, 75%): R_f 0.20 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H), 7.29-7.19 (m, 3H), 4.12 (ddd, J = 4.1, 8.2, 12.7 Hz, 1H), 4.01 (ddd, J = 6.8, 8.2, 8.2 Hz, 1H), 3.94 (ddd, J = 2.7, 5.1, 8.2 Hz, 1H), 3.75, (dd, J = 2.7, 12.0 Hz, 1H), 3.54 (dd, J = 5.1, 12.0 Hz, 1H), 3.20 (ddd, J = 8.5, 8.5, 8.5 Hz, 1H), 2.45 (br s, 1H), 2.43-2.34 (m, 1H), 2.23-2.12 (m 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 128.6, 127.6, 126.7, 86.3, 68.2, 62.7, 46.0, 35.4; HRMS *m/z* 179.1070 (calc'd for $C_{11}H_{15}O_2$ $[M+H]^+$, 179.1072).



2.41b

(5-Hydroxymethylhexahydrofuro[3,2-b]furan-2-yl)-methanol (2.41b). The title compound was prepared from diol **2.41a** (170 mg, 1.0 mmol) according to the general procedure described for **2.27b** except 1% (v/v) H_2O was added to the reaction mixture (79 mg, 50%): R_f 0.31 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (d, J = 4.4 Hz, 2H), 4.17 (dddd, J = 2.1, 5.5, 5.5, 9.9 Hz, 2H), 3.71 (dd, J = 2.1, 12.0 Hz, 2H), 3.44 (dd, J = 5.5, 12.0 Hz, 2H), 2.50 (br s, 2H), 2.04 (dd, J = 5.5, 13.3 Hz, 2H), 1.83 (ddd, J = 4.4, 9.9, 13.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ; HRMS *m/z* 175.0974 (calc'd for $C_8H_{15}O_4$ $[M+H]^+$, 175.0970).

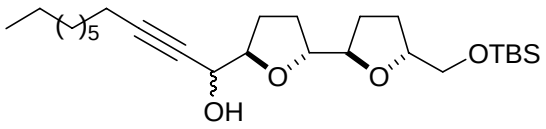
5.7 SYNTHESIS OF THE TETHER-ELONGATED ANALOG OF BULLATACIN



4.78

(2*R*,2'*R*,5*R*,5'*R*)-5'-(*tert*-Butyldimethylsiloxymethyl)octahydro-[2,2']bifuranyl-5-carbaldehyde (4.78). A solution of DMSO (1.2 mL, 18 mmol) in CH_2Cl_2 (4.7 mL) was added dropwise to a -78 °C solution of oxalyl chloride (0.69 mL, 8.0 mmol) in CH_2Cl_2 (36 mL). After 30 min, a solution of alcohol **2.18b** (0.95 g, 3.0 mmol) in CH_2Cl_2 (4.7 mL) was added dropwise to the reaction mixture. After 45 min, Et_3N (3.8 mL, 27 mmol) was added and the reaction mixture was allowed to warm to rt. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Purification of the residual oil by flash chromatography on SiO_2 (elution gradient: 20% EtOAc/hexanes

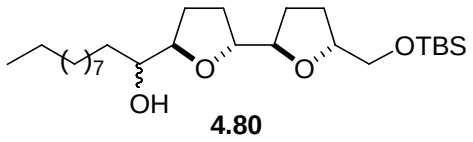
to 30% EtOAc/hexanes) provided the title compound as a colorless oil (0.91 g, 2.9 mmol, 96%): R_f 0.42 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, J = 2.0 hz, 1H), 4.36-4.31 (m, 1H), 4.11-3.99 (m, 2H), 3.96-3.91 (m, 1H), 3.67 (dd, *J* = 4.0, 10.4 Hz, 1H), 3.58 (dd, *J* = 5.2, 10.4 Hz, 1H), 2.24-2.17 (m, 1H), 2.07-1.89 (m, 4H), 1.82-1.65 (m, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 83.4, 83.2, 81.7, 80.0, 65.8, 28.5, 28.3, 28.0, 27.4, 25.9, 18.3, -5.3.



4.79

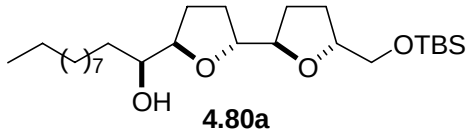
(2*R*,2'*R*,5*R*,5'*R*)-5-*tert*-Butyldimethylsiloxymethyl-5'-[(1*R/S*)-1-hydroxytriundec-2-ynyl]octahydro-[2,2']bifuran (4.79). To a 0 °C solution of 1-decyne (2.1 mL, 12 mmol) in Et_2O (40 mL), *n*-BuLi (4.8 mL 2.4 M solution in hexanes, 12 mmol) was added dropwise. After cooling the reaction mixture to −78 °C, TiCl(Oi-Pr)$_3$ (5.1 mL 2.26 M solution in toluene, 12 mmol) was added dropwise. After 30 min, a solution of aldehyde **4.78** (0.78 g, 2.5 mmol) in Et_2O (10 mL) was added dropwise. The reaction mixture was allowed to warm up to 0 °C over 1 h and after 8 h, an aqueous solution of tartaric acid (100 mL, 1.0 M, 100 mmol) was added to the reaction mixture and the ice bath was removed. After 1 h at rt, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: 14% EtOAc/hexanes to 25% EtOAc/hexanes) provided the title compound as an

inseparable mixture of epimers (0.90 g, 2.0 mmol, 82%): R_f 0.25 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (m, 1H), 4.16-4.10 (m, 1H), 4.10-4.01 (m, 1H), 4.02-3.94 (m, 1H), 3.92-3.82 (m, 1H), 3.67 (dd, *J* = 4.0, 10.4 Hz, 1H), 3.55 (dd, *J* = 6.0, 10.4 Hz, 1H), 2.38 (brs, 1H), 2.17 (dt, *J* = 2.0, 6.8 Hz, 2H), 2.06-1.90 (m, 5H), 1.82-1.70 (m, 1H), 1.70-1.54 (m, 2H), 1.54-1.40 (m, 2H), 1.40-1.22 (m, 10H), 0.87 (s, 9H), 0.86 (dd, *J* = 6.8, 6.8 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5, 83.4, 82.3, 82.1, 79.8, 77.6, 65.8, 63.9, 38.0, 31.8, 29.1, 29.0, 28.8, 28.6, 28.5, 28.4, 28.3, 25.9, 22.6, 18.7, 18.3, 14.1, -5.3; HRMS *m/z* 453.3403 (calc'd for $C_{26}H_{49}O_4Si$ $[M+H]^+$, 453.3400).



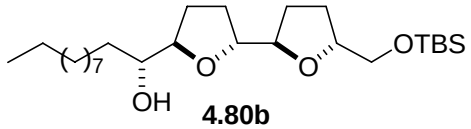
4.80

(2*R*,2'*R*,5*R*,5'*R*)-5-*tert*-Butyldimethylsiloxymethyl-5'-[(1*R*/1S)-1-hydroxytriundecanyl]octahydro-[2,2']bifuran (4.80) To a solution of the diastereomeric mixture of **4.79** (0.90 g, 2.0 mmol) in benzene (20 mL) was added Pd/C (10% by wt, 0.20 g, 0.20 mmol). The mixture was stirred under 1 atm of H_2 for 8 h. The reaction mixture was filtered (Celite) and concentrated, and the residue was purified by flash chromatography on SiO_2 (elution gradient: 15% EtOAc/hexanes to 30% EtOAc/hexanes), providing the title compound (789 mg, 1.7 mmol, 85%) and its epimer (53 mg, 0.1 mmol, 5%):



4.80a

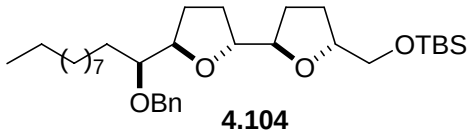
4.80a: R_f 0.25 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13-4.04 (m, 1H), 3.94-3.84 (m, 4H), 3.70 (dd, *J* = 3.9, 10.5 Hz, 1H), 3.56 (dd, *J* = 6.0, 10.2 Hz, 1H), 2.05-1.71 (m, 7H), 1.64-1.40 (m, 3H), 1.32-1.22 (m, 16H), 0.87 (s, 9H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 82.51, 82.46, 79.8, 71.1, 65.8, 32.4, 31.9, 29.64, 29.55, 29.5, 29.3, 28.7, 28.4, 28.3, 26.0, 25.9, 24.4, 22.6, 18.2, 14.1, -5.4; HRMS m/z 457.3706 (calc'd for $C_{26}H_{53}O_4Si$ $[M+H]^+$, 457.3713).



4.80b

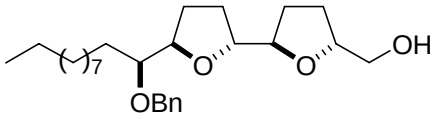
4.80b: R_f 0.30 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10-4.03 (m, 1H), 3.92-3.78 (m, 3H), 3.66 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.56 (dd, *J* = 6.4, 10.4 Hz, 1H), 3.40-3.34 (m, 1H), 2.27 (brs, 1H), 2.04-1.90 (m, 4H), 1.80-1.58 (m, 4H), 1.58-1.20 (m, 18H), 0.87 (s, 9H), 0.86 (dd, *J* = 6.9, 6.9 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.9, 82.0, 81.9, 79.9, 74.0, 65.8, 33.4, 31.9, 29.7, 29.59, 29.57, 29.3, 28.8, 28.5, 28.32, 28.31, 25.9, 25.6, 22.6, 18.3, 14.1, -5.3.

Relative stereochemistry was assigned by Swern oxidation of the mixture and L-Selectride® reduction.[100] The ^{1}H NMR and ^{13}C NMR spectra of the major *threo* epimer from this reduction were identical to that of the minor product from the titanium acetylide/hydrogenation sequence.



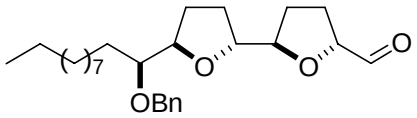
4.104

(2*R*,2'*R*,5*R*,5'*R*)-5-*tert*-Butyldimethylsiloxymethyl-5'-[(1*S*)-1-benzyloxytriundecanyl]octahydro-[2,2']bifuran (4.104). A solution of alcohol **4.80a** (726 mg, 1.59 mmol) in DMF (1 mL) was added to a suspension of NaH (60%, 190 mg, 4.7 mmol) in DMF (9 mL) at 0 °C. After stirring for 15 min, benzyl bromide (598 mg, 3.5 mmol) and Bu_4NI (29.4 mg, 0.08 mmol) were added. After 16 h, the reaction mixture was diluted with Et_2O and washed with H_2O and brine. The organic fraction was separated, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: 2% EtOAc/hexanes to 8% EtOAc/hexanes) provided the title compound as a colorless oil (800 mg, 1.5 mmol, 92%): R_f 0.35 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 4.73 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.16-3.99 (m, 2H), 3.96-3.85 (m, 2H), 3.70 (dd, *J* = 4.2, 10.2 Hz, 1H), 3.66-3.59 (m, 1H), 3.55 (dd, *J* = 5.7, 10.2 Hz, 1H), 2.08-1.86 (m, 5H), 1.82-1.56 (m, 3H), 1.52-1.37 (m, 3H), 1.36-1.19 (m, 16H), 0.89 (s, 9H), 0.88 (dd, *J* = 6.9, 6.9 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 128.2, 127.7, 127.3, 82.5, 82.0, 81.8, 80.7, 79.8, 73.3, 65.9, 32.0, 31.9, 29.7, 29.59, 29.57, 29.3, 28.7, 28.5, 28.3, 26.2, 25.9, 25.8, 22.7, 18.3, 14.1, -5.3; HRMS m/z 547.4174 (calc'd for $C_{33}H_{59}O_4Si$ $[M+H]^+$, 547.4183).



4.105

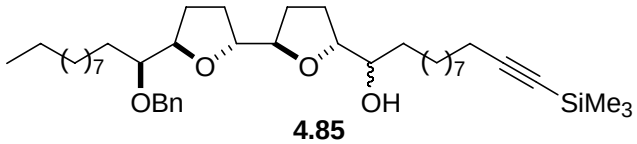
(2*R*,2'*R*,5*R*,5'*R*)-5-hydroxymethyl-5'-[(1*S*)-1-benzyloxytriundecanyl]octahydro-[2,2']bifuran (4.105). A solution of **4.104** (869 mg, 1.59 mmol) in MeOH (10 mL) and HCl (3.4 mL, 7.0 M solution in MeOH, 24 mmol) was added at rt. After 2 h, the mixture was concentrated and purification of the residue by flash chromatography on silica gel (elution gradient: CH_2Cl_2 to 2% MeOH/CH_2Cl_2) provided the title compound as colorless oil (674 mg, 1.56 mmol, 98%): R_f 0.54 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 4.73 (d, *J* = 11.1 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.16-4.01 (m, 2H), 3.95-3.85 (m, 2H), 3.76-3.62 (m, 2H), 3.50 (dd, *J* = 5.1, 11.7 Hz, 1H), 2.39 (brs, 1H), 2.02-1.85 (m, 5H), 1.80-1.52 (m, 3H), 1.52-1.36 (m, 3H), 1.36-1.18 (m, 15H), 0.87 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.2, 128.1, 127.6, 127.2, 82.6, 82.1, 81.9, 80.5, 79.8, 73.3, 64.5, 31.9, 31.8, 29.6, 29.49, 29.47, 29.2, 28.7, 27.4, 25.9, 25.7, 22.6, 14.0; HRMS *m/z* 433.3316 (calc'd for $C_{27}H_{45}O_4$ $[M+H]^+$, 433.3318).



4.84

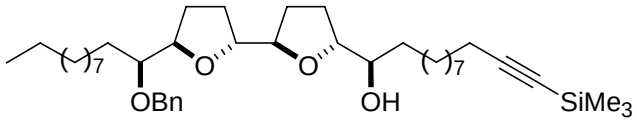
5'-{(2*R*,2'*R*,5*R*,5'*R*)-[(1*S*)-1-Benzyloxyundecanyl)]octahydro-[2,2']bifuran-5-yl}-carbaldehyde (4.84). The title compound was prepared according to the procedure described for **4.78** as a yellow oil (651 mg, 1.51 mmol, 97%): R_f 0.39 (2.5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 0.8 Hz, 1H), 7.39-7.23 (m,

5H), 4.73 (d, *J* = 11.1 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.35 (t, *J* = 6.4 Hz, 1H), 4.10-3.98 (m, 2H), 3.97-3.90 (m, 1H), 3.67-3.61 (m, 1H), 2.27-2.16 (m, 1H), 2.06-1.88 (m, 5H), 1.78-1.62 (m, 2H), 1.52-1.37 (m, 3H), 1.34-1.19 (m, 16H), 0.88 (dd, *J* = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 139.3, 128.2, 127.7, 127.3, 83.4, 83.3, 82.8, 81.4, 80.6, 73.3, 32.0, 31.9, 29.7, 29.6, 29.3, 28.8, 28.0, 27.3, 26.0, 25.8, 22.6, 14.1; HRMS *m/z* 551.4083 (calc'd for $C_{27}H_{43}O_4$ $[M+H]^+$, 551.4100).



4.85

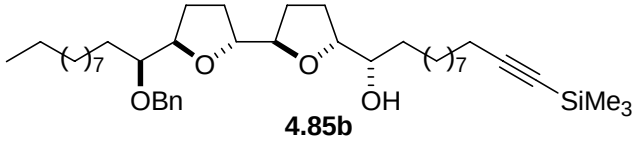
(2*R*,2'*R*,5*R*,5'*R*)-5-[(1*R*/*S*)-1-Hydroxy-12-trimethylsilyldodec-11-ynyl]-5'-[(1*S*)-1-benzyloxyundecyl]octahydro-[2,2']bifuran (4.85). The title compound was prepared as a mixture of *erythro*/*threo* isomers from aldehyde **4.84** (645 mg, 1.17 mmol) and bromide **4.82** (2.73 g, 9.0 mmol) using the general procedure described for **4.96** (colorless oil, 770 mg, 79%, dr: 2:1).



4.85a

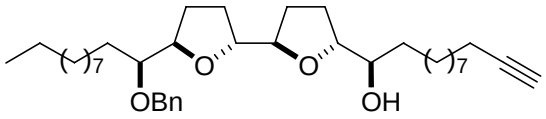
4.85a: R_f 0.29 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (m, 4H), 7.28-7.22 (m, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.59 (d, J =11.6 Hz, 1H), 4.05 (ddd, J = 3.4, 6.8, 6.8 Hz, 1H), 3.93-3.85 (m, 2H), 3.82 (ddd, J = 6.8, 6.8, 6.8 Hz, 1H), 3.62 (ddd, J = 4.1, 4.1, 7.5 Hz, 1H), 3.54 (ddd, J = 4.1, 4.1, 6.8 Hz, 1H), 2.45 (br s, 1H), 2.19 (dd, J = 7.2, 7.2 Hz, 2H), 2.01-1.88 (m, 5H), 1.73-1.55 (m, 3H), 1.55-1.17 (m, 32H), 0.88 (dd, J =

6.5, 6.5 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 128.2, 127.7, 127.2, 107.7, 84.1, 82.9, 82.6, 81.9, 81.7, 80.5, 73.9, 73.3, 33.4, 31.89, 31.85, 29.7, 29.6, 29.53, 29.48, 29.4, 29.3, 29.0, 28.8, 28.7, 28.6, 28.3, 26.1, 25.7, 25.6, 22.6, 19.8, 14.1, 0.1; HRMS *m/z* 655.5130 (calc'd for $C_{41}H_{71}O_4Si$ $[M+H]^+$, 655.5122).



4.85b

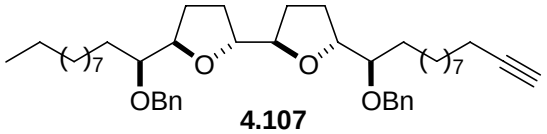
4.85b: R_f 0.24 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H), 4.71 (d, J = 11.8 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.04 (ddd, J = 3.3, 3.3, 6.7 Hz, 1H), 3.94-3.81 (m, 4H), 3.62 (ddd, J = 6.7, 6.7 Hz, 1H), 2.18 (ddd, J = 1.8, 6.9, 6.9 Hz, 2H), 2.01-1.70 (m, 8H), 1.64-1.16 (m, 32H), 0.86 (dd, J = 6.7, 6.7 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 128.5. 127.6, 108.03, 108.00, 107.99, 84.5, 83.0, 82.8, 82.5, 80.9, 73.7, 71.4, 63.3, 30.0, 29.9, 29.8, 29.73, 29.67, 29.6, 29.32, 29.25, 29.05, 29.00, 28.88, 28.85, 26.3, 26.1, 26.0, 22.9, 20.1, 14.4, 0.4; HRMS *m/z* 655.5115 (calc'd for $C_{41}H_{71}O_4Si$ $[M+H]^+$, 655.5122).



4.106

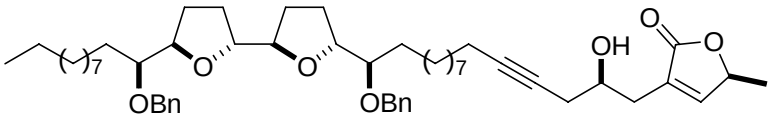
(2*R*,2'*R*,5*R*,5'*R*)-5-[(1*R*)-1-Hydroxydodec-11-ynyl]-5'-[(1*S*)-1-benzyloxyundecyl]octahydro-[2,2']bifuran (4.106). The title compound was prepared from **4.85a** (245 mg, 0.38 mmol) using the general procedure for **4.112** (colorless oil, 200 mg, 92%): R_f 0.27 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m,

4H), 7.28-7.22 (m, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.05 (ddd, J - 3.4, 6.8, 6.8 Hz, 1H), 3.93-3.85 (m, 2H), 3.82 (ddd, J = 7.9, 7.9, 7.9 hz, 1H, 3.61 (ddd, J = 3.8, 3.8, 7.5 Hz, 1H), 3.39 (ddd, J = 4.1, 6.8, 6.8 Hz, 1H), 2.45 (br s, 1H), 2.16 (app ddd, J = 2.4, 6.8, 6.8 Hz, 2H), 2.01-1.86 (m, 6H), 1.73-1.56 (m, 3H), 1.55-1.21 (m, 34H), 0.87 (dd, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 128.1, 127.7, 127.2, 84.7, 82.9, 82.6, 81.8, 81.7, 80.5, 73.9, 73.2, 68.0, 33.4, 31.85, 31.82, 29.63, 29.62, 29.52, 29.49, 29.44, 29.35, 29.26, 29.0, 28.8, 28.6, 28.4, 28.3, 26.1, 25.7, 25.6, 22.6, 18.3, 14.0.



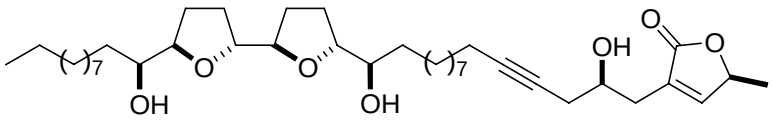
4.107

(2*R*,2'*R*,5*R*,5'*R*)-5-[(1*R*)-1-Benzyloxydodec-11-ynyl]-5'-[(1*S*)-1-benzyloxyundecyl]octahydro-[2,2']bifuran (4.107). The title compound was prepared from **4.106** (200 mg, 0.34 mmol) using the general procedure for **4.97** (colorless oil, 195 mg, 86%): R_f 0.24 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 8H), 7.30-7.23 (m, 2H), 4.78 (d, J = 11.6, 1H), 4.75 (d, J = 11.6, 1H), 4.62 (app d, J = 11.6, 2H), 4.16-4.04 (m, 2H), 4.00-3.91 (m, 2H), 3.62 (ddd, J = 3.1, 3.1, 6.8 Hz, 1H), 3.41 (ddd, J = 7.2, 7.2, 7.2 Hz, 1H), 2.19 (app ddd, J = 2.4, 7.2, 7.2, 2H), 2.05-1.89 (m, 6H), 1.81-1.62 (m, 3H), 1.58-1.20 (m, 34H), 0.90 (dd, J = 6.5, 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 139.2, 128.13, 128.10, 127.9, 127.7, 127.25, 127.20, 84.6, 82.4, 81.78, 81.6, 81.4, 81.2, 80.6, 73.1, 72.7, 68.0, 31.9, 31.8, 30.1, 29.7, 29.54, 29.48, 29.4, 29.3, 29.0, 28.7, 28.6, 28.4, 28.3, 28.1, 26.3, 25.8, 25.7, 22.6, 18.3, 14.1; HRMS *m/z* 671.5041 (calc'd for $C_{45}H_{67}O_4$ $[M+H]^+$, 671.5039).



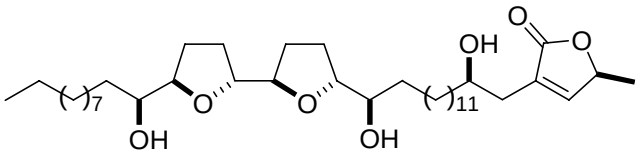
4.88

(5*S*)-3-{(2*S*,14*R*)-14-[(2*R*,2'*R*,5*R*,5'*R*)-5'-[(1*S*)-1-Benzyloxyundecyloctahydro-[2,2']bifuran-5-yl]-14-benzyloxy-2-hydroxytetradec-4-ynyl}-5-methyl-5*H*-furan-2-one (4.88). The title compound was prepared from **4.108** (80 mg, 0.12 mmol) using the general procedure for **4.98** (colorless oil, 51 mg, 51%, 78% BRSM): R_f 0.38 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.24 (m, 10H), 7.24 (d, J = 1.3 Hz, 1H), 5.07 (dq, J = 1.3, 6.9 Hz, 1H), 4.78 (d, J = 11.5 Hz, 1H), 4.74 (J = 11.5 Hz, 1H), 4.61 (app d, J = 11.5 Hz, 2H), 4.17-4.03 (m, 2H), 4.03-3.90 (m, 3H), 3.63 (ddd, J = 3.8, 3.8, 7.7 Hz, 1H), 3.45-3.35 (m, 1H), 2.73 (br s, 1H), 2.62 (app dddd, J = 1.5, 1.5, 3.8, 15.1 Hz, 2H), 2.53 (app dd, J = 7.9, 15.1 Hz, 2H), 2.20 (ddd, J = 2.3, 2.3, 6.9 Hz, 1H), 2.17 (ddd, J = 2.3, 2.3, 6.9 Hz, 1H), 2.02-1.90 (m, 5H), 1.80-1.61 (m, 3H), 1.57-1.20 (m, 33H), 1.44 (d, J = 6.9H, 3H), 0.90 (dd, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 152.0,139.3, 139.2, 130.6, 128.2, 128.1, 127.9, 127.7, 127.30, 127.26, 83.8, 82.5, 81.7, 81.6, 81.5, 81.3, 80.7, 78.0, 75.3, 73.2, 72.7, 68.3, 31.94, 31.86, 30.6, 29.7, 29.6, 29.4, 29.3, 29.1, 28.90, 28.87, 28.6, 28.3, 28.1, 27.5, 26.3, 25.9, 25.7, 22.6, 19.0, 18.7, 14.1; HRMS *m/z* 827.5814 (calc'd for $C_{53}H_{79}O_7$ $[M+H]^+$, 827.5826).



4.109

(5*S*)-3-{(2*S*,14*R*)-14-[(2*R*,2'*R*,5*R*,5'*R*)-5'-[(1*S*)-1-Hydroxyundecyloctahydro-[2,2']bifuran-5-yl]-2,14-dihydroxytetradec-4-ynyl}-5-methyl-5*H*-furan-2-one (4.109). The title compound was prepared from **4.88** (50 mg, 61 μmol) using the general procedure for **4.99** (colorless oil, 35 mg, 90%): R_f 0.50 (80% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 1.3 Hz, 1H), 5.04 (dq, J = 1.3, 6.7, 1H), 4.02-3.76 (m, 6H), 3.38 (ddd, J = 5.1, 5.1, 5.1 Hz, 1H), 3.38, (ddd, J = 5.1, 5.1, 5.1 Hz, 1H), 2.68 (br s, 1H), 2.64-2.44 (m, 3H), 2.39 (dd, J = 2.6, 5.4 Hz, 1H), 2.37 (J = 2.6, 5.9 Hz, 1H), 2.33 (br s, 1H), 2.15 (ddd, J = 2.3, 3.3, 6.9 Hz, 1H), 2.13 (ddd, J = 2.3, 2.3, 6.9 Hz, 1H), 2.04-1.91 (m, 5H), 1.68-1.18 (m, 35H), 1.42 (d, J = 6.7 Hz, 3H), 0.86 (dd, J = 6.9, 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 152.0, 130.6, 83.7, 83.2, 82.8, 82.5, 82.2, 78.0, 75.3, 74.1, 71.2, 68.3, 33.2, 32.3, 31.9, 31.8, 29.63 29.55, 29.49, 29.46, 29.4, 29.3, 29.0, 28.93, 28.85, 28.8, 28.4, 27.5, 26.0, 24.4, 22.6, 19.0, 18.7, 14.1; HRMS *m/z* 647.4885 (calc'd for $C_{39}H_{67}O_7$ $[M+H]^+$, 647.4887).

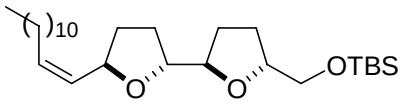


4.89

(5*S*)-3-{(2*S*,14*R*)-14-[(2*R*,2'*R*,5*R*,5'*R*)-5'-[(1*S*)-1-Hydroxyundecyloctahydro-[2,2']bifuran-5-yl]-2,14-dihydroxytetradecyl}-5-methyl-5*H*-furan-2-one (4.89). The title compound was prepared from **4.109** (25 mg, 39 μmol) using the general procedure

for **4.113** (colorless oil, 23 mg, 91%): R_f 0.56 (80% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (app s, 1H), 5.03 (app a, J = 6.8 Hz, 1H), 3.92-3.75 (m, 6H), 3.37 (ddd, J = 5.1, 5.1, 5.1 Hz, 1H), 2.60-2.32 (m, 6H), 2.10-1.72 (m, 6H), 1.65-1.18 (m, 43H), 1.40 (d, J = 6.8 Hz, 3H), 0.84 (dd, J = 6.4 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 151.8, 131.1, 83.2, 82.7, 82.5, 82.3, 78.0, 74.1, 71.3, 70.0, 37.4, 33.3, 33.2, 31.9, 29.7, 29.6, 29.54, 29.52, 29.3, 28.95, 28.91, 28.37, 26.02, 26.00, 24.4, 22.6, 19.1, 14.1; HRMS *m/z* 651.5207 (calc'd for $C_{39}H_{71}O_7$ $[M+H]^+$, 651.5200).

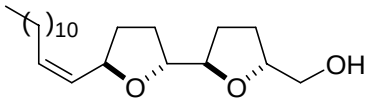
5.8 SYNTHESIS OF 22-DEOXY-SQUAMOTACIN



4.90

(2*R*,2'*R*,5*R*,5'*R*)-5-*tert*-Butyldimethylsiloxymethyl-5'-[(*Z*)-tridec-1-enyl]octahydro-[2,2']bifuran (4.90). To a 0 °C solution of dodecyltriphenylphosphonium bromide (2.55g, 5 mmol) in THF (24 mL) was added *n*-BuLi (1.7 mL, 2.62M, 4.5 mmol) dropwise. After 20 min, the reaction mixture was cooled to -78 °C and a solution of aldehyde **4.91** (1.25g, 4.0 mmol) in THF (7 mL) was added dropwise via cannula and after an additional 30 min, the cooling bath was replaced with an ice bath. The ice bath was removed after 1 h and the reaction mixture was allowed to warm to rt. After 12 h, NH_4Cl (10 mL, sat'd) was added and the resulting mixture was extracted with Et_2O. The combined extracts were washed with $NaHCO_3$ and brine, dried (Na_2SO_4) filtered and concentrated. The residue was purified by flash chromatography on SiO_2 (elution

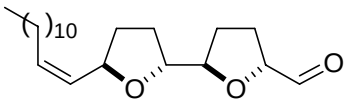
gradient: 2.5% EtOAc/hexanes to 10% EtOAc/hexanes) to give the title compound as a colorless liquid (1.45 g, 81%): R_f 0.71 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47-5.36 (m, 2H), 4.68 (ddd, J = 5.8, 7.9, 8.9 Hz, 1H), 4.05 (ddd, J = 6.2, 6.2, 10.9, 1H), 3.96-3.86 (m, 2H), 3.66 (dd, J = 8.1, 10.3 Hz, 1H), 3.53 (dd, J = 5.8, 10.3 Hz, 1H), 2.10-1.89 (m, 6H), 1.78-1.61 (m, 3H), 1.59-1.47 (m, 1H), 1.34-1.20 (m, 18H), 0.86 (s, 9H), 0.85 (dd, J = 5.8, 5.8 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 130.8, 81.9, 81.3, 79.8, 75.2, 65.9, 33.4, 31.9, 29.7, 29.64, 29.62, 29.59, 29.5, 29.32, 29.26, 28.8, 28.5, 28.2, 27.7, 25.9, 22.7, 18.3, 14.1, -5.3; HRMS *m/z* 467.3910 (calc'd for $C_{28}H_{55}O_3Si$ $[M+H]^+$, 467.3920).



4.110

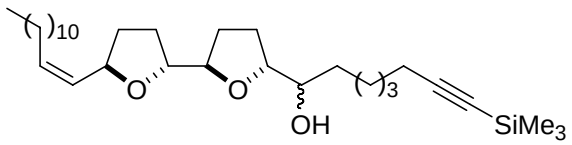
(2*R*,2'*R*,5*R*,5'*R*)-5-hydroxymethyl-5'-[(*Z*)-tridec-1-enyl]octahydro-[2,2']bifuran (4.110). A solution of **4.90** (1.14 g, 2.57 mmol) in THF (26 mL) was cooled to 0 °C and NBu4F (3.1 mL, 1.0 M, 3.1 mmol) was added dropwise. The ice bath was removed and after 12 h, the reaction mixture was extracted with EtOAc. The combined extracts were washed with NH_4Cl and brine, dried (Na_2SO_4) and concentrated. Purification of the residual oil by flash chromatography on SiO_2 (elution gradient: 25% EtOAc/hexanes to 50% EtOAc/hexanes) provided the title compound as a colorless oil (0.84 g, 98%): R_f 0.32 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46-5.34 (m, 2H), 4.69 (ddd, J = 5.8, 7.5, 8.6, 1H), 4.10 (dddd, J = 3.4, 3.4, 5.1, 8.9 Hz, 1H), 3.95- 3.83 (m, 2H), 3.66 (dd, J = 3.4, 11.6 Hz, 1H), 3.46 (dd, J = 5.1, 11.6 Hz, 1H), 2.22 (br s, 1H), 2.08-1.86 (m,

6H, 1.76-1.47 (m, 4H), 1.38-1.08 (m, 18H), 0.84 (dd, J = 7.1, 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 130.9, 110.0, 82.5, 81.9, 80.1, 77.3, 75.7, 64.8, 33.6, 32.2, 30.0, 29.91, 29.88, 29.87, 29.8, 29.6, 29.5, 29.2, 29.0, 27.9, 27.7, 22.9, 14.4; HRMS *m/z* 353.3049 (calc'd for $C_{22}H_{41}O_3$ $[M+H]^+$, 353.3056).



4.91

(2*R*,2'*R*,5*R*,5'*R*)-5'--[(*Z*)-Tridec-1-enyl]octahydro-[2,2']bifuranyl-5-carbaldehyde (4.91). The title compound was prepared from **4.110** (630 mg, 1.9 mmol) using the procedure described for **4.78** (560 mg, 89%).R_f 0.41 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, J = 2.05 Hz, 1H), 5.48-5.33 (m, 2H), 4.69 (ddd, J = 6.2, 8.9, 8.9 Hz, 1H), 4.32 (ddd, J = 2.05, 6.8, 7.6 Hz, 1H), 4.03 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 3.96 (ddd, J = 6.5, 6.5, 8.2 Hz, 1H), 2.24-2.15 (m, 1H), 2.10-1.85 (m, 7H), 1.82-1.70 (m, 2H), 1.61-1.50 (m, 1H), 1.34-1.19 (m, 19H), 0.84 (dd, J = 6.8, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 132.4, 130.4, 83.28, 83.26, 80.9, 75.5, 33.3, 31.9, 29.7, 29.57, 29.55, 29.5, 29.3, 29.2, 28.9, 27.9, 27.6, 27.4, 22.6, 14.1; HRMS *m/z* 351.2903 (calc'd for $C_{22}H_{39}O_3$ $[M+H]^+$, 351.2899).

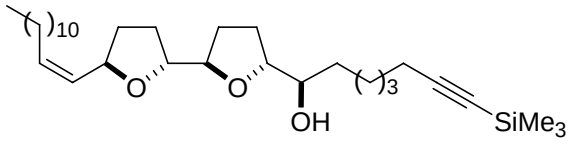


4.96

(2*R*,2'*R*,5*R*,5'*R*)-5-[(1*R*/*S*)-1-Hydroxy-8-trimethylsilyloct-7-ynyl]-5'-[(*Z*)-tridec-1-enyl]octahydro-[2,2']bifuran (4.96). To a suspension of Mg (1.0 g, 42 mmol) in Et_2O was added dibromoethane (0.30 mL, 3.5 mmol) at rt. After the exotherm concluded, a solution of alkyl bromide **4.92** (0.96 g, 3.9 mmol) in Et_2O (5 mL) was added and the reaction mixture was heated to reflux for 1 h. After transferring the solution away from excess Mg to a new flask and heating to reflux, a solution of aldehyde **4.91** (320 mg, 1.0 mmol) in Et_2O (4 mL) was added dropwise. After 45 min, the reaction mixture was allowed to cool to rt and NH_4Cl (5 mL, 50% sat'd) was added. The layers were separated, the aqueous layer was extracted with Et_2O and the combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on SiO_2 (10% EtOAc/hexanes) provided the title compound as a mixture of *anti*/*syn* diastereomers (400 mg, 77%, dr 2:1).

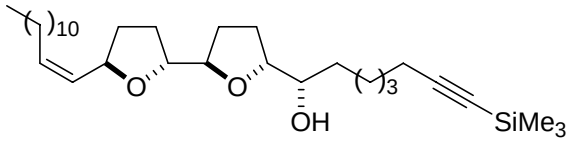
The title compound was also prepared by L-Selectride™ reduction of ketone **4.111**. A solution of **4.111** (315 mg, 0.61 mmol) in THF (6 mL) was cooled to -100 °C and L-Selectride™ was added dropwise using a cold finger cooled to -78 °C. After 2 h, the internal temperature was allowed to warm to -60 °C and NaOH (2 mL, 2 M, 4 mmol) and H_2O_2 (2 mL, 30%, 19 mmol) were added dropwise. The resulting mixture was extracted with EtOAc and the combined extracts were washed with $Na_2S_2O_3$ (sat'd), $NaHCO_3$ and

brine, dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (10% EtOAc/hexanes) provided the title compound as a mixture of *erythro*/*threo* isomers (287 mg, 91%, dr 10:1).



4.96a

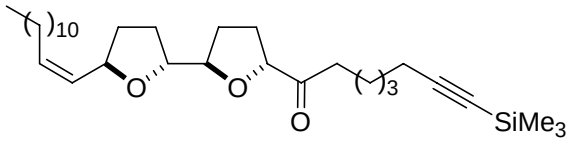
4.96a: R_f 0.59 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.34 (m, 2H), 4.68 (ddd, J = 5.5, 8.2, 8.2 Hz, 1H), 3.92 (ddd, J = 5.8, 5.8, 7.9 Hz, 1H), 3.87 (ddd, J = 5.8, 5.8, 7.9 Hz, 1H), 3.81 (ddd, J = 6.5, 6.5, 6.5 Hz, 1H), 3.36 (ddd, J = 4.1, 7.2, 7.2 Hz, 1H), 2.29 (br s, 1H), 2.18 (dd, J = 7.2, 7.2 Hz, 2H), 2.07-1.90 (m, 6H), 1.76-1.44 (m, 7H), 1.44-1.19 (m, 23H), 0.85 (dd, J = 6.8, 6.8 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 130.6, 107.6, 84.2, 83.0, 81.9, 81.4, 75.4, 73.9, 33.4, 33.3 29.7, 29.63, 29.60, 29.58, 29.5, 29.3, 29.2, 29.0, 28.9, 28.8, 28.6, 28.4, 27.7, 22.6, 19.8, 14.1; HRMS *m/z* 519.4248 (calc'd for $C_{32}H_{59}O_3Si$ $[M+H]^+$, 519.4234).



4.96b

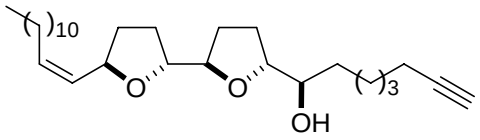
4.96b: R_f 0.56 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46-5.33 (m, 2H), 4.69 (ddd, J = 7.2, 7.2, 7.2 Hz, 1H), 3.94-3.85 (m, 2H), 3.85-3.79 (m, 1H), 2.18 (dd, J = 8.5, 8.5 Hz, 2H), 2.14-1.90 (m, 6H), 1.90-1.71 (m, 2H), 1.67-1.42 (m, 6H), 1.42-1.19 (m, 21 H), 0.83 (dd, J = 6.8, 6.8 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.9, 130.7, 109.7, 107.5, 84.2, 82.5, 81.8, 75.4, 71.1, 33.3, 32.2, 31.9, 29.7, 29.60, 29.55, 29.5,

29.3, 29.2, 28.84, 28.81, 28.7, 28.5, 27.6, 25.6, 24.5, 22.6, 19.7, 14.1, 0.1; HRMS *m/z* 519.4243 (calc'd for $C_{32}H_{59}O_3Si$ $[M+H]^+$, 519.4234).



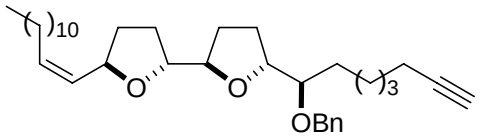
4.110

(2*R*,2'*R*,5*R*,5'*R*)-5-(1-Oxo-8-trimethylsilyloct-7-ynyl)-5'-[(*Z*)-tridec-1-enyl]octahydro-[2,2']bifuran (4.111). To a rt solution of the isomeric mixture of **4.96** (380 mg, 0.73 mmol) in CH_2Cl_2/CH_3CN (2 mL, 9:1) was added TPAP (13 mg, 37 μmol), N-methylmorpholine oxide (200 mg, 1.5 mmol) and 4 Å MS. After 3 h, the reaction mixture was filtered through a SiO_2 plug (EtOAc) and concentrated. Purification of the residual oil using flash chromatography on SiO_2 (10% EtOAc/hexanes) provided the title compound as a colorless oil (319 mg, 85%). R_f 0.42 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56- 5.36 (m, 2H), 4.73 (ddd, J = 5.0, 8.5, 8.5 Hz, 1H), 4.43 (dd, J = 2.8, 2.8 Hz, 1H), 4.09 (ddd, J = 6.7, 6.7, 6.7, 1H), 3.99 (ddd, J = 6.7, 6.7, 8.2 Hz, 1H), 2.64 (ddd, J = 7.2, 7.2, 17.9 Hz, 1H), 2.53 (ddd, J = 7.4, 7.4, 17.9 Hz, 1H), 2.32-2.18 (m, 1H), 2.22 (dd, J = 7.2, 7.2 Hz, 2H), 2.16, 1.70 (m, 8H), 1.67-1.46 (m, 5H), 1.45-1.19 (m, 20H), 0.89 (dd, J = 6.1, 6.1 Hz, 3H), 0.15, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 132.3, 130.6, 107.3, 84.4, 83.4, 82.9, 80.9, 75.5, 37.9, 33.4, 31.9, 29.7, 29.63, 29.60, 29.58, 29.5, 29.4, 29.31, 29.25, 28.9, 28.39, 28.35, 28.0, 27.7, 22.6, 22.5, 19.7, 14.1, 0.1.



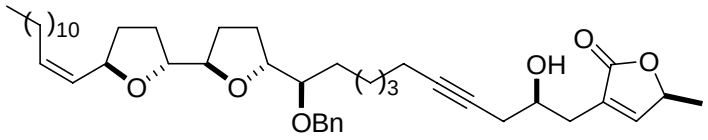
4.112

(2*R*,2'*R*,5*R*,5'*R*)-5-[(1*R*)-1-Hydroxyoct-7-ynyl]-5'-[(*Z*)-tridec-1-enyl]octahydro-[2,2']bifuran (4.112). To a rt solution of **4.96a** (261 mg, 0.50 mmol) in MeOH (1.8 mL) and Et_2O (0.4 mL) was added K_2CO_3 (50 mg, 0.36 mmol). After 8 h, the reaction mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (11% EtOAc/hexanes) provided the title compound as a colorless oil (213 mg, 95%): R_f 0.58 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.34 (m, 2H), 4.68 (ddd, J = 5.5, 8.2, 8.2 Hz, 1H), 3.92 (ddd, J = 6.2, 6.2, 8.5 Hz, 1H), 3.86 (ddd, J = 5.8, 5.8, 7.9 Hz, 1H), 3.80 (ddd, J = 6.5, 6.5, 8.2 Hz, 1H), 3.36 (ddd, J = 4.1, 6.8, 7.6 Hz, 1H), 2.39 (br s, 1H), 2.15 (ddd, J = 2.7, 7.2 Hz, 2H), 2.10-1.80 (m, 7H), 1.76-1.43 (m, 7H), 1.43-1.18 (m, 24H), 0.84 (dd, J = 6.8, 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2, 130.6, 84.6, 83.0, 81.9, 81.4, 75.4, 73.9, 68.1, 33.34, 33.26, 31.9, 29.7, 29.59, 29.58, 29.5, 29.3, 29.2, 29.0, 28.8, 28.7, 28.38, 28.36, 27.7, 25.1, 22.6, 18.3, 14.1; HRMS *m/z* 447.3838 (calc'd for $C_{29}H_{51}O_3$ $[M+H]^+$, 447.3838).



4.97

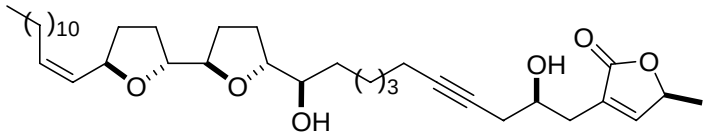
(2*R*,2'*R*,5*R*,5'*R*)-5-[(1*R*)-1-Benzyloxyocty-7-nyl]-5'-[(*Z*)-tridec-1-enyl]octahydro-[2,2']bifuran (4.97). A solution of **4.112** (207 mg, 0.46 mmol) in DMF (2.5 mL) was added dropwise to a suspension of NaH (29 mg, 0.95%, 1.2 mmol) and NBu_4I (17 mg, 46 μmol) in DMF (2.5 mL) at 0 °C. After 15 min, BnBr (0.18 mL, 1.4 mmol) was added dropwise. After 2 h, NH_4Cl (5 mL, sat'd) was added and the resulting mixture was extracted with Et_2O. The combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (8% EtOAc/hexanes) provided the title compound as a colorless oil (234 mg, 94%): R_f 0.72 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H), 7.28-7.26 (m, 1H), 5.51-5.37 (m, 2H), 4.74 (d, J = 11.6 Hz, 1H), 4.75-4.70 (m, 1H), 4.59 (d, J = 11.6, 1H), 4.12 (ddd, J = 5.8, 5.8, 8.9 Hz, 1H), 4.02-3.92 (m, 2H), 3.38 (ddd, J = 5.8, 5.8, 5.8 Hz, 1H), 2.16 (ddd, J = 2.7, 7.2, 7.2 Hz, 2H), 2.12-1.90 (m, 7H), 1.90-1.19 (m, 29H), 0.88 (dd, J = 6.5, 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 132.2, 130.8, 128.2, 127.9, 127.3, 84.6, 81.7, 81.6, 81.15, 81.10, 75.3, 72.7, 68.1, 33.4, 31.9, 30.5, 29.7, 29.65, 29.62, 29.60, 29.5, 29.32, 29.26, 28.83, 28.80, 28.2, 27.7, 25.3, 22.7, 18.3, 14.1; HRMS *m/z* 537.4298 (calc'd for $C_{36}H_{57}O_3$ $[M+H]^+$, 537.4308).



4.98

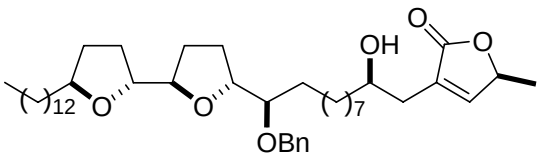
3-{(2*S*,11*R*)-11-[(2*R*,2'*R*,5*R*,5'*R*)-5'-(*Z*)-Tridec-1-enyloctahydro-[2,2']bifuran-5-yl]-11-benzyloxy-2-hydroxyundec-4-ynyl}-5-methyl-5*H*-furan-2-one (4.98). A solution of **4.97** (217 mg, 0.41 mmol) in THF (1 mL) was cooled to -78 °C and *n*-BuLi (150 μL, 2.59 M, 0.39 mmol) was added dropwise. After 15 min, BF_3•OEt_2 (51 μL, 0.40 mmol) was added dropwise and after an additional 30 min, a solution of **4.75** (37 mg, 0.24 mmol) in THF (0.5 mL) was added dropwise. After 3 h, MeOH (1 mL) was added and the reaction mixture was poured cold into a stirred solution of NH_4Cl (20 mL, sat'd). The resulting mixture was extracted with Et_2O and the combined extracts were dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (40% EtOAc/hexanes) provided the title compound as a colorless oil (90 mg, 62%, 89% BRSM): R_f 0.43 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 4H), 7.26-7.21 (m, 1H), 7.20 (d, J = 1.0 Hz, 1H), 5.49- 5.32 (m, 2H), 5.02 (dddd, J = 1.4, 6.8, 6.8, 6.8 Hz, 1H), 4.74-4.67 (m, 1H), 4.72 (d, J = 11.6, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.14-4.06 (m, 1H), 4.00-3.89 (m, 3H), 3.36 (ddd, J = 7.9, 7.9, 7.9 Hz, 1H), 2.57 (dddd, J = 1.7, 1.7, 3.8, 15.4 Hz, 1H), 2.49 (dddd, J = 1.5, 1.5, 8.2, 15.4 Hz, 1H), 2.39 (dddd, J = 2.4, 2.4, 5.8, 16.8 Hz, 1H), 2.33 (dddd, J = 2.4, 2.4, 6.2, 16.8 Hz, 1H), 2.16-1.85 (m, 8H), 1.85-1.18 (m, 28H), 1.40 (d, J = 6.8 Hz, 3H), 0.85 (dd, J = 6.5, 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 152.1, 139.1, 132.2, 130.8, 130.6, 128.2, 127.9, 127.3, 83.7, 81.64, 81.60, 81.2, 81.1, 78.0, 75.4, 75.3, 72.7, 68.3, 33.4, 32.0, 31.9, 30.5, 29.7, 29.62,

29.60, 29.58, 29.3, 29.2, 29.0, 28.9, 28.8, 28.2, 28.1, 27.7, 27.5, 25.4, 22.6, 19.0, 18.6, 14.1; HRMS *m/z* 691.4953 (calc'd for $C_{44}H_{67}O_6$ $[M+H]^+$, 691.4938).



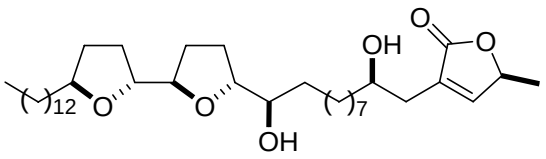
4.99

3-{(2*S*,11*R*)-11-[(2*R*,2'*R*,5*R*,5'*R*)-5'-(*Z*)-Tridec-1-enyloctahydro-[2,2']bifuran-5-yl]-2,11-dihydroxy-undec-4-ynyl}-5-methyl-5*H*-furan-2-one (4.99). A solution of **4.98** (75 mg, 0.11 mmol) in 1,2-dichloroethane (2 mL), H_2O (0.16 mL), and pH 7 buffer solution (0.16 mL) was protected from light and heated to 50 °C. To this solution was added DDQ (184 mg, 0.8 mmol) in one portion, and the resulting mixture was stirred at 50 °C for 2 h. The mixture was allowed to cool and diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ (sat'd), dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography on SiO_2 (elution gradient: 60% EtOAc/hexanes to 80% EtOAc/hexanes) provided the title compound as a colorless oil (15 mg, 23%): R_f 0.24 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 1.0 Hz, 1H), 5.52-5.36 (m, 2H), 5.03 (dq, J = 1.4, 6.8 Hz, 1H), 4.72 (ddd, J = 7.2, 7.2, 7.2 Hz, 1H), 4.01-3.78 (m, 4H), 3.42-3.36 (m, 1H), 2.63-2.43 (m, 2H), 2.43-1.84 (m, 12H), 1.76-1.17 (m, 35H), 1.84 (dd, J = 6.5, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 152.1, 132.2, 130.63, 130.58, 83.6, 83.0, 82.0, 81.5, 78.0, 75.4, 74.0, 68.4. 33.4, 33.3, 32.0, 31.9, 29.7, 29.64, 29.61, 29.59, 29.5, 29.32, 29.26, 29.0, 28.9, 28.84, 28.78, 28.4, 27.7, 27.5, 25.1, 22.7, 19.0, 18.6, 14.1; HRMS *m/z* 601.4469 (calc'd for $C_{37}H_{61}O_6$ $[M+H]^+$, 601.4468).



4.113

3-{(2*S*,11*R*)-11-[(2*R*,2'*R*,5*R*,5'*R*)-5'-tridecanyloctahydro-[2,2']bifuran-5-yl]-11-benzyloxy-2-hydroxyundecanyl}-5-methyl-5*H*-furan-2-one (4.113). A solution of **4.98** (52 mg, 75 μmol) and *p*-toluenesulfonyl hydrazide (2.6 g, 14 mmol) in ethylene glycol dimethyl ether (13 mL) was heated at reflux. An aqueous solution of NaOAc (10.9 mL, 1.6 M, 17 mmol) was added over 4 h by syringe pump. The mixture was refluxed for an additional 1 h and allowed to cool to rt. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification of the crude material by flash chromatography on SiO_2 (elution gradient: 40% EtOAc/hexanes to 60% EtOAc/hexanes) gave a colorless oil (48 mg, 69 μmol, 92%): R_f 0.28 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 7.16 (d, J = 1.0 Hz, 1H), 5.02 (dq, J = 1.3, 6.7 Hz, 1H), 4.71 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.14-4.02 (m, 1H), 3.88-3.76 (m, 1H), 2.55-2.25 (m, 3H), 2.06-1.82 (m, 4H), 1.79-1.52 (m, 4H), 1.50-1.15 (m, 41H), 1.40 (d, J = 6.7 Hz, 3H), 0.85 (dd, J = 6.9, 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 151.8, 139.2, 131.1, 128.1, 127.9, 127.3, 81.8, 81.5, 81.3, 79.8, 77.9, 72.7, 69.9, 37.4, 35.8, 33.3, 31.9, 30.5, 29.8, 29.7, 29.63, 29.60, 29.59, 29.5, 29.3, 28.3, 28.1, 26.2, 25.8, 25.5, 22.6, 19.1, 14.1.



22-Deoxysquamotacin

22-Deoxysquamotacin. The title compound was prepared from **4.113** (35 mg, 50 μmol) using the general procedure described for **4.99** (colorless oil, 28 mg, 94%): R_f 0.38 (60% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 1.4 Hz, 1H), 5.02, (dq, J = 1.4, 6.8 Hz, 1H), 3.94-3.76 (m, 5H), 3.35 (ddd, J = 6.8, 6.8, 6.8 Hz; 1H), 2.49 (dddd, J = 1.7, 1.7, 3.4, 15.0 Hz, 1H), 2.39 (br s, 2H), 2.36 (dddd, J = 1.4, 1.4, 8.2, 15.0 Hz, 1H), 2.02-1.86 (m, 5H), 1.68-1.55 (m, 5H), 1.50-1.17 (m, 50H), 0.84 (dd, J = 6.8, 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 151.8, 151.1, 83.0, 82.1, 81.2, 78.0, 74.0, 69.9, 37.3, 35.8, 33.3, 32.0, 31.9, 29.7, 29.64, 29.62, 29.56, 29.4, 29.3, 28.9, 28.3, 26.1, 25.6, 25.5, 22.6, 19.1, 14.1; HRMS *m/z* 607.4938 (calc'd for $C_{37}H_{67}O_6$ $[M+H]^+$, 607.4938).

References

1 Wilkinson, G.; Birmingham, J. M. *J. Am. Chem. Soc.* **1954**, *76*, 4281.

2 Negishi, E.-I.; Montchamp, J.-L. in *Metallocenes*, vol. 1; Togni, A.; Halterman, R. L., Eds.; Wiley-VCH: New York, **1998**, pp 241-319.

3 a) Kautzner, B.; Wailes, P. C.; Weigold, H. *J. Chem. Soc. D: Chem. Commun*. **1969**, 1105. b) Wailes, P. C.; Weigold, H. *J. Organomet. Chem*., **1970**, *24*, 405-411. c) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1971**, *27*, 373-378.

4 a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc*.**1974**, *96*, 8115-8116. b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 333-340. c) Labinger, J. A. in *Comprehensive Organic Synthesis*, vol. 8, Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, pp 667-702.

5 Blackburn, T. F.; Labinger, J. A.; Schwartz, J. *Tetrahedron Lett.* **1975**, *16*, 3041-3044.

6 Bertelo, C. A.; Schwartz, J. J. Am. Chem. Soc. 1975, 97, 228-230.

7 Cardin, C. J.; Cardin, D. J.; Kelly, J. M.; Norton, R. J.; Roy, A. *J. Organomet. Chem*. **1977**, *132*, C23-C25. b) Lappert, M. F.; Luong-Thi, N. T.; Milne, C. R. C. *J. Organomet. Chem*. **1979**, *174*, C35-37.

8 Buchwald, S. L.; Lamaire, S. J. *Tetrahedron Lett*. **1987**, *28*, 295-298.

9 Negishi, E.-I.; Swanson, D. R.; Miller, S. R. *Tetrahedron Lett.* **1988**, *29*, 1631-1634.

10 For a report of addition of hydrozirconation products and zirconocycles to activated alkenes, see Liu, Y.; Shen, B.; Kotora, M.; Nakajima, K.; Takahashi, T. *J. Org. Chem*. **2002**, *67*, 7019-7028.

11 a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett*. **1992**, *33*, 5965-5968. b) Wipf, P.; Xu, W. *J. Org. Chem*., **1993**, *58*, 825-826.

12 a) Wipf, P.; Jahn, H. *Tetrahedron*, **1996**, *52*, 12853-12910. b) Wipf, P. *Synthesis*, **1993**, 537-557. c) Lipshutz, B.H.; Sengupta, S. *Org. React*. **1992**, *41*, 135-631.d) Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett*. **1977**, *18*, 1303-1306. Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc*. **1990**, *112*, 7440-7441. e) Wipf, P.; Smitrovitch, J. H. *J. Org. Chem*. **1991**, *56*, 6494-6496. f) Wipf, P.; Xu, W. J.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1994**, *50*, 1935-1954.

13 Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5647-5650.

14 Venanzi, L. M.; Lehmann, R.; Keil, R.; Lipshutz, B. H. *Tetrahedron Lett*. **1992**, *33*, 5857-5860.

15 a) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045-8046. b) Negishi, E.-I.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168-3170. c) Negishi, E.-I.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem Soc*. **1987**, *109*, 2393-2401.d) Okukado, N,; Van Horn, D. E. Klima, W. E.; Negishi.E.-I. *Tetrahedron Lett*. **1978**, *19*, 1027-1030.

16 Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5198-5200.

17 Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc*. **1978**, *100*, 2254-2256. b) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc*. **1994**, *116*, 11689-11702.

18 a) Cole, T. E.; Quintanilla, R.; Rodewald, S. *Organometallics* **1991**, *10*, 3777. b) Quintanilla, R.; Cole, T. E.; *Tetrahedron*, **1995**, *51*, 4297-4308. c) Cole, T. E.; Rodewald, S.; Watson, C. *Tetrahedron, Lett*. **1992**, *33*, 5295-5298. d) Cole, T. E. Gonzalez, T. *Tetrahedron Lett.* **1997**, *38*, 8487-8490.

19 Alt, H.; Rausch, M. D. *J. Am. Chem. Soc*. **1974**, 5936-5937.

20 a) Famili, A.; Farona, M. F.; Thanedar, S. *J. Chem. Soc. Chem. Commun*. **1983**, 435-436. b) Shur, V. B.; Bekovich, E. G.; Vol'pin, M. E.; Lorenze, B.; Wahren, M. J. *J. Organomet. Chem.* **1982**, *228*, C36-C38.

21 Erker, G.; Kropp, K. *J. Am. Chem. Soc*. **1979**, *101*, 3659-3660.

22 Erker, G. *J. Organomet. Chem*. **1977**, *134*, 189-202.

23 a) Buchwald, S. L; Nielsen, R. B. Chem. Rev. 1988, 88, 1047-1058. b) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc*. **1987**, *109*, 2544-2546.

24 Negishi, E.-I.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *28*, 2829-2832.

25 Negishi, E.-I.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc*., **1985**, *107*, 2568-2569.

26 Negishi, E.-I.; Maye, J. P.; Choueiry, D. *Tetrahedron*, **1995**, *51*, 4447-4462.

27 a) Fagan, P. J.; Nugent, W. A. J. *Am. Chem. Soc.* **1988**, *110*, 2310-2312. b) Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc*. **1994**, *116*, 1880-1889.

28 Dumond, Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1999**, *121*, 11223-11224.

29 Gordon, G. J.; Whitby, R. J. *Chem. Commun*. **1997**, 1321-1322.

30 Copéret, C.; Negishi, E.-I. *Tetrahedron Lett*. **1994**, *35*, 695-698.

31 Takahashi, T.; Aoyagi, K; Hara, R.; Suzuki, N. *J. Chem. Soc., Chem. Commun.* **1993**, 1042-1044.

32 a) Takahashi, T.; Aoyagi, K.; Kondakov, D. Y. *J. Chem. Soc., Chem. Commun.* **1994**, 747-748. b) Aoyagi, K.; Kasai, K.; Kondakov, D. Y. Hara, R.; Suzuki, N.; Takahashi, T. *Inorganica Chimica Acta*, **1994**, *220*, 319-326.

33 a) Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407-4420. b) Venanzi, L. M.; Lehmann, R.; Kell, R.; Lipshutz, B. H. *Tetrahedron Lett*. **1992**, *33*, 5857-5860.

34 Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 109-110.

35 Brown, H. C.; Singh, S. M. *Organometallics*. **1986**, *5*, 998-1001.

36 Brown, H. C.; Negishi, E.-I. *J. Am. Chem. Soc*. **1967**, *89*, 5477-5478.

37 Kirchoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 1945-1947.

38 Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett*. **2002**, *4*, 2993-2995.

39 Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis*, **1980**, 627-630.

40 Magnus, P.; Exon C.; Albaugh-Robertson, P.. *Tetrahedron* **1985**, *41*, 5861-5869.

41 Iacono, S. T. *Advances in Transition Metal Mediated Inramolecular Cycloisomerizations of 1,6-Substituted Enynes*, Masters Thesis, University of Texas at Austin.

42 a) Beesley, R. M.; Ingold, C. K. Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080-1106. b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735-1766.

43 a) Lund, E. C.; Livinghouse, T. *J. Org. Chem*, **1989**, *54*, 4487. b) Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421-4438.

44 RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc*., **1988**, *110*, 7128-7135.

45 a) Sommer, L. H.; Bailey, D. L.; Goldberg, G. M.; Buck, C. E.; Bye, T. S.; Evans, F. J.; Whitmore, F. C. *J. Am. Chem. Soc.* **1954**, *76*, 1613-1618. b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev*. **1986**, *86*, 857-873.

46 Gorman, J. S. T.; Iacono, S. T.; Pagenkopf, B. L. *Org. Lett*. **1994**, *6*, 67-70.

47 For reviews: a) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K. McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275-306. b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L *J. Nat. Prod*., **1999**, *62*, 504-540. c) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod*. **1990**, *53*, 237-278. d) Gu, Z.-M.; Zhoa, G.-X.; Oberlies, N. H.; Zeng, L.; McLaughlin, J. L. In *Recent Advances in Phytochemistry*, vol. 29, Plenum Press: New York, **1995**, pp 249-310.

48 a) O'Hagan, D. *Nat. Prod. Rep*. **1989**, *6*, 205-219. b) Westley, J. W. *J. Nat. Prod*. **1986**, *49*, 35-47.

49 Postema, M. H. D. *Tetrahedron*, **1992**, *48*, 8545-8599.

50 a) Harmange, J.-C.; Figadére, B. *Tetrahedron: Asymmetry* **1993**, 1711-1754. b) Boivin, T. L. B., *Tetrahedron*, **1987**, *43*, 3309-3362.

51 Hui, Y. H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat Prod.* **1989**, *52*, 463-77.

52 Hopp, D. C.; Zeng, L.; Gu, Z. M.; McLaughlin, J. L. *J. Nat. Prod.* **1996**, *59*, 97-99.

53 Wagner, H.; Koert, U.; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 1873-1875. b) Emde, U.; Koert, U. *Tetrahedron Lett*. **1999**, *40* 5979-5982.

54 a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768-2771. b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-547.

55 a) Tian, S.-K.; Wang, Z.-M.; Jiang, J. K.; Shi, M. *Tetrahedron: Asymmetry*, **1999**, *10*, 2551-2562. b) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Eur. J. Org. Chem.* **2000**, 349-356. The authors also reported use of the Mukaiyama method for synthesis of the mono-THF unit of the acetogenin gigantetrocin A: c) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron: Asymmetry*, **1999**, *10*, 667-670. d) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Chirality*, **2000**, *12*, 581-589.

56 Inoki, S.; Mukaiyama, T. *Chem. Lett*. **1990**, 67-70.

57 a) Isayama, S.; Mukaiyama, T. *Chem. Lett*. **1989**, 573-576. b) Isayama, *Bull. Chem. Soc.* Jpn., **1990**, *63*, 1305-1310. c) Mukaiyama, T.; Yamada, T. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 17-35.

58 Inoki, S.; Kato, T.; Takai, S.; Isayama, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett*. **1989**, 515-518.

59 a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc*. **1973**, *95*, 6136-6137. b) Mihelich, E. D.; Daniels, K. Eickhoff, D. J. *J. Am. Chem. Soc*. **1981**, *103*, 7690-7692. c) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc*. **1978**, *100*, 2933-2934.

60 a) Kennedy, R. M.; Tang, S. *Tetrahedron Lett*. **1992**, *33*, 3729-3732. b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett*. **1992**, *33*, 5299-5302. c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett*. **1992**, *33*, 5303-5306. d) Boyce, R. S.; Kennedy, R. M. *Tetrahedron Lett*. **1994**, *35*, 5133-5136.

61 Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc*. **2003**, *125*, 14702-14703.

62 Takahashi, S.; Kubota, A. Nakata, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 4751-4754.

63 Drees, S.; Greb, M. Hartung, J. Schmidt, P. In *Peroxide Chemistry: Mechanistic and Preparative Aspects of Oxygen Transfer*, Adam, W., Ed. Wiley-VCH: Weingheim, Germany, **2000**, pp 281-300.

64 Isayama, S. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 1305-1310.

65 Vogel, D. E.; Buchi, G. H. *Org. Synth*. **1988**, *66*, 29-36.

66 Robbins, M. A.; Devine, P. N.; Oh, T. *Org. Synth.* **1999**, *76,* 101-109.

67 Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem*. **1990**, *55*, 4417-4422.

68 Hoye, T. R.; Ramirez, E. A. in *Studies in Natural Products Chemistry*, vol. 17, ur-Rahman, A., Ed., Elsevier Science B. V.: Amsterdam, **1995**, 251-282.

69 Hartung, J.; Drees, S.; Greb, M.; Schmidt, P.; Svoboda, I.; Fuess, H.; Murso, A.; Stalke, D. *Eur. J. Org. Chem.* **2003**, 2388-2408.

70 a) Londershausen, M.; Leicht, W.; Lieb, F.; Moeschler, H. *Pestic. Sci.* **1991**, *33*, 427-438. b) Ahammadsahib, K. I.; Hollingworth, R. M.; McGovern, J. P.; Hui, Y.-H.; McLaughlin, J. L. *Life Sci*. **1993**, *53*, 1113-1120. c) Morré, D. J.; de Cabo, R.; Farley, C.; Oberlies, N. H.; McLaughlin, J. L. *Life Sci*., **1995**, *56*, 343-348.

71 a) He, K.; Zeng, L.; Ye, Q.; Shi, G.; Oberlies, N. H.; Zhao, G.-X.; Njoku, C. J.; McLaughlin, J. L. *Pestic. Sci.* **1997**, *49*, 372-378. b) Ye, Q.; He, K.; Oberlies, N. H.; Zeng, L.; Shi, G.; Evert, D.; McLaughlin, J. L. *J. Med. Chem.* **1996**, *39*, 1790-1796. c) Oberlies, N. H.; Chang, C.-j.; McLaughlin, J. L. *J. Med. Chem*. **1997**, *40*, 2102-2106. d) Tormo, J. R.; DePedro, N.; Royo, I.; Barrachina, I.; Zafra-Polo, M. C.; Cuadrillero, C.; Hernández, P.; Cortes, D.; Peláez, F. *Oncol. Res*. **2005**, *15*, 129-138. e) Royo, I.; DePedro, N.; Estornell, E.; Cortes, D.; Peláez, F; Tormo, J. R. *Oncol. Res*. **2003**, *13*, 521-528. f) Tormo, J. R; Royo, I.; Gallardo, T.; Zafra-Polo, M. C.; Hernández, P.; Hernández, P.; Cortes, D.; Peláez, F. *Oncol. Res*. **2003**, *14*, 147-154. g) Takada, M.; Kuwabara, K.; Nakato, H.; Tanaka, A.; Iwamura, H.; Miyoshi, H. *Biochim. Biophys. Acta* **2000**, *1460*, 302-310. h) Abe, M.; Kenmochi, A, Ichimaru, N.; Hamada, T.; Nishioka, T.; Miyoshi, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 779-782. i) Landolt, J. L.; Ahammadsahib, K. I.; Hollingworth, R. M.; Barr, R.; Crane, F. L. Buerck, N.L.; McCabe, G. P.; McLaughlin, J. L. *Chemico-Biol. Interact*. **1995**, *98*, 1-13. j) Alfonso, D.; Johnson, H. A.; Colman-Salzarbitoria, T.; Presley, C. P.; McCabe, G. P.; McLaughlin, J. L. *Nat. Toxins*, **1996**, *4*, 181-188. k) Miyoshi, H.; Ohshima, M.; Shimada, H.; Akagi, T.; Iwamura, H.; McLaughlin, J. L. *Biochim. Biophys. Acta*, **1998**, *1365*, 443-452.

l) Gallardo, T.; Zafra-Polo, C.; Tormo, J. R. González, M. C.; Franck, X.; Estornell, E.; Cortes, D. *J. Med. Chem*. **2000**, *43*, 4793-4800. m) Kuwabara, K.; Takada, M.; Iwata, J. Tatsumoto, K.; Sakamoto, K; Iwamura, H.; Miyoshi, H. *Eur. J. Biochem.* **2000**, *267*, 2548-2546.

72 For reviews: a) Marshall, J. A.; Hinkle, K. W.; Hagedorn, C. E. *Isr. J. Chem*. **1997**, *37*, 97-107. b) Figadere, B. *Acc. of Chem. Res*. **1995**, *28*, 359-365. c) Bermejo, A.; Figadere, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep*. **2005**, *22*, 269-303. d) Hoppe, R.; Scharf, H. D.; *Synthesis*, **1995**, *1447*-1464. e) Casiraghi, G.; Zanardi, F. Battistini, L.; Rassu, G. *Chemtracts: Org. Chem*, **1998**, *11*, 803-827.

73 Okun, J. G.; Lümmen, P.; Brandt, U. *J. Biol. Chem.,* **1999**, *274*, 2625-2630.

74 Shimada, H.; Grutzner, J. B.; Kozlowski, J. F.; McLaughlin, J. L. *Biochem*. **1998**, *37*, 854-866.

75 Oberlies, N. H.; Croy, V. L.; Harrison, M. L.; McLaughlin, J. L. *Cancer Lett*. **1997**, *115*, 73-79.

76 Ling, V. *Cancer Res*. **1992**, *69*, 385-427.

77 Zhao, H. Stereospecific Alkynylation at the More Hindered Carbon of Trisubstituted Epoxides and Concise Syntheses of Bis-THF Acetogenins and Analogues Ph.D. Dissertation, University of Texas at Austin.

78 Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M, Sasaki, S. *J. Org. Chem*. **1995**, *60*, 4419-4427.

79 Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H., Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

80 Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. *Tetrahedron Lett*. **1995**, *36*, 9257-9260.

81 Sinha, S. C.; Sinha, S. C.; Keinan, Ehud *J. Org. Chem*. **1999**, *64*, 7067-7073.

82 Hoye, T. R.; Lushi, T. *Tetrahedron Lett.* **1995**, *36*, 1981-1984.

83 Hughes, David L. *Org Prep Proc. Int*. **1996**, *28*, 127-64.

84 Tinsley, J. M.; Mertz, E.; Chong, P. Y.;Rarig, R.-A. F.; Roush, W. R. *Org. Lett*. **2005**, *7*, 4245-4248.

85 Masse, C. E.; Panek, J. S. *Chem. Rev*. **1995**, *95*, 1293-1316.

86 White, J. D.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc*. **1986**, *108*, 5352-5253.

87 Shunya, T.; Kenji, F.; Nobuo, S.; Tadashi, N. *Heterocycles* **2000**, *53*, 1361-1370.

88 Harmange, J.-C.; Figadére, B.; Cavé, A. *Tetrahedron Lett*. **1992**, *33*, 5749-5752.

89 Harms, A. E.; Stille, J. R. *Tetrahedron Lett*.**1992**, *33*, 6565-6568.

90 Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885-888.

91 Cominetti, F.; Deagostino, A.; Prandi, C.; Venturello, P. *Tetrahedron* **1998**, *54*, 14603-14608.

92 Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; 4th Ed.; Oxford: Butterworth-Heinemann, 1996.

93 Adrio, J.; Rivero, M. R.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 2435 - 2448.

94 Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc*. **1988**, *110*, 1286.

95 Sugawara, M.; Yoshida, J.-i.; *Tetrahedron*, **2000**, *56*, 4683-4690.

96 Kim, D. H.; Li, Z.-H.; Lee, S. S.; Park, J.-i.; Chung, S. J. *Bioorg. Med. Chem.* **1998**, *6*, 239-250.

97 Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem*. **1992**, *11*, 2986-2987.

98 Igner, E.; Paynter, O. I.; Simmonds, D. J.; Whiting, M. C. *J. Chem. Soc. Perkin Trans.* **1987**, *1*, 2447-2454.

99 Spino, C.; Barriault, N. *J. Org. Chem*. **1999**, *6*4, 5292-5298.

100 Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889-1904.

Vita

Jeff Gorman, the youngest of Thomas and Roberta Gorman's eight children, was born in Richmond, Virginia in the summer of 1976. In 1994, he matriculated at the Virginia Military Insititute, where researching the chemistry of ant venoms under the tutelage of Dr. Tappey Jones spawned his interest in organic chemistry. After earning a B.S. in Chemistry in May 1998, Jeff worked two years for Wyeth-Ayerst Pharmaceuticals at their Richmond production plant, conducting manufacturing and packaging equipment validations to ensure cGMP compliance. Anxious to return to organic chemistry, he enrolled in the Ph.D. program at the University of Texas at Austin in the fall of 2000. There, under the guidance and support of Dr. Brian Pagenkopf, Jeff has conducted research in a variety of areas including ligand design and synthesis, methodologies involving transition metal-mediated cyclizations and syntheses of natural product analogs. Upon completion of his Ph.D., he plans to teach in a postdoctoral position at St. Edward's University in Austin, Texas.

Permanent Address: 6530 Buckhill Rd.
Richmond, Virginia 23225

This dissertation was typed by the author