MACROCYCLIZATION THROUGH ENE–YNE CROSS-COUPLING/ALKYNE REDUCTION TANDEM REACTION AND ITS APPLICATION IN NATURAL PRODUCT SYNTHESIS

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Abstract

Chapter 1 — Macrocyclization Through Copper-Catalyzed Castro–Stephens Coupling/Alkyne Reduction Tandem Reaction

Macrocycles, incorporating conjugated polyene subunits within the ring, are structural features found in a number of natural products that exhibit diverse and potent biological activities. Existing methods for the construction of such structures are limited and in many cases inefficient. We discovered an unprecedented copper-mediated reductive ene–yne macrocyclization reaction during our pursuit of the total synthesis of oximidine II. The reaction selectively generates an endocyclic *Z*-double bond through an intramolecular coupling of a vinyl iodide and a terminal alkyne fragment followed by *in situ* alkyne reduction. We developed this transformation as a general method for the preparation of polyunsaturated macrocycles. The reaction conditions were optimized and the scope of the reaction was extensively explored. It was found that the alkyne reduction step is driven by the release of the ring strain. Thus, the reaction is particularly efficient for suitably strained 11- to 13-membered *E*,*Z*-1,3-diene macrocycles. A complementary stepwise procedure was employed for the synthesis of larger rings. Finally, a plausible reaction mechanism was proposed based on experimental findings.

Chapter 2 — Formal Total Synthesis of Lactimidomycin

Lactimidomycin is a macrocyclic natural product that possesses potent *in vitro* and *in vivo* anti-tumor activities. We accomplished a facile, 9-step synthesis of an advanced intermediate for the total synthesis of lactimidomycin. The crucial 12-membered polyene lactone core structure was constructed employing our newly developed Castro–Stephens coupling/alkyne reduction tandem reaction. The stereocenters were established via asymmetric a vinylogous aldol reaction and a Marshall's propargylation reaction.

Chapter 3 — Synthesis and Biological Evaluation of Oximidine II Analogues

Oximidine II belongs to a family of benzolactone enamide natural products that exert their cytotoxic effects through inhibition of V-ATPases. Unlike other members of this family, the structure-activity relationship (SAR) of oximidines has not been extensively investigated. Guided by computational analysis and previous studies in our group, we designed and synthesized two oximidine II analogues with simplified scaffold. The simplified benzolactone core was accessed through a ring-closing metathesis (RCM) reaction and the enamide side chain was installed via a copper-mediated *C–N* coupling reaction. The analogues were evaluated for their biological activity. The results revealed that these molecules were weakly cytotoxic to a number of cancer cell lines.

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3D-QSAR	3-dimensional quantitative structure-activity relationship
Ac	acetyl
AIBN	azobisisobutyronitrile
APC	allylpalladium chloride dimer
Ar	aryl
BHT	butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
br	broad
CoMSIA	comparative molecular similarity indices analysis
Cp	cyclopentadienyl
CuTC	copper(I) thiophene-2-carboxylate
Cy	cyclohexyl
d	doublet
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMB	dimethoxybenzyl
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin Periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
e.r.	enantiomeric ratio
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl
h	hour(s)
HMPA	hexamethylphosphoramide
Hsp90	heat shock protein 90
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocampheyl

IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
^{i}Pr	isopropyl
IR	infrared
KHMDS	potassium hexamethyldisilazide
L	ligand
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
min	minute(s)
MOM	methoxymethyl
MS	molecular sieve
Ms	mesyl
NaHMDS	sodium hexamethyldisilazide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
^{n}Bu	butyl
p-TSA	*para*-toluenesulfonic acid
Ph	phenyl
phanephos	4,12-bis(diphenylphosphino)-[2.2]-paracyclophane

piv	pivaloyl
PMB	*para*-methoxybenzyl
PMHS	polymethylhydrosiloxane
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Py	pyridine
q	quartet
quint	quintet
rac	racemic
RCAM	ring-closing alkyne metathesis
RCM	ring-closing metathesis
rt	room temperature
s	singlet
SAR	structure-activity relationship
^{s}Bu	*sec*-butyl
Sphos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
^{t}Bu	*tert*-butyl
Teoc	trimethylsilylethoxycarbonyl

TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMAD	tetramethylazodicarboxamide
TME	trimethylolethane
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
tol	tolyl
Ts	tosyl
V-ATPase	vacuolar-type (H^+)-ATPase

Chapter I. Macrocyclization Through Copper-Catalyzed Castro–Stephens Coupling/Alkyne Reduction Tandem Reaction

1.1 Background

Macrocycles are recurring structural units present in a myriad of biologically important natural products and more than 100 marketed drugs.[1-7] By virtue of their intrinsically restrained conformation, macrocyclic compounds have been found to exhibit higher binding affinities and selectivities to proteins, and better oral bioavailability than their acyclic analogues. Established methods of synthesizing macrocycles include lactonization,[8-9] lactamization,[10] radical cyclizations,[11] ring-closing metathesis (RCM),[12] palladium-catalyzed coupling reactions,[13] *etc*. Despite their successful application in obtaining certain macrocycles, these methods have some limitations. For example, RCM reactions could potentially generate a mixture of stereoisomers and ring-contraction products.[14-21] Palladium chemistry-based methods usually produce stoichiometric amounts of useless, sometimes toxic byproducts, and the introduction of the required coupling components (e.g., organoboron, organostannane) is often a multi-step, yet inefficient process. Due to the unique drug-like properties of macrocyclic compounds and the limitations of existing technology, continuing efforts are aimed at improving the efficiency of their chemical synthesis through developing new methodologies.

We are particularly interested in macrocycles possessing conjugated *E*,*Z*-diene units within the ring since this motif exists in a number of natural products with diverse and potent bioactivities such as latrunculin A,[22-25] radicicol,[26-29] lactimidomycin,[30-31] and oximidine II (Figure 1–1).[32] The rigid nature of unsaturated bonds contributes additional ring strain, making these compounds even more synthetically challenging than their saturated analogues. Most reported total syntheses of these natural products have so far relied on variants of RCM reactions.[14, 33-41] A palladium-catalyzed Suzuki cross-coupling reaction was also employed for the synthesis of oximidine II.[42]

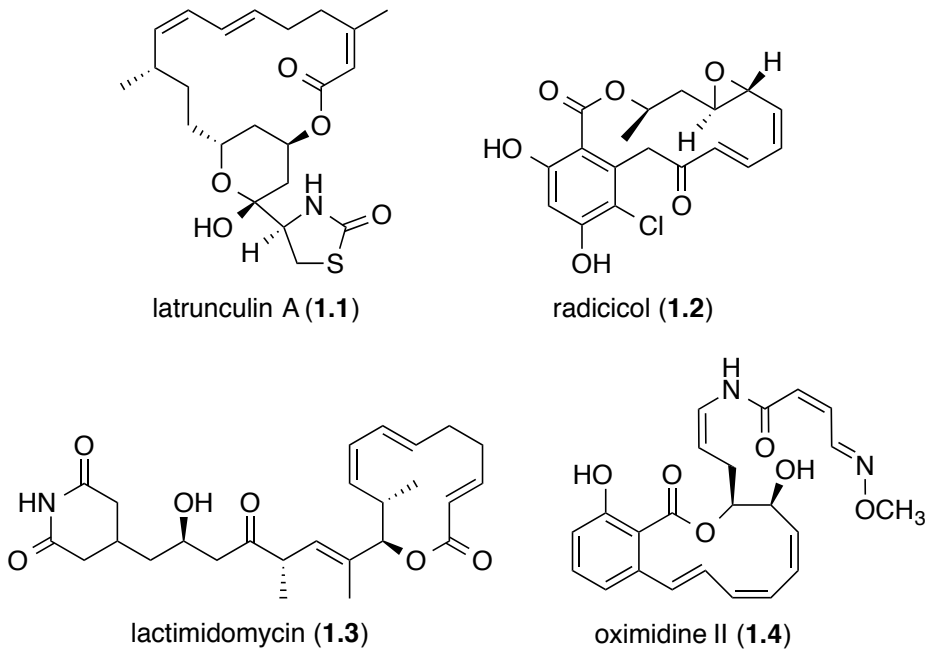


Figure 1–1. Selected examples of polyunsaturated macrocyclic natural products.

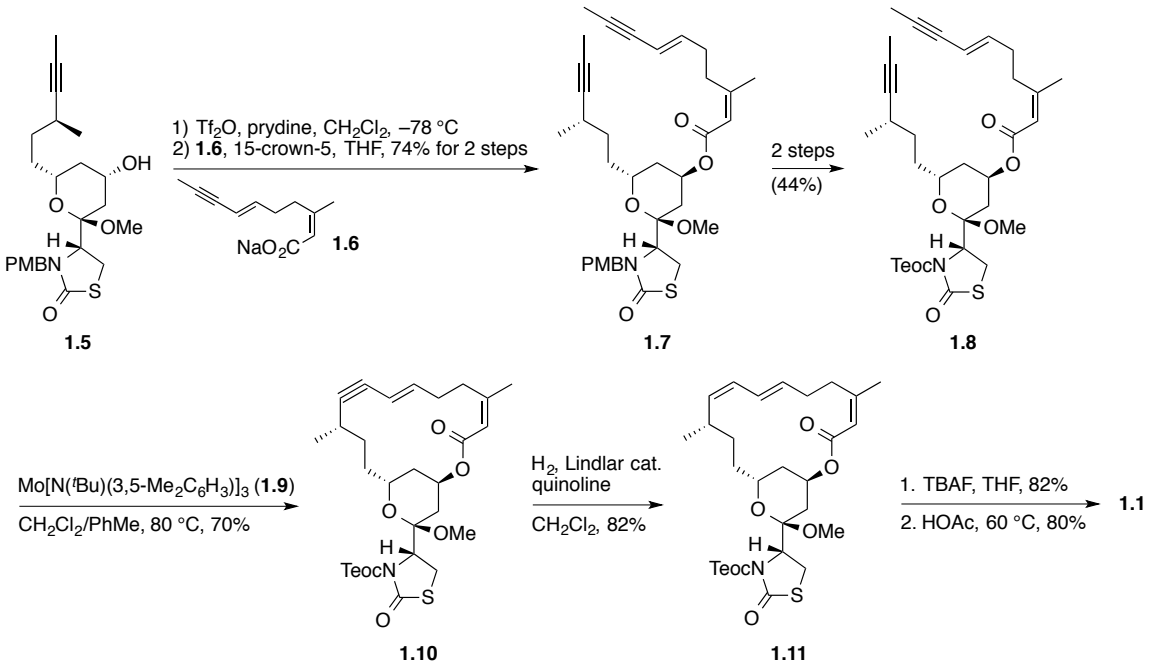
1.1.1 Total Syntheses of Latrunculin A

Latrunculin A (**1.1**) was first isolated from the Red Sea sponge *Negombata magnifica* (formerly *Latrunculia magnifica*).[22-23] It was shown to bind reversibly to the cytoskeletal protein actin with 1:1 stoichiometry and prohibit actin polymerization.[43] Thus, latrunculin

A and its structurally related congeners have been widely used as chemical probes for exploring the biological behavior of the actin cytoskeleton.[44] The remarkable biological profiles have prompted synthetic investigations and three total syntheses have been reported.

Both of the early two total syntheses in 1990, accomplished by Smith[45-46] and White[47-48] respectively, constructed the *E*,*Z*-1,3-diene structure through a Wittig olefination reaction and the macrocycle by Mitsunobu lactonization. However, the ring-closing steps were extremely inefficient with yields of 28-44%.

Scheme 1–1. Fürstner's Total Synthesis of Latrunculin A



The more recent total synthesis of latrunculin A (**1.1**, Figure 1–1) by Fürstner et al. employed a ring-closing alkyne metathesis (RCAM) approach (Scheme 1–1).[33-34] The triflate of alkynyl alcohol **1.5** underwent an S_N2 reaction with the sodium salt of alkynyl carboxylic acid **1.6** to provide diyne ester **1.7**. Replacement of the *N*-PMB group with a

Teoc protecting group set compound **1.8** ready for the key macrocyclization step. Chemoselective alkyne metathesis of the two triple bonds of compound **1.8** was effectuated upon treatment with molybdenum catalyst **1.9**, affording the 16-membered enyne lactone **1.10** in 70% percent yield. It was claimed that this is the smallest ring size ever to be formed by ring-closing enyne–yne metathesis. *Z*-Selective semihydrogenation of the triple bond with Lindlar's catalyst and subsequent cleavage of the protecting groups completed the total synthesis of latrunculin A. This concise and practical synthesis inspired the preparation of a library of natural and unnatural analogues of latrunculin A and related biological studies.[49-50]

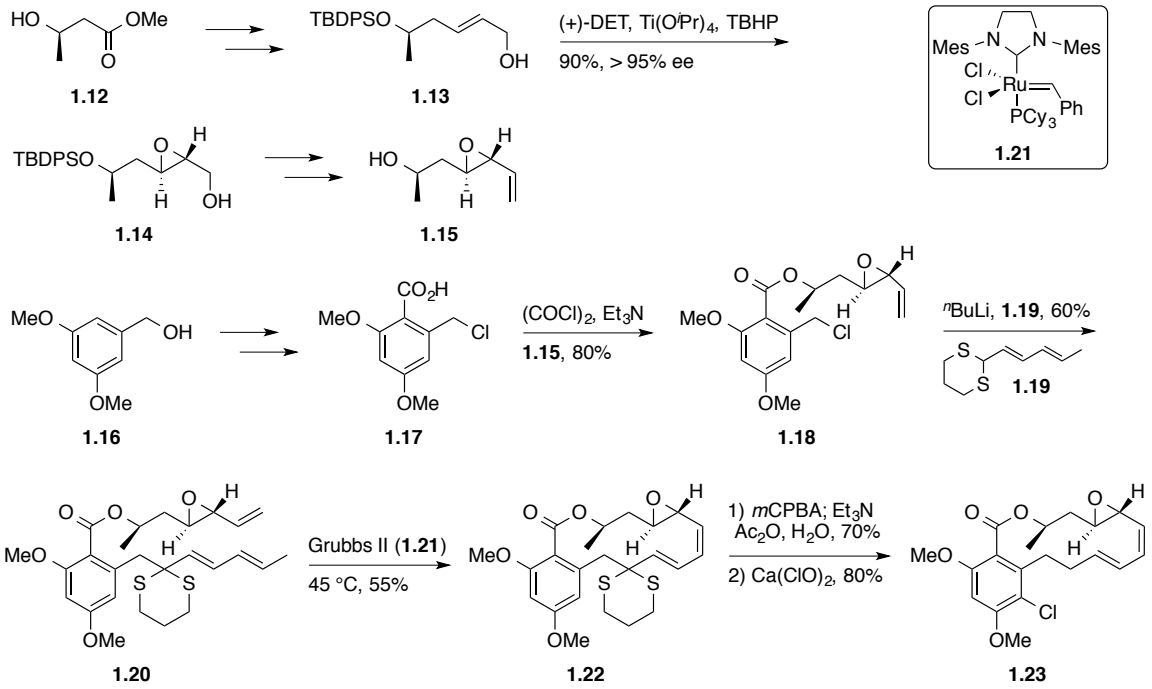
1.1.2 Total Syntheses of Radicicol

Radicicol (**1.2**, Figure 1–1) was first isolated decades ago from *Monocillium nordinii*, and later found to have mild sedative and antibiotic activities.[26, 28] The initially reported biological properties did not attract much interest until the natural product was identified in the late 1990s as a potent inhibitor of Hsp90,[51-52] which is an appealing target for cancer chemotherapy.

Danishefsky disclosed a concise synthesis of radicicol dimethyl ether based on the RCM reaction (Scheme 1–2).[35] Enantioenriched alcohol **1.15** was prepared from methyl (*R*)-3-hydroxybutyrate (**1.12**) in nine steps including a Sharpless asymmetric oxidation that set up the chiral epoxide. Chloromethylbenzoic acid **1.17** was conveniently derived from commercially available 3,5-dimethoxybenzyl alcohol (**1.16**). Esterification between carboxylic acid **1.17** and alcohol **1.15** proceeded via the acid chloride to afford ester **1.18**. Chemoselective addition of lithiated allylic dithiane **1.19** to the benzyl chloride center provided triene **1.20** ready for ring formation. The RCM reaction of triene **1.20** was

catalyzed by the second-generation Grubbs catalyst **1.21** and generated 14-membered macrolactone **1.22** in 55% yield. Notably, the transformation tolerated the vinyl expoxide and was not poisoned by the two sulfur atoms. Subsequent removal of the dithiane and aromatic chlorination finalized the synthesis of the radicicol dimethyl ether **1.23**. In a subsequent publication, this group reported the total synthesis of the natural product itself through the same strategy with modified manipulation of protecting groups.[6]

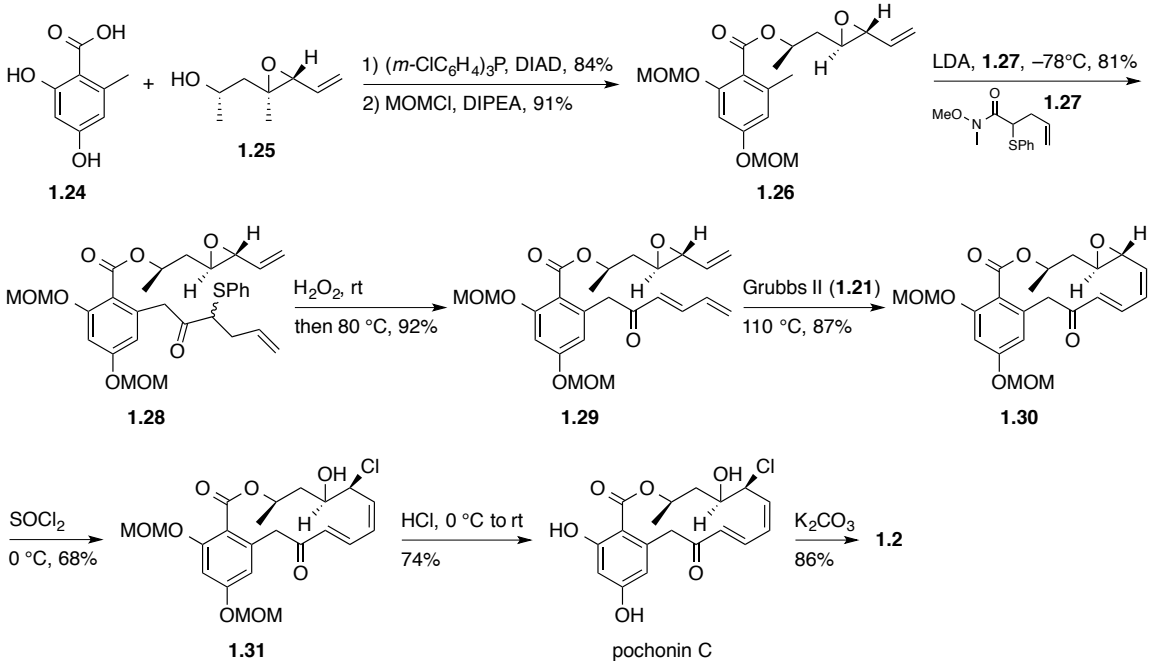
Scheme 1–2. Danishefsky's Synthesis of Radicicol Dimethyl Ether



Wissinger presented another RCM based total synthesis of radicicol with improved cyclization efficiency (Scheme 1–3).[37] Mitsunobu esterification of resorcylic acid **1.24** and epoxide alcohol **1.25** followed by MOM protection yielded ester **1.26**. Addition of the deprotonated compound **1.26** to Weinreb amide **1.27** afforded ketone **1.28**. Oxidation of the thioether **1.28** and subsequent sulfoxide elimination led to triene **1.29**. Exposing triene **1.29** to RCM conditions in refluxing toluene produced exclusively macrocycle **1.30**

in a very good yield of 87%. Chlorination of compound **1.30** was accompanied by stereospecific epoxide ring opening to give chloride **1.31**. Completion of the total synthesis was achieved after deprotection of phenols and reforming of the epoxide.

Scheme 1–3. Wissinger's Total Synthesis of Radicicol

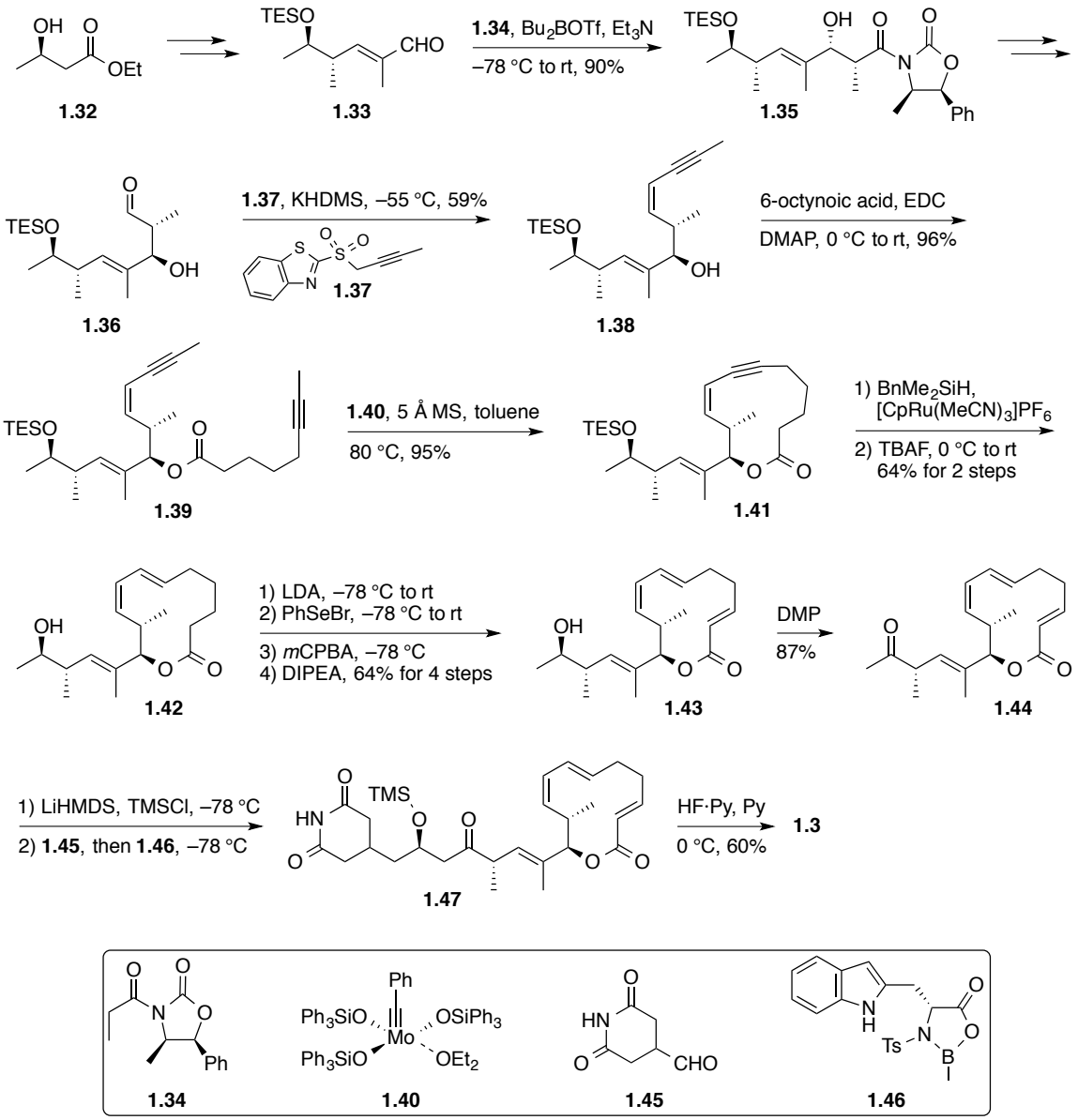


1.1.3 Total Syntheses of Lactimidomycin

Lactimidomycin (**1.3**, Figure 1–1) was isolated from *Streptomyces amphibioporus* ATCC 53964, which exhibited antiproliferative and cytotoxic activities.[30] Fürstner developed two total syntheses utilizing different versions of metathesis reactions. The first-generation synthesis relied on an RCAM reaction (Scheme 1–4).[38-39] Alcohol **1.38** was synthesized from commercial (*R*)-ethyl 3-hydroxybutyrate (**1.32**) in a 10-step sequence including an enantioselective Evans aldol reaction and a *Z*-selective Julia olefination. Steglich esterification of alcohol **1.38** with 6-octynoic acid provided diyne ester **1.39**, which was converted to the 12-membered enyne lactone **1.41** via RCAM

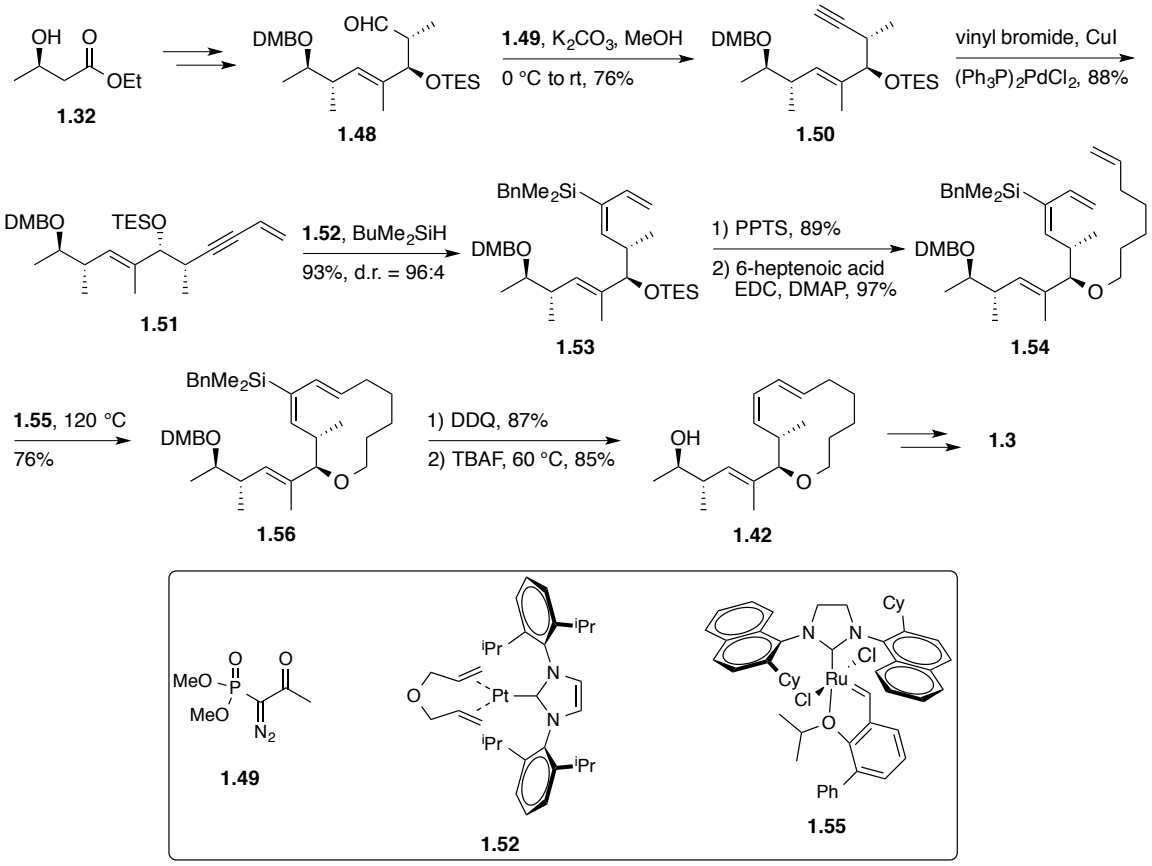
reaction in the presence of the molybdenum catalyst **1.40**. A ruthenium-catalyzed *trans*-hydrosilylation/desilylation sequence commenced with enyne **1.41** and established the requisite *E*,*Z*-configured 1,3-diene unit to yield lactone **1.42**. The enoate moiety was then installed by successive α-selenylation and oxidative elimination to give triene cycle **1.43**.

Scheme 1–4. Fürstner's First-Generation Total Synthesis of Lactimidomycin



Dess–Martin oxidation of alcohol **1.43** furnished ketone **1.44**. The glutarimide fragment was installed via asymmetric Mukaiyama aldol reaction of the silyl enolate of ketone **1.44** and aldehyde **1.45** under the catalysis of chiral oxazaborolidine **1.46**. The total synthesis of the natural product was accomplished after the final desilylation by fluoride in a carefully buffered medium.

Scheme 1–5. Fürstner's Second-Generation Synthesis of Lactimidomycin



Their second-generation synthesis of lactimidomycin employed a regio- and stereoselective diene–ene RCM reaction with a silyl group on the diene unit (Scheme 1–5).[14] Aldehyde **1.48** was derived from compound **1.32** in similar fashion to aldehyde **1.36** that they had described in the first-generation synthesis. The aldehyde was converted to

alkyne **1.50** through an Ohira–Bestmann modification of the Seyferth–Gilbert homologation. Sonogashira coupling of alkyne **1.50** with vinyl bromide afforded enyne **1.51**, which engaged in a platinum-catalyzed *cis*-hydrosilylation with excellent regio-control. *O*-Desilylation of the resultant compound **1.53** followed by esterification with 6-heptenoic acid yielded triene ester **1.54**. The key RCM reaction of triene **1.54** was prompted by ruthenium catalyst **1.55** to furnish the 12-membered lactone **1.56**. Ring contraction and formation of the *Z*,*Z*-isomer were effectively suppressed as a consequence of the *C*-silyl substitution. Deprotection of the dimethoxybenzyl (DMB) ether and removal of the stereo-directing silyl substituent delivered alcohol **1.42**, which could be elaborated to lactimidomycin according to their previously reported total synthesis.

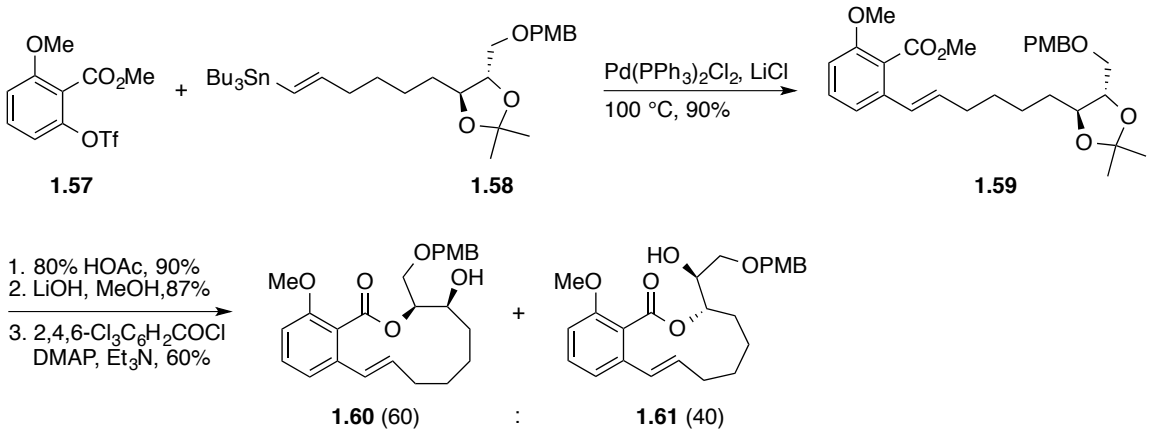
1.1.4 Total Syntheses and Synthetic Studies of Oximidines

In 1999 Hayakawa and co-workers reported the isolation of oximidines I and II (**1.4**, Figure 1–1) from *Pseudomonas* sp. Q52002.[32] Oximidine III was isolated and its structure was elucidated by the same group in 2003.[53-54] The oximidines exhibited selective cytotoxicity at ng/mL levels for cells transformed with either the ras or src oncogens. A variety of macrocyclization strategies including RCM and transition metal catalyzed couplings have been investigated to synthesize oximidines. These investigations have led to the completion of two total syntheses and one formal total synthesis of oximidine II,[40, 42, 55] one total synthesis of oximidine III,[41] and several model studies.[56-57] However, these approaches usually suffer from low efficiency for the critical ring-forming steps, particularly in the case of oximidine II due to its extremely strained structure with three consecutive double bonds.

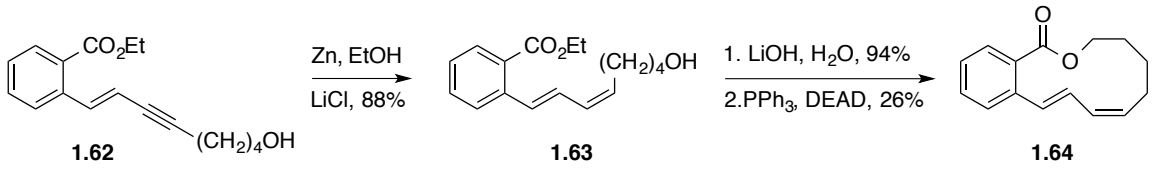
1.1.4.1 Macrolactonization Approaches

The Maier group reported synthetic studies towards a functionalized oximidine core using the Stille coupling/macrolactonization strategy (Scheme 1–6).[57] Stille coupling of chiral stannane **1.58** with triflate **1.57** generated styrene **1.59**. Acidic removal of the acetonide followed by basic hydrolysis released a dihydroxy carboxylic acid, which underwent Yamaguchi lactonization to afford benzolactones **1.60** and **1.61** in a ratio of 60:40, in favor of the desired larger 12-membered-ring.

Scheme 1–6. Maier's Synthesis of Oximidine's Macrolactone Core



Scheme 1–7. Coleman's Approach to the Oximidine Core Structure

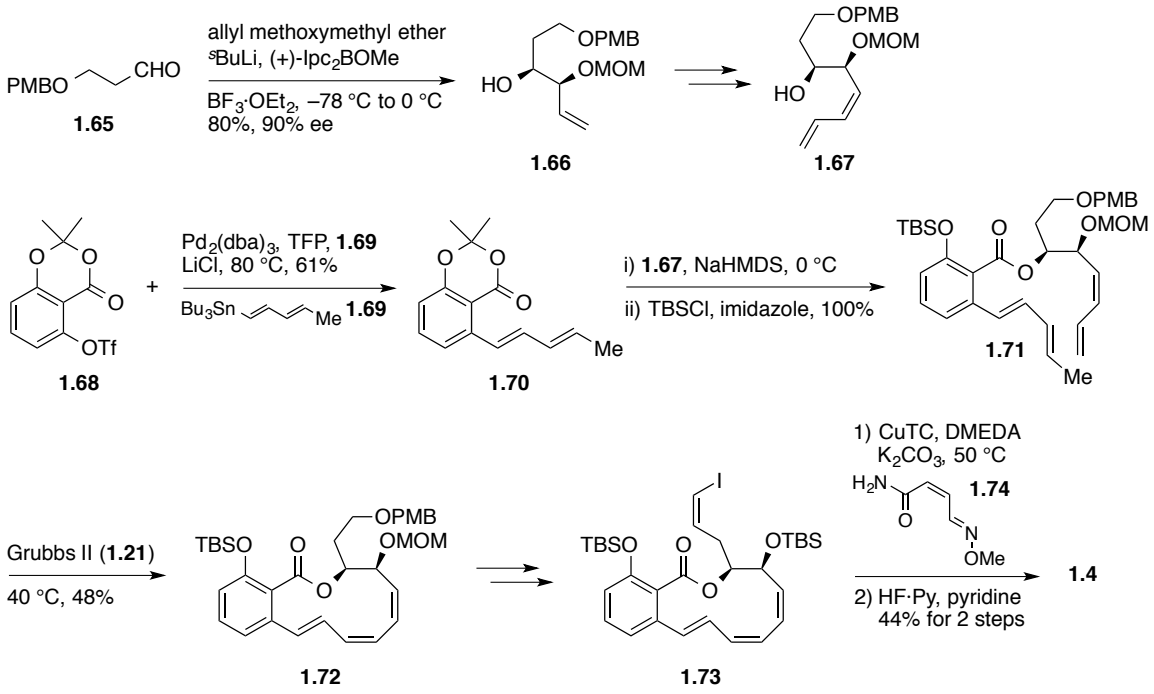


Coleman and Garg published their model studies towards oximidines through both macrolactonization and Castro–Stephens ene–yne coupling/reduction strategies.[56] In the macrolactonization approach (Scheme 1–7), enyne **1.62** was partially reduced to diene ester **1.63** with zinc metal. Ester **1.63** was then saponified and subjected to a Mitsunobu

macrolactonization reaction. The expected diene lactone was successfully formed, however in a yield of only 26%.

1.1.4.2 RCM Approaches

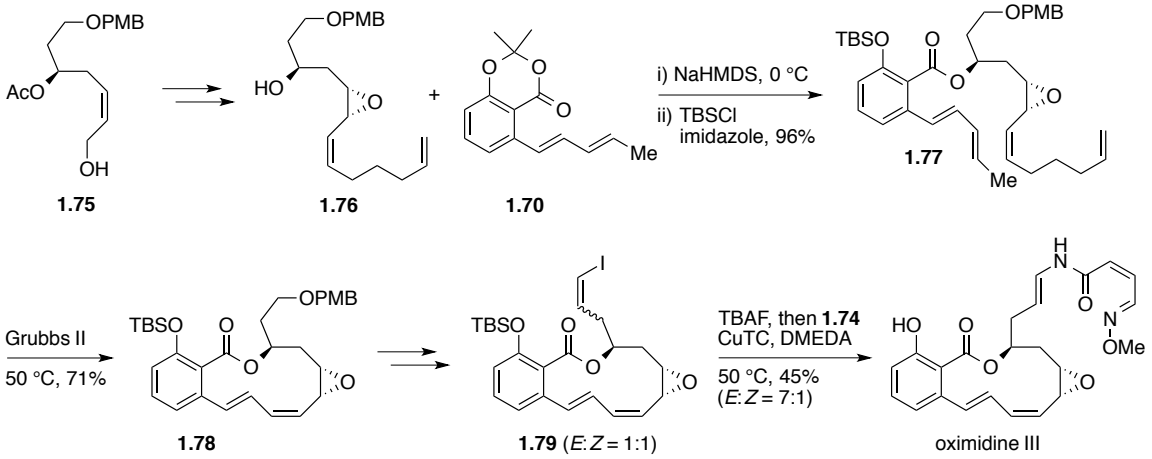
Scheme 1–8. Porco's Total Synthesis of Oximidine II



Porco reported the first total synthesis of oximidine II that adapted an RCM reaction of a well-defined bis-diene substrate (Schem 1–8),[40] in which chiral alcohol **1.67** was prepared from aldehyde **1.65**. The stereocenters were established with a Brown asymmetric allylation reaction. *E,E*-Diene acetonide **1.70** was synthesized from triflate **1.68**[58-59] and stannane **1.69** through a Stille coupling reaction. Transesterification of salicylate **1.70** with the anion of alcohol **1.67** followed by phenolate silylation provided bis-diene **1.71** in a one-pot procedure. RCM reaction of bis-diene **1.71** proceeded upon treatment with second-generation Grubbs catalyst to afford the triene lactone core **1.72** in

48% yield after one recycle. Positioning the terminal methyl group on the *E*,*E*-diene fragment was essential for the success of this reaction. Lactone **1.72** was then transformed to *Z*-vinyl iodide **1.73**, which underwent copper-mediated *C*–*N* coupling reaction with oxime amide **1.74**[60] to install the enamide side chain. The total synthesis was finally finished after global deproctetion of the TBS groups.

Scheme 1–9. Porco's Total Synthesis of Oximidine III

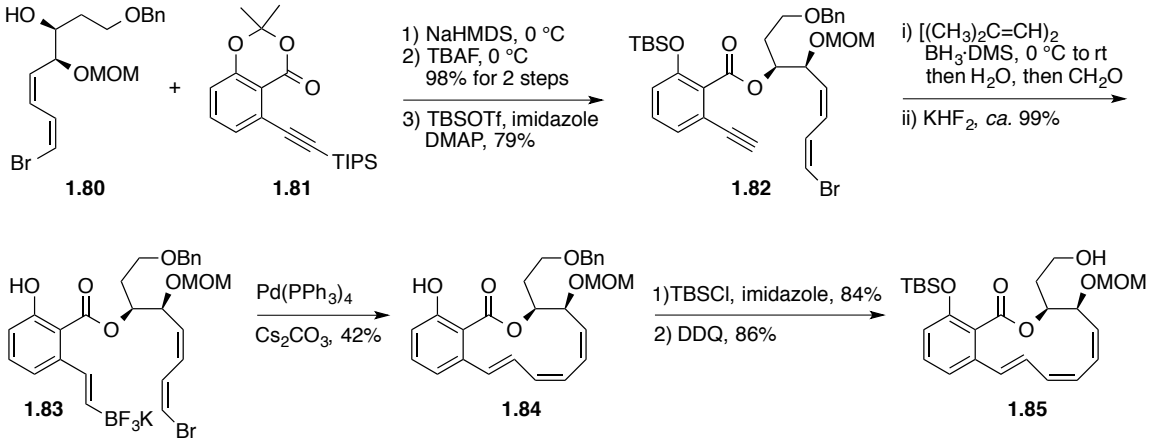


Shortly afterwards, the same group reported a total synthesis of oximidine III following a relay RCM strategy (Scheme 1–9).[41] Transesterification reaction of salicylate **1.70** with alcohol **1.76** and *in situ* silyl protection of phenol provided tetraene ester **1.77**. The RCM reaction of tetraene **1.77** afforded diene epoxide macrocycle **1.78** in good yield. The introduction of a relay moiety (the three-methylene-spaced terminal olefin) helped to initiate the reaction at the epoxide site. Sequential elaboration to vinyl iodide, TBS deprotection and side chain installation finalized the total synthesis of oximidine III.

1.1.4.3 Suzuki Coupling Approach

Molander's formal total synthesis of oximidine II employing a Suzuki-type coupling reaction (Scheme 1–10) represented the first application of potassium trifluoroborates to natural product synthesis.[42] The transesterification between alcohol **1.80** and salicylate **1.81** was followed by alkyne desilylation and phenol protection to generate ester **1.82**. The use of Snieckus' reagent ($^{i}P_2BH$) allowed regioselective hydroboration of the terminal alkyne, and the resultant organoborane was readily converted to the corresponding potassium trifluoroborate **1.83** in quantitative yield. Palladium-catalyzed intramolecular Suzuki coupling of seco-cycle **1.83** furnished the cyclized product **1.84**. The reprotection of phenol **1.84** and removal of the benzyl protecting group yielded alcohol **1.85**, a late-stage intermediate in Porco's synthesis of oximidine II.

Scheme 1–10. Molander's Formal Total Synthesis of Oximidine II

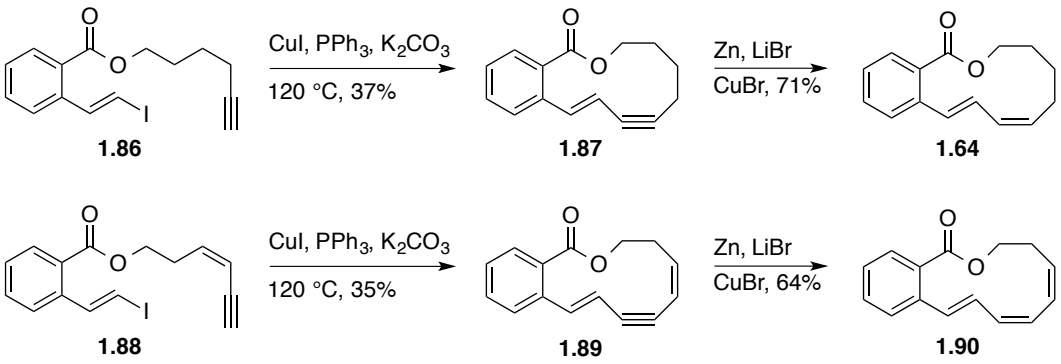


1.1.4.4 Castro–Stephens Ene–Yne Coupling Approach

Coleman and Garg also reported an access to oximidine cores structure though a copper-catalyzed Castro–Stephens coupling reaction.[56] Vinyl iodide **1.86** engaged in an intramolecular ene–yne coupling with the alkyne moiety to afford cyclic enyne **1.87** in

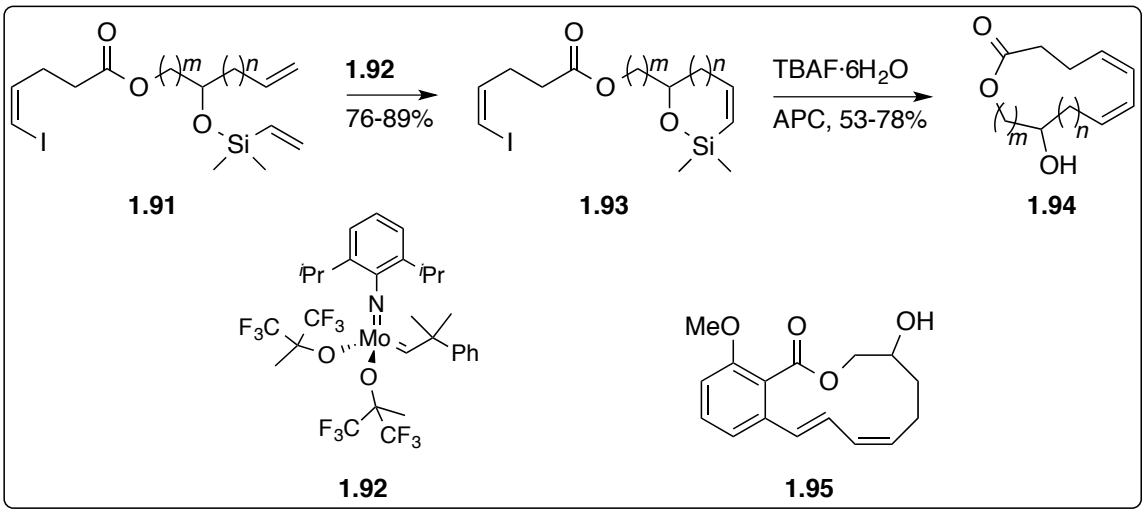
37% yield. The enyne was chemo- and stereoselectively reduced with activated zinc metal, providing *E*,*Z*-diene lactone **1.64** in 26% yield over two steps. Similarly, lactone **1.90** possessing the *E*,*Z*,*Z*-triene subunit of oximidine II was prepared from vinyl iodide **1.88** in 22% overall yield.

Scheme 1–11. Coleman's Ene–Yne Coupling Strategy Model Studies



1.1.5 General Synthetic Methods

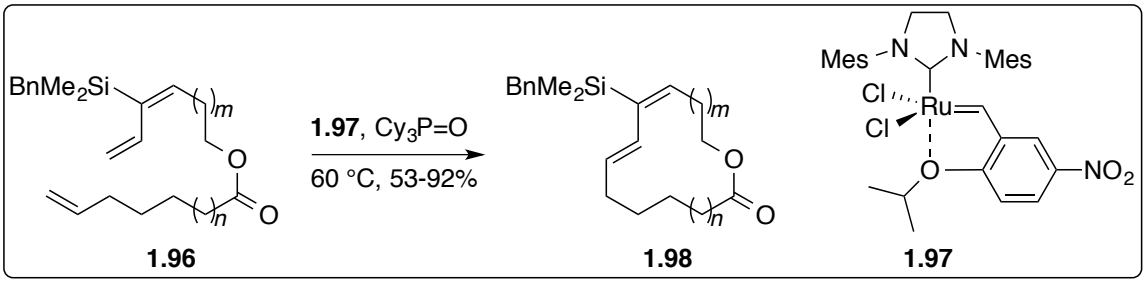
Scheme 1–12. Denmark's RCM/Cross-Coupling Method



In spite of the successful total syntheses of natural products and related model studies, general methods to prepare conjugated polyene macrocycles are underexplored. One

example of this exploration is that Denmark described a general 2-step sequence combining a RCM reaction and a silicon-assisted cross-coupling reaction for the synthesis of 1,3-diene lactones (Scheme 1–12).[61] RCM reaction of alkenylsilyl ethers **1.91** was facilitated by the Schrock catalyst **1.92** to provide alkenylsiloxanes **1.93**, which participated in an allylpalladium chloride dimer (APC)-catalyzed intramolecular cross-coupling reaction with the pendent vinyl iodide moiety in the presence of TBAF hexahydrate as an activator to furnish macrocycles **1.94**. Six examples of 11- to 14-membered *Z*,*Z*-diene lactones were showcased with yields of 76-89% for the RCM step and 53-78% for the coupling step. Benzolactone **1.95** with the oximidine core structure was also shown as an example of *E*,*Z*-diene lactones.

Scheme 1–13. Fürstner's Diene–Ene RCM Method



In Fürstner's second-generation synthesis of lactimidomycin, a general method for the construction of *E*,*Z*-diene lactones through a diene–ene RCM strategy was reported as well (Scheme 1–13).[14] Although diene–ene RCM reactions have found numerous applications in natural product synthesis, an obvious drawback is their susceptibility to *E*/*Z* isomer formation and ring contraction. This situation was circumvented in Fürstner's approach by the introduction of a *C*-silyl substituent on the diene unit. The steric hindrance of the bulky silyl group would protect the internal double bond against attack

by ruthenium species, so that undesired ring contraction would be prevented. At the same time, the silyl residue would also exhibit repulsive non-bonding interactions with the alkyl chain in the [2+2] cycloaddition intermediate that would lead to the *Z*,*Z*-diene (after desilylation) isomer. Following this strategy, esters **1.96** were subjected to RCM reactions with catalyst **1.97**, generating lactones **1.98** that would furnish *E*,*Z*-diene cycles after desilylation as the only products. Eight examples of 12- to 18-membered lactones were synthesized using this method in good to excellent yields.

In summary, natural products containing conjugated polyene macrocycle structural units were successfully synthesized through various ring-closing strategies including metathesis, macrolactonization, and metal catalyzed intramolecular cross-couplings. However, these methods were not universally efficient, especially for highly strained ring systems (yields < 50% for oximidine II). Two general methodologies have been reported, both of which required involvement of a silyl substituent Thus, new efficient methods that are tolerant of diverse functional groups are still in need to further explore these types of structures for biomedical applications.

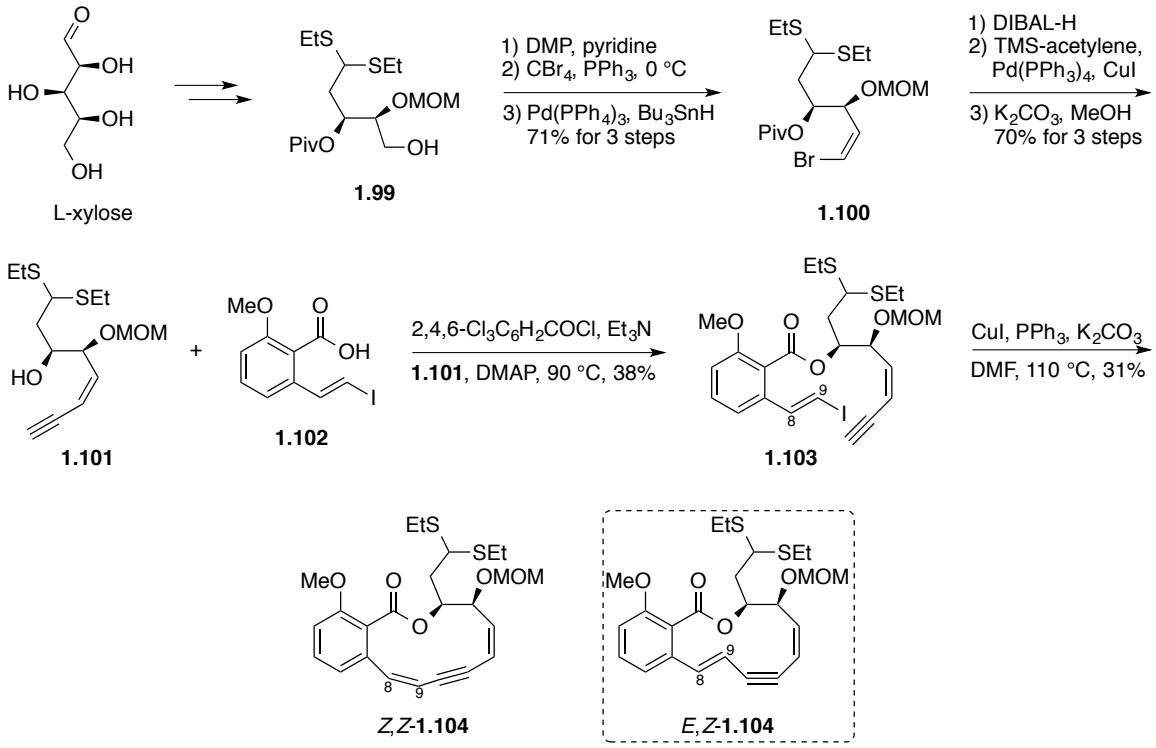
1.1.6 Discovery of Ene–Yne Coupling/Alkyne Reduction Tandem Reaction

Attracted by its promising anti-tumor property, the Georg group has been involved in the studies towards the synthesis and medicinal chemistry of oximidine II and its synthetic analogues. The initial plan included a two-step, two-pot procedure similar to Coleman's approach in which a Castro–Stephens coupling would form the macrocycle and a chemoselective alkyne-to-alkene reduction would yield the triene system.

The Georg group's first-generation synthesis commenced with L-xylose (Scheme 1–14),[62] in which enantio-enriched alcohol **1.99** was prepared over nine steps with two

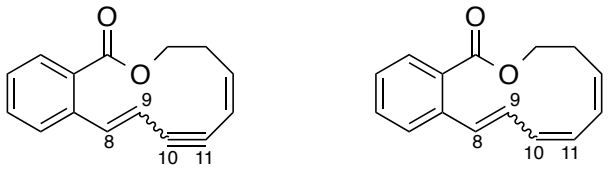
chiral centers derived from L-xylose. A Dess–Martin oxidation of the alcohol followed by a Corey–Fuchs reaction and stereoselective debromination provided *Z*-vinyl bromide **1.100**. Subsequent cleavage of the pivalate, Sonogashira coupling with TMS acetylene and desilylation afforded enyne alcohol **1.101**. Yamaguchi esterification reaction of salicyclic acid derivative **1.102** with alcohol **1.101** engendered ester **1.103** as the macrocyclization precursor. The treatment of iodide **1.103** under modified Castro–Stephens conditions[63] formed the macrocyclic dienyne lactone **1.104** in a yield of 31%. Unfortunately, the *E*-C_8–C_9 double bond had isomerized to the *Z*-configuration during the course of the reaction, resulting in exclusively the undesired *Z*,*Z*-diene isomer.

Scheme 1–14. Synthetic Studies Towards Oximidine II by Georg Group



The next step was to complete an exhaustive conformational analyses on model structures **A**-*Z*,*Z* and **A**-*E*,*Z*, as well as on the corresponding dihydro analogues **B**-*Z*,*Z*,*Z*

and **B**-*E*,*Z*,*Z* in order to rationalize this unexpected outcome (Figure 1–2). Both molecular mechanics and quantum chemical relative energies indicated that the *Z*,*Z*-configuration (**A**-*Z*,*Z*) was more stable than its *E*,*Z*-counterpart (**A**-*E*,*Z*) by 11-16 kcal/mol for dienyne structure **A**, highlighting the thermodynamic basis for the isomerization. However, upon the partial reduction of the C_{10}–C_{11} alkyne to *cis*-olefin, the latter triene **B**-*E*,*Z*,*Z* was favored by 2-5 kcal/mol over the all *Z*-triene compound.



A-*Z*,*Z*
A-*E*,*Z*

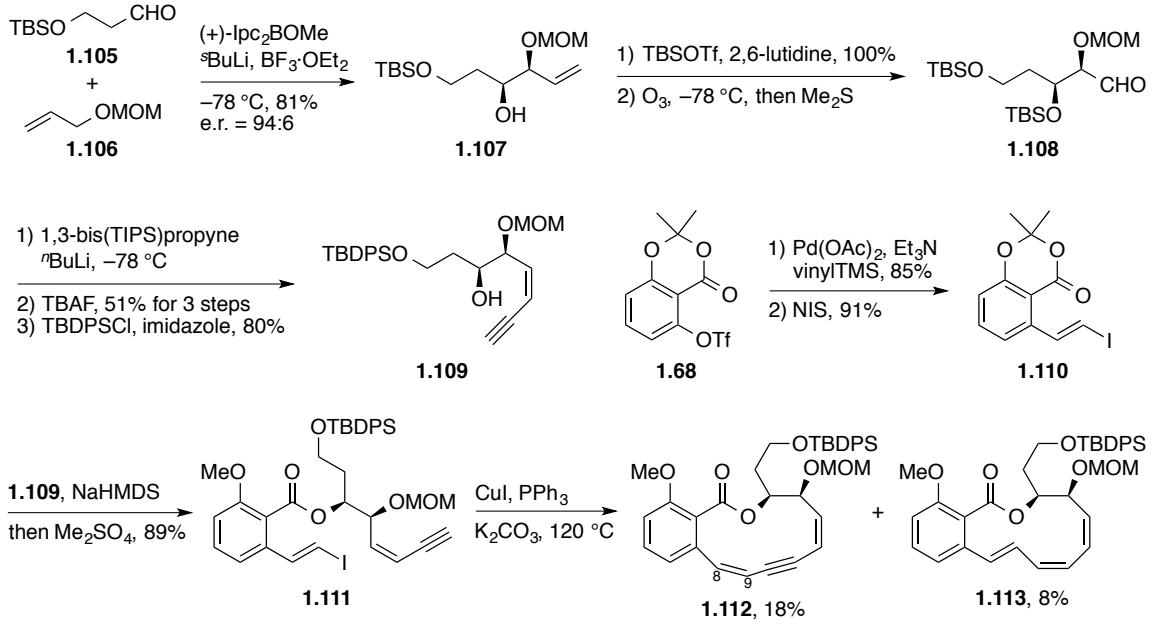
B-*Z*,*Z*,*Z*
B-*E*,*Z*,*Z*

Figure 1–2. Model compounds for rationalizing C_8–C_9 double bond isomerization.

We therefore resorted to a second-generation synthesis (Scheme 1–15), which led to the discovery of the unprecedented ene–yne coupling/alkyne reduction tandem reaction.[55]

The synthesis of the alkyne fragment **1.109** began with a Brown asymmetric allylation of aldehyde **1.105** and alkene **1.106** in which enantioenriched alcohol **1.107** was obtained in 81% yield as a single diastereomer with an e.r. of 94:6. TBS protection of the alcohol followed by ozonolysis of the resultant intermediate yielded aldehyde **1.108**, which underwent Peterson olefination to give selectively a *Z*-enyne. Global desilylation and mono-reprotection of the diol afforded enyne alcohol **1.109**. The aromatic vinyl iodide fragment **1.110** was prepared from triflate **1.68** via sequential Heck-coupling and iodine-silicon exchange. A one-pot process involving base-induced transesterification of salicylate **1.110** with alcohol **1.109** and phenolate methylation produced ester **1.111**, the key intermediate for the macrocyclization step.

Scheme 1–15. Second-Generation Total Synthesis of Oximidine II

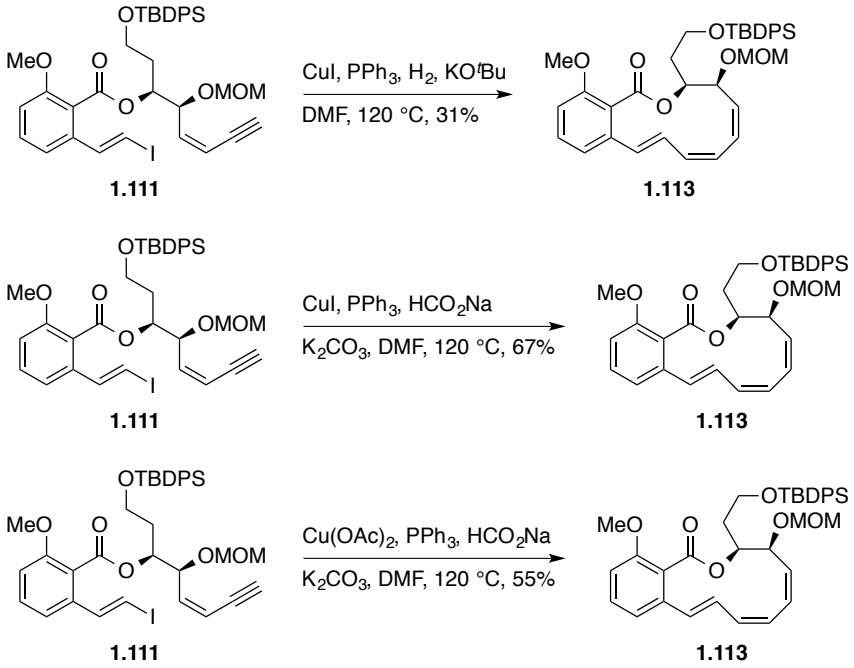


When seco-cycle **1.111** was subjected to catalytic Castro–Stephens conditions the *Z,E*-dienyne lactone **1.112** was obtained in 18% yield with simultaneous C_8–C_9 double bond isomerization (Scheme 1–15), which was in accordance with previous experimental and computational results from the first generation synthesis.[62] Careful analysis of the reaction mixture revealed the existence of a small amount (8%) of the partially reduced triene **1.113** (Scheme 1–15), implying that coupling and alkyne reduction reactions were proceeding in a single step.

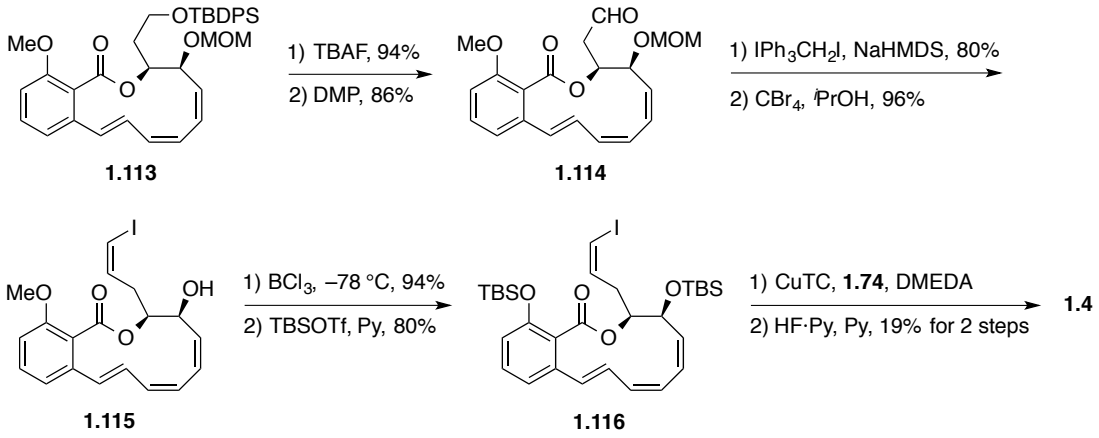
The reductant source was hypothesized to be a copper hydride (CuH) species, which was verified experimentally. Thus, exposing iodide **1.111** to the reaction conditions reported by Stryker[64] for the generation of $[CuH(PPh_3)]_6$ resulted in the isolation of only the reduced triene product **1.113** in 31% yield (Scheme 1–16). The optimal source of hydride for this macrocyclization/reduction tandem transformation proved to be sodium formate and the reaction with the weaker base K_2CO_3 increased the yield of triene **1.113**

to 67%. This cyclization was also mediated by $Cu(OAc)_2$, albeit furnishing a lower yield (55%) of triene **1.113**, but producing cleaner reactions.

Scheme 1–16. Castro–Stephens Coupling/Alkyne Reduction Tandem Reactions



Scheme 1–17. Completion of the Total Synthesis of Oximidine II



With the crucial triene lactone core structure established, we thereafter completed the total synthesis of oximidine II (Scheme 1–17). Desilylation of triene **1.113**, oxidation to

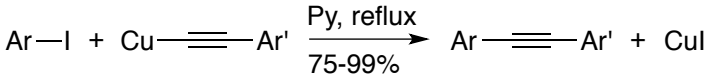
the corresponding aldehyde, Stork–Zhao iodo-olefination, and protecting group interconversion generated *Z*-vinyl iodide **1.116** for the penultimate amide coupling. Iodide **1.116** was finally converted to oximidine II following the Porco protocol.

Encouraged by its high efficiency (67% *vs*. less than 50% using other methods in literature) for the cyclization step in the total synthesis of oximidine II, we decided to develop the newly discovered one-pot reductive ene–yne coupling reaction as a general method for the construction of conjugated polyene macrocycles. To better understand the nature of this coupling/reduction cascade, a brief overview of the Castro–Stephens-type coupling reactions and CuH-mediated alkyne reductions will be presented in the following sections.

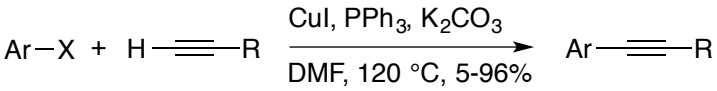
1.1.7 Castro–Stephens-Type Coupling Reactions

The Castro–Stephens coupling is a copper-mediated *C–C* bond forming reaction between a terminal alkyne and an organic halide.[65] The original report in 1963 described the coupling of copper(I) acetylides with aryl iodides in refluxing pyridine under a nitrogen atmosphere to form disubstituted alkynes in good to excellent yields (Scheme 1–18).[65] The copper(I) acetylide reagent was prepared and isolated beforehand and hence, a stoichiometric amount of copper species was needed.

Scheme 1–18. Castro–Stephens Coupling



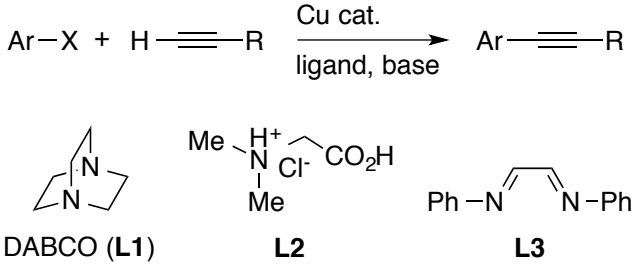
Scheme 1–19. Miura's Modification Under Catalytic Conditions



In 1993, Miura and co-workers reported the first Castro–Stephens-type coupling reaction under catalytic conditions (Scheme 1–19). The coupling of aryl halides and alkynes was catalyzed with the combination of CuI (10 mmol%) and ligand PPh_3 (10 mmol%), using K_2CO_3 as the base and DMF as the solvent.[63] Although aryl iodides were found to be efficient for this reaction (37-96% yields), aryl bromides gave decreased product formation (5-23% yields). Since this report, the copper catalyzed alkyne coupling reaction has spurred numerous studies. The development of new catalytic systems has brought about enhanced yields and extension of the reaction scope.

1.1.7.1 Cross-Coupling Reactions of Terminal Alkynes with Aryl Halides

Scheme 1–20. Copper-Catalyzed Aryl–Yne Couplings

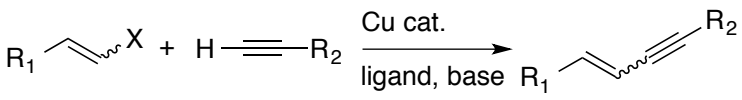


Li and co-workers reported that a catalytic amount of CuI combined with 1,4-diazabicyclo[2.2.2]octane (DABCO, **L1**) and Cs_2CO_3 promoted the smooth coupling of alkynes with both electron-rich and electron-poor aryl halides, including aryl chlorides, in moderate to quantitative yields (51-99%).[66] Ma et al. reported a catalytic system consisting of CuI, *N*,*N*-dimethylglycine hydrochloride (**L2**) and K_2CO_3 in DMF that

effected the coupling of alkynes with aryl iodides and bromides in 60-98% yields.[67] A broad scope of reactants was examined and functional groups such as halo, nitro, carbonyl derivatives, carboxylic acids, and alkyl and silyl ethers were tolerated using these conditions. A $Cu(OAc)_2$/1,4-diphenyl-1,4-diazabuta-1,3-diene (**L3**) catalyzed aryl–yne coupling under aerobic and solvent-free conditions was reported by Li.[68] The aryl iodides afforded the desired cross-coupling products in decent yields; however, higher loadings of catalyst were needed in aryl bromide reactions to suppress the oxidative homo-coupling of terminal alkynes. Li and Zhang developed another solvent free methodology utilizing octahedral Cu_2O nanoparticles supported by PPh_3 and tetra-*n*-butylammonium bromide (TBAB).[69] Their coupling reaction was compatible with a wide range of functionalities, including free alcohols, and the scope was extended to include *N*-heteroaryl halides. It should be noted that this catalyst could be recovered and reused several times without loss of activity.

1.1.7.2 Cross-Coupling Reactions of Terminal Alkynes with Vinyl Halides

Scheme 1–21. Copper-Catalyzed Ene–Yne Couplings

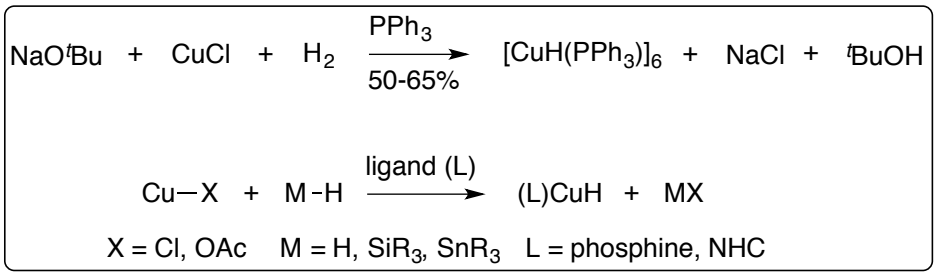


Miura and co-workers reported a stereospecific cross-coupling of alkynes with vinyl halides,[63] in which the *E*/*Z* ratio of the products remained unchanged from that of the vinyl halides employed. In this reaction the *E*-vinyl iodides were more reactive than the corresponding *Z*-isomers. The catalytic system reported by Li (CuI, DABCO, Cs_2CO_3) proved to be efficient for coupling alkyne and vinyl halide substrates as well upon

addition of 1 equivalent of TBAB.[66] The ene–yne coupling reaction was also effected by Ma's catalytic system (CuI, *N*,*N*-dimethylglycine (**L2**) hydrochloride, Cs_2CO_3) under mild conditions (dioxane, 80 ^oC). A variety of functional groups were accommodated and enyne products were obtained in good to excellent yields (60-91%).[70]

1.1.8 CuH-Mediated Alkyne Reductions

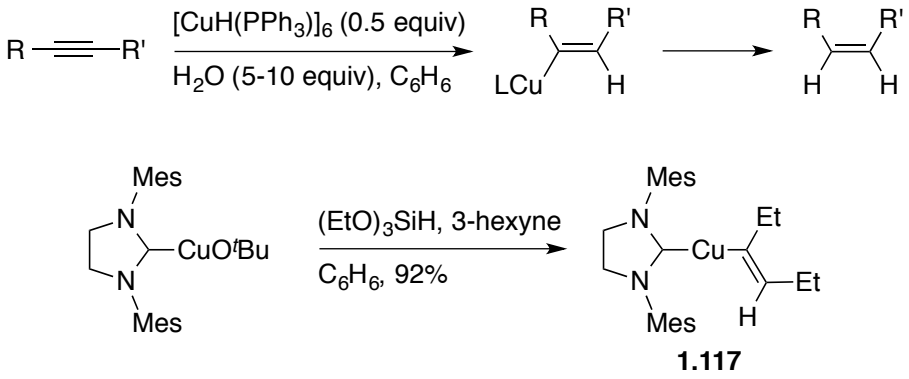
Scheme 1–22. Preparation of CuH Complexes



Copper(I) hydride (CuH) complexes have been the topic of interest as both mild and selective reducing agents for a broad spectrum of substrates including α,β-unsaturated carbonyl derivatives and alkynes.[71-73] The most frequently used CuH species is the phosphine stabilized hexamer $[CuH(PPh_3)]_6$, known as Stryker's reagent[64] or Osborn complex.[74] In the original report, the compound was prepared by the hydrogenation of CuO^tBu, which was produced *in situ* from CuCl and NaO^tBu (Scheme 1–22). Alternative methods for preparation of Stryker's reagent and other CuH complexes have been developed to avoid the extremely air-sensitive system (Scheme 1–22).[75-76] Replacement of CuO^tBu with $Cu(OAc)_2 \cdot H_2O$ as the copper source allowed the formation of Stryker's reagent in high purity without the need of repeated recrystallization. Hydrosilanes have been used as a more convenient hydride source instead of hydrogen gas. At the initial stage, CuH-mediated reductions required stoichiometric use of copper species,[77-79] but

were later discovered to proceed catalytically in copper in the presence of a stoichiometric amount of hydride source.[80-86] For most reactions, the active CuH species was generated *in situ* prior to the addition of the substrate to be reduced and stabilized with phosphines or *N*-heterocyclic carbenes (NHC) through complexation.

Scheme 1–23. Alkyne Reduction with Stryker's Reagent and Isolation of a Vinyl Copper(I) Species

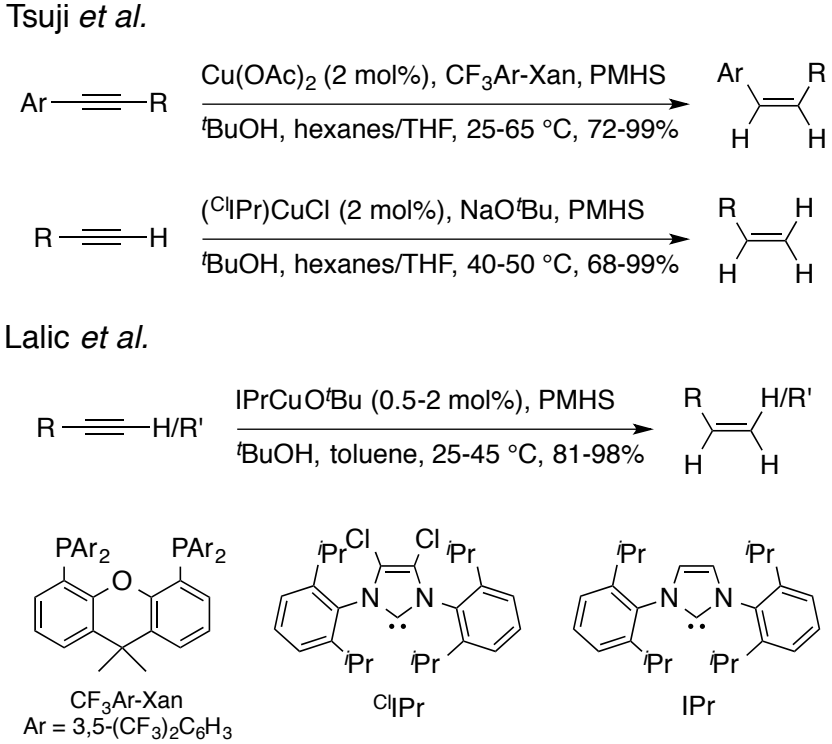


1.117

Stryker reported in 1990 that $[CuH(PPh_3)]_6$ could prompt reduction of alkynes to furnish the corresponding alkenes with high *Z*-selectivity (Scheme 1–23).[87] This reaction was carried out in the presence of water and employed stoichiometric amounts of Stryker's reagent. Functionalities such as esters, tertiary ethers, acetals, and free alcohols were unaffected under the conditions. Terminal alkynes were reduced at room temperature whereas unactivated internal alkynes reacted only at elevated temperature. The reduction was conjectured to proceed via vinyl copper(I) intermediates through hydrocupration of alkynes. This hypothesis was later supported by the isolation and crystallographic study of a vinyl copper complex **1.117** as a result of the addition of an NHC-stabilized CuH species to 3-hexyne (Scheme 1–23).[88]

The catalytic version of the alkyne semi-reduction using CuH species has been underdeveloped until very recently. Tsuji revealed in 2012 that partial reduction of aromatic internal alkynes could be catalyzed by an *in situ* generated CuH-bisphosphine complex to afford *Z*-alkenes in high yields (Scheme 124).[89] In the example polymethylhydrosiloxane (PMHS) was employed as the stoichiometric hydride source. The reaction exhibited exceptional tolerance to various functionalities such as hydroxy, siloxy, phthalimido, chloro, cyano, and vinylsilane. The catalyst was less reactive with dialkyl substrates and terminal alkynes, for which better yields were obtained with the NHC ligand ^{Cl}IPr.

Scheme 1–24. Catalytic Alkyne Reductions with CuH Complexes

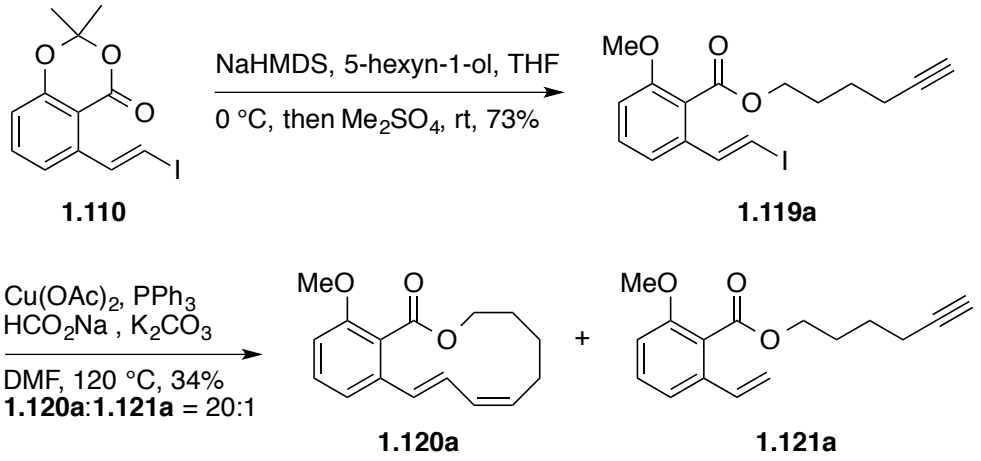


Lalic reported later a similar catalytic system using NHC ligand IPr for this transformation (Scheme 1–24).[90] The method was universally efficient for

aliphatic/aromatic internal and terminal alkynes although the reaction of internal alkynes required mild heating; thirty examples were showcased with excellent yields of 81-98%. Functionalities that are sensitive to hydrogenations such as cyano, nitro, and ketone were compatible with the reaction conditions.

1.2 Reaction Optimization

Scheme 1–25. Synthesis and Macrocyclization of Model Compound



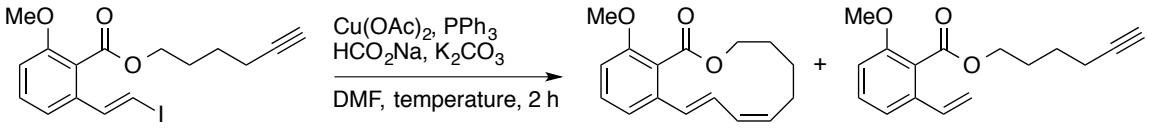
For optimization studies, we investigated the reaction of a model compound vinyl iodide **1.119a** (Scheme 1–25). The compound was synthesized from salicylate **1.110** through transesterification with 5-hexyn-1-ol followed by *in situ* phenolate methylation. The coupling/reduction tandem reaction of iodide **1.119a** was performed under the previously reported conditions[55] for the total synthesis of oximidine II (HCO_2Na (4 equiv), K_2CO_3 (1.5 equiv), $Cu(OAc)_2$ (0.33 equiv), and PPh_3 (1 equiv) at 120 °C in DMF (0.005 M) for 2 h). We employed $Cu(OAc)_2$ as the metal source rather than CuI, because it provided better reproducibility of the reaction on a large scale.[91] The reaction furnished

the expected 12-membered *E,Z*-diene lactone **1.120a** in a modest 34% yield, along with an undesired acyclic product **1.121a** as a result of dehalogenation. The ratio of the two products was 20:1 favoring the desired lactone product. Extensive screening of various reaction conditions was carried out on the model system to increase the yield while maintaining the high selectivity for macrocyclization.

1.2.1 Screening of Reaction Temperature

The reaction of iodide **1.119a** using PPh_3 as the ligand was conducted at different temperatures; the results are listed in Table 1–1.

Table 1–1. Optimization of Reaction Temperature[a]



1.119a **1.120a** **1.121a**

entry	temperature (°C)	yield (%)[b]	ratio (**1.120a**:**1.121a**)[c]
1	**120**	**34**	**20:1**
2	100	0	N/A
3	140	19	6:1

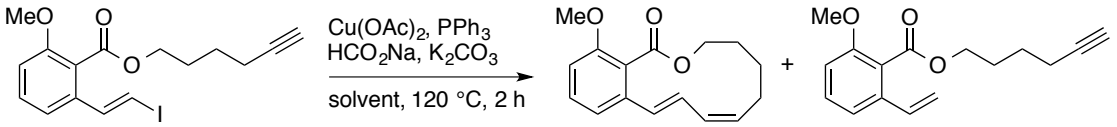
[a] Reaction conditions: **1.119a** (0.005 M), $Cu(OAc)_2$ (0.33 equiv), PPh_3 (1 equiv), HCO_2Na (4 equiv), and K_2CO_3 (1.5 equiv) in DMF under N_2 for 2 h. [b] Isolated yield as mixture of **1.120a** and **1.121a**. [c] Calculated from ^1H NMR.

The reaction was found to perform well, but only at a specific temperature (120 °C, Table 1–1, entry 1). At lower temperature (110 °C, entry 2), the reaction was not initiated and only starting material was recovered. However, at an elevated temperature (140 °C, entry 3) a sharp decrease in both yield and selectivity was observed.

1.2.2 Screening of Solvent

A selection of solvents was applied in the reductive ene–yne coupling reaction (Table 1–2). Employing less polar solvent such as 1,4-dioxane and toluene (Table 1–2, entries 2 and 3) did not provide any product. All the polar aprotic solvents tested (entries 1, and 4-6) promoted the reaction with DMF and NMP (entries 1 and 6) slightly more efficient than the other two (entries 4 and 5). Considering the higher toxicity and price of NMP, the original DMF was our choice of solvent for further optimization studies.

Table 1–2. Optimization Studies of Solvent[a]



1.119a **1.120a** **1.121a**

entry	solvent	yield (%)[b]	ratio (**1.120a**:**1.121a**)[c]
1	**DMF**	**34**	**20:1**
2	1,4-dioxane	0	N/A
3	toluene	0	N/A
4	DMA	34	14:1
5	DMSO	31	20:1
6	**NMP**	**35**	**20:1**

[a] Reaction conditions: **1.119a** (0.005 M), $Cu(OAc)_2$ (0.33 equiv), PPh_3 (1 equiv), HCO_2Na (4 equiv), and K_2CO_3 (1.5 equiv) at 120 °C under N_2 for 2 h. [b] Isolated yield as mixture of **1.120a** and **1.121a**. [c] Calculated from ^1H NMR.

1.2.3 Screening of Ligands

The ligand effect on the Castro–Stephens coupling/alkyne reduction tandem reaction was rigorously examined. All the ligands screened were shown to promote the reaction, as listed in Table 1–3. The chemical structures of some of the ligands are depicted in Figure 1–3.

Substitutions on PPh_3, either with electron-donating (Table 13, entries 2 and 3) or electron-withdrawing (entry 4) groups, did not increase the product formation. Alkyl phosphines (entries 5, 6 and 8) and a phosphite ligand (entry 7) displayed slightly better efficiency than PPh_3, but the yields of 40-50% were still not practical. Next, we were pleased to find that high yields of over 70% could be achieved with chelating bisphosphine ligands (entries 9-11). Among them, dppe (entry 9) was the most inexpensive and easy-to-handle due to its high solubility. Although this ligand provided lower selectivity for macrocyclization (ratio of **1.120a**:**1.121a** = 11:1), it should be useful when a substrate does not generate the acyclic product or the two products are separable. Phanephos (entry 11) afforded the best selectivity for the desired diene product **1.120a**. Chelating *O*-ligands BINOL and TME (entries 12 and 13) gave comparable yields with bisphosphines, but were not as selective. Lastly, we also evaluated a few *N*-ligands, which exhibited inferior reactivities (entries 14-16).

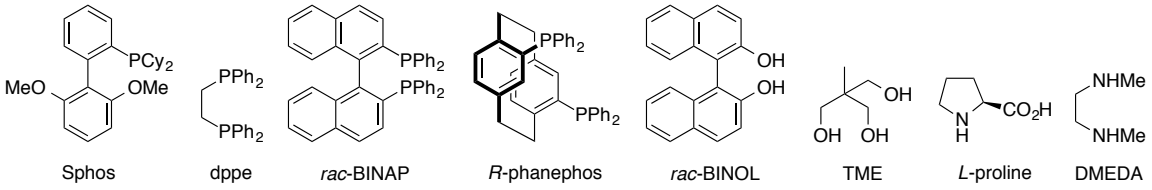
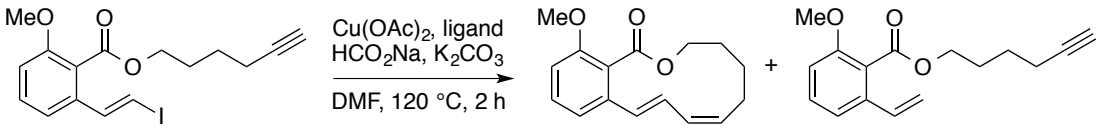


Figure 1–3. Structures of ligands.

Table 1–3. Optimization of Ligand[a]



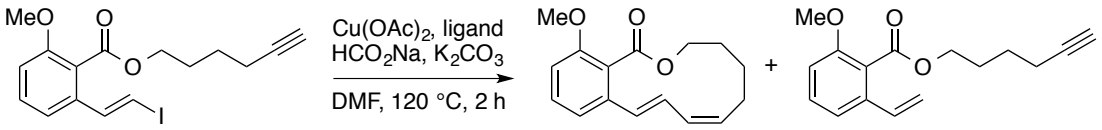
1.119a **1.120a** **1.121a**

entry	ligand	yield (%)[b]	ratio (**1.120a**:**1.121a**)[c]
1	PPh_3	34	20:1
2	$P(2\text{-tol})_3$	37	40:1
3	$P(4\text{-MeOC}_6H_4)_3P$	19	11:1
4	$P(4\text{-FC}_6H_4)_3P$	21	20:1
5[d]	P^nBu_3	40	7:1
6	P^tBu_3	49	20:1
7	$P(OEt)_3$	53	18:1
8	Sphos	45	9:1
9	**dppe**	**73**	**11:1**
10	***rac*-BINAP**	**72**	**25:1**
11	**(*R*)-phanephos**	**71**	**44:1**
12	*rac*-BINOL	70	5.9:1
13	TME	69	17:1
14	2,2'-bipyridyl	25	5:1
15	DMEDA	39	20:1
16	*L*-proline	30	4:1

[a] Reaction conditions unless otherwise specified: **1.119a** (0.005 M), $Cu(OAc)_2$ (0.33 equiv), ligand (donor atom/Cu = 3), HCO_2Na (4 equiv) and K_2CO_3 (1.5 equiv) in DMF at 120 °C under N_2 for 2 h. [b] Isolated yield as mixture of **1.120a** and **1.121a**. [c] Calculated from ^1H NMR. [d] At 100 °C.

1.2.4 Optimization of Catalyst Loading

Table 1–4. Optimization of Catalyst Loading[a]



1.119a **1.120a** **1.121a**

entry	ligand	copper loading (equiv)	ligand loading (equiv)	yield (%)[b]	ratio (**1.120a**:**1.121a**)[c]
1	PPh_3	0.33	1	34	20:1
2	PPh_3	1	3	64	90:1
3	dppe	0.33	0.5	73	11:1
4	dppe	1	1.5	73	20:1
5	(*R*)-phanephos	0.33	0.5	71	44:1
6	**(*R*)-phanephos**	**0.2**	**0.3**	**73**	**44:1**
7	(*R*)-phanephos	0.1	0.15	N/A[d]	28:1

[a] Reaction conditions: **1.119a** (0.005 M), HCO_2Na (4 equiv) and K_2CO_3 (1.5 equiv) in DMF at 120 °C under N_2 for 2 h. [b] Isolated yield as mixture of **1.120a** and **1.121a**. [c] Calculated from ^1H NMR. [d] Proceeded to 70% conversion after 4 h.

The reductive ene–yne macrocyclization reaction had been operated with 0.33 equivalent of $Cu(OAc)_2$ catalyst and thus, we next investigated the impact of catalyst loading on the reaction (Table 1–4). For reactions employing simple phosphine PPh_3, stoichiometric amounts of $Cu(OAc)_2$ and 3 equivalents of the ligand resulted in a remarkable increase in both yield and selectivity (Table 1–4, entry 2, compared with entry 1). Similarly, the stoichiometric use of copper and 1.5 equivalents of bisphosphine dppe inhibited the formation of the undesired dehalogenation product **1.121a** to an

acceptable level (entry 4, compared with entry 3). On the other hand, we hoped to decrease the consumption of the expensive ligand phanephos. We were pleased to find that the efficiency of this ligand was not diminished under reduced catalyst loading ($Cu(OAc)_2$ (0.2 equiv), phanephos (0.3 equiv), entry 6). Further lowering the loading of the catalyst (entry 7) led to incomplete reaction even after 4 h. Eventually, conditions for entry 6 were identified as the optimal conditions and would be used for exploring the scope of the reaction. However, the best conditions for each individual compound may vary as will be discussed in the following section.

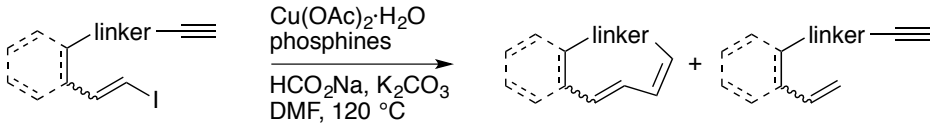
1.3 Reaction Scope

We next applied this coupling/reduction tandem reaction to the synthesis of a diverse set of macrocyclic compounds. The scope of this reaction will be discussed here in terms of ring size, functionality, and vinyl iodide double bond configuration.

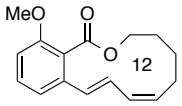
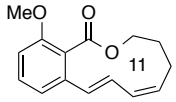
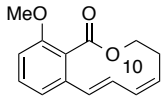
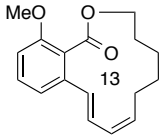
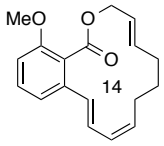
1.3.1 Ring Size

Analogues of *E*,*Z*-1,3-diene lactone **1.120a** with different tether lengths were prepared through the Castro–Stephens coupling/alkyne reduction tandem reaction (Table 1–5). We found that 11- to 13-membered rings **1.120a**, **1.120b** and **1.120d** were obtained in good yields (Table 1–5, entries 1, 2 and 4). The 10-membered homologue **1.120c** (entry 3) was also accessible, albeit in a low efficiency of 26%. The attempt to synthesize the 14-membered diene lactone **1.120e** (entry 5) was unfruitful. Instead, NMR analysis of the crude mixture suggested that the unreduced enyne cycle **1.122e** was the major component (Scheme 1–26).

Table 1–5. Preparation of Macrocycles with Different Ring Sizes[a]



1.119 **1.120** **1.121**

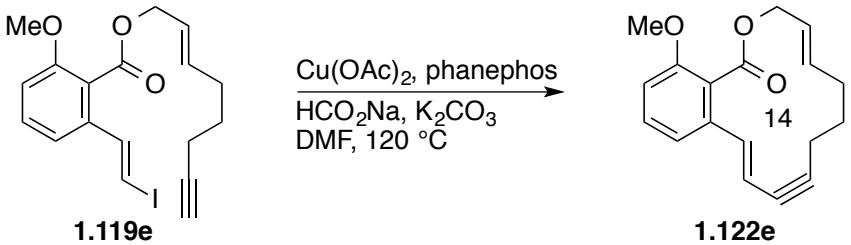
entry	product	ligand	Cu loading (equiv)	time (h)	yield (%)[b]	ratio (**1.120**:**1.121**)[c]
1	 **1.120a**	phanephos	0.2	2	73	44:1
2A	 **1.120b**	phanephos	0.2	2	62	59:1
2B		BINAP	0.3	2.5	68	36:1
3	 **1.120c**	dppe	0.3	2	28	**1.120c** only
4A	 **1.120d**	BINAP	0.3	24	72	12:1
4B		PPh_3	1	22	53	**1.120d** only
5	 **1.120e**	phanephos	0.2	24	0[d]	N/A

[a] Reaction conditions unless otherwise specified: **1.119** (0.005 M), ligand (donor atom/Cu = 3), HCO_2Na (4 equiv) and K_2CO_3 (1.5 equiv) in DMF at 120 °C under N_2. Reaction times were not fully optimized. [b] Isolated yield as mixture of **1.120** and **1.121**. [c] Calculated from ^1H NMR. [d] Only enyne was detected.

We concluded that the alkyne reduction step of the tandem reaction is driven by the release of ring strain from the ene–yne coupling intermediate. For 12-membered or smaller rings, this intermediate was highly strained and susceptible to isomerization, as

discussed in Section 1.1.6. Thus, the substrates readily underwent alkyne reduction in the presence of a reducing agent. In the case of a 13-membered ring system (entry 4), the enyne cycle was moderately strained and stable enough to be observed without isomerization by NMR after 2 h. An extended reaction time (22-24 h) was needed to convert the enyne to the desired diene **1.120d**. 14-Membered (entry 5) or larger rings formed a stable enyne that might offset the ring strain through conformation changes and did not produce any diene even after prolonged reaction time.

Scheme 1–26. Reaction of Substrate 1.119e

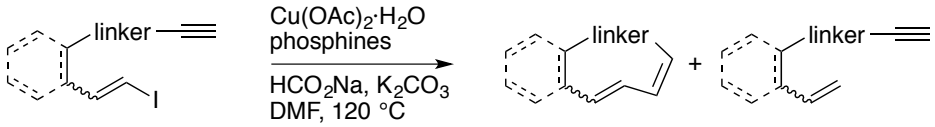


1.119e **1.122e**

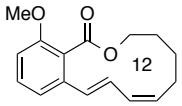
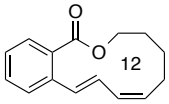
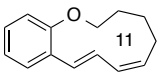
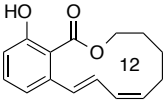
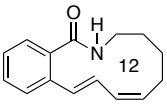
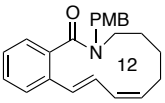
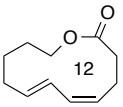
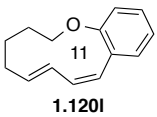
1.3.2. Functionality

The 11- or 12-membered macrocycles with various linkages were synthesized employing the coupling/reduction tandem reaction (Table 1–6) demonstrating that a methoxy substitution on the aromatic ring was not necessary for implementing the macrocyclization (Table 1–6, entry 2 *vs*. entry 1). A phenyl iodide with an ether linkage (entry 3) worked equally well as the ester linkages. Labile functionalities such as an unprotected phenol and a secondary amide (entries 4 and 5) were not well tolerated. In contrast, a protected amide (entry 6) provided the corresponding lactam **1.120j** in a decent yield of 79%.

Table 1–6. Preparation of Macrocycles with Different Functionalities[a]



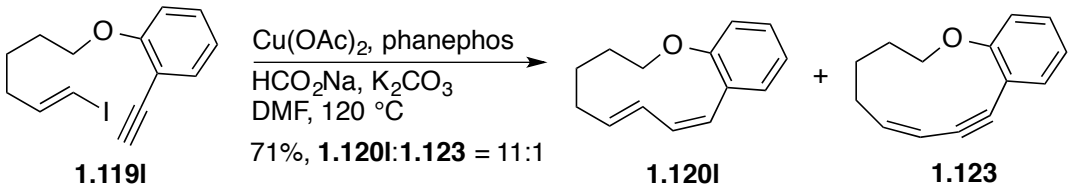
1.119 **1.120** **1.121**

entry	product	ligand	Cu loading (equiv)	time (h)	yield (%)[b]	ratio (**1.120**:**1.121**)[c]
1	 **1.120a**	phanephos	0.2	2	73	44:1
2A	 **1.120f**	phanephos	0.2	2	60	5.6:1
2B		PPh_3	1	2	60	**1.120f** only
3	 **1.120g**	phanephos	0.1	6	62	**1.120g** only
4	 **1.120h**	PPh_3	1	3	12	**1.120h** only
5	 **1.120i**	phanephos	0.2	2	0[e]	N/A
6	 **1.120j**	phanephos	0.2	3.5	79	**1.120j** only
7A	 **1.120k**	phanephos[d]	0.3	3	62	**1.120k** only
7B		BINAP	0.3	3	70	**1.120k** only
8A	 **1.120l**	phanephos	0.2	4	71[f]	
8B		dppe	0.3	4	82	**1.120l** only

[a] Reaction conditions unless otherwise specified: **1.119** (0.005 M), ligand (donor atom/Cu = 3), HCO_2Na (4 equiv) and K_2CO_3 (1.5 equiv) in DMF at 120 °C under N_2.

Reaction times were not fully optimized. [b] Isolated yield as mixture of **1.120** and **1.121**. [c] Calculated from ^{1}H NMR. [d] ligand (donor atom/Cu = 2). [e] Decomposed. [f] Combined yield of an inseparable mixture of diene **1.120l** and enyne **1.123** (ratio 11:1).

Scheme 1–27. Reaction of Substrate 1.119l



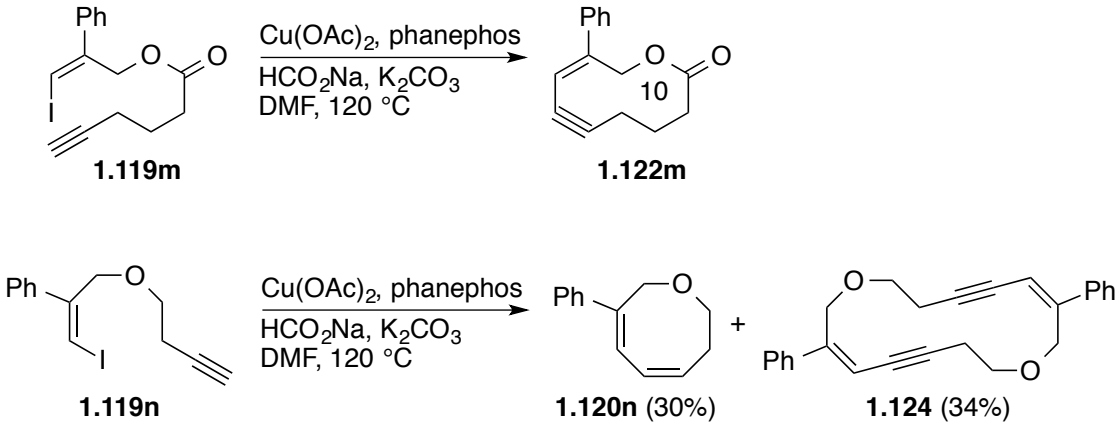
1.119l **1.120l** **1.123**

Both vinyl iodide and terminal alkyne coupling partners can be aromatic or aliphatic (entries 11 and 12). Vinyl iodide double bond isomerization was observed for substrate **1.119l** (entry 8A and Scheme 1–27), which furnished an inseparable mixture (11:1) of diene **1.120l** and enyne **1.123**. Using dppe as the ligand, diene **1.120l** was obtained in 82% yield as the sole product. In the majority of the above examples (Tables 1–5 and 1–6), the undesired acyclic product **1.121** was negligible. For those substrates that produce a significant quantity of compound **1.121**, the use of stoichiometric amounts of copper and ligand could completely suppress the side reaction (Table 1–5, entry 4B and Table 1–6, entry 2B).

1.3.3 *Z*-Vinyl Iodide Substrates

Z,*Z*-Diene macrocycles were difficult to access from the corresponding Z-vinyl iodide substrates (Scheme 1–28). The Z-enyne cycle intermediate is much less strained than its *E*-counterpart and therefore, did not undergo alkyne reduction even for the 10-membered ring system **1.122m**. The 8-membered ring system was strained enough to afford the desired diene **1.120n** in 30% yield; however, a significant amount of dimer **1.124** (34%) was formed at the same time.

Scheme 1–28. Reactions of Z-Vinyl Iodides

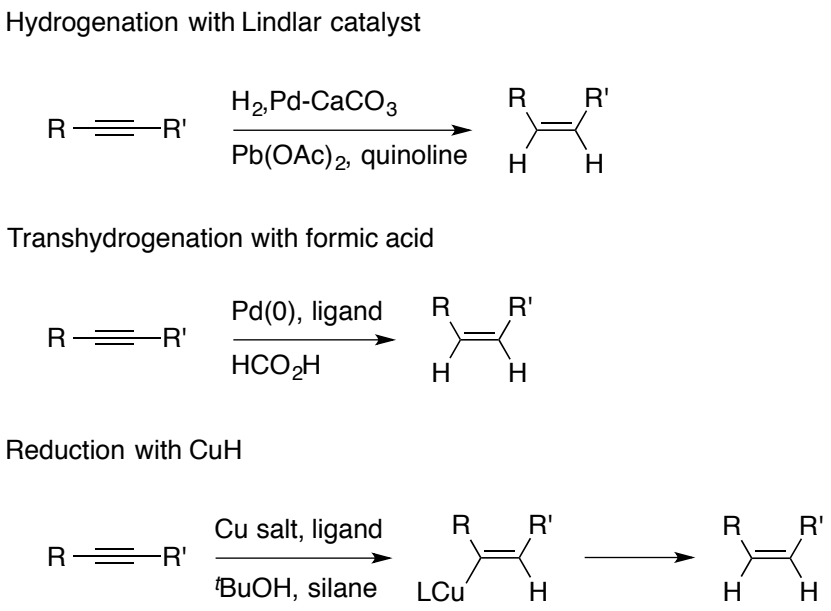


1.4 Stepwise Synthesis for Non-Strained Ring Systems

Ring systems that were not strained enough to trigger the *in situ* alkyne reduction generated macrocyclic enynes (**1.122e** and **1.122m**). This transformation is worth noting, since the intramolecular ene–yne *C*–*C* couplings (Sonogashira or Castro–Stephens) have not been widely applied to macrocyclizations and most previous reactions employed

phenyl iodide substrates.[92-98] In addition, the desired diene macrocycles could be obtained from the enynes through a separate reduction step.

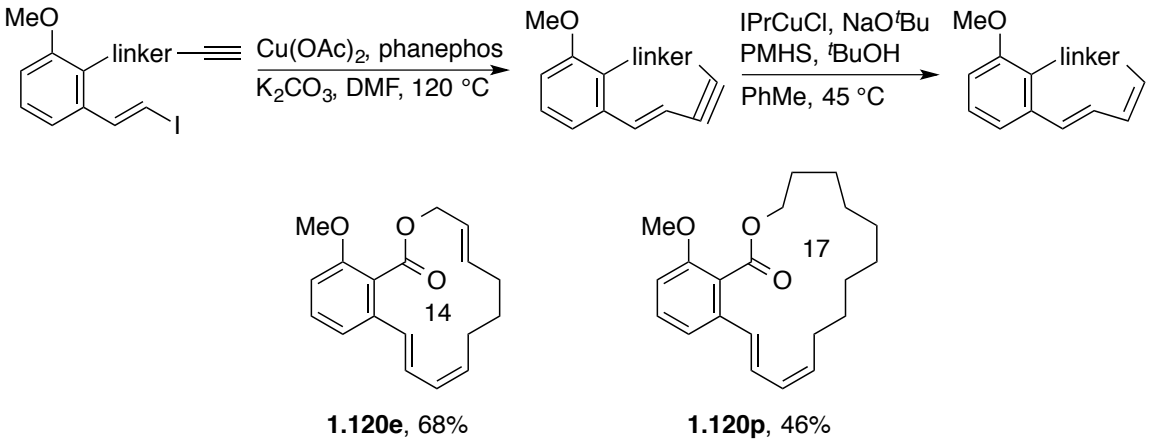
Scheme 1–29. Methods for Alkyne Semi-reduction



Convenient protocols for this semi-reduction include hydrogenation using H_2 gas and the Lindlar catalyst,[99-100] palladium-catalyzed trans-hydrogenation using formic acid or its ammonium salts,[101-107] and CuH-mediated reactions[89-90, 108-111] (Scheme 1–29). The Lindlar catalyst may suffer from a number of major problems such as partial *E*/*Z* isomerization, double bond shift, and over-reduction to alkanes.[112-114] Therefore, close monitoring of the reaction progress is often necessary. Palladium-catalyzed trans-hydrogenation with formic acid is known to induce double bond isomerization in conjugated systems,[104] whereas CuH-mediated reductions exhibited excellent efficiency and selectivity, giving almost quantitative yields of *Z*-alkenes as the sole product in most cases.[90] The conditions were also compatible with a plethora of functional groups, including nitro and aromatic iodides that are extremely labile to hydrogenations. Thus,

we prepared 14-membered or larger macrocycles through the combination of a Castro–Stephens coupling and the CuH-mediated alkyne reduction (Scheme 130).

Scheme 1–30. Stepwise Coupling/Reduction Synthesis of 14- and 17-Membered Macrocycles



1.120e, 68% **1.120p**, 46%

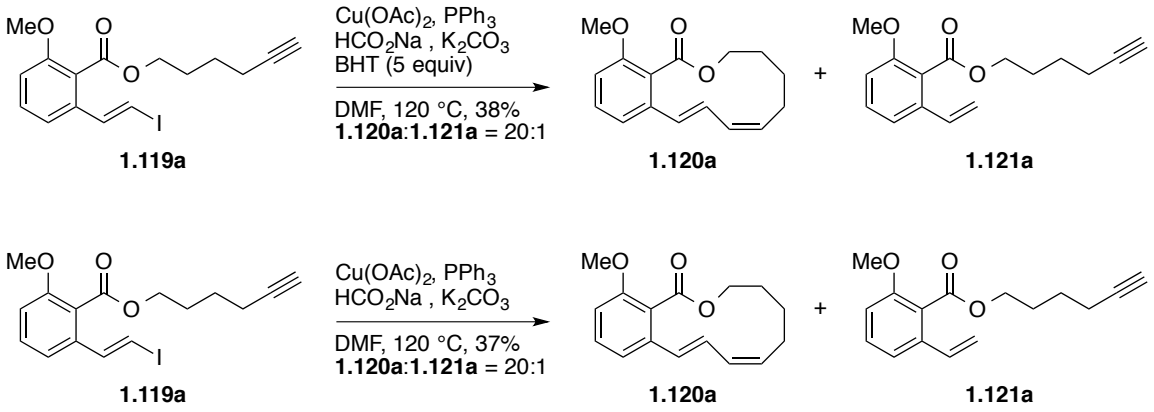
The iodides were exposed to the ene–yne coupling conditions in the absence of HCO_2Na and the crude enyne was then treated with *in situ* formed CuH.[90] The 14-membered macrolactone **1.120e** and 17-membered macrolactone **1.120p** were synthesized using these conditions and double bond isomerization as seen in palladium-catalyzed trans-hydrogenation of enyne was not detected herein.

1.5 Mechanistic Insights

A series of experiments was conducted in order to gain insights into the possible mechanism of the unprecedented reductive ene–yne coupling reaction. We hoped that an in-depth understanding of the reaction would give rise to further expansion of its scope and applications. We first added radical scavenger butylated hydroxytoluene (BHT, 5

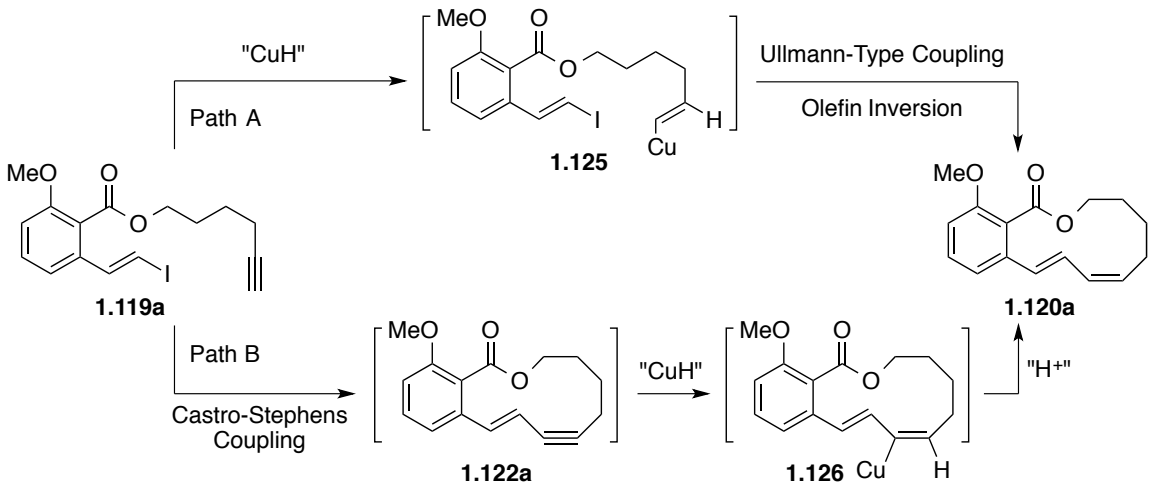
equiv) to the reaction of iodide **1.119a** under the previously described conditions (HCO_2Na (4 equiv), K_2CO_3 (1.5 equiv), $Cu(OAc)_2$ (0.33 equiv), and PPh_3 (1 equiv) at 120 °C in DMF (0.005 M) for 2 h) to determine whether the reaction proceeded through a radical or non-radical pathway (Scheme 1–31). Addition of the reagent exerted no perceptible effect on the rate, efficiency, or selectivity of the reaction in comparison with a control experiment. Both reactions went to completion in 2 h and gave nearly identical yields (~38%) and product ratios (**1.120a**:**1.121a** = 20:1), suggesting that radicals were not likely to be involved in the reaction pathway.

Scheme 1–31. Reactions with or without BHT



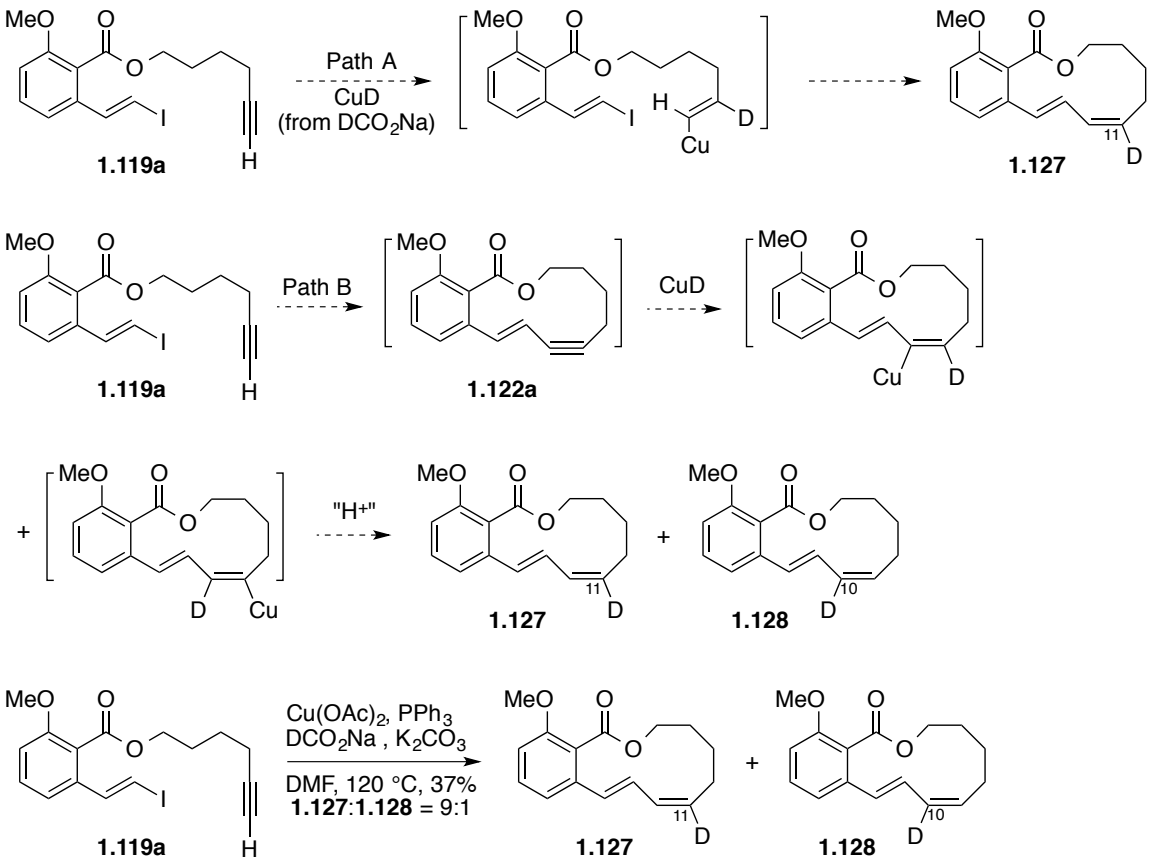
After ruling out the possibility of radical mechanisms, we postulated two non-radical pathways that would lead to the formation of diene lactone **1.120a** (Scheme 1–32). Both mechanisms consisted of a coupling step and a reduction step via hydrocupration of an alkyne with a CuH species. However, we were uncertain whether the hydrocupration occurred prior to (path A) or after (path B) the ring-forming coupling reaction.

Scheme 1–32. Possible Reaction Mechanisms



To determine the plausibility of the hypothesized mechanisms, deuterium-labeling experiments for the reductive coupling reaction were carried out through replacing HCO_2Na, the hydride source, with DCO_2Na. We assumed that the active reducing species under otherwise the same conditions to be copper deuteride (CuD). If path A was the actual mechanistic pathway, the reaction with DCO_2Na should generate exclusively the 11-deuterated product **1.127** (Scheme 1–33). In contrast, if the reaction proceeded through path B and the hydrocupration was not absolutely regioselective, both 11-deuterated product **1.127** and 10-deuterated product **1.128** could be obtained (Scheme 1–33). In fact, ^{1}HNMR analysis identified the product of the labeling experiment as a 9:1 mixture of both regioisomers **1.127** and **1.128**, implying that path B was more likely the operating mechanism. The preference for deuteration at the C_{11} position might be ascribed to the electronic properties of the enyne intermediate.

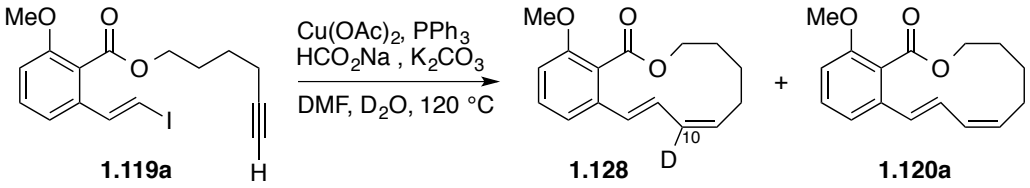
Scheme 1–33. Reaction with DCO_2Na



In path B, a conjectured vinyl copper intermediate **1.126** (Scheme 1–32) extracts a proton to furnish the final product. Since we did not observe the bis-deuterated product in the reaction with DCO_2Na, we deduced that the vinylcopper intermediate was likely quenched by external proton donors present in the solution (for example, $Cu(OAc)_2 \cdot H_2O$, alkynyl proton, or residual water in the solvent). This hypothesis was supported by the experiments performed with iodide **1.119a** in the presence of anhydrous $Cu(OAc)_2$, HCO_2Na and D_2O (Table 1–7), which resulted in deuterium incorporation at the C_{10} position (**1.128**). The proportion of deuterated product **1.128** increased along with the amount of D_2O added to the reaction (Table 1–7, entries 1-3). However, 75% of the

product remained undeuterated even with large excess of D_2O (15 equiv, entry 3). The quenching proton might come from the non-dry solvent or diethylamine due to the decomposition of DMF at the high reaction temperature. In order to exclude proton sources to the greatest extent, one experiment was operated in pre-dried d_6-DMSO (entry 4). A high degree of 68% deuterium incorporation was achieved under these conditions.

Table 1–7. Reactions with D_2O[a]

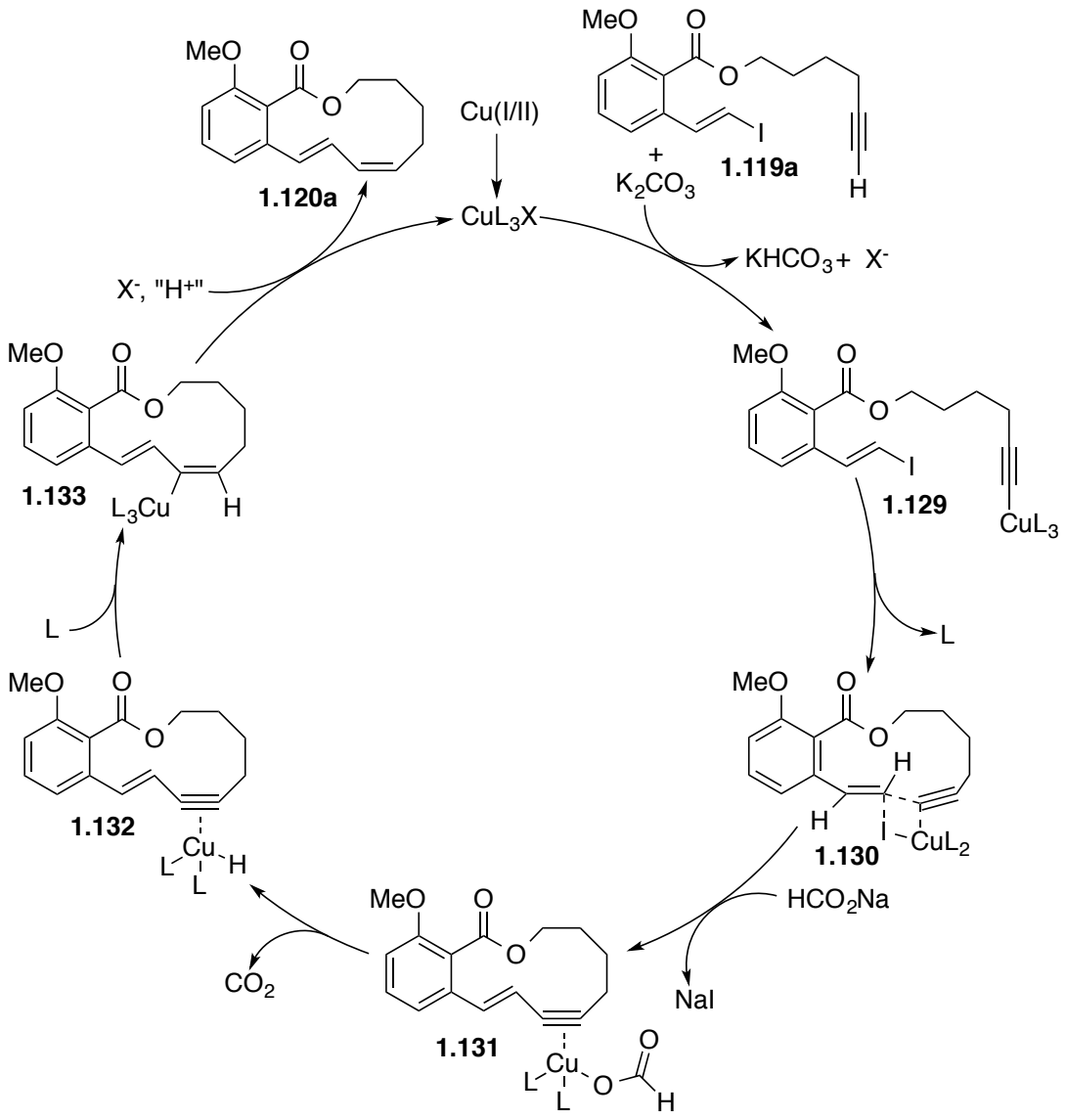


entry	solvent	amount of D_2O (equiv)	yield (%)[b]	ratio (**1.128**:**1.120a**)[c]
1	DMF	2	N/A[d]	10:90
2	DMF	5	N/A[d]	25:75
3	DMF	15	34	29:71
4	d_6-DMSO	15	36	68:32

[a] Reaction conditions: **1.119a** (0.005 M), anhydrous $Cu(OAc)_2$ (0.33 equiv), PPh_3 (1 equiv), HCO_2Na (4 equiv), and K_2CO_3 (1.5 equiv) at 120 °C under N_2 for 2 h. [b] Isolated yield as mixture of **1.128** and **1.120a**. [c] Calculated from ^1H NMR. [d] Not isolated. Crude NMR was analyzed.

One the basis of the above experimental results and literature reports, we proposed the detailed catalytic cycle following path B as shown in Scheme 1–34.

Scheme 1–34. Proposed Mechanism for Reductive Coupling Reaction



The interaction of terminal alkyne **1.119a** with the copper catalyst generates copper acetylide **1.129** *in situ* in the presence of the weak base K_2CO_3. An intramolecular Castro–Stephens coupling reaction between the acetylide and the vinyl iodide units forms *E*-enyne **1.131** via a four-centered transition state.[63, 115] The copper atom remains coordinated to the triple bond through π-complexation, stabilizing the highly strained enyne and preventing the C_8–C_9 olefin isomerization. Subsequent expulsion of CO_2 from

the copper-formate complex provides the requisite CuH species **1.132**, which undergoes 1,2-addtion across the alkyne to afford vinyl copper **1.133**. A final protonation of the vinyl copper delivers the desired diene macrocyle **1.120a** and regenerates the copper catalyst.

1.6 Summary

A copper-mediated tandem reaction involving an intramolecular Castro–Stephens coupling and *in situ* alkyne semi-reduction has been developed for the construction of macrocycles containing conjugated *E*,*Z*-diene units. Both extensive optimization studies and scope explorations have been conducted, demonstrating that the reaction is ring strain dependent and particularly efficient for 11- to 13-membered rings. The synthesis of larger and hence, less strained macrocycles can be achieved through an alternative stepwise sequence. The method is tolerant of linkages such as an ether, ester, and tertiary amide, but not compatible with acidic functionalities like an unprotected phenol or a secondary amide. A plausible mechanism has been proposed based on preliminary experimental observations. The deuterium-labeling studies reveal that the coupling reaction precedes the alkyne reduction.

We believe that this facile transformation, which we previously utilized in the total synthesis of the benzolactone enamide natural product oximidine II, will be of great synthetic value for other complex macrocyclic molecules. In the next chapter, this will be demonstrated through an expeditious formal total synthesis of lactimidomycin, a potent antiproliferative agent.

Chapter II. Formal Total Synthesis of Lactimidomycin

2.1 Background

2.1.1 Biological Profile

The glutarimide-containing macrolide lactimidomycin (**1.3**, Figure 2–1), isolated in 1992 from the fermentation broth of *Streptomyces amphibiosporus* ATCC 53964, displays a wide spectrum of biological effects including cytotoxicity, antifungal activity, and inhibition of DNA/protein biosynthesis.[30] The optimization of the fermentation conditions led to the production of lactimidomycin in appreciable quantities and as a consequence, the determination of its absolute stereochemistry.[31] Further biological studies also identified it as an outstanding cell-migration inhibitor with an IC_{50} value of 0.6 nM against the highly invasive MDA-MB-231 human breast adenocarcinoma cell line.[116] However, a more recent report claimed that lactimidomycin was acutely cytotoxic and no significant cell-inhibition was observed at sub-toxic doses.[39] Regardless of these contradictory results, lactimidomycin is still considered to be a promising anticancer drug lead because of its potent and selective antiproliferative effect on tumor cells both *in vitro* and *in vivo*.[30, 117] Recently, details of its mechanism of action were unveiled when a lactimidomycin co-crystal structure with the 80S ribosome of *Saccharomyces cerevisia* revealed that the natural product binds to the tRNA E-site of the S60 subunit, thereby

preventing the binding of tRNA.[118] In addition, kinetic experiments showed that lactimidomycin targets the first elongation cycle.

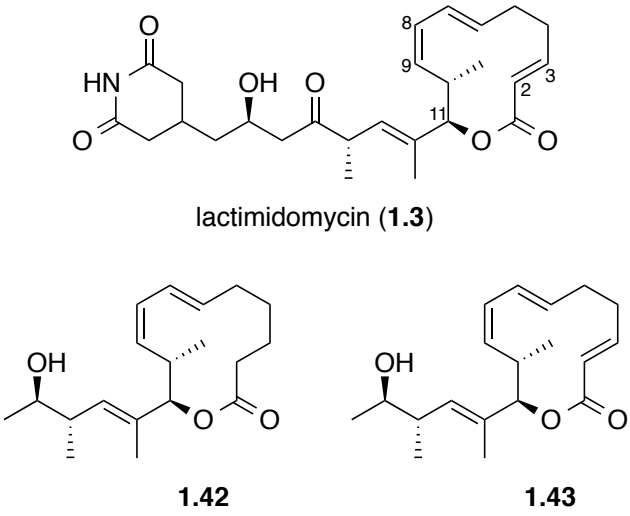
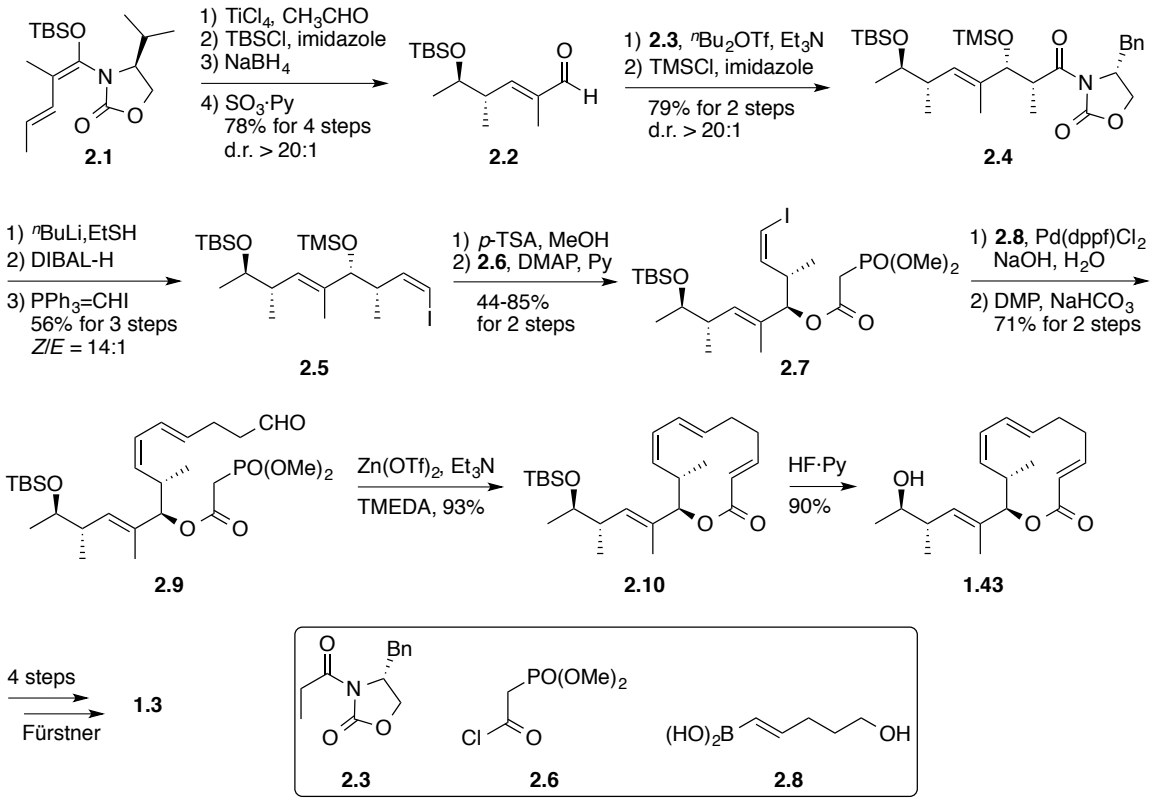


Figure 2–1. Lactimidomycin (**1.3**) and its synthetic precursors **1.42** and **1.43**.

2.1.2 Reported Synthesis

In addition to the continuous interest in its biological and pharmacological properties, lactimidomycin has also attracted attention from the organic chemistry community. Two total syntheses and two formal total syntheses have been disclosed, all with efforts focused on the construction of the unsaturated 12-membered lactone subunit. Fürstner developed two distinct approaches through RCM reations,[14, 38] as discussed in Section 1.1.3. The two latest syntheses, independently reported by Nagorny and Kuwahara, were published back-to-back in 2013.

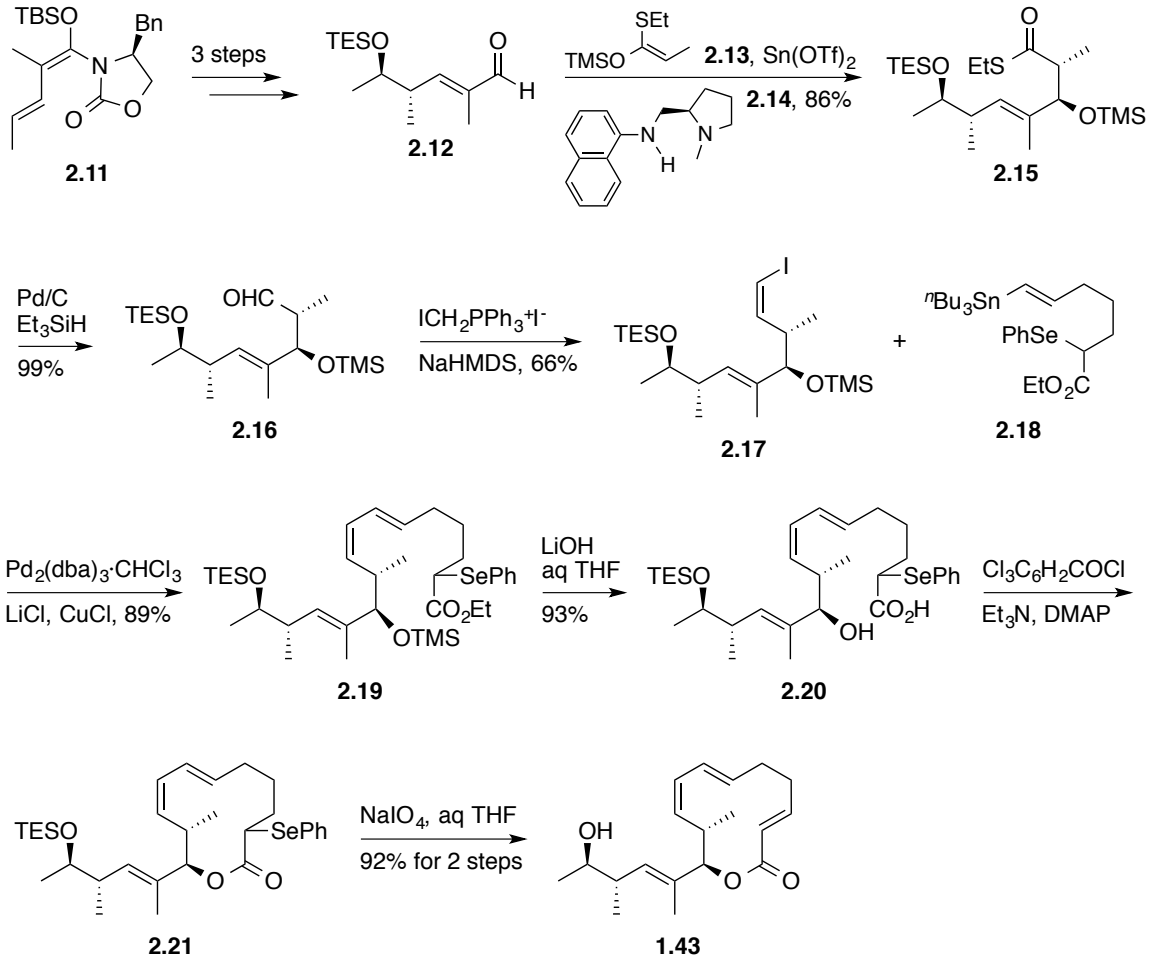
Scheme 2–1. Nagorny's Total Synthesis of Lactimidomycin



Nagorny et al. carried out their total synthesis by employing a Horner–Wadsworth–Emmons macrocyclization strategy (Scheme 2–1).[119] Here chiral aldehyde **2.2** was derived from the known vinylketene silyl *N*,*O*-acetal **2.1** in four steps including an asymmetric vinylogous aldol reaction, silyl protection, the reductive removal of the auxiliary, and a Parikh–Doering oxidation of the resultant alcohol. The aldehyde was then subjected to an Evans *syn*-selective aldol reaction followed by silyl protection to yield the protected aldol adduct **2.4**. The oxazolidinone auxiliary was removed through sequential thioesterification and DIBAL-H reduction to form an aldehyde, which was converted to *Z*-vinyl iodide **2.5** through a Stork–Zhao olefination. The TMS protecting group of compound **2.5** was selectively removed and the resultant alcohol underwent an acylation

reaction with acyl chloride **2.6** to provide iodovinyl phosphate **2.7**. The Suzuki coupling reaction of iodide **2.7** with boronic acid **2.8** installed the *E*,*Z*-1,3-diene structural unit and succeeding Dess–Martin oxidation furnished aldehyde **2.7** ready for the critical ring-closing step. A Lewis acid Zn(II)-mediated intramolecular HWE reaction of compound **2.7** generated the desired triene macrolactone **2.10** in a remarkably high yield of 93%. Model studies revealed that conventional Brønsted base-mediated conditions (e.g., LiHMDS) gave only the dimerized product. Desilylation of compound **2.10** delivered alcohol **1.43**, which was elaborated to lactimidomycin following Fürstner's report.[38]

Scheme 2–2. Kuwahara's Formal Total Synthesis of Lactimidomycin

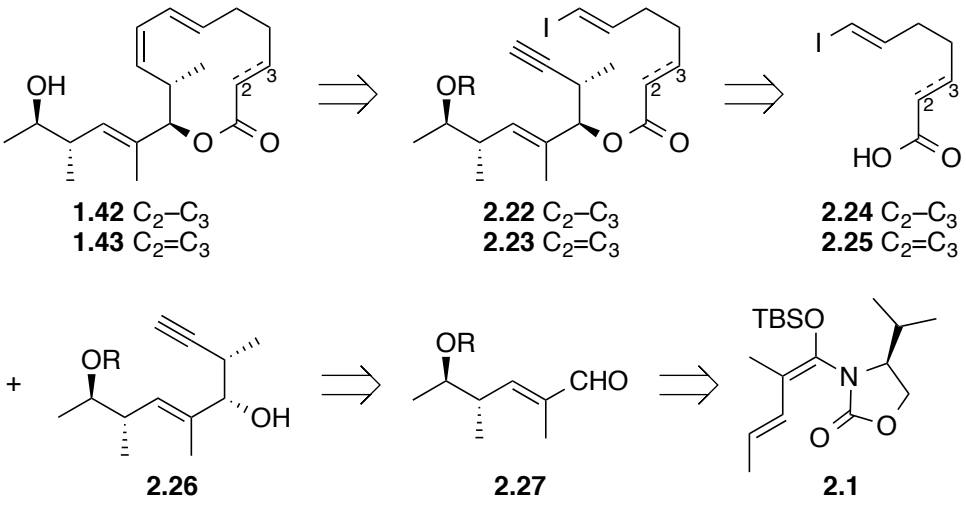


Kuwahara's formal total synthesis of lactimidomycin employed a Yamaguchi macrolactonization (Scheme 2–2).[120] Aldehyde **2.12** was prepared similarly to aldehyde **2.2** in the Nagorny's synthesis. Exposing the aldehyde to ketene silyl *S*,*O*-acetal **2.13** in the presence of $Sn(OTf)_2$ and chiral amine **2.14** led to the asymmetric formation of thioester **2.15**. Reduction of thioester **2.15** to aldehyde **2.16** followed by a *Z*-selective Stork–Zhao olefination reaction afforded iodide **2.17**, which was converted to *Z*,*E*-diene **2.19** through Stille coupling reaction with stannane **2.18**. Saponification of ester **2.19** under basic conditions also induced the selective deprotection of the TMS ether to give directly the seco-acid **2.20**. Yamaguchi macrocyclization of hydroxy acid **2.20** followed by oxidative elimination of the selenide and simultaneous desilylation furnished the triene lactone **1.43** in an excellent yield of 92% over two steps. Since compound **1.43** is a known intermediate in Fürstner's and Nagorny's total syntheses, this 10-step sequence constituted a formal total synthesis of lactimidomycin.

2.2 Retrosynthesis

Having developed the Castro–Stephens coupling/alkyne reduction tandem reaction for macrocyclization and having found that it was efficient for aliphatic substrates as well, we implemented the use of this method for the enantiospecific formal total synthesis of lactimidomycin. We selected truncated macrolides **1.42** and **1.43** (Figure 2–1) as the synthetic target, since both compounds have been converted to lactimidomycin in previously reported total syntheses.

Scheme 2–3. Retrosynthesis



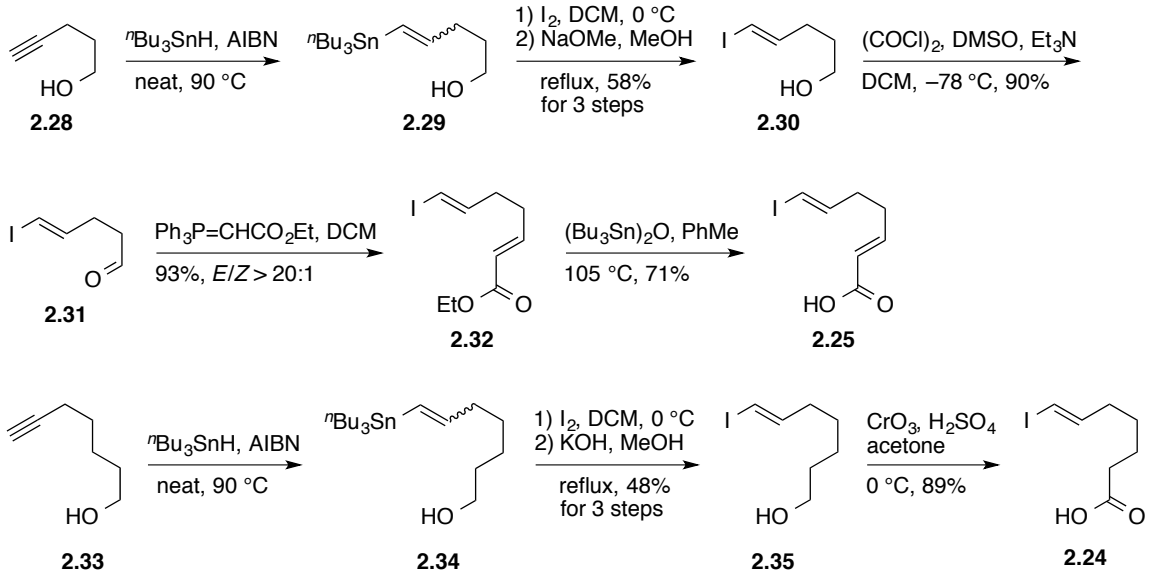
The retrosynthetic analysis is depicted in Scheme 2–3. We expected that the 12-membered macrocycles **1.42** or **1.43** could be obtained from iodides **2.22**/**2.23** via our coupling/reduction tandem reaction. Esters **2.22**/**2.23** could be readily prepared from propargyl alcohol **2.26** and the corresponding carboxylic acids **2.24**/**2.25** using Mitsunobu conditions. Enantioenriched alcohol **2.26** was envisioned to arise from aldehyde **2.27** through Marshall's asymmetric propargylation reaction. We also hypothesized that an *anti*-selective Kobayashi's vinylogous aldol reaction of the known compound **2.1** would be able to deliver aldehyde **2.27**.

2.3 Preparation of Acids 2.24/2.45

The Acid **2.24** was prepared from 4-pentyn-1-ol (**2.28**) in a 6-step sequence as shown in Scheme 2–4. Radical hydrostannylation of alcohol **2.28** was initiated by AIBN to generate vinyl stannane **2.29**, which was converted via tin-iodine exchange to the corresponding vinyl iodide as a mixture of *E*/*Z* isomers.[121] The mixture was then treated

with NaOMe in refluxing methanol.[122] Under these conditions, only the *Z*-isomer was susceptible to an elimination reaction, leaving the untouched *E*-vinyl iodide **2.30** to be isolated in 58% yield over three steps. Next, alcohol **2.30** was oxidized to aldehyde **2.31** under Swern conditions.[123] The Wittig olefination reaction[124] of aldehyde **2.31** with (ethoxycarbonyl)triphenylphosphorane afforded *α,β*-unsaturated ester **2.32** in high yield and *E*-selectivity (93%, *E*/*Z* > 20:1). While common basic saponification conditions failed to cleave the ethyl ester **2.32**, this transformation was promoted by bis(tributyl)tin oxide with heating, furnishing the acid **2.25** in 71% yield.

Scheme 2–4. Preparation of Acids 2.24/2.25

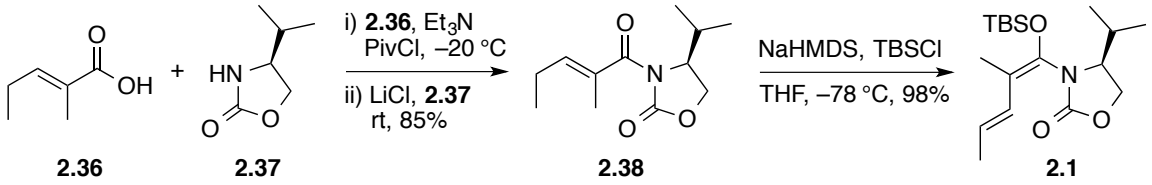


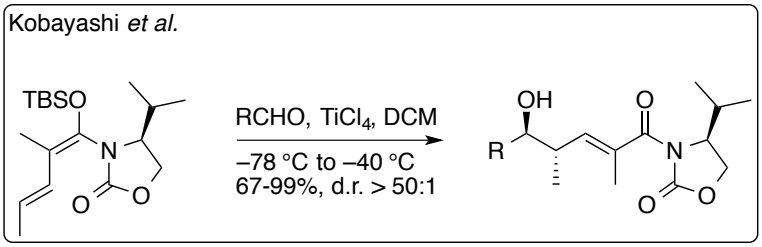
Acid **2.24** was synthesized from 6-heptyn-1-ol (Scheme 2–4). *E*-iodovinyl alcohol **2.35** was obtained in a manner analogous to alcohol **2.30**. Jones oxidation[125] of alcohol **2.35** gave directly the acid **2.24**.

2.4 Synthesis of Esters 2.22/2.23

The preparation of esters **2.22**/**2.23** was started from the commercially available (*E*)-2-methyl-2-pentenoic acid (**2.36**), which was converted to the known vinylketene silyl *N*,*O*-acetal **2.1** following literature procedures (Scheme 2–5).[126-127] Evans' oxazolidinone **2.37** was acylated with the mixed anhydride of acid **2.36** and pivalic acid in the presence of LiCl[128] to yield chiral imide **2.38** and subsequent enol silyation of imide **2.38** with TBSCl generated compound **2.1** in almost quantitative yield.

Scheme 2–5. Preparation of Ketene *N*,*O*-Acetal 2.1 and Its Vinylogous Aldol Reactions Reported by Kobayashi

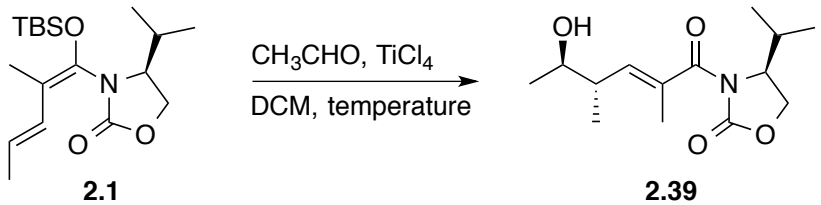




We intended to obtain the aldol adduct **2.39** by coupling compound **2.1** with acetaldehyde through a vinylous Mukaiyama-type aldol reaction following Kobayashi's protocol (Scheme 2–5 and Table 2–1).[129-130] In the original publication of 2004, compound **2.1** was reacted with long-chain or α-branched aldehydes to provide the corresponding aldol adducts with exceedingly high stereoselectivity (d.r. > 50:1). We

were concerned whether the reaction with acetaldehyde would retain the selectivity owing to its small size and lack of steric hindrance.

Table 2–1. Vinylogous Aldol Reaction of Compound 2.1 with Acetaldehyde[a]



2.1 **2.39**

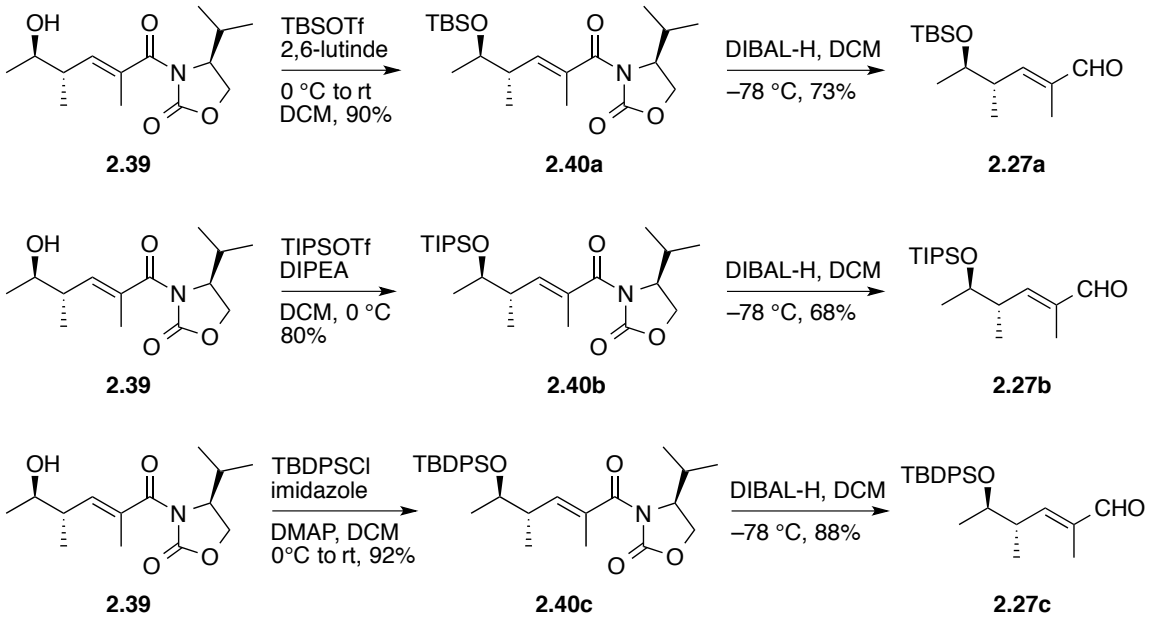
entry	temperature (°C)	equiv of CH_3CHO	yield (%)[b]	d.r.[c]
1	–78 to –40	2	39	2.5:1
2	–78 to –65	2	81	20:1
3	–78	2	71	> 30:1
4	**–78**	**4**	**80**	**> 30:1**

[a] Reaction conditions: **2.1** (0.1 M), CH_3CHO, and $TiCl_4$ (1 equiv) in DCM under N_2 overnight. [b] Isolated yield. [c] Calculated from ^1H NMR.

We first mixed the reactants at –78 °C, allowed the mixture to warm to –40 °C, and left the reaction at this temperature overnight (Table 2–1, entry 1). The aldol adduct was obtained in 39% yield and this low yield might be attributed to the quality of compound **2.1**, which was improperly stored at room temperature for a few days, resulting in visible decomposition by TLC analysis. Nonetheless, the modest selectivity (d.r. = 2.5:1) implied the necessity of maintaining the reaction at a lower temperature. Indeed, a drastic increase in both diastereomeric ratio (20:1) and yield (81%) was observed when the reaction was executed at –65 °C (entry 2). Further enhancement of the stereoselectivity (d.r. > 30:1) was achieved by keeping the reaction temperature constant at –78 °C (entry 3), with somewhat diminished efficiency (71% yield). Finally, we were gratified to obtain

compound **2.39** in 80% yield at –78 °C, meanwhile maintaining the selectivity upon using an excess amount of acetaldehyde (entry 4).

Scheme 2–6. Synthesis of Aldehyde 2.27



The aldol adduct **2.39** was protected by various silyl protecting groups to afford compounds **2.40a-c**. The conversion of imides **2.40a-c** to the corresponding aldehydes **2.27a-c** was accomplished by reductive removal of the chiral auxiliary while the reaction progress was strictly monitored to avoid over-reduction to alcohols.

We next aimed at the stereoselective installation of the methylpropargyl moiety onto the molecule. Marshall developed a series of asymmetric propargylation reactions mediated by an assortment of metals (Scheme 27).[131-135] Depending on the metal reagent employed, the stereochemical outcome can be regulated. In the tin-mediated reactions, an aldehyde was coupled with a chiral allenylstannane, yielding an alcohol with the hydroxy and adjacent methyl groups syn to each other as the major stereoisomer.[131] To the

contrary, the zinc/indium-assisted reactions involved allenyl metal species formed *in situ* from chiral mesylates and preferred anti product formation.[134]

Scheme 2–7. Marshall's Asymmetric Propargylation Reactions and Synthesis of Propargylation Reagents

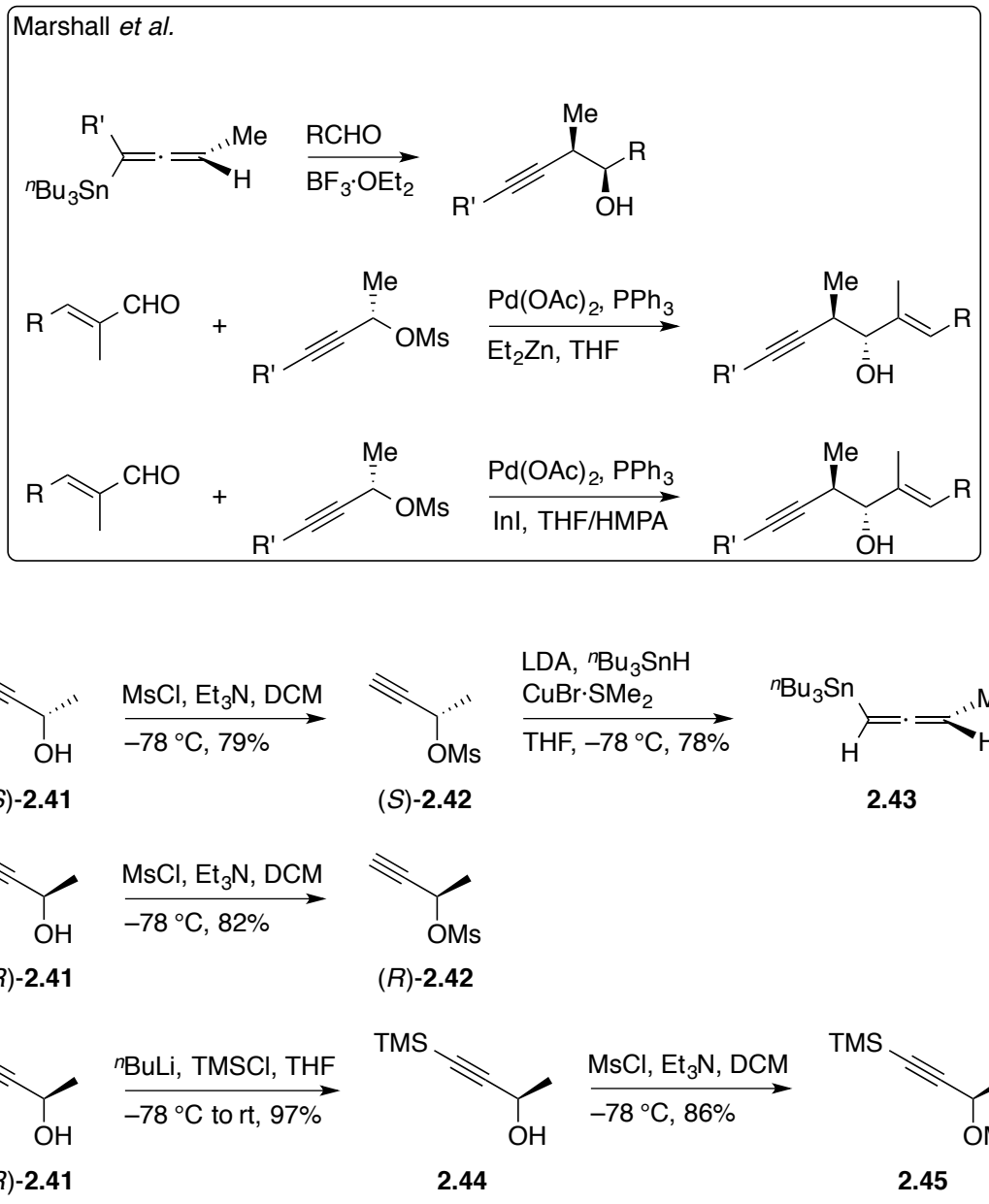
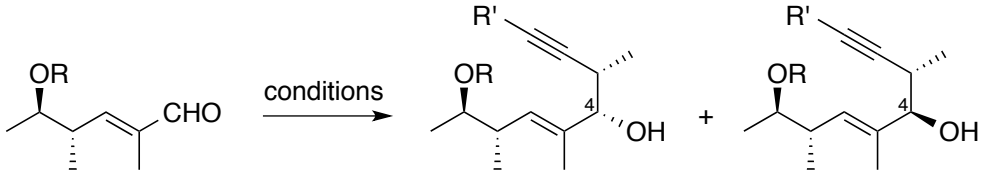
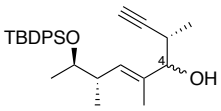
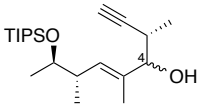
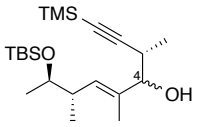
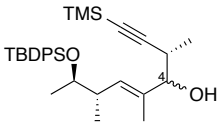


Table 2–2. Propargylation of Aldehyde 2.27



2.27 (4*S*)-**2.26** (4*R*)-**2.26**

entry	reactants	scale[a] (mg)	conditions[b]	product	yield (%)[c]	ratio (4*S*/4*R*)[d]
1	**2.27c** + **2.43**	42.5	A (Sn)	 **2.26c**	ca. 100	44:56
2	**2.27b** + (*R*)-**2.42**	46.3	B (In)	 **2.26b**	76	72:28
3	**2.27c** + (*R*)-**2.42**	35.0	B (In)	**2.26c**	84	83:17
4	**2.27c** + (*R*)-**2.42**	679	B (In)	**2.26c**	71	63:37
5	**2.27a** + **2.45**	26.2	C (Zn)	 TMS-**2.26a**	0[e]	N/A
6	**2.27c** + **2.45**	14.8	C (Zn)	 TMS-**2.26c**	0[e]	N/A
7	**2.27c** + (*R*)-**2.42**	49.3	C (Zn)	**2.26c**	70	82:18
8	**2.27c + (*R*)-2.42**	**382**	**C (Zn)**[f]	**2.26c**	**79**	**82:18**

[a] Weight of aldehyde. [b] Reaction conditions unless otherwise specified: A: aldehyde (0.1 M), stannane (2 equiv), and $BF_3{\cdot}OEt_2$ (3.5 equiv) in DCM at –78 °C under N_2 overnight; B: aldehyde (0.15 M), mesylate (1.2 equiv), $Pd(OAc)_2$ (0.07 equiv), PPh_3 (0.07 equiv), and InI (1.6 equiv) in THF/HMPA (3:1) at 0 °C under N_2 for 15 min, then

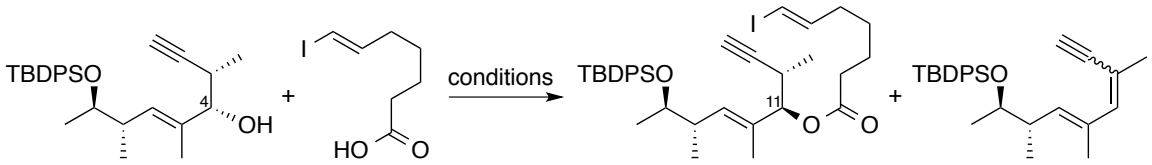
room temperature for 2 h; C: aldehyde (0.05 M), mesylate (1.2 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.05 equiv), and Et_2Zn (3 equiv) in THF at –78 °C under N_2 for 10 min, then –20 °C overnight. [c] Isolated yield as mixture of diastereomers. [d] Calculated from ^1H NMR. [e] Only starting materials remained. [f] Dried THF was further treated with 3 Å molecular sieves before reaction.

Thus, propargylation reagents **2.43**, (*R*)-**2.42** and **2.45** were prepared from enantiomerically pure alcohols (*R*)- or (*S*)-**2.41** according to literature reports (Scheme 2–7)[136-138] and subjected to propargylation reactions with aldehyde **2.27** (Table 2–2). We first investigated the tin-mediated reaction, since the expected major isomer product (*4R*)-**2.26** possesses the same stereochemical configuration as the lactimidomycin at all chiral centers. The reaction of aldehyde **2.27a** and allenylstannane **2.43** (Table 2–2, entry 1) produced alcohol **2.26c** as an inseparable mixture of both (*4S*)- and (*4R*)-epimers, in an almost quantitative yield. However, the transformation was barely selective with a diastereomeric ratio of 44:56. Reactions involving allenylindium intermediates (entries 2-4) provided alcohols **2.26b** and **2.26c** in good yields and exhibited appreciable selectivities for the (*4S*)-epimer, but the results were not well reproducible, especially on large scales (entry 4). We eventually sought to examine the zinc version reaction. Placing a silyl group at the alkyne terminus is known to improve the stereoselectivity of the reaction and may help to resolve the diastereomers by column chromatography. Thereby, we exposed aldehydes **2.27a** and **2.27c** to the silylated mesylate **2.45** (entries 5 and 6) and anticipated the formation of the corresponding alcohols TMS-**2.26a** and TMS-**2.26c**. Unfortunately, both attempts met with failure and no conversion of starting materials was observed. In contrast, exposure of aldehyde **2.27c** to simple mesylate (*R*)-**2.42** furnished alcohol **2.26c** in a yield of 70% (entry 7). The diatereomeric ratio was 82:18, preferring

the (*4S*)-epimer. The reaction was performed on multi-hundred milligram scale with the product ratio unchanged, whereas the yield was increased to 79% upon carefully drying the solvent before use (entry 8).

In order to invert the C_4 center of alcohol (4*S*)-**2.26c** to match the stereochemistry of lactimidomycin C_{11} center (numbering see Figure 2–1), a Mitsunobu esterification reaction[139-140] was implemented to install the vinyl iodide fragment (Table 2–3).

Table 2–3. Mitsunobu Reaction between Alcohol (4*S*)-2.26c and Acid 2.24



(4*S*)-**2.26c** **2.24** **2.22** **2.46**

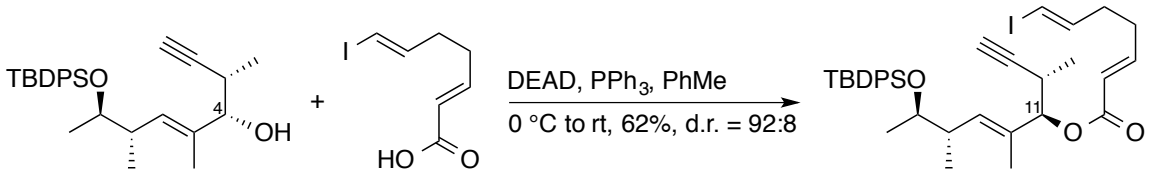
entry	conditions[a]	yield of **2.22** (%)[b]	yield of **2.46** (%)[b]
1	(*4S*)-**2.26c** (0.1 M), **2.24** (2 equiv), PPh_3 (2 equiv), and DEAD (2 equiv) in THF, 0 °C to rt	16	6.4
2	(*4S*)-**2.26c** (0.3 M), **2.24** (3 equiv), P^nBu_3 (3 equiv), and TMAD (3 equiv) in toluene, 0 °C to rt	65	N/A[c]
3	**(*4S*)-2.26c (0.1 M), 2.24 (3 equiv), PPh_3 (3 equiv), and DEAD (3 equiv) in toluene, 0 °C to rt**	**64**	**20**
4	(*4S*)-**2.26c** (0.3 M), **2.24** (3 equiv), PPh_3 (3 equiv), and DEAD (3 equiv) in toluene, 0 °C to rt	50	14

[a] All reactions were carried out under N_2 overnight. [b] Isolated yield. [c] Detected by TLC but not isolated.

The coupling of alcohol (*4S*)-**2.26c** and acid **2.24** under routine Mitsunobu conditions (DEAD, PPh_3, in THF) generated the desired ester **2.22** in an extremely low yield of 16% (Table 2–3, entry 1). The alcohol was vulnerable to dehydration, leading to the formation

of highly conjugated dienyne **2.46** as a side product. We used modified conditions with *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)/P^{n}Bu$_3$ as the reagent system[141] that dramatically increased the yield of ester **2.22** to 65% (entry 2). We later found that simply conducting the reaction with DEAD/PPh$_3$ system in toluene instead of in THF provided a comparable yield (64%) of ester to that with the TMAD/ P^{n}Bu$_3$ system (entry 3). The diastereomeric ratio of the product was 93:7 in favor of the (11*R*)-ester (lactimidomycin numbering). This ratio was greater than that of the starting alcohol (82:18), which is presumably due to the higher proclivity of the minor (4*R*)-epimer of alcohol **2.26c** to generate the dehydration product. Elevating the concentration of reactants did not exert any positive effects on the reaction (entry 4). Similarly, conjugated ester **2.23** was prepared from alcohol **2.26c** and acid **2.25** following the same procedure as in entry 2 (Scheme 2–8).

Scheme 2–8. Preparation of Ester 2.23



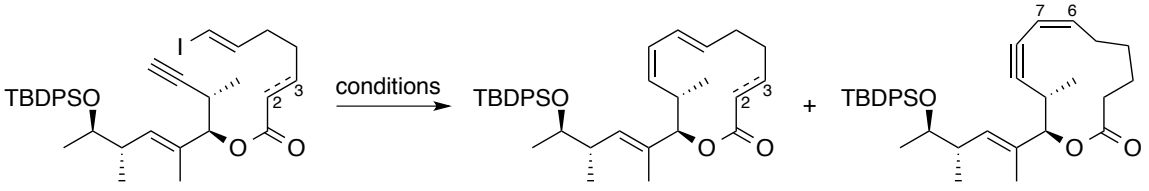
(4*S*)-**2.26c** **2.25** **2.23**

2.5 Macrocyclization and Completion of Formal Total Synthesis

We then subjected esters **2.22**/**2.23** to the macrocyclization method based on the Castro–Stephens coupling and the *in situ* alkyne reduction (Table 2–4). Ligand phanephos induced significant C_6–C_7 double bond isomerization after cyclization of iodide **2.22**, producing *Z*-enyne macrocycle **2.49** in 42% yield, along with 33% of the

desired *E*,*Z*-diene lactone **2.47** (Table 2–4, entry 1). Switching the ligand to BINAP increased the yield of diene **2.47** to around 80% (entry 2). Fortunately, the reaction was quite scalable, with 102 mg of the diene lactone obtained from 150 mg of the iodide starting material (83%) without incident. We also attempted to convert the conjugated ester **2.23** to triene lactone **2.48** under the Cu/BINAP conditions. However, the reaction with ester **2.23** resulted in complete decomposition to form a complex mixture of unidentifiable components. We hypothesized that the C_2–C_3 *E*-conjugated double bond might reduce the flexibility of the molecule, so that it could not adapt a conformation in which the reacting centers were close enough to facilitate the macrocyclization.

Table 2–4. Macrocyclization[a]



2.22 C_2–C_3
2.23 C_2=C_3

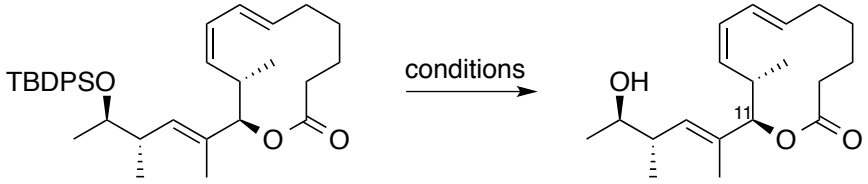
2.47 C_2–C_3
2.48 C_2=C_3

2.49

entry	iodide	catalyst & loading	yield of **2.47**/**2.48** (%)[b]	yield of **2.49** (%)[b]
1	**2.22**	$Cu(OAc)_2$ (0.33 equiv), phanephos (0.33 equiv)	33	42
2	**2.22**	**$Cu(OAc)_2$ (0.33 equiv), BINAP (0.5 equiv)**	**77-83**[c]	**N/A**[d]
3	**2.23**	$Cu(OAc)_2$ (0.33 equiv), BINAP (0.5 equiv)	0[e]	0

[a] Reaction conditions unless otherwise specified: iodide (0.005 M), HCO_2Na (4 equiv) and K_2CO_3 (1.5 equiv) in DMF at 120 °C under N_2 for 4h. [b] Isolated yield. [c] Variation among batches. [d] Observed by TLC in minor quantities, but not isolated. [e] Decomposed.

Table 2–5. TBDPS Deprotection



2.47 **1.42**

entry	conditions[a]	yield (%)
1	**2.47**, HF (48% aq. solution), in MeCN, 0 °C, overnight	0[b]
2	**2.47**, HF·Py, in MeCN, rt, overnight	0[b]
3	**2.47**, TBAT, in THF, rt, overnight	0[c]
4	**2.47**, TBAF, in THF, rt, overnight	N/A[d]
5	**2.47, TBAF, in THF, 50 °C, 4 h**	**91**[e]

[a] All reactions were carried out in open air. [b] Decomposed. [c] Only starting material remained. [d] New spot detected at low conversion, not isolated. [e] Combined isolated yields of C_{11}-epimers, d.r. = 93:7 by weight.

Having constructed the 12-membered *E*,*Z*-1,3-diene macrocyclic core, we were left with only the last desilylation step for the formal total synthesis. A number of fluoride sources were explored for the cleavage of the TBDPS protecting group from compound **2.47** (Table 2–5). The lactone ring was surprisingly sensitive to acidic conditions (Table 2–5, entries 1 and 2), which provoked complete decomposition even at low temperature. A mild fluoride donor tetrabutylammonium difluorotriphenylsilicate (TBAT) did not initiate any desilylation at room temperature, even after a long reaction time (entry 3). The TBAF-mediated reaction was encouraging, generating a new spot on TLC plate in a small but notable amount (entry 4). Finally, we were pleased to find that exposure of lactone **2.47** to TBAF at elevated temperature (50 °C, entry 5) furnished the known

alcohol **1.42** and its C_{11} epimer in a combined yield of 91%. The diastereomeric ratio of 93:7 was identical to that of ester **2.22** and the epimers were separable by column chromatography. Spectra data and optical rotation ($[\alpha]_D^{22} = -85$ (*c*, 0.10, $CHCl_3$)) of the major isomer were in excellent agreement with those of the same compound reported by Fürstner ($[\alpha]_D^{20} = -86$ (*c*, 0.9, $CHCl_3$)).[38] Therefore, a formal total synthesis of lactimidomycin had been achieved at this point.

2.6 Summary

The synthesis of macrolactone **1.42**, an advanced intermediate in the total synthesis of the antiproliferative natural product lactimidomycin, has been accomplished from commercially available starting materials in a total of nine steps (longest linear sequence) using minimal functional group protection. To our knowledge, this is the shortest route to lactimidomycin intermediates with similar structure. The key step was a copper-catalyzed ene–yne coupling/alkyne reduction tandem reaction that formed the 12-membered *E*,*Z*-diene macrocycle. Other featured reactions included a Kobayashi vinylogous aldol reaction and a Marshall propargylation reaction to generate the four stereocenters.

Chapter III. Synthesis and Biological Evaluation of Oximidine II Analogues

3.1 Background

Oximidine II (**1.4**) and its congener oximidine I were isolated in 1999 from the fermentation broth of *Pseudomonas* sp. Q52002[32] and belong to a family of benzolactone enamide natural products that possess an acyl enamine (enamide) side chain appended to a salicylate macrolactone core.[142] Other members of this family include salicylihalamides,[143-144] lobatamides,[145-146] CJ-compounds,[147] and apicularens[148-149] (representative examples in Figure 3–1). These molecules are potent cytotoxic agents and share a unique differential cytotoxicity profile in the NCI 60-cell line human tumor assay with no significant correlations to those of any other anti-tumor compounds, which implied a new mechanism of action.[143, 149-150] Using the COMPARE algorithm,[151] Boyd and co-workers deduced that the benzolactone enamides target the eukaryotic transport protein vacuolar-type (H^+)-ATPase (V-ATPase). Further biological assessments revealed that these compounds selectively inhibit mammalian types of V-ATPases. V-ATPases are important membrane-bound enzymes that energize proton transport processes across eukaryotic membranes.[152-154] They regulate the pH level of various intracellular and intraorganellar compartments, thereby playing a crucial role in the processes of renal acidification,[155] bone resorption and degradation,[156] cytoplasmic pH homeostasis,[153] and

sperm maturation.[157] Malfunction of V-ATPases has been related to an assortment of diseases, including HIV, osteoporosis, diabetes, and cancer.[153, 158]

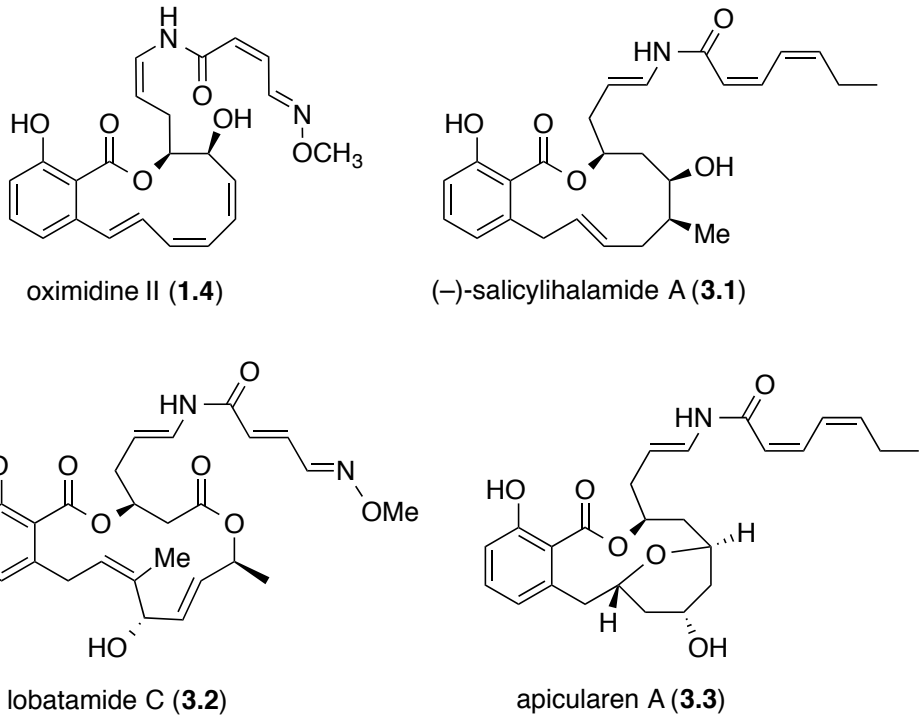


Figure 3–1. Structures of representative benzolactone enamide natural products.

Owing to their unique structural architecture and biological properties as V-ATPase inhibitors, the benzolactone enamide natural products have been the topic of interest in both the synthetic and medicinal chemistry communities. Successful total syntheses[142] of these molecules facilitated the development of synthetic analogues and subsequent exploration of the structure-activity relationships (SARs).

3.1.1 SAR Studies Towards Salicylihalamides

The SARs of salicylihalamides have been extensively studied in the De Brabander group.[159-161] A plethora of analogues of salicylihalamide A were synthesized with modifications on both the enamide side chain and the macrolactone core. The Smith

group also reported on the synthesis and biological evaluation of two simplified congeners.[162] The structures of the synthetic analogues are depicted in Figure 3–2. Their biological activities are summarized in Table 3–1.

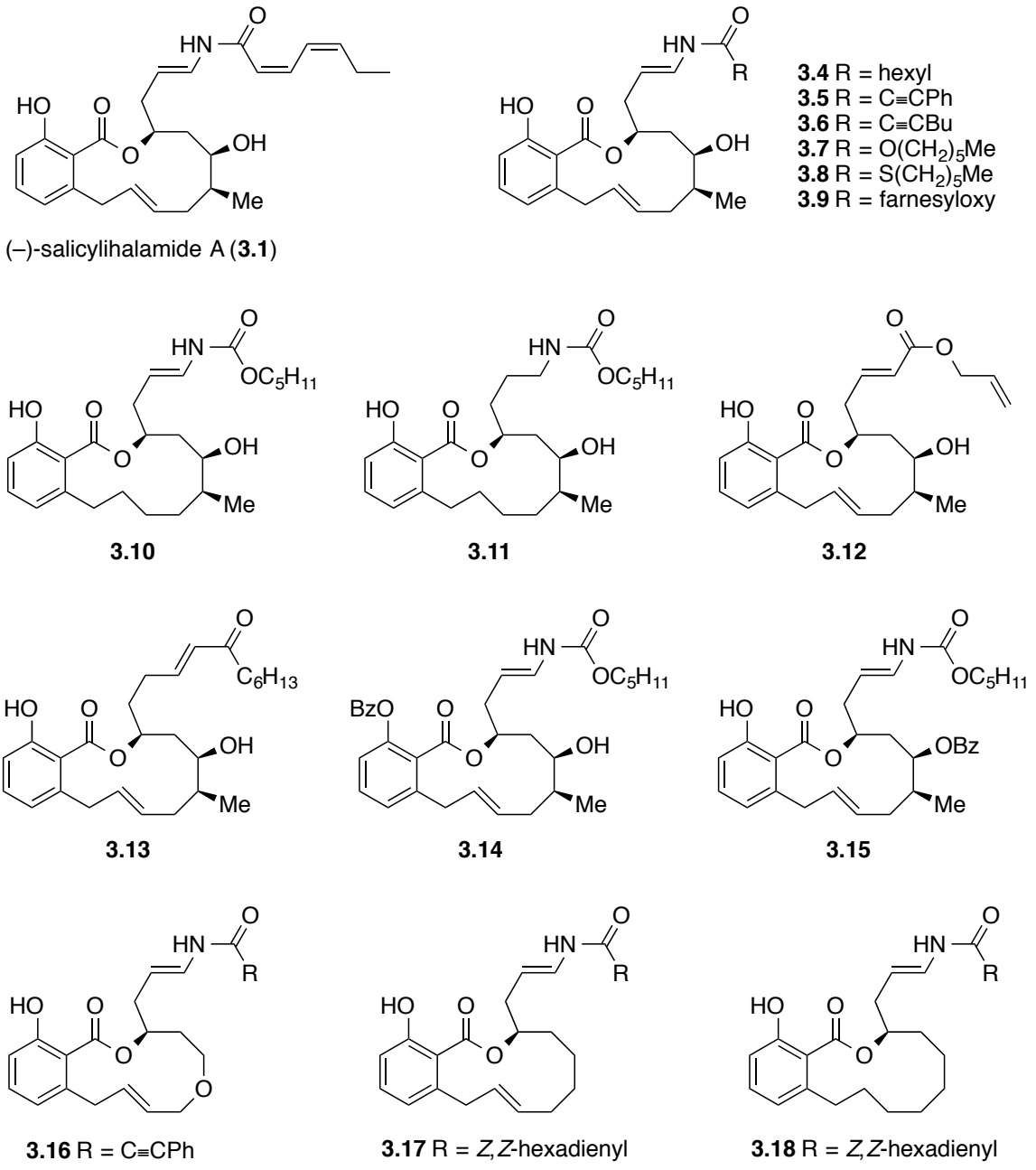


Figure 3–2. Structures of salicylihalamide analogues.

Table 3–1. Biological Evaluation of Salicylihalamide Analogues

entry	compound	V-ATPase IC_{50} (nM)	cytotoxicity[a]	reference
1	**3.1**	< 1.0	IC_{50} = 0.06 μM GI_{50} = 38-81 nM[c]	159, 160 162
2	**3.4**	1.0	IC_{50} = 0.38 μM	159, 160
3	**3.5**	<1.0	IC_{50} = 0.3 μM IC_{50} = 0.018-0.086 μM[d]	159, 160 161
4	**3.6**	1.0	IC_{50} = 0.3 μM	159, 160
5	**3.7**	1.6	IC_{50} = 0.5 μM	159, 160
6	**3.8**	1.8	IC_{50} = 0.45 μM	159, 160
7	**3.9**	>1000	IC_{50} = 1.5 μM	159, 160
8	**3.10**	3.0	IC_{50} = 8 μM	159, 160
9	**3.11**	30[b]	IC_{50} > 20 μM	159, 160
10	**3.12**	230	IC_{50} > 20 μM	159, 160
11	**3.13**	7.5[b]		160
12	**3.14**	300	IC_{50} = 1 μM	159
13	**3.15**	180	IC_{50} >20 μM	159
14	**3.16**	4.5	IC_{50} = 0.20-1.03 μM[d]	161
15	**3.17**		GI_{50} = 110-870 nM[c]	162
16	**3.18**		GI_{50} = 370-880 nM[c]	162

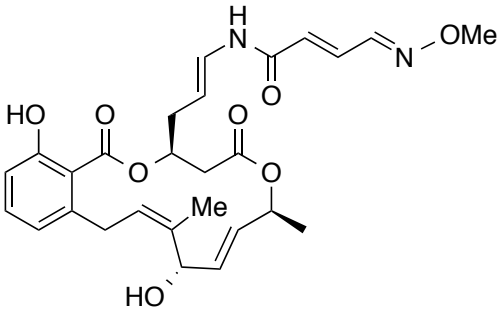
a Against SK-MEL-5 unless otherwise noted. b Reversible binding. c Against BXPC-3, MCF-7, SF268, NCI-H460, KM20L2, and DU-145 cell lines. d Against A549 and NCI-H460 cell lines.

The side-chain-modified analogues retaining the enamide functionality (Table 3–1, entries 2-6) all showed the ability to inhibit proton-pumping activity at similar concentrations to that of salicylihalamide A.[159-160] One exception was the farnesylated compound **3.9**, which exhibited a 1000-fold drop in activity (entry 7). However, the cytotoxicity of these molecules were mostly 5- to 10-fold less potent than the natural product. Analogue **3.10** (entry 8) with a saturated macrolactone retained significant potency, while the similar carbamate **3.11** (entry 9) lacking the enamide double bond displayed a 10-fold decreased activity and a reversible binding mode.[159-160] The significantly attenuated potency of allyl ester **3.12** (entry 10) emphasized again the importance of the enamide moiety.[159-160] The α,β-unsaturated ketone **3.13** (entry 11) exhibited potent V-ATPase inhibition, but was a revesible inhibitor in a variety of assays.[160] Benzyl protection at either the phenol (entry 12) or the secondary alcohol (entry 13) substantially impaired the biological activities, highlighting the neccesity of hydron bonding for the interaction of salicylihalamides with the enzyme.[159] The ether analogue[161] (entry 14) and Smith's analogues[162] (entries 15 and 16) devoid of methyl and hydroxy groups appended to the lactone ring retained considerable, although reduced activity. This implied that the structural elements on the macrocylic core might be important, but not critical. Smith et al. surmised that their function is to orchestrate the optimal orientation between the side chain and salicylate substituents for receptor binding.[162]

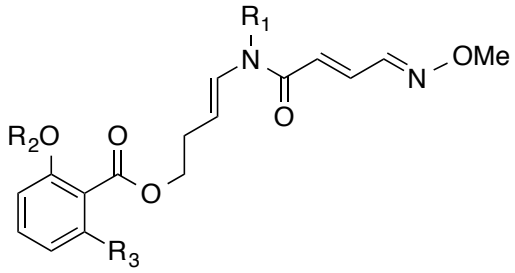
3.1.2 SAR Studies Towards Lobatamides

The Porco group prepared a series of open-chain analogues and one lactone analogue of lobatamide C (Figure 3–3).[163-165] All of the compounds bear the enamide side chain.

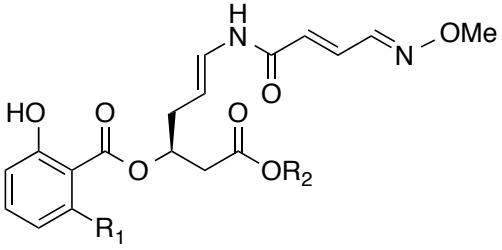
Their bioactivity was evaluated by examining the inhibition against bovine V-ATPase activity (Table 3–2).



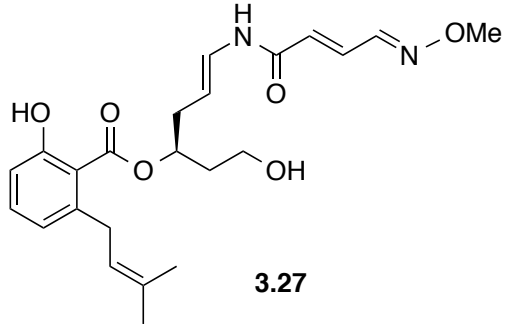
lobatamide C (**3.2**)



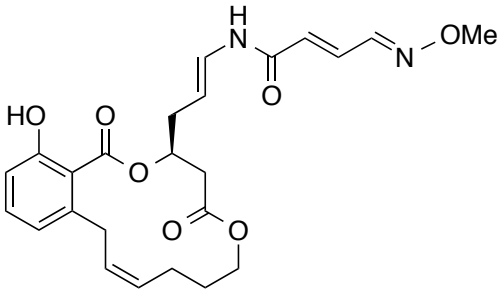
3.19 R_1 = H, R_2 = H, R_3 = H
3.20 R_1 = Me, R_2 = H, R_3 = H
3.21 R_1 = H, R_2 = Me, R_3 = H
3.22 R_1 = H, R_2 = H, R_3 = Me



3.23 R_1 = H, R_2 = Et
3.24 R_1 = Me, R_2 = Me
3.25 R_1 = I, R_2 = Me
3.26 R_1 = prenyl, R_2 = Me



3.27



3.28

Figure 3–3. Structures of lobatamide analogues.

Table 3–2. Biological Evaluation of Lobatamide Analogues

entry	compound	V-ATPase inhibition (IC_{50} in μM)	reference
1	**3.2**	0.002	163
2	**3.19**	25% inhibition at 20 μM	163
3	**3.20**	200	163
4	**3.21**	no effect	163
5	**3.22**	1.6	164
6	**3.23**	18	163
7	**3.24**	0.1	163
8	**3.25**	0.21	164
9	**3.26**	0.06	164
10	**3.27**	0.01	165
11	**3.28**	1.2	163

The minimally functionalized analogue **3.19** exhibited only week inhibition against proton-pumping activity even at high concentration (Table 3–2, entry 2).[163] The methylation at either the enamide or the phenol moieties led to an almost total loss of biological activity (entries 3 and 4), indicating the importance of the hydrogen bond donor.[163] The simple salicylate analogue **3.23**, lacking an ortho substitution showed intensely compromised potency compared to the lobatamide C natural product (entry 6).[163] However, substitution at this position with a methyl (entries 5 and 7), iodo (entry 8) or prenyl (entry 9) group regained some inhibitory property.[163-164] Notably, primary alcohol **3.27** displayed nanomolar inhibition in line with the activity of lobatamide C (entry 10).[165] The simplified ring-contracted macrolactone **3.28** proved to be 600-fold

less potent than the natural product (entry 11), suggesting that a certain ring size and substitutions on the ring are indispensable.[163]

3.1.3 SAR Studies Towards Apicularens

Analogues of apicularen A have been prepared by a number of research groups,[166-168] with focus mainly on the enamide side chain (Figure 3–4). The biological property data are listed in Table 3–3.

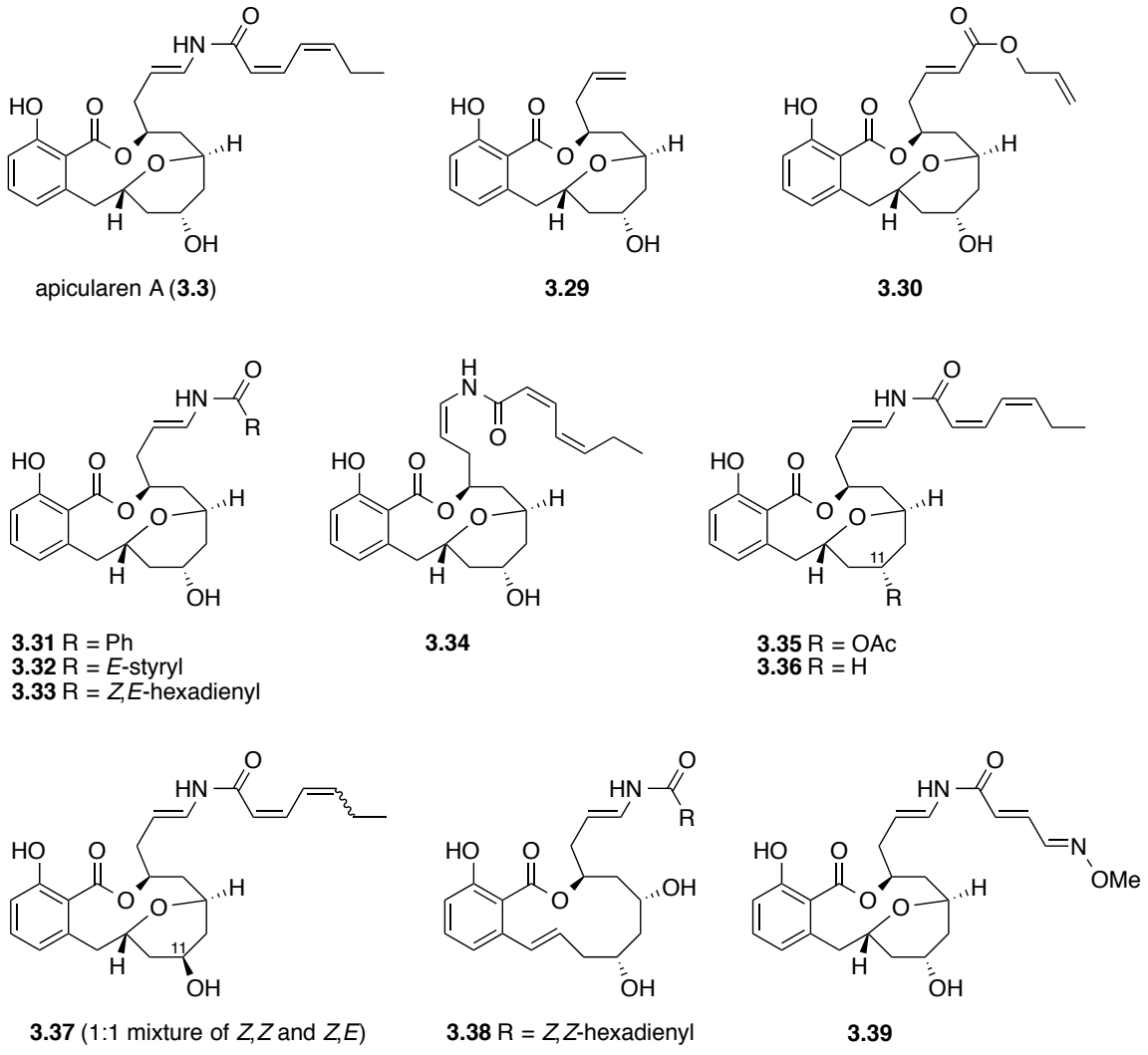


Figure 3–4. Structures of apicularen analogues.

Table 3–3. Biological Evaluation of Apicularen Analogues

entry	compound	cytotoxicity	cell line	reference
1	**3.3**	GI_{50} = 0.006 μM	SK-MEL-5	166
		IC_{50} = 0.78 nM	1A9	167
		IC_{50} = 2.3 nM	KB-3-1	168
		IC_{50} = 15.9 nM	KB-V1[a]	168
2	**3.29**	GI_{50} > 20 μM	SK-MEL-5	166
3	**3.30**	GI_{50} > 20 μM	SK-MEL-5	166
4	**3.31**	IC_{50} > 1500 nM	1A9	167
5	**3.32**	IC_{50} = 50 nM	1A9	167
6	**3.33**	GI_{50} = 0.06 μM	SK-MEL-5	166
7	**3.34**	IC_{50} = 71 nM	1A9	167
8	**3.35**	IC_{50} = 3.2 nM	1A9	167
9	**3.36**	IC_{50} = 7.1 nM	KB-3-1	168
		IC_{50} = 2.4 nM	KB-V1 [a]	168
10	**3.37**	GI_{50} = 0.45 μM	SK-MEL-5	166
11	**3.38**	IC_{50} = 180 nM	KB-3-1	168
12	**3.39**	IC_{50} = 1130 nM	KB-3-1	168

[a] Multiple drug-resistant cell line.

Similar to the SAR investigation of salicylihalamides, analogue studies of apicularens also demonstrated the importance of the enamide functionalized side chain. Analogues lacking this moiety exhibited almost no activity (Table 3–3, entries 2 and 3).[166] The short chain substituent with a bulky phenyl group (entry 4) resulted in more than 1000-fold attenuated potency.[167] In contrast, the longer chain with a linear conjugated spacer between the acyl and phenyl groups (entry 5) restored significant anti-tumor property.[167]

Variations of the double bond configuration on side chain reduced the potency by a factor of 10 to 100 (entries 6 and 7).[166-167] Acylation (entry 8) or removal (entry 9) of the 11-hydroxy group had only a marginal effect on the IC_{50} values.[167-168] Particularly, the 11-deoxy analogue **3.36** was even more potent than apicularen A against the multi-drug-resistant KB-V1 cell line (entry 9),[168] suggesting that this hydroxy group is not responsible for activity. However, inversion of this C_{11} stereocenter (entry 10) led to a 75-fold decrease in potency.[166] Opening of the pyran ring afforded analogue **3.38** similar in structure to salicilyhalamide A and analogue **3.39** bears a lobatamide-like side chain. Nonetheless, both molecules showed substantially declined cytotoxicity (entries 11 and 12), underlining the importance of the 3D conformation of the molecule for biological activity.[168]

3.1.4 SAR Studies Towards Oximidine II in Georg Group

Unlike the other benzolactone enamide natural products, the SAR of oximidines has not been the subject of exhaustive exploration. Albeit the analogue studies of salicylihalamide A and lobatamide C indicated the essentiality of the enamide side chain for anti-cancer activity, this structural unit is known for its instability under physiological conditions.[143] The enamide could be hydrolyzed into the corresponding aldehyde and amide fragments in aqueous media or more importantly, from a chemotherapeutic discovery perspective, be inactivated prior to reaching its intended target. The hydrolysis inside the acidic environment of cancer cells is also a possible concern. In an endeavor to discover bioactive analogues with better chemical stability, we set out to install physiologically stable warheads onto the oximidine framework to create analogues that would retain the cytotoxic properties observed with this natural product class. Drawing

experience from our syntheses of salicylihalamides and oximidine II,[55, 169-171] we envisioned that we could rapidly assemble the benzolactone scaffolds and affix different side chains for investigation of the anti-cancer properties of the analogues.

Dr. Schneider prepared oximidine analogue **3.41** with an allylic amide side chain,[91] inspired by the structure of another benzolactone natural product cruentaren A (**3.40**, Figure 3–5). Cruentaren A contains the allylic amide side chain, not a conjugated enamide, yet still possesses potent cytotoxicity. On the other hand, Dr. Khownium designed and synthesized analogues **3.42** and **3.43** employing a vinyl sulfone as the electrophilic functionality group that would mimic the mode-of-action of the enamide.[172] The unique property of the vinyl sulfone groups is that under physiological conditions, they do not undergo nucleophilic addition. Nucleophilic addition occurs only when hydrogen bonding interactions, typically within an active site of an enzyme, are present to activate the functionality.[173] These analogues were designed assuming that the acidic environment of the V-ATPase enzyme would activate the electrophilic vinyl sulfone moiety for nucleophilic addition analogously to the activation of the enamide moiety.[160]

For facile preparation of analogues, Dr. Khownium also developed a simplified benzolactone scaffold with the aid of computational analysis studies. Using molecular modeling data obtained from a previous comparative molecular similarity indices analysis (CoMSIA)[174]/3-dimensional quantitative structure-activity relationship (3D-QSAR) study completed by our group as the training set,[175] a simplified, partially saturated, oximidine-like scaffold was identified with predicted V-ATPase activity comparable to the parent oximidine II molecule. Thus, analogues **3.44** and **3.45** carrying this scaffold were synthesized with the attachment of vinyl sulfone chains. Both

compounds, varying in the number of methylene spacers, aligned well with the CoMSIA features. Structures of analogues **3.41**-**3.45** are shown in Figure 3–5.

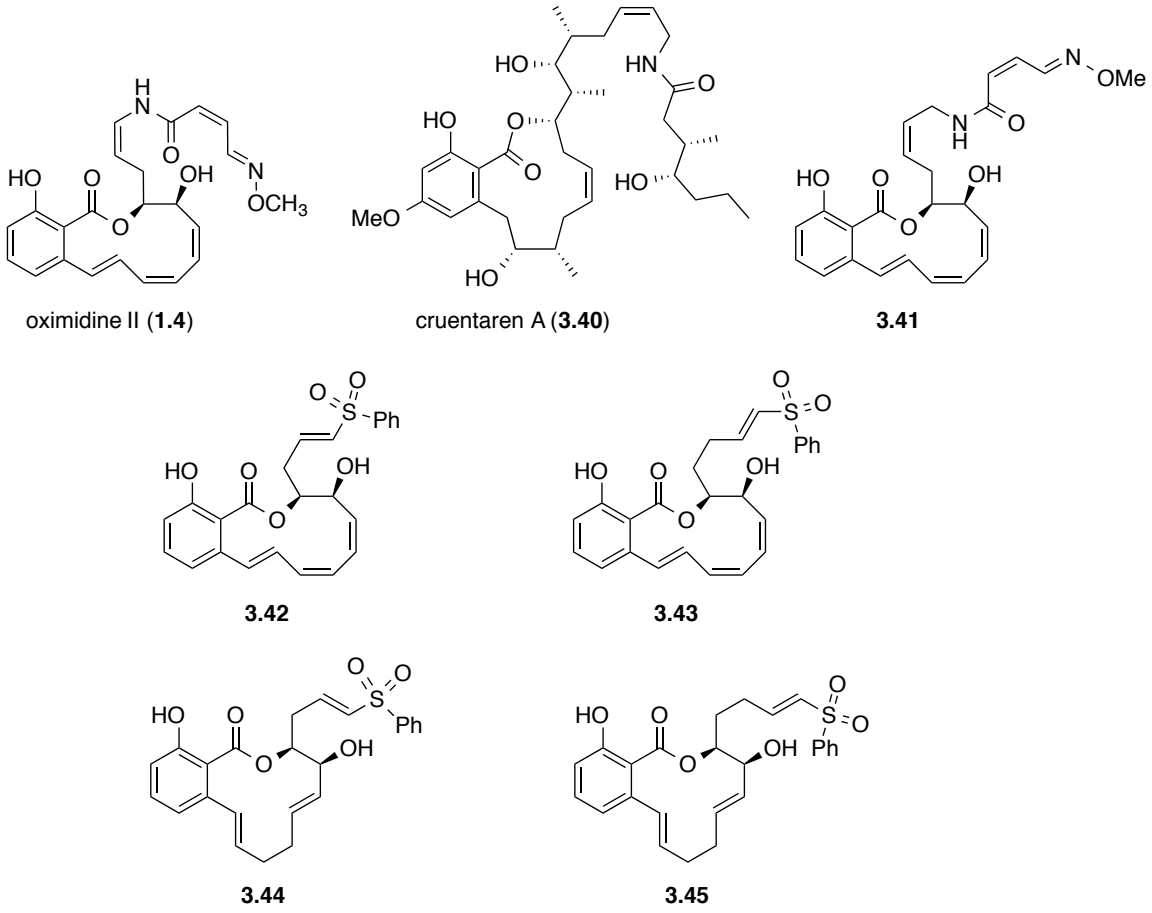


Figure 3–5. Structures of oximidine II, cruentaren A, and oximidine analogues.

Cytotoxic activity of the analogues was evaluated by testing the compounds against melanoma cell lines SK-MEL-5 and SK-MEL-28, leukemia cell line HL-60 and breast cancer cell line MCF-7 (Table 3-4). Oximidine II (entry 2) obtained through total synthesis exhibited submicromolar activity against SK-MEL-5 cell line (IC_{50} = 590 nM) and much lower potency against SK-MEL-28 cell line (60% inhibition at 100 μM).[91] All the synthetic analogues showed greatly compromised cytotoxicity compared to the parent natural product. The allylic amide analogue displayed only 40% inhibition against SK-

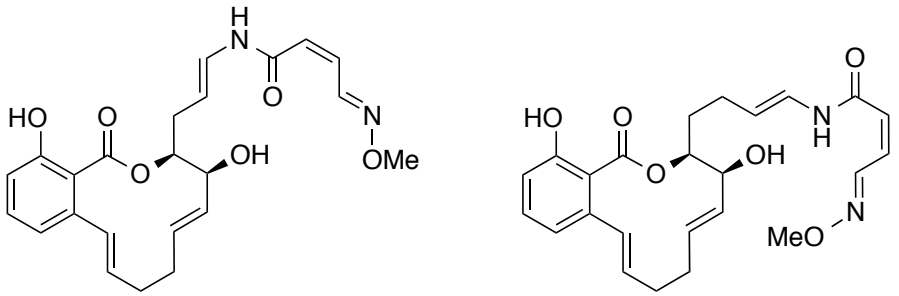
MEL-5 cell line and was barely active towards SK-MEL-28 cells (entry 3).[91] The vinyl sulfone analogues were micromolar inhibitors towards SK-MEL-5 cancer cells with IC_{50} in the range of 20-60 μM (entries 4-7), slightly more potent than the allylic amide counterpart.[172] Analogues **3.44** and **3.45** also exerted weak cytotoxic effects against leukemia and breast cancer cell lines (entries 6 and 7).[172]

Table 3–4. Cytotoxicity Evaluation of Synthesized Analogues[91, 172]

entry	compound	SK-MEL-5 (IC_{50} in μM)	SK-MEL-28 (IC_{50} in μM)	HL-60 (IC_{50} in μM)	MCF-7 (IC_{50} in μM)
1	taxol	2.90 nM	N/A[a]	2.64 nM	0.282
2	**1.4**	0.59	> 20	ND[b]	ND
3	**3.41**	> 100	> 100	ND	ND
4	**3.42**	> 100	ND	ND	ND
5	**3.43**	> 20	ND	ND	ND
6	**3.44**	> 20	> 100	> 20	> 20
7	**3.45**	> 20	> 20	> 20	100

[a] 10% inhibition at 100 μM. [b] ND = not determined.

Although the side chain modifications of oximidine II resulted in significant loss in bioactivity, the vinyl sulfone analogues with the simplified lactone core derived from CoMSIA/QSAR analysis were equipotent to those bearing the triene core of the natural product. We next decided to prepare analogues **3.46** and **3.47** (Figure 3–6) to probe whether the simplified scaffold carrying the enamide side chain could retain the anti-tumor activity of this family of natural products.

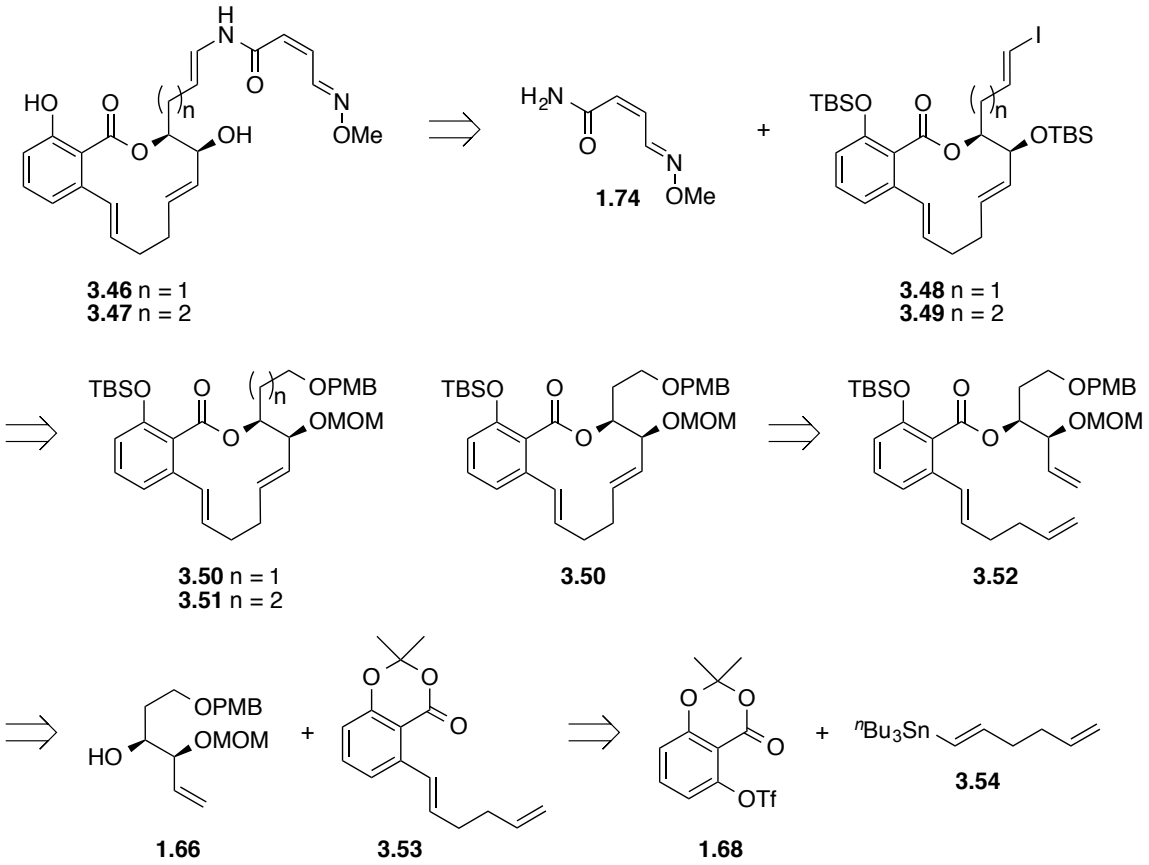


3.46 **3.47**

Figure 3–6. Structures of the newly proposed analogues with enamide side chain.

3.2 Retrosynthesis of Oximidine II Analogues

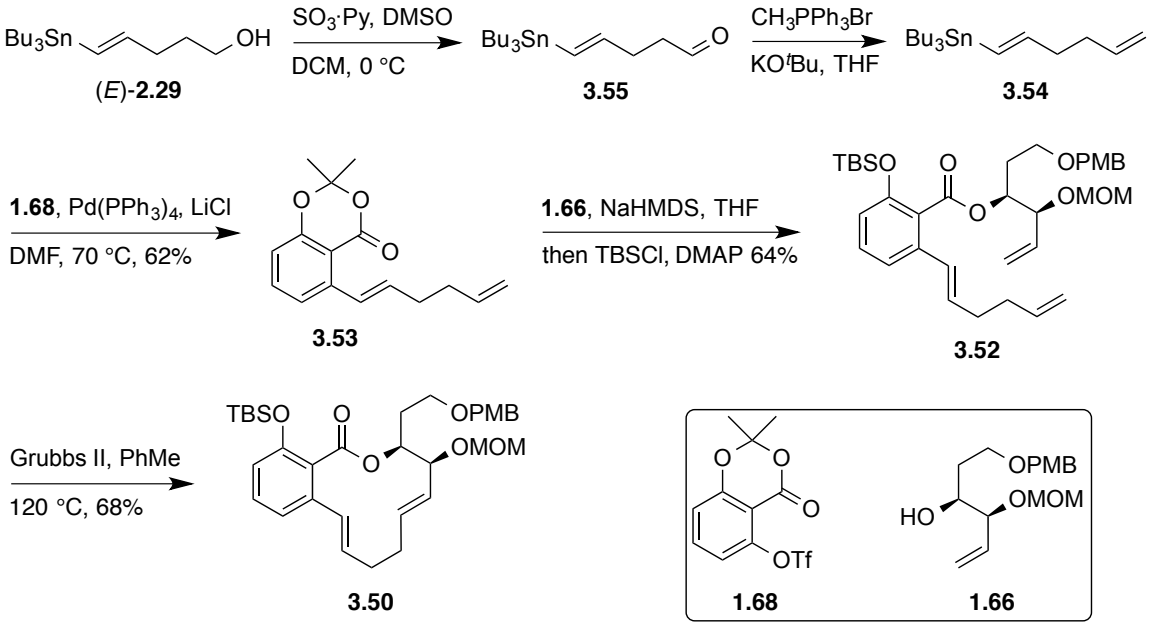
Scheme 3–1. Retrosynthesis of Analogues 3.46 and 3.47



The retrosynthetic analysis of the proposed analogues is displayed in Scheme 3–1. We envisioned a late-stage installation of the enamide chain through the coupling of bis-TBS protected iodides **3.48**/**3.49** with amide **1.74**. The iodides would be derived from protected triols **3.50**/**3.51** following Porco's strategy.[40] Compound **3.51** was kindly provided by Dr. Khownium, whereas lactone **3.50** could be prepared via the RCM reaction of triene ester **3.52**. Transesterification of salicylate **3.53** with enantioenriched alcohol **1.66**[40] would presumably provide the RCM precursor. Compound **3.53** could be obtained from triflate **1.68**[58] and vinyl stannane **3.54** through a Stille coupling reaction.

3.3 Preparation of Oximidine II Analogues

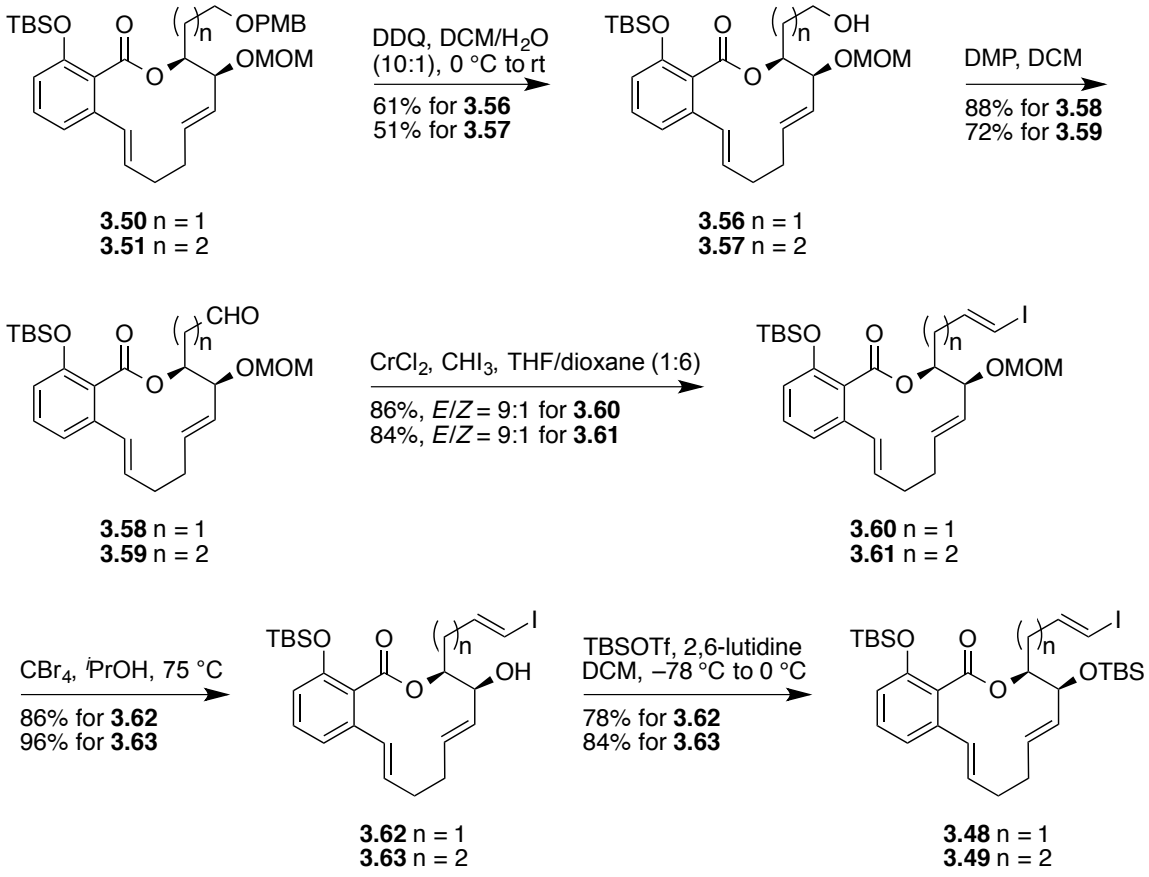
Scheme 3–2. Synthesis of Lactone 3.50



We synthesized stannane **3.54** from the known alcohol (*E*)-**2.29**[176] in two steps including a Parikh–Doering oxidation[177] and a Wittig olefination reaction (Scheme 3–2).

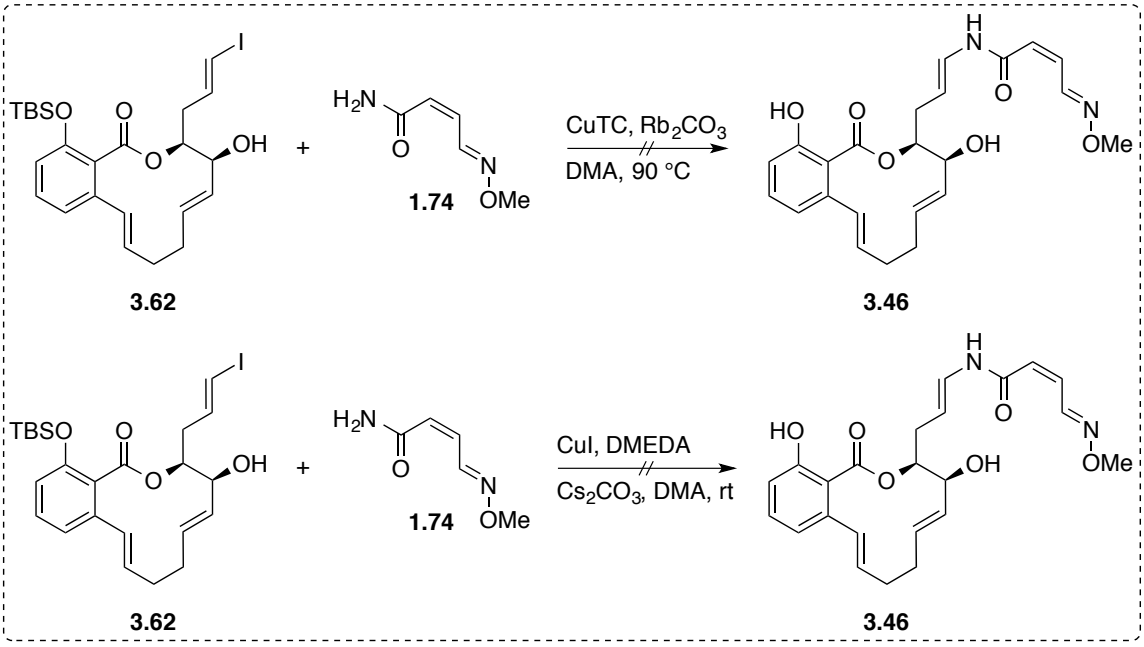
The crude stannane was directly subjected to a palladium-catalyzed Stille coupling reaction with triflate **1.68** in the presence of LiCl to form diene acetonide **3.53**.[178] The one-pot transesterification of salicylate **3.53** with alcohol **1.66** and the *in situ* phenol protection furnished the crucial triene intermediate **3.52** for macrocyclization. The RCM reaction of triene **3.52** proceeded smoothly with the second-generation Grubbs catalyst[179] to generate the thermodynamically favored product **3.50** in 68% yield. The *E*-configuration of the endocyclic double bonds was confirmed by the coupling constants of 15-16 Hz observed in the ^{1}H NMR spectrum.

Scheme 3–3. Synthesis of Iodides 3.48/3.49



The side chain elaboration commenced with lactones **3.50**/**3.51** (Scheme 3–3). Oxidative cleavage of the PMB ether with DDQ[180] followed by Dess–Martin oxidation[181] of the resultant alcohol yielded aldehydes **3.58**/**3.59**, which were converted to vinyl iodides **3.60**/**3.61** via Takai olefination.[182] The use of a mixed solvent system of THF and 1,4-dioxane (1:6)[183] provided high yields (> 80%) and good *E*-selectivity (9:1). MOM deprotection under mild acidic conditions (CBr_4, ^{i}PrOH)[184] transformed compounds **3.60**/**3.61** into alcohols **3.62**/**3.63**. The alcohols were silylated to prepare the bis-TBS ethers **3.48**/**3.49** for installation of the enamide moiety.

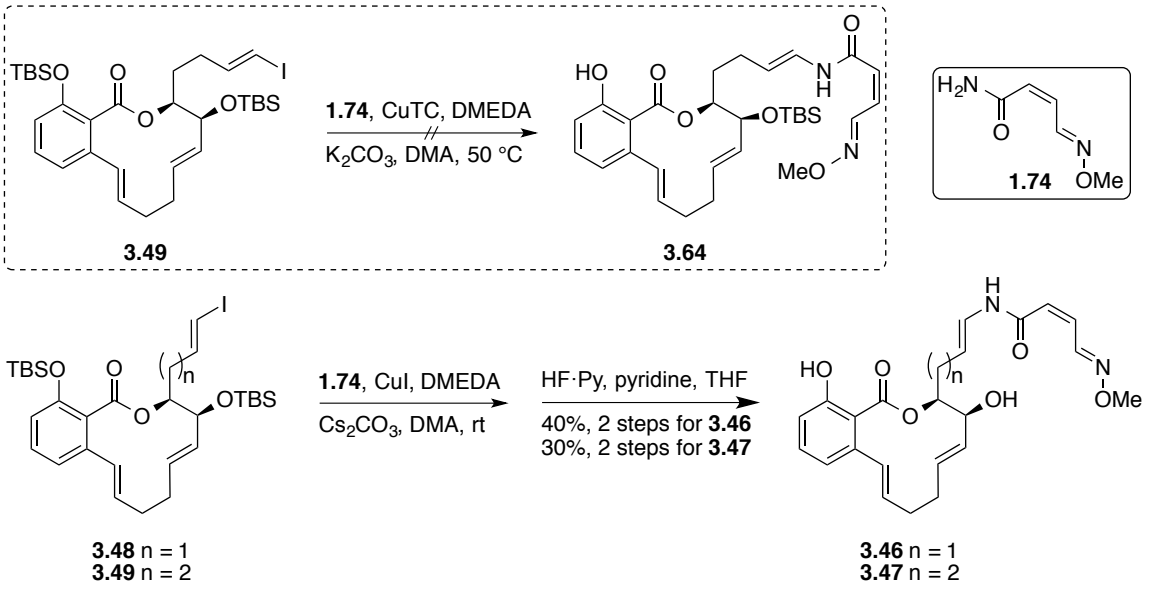
Scheme 3–4. Failed Enamide Coupling of Iodide 3.62



To attach the enamide, we first ventured into the direct coupling of vinyl iodide **3.62** containing a free alcohol with amide **1.74**, since this would bypass a 2-step silylation/desilytion sequence to accomplish the synthesis of analogue **3.46** (Scheme 3–4). Unfortunately, performing the reaction under either Fürstner's conditions (CuTC,

Rb_2CO_3, DMA, 90 °C)[59] or Buchwald's conditions (CuI, DMEDA, Cs_2CO_3, DMA, rt)[185] brought about total decomposition of the iodide. We then sought to use the bis-TBS protected substrates **3.48**/**3.49** (Scheme 3–5). While exposure of iodide **3.49** to Porco's conditions (CuTC, DMEDA, K_2CO_3, DMA, 50 °C)[40] for the total synthesis of oximidine II also decomposed the starting material, modified Buchwald's conditions[186] using an excess of CuI (2 equiv) successfully facilitated the desired coupling of iodides **3.48**/**3.49** with amide **1.74**. The resultants enamide intermediates were finally desilylated with a buffered solution of HF/Pyridine[159] to afford the target molecules **3.46**/**3.47**.

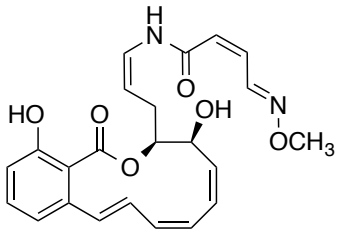
Scheme 3–5. Enamide Coupling of Iodides 3.48/3.49 and TBS Deprotection



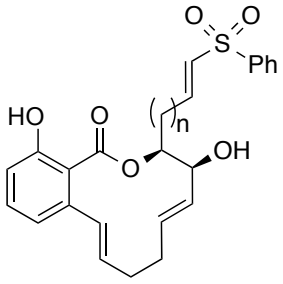
3.4 Biological Evaluation of Oximidine II Analogues

Synthetic analogues **3.46**/**3.47** were tested against SK-MEL-5, SK-MEL-28, HL-60, and MCF-7 cell lines for evaluation of biological activity (Table 3–5). The analogues showed 40-55 fold attenuated potency against SK-MEL-5 cells compared to the parent natural product oximidine II (entries 4 and 5, *vs.* entry 1). They are also weak inhibitors towards SK-MEL-28, HL-60, MCF-7 cell lines with IC_{50} values in the range of 20-80 μM.

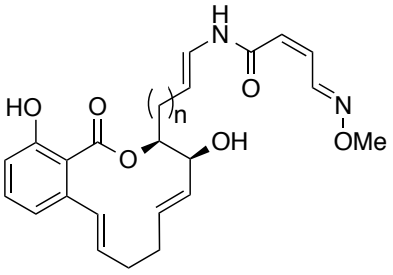
Table 3–5. Biological Evaluation of Oximidine II Analogues[a]



oximidine II (**1.4**)



3.44 n = 1
3.45 n = 2



3.46 n = 1
3.47 n = 2

entry	compound	SK-MEL-5 (IC_{50} in μM)	SK-MEL-28 (IC_{50} in μM)	HL-60 (IC_{50} in μM)	MCF-7 (IC_{50} in μM)
1	taxol	0.014	0.194	0.00075	0.111
2	**1.4**	0.59	> 20	ND[b]	ND
3	**3.44**	> 20	> 100	> 20	> 20
4	**3.45**	> 20	> 20	> 20	100
5	**3.46**	24.2	57	24.9	N/A
6	**3.47**	32.2	44.4	50.1	74

[a] The assay was performed in triplicate wells. [b] ND = not determined.

3.6 Summary

Two analogues of the benzolactone enamide natural product oximidine II with a simplified core structure have been designed and synthesized based on previous SAR studies. The biological assays revealed that the analogues exhibited weak cytotoxic activity against leukemia (HL-60), breast (MCF-7) and melanoma (SK-MEL-5 and SK-MEL-28) cells.

Chapter IV. Experimental Data

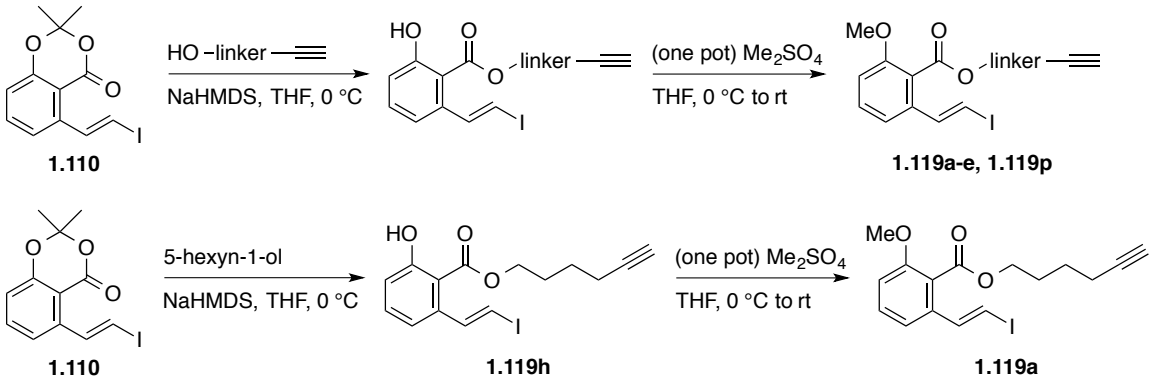
4.1 Materials and Methods

Anhydrous THF, DCM, Et_2O and toluene were dried and deoxygenated by passing the nitrogen-purged solvents through activated alumina columns on a solvent purification system. DMF was similarly dried by passing through a column of activated 4Å molecular sieves. All other commercially available reagents and solvents were used as received without further purification. Copper acetate (hydrates, 98%) was purchased from Sigma-Aldrich. (*R*)-Phanephos (98%) was purchase from Alfa Aesar and all other ligands were from Sigma-Aldrich. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. Flash column chromatography was carried out on silica gel. TLC was conducted on 250 micron, F_{254} silica gel plates. ^1H NMR analyses were performed on a 400 MHz spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts were reported as ppm relative to the solvent residual peak ($CHCl_3$: 7.26 ppm for ^1H, 77.2 ppm for ^{13}C; acetone-d_6: 2.05 ppm for ^1H, 29.9 ppm for ^{13}C; D_2O: 4.80 ppm for ^1H; DMSO-d_6: 39.5 ppm for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. IR spectra were obtained on a FT-IR instrument from thin films on a NaCl plate. High-resolution mass spectra were acquired on an ESI-TOF instrument using PEG or PPG as an internal calibrant.

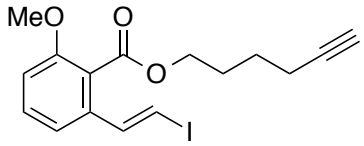
4.2 Chapter 1

4.2.1 Substrate Synthesis

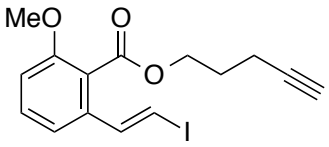
Synthesis of Substrates 1.119a-e, 1.119h, and 1.119p



General Procedure 1: Alkynyl alcohol (1.05 equiv) was dissolved in THF (2.67 mL per 1 mmol of alcohol) and cooled to 0 °C. A solution of NaHMDS (1.0 M in THF, 1.07 equiv) was added dropwise to the alcohol solution and the mixture was stirred at 0 °C for 1 h. (*E*)-5-(2-Iodovinyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**1.110**)[61, 91] (1 equiv) was dissolved in THF (1.33 mL per 1 mmol of **1.110**) and added to the above anion solution. The mixture was further stirred at 0 °C for 2 h before Me_2SO_4 (4 equiv) was added. The reaction was then allowed to warm to room temperature, left overnight, and quenched with water. The mixture was extracted with EtOAc and separated. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 10:1 hexanes/EtOAc).

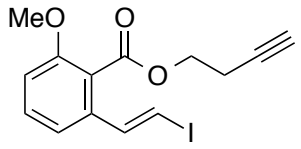


5-Hexyn-1-yl (*E*)-2-(2-Iodovinyl)-6-methoxybenzoate (1.119a). General Procedure 1 was followed using iodide **1.110** (4.29 g, 13.0 mmol), 5-hexyn-1-ol (1.5 mL, 1.3 g, 13.7 mmol). Compound **1.119a** (3.66 g, 73%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 14.8 Hz, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 14.8 Hz, 1H), 4.39 (t, *J* =6.3 Hz, 2H), 3.83 (s, 3H), 2.28 (td, *J* = 7.0, 2.6 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.92 — 1.85 (m, 2H), 1.69 (quint, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.7, 141.9, 136.6, 130.8, 122.2, 118.1, 111.0, 84.1, 80.4, 69.0, 65.2, 56.2, 27.9, 25.1, 18.3; IR (film, cm^{-1}) 3295, 3063, 2944, 2116, 1726, 1602, 1571, 1471, 1271, 1117, 1067, 944, 762; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{16}H_{17}IO_3Na$: 407.0115, found 407.0131.

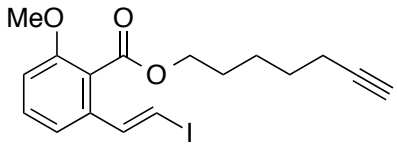


4-Pentyn-1-yl (*E*)-2-(2-Iodovinyl)-6-methoxybenzoate (1.119b). General Procedure 1 was followed using iodide **1.110** (118 mg, 0.357 mmol) and 4-pentyn-1-ol (35 μL, 32 mg, 0.38 mmol). Compound **1.119b** (108 mg, 82%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 14.8 Hz, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 14.8 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.46 (t, *J* = 6.2 Hz, 2H), 3.83 (s, 3H), 2.37 (td, *J* = 7.1, 2.6 Hz, 2H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.98 (quint, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 156.7, 141.8, 136.5, 130.8, 122.0,

118.0, 110.9, 83.1, 80.5, 69.4, 64.1, 56.2, 27.7, 15.3; IR (film, cm^{-1}) 3303, 3058, 2964, 2119, 1725, 1602, 1571, 1472, 1266, 1117, 1068, 944, 736, 639; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{15}IO_3Na$: 392.9958, found 392.9962.

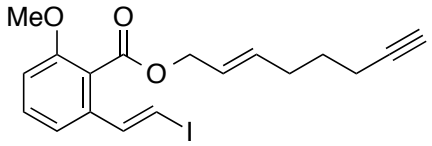


3-Butyn-1-yl (*E*)-2-(2-Iodovinyl)-6-methoxybenzoate (1.119c). General Procedure 1 was followed using iodide **1.110** (203 mg, 0.615 mmol) and 3-butyn-1-ol (49 μL, 45 mg, 0.65 mmol). Compound **1.119c** (168 mg, 77%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 14.8 Hz, 1H), 7.32 (t, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 14.7 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.46 (t, *J* = 6.7 Hz, 2H), 3.83 (s, 3H), 2.66 (td, *J* = 6.7, 2.4 Hz, 2H), 2.09 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 156.8, 141.7, 136.7, 131.0, 121.7, 118.1, 110.9, 80.6, 80.2, 70.5, 63.3, 56.3, 19.2; IR (film, cm^{-1}) 3294, 3063, 1729, 1601, 1571, 1472, 1271, 1115, 1070, 944, 762; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{13}IO_3Na$: 378.9802, found 378.9814.

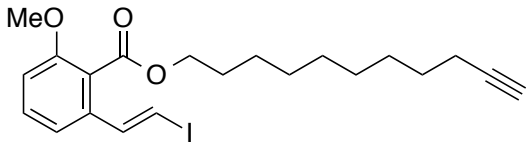


6-Heptyn-1-yl (*E*)-2-(2-Iodovinyl)-6-methoxybenzoate (1.119d). General Procedure 1 was followed using iodide **1.110** (250 mg, 0.757 mmol) and 6-heptyn-1-ol (0.10 mL, 89 mg, 0.80 mmol). Compound **1.119d** (235 mg, 78%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 14.8 Hz, 1H), 7.32 (t, *J* = 8.1 Hz,

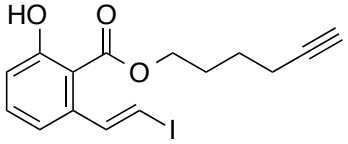
1H), 6.99 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.86 (d, J = 14.9 Hz, 1H), 4.36 (t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 2.23 (td, J = 6.5, 2.4 Hz, 2H), 1.94 (t, J = 2.5 Hz, 1H), 1.78 (quint, J = 6.8 Hz, 2H), 1.65 — 1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.7, 141.9, 136.5, 130.8, 122.3, 118.0, 110.9, 84.5, 80.4, 68.6, 65.6, 56.3, 28.4, 28.3, 25.4, 18.6; IR (film, cm^{-1}) 3296, 3063, 2940, 2116, 1726, 1602, 1571, 1471, 1271, 1118, 1069, 944, 762, 623; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{17}H_{19}IO_3Na$: 421.0271, found 421.0275.



(*E*)-2-Octen-7-yn-1-yl (*E*)-2-(2-Iodovinyl)-6-methoxybenzoate (1.119e). General Procedure 1 was followed using iodide **1.110** (204 mg, 0.619 mmol) and (*E*)-2-Octen-7-yn-1-ol[187] (82 mg, 0.65 mmol). Compound **1.119e** (123 mg, 54%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 14.8 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 14.8 Hz, 1H), 5.92 — 5.85 (m, 1H), 5.76 — 5.69 (m, 1H), 4.80 (d, J = 6.5 Hz, 2H), 3.83 (s, 3H), 2.23 (quint, J = 7.1 Hz, 2H), 2.22 (td, J = 7.1, 2.6 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.67 (quint, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 156.7, 141.9, 136.6, 136.2, 130.8, 124.6, 122.0, 118.1, 111.0, 84.3, 80.4, 68.8, 66.2, 56.3, 31.4, 27.8, 18.1; IR (film, cm^{-1}) 3296, 3063, 3009, 2940, 2116, 1726, 1602, 1571, 1472, 1270, 1113, 1066, 944, 762, 623; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{18}H_{19}IO_3Na$: 433.0271, found 433.0286.



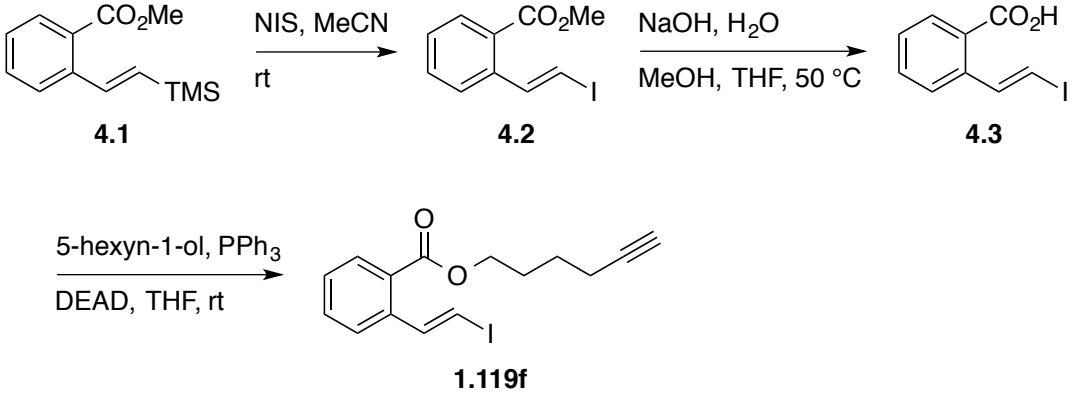
10-Undecyn-1-yl (*E*)-2-(2-Iodovinyl)-6-methoxybenzoate (1.119p). General Procedure 1 was followed using iodide **1.110** (78.8 mg, 0.239 mmol) and 10-undecyn-1-ol (48 μL, 42 mg, 0.25 mmol). Compound **1.119p** (64.7 mg, 57%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 14.8 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 14.8 Hz, 1H), 4.35 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 2.17 (td, *J* = 7.0, 2.6 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.75 (quint, *J* = 6.8 Hz, 2H), 1.52 (quint, *J* = 7.5 Hz, 2H), 1.43 — 1.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 156.7, 141.9, 136.5, 130.7, 122.4, 118.0, 110.0, 85.0, 80.3, 68.3, 65.9, 56.3, 29.6, 29.4, 29.2, 28.9, 28.9, 28.7, 26.2, 18.6; IR (film, cm^{-1}) 3303, 2930, 1727, 1602, 1571, 1471, 1270, 1071, 943, 761; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{21}H_{27}IO_3Na$: 477.0897, found 477.0911.

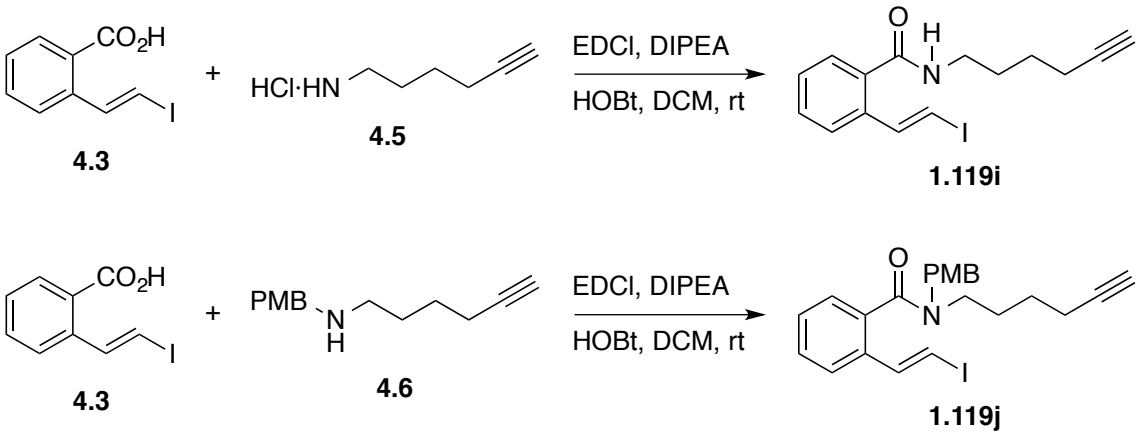


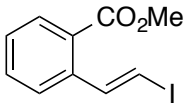
5-Hexyn-1-yl (*E*)-2-Hydroxy-6-(2-iodovinyl)benzoate (1.119h). Compound **1.119h** (0.86 g, 18%) was isolated as the unreacted intermediate during the preparation of compound **1.119a**, white solid (mp 64 — 65 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 7.93 (d, *J* = 14.6 Hz, 1H), 7.37 (t, *J* = 8.0 Hz), 6.97 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.50 (d, *J* =14.6 Hz, 1H), 4.40 (t, *J* = 6.2 Hz, 2H), 2.33 (td, *J* = 6.9, 2.6 Hz, 2H), 1,99 — 1.93 (m, 3H), 1.75 (quint, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

171.0, 162.8, 146.5, 141.3, 134.8, 120.3, 118.2, 110.0, 83.9, 77.9, 69.3, 66.0, 27.7, 25.4, 18.4; IR (film, cm^{-1}) 3282, 3057, 2952, 1665, 1585, 1448, 1254, 1207, 1168, 943, 827; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{15}IO_3Na$: 392.9958, found 392.9954.

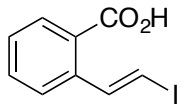
Synthesis of Substrates 1.119f, 1.119i, and 1.119j





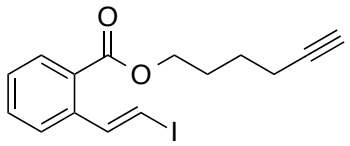


Methyl (*E*)-2-(2-Iodovinyl)benzoate (4.2). To a solution of methyl (*E*)-2-(2-(trimethylsilyl)vinyl)benzoate (**4.1**)[188] (857 mg, 3.65 mmol) in MeCN (37 mL) was added *N*-iodosuccinimide (4.12 g, 18.3 mmol). The mixture was then stirred at room temperature for 30 min before it was quenched with saturated $Na_2S_2O_3$ solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **4.2** (959 mg, 91%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 14.8 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 14.8 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 144.3, 139.6, 132.6, 130.8, 128.2, 127.7, 127.7, 79.2, 52.5; IR (film, cm^{-1}) 3066, 2950, 1719, 1560, 1433, 1259, 1131, 1078, 738; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{10}H_9IO_2Na$: 310.9539, found 310.9547.



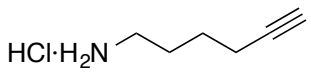
(*E*)-2-(2-iodovinyl)benzoic Acid (4.3). Ester **4.2** (909 mg, 3.15 mmol) was dissolved in THF (8 mL) and MeOH (8 mL). An aqueous solution of NaOH was prepared by dissolving NaOH (3.78 g, 94.4 mmol) in water (19 mL) and added to the ester solution. The mixture was heated to 50 °C and stirred overnight. The organic solvent was evaporated and the residue was neutralized with 10% HCl solution. The precipitated

product was extracted with DCM, washed with brine and dried over Na_2SO_4. Compound **4.3** (785 mg, 91%) was obtained as yellow crystals (mp 173 °C) after removing the solvent, and used directly without further purification. ^{1}H NMR (400 MHz, acetone-d_6, COO-H missing) δ 8.36 (d, J = 14.8 Hz, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 14.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3, 144.9, 140.0, 133.3, 131.7, 129.1, 128.8, 128.2, 80.2; HRMS (ESI+) *m/z* calc'd for $[M-H+2Na]^+$ $C_9H_6IO_2Na_2$: 318.9202, found 318.9212.

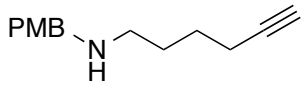


5-Hexyn-1-yl (*E*)-2-(2-Iodovinyl)benzoate (1.119f). Acid **4.3** (70.0 mg, 0.255 mmol), 5-hexyn-1-ol (28 μL, 25 mg, 0.26 mmol), and PPh_3 (66.9 mg, 0.730 mmol) were dissolved in THF (2.6 mL) and the solution was cooled to 0 °C. A solution of DEAD (40% in toluene, 0.12 mL, 45 mg, 0.26 mmol) was added and the mixture was stirred for 5 min before the cold bath was removed. The reaction was left overnight and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **1.119f** (80.8 mg, 89%) was isolated as a yellow solid (mp 33 — 35 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 14.8 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 14.8 Hz, 1H), 4.35 (t, J = 6.4 Hz, 2H), 2.30 (td, J = 7.0, 2.6 Hz, 2H), 1.98 (t, J = 2.5 Hz, 1H), 1.95 — 1.88 (m, 2H), 1.72 (quint, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 144.5, 139.5, 132.6, 130.9, 128.2, 128.0, 127.8, 84.0, 79.1, 69.1, 65.0, 27.9, 25.3, 18.4; IR (film, cm^{-1}) 3298, 3066, 2953, 2116,

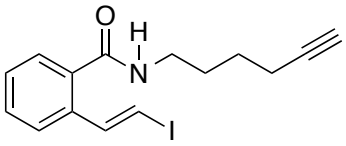
1718, 1599, 1561, 1447, 1280, 1254, 1132, 1074, 944. 743, 638; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{15}IO_2Na$: 377.0009, found 377.0014.



5-Hexyn-1-amine Hydrochloride (4.5). 6-Phthalimido-1-hexyne (**4.4**)[189] (3.03 g, 13.3 mmol) was suspended in a mixture of isopropanol and water (6:1, 67 mL), and $NaBH_4$ (2.52 g, 66.6 mmol) was added. The mixture was stirred overnight under ambient atmosphere before the addition of glacial acetic acid (15 mL). After gas evolution ceased, the solution was heated to 80 °C and stirred at this temperature for 2 h. The reaction mixture was then cooled to room temperature and treated with NaOH solution (1 N) until pH = 12. The basic aqueous solution was extracted with 1:1 EtOAc/hexanes. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was dissolved in a minimum amount of Et_2O, treated with HCl solution (2 M in Et_2O), and cooled in an ice-water bath. Compound **4.5** (1.46 g, 82%) precipitated as light brown crystals and was collected by vacuum filtration. ^{1}H NMR (400 MHz, D_2O, N-H missing) δ 3.06 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 2.6 Hz, 1H), 2.31 (td, *J* = 7.0, 2.6 Hz, 2H), 1.85 — 1.78 (m, 2H), 1.67 — 1.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 84.0, 71.7, 38.2, 26.1, 24.9, 17.3; LRMS (ESI+) *m/z* calc'd for $[M-Cl]^+$ $C_6H_{12}N$: 98.1, found 98.1.

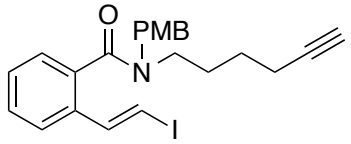


***N*-(4-Methoxybenzyl)-5-hexyn-1-amine (4.6).** Hydrochloride **4.5** (400 mg, 2.99 mmol) was dissolved in MeOH (15 mL) and cooled to 0 °C. Triethylamine (0.42 mL, 303 mg, 2.99 mmol) was added and the solution was stirred at 0 °C for 10 min before 4-methoxybenzaldehye (0.40 mL, 448 mg, 3.29 mmol) was added. The reaction was allowed to warm to room temperature, stirred for 3 h, and re-cooled to 0 °C. $NaBH_4$ (452 mg, 12.0 mmol) was added in 2 portions. The reaction was left under ambient conditions overnight, quenched with 10% K_2CO_3, and extracted with Et_2O. The combine organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (60:40:1 hexanes/EtOAc/Et_3N). Compound **4.6** (432 mg, 66%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 2H), 2.63 (t, *J* = 6.7 Hz, 2H), 2.20 (td, *J* = 6.8, 2.5 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.66 — 1.53 (m, 4H), 1.35 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 132.8, 129.4, 113.9, 84.6, 68.6, 55.5, 53.6, 48.9, 29.3, 26.4, 18.5; IR (film, cm^{-1}) 3636, 3293, 3031, 2999, 2936, 2116, 1612, 1510, 1463, 1301, 1247, 1177, 1110, 1036, 820.



(*E*)-*N*-(5-Hexyn-1-yl)-2-(2-iodovinyl)benzamide (1.119i). Acid **4.3** (300 mg, 1.09 mmol), 1-hydroxybenzotriazole (296 mg, 2.19 mmol) and EDCl (420 mg, 2.19 mmol) were dissolved in DCM (5 mL) and stirred at room temperature for 30 min. To the above

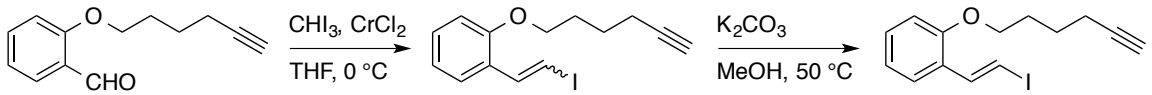
solution was added a solution of hydrochloride **4.5** (219 mg, 1.64 mmol) and diisopropylethylamine (0.67 mL, 495 mg, 3.83 mmol) in DCM/DMF (1:1, 8 mL). The reaction mixture was stirred overnight, quenched with aqueous HCl solution (1 N), and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 70:30 hexanes/EtOAc). Compound **1.119i** (341 mg, 89%) was isolated as a light yellow solid (mp 77 — 80 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 14.8 Hz, 1H), 7.43 — 7.37 (m, 3H), 7.33 — 7.30 (m, 1H), 6.84 (d, *J* = 14.8 Hz, 1H), 5.84 (s, 1H) 3.47 (q, *J* = 6.4 Hz, 2H), 2.28 (td, *J* = 6.8, 2.2 Hz, 2H), 1.97 (t, *J* = 2.3 Hz, 1H), 1.79 — 1.71 (m, 2H), 1.67 — 1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 142.7, 135.9, 134.8, 130.4, 128.4, 127.6, 126.6, 84.1, 79.6, 69.1, 39.7, 28.8, 25.9, 18.3; IR (film, cm^{-1}) 3304, 3054, 2986, 1660, 1519, 1422, 1265, 896, 738; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{16}INONa$: 376.0169, found 376.0163.



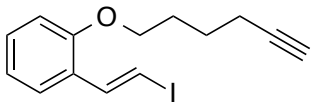
(*E*)-*N*-(5-Hexyn-1-yl)-2-(2-iodovinyl)-*N*-(4-methoxybenzyl)benzamide (1.119j). Acid **4.3** (149 mg, 0.543 mmol), 1-hydroxybenzotriazole (147 mg, 1.09 mmol) and EDCl (209 mg, 1.09 mmol) were dissolved in DCM (3 mL) and stirred at room temperature for 30 min. To the above solution was added a solution of amine **4.6** (166 mg, 0.764 mmol) and diisopropylethylamine (0.19 mL, 141 mg, 1.09 mmol) in DCM (3 mL). The reaction mixture was stirred overnight, quenched with aqueous HCl solution (1 N), and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and

concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 75:25 hexanes/EtOAc). Compound **1.119j** (213 mg, 83%) was isolated as a colorless oil (1:1 amide rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 14.8 Hz, 0.5H), 7.45 — 7.39 (m, 1.5H), 7.36 — 7.30 (m, 3H), 7.28 — 7.22 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.91 — 6.83 (m, 2H), 5.11 (br, 0.5 H), 4.39 (br, 0.5H), 4.20 (s, 1H), 3.82 (s, 1.5H), 3.79 (s, 1.5H), 3.70 (br, 0.5H), 3.28 (br, 0.5H), 2.92 (t, *J* = 7.4 Hz, 1H), 2.27 (td, *J* = 7.0, 2.5 Hz, 1H), 2.01 (td, *J* = 6.9, 2.5 Hz, 1H), 1.97 (t, *J* = 2.5 Hz, 0.5H), 1.92 (t, *J* = 2.5 Hz, 0.5H), 1.77 (quint, *J* = 7.3 Hz, 1H), 1.62 — 1.56 (m, 2H), 1.25 (quint, *J* = 7.2 Hz, 1H); IR (film, cm^{-1}) 3300, 3058, 2938, 2116, 1629, 1512, 1418, 1247, 1176, 1034, 954, 736, 645; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{23}H_{24}INO_2Na$: 496.0744, found 496.0758.

Synthesis of Substrate 1.119g



4.7 (*E*/*Z*)-**1.119g** **1.119g**

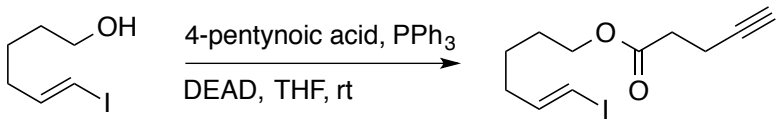


(*E*)-1-(5-Hexyn-1-yloxy)-2-(2-iodovinyl)benzene (1.119g). $CrCl_2$ (1.56 g, 12.72 mmol) was suspended in THF (10 mL) and cooled to 0 °C. To the above mixture was slowly added a solution of 2-(5-hexyn-1-yloxy)benzaldehyde (**4.7**)[190] (214 mg, 1.06 mmol) and iodoform (1.67 g, 4.24 mmol) in THF (10 mL). The resultant red-brown solution was stirred at 0 °C for 3 h, diluted with brine, and extracted with EtOAc. The

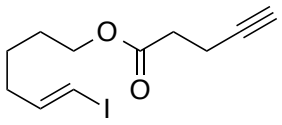
combined organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/DCM) to afford 1-(5-hexyn-1-yloxy)-2-(2-iodovinyl)benzene (168 mg, 48%) as a 1:1 *E*/*Z* isomer mixture.

The *E*/*Z* mixture (164 mg, 0.503 mmol) was dissolved in MeOH (5 mL), mixed with K_2CO_3 (347 mg, 2.51 mmol), and heated at 50 °C overnight. The solvent was evaporated under vacuum and the residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/DCM). Compound **1.119g** (57.0 mg, 35%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 14.9 Hz, 1H), 7.28 — 7.22 (m, 2H), 6.92 (d, *J* = 14.9 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 4.02 (d, *J* = 6.3 Hz, 2H), 2.30 (td, *J* = 6.9, 2.5 Hz, 2H), 2.01 (t, *J* = 2.4 Hz, 1H), 1.99 — 1.94 (m, 2H), 1.74 (quint, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 140.8, 129.6, 127.8, 126.8, 120.8, 112.1, 84.2, 78.1, 69.1, 67.9, 28.4, 25.3, 18.3; IR (film, cm^{-1}) 3298, 3061, 2947, 2117, 1597, 1453, 1245, 1103, 1051, 953, 750, 631; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{15}IONa$: 349.0060, found 349.0047.

Synthesis of Substrate 1.119k

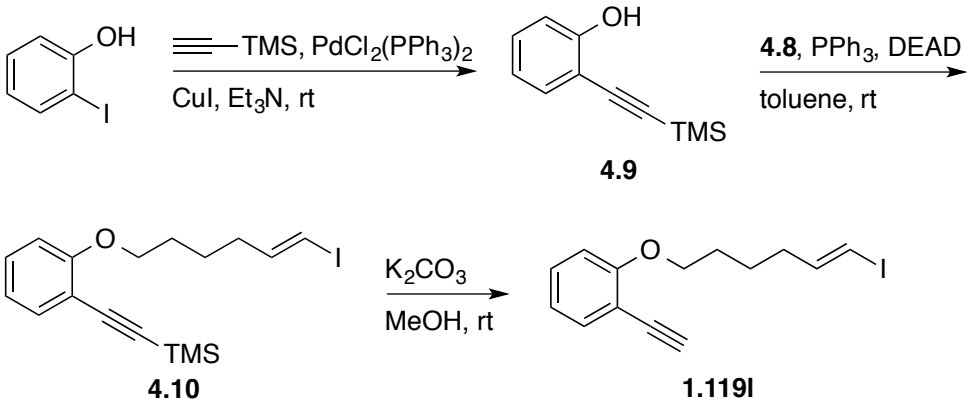


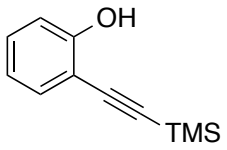
4.8 **1.119k**



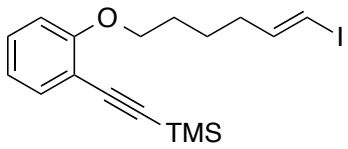
(*E*)-6-Iodo-5-hexen-1-yl 4-Pentynoate (1.119k). 6-Iodo-5-hexen-1-ol (**4.8**)[191] (150 mg, 0.664 mmol), 4-pentynoic acid (78.0 mg, 0.796 mmol), and PPh_3 (209 mg, 0.796 mmol) were dissolved in THF (6.6 mL) and the solution was cooled to 0 °C. A solution of DEAD (40% in toluene, 0.36 mL, 138 mg, 0.796 mmol) was added and the mixture was stirred for 5 min before the cold bath was removed. The reaction was left overnight and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **1.119k** (194 mg, 95%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dt, *J* = 14.3, 7.2 Hz, 1H), 6.02 (dt, *J* = 14.4, 1.4 Hz, 1H), 4.11 (t, *J* = 6.5 Hz, 2H), 2.58 — 2.48 (m, 4H), 2.09 (qd, *J* = 7.3, 1.2 Hz, 2H), 1.98 (t, *J* = 2.5 Hz, 1H), 1.68 — 1.61 (m, 2H), 1.51 — 1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 146.1, 82.7, 75.2, 69.2, 64.5, 35.7, 33.5, 28.1, 24.9, 14.6; IR (film, cm^{-1}) 3296, 2919, 1733, 1605, 1358, 1166, 1058, 950; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{11}H_{15}IO_2Na$: 329.0009, found 329.0023.

Synthesis of Substrate 1.119l



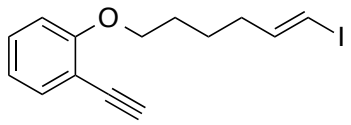


2-((Trimethylsily)ethynyl)phenol (4.9). To a stirred suspension of 2-iodophenol (700 mg, 3.18 mmol), $PdCl_2(PPh_3)_2$ (112 mg, 0.159 mmol), and CuI (60.6 mg, 0.318 mmol) in triethylamine (10 mL) was added trimethylsilylacetylene (0.67 mL, 468 mg, 4.77 mmol). The mixture was stirred at room temperature overnight, quenched with saturated NH_4Cl solution, and extracted with Et_2O. The combined organic layer was washed with aqueous HCl solution (1N), brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 97:3 hexanes/EtOAc). Compound **4.9** (519 mg, 86%) was isolated as a light brown liquid, which solidified (mp 46 — 47 °C) slowly upon storage in a refrigerator. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6.86 (t, J = 7.5 Hz, 1H), 5.86 (s, 1H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 131.8, 130.9, 120.4, 114.7, 109.7, 102.6, 99.1, 0.2; IR (film, cm^{-1}) 3511, 3065, 2960, 2151, 1577, 1484, 1251, 1097, 1031, 870, 843, 776, 753.



(*E*)-1-(6-Iodo-5-hexyn-1-yloxy)-2-((trimethylsilyl)ethynyl)benzene (4.10). Phenol **4.9** (110 mg, 0.578 mmol), alcohol **4.8** (157 mg, 0.694 mmol), and PPh_3 (182 mg, 0.694 mmol) were dissolved in toluene (5.8 mL) and the solution was cooled to 0 °C. A solution of DEAD (40% in toluene, 0.32 mL, 121 mg, 0.694 mmol) was added and the

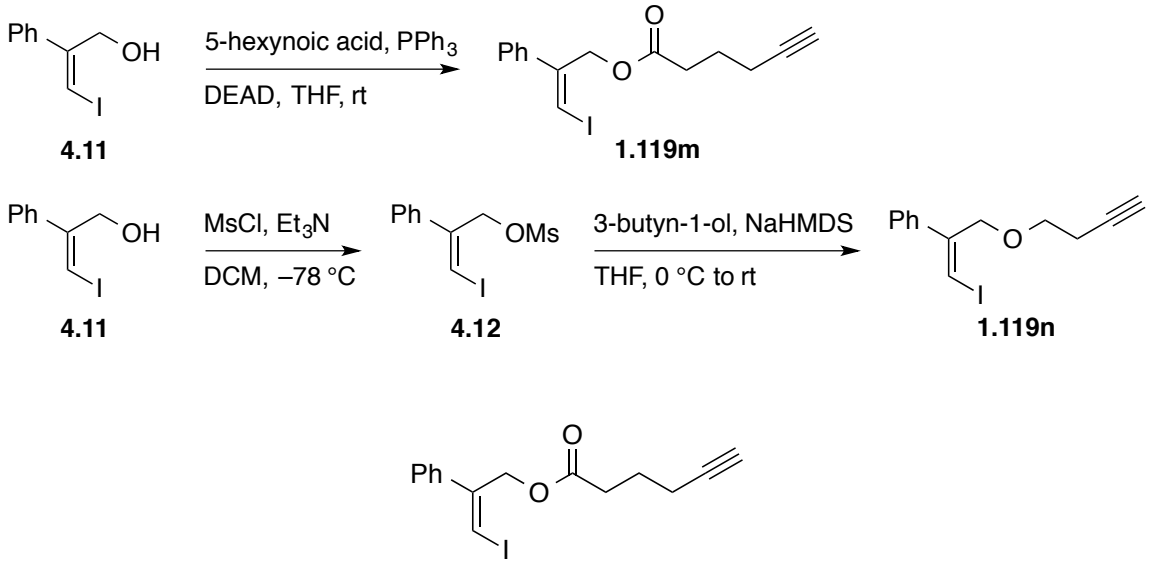
mixture was stirred for 5 min before the cold bath was removed. The reaction was left overnight and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **4.10** (210 mg, 91%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.27 — 7.23 (m, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.54 (dt, *J* = 14.3, 7.2 Hz, 1H), 6.03 (d, *J* = 14.4 Hz, 1H), 4.01 (t, *J* = 6.0 Hz, 2H), 2.16 (q, *J* = 7.2 Hz, 2H), 1.87 — 1.80 (m, 2H), 1.67 (quint, *J* = 7.7 Hz, 2H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 146.4, 133.9, 130.1, 120.5, 112.9, 112.1, 101.5, 98.6, 75.1, 68.3, 36.0, 28.7, 25.2, 0.3; IR (film, cm^{-1}) 3052, 2954, 2158, 1594, 1490, 1250, 1204, 1113, 842, 752, 645; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{17}H_{23}IOSiNa$: 421.0455, found 421.0475.



(*E*)-1-Ethynyl-2-(6-iodo-5-hexyn-1-yloxy)benzene (1.119l). To a solution of compound **4.10** (285 mg, 0.715 mmol) in MeOH (3.6 mL) was added K_2CO_3 (198 mg, 1.43 mmol). The mixture was stirred overnight, diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **1.119l** (197 mg, 84%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.31 — 7.27 (m, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.54 (dt, *J* = 14.3, 7.1 Hz, 1H), 6.04 (d, *J* = 14.3 Hz, 1H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.27 (s, 1H), 2.16 (q, *J* =

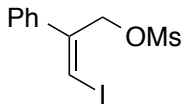
7.2 Hz, 2H), 1.88 — 1.81 (m, 2H), 1.63 (quint, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 146.4, 134.3, 130.3, 120.6, 112.1, 111.8, 81.3, 80.3, 75.2, 68.5, 35.8, 28.4, 25.0; IR (film, cm^{-1}) 3287, 3051, 2939, 2106, 1595, 1490, 1280, 1252, 1110, 751; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{15}IONa$: 349.0060, found 349.0067.

Synthesis of Substrates 1.119m and 1.119n

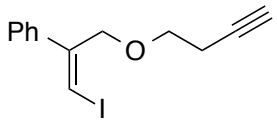


(*Z*)-3-Iodo-2-phenylallyl 5-Hexynoate (1.119m). 3-Iodo-2-phenyl-2-propen-1-ol (**4.11**)[192] (189 mg 0.726 mmol), 5-hexynoic acid (80 μL, 81 mg, 0.73 mmol), and PPh_3 (190 mg, 0.726 mmol) were dissolved in THF (7.3 mL) and the solution was cooled to 0 °C. A solution of DEAD (40% in toluene, 0.33 mL, 126 mg, 0.726 mmol) was added and the mixture was stirred for 5 min before the cold bath was removed. The reaction was left overnight and the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **1.119m** (193 mg, 75%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 — 7.30 (m, 5H), 6.79 (s, 1H), 5.16 (s, 2H), 2.38 (t, J = 7.4 Hz, 2H), 2.14 (td, J = 7.0, 2.6

Hz, 2H), 1.93 (t, J = 2.6 Hz, 1H), 1.74 (quint, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 146.2, 138.8, 128.7, 128.5, 126.6, 83.6, 83.3, 69.3, 67.8, 32.8, 23.7, 17.9; IR (film, cm^{-1}) 3301, 3061, 2942, 2118, 1736, 1596, 1442, 1204, 1152, 1027, 974, 729, 700; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{15}IO_2Na$: 377.0009, found 377.0005.

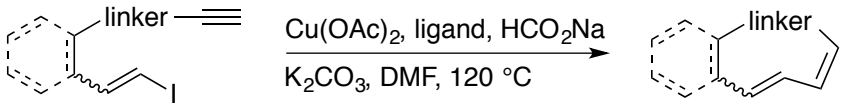


(*Z*)-3-Iodo-2-phenylallyl Methanesulfonate (4.12). To a solution of alcohol **4.11** (84.7 mg, 0.326 mmol) in DCM (3.3 mL) were added sequentially triethylamine (91 μL, 66 mg, 0.65 mmol) and methanesulfonyl chloride (38 μL, 56 mg, 0.49 mmol) at –78 °C. The solution was stirred at –78 °C for 2 h before it was quenched with saturated $NaHCO_3$ solution. The reaction mixture was warmed to room temperature and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum to afford a crude product. This crude compound **4.12** (99.5 mg, 90%) was directly used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 5H), 6.98 (s, 1H), 5.30 (s, 2H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.9, 129.0 (overlapping), 126.6, 86.4, 72.6, 38.1; IR (film, cm^{-1}) 3061, 2963, 1355, 1262, 1174, 1025, 802; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{10}H_{11}IO_3SNa$: 360.9366, found 360.9368.



(*Z*)-4-((3-iodo-2-phenylallyl)oxy)-1-butyne (1.119n). To a solution of 3-butyn-1-ol (17 μL, 016 mg, 0.23 mmol) in THF (1.1 mL) was added NaHMDS (1.0 M in THF, 0.23 mL, 0.23 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h before mesylate **S13** (73.0 mg, 0.216 mmol) in THF (1.1 mL) was added. The reaction was left at room temperature overnight, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **1.119n** (40.3 mg, 60%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 — 7.41 (m, 2H), 7.36 — 7.31 (m, 3H), 6.78 (s, 1H), 4.62 (s, 2H), 3.60 (t, *J* =6.9 Hz, 2H), 2.43 (td, *J* = 6.9, 2.6 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 139.3, 128.7, 128.3, 126.8, 83.2, 81.4, 74.1, 69.6, 68.2, 20.0; IR (film, cm^{-1}) 3298, 3058, 2917, 2867, 2120, 1592, 1493, 1442, 1201, 1099, 753, 698, 636; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{13}H_{13}IONa$: 334.9903, found 334.9936.

4.2.3 Castro–Stephens/Alkyne Reduction Tandem Reaction



1.119 **1.120**

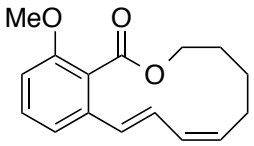
General Procedure 2: Conditions A: $Cu(OAc)_2$ (0.2 equiv), phanephos (0.3 equiv), HCO_2Na (4 equiv), K_2CO_3 (1.5 equiv) were suspended in DMF (100 mL per 1 mmol of

iodide **1.119**). This suspension was heated with stirring at 120 °C for 30 min. In a separate container, iodide **1.119** (1 equiv) was dissolved in DMF (100 mL per 1 mmol of iodide **1.119**) and the solution was transferred dropwise via syringe to the above suspension in one portion. The reaction was further stirred at 120 °C for the time listed in Table 1–5 and Table 1–6, and then cooled to room temperature. To the cooled reaction mixture was added saturated NH_4Cl solution. The mixture was stirred at room temperature for 15 min, diluted with water and extracted with hexanes/EtOAc (1:1). The combined organic layer was sequentially washed with NH_4Cl/NH_3 buffer (3:1 mixture of saturated NH_4Cl/28% aqueous ammonium hydroxide), water, and brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel.

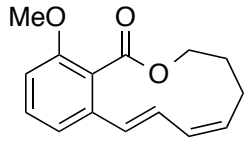
Conditions B were the same as **Conditions A** except that $Cu(OAc)_2$ (0.3 equiv) and BINAP (0.5 equiv) were employed instead of $Cu(OAc)_2$ (0.2 equiv) and phanephos (0.3 equiv).

Conditions C were the same as **Conditions A** except that $Cu(OAc)_2$ (1 equiv) and PPh_3 (3 equiv) were employed instead of $Cu(OAc)_2$ (0.2 equiv) and phanephos (0.3 equiv).

Conditions D were the same as **Conditions A** except that $Cu(OAc)_2$ (0.3 equiv) and dppe (0.5 equiv) were employed instead of $Cu(OAc)_2$ (0.2 equiv) and phanephos (0.3 equiv).

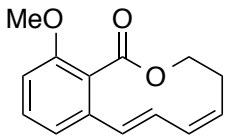


(7*Z*,9*E*)-14-Methoxy-3,4,5,6-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (1.120a). Prepared from iodide **1.119a** (26.2 mg, 0.0682 mmol) using Conditions A. Compound **1.120a** (12.7 mg) was isolated as a colorless oil or white waxy solid after flash column chromatography (100:0 — 90:10 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 8.0 Hz, 1H), 6.92 — 6.80 (m, 3H), 6.53 (d, *J* = 16.2 Hz, 1H), 6.15 (t, *J* = 10.4 Hz, 1H), 5.65 (dt, *J* = 10.8, 7.4 Hz, 1H), 4.50 (t, *J* = 5.1 Hz, 2H), 3.84 (s, 3H), 2.35 (q, *J* = 6.9 Hz, 2H), 1.85 — 1.80 (m, 2H), 1.71 (quint, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 156.9, 137.9, 133.0, 131.1, 130.3, 128.7, 128.5, 122.8, 120.7, 109.8, 66.2, 56.2, 27.5, 26.4, 26.2; IR (film, cm^{-1}) 3061, 3008, 2956, 1725, 1571, 1469, 1267, 1113, 1063, 954, 736; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{16}H_{18}O_3Na$: 259.1148, found 259.1151.

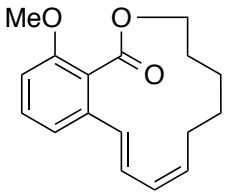


(6*Z*,8*E*)-13-Methoxy-4,5-dihydrobenzo[*c*][1]oxacycloundecin-1(3*H*)-one (1.120b). Prepared from iodide **1.119b** (29.8 mg, 0.0805 mmol) using Conditions A. Compound **1.120b** (12.1mg, 62%) was isolated as a colorless oil or white waxy solid after flash column chromatography (100:0 — 90:10 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.79 — 6.73 (m, 1H), 6.55 (d, *J* = 16.3 Hz, 1H), 6.22 — 6.17 (m, 1H), 5.86 — 5.81 (m, 1H), 4.34 (t, *J*

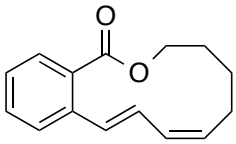
= 5.4 Hz, 2H), 3.85 (s, 3H) , 2.44 (q, *J* = 7.2 Hz, 2H), 1.92 — 1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 156.5, 139.3, 133.9, 132.5, 130.3, 129.3, 128.1, 124.3, 120.2, 109.9, 64.8, 56.2, 29.2, 23.3; IR (film, cm^{-1}) 3010, 3058, 3011, 2959, 1724, 1571, 1469, 1263, 1106, 1086, 1059, 734; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{16}O_3Na$: 267.0992, found 267.0996.



(5*Z*,7*E*)-12-Methoxy-3,4-dihydro-1*H*-benzo[*c*]oxecin-1-one (1.120c). Prepared from iodide **1.119c** (59.4 mg, 0.167 mmol) using Conditions D. Compound **1.120c** (10.7 mg, 28%) was isolated as a yellow oil after flash column chromatography (100:0 — 90:10 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1H), 6.89 — 6.82 (m, 3H), 6.49 — 6.44 (m, 1H), 6.37 (d, *J* = 16.6 Hz, 1H), 5.78 (dtd, *J* = 10.5, 7.6, 1.4 Hz, 1H), 4.45 (br, 2H), 3.86 (s, 3H), 2.66 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 157.9, 140.4, 135.8, 131.7, 130.7, 129.3, 125.7, 124.5, 121.5, 110.4, 66.6, 56.2, 26.0; IR (film, cm^{-1}) 3062, 3008, 2954, 2840, 1721, 1599, 1568, 1469, 1437, 1266, 1251, 1106, 1085, 1061, 1002, 846, 725; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{14}O_3Na$: 253.0835, found 253.0848.

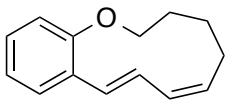


(8*Z*,10*E*)-15-Methoxy-4,5,6,7-tetrahydrobenzo[*c*][1]oxacyclotridecin-1(3*H*)-one (1.120d). Prepared from iodide **1.119d** (26.2 mg, 0.0658 mmol) using Conditions C. Compound **1.120d** (8.3 mg, 53%) was isolated as a colorless oil or white waxy solid after flash column chromatography (100:0 — 90:10 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.74 (dd, *J* = 16.0, 10.8 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.20 (t, *J* = 10.8 Hz, 1H), 5.64 — 5.57 (m, 1H), 4.44 (t, *J* = 5.1 Hz, 2H), 3.83 (s, 3H), 2.19 (br, 2H), 1.92 (br, 2H), 1.46 — 1.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 157.0, 135.9, 133.4, 131.0, 130.2, 130.0, 129.3, 123.0, 122.0, 110.1, 66.7, 56.4, 27.8, 27.5, 24.6, 22.0; IR (film, cm^{-1}) 3060, 2941, 1726, 1575, 1463, 1268, 1114, 1068, 736; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{17}H_{20}O_3Na$: 295.1305, found 295.1308.

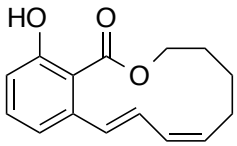


(7*Z*,9*E*)-3,4,5,6-Tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (1.120f). Prepared from iodide **1.119f** (39.8 mg, 0.112 mmol) using Conditions C. Compound **1.120f** (15.3 mg, 60%) was isolated as a colorless oil after flash column chromatography (100:0 — 60:40 hexanes/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.50 (d, *J* = 6.8 Hz, 1H), 7.45 (td, *J* = 7.1, 1.2 Hz, 1H), 7.31 — 7.27 (m, 1H), 6.93 (d, *J* = 16.2 Hz, 1H), 6.44 (dd, *J* = 16.2, 5.5 Hz, 1H), 6.13 (ddd, *J* = 11.0, 5.5, 0.8 Hz,

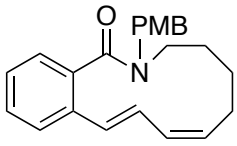
1H), 5.75 (dt, *J* = 10.9, 8.3 Hz, 1H), 4.38 (t, *J* = 5.6 Hz, 2H), 2.38 (q, *J* = 8.1 Hz, 2H), 1.87 — 1.81 (m, 2H), 1.72 — 1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.9, 133.7, 131.7, 131.5, 130.9, 130.8, 128.9, 128.1, 127.2, 127.1, 67.0, 29.0, 27.4, 26.6; IR (film, cm^{-1}) 3055, 2930, 1707, 1600, 1265, 1124, 737, 705; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{16}O_2Na$: 251.1043, found 251.1049.



(6*Z*,8*E*)-2,3,4,5-Tetrahydrobenzo[*b*][1]oxacycloundecine (1.120g). Prepared from iodide **1.119g** (26.3 mg, 0.0806 mmol) using Conditions A except that $Cu(OAc)_2$ (0.1 equiv) and phanephos (0.15 equiv) were used. Compound **1.120g** (10.0 mg, 62%) was isolated as a colorless oil or white waxy solid after flash column chromatography (100:0 — 80:20 hexanes/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 1H), 7.21 — 7.17 (m, 1H), 7.12 — 7.08 (m, 2H), 6.96 (d, *J* = 16.7 Hz, 1H), 6.46 (dd, *J* = 16.7, 4.6 Hz, 1H), 6.21 (dd, *J* = 10.5, 4.5 Hz, 1H), 5.95 — 5.88 (m, 1H), 4.04 (t, *J* = 5.4 Hz, 2H), 2.23 (q, *J* = 7.8 Hz, 2H), 1.95 — 1.88 (m, 2H), 1.79 — 1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 134.4, 132.1, 130.6, 129.1, 128.4, 128.1, 127.0, 124.5, 122.4, 72.4, 28.2, 25.9, 25.6; IR (film, cm^{-1}) 3062, 3008, 2931, 1599, 1454, 1232, 1219, 1202, 994, 745, 732, 703; HRMS (EI) *m/z* calc'd for $[M\cdot]^+$ $C_{14}H_{16}O$: 200.1196, found 200.1196.

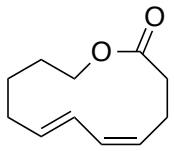


(7*Z*,9*E*)-14-Hydroxy-3,4,5,6-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (1.120h). Prepared from iodide **1.119h** (30.7 mg, 0.0829 mmol) using Conditions C. Compound **1.120h** (2.5 mg, 12%) was isolated as a colorless oil or white waxy solid after flash column chromatography (100:0 — 50:50 hexanes/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.9 (s, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 16.6 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.30 (dd, *J* = 16.1, 4.2 Hz, 1H), 6.09 (dd, *J* = 10.8, 4.2 Hz, 1H), 5.76 (dt, *J* =10.9, 8.4 Hz, 1H), 4.41 (t, *J* = 5.9 Hz, 2H), 2.37 (q, *J* = 8.2 Hz, 2H), 1.88 — 1.83 (m, 2H), 1.74 — 1.68 (m, 2H);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 162.3, 140.9, 134.4, 133.7, 133.4, 129.0, 127.4, 118.6, 116.6, 112.0, 67.3, 29.6, 27.6, 26.4; IR (film, cm^{-1}) 3431, 2926, 1655, 1451, 1264, 1211, 1120; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{15}H_{16}O_3Na$: 267.0992, found 267.0997.

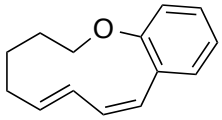


(7*Z*,9*E*)-2-(4-Methoxybenzyl)-3,4,5,6-tetrahydrobenzo[*c*][1]azacyclododecin-1(2*H*)-one (1.120j). Prepared from iodide **1.119j** (21.6 mg, 0.0456 mmol) using Conditions A. Compound **1.120j** (12.5mg, 79%) was isolated as a colorless oil after flash column chromatography (100:0 — 75:25 hexanes/EtOAc). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.37 — 7.23 (m, 4H), 7.14 — 7.07 (m, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 16.3 Hz, 1H), 6.31 (t, *J* = 10.4 Hz, 1H), 5.72 — 5.65 (m, 1H), 4.40 (dt, *J* = 14.3, 5.3 Hz,

1H), 4.20 (d, J = 15.6 Hz, 1H), 4.04 (d, J = 15.6 Hz, 1H), 3.77 (s, 3H), 2.78-2.71 (m, 1H), 2.54 — 2.44 (m, 1H), 2.16 — 2.10 (m, 1H), 1.74 — 1.70 (m, 1H), 1.64 — 1.42 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.4, 160.2, 136.5, 135.5, 134.4, 131.5, 130.4, 130.3, 129.5, 129.5, 129.4, 128.5, 128.3, 128.0, 114.9, 55.6, 50.2, 40.8, 27.0, 26.8, 23.9; IR (film, cm^{-1}) 3009, 2933, 1618, 1513, 1458, 1249, 1175, 1034, 737; *m/z* calc'd for $[M+Na]^+$ $C_{23}H_{25}NO_2Na$: 370.1778, found 370.1783.

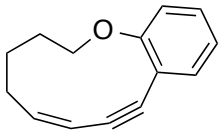


(5*Z*,7*E*)-Oxa-5,7-cyclododecadien-2-one (1.120k). Prepared from iodide **1.119k** (27.4 mg, 0.0895 mmol) using Conditions B. Compound **1.120k** (11.3 mg, 70%) was isolated as a colorless oil after flash column chromatography (100:00 — 30:70 hexanes/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (dd, J =15.9, 10.8 Hz, 1H), 6.18 (t, J = 10.6 Hz, 1H), 5.74 (dt, J = 16.0, 4.9 Hz, 1H), 5.51 — 5.45 (m, 1H), 4.00 (t, J = 5.3 Hz, 2H), 2.61 — 2.55 (m, 2H), 2.44 — 2.40 (m, 2H), 2.15 (q, J = 4.8 Hz, 2H), 1.84 — 1.79 (m, 2H), 1.74 — 1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 130.8, 129.9, 127.0, 126.1, 64.9, 36.2, 29.5, 27.4, 23.5, 21.8; IR (film, cm^{-1}) 3013, 2932, 1732, 1655, 1462, 1432, 1339, 1156, 1021, 724; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{11}H_{16}O_2Na$: 203.1043, found 203.1043.

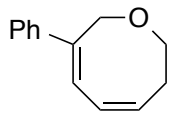


(6*E*,8*Z*)-2,3,4,5-Tetrahydrobenzo[*b*][1]oxacycloundecine (1.120l). Prepared from iodide **1.119l** (37.7 mg, 0.116 mmol) using Conditions D. Compound **1.120l** (19.0 mg, 82%) was isolated as a colorless oil after flash column chromatography (100:0 — 80:20 hexanes/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 — 7.19 (m, 2H), 6.93 (td, *J* = 7.6, 0.9 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.31 — 6.24 (m, 2H), 6.10 (ddd, *J* = 16.0, 6.3, 1.2 Hz, 1H), 5.68 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.17 (br, 2H), 2.21 (br, 2H), 1.85 — 1.82 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 132.5, 132.1, 130.1, 128.8, 128.5, 126.7, 125.4, 120.2, 112.7, 70.4, 31.6, 28.3, 28.0; IR (film, cm^{-1}) 3054, 2934, 1652, 1600, 1490, 1453, 1265, 1123, 972, 736, 704; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{16}ONa$: 223.1093, found 223.1105.

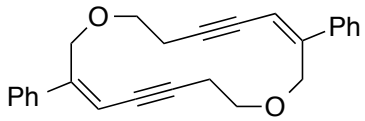
When prepared using Conditions A, an inseparable mixture of compound **1.120l** and enyne **1.123** (71% combined yield, **1.120l**:**1.123** = 11:1) was obtained.



(*Z*)-Benzo[*b*][1]oxa-6-cycloundecen-8-yne (1.123). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.10 — 7.04 (m, 4H), 6.41 (dt, *J* = 10.2, 7.6 Hz, 1H), 4.19 (br, 2H), 2.38 (q, *J* = 7.0 Hz, 2H), 1.85 — 1.82 (m, 4H).

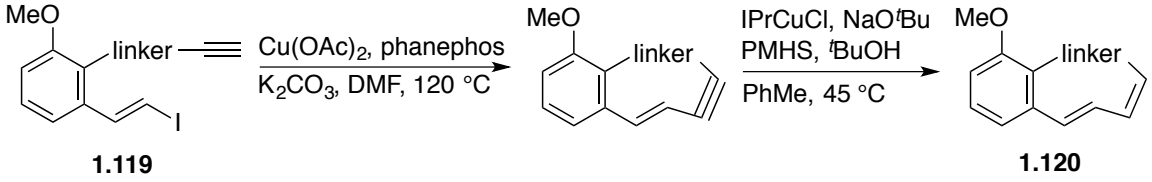


(4*Z*,6*Z*)-7-Phenyl-3,8-dihydro-2*H*-oxocine (1.120n). Prepared from iodide **1.119n** (17.8 mg, 0.0570 mmol) using Conditions A. Compound **1.120n** (3.2 mg, 30%) was isolated as a yellow oil after flash column chromatography (100:0 — 30:70 hexanes/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 — 7.52 (m, 2H), 7.35 (d, J = 7.4 Hz, 2H), 7.28 (d, J = 7.5 Hz, 1H), 6.46 (d, J = 4.2 Hz, 1H), 6.18 (dd, J = 11.3, 4.3 Hz, 1H), 5.89 (dt, J = 11.1, 7.4 Hz, 1H), 4.40 (s, 2H), 3.65 (t, J = 5.0 Hz, 2H), 2.39 — 2.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.73, 138.09, 131.23, 128.64, 128.22, 127.50, 127.09, 126.18, 69.6, 64.2, 31.5; IR (film, cm^{-1}) 3011, 2924, 1459, 1089, 759, 727, 698; HRMS (EI) *m/z* calc'd for $[M\cdot]^+$ $C_{13}H_{14}O$: 186.1139, found 186.1141.



(3*Z*,11*Z*)-3,11-Diphenyl-1,9-dioxa-3,11-cyclohexadecadien-5,13-diyne (1.124). Dimer **1.124** (3.6 mg, 34%) was isolated as a white wax. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 — 7.50 (m, 4H), 7.36 — 7.29 (m, 6H), 6.10 (t, J = 2.3 Hz, 2H), 4.77 (s, 4H), 3.81 (t, J = 6.0 Hz, 4H), 2.72 (td, J = 5.9, 2.3 Hz, 4H). LC-MS *m/z* calc'd for $[M+H]^+$ $C_{26}H_{25}O_2$: 369, found 369.

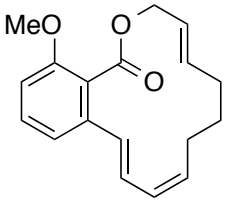
4.2.4 Stepwise Castro–Stephens/Alkyne Reduction Sequence



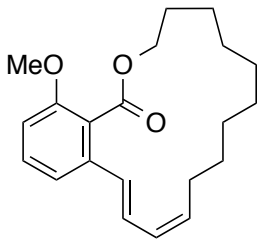
1.119 **1.120**

General Procedure 3: A suspension of iodide substrate (1 equiv), $Cu(OAc)_2$ (0.2 equiv), phanephos (0.3 equiv), and K_2CO_3 (1.5 equiv) in DMF (200 mL per 1 mmol of iodide) was stirred at 120 °C overnight, and then cooled to room temperature. To the cooled reaction mixture was added saturated NH_4Cl solution. The mixture was stirred at room temperature for 15 min, diluted with water and extracted with hexanes/EtOAc (1:1). The combined organic layer was washed with NH_4Cl/NH_3 buffer (3:1 mixture of saturated NH_4Cl/28% aqueous ammonium hydroxide), water, and brine, dried over $MgSO_4$, and concentrated under vacuum to afford the crude enyne intermediate.

The crude enyne, polymethylhydrosiloxane (PMHS, equiv), and *tert*-butanol (equiv) were dissolved in toluene (0.5 mL). To a separate container was added chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) (IPrCuCl, 0.05 equiv), NaO^{t}Bu (0.05 equiv) and THF (0.1 mL). The copper catalyst solution was stirred at room temperature for 15 min and then transferred to the enyne solution via syringe. The combined mixture was heated with stirring at 45 °C for 8 h, after which it was cooled to room temperature and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 40:60 hexanes/DCM) to afford the pure diene product.



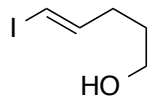
(4*E*,9*Z*,11*E*)-16-Methoxy-3,6,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (1.120e). Prepare from iodide **1.119e** (28.2 mg, 0.0687 mmol) following General Procedure 3. Compound **1.120e** (13.2 mg, 68%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.0 Hz, 1H, overlapping with solvent), 6.82 — 6.75 (m, 3H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.13 (t, *J* = 10.8 Hz, 1H), 5.75 — 5.68 (m, 1H), 5.49 — 5.41 (m, 1H), 7.36 (dt, *J* = 10.2, 8.3 Hz, 1H), 4.80 (d, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 2.29 — 2.23 (m, 2H), 2.10 (q, *J* = 6.6 Hz, 2H), 1.66 — 1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 156.7, 137.0, 136.8, 133.6, 130.6, 130.1, 129.7, 129.1, 126.4, 122.3, 121.8, 109.8, 66.3, 56.3, 30.3, 25.7, 25.5; IR (film, cm^{-1}) 3004, 2925, 2850, 1729, 1571, 1465, 1268, 1111, 1092, 1059, 740; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{18}H_{20}O_3Na$: 307.1305, found 307.1303.



(12*Z*,14*E*)-19-Methoxy-4,5,6,7,8,9,10,11-octahydrobenzo[*c*][1]oxacycloheptadecin-1(3*H*)-one (1.120p). Prepare from iodide **1.119p** (17.9 mg, 0.0394 mmol) following General Procedure 3. Compound **1.120p** (6.0 mg, 41%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.1

Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.84 — 6.78 (m, 2H), 6.54 (d, J = 15.4 Hz, 1H), 6.14 (t, J = 10.8 Hz, 1H), 5.50 (dt, J = 10.6, 7.9 Hz, 1H), 4.32 (t, J = 5.7 Hz, 2H), 3.84 (s, 3H), 2.29 (q, J = 6.8 Hz, 2H), 1.66 — 1.59 (m, 2H), 1.55 — 1.47 (m, 2H), 1.32 — 1.15 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 156.3, 137.9, 134.7, 130.6, 130.2, 129.0, 128.9, 122.7, 120.1, 110.0, 65.8, 56.3, 28.9, 28.4, 27.6, 27.2, 27.1, 26.4, 25.8, 25.6; IR (film, cm^{-1}) 3050, 2925, 2853, 1729, 1574, 1470, 1270, 1156, 1072; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{21}H_{28}O_3Na$: 351.1931, found 351.1935.

4.3 Chapter 2

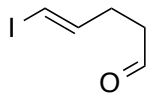


(*E*)-5-Iodo-4-penten-1-ol (2.30). A mixture of 4-pentyn-1-ol (**2.28**, 1.7 mL, 1.5 g, 18 mmol), Bn_3SnH (7.2 mL, 7.8 g, 27 mmol), and AIBN (292 mg, 1.78 mmol) was stirred in a vial at 90 °C for 28 h, and then cooled to room temperature. The resultant liquid containing stannane **2.29** was used for the next step without further purification.

The crude stannane **2.29** was transferred to a round-bottomed flask and diluted with DCM (89 mL). To this solution was added I_2 (6.78 g, 26.7 mmol) in one portion. The mixture was stirred at 0 °C for 1 h and quenched with saturated $Na_2S_2O_3$ solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was dissolved in a minimal amount of DCM and passed through a short column of silica gel (100:0 — 70:30 hexanes/EtOAc) to remove organic

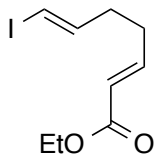
stannanes. The eluting solvent was evaporated under vacuum to afford the crude alcohol **2.30** as a mixture of *E*/*Z* isomers.

The above mixture was dissolved in MeOH (36 mL) and NaOMe (0.5 M in MeOH, 53.4 mL, 26.7 mmol) was added. The solution was refluxed overnight before it was cooled and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 70:30 hexanes/EtOAc). Compound **2.30** (2.20 g, 58%) was isolated as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.02 (dt, *J* = 14.4, 1.3 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.13 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.95 (s, 1H), 1.67 — 1.60 (m, 2H).

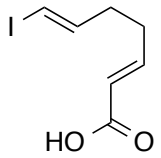


(*E*)-5-Iodo-4-pentenal (2.31). To a solution of oxalyl chloride (0.93 mL, 1.4 g, 11 mmol) in DCM (73 mL) was added DMSO (1.5 mL, 1.7 g, 22 mmol) dropwise at –78 °C. The solution was stirred for 10 min, after which alcohol **2.30** (1.54 g, 7.25 mmol) was added over 5 min. The solution was further stirred for 30 min. Triethylamine (6.6 mL, 4.8 g, 47 mmol) was added over 5 min and the solution was further stirred for 1 h at –78 °C. The reaction was allowed to warm to room temperature and stirred for another 1 h before it was quenched with saturated NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by

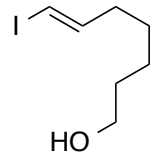
flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **2.31** (1.38 g, 90%) was isolated as a nearly colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.2 Hz, 1H), 6.52 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.12 (dt, *J* = 14.4, 1.5 Hz, 1H), 2.59 — 2.55 (m, 2H), 2.41 — 2.35 (m, 2H).



Ethyl (2*E*,6*E*)-7-Iodo-2,6-heptadienoate (2.32). To a solution of aldehyde **2.31** (1.06 g, 5.04 mmol) in DCM (50 mL) was added (ethoxycarbonylmethylene)triphenyl-phosphorane (2.64 g, 7.56 mmol) in one portion and the solution was stirred at room temperature for 1 h. The mixture was quenched with saturated NH_4Cl solution and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **2.32** (1.32 g, 93%) was isolated as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, *J* = 15.7, 6.6 Hz, 1H), 6.50 (dt, *J* = 14.4, 6.9 Hz, 1H), 6.08 (dt, *J* = 14.4, 1.4 Hz, 1H), 5.83 (dt, *J* = 15.7, 1.6 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.33 — 2.28 (m, 2H), 2.24 — 2.19 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 147.1, 144.6, 122.4, 76.1, 60.4, 34.4, 30.9, 14.4; IR (film, cm^{-1}) 3058, 2980, 2935, 2905, 2848, 1717, 1655, 1606, 1367, 1269, 1182, 976, 948.



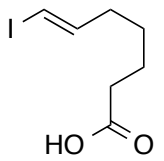
(2*E*,6*E*)-7-Iodo-2,6-heptadienoic Acid (2.25). Ester **2.32** (572 mg, 2.04 mmol) and bis(tributyltin) oxide (2.1 mL, 2.4 g, 4.1 mmol) were dissolved in toluene. The solution was heated with stirring at 105 °C for 48 h. The mixture was cooled to room temperature and partitioned between aqueous HCl solution (1 M) and EtOAc. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 70:30 hexanes/EtOAc). Compound **2.25** (364 mg, 71%) was isolated as white crystals (mp 155 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.08 (br, 1H), 7.03 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.50 (dt, *J* = 14.4, 7.1 Hz, 1H), 6.10 (d, *J* = 14.4 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 2.38 — 2.32 (m, 2H), 2.27 — 2.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 150.3, 144.5, 121.8, 76.4, 34.4, 31.1; IR (film, cm^{-1}) 3054, 2986, 1697, 1654, 1421, 1262, 896, 750; HRMS (ESI+) *m/z* calc'd for $[M–H+2Na]^+$ $C_7H_8IO_2Na_2$: 296.9359, found 296.9372.



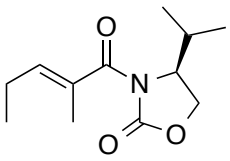
(*E*)-7-Iodo-6-hepten-1-ol (2.35). A mixture of 6-heptyn-1-ol (**2.33**, 696 mg, 6.21 mmol), Bn_3SnH (2.5 mL, 2.7 g, 9.3 mmol), and AIBN (30.6 mg, 0.186 mmol) was stirred in a vial at 90 °C for 24 h, and then cooled to room temperature. The resultant liquid containing stannane **2.34** was used for the next step without further purification.

The crude stannane **2.34** was transferred to a round-bottomed flask and diluted with DCM (6.2 mL). To this solution was added I_2 (2.52 g, 9.94 mmol) in one portion. The mixture was stirred at 0 °C for 1 h and quenched with saturated $Na_2S_2O_3$ solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was dissolved in a minimal amount of DCM and passed through a short column of silica gel (100:0 — 70:30 hexanes/EtOAc) to remove organic stannanes. The eluting solvent was evaporated under vacuum to afford the crude alcohol **2.35** as a mixture of *E*/*Z* isomers.

The above mixture was dissolved in MeOH (12 mL) and KOH (3.48 g, 62.1 mmol) was added. The solution was refluxed overnight before it was cooled and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 DCM/EtOAc). Compound **2.35** (711 mg, 48%) was isolated as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dt, *J* = 14.3, 7.2 Hz, 1H), 5.97 (dt, *J* = 14.3, 1.3 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.05 (qd, *J* = 7.1, 1.2 Hz, 2H), 1.59 (s, 1H), 1.58 — 1.51 (m, 2H), 1.45 — 1.30 (m, 2H, contaminated by unidentified impurity); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 74.8, 62.9, 36.1, 32.6, 28.3, 25.2.

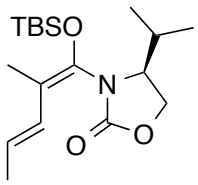


(*E*)-7-Iodo-6-heptenoic Acid (2.24). To a solution of alcohol **2.35** (631 mg, 2.63 mmol) in acetone (26 mL) was added Jones reagent (2.76 M CrO_3 in H_2SO_4, 3.8 mL, 10.5 mmol) at 0 °C and the mixture was stirred at this temperature for 3 h. The reaction mixture was then diluted with water and extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/EtOAc). Compound **2.24** (601 mg, 89%) was isolated as white crystals (mp 64 — 65 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (br, 1H), 6.50 (dt, *J* = 14.4, 7.1 Hz, 1H), 6.02 (d, *J* = 14.4 Hz, 1H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.09 (q, *J* = 7.2 Hz, 2H), 1.69 — 1.61 (m, 2H), 1.50 — 1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 146.0, 75.2, 35.8, 33.9, 27.9, 24.1; IR (film, cm^{-1}) 3047, 2937, 1699, 1412, 1291, 1210, 950; HRMS (ESI+) *m/z* calc'd for $[M–H+2Na]^+$ $C_7H_{10}IO_2Na_2$: 298.9515, found 298.9521.



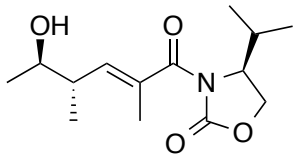
(*S*,*E*)-4-Isopropyl-3-(2-methyl-2-pentenoyl)-2-oxazolidinone (2.38). A solution of (*E*)-2-methyl-2-pentenoic acid (**2.36**, 1.33 g, 11.6 mmol) and triethylamine (3.3 mL, 2.4 g, 24 mmol) in THF (26 mL) was cooled to –20 °C and pivaloyl chloride (1.4 mL, 1.4 g, 12 mmol) was added. The resultant white slurry was stirred at –20 °C for 1 h before the addition of LiCl (984 mg, 23.2 mmol) and (*S*)-4-isopropyl-2-oxazolidinone (**2.37**, 1.00 g,

7.74 mmol). The reaction mixture was allowed to warm to room temperature, stirred overnight, quenched with aqueous HCl solution (0.2 N), and extracted with EtOAc. The combined organic layer was washed sequentially with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **2.38** (1.49 g, 85%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (td, *J* = 7.2, 1.1 Hz, 1H), 4.54 — 4.49 (m, 1H), 4.31 (t, *J* = 8.9 Hz, 1H), 4.17 (dd, *J* = 9.0, 5.5 Hz, 1H), 2.37 (septd, *J* = 7.0, 4.4 Hz, 1H), 2.04 (quint, *J* = 7.5 Hz, 2H), 1.90 (s, 3H), 1.05 (t, *J* = 7.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 153.8, 141.3, 130.4, 63.5, 58.4, 28.4, 21.8, 18.0, 15.2, 13.6, 12.9.



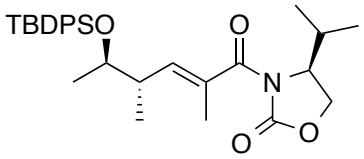
(*S*)-3-((1*E*,3*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-1,3-pentadien-1-yl)-4-isopropyl-2-oxazolidinone (2.1). To a solution of imide **2.38** (1.48 g, 6.57 mmol) in THF (60 mL) was added NaHMDS (1.0 M in THF, 9.9 mL, 9.9 mmol) at –78 °C. After stirring for 90 min, a solution of TBSCl (2.97 g, 19.7 mmol) in THF (24 mL) was added and stirring was continued for another 90 min. The reaction mixture was quenched with saturated NH_4Cl solution, warmed to room temperature, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **2.1** (2.18 g, 98%) was isolated as a

colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (d, *J* = 15.6 Hz, 1H), 5.63 (qd, *J* = 15.5, 6.6 Hz, 1H), 4.32 (t, *J* = 8.7 Hz, 1H), 4.12 (t, *J* = 8.3 Hz, 1H), 4.05 — 3.95 (m, 1H), 1.98 — 1.90 (m, 1H), 1.79 — 1.77 (m, 6H), 0.98 (s, 9H), 0.92 (d, *J* = 7.7 Hz, 6H), 0.19 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 134.8, 128.3, 124.4, 115.1, 64.5, 59.5, 29.5, 25.8, 18.9, 18.4, 18.2, 16.4, 12.4, –4.2, –4.8.



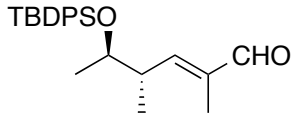
(*S*)-3-((4*S*,5*R*,*E*)-5-Hydroxy-2,4-dimethyl-2-hexenoyl)-4-isopropyl-2-oxazolidinone (2.39). At –78 °C, to a solution of acetaldehyde (0.898 g, 20.4 mmol) in DCM (25 mL) were sequentially added $TiCl_4$ solution (1 M in DCM, 5.1 mL, 5.1 mmol) and a solution of vinylketene silyl *N*,*O*-acetal **2.1** (1.73 g, 5.09 mmol) in DCM (25 mL). The resultant dark orange solution was stirred at –78 °C for 24 h, after which the color turned bright yellow. The reaction was quenched with aqueous saturated Rochelle salt solution and stirred at room temperature for several hours until precipitates disappeared. The mixture was extracted with DCM. The combine organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (90:10 — 60:40 hexanes/EtOAc). Compound **15** (1.10 g, 80%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +11 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.58 (ddd, *J* = 8.9, 5.8, 4.6Hz, 1H), 4.34 (t, *J* = 9.0 Hz, 1H), 4.19 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.51 (quint, *J* = 6.6 Hz, 1H), 3.24 (s, 1H), 2.49 (ddq, *J* = 10.4, 8.3, 6.6 Hz, 1H), 2.34 (septd, *J* = 7.0, 4.5 Hz, 1H), 1.95 (d, *J*

= 1.4 Hz, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 154.6, 142.0, 131.3, 71.6, 63.6, 58.1, 41.9, 28.5, 20.1, 17.8, 16.2, 15.2, 14.0; IR (film, cm^{-1}) 3517, 2968, 2931, 2876, 1773, 1685, 1390, 1366, 1301, 1210; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{23}NO_4Na$: 292.1519, found 292.1514.

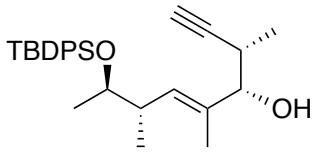


(*S*)-3-((4*S*,5*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethyl-2-hexenoyl)-4-isopropyl-2-oxazolidinone (2.40c). A solution of alcohol **2.39** (1.02 g, 3.79 mmol), imidazole (774 mg, 11.4 mmol) and DMAP (92.5 mg, 0.757 mmol) in DCM (19 mL) was cooled to 0 °C and *tert*-butylchlorodiphenylsilane (1.9 mL, 2.1 g, 7.6 mmol) was added. The solution was stirred at room temperature overnight and then water was added. The mixture was extracted with DCM. The combine organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **2.40c** (1.78 g, 92%) was isolated as a colorless syrup. $[\alpha]_D^{21}$ = +16 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 — 7.68 (m, 4H), 7.45 — 7.36 (m, 6H), 6.08 — 6.05 (m, 1H), 4.52 (ddd, *J* = 8.8, 5.5, 4.3 Hz, 1H), 4.32 (t, *J* = 8.9 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.6 Hz, 1H), 3.89 (qd, *J* = 6.4, 3.4 Hz, 1H), 2.54 (dqd, *J* = 10.2, 6.8, 3.4 Hz, 1H), 2.37 (septd, *J* = 6.9, 4.2 Hz, 1H), 1.70 (d, *J* = 1.4 Hz, 3H), 1.07 (s, 9H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 172.2, 153.7, 141.2, 136.1, 134.7, 134.2, 131.1, 129.8, 129.6, 127.7, 127.6, 72.2, 63.5, 58.3, 40.1, 28.3, 27.2, 20.5, 19.6, 18.0, 15.3, 15.2, 13.6; IR (film, cm^{-1}) 3072, 3049, 2964, 2931, 1789, 1683, 1428, 1300, 1111, 703; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{30}H_{41}NO_4SiNa$: 530.2697, found 530.2703.

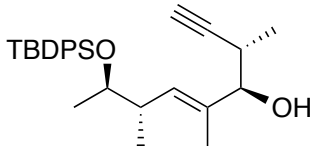


(4*S*,5*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethyl-2-hexenal (2.27c). A solution of compound **2.40c** (1.16 g, 2.28 mmol) in DCM (50 mL) was cool to –78 °C and DIBAL-H solution (1.49 M in toluene, 3.3 mL, 4.9 mmol) was added dropwise. The reaction was stirred at –78 °C for 20 min before it was quenched by MeOH and then aqueous saturated Rochelle salt solution. The mixture was stirred at room temperature until precipitates disappeared and then extracted with DCM. The combine organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **2.27c** (761 mg, 88%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +1.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.70 — 7.65 (m, 4H), 7.46 — 7.35 (m, 6H), 6.40 (dq, *J* = 9.8, 1.3 Hz, 1H), 3.85 (qd, *J* = 6.2, 4.4 Hz, 1H), 2.71 (dqd, *J* = 9.8, 6.8, 4.4 Hz, 1H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.05 (s, 9H), 1.04 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 157.1, 139.3, 136.1 134.6, 133.9, 130.0, 129.8, 127.8, 127.7, 72.4, 41.2, 27.2, 21.0, 19.6, 15.6, 9.5; IR (film, cm^{-1}) 3071, 3050, 2964, 2931, 2858, 2820, 2708, 1690, 1641, 1428, 1377, 1111, 1025, 703; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{24}H_{32}O_2SiNa$: 403.2064, found 403.2064.

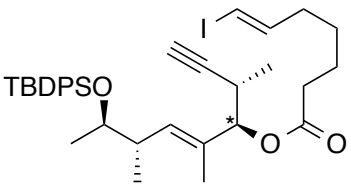


(3*S*,4*S*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethyl-5-nonen-1-yn-4-ol ((4*S*)-2.26c). Anhydrous THF used in this reaction was pretreated with 3Å molecular sieves (20% M/V) overnight. A solution of palladium acetate (11.2 mg, 0.0500 mmol) and triphenylphosphine (13.1 mg, 0.0500 mmol) in THF (18 mL) was cooled to –78 °C. To this solution were sequentially added mesylate (*R*)-**2.42**[136] (0.15 mL, 178 mg, 1.20 mmol), a solution of aldehyde **2.27c** (382 mg, 1.00 mmol) in THF (2mL), and diethylzinc (1.0 M in hexanes, 3.0 mL, 3.0 mmol). The mixture was stirred at –78 °C for 10 min, warmed up to –20 °C, and stirred at this temperature for 20 h. The sealed reaction container was then left in a 0 °C refrigerator for another 16 h before EtOAc and saturated NH_4Cl solution were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). An inseparable mixture of compound (4*S*)-**2.26** and its C_4-epimer (342 mg, 79%, d.r. = 82:18) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +2.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 — 7.66 (m, 4H), 7.44 — 7.34 (m, 6H), 5.32 — 5.29 (m, 1H), 3.80 (qd, *J* = 6.3, 4.0 Hz, 1H), 3.76 (d, *J* = 8.0 Hz, 1H), 2.65 — 2.55 (m, 1H), 2.47 (dqd, *J* = 9.6, 6.8, 4.1 Hz, 1H), 2.12 (d, *J* = 2.4 Hz, 1H), 1.86 (br, 1H), 1.39 (d, *J* = 1.3 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.06 (s, 9H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 134.9, 134.5, 134.1, 132.0, 129.7, 129.6, 127.7, 127.6, 86.3, 81.2, 72.5, 70.7, 39.3, 31.3, 27.3, 19.9, 19.6, 17.7, 15.6, 11.3; IR (film, cm^{-1}) 3308, 3071, 2964, 2932, 2858, 1473,

1460, 1428, 1376, 1111, 1027, 961, 822, 739, 702, 612; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{28}H_{38}O_2SiNa$: 457.2533, found 457.2528.

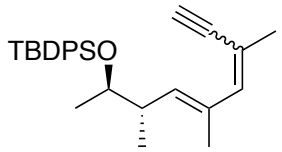


(3*S*,4*R*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethyl-5-nonen-1-yn-4-ol ((4*R*)-2.26c). Featured ^{1}H NMR (400 MHz, $CDCl_3$) peaks: δ 5.39 — 5.36 (m, 1H), 3.91 (d, *J* = 7.0 Hz, 1H), 1.96 (d, *J* = 2.5 Hz, 1H), 1.42 (d, *J* = 1.4 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H). The minor isomer is in an inseparable mixture and therefore not all signals are visible in the spectrum.

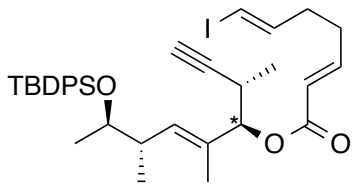


(3*S*,4*R*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethyl-5-nonen-1-yn-4-yl (*E*)-7-Iodo-6-heptenoate (2.22). A solution of alcohol (4*S*)-**2.26** (78.8 mg, 0.181 mmol), acid **2.24** (139 mg, 0.543 mmol), and triphenylphosphine (142 mg, 0.543 mmol) in toluene (1.8 mL) was cooled to 0 °C and DEAD (40% in toluene, 0.25 mL, 95 mg, 0.54 mmol) was added. The mixture was stirred at room temperature for 20 h before the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (100:0 — 50:50 hexanes/DCM). Compound **2.22** along with its inseparable epimer (77.8 mg, 64%, d.r. = 93:7) was isolated as a colorless oil. $[\alpha]_D^{22}$ = +7.4 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 — 7.66 (m, 4H), 7.44 — 7.34 (m, 6H), 6.48

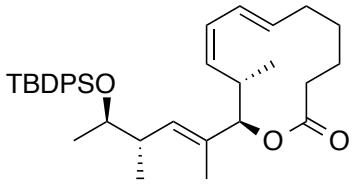
(dt, *J* = 14.2, 7.1 Hz, 1H), 6.02 (dt, *J* = 14.3, 1.5 Hz, 1H), 5.40 (d, *J* = 9.6 Hz, 1H), 5.06 (d, *J* = 7.8 Hz, 1H), 3.78 (qd, *J* = 6.3, 3.3 Hz, 1H), 2.75 (quintd, *J* = 6.9, 2.4 Hz, 1H), 2.43 (dqd, *J* = 9.9, 6.8, 3.4 Hz, 1H), 2.31 (td, *J* = 7.5, 1.8 Hz, 2H), 2.06 (qd, *J* = 7.3, 1.6 Hz, 2H), 1.92 (d, *J* = 2.4 Hz, 1H), 1.66 — 1.58 (m, 2H), 1.45 — 1.37 (m, 5H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 146.0, 136.1, 134.9, 134.4, 132.7, 131.4, 129.7, 129.6, 127.9, 127.5, 85.1, 80.9, 75.1, 72.3, 70.4, 39.0, 35.8, 34.3, 29.1, 27.9, 27.2, 24.4, 19.8, 19.6, 17.1, 15.4, 12.5; IR (film, cm^{-1}) 3308, 3070, 2931, 2857, 1736, 1427, 1110, 702, HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{35}H_{47}IO_3SiNa$: 693.2231, found 693.2236.



***tert*-Butyldiphenyl(((2*R*,3*S*,4*E*)-3,5,7-trimethyl-4,6-nonadien-8-yn-2-yl)oxy)silane (2.46).** Elimination product **2.46** (15.9 mg, 21%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 — 7.68 (m, 4H), 7.52 — 7.30 (m, 6H), 6.12 (br, 1H), 5.51 (d, *J* = 9.7 Hz, 1H), 3.80 (qd, *J* = 6.2, 4.1 Hz, 1H), 3.15 (s, 1H), 2.55 (dqd, *J* = 9.5, 6.8, 4.2, 1H), 1.95 (d, *J* = 1.4 Hz, 3H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.08 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 127.2, 136.2, 135.1, 134.5, 133.8, 129.7, 129.6, 127.7, 127.6, 112.9, 85.0, 82.5, 72.6, 39.8, 27.3, 25.9, 20.0, 19.6, 15.6, 15.1.

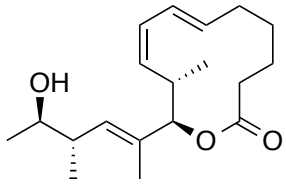


(3*S*,4*R*,7*S*,8*R*,*E*)-8-((*tert*-Butyldiphenylsilyl)oxy)-3,5,7-trimethyl-5-nonen-1-yn-4-yl (2*E*,6*E*)-7-Iodo-2,6-heptadienoate (2.23). A solution of alcohol (4*S*)-**2.26** (56.8 mg, 0.131 mmol), acid **2.25** (98.8 mg, 0.392 mmol), and triphenylphosphine (103 mg, 0.392 mmol) in toluene (1.3 mL) was cooled to 0 °C and DEAD (40% in toluene, 0.18 mL, 69 mg, 0.39 mmol) was added. The mixture was stirred at room temperature for 22 h before the solvent was evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 50:50 hexanes/DCM). Compound **2.23** along with its inseparable epimer (54.2 mg, 62%, d.r. = 92:8) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 — 7.65 (m, 4H), 7.43 — 7.34 (m, 6H), 6.92 (dt, *J* = 15.6, 6.5 Hz, 1H), 6.49 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.07 (dt, *J* = 14.4, 1.5 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.42 (d, *J* = 9.4 Hz, 1H), 5.12 (d, *J* = 7.9 Hz, 1H), 3.78 (qd, *J* = 6.2, 3.2 Hz, 1H), 2.78 (quintd, *J* = 7.0, 2.5 Hz, 1H), 2.43 (dqd, *J* = 9.8, 6.7, 3.2 Hz, 1H), 2.31 — 2.26 (m, 2H), 2.23 — 2.19 (m, 2H), 1.93 (d, *J* = 2.4 Hz, 1H), 1.42 (d, *J* = 1.5 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 9H), 1.02 (d, *J* = 6.8, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 147.6, 144.7, 136.1, 135.0, 134.4, 132.9, 131.4, 129.7, 129.6, 127.7, 127.6, 122.4, 85.1, 81.1, 76.2, 72.4, 70.5, 39.1, 34.5, 31.0, 29.3, 27.3, 19.8, 19.6, 17.2, 15.4, 12.5; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{35}H_{45}IO_3Si$: 691.2075, found 691.2096.



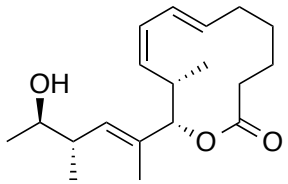
(7*E*,9*Z*,11*S*,12*R*)-12-((4*S*,5*R*,*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)-4-methyl-2-hexen-2-yl)-11-methyloxa-7,9-cyclododecadien-2-one (2.47). A suspension of copper acetate (13.4 mg, 0.0738 mmol), BINAP (69.7 mg, 0.112 mmol), sodium formate (60.9 mg, 0.896 mmol) and potassium carbonate (46.4 mg, 0.336 mmol) in DMF (22 mL) was stirred at 120 °C for 30 min, after which a solution of ester **2.2** (150 mg, 0.224 mmol) in DMF (23 mL) was added dropwise in one portion. The resultant mixture was stirred at 120 °C for an additional period of 4h before it was cooled and quenched with saturated NH_4Cl solution. After stirring at room temperature for 15 min, the mixture was diluted with water and extracted with EtOAc/hexanes (1:1). The combine organic layer was sequentially washed with NH_4Cl/NH_3 buffer (3:1 mixture of saturated NH_4Cl/28% aqueous ammonium hydroxide), water and brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 50:50 hexanes/DCM). Compound **2.47** (102 mg, 83%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = –25 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 — 7.66 (m, 4H), 7.44 — 7.35 (m, 6H), 6.21 (dd, *J* = 15.8, 10.5 Hz, 1H), 6.10 (t, *J* = 10.4 Hz, 1H), 5.74 (dt, *J* = 15.8, 5.3 Hz, 1H), 5.30 (d, *J* = 9.6 Hz, 1H), 5.10 (d, *J* = 5.0 Hz, 1H), 4.99 (t, *J* = 10.0 Hz, 1H), 3.78 (qd, *J* = 6.2, 3.1 Hz, 1H), 3.38 — 3.29 (m, 1H), 2.44 — 2.23 (m, 4H), 2.04 — 1.93 (m, 2H), 1.90 — 1.84 (m, 1H), 1.59 — 1.50 (m, 2H), 1.35 (d, *J* = 1.3 Hz, 3H), 1.07 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 136.2, 136.1, 135.0, 134.4, 133.6,

131.6, 131.3, 131.1, 130.1, 129.7, 129.6, 127.7, 127.6, 126.7, 83.5, 72.5, 39.2, 33.6, 33.4, 30.5, 27.2, 24.1, 23.2, 20.1, 19.6, 17.8, 15.6, 14.3; IR (film, cm^{-1}) 3071, 2962, 2930, 2857, 1728, 1427, 1376, 1200, 1111, 739, 702; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{35}H_{48}O_3SiNa$: 567.3265, found 567.3267.



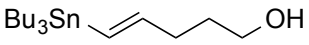
(7*E*,9*Z*,11*S*,12*R*)-12-((4*S*,5*R*,*E*)-5-Hydroxy-4-methyl-2-hexen-2-yl)-11-methyloxa-7,9-cyclododecadien-2-one (1.42). To a vial containing lactone **2.47** (71.5 mg, 0.131 mmol) was added TBAF solution (1.0 M in THF, 3.4 mL, 3.4 mmol). The solution was then heated with stirring at 50 °C for 4 h. The mixture was cooled, diluted with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **1.42** (34 mg, 85%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = –85 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.12 (t, *J* = 10.4 Hz, 1H), 5.74 (dt, *J* = 15.6, 5.2 Hz, 1H), 5.24 (d, *J* = 9.8 Hz, 1H), 5.13 (d, *J* = 5.0 Hz, 1H), 5.05 (t, *J* = 9.9 Hz, 1H), 3.58 (quint, *J* = 6.2 Hz, 1H), 3.40 — 3.32 (m, 1H), 2.41 (dquint, *J* = 9.9, 6.7 Hz, 1H), 2.34 — 2.24 (m, 3H), 2.04 — 1.96 (m, 2H), 1.93 — 1.83 (m, 1H), 1.64 (d, *J* = 1.1 Hz, 3H), 1.59 — 1.48 (m, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.8, 3H), 0.95 (d, *J* = 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 133.3, 133.0, 131.6, 131.3, 130.3, 126.7, 83.3, 71.7, 40.2, 33.5, 33.4, 30.5, 24.1, 23.2, 20.4, 17.9, 16.6, 14.8; IR (film, cm^{-1}) 3449,

3008, 2966, 2929, 2876, 1726, 1453, 1376, 1201, 1146, 1093, 994, 955; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{19}H_{30}O_3Na$: 329.2087, found 329.2085.



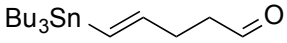
(7*E*,9*Z*,11*S*,12*S*)-12-((4*S*,5*R*,*E*)-5-Hydroxy-4-methyl-2-hexen-2-yl)-11-methyloxa-7,9-cyclododecadien-2-one (*epi*-1.42). The epimer (2.5 mg, 6%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = +16 (*c* 0.050, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.13 (t, *J* = 10.4 Hz, 1H), 5.75 (dt, *J* = 15.6, 5.2 Hz, 1H), 5.24 (d, *J* = 9.8 Hz, 1H), 5.15 (d, *J* = 4.9 Hz, 1H), 5.05 (t, *J* = 9.9 Hz, 1H), 3.55 (quint, *J* = 6.3 Hz, 1H), 3.41 — 3.33 (m, 1H), 2.41 (dquint, *J* = 9.8, 6.8 Hz, 1H), 2.38 — 2.25 (m, 3H), 2.05 — 1.95 (m, 2H), 1.93 — 1.81 (m, 1H), 1.66 (s, 3H, overlapping with water signal), 1.60 — 1.52 (m, 3H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 6H).

4.4 Chapter 3

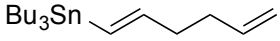


(*E*)-5-(Tributylstannyl)-4-penten-1-ol ((*E*)-2.29). Pd_2dba_3 (50.3 mg, 0.0549 mmol), tricyclohexylphosphonium tetrafluoroborate (79.2 mg, 0.215 mmol) and DIPEA (0.30 mL, 220 mg, 1.7 mmol) were dissolved in DCM (100 mL) and the solution was stirred at room temperature for 10 min. 4-Pentyn-1-ol (1.0 mL, 900 mg, 11 mmol) was added and the reaction mixture was cooled to 0 °C. A solution of Bu_3SnH (3.5 mL, 3.8 g, 13 mmol) in DCM (30 mL) was added dropwise via syringe over 15 min. The reaction mixture was

then stirred at 0 °C for 4 h before it was concentrated to afford a crude product. This crude compound (*E*)-**2.29** was directly used for the next step without further purification.

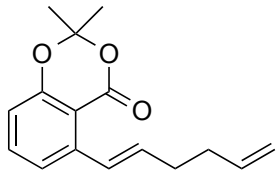


(*E*)-5-(Tributylstannyl)-4-pentenal (3.55). To a solution of the above crude alcohol (*E*)-**2.29** in DCM (30 mL) was added triethylamine (7.6 mL, 5.5 g, 54 mmol) and DMSO (30 mL). The mixture was cooled to 0 °C, and $SO_3 \cdot Py$ (52.0 mg, 0.324 mmol) was added in portions over 2 min. The mixture was stirred at 0 °C for an additional period of 1 h, and then diluted with hexanes (100 mL) and phosphate (pH = 7) buffer (20 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford a bright yellow crude product. This crude compound **3.55** was directly used for the next step without further purification.

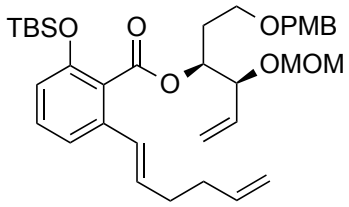


(*E*)-Tributyl(1,5-hexadien-1-yl)stannane (3.54). Methyltriphenylphosphonium bromide (8.50 g, 23.8 mmol) was suspended with stirring in THF (30 mL) at 0 °C and a solution of KO^{t}Bu (1.0 M in THF, 22 mL, 22 mmol) was added over 3 min. After the addition was completed, the bright yellow mixture was stirred at 0 °C for 30 min. A solution of crude aldehyde **3.55** from the previous step in THF (30 mL) was then added dropwise over 10 min. The reaction mixture was stirred at 0 °C and warmed to room temperature overnight before it was diluted with hexanes (100 mL) and quenched with phosphate (pH = 7) buffer (50 mL). The organic layer was separated, and the aqueous

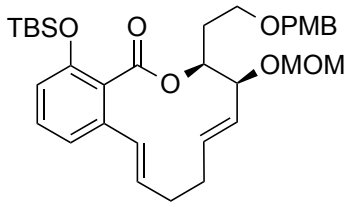
layer was extracted with hexanes. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum to afford a crude product. This crude compound **3.54** was directly used for the next step without further purification.



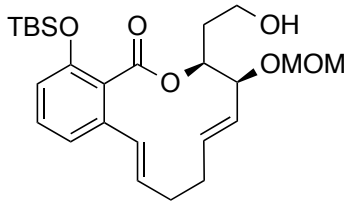
(*E*)-5-(1,5-Hexadien-1-yl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3.53). A mixture of $Pd(PPh_3)_4$ (78.0 mg, 0.0675 mmol), LiCl (286 mg, 6.75 mmol), and 2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl trifluoromethanesulfonate (**1.68**)[58, 91] (439 mg, 1.35 mmol) in degassed DMF (6.8 mL) was stirred at room temperature for 15min, after which crude stannyl diene **3.54** (0.56 mL, *ca.* 600 mg, 1.6 mmol) was added dropwise via syringe. The resulting mixture was stirred and heated at 70 °C for 24 h, cooled to room temperature, and diluted with water and hexanes. The aqueous layer was extracted with EtOAc/hexanes (1:1). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **3.53** (215 mg, 62%) was isolated as a colorless oil, which solidified slowly upon storage in a refrigerator. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 15.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.22 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.87 (ddt, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 2.41 — 2.36 (m, 2H), 2.29 — 2.24 (m, 2H), 1.70 (s, 6H).



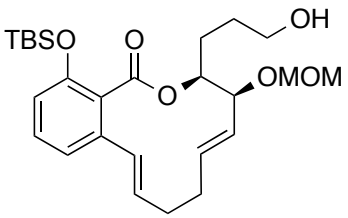
(3*S*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-(methoxymethoxy)-5-hexen-3-yl 2-((*tert*-Butyldimethylsilyl)oxy)-6-((*E*)-1,5-hexadien-1-yl)benzoate (3.52). A solution of alcohol **1.66**[40] (91.1 mg, 0.308 mmol) in THF (0.5 mL) was cooled to 0 °C and NaHMDS (1.0 M in THF, 0.59 mL, 0.59 mmol) was added. After stirring at 0 °C for 30 min, a solution of salicylate **3.53** (75.7 mg, 0.293 mmol) in THF (0.5 mL) was added dropwise via syringe. The reaction was warmed to room temperature, and stirred for 2 h before TBSCl (88.3 mg, 0.586 mmol) and imidazole (39.9 mg, 0.586 mmol) were added as solids. The mixture was stirred overnight and then diluted with water and hexanes. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 90:10 hexanes/EtOAc). Compound **3.52** (115 mg, 64%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.4 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 6.17 (dt, *J* = 15.7, 6.6 Hz, 1H), 5.86 — 5.77 (m, 2H), 5.36 — 5.27 (m, 3H), 5.04 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.98 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 6.7 Hz, 1H), 4.49 — 4.41 (m, 2H), 4.31 (dd, *J* = 6.9, 4.7 Hz, 1H), 3.80 (s, 3H), 3.67 — 3.57 (m, 2H), 3.32 (s, 3H), 2.29 — 2.10 (m, 5H, overlapping with residual acetone), 2.04 — 1.97 (m, 1H), 0.98 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H).



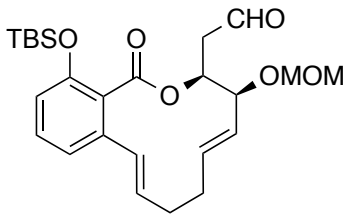
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-3-(2-((4-methoxybenzyl)oxy) ethyl)-4-(methoxymethoxy)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.50). A solution of ester **3.52** (604 mg, 0.989 mmol) and second-generation Grubbs catalyst (42.0 mg, 0.0495 mmol) in toluene (620 mL) was degassed and heated to reflux. The refluxing solution was stirred for 26 h and then cooled to room temperature. DMSO (0.18 mL, 190 mg, 2.4 mmol) was added into the reaction flask, and the mixture was stirred at room temperature overnight before the solvent was removed under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/EtOAc). Compound **3.50** (392 mg, 68%) was isolated as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.89 — 6.85 (m, 3H), 6.68 (d, *J* = 8.2, 1H), 6.22 (d, *J* = 15.9 Hz, 1H), 5.77 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.50 (dt, *J* = 15.8, 6.2 Hz, 1H), 5.35 — 5.27 (m, 2H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.40 — 4.38 (m, 1H), 3.81 (s, 3H), 3.68 — 3.59 (m, 2H), 3.35 (s, 3H), 2.41 — 2.30 (m, 2H), 2.24 — 2.13 (m, 4H), 0.98 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H).



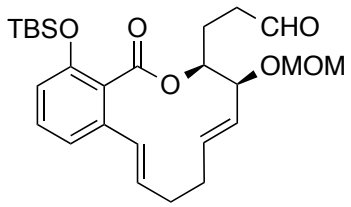
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-3-(2-hydroxyethyl)-4-(methoxymethoxy)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.56). To a flask containing macrocyclic diene **3.50** (385 mg, 0.661 mmol) was added DCM (20 mL) and H_2O (2 mL). The mixture was cooled to 0 °C and DDQ (165 mg, 0.727 mmol) was added in one portion. The cooling bath was removed and the reaction was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution and then extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 65:35 hexanes/EtOAc). Compound **3.56** (188 mg, 61%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 5.79 (dt, *J* = 15.7, 5.9 Hz, 1H), 5.53 (dt, *J* = 15.7, 5.8 Hz, 1H), 5.35 — 5.29 (m, 2H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.39 — 4.37 (m, 1H), 3.83 — 3.72 (m, 2H), 3.38 (s, 3H), 2.59 (s, 1H), 2.43 — 2.33 (m, 2H), 2.23 — 2.13 (m, 2H), 2.12 — 2.00 (m, 2H), 0.97 (s, 9H), 0.26 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 152.3, 137.7, 132.3, 131.6, 131.0, 130.3, 130.0, 125.4, 118.7, 117.4, 95.0, 77.4, 75.7, 58.9, 56.3, 34.1, 30.6, 29.9, 26.0, 18.7, –3.87, –3.94.



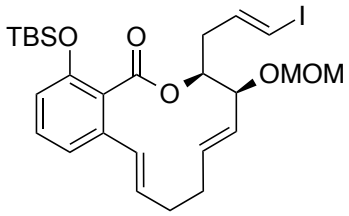
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-3-(3-hydroxypropyl)-4-(methoxymethoxy)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.57). To a flask containing macrocyclic diene **3.51**[172] (68.1 mg, 0.114 mmol) was added DCM (3 mL) and H_2O (0.3 mL). The mixture was cooled to 0 °C and DDQ (28.4 mg, 0.125 mmol) was added in one portion. The cooling bath was removed and the reaction was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution and then extracted with DCM. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 65:35 hexanes/EtOAc). Compound **3.57** (27.7 mg, 51%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.0, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.23 (d, *J* = 16.0 Hz, 1H), 5.77 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.51 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.34 (dd, *J* = 15.7, 5.0 Hz, 1H), 5.17 (td, *J* = 7.0, 3.1 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.44 — 4.42 (m, 1H), 3.75 — 3.65 (m, 2H), 3.40 (s, 3H), 2.41 — 2.30 (m, 2H), 2.28 — 2.16 (m, 2H), 2.07 — 1.98 (m, 1H), 1.92 — 1.83 (m, 1H), 1.80 — 1.66 (m, 2H), 1.47 (br, 1H), 0.97 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 152.3, 137.8, 132.5, 132.1, 131.0, 129.9, 129.5, 125.8, 119.1, 117.4, 95.1, 77.4, 76.2, 63.0, 56.4, 30.8, 30.3, 28.9, 27.0, 26.0, 18.5, –3.9, –4.1.



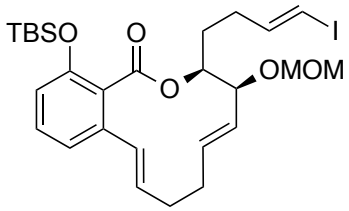
2-((3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-4-(methoxymethoxy)-1-oxo-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-3-yl)ethanal (3.58). To a solution of alcohol **3.56** (188 mg, 0.406 mmol) in DCM (4.1 mL) was added Dess–Martin periodinane (259 mg, 0.610 mmol) as solid. The resultant mixture was stirred at room temperature for 2.5 h before it was filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/EtOAc). Compound **3.58** (165 mg, 88%) was isolated as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.16 (t, *J* = 8.0, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.14 (d, *J* = 15.9 Hz, 1H), 5.76 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.57 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.52 — 5.48 (m, 1H), 5.30 (dd, *J* = 15.8, 6.3 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.51 — 4.49 (m, 2H), 3.32 (s, 3H), 3.07 (ddd, *J* = 17.3, 4.8, 2.1 Hz, 1H), 2.83 (ddd, *J* = 17.3, 4.8, 2.1 Hz, 1H), 2.43 — 2.34 (m, 2H), 2.16 — 2.05 (m, 2H), 0.96 (s, 9H), 0.234 (s, 3H), 0.230 (s, 3H).



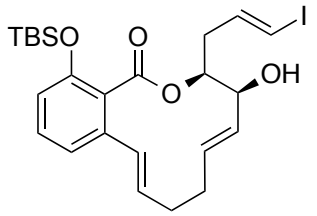
3-((3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-4-(methoxymethoxy)-1-oxo-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-3-yl)propanal (3.59). To a solution of alcohol **3.57** (28.4 mg, 0.0596 mmol) in DCM (1.2 mL) was added Dess–Martin periodinane (37.9 mg, 0.0894 mmol) as solid. The resultant mixture was stirred at room temperature for 3 h before it was filtered. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 80:20 hexanes/EtOAc). Compound **3.59** (20.3 mg, 72%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +150 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 5.76 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.55 — 5.48 (m, 1H), 5.32 (dd, *J* = 15.6, 5.3 Hz, 1H), 5.16 (ddd, *J* = 7.8, 5.8, 3.2 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.43 — 4.41 (m, 1H), 3.39 (s, 3H), 2.68 — 2.63 (m, 2H), 2.41 — 2.30 (m, 2H), 2.23 — 2.13 (m, 4H), 0.98 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H).



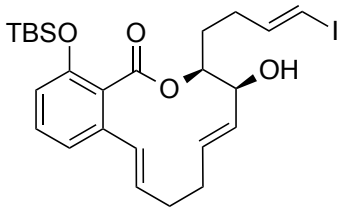
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-3-((*E*)-3-iodoallyl)-4-(methoxymethoxy)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.60). To a suspension of $CrCl_2$ (350 mg, 2.84 mmol) in THF (1.7 mL) was added a solution of aldehyde **3.58** (109 mg, 0.237 mmol) and iodoform (373 mg, 0.947 mmol) in dioxane (10.2 mL). The resultant mixture was stirred at room temperature for 22 h, quenched with brine, and then extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **3.60** (120 mg, 86%) was isolated as a colorless oil (*E*/*Z* = 9:1 vinyl iodide isomers). $[\alpha]_D^{23}$ = +96.7 (*c* 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.60 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.25 (d, *J* = 14.4 Hz, 1H), 6.17 (d, *J* = 15.9 Hz, 1H), 5.77 (dt, *J* = 15.7, 6.1 Hz, 1H), 5.52 (dt, *J* = 15.7, 6.1 Hz, 1H), 5.30 (dd, *J* = 15.8, 5.6 Hz, 1H), 5.04 (ddd, 8.5, 5.4, 3.1 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.7, 1H), 4.42 — 4.40 (m, 1H), 3.41 (s, 3H), 2.78 — 2.70 (m, 1H), 2.59 — 2.52 (m, 1H), 2.42 — 2.32 (m, 2H), 2.20 — 2.12 (m, 2H), 0.98 (s, 9H), 0.244 (s, 3H), 0.237 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 168.3, 152.3, 141.0, 137.8, 132.4, 132.2, 131.1, 130.1, 129.9, 125.5, 119.0, 117.2, 95.1, 78.7, 76.4, 75.6, 56.5, 36.7, 30.9, 30.3, 26.0, 18.4, –3.8, –4.2; IR (film, cm^{-1}) 3064, 2928, 2856, 1730, 1574, 1466, 1290, 1255, 1107, 1036, 841, 784; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{26}H_{37}IO_5SiNa$: 607.1347, found 607.1357.



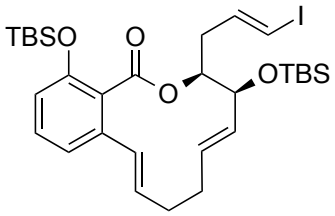
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-3-((*E*)-4-iodo-3-buten-1-yl)-4-(methoxymethoxy)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.61). To a suspension of $CrCl_2$ (114 mg, 0.924 mmol) in THF (0.55 mL) was added a solution of aldehyde **3.59** (36.7 mg, 0.0770 mmol) and iodoform (121 mg, 0.308 mmol) in dioxane (3.3 mL). The resultant mixture was stirred at room temperature for 23 h, quenched with brine, and then extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **3.61** (38.9 mg, 84%) was isolated as a colorless oil (*E*/*Z* = 9:1 vinyl iodide isomers). $[\alpha]_D^{22}$ = +110 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.55 (dt, *J* = 14.1, 6.9 Hz, 1H), 6.24 (d, *J* = 15.7 Hz, 1H), 6.08 (d, *J* = 14.4 Hz, 1H), 5.77 (dt, *J* = 15.8, 6.1 Hz, 1H), 5.53 — 5.46 (m, 1H), 5.32 (dd, *J* = 15.7, 5.1 Hz, 1H), 5.14 (td, *J* = 6.9, 3.1 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.40 — 4.38 (m, 1H), 3.39 (s, 3H), 2.42 — 2.13 (m, 6H), 2.00 — 1.89 (m, 2H), 0.97 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 152.4, 145.5, 137.7, 132.6, 132.4, 131.0, 129.9, 129.1, 125.8, 119.1, 117.4, 95.1, 76.4, 76.2, 75.4, 56.4, 32.4, 30.7, 30.3, 29.2, 26.0, 18.6, –3.8, –4.0; IR (film, cm^{-1}) 3065, 2929, 2857, 1728, 1573, 1466, 1032, 841; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{27}H_{39}IO_5SiNa$: 621.1504, found 621.1509.



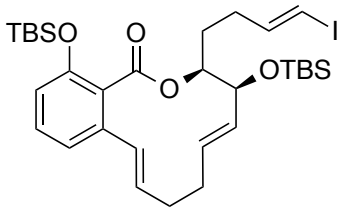
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-3-((*E*)-3-iodoallyl)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.62). To a flask containing iodide **3.60** (117 mg, 0.200 mmol) was added ^{i}PrOH (4 mL) and CBr_4 (266 mg, 0.801 mmol) in one portion. The mixture was heated with stirring at 75 °C for 2 h, cooled to room temperature, and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **3.62** (93.1 mg, 86%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = +37.6 (*c* 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.57 (ddd, *J* = 15.0, 8.5, 6.8 Hz, 1H), 6.28 (d, *J* = 14.4 Hz, 1H), 6.21 (d, *J* = 16.1 Hz, 1H), 5.75 (dt, *J* = 15.8, 5.8 Hz, 1H), 5.47 (s, 2H), 5.13 (ddd, *J* = 9.9, 4.9, 2.0 Hz, 1H), 4.36 (s, 1H), 2.77 — 2.69 (m, 1H), 2.50 — 2.43 (m, 1H), 2.38 — 2.23 (m, 4H), 1.73 (br, 1H), 0.98 (s, 9H), 0.25 (s, 3H), 0.24 (3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 152.4, 140.7, 137.6, 133.2, 132.9, 130.4, 130.1, 129.5, 125.4, 119.0, 117.2, 79.4, 75.7, 71.0, 37.1, 30.9, 30.0, 25.9, 18.4, –3.8, –4.2; IR (film, cm^{-1}) 3435, 2955, 2929, 2856, 1726, 1645, 1573, 1466, 1253, 1106, 840, 783; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{24}H_{33}IO_4SiNa$: 563.1085, found 563.1085.



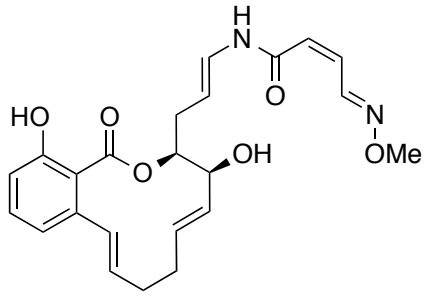
(3*S*,4*S*,5*E*,9*E*)-14-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-3-((*E*)-4-iodo-3-buten-1-yl)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.63). To a flask containing iodide **3.61** (38.9 mg, 0.0650 mmol) was added ^{i}PrOH (1.3 mL) and CBr_4 (86.2 mg, 0.260 mmol) in one portion. The mixture was heated with stirring at 75 °C for 2 h, cooled to room temperature, and then concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 85:15 hexanes/EtOAc). Compound **3.62** (34.5 mg, 96%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +31 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.54 (dt, *J* = 14.1, 7.0 Hz, 1H), 6.26 (d, *J* = 15.6 Hz, 1H), 6.08 (d, *J* = 14.4 Hz, 1H), 5.79 — 5.72 (m, 1H), 5.55 — 5.43 (m, 2H), 5.19 (td, *J* = 7.1, 2.0 Hz, 1H), 4.31 (d, *J* = 8.8 Hz, 1H), 2.41 — 2.13 (m, 6H), 1.98 — 1.86 (m, 2H), 1.65 (d, *J* = 9.7 Hz, 1H), 0.97 (s, 9H), 0.233 (s, 3H), 0.227 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 152.5, 145.4, 137.5, 133.3, 132.8, 130.3, 130.0, 129.6, 125.6, 119.2, 117.5, 76.6, 75.6, 72.3, 32.5, 30.8, 30.1, 29.6, 26.0, 18.6, –3.8, –4.0; IR (film, cm^{-1}) 3326, 3065, 2954, 2928, 2856, 1730, 1572, 1465, 1106, 840; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{25}H_{35}IO_4SiNa$: 577.1242, found 577.1246.



(3*S*,4*S*,5*E*,9*E*)-4,14-Bis((*tert*-butyldimethylsilyl)oxy)-3-((*E*)-3-iodoallyl)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.48). A solution of alcohol **3.62** (76.9 mg, 0.142 mmol) and 2,6-lutidine (33 μL, 30.5 mg, 0.28 mmol) in DCM (1.4 mL) was cool to –78 °C and TBSOTf (65 μL, 75.2 mg, 0.28 mmol) was added. The solution was stirred at –78 °C for 3 h and then left in a 0 °C refrigerator overnight. EtOAc was added and the organic mixture was washed with saturated $NaHCO_3$ solution. The aqueous layer was re-extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **3.48** (72.3 mg, 78%) was isolated as a colorless oil. $[\alpha]_D^{22}$ = +79.8 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.54 (dt, *J* = 14.6, 7.3 Hz, 1H), 6.18 (d, *J* = 14.5 Hz, 1H), 6.13 (d, *J* = 15.8 Hz, 1H), 5.76 — 5.69 (m, 1H), 5.48 — 5.39 (m, 1H), 5.32 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.84 (ddd, *J* = 7.4, 6.2, 3.7 Hz, 1H), 4.46 (dd, *J* = 6.6, 3.7 Hz, 1H), 2.74 — 2.61 (m, 1H), 2.59 — 2.43 (m, 1H), 2.41 — 2.25 (m, 2H), 2.21 — 1.91 (m, 2H), 0.98 (s, 9H), 0.88 (s, 9H), 0.24 (s, 6H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 152.0, 141.8, 138.1, 133.5, 132.3, 131.5, 130.6, 130.0, 126.0, 119.1, 117.5, 78.6, 78.0, 72.9, 36.2, 31.1, 30.7, 26.1, 26.0, 18.44, 18.37, –3.5, –3.9, –4.1, –4.7.



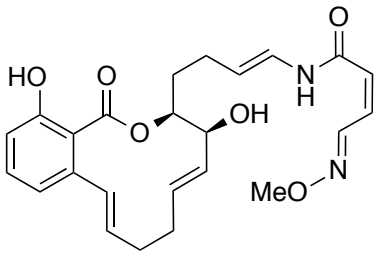
(3*S*,4*S*,5*E*,9*E*)-4,14-Bis((*tert*-butyldimethylsilyl)oxy)-3-((*E*)-4-iodo-3-buten-1-yl)-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (3.49). A solution of alcohol **3.63** (34.5 mg, 0.0622 mmol) and 2,6-lutidine (14 μL, 13 mg, 0.12 mmol) in DCM (0.6 mL) was cool to –78 °C and TBSOTf (29 μL, 33 mg, 0.12 mmol) was added. The solution was stirred at –78 °C for 3 h and then left in a 0 °C refrigerator overnight. EtOAc was added and the organic mixture was washed with saturated $NaHCO_3$ solution. The aqueous layer was re-extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 95:5 hexanes/EtOAc). Compound **3.49** (35.1 mg, 84%) was isolated as a colorless oil. $[\alpha]_D^{21}$ = +75 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 6.54 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.22 (d, *J* = 16.2 Hz, 1H), 6.04 (d, *J* = 14.4 Hz, 1H), 5.73 (dt, *J* = 15.9, 6.4 Hz, 1H), 5.47 — 5.33 (m, 2H), 4.95 (ddd, *J* = 7.8, 5.4, 3.6 Hz, 1H), 4.43 (dd, *J* = 5.5, 3.7 Hz, 1H), 2.37 — 2.01 (m, 6H), 1.94 — 1.80 (m, 2H), 0.97 (s, 9H), 0.89 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 152.2, 145.8, 138.1, 132.52, 132.50, 131.3, 131.2, 129.9, 126.2, 119.3, 117.6, 78.1, 75.2, 73.5, 32.7, 30.9, 30.7, 28.7, 26.1, 26.0, 18.6, 18.4, –3.8, –3.9, –4.0, –4.7; IR (film, cm^{-1}) 3066, 2955, 2929, 2857, 1728, 1465, 1107, 840, 779; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{31}H_{49}IO_4Si_2Na$: 691.2106, found 691.2120.



(2*Z*,4*E*)-*N*-((*E*)-3-((3*S*,4*S*,5*E*,9*E*)-4,14-Dihydroxy-1-oxo-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-3-yl)-1-propen-1-yl)-4-(methoxyimino)-2-butenamide (3.46). To a flask containing iodide **3.48** (71.4 mg, 0.109 mmol), amide **1.74**[91, 193] (69.8 mg, 0.545 mmol), CuI (41.5 mg, 0.218 mmol) and Cs_2CO_3 (178 mg, 0.545 mmol) was charged dimethylacetamide (DMA) (11 mL). The resultant mixture was degassed under high vacuum for 5 min before *N*,*N*'-dimethylethylenediamine (DMEDA) (59 μL, 48 mg, 0.55 mmol) was added. The reaction was stirred at room temperature for 24 h and then water was added. The crude mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude bis-TBS enamide was directly used in the next step without further purification.

The crude bis-TBS enamide was dissolved in THF (1 mL) and 5 M HF·Py solution (1:2:4.7 mixture of HF·Py (70% HF)/pyridine/THF, 1.3 mL, 6.5 mmol) was added. The reaction was stirred for 48 h and quenched with phosphate (pH = 7) buffer. The aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 40:60 hexanes/EtOAc). Compound **3.46** (18.6 mg, 40%) was isolated as a colorless syrup. $[\alpha]_D^{21}$ = –45.4 (*c* 0.372, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 9.90 (s, 1H), 9.33 (d, *J* = 10.4 Hz, 1H), 9.08 (d, *J* = 10.2 Hz, 1H), 7.27 (t, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 14.4, 10.3 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H),

6.79 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 15.8 Hz, 1H), 6.47 (t, J = 10.8 Hz, 1H), 6.12 (d, J = 11.5 Hz, 1H), 5.76 — 5.67 (m, 1H), 5.64 — 5.51 (m, 2H), 5.37 (dt, J = 14.4, 7.2 Hz, 1H), 5.17 (ddd, J = 7.7, 5.9, 3.2 Hz, 1H), 4.38 (s, 1H), 4.20 (d, J = 6.4 Hz, 1H), 3.87 (s, 3H), 2.74 — 2.67 (m, 1H), 2.60 — 2.50 (m, 1H), 2.42 – 2.20 (m, 4H); ^{13}C NMR (100 MHz, acetone-d_6) δ 170.4, 162.6, 159.4, 148.5, 141.1, 134.9, 134.2, 133.3, 132.5, 132.1, 131.5, 126.5, 126.1, 119.5, 117.0, 115.9, 109.8, 78.5, 72.5, 62.5, 32.5, 31.4, 30.7; IR (film, cm^{-1}) 3419, 2928, 2852, 1652, 1526, 1465, 1259, 1118, 1043, 966, 819; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{23}H_{26}N_2O_6Na$: 449.1683, found 449.1686.



(2*Z*,4*E*)-*N*-((*E*)-4-((3*S*,4*S*,5*E*,9*E*)-4,14-Dihydroxy-1-oxo-3,4,7,8-tetrahydro-1*H*-benzo[*c*][1]oxacyclododecin-3-yl)-1-buten-1-yl)-4-(methoxyimino)-2-butenamide (3.47). To a flask containing iodide **3.49** (18.6 mg, 0.0278 mmol), amide **1.74**[91, 193] (17.8 mg, 0.139 mmol), CuI (10.6 mg, 0.0556 mmol) and Cs_2CO_3 (45.3 mg, 0.139 mmol) was charged DMA (2.8 mL). The resultant mixture was degassed under high vacuum for 5 min before DMEDA (15 μL, 12 mg, 0.14 mmol) was added. The reaction was stirred at room temperature for 24 h and then water was added. The crude mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude bis-TBS enamide was directly used in the next step without further purification.

The crude bis-TBS enamide was dissolved in THF (0.28 mL) and 5 M HF·Py solution (1:2:4.7 mixture of HF·Py (70% HF)/pyridine/THF, 0.17 mL, 0.83 mmol) was added. The reaction was stirred for 48 h and quenched with phosphate (pH = 7) buffer. The aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (100:0 — 40:60 hexanes/EtOAc). Compound **3.47** (3.7 mg, 30%) was isolated as a white solid. $[\alpha]_D^{22}$ = –62 (*c* 0.050, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 9.01 (d, *J* = 10.3 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.12 — 7.05 (m, 1H), 6.88 — 6.77 (m, 3H), 6.65 (d, *J* = 15.7 Hz, 1H), 6.50 (dd, *J* = 11.3, 10.5 Hz, 1H), 5.84 (d, *J* = 11.5 Hz, 1H), 5.66 — 5.57 (m, 2H), 5.49 (dd, *J* = 15.7, 5.7 Hz, 1H), 5.28 (dt, *J* = 14.2, 7.1 Hz, 1H), 5.21 (ddd, *J* = 7.6, 5.4, 3.9 Hz, 1H), 4.36 (d, *J* = 5.0 Hz, 1H), 3.94 (s, 3H), 2.47 — 2.33 (m, 2H), 2.28 — 2.15 (m, 4H), 2.11 — 2.03 (m, 1H), 1.90 — 1.83 (m, 1H), 1.79 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 161.8, 161.4, 147.9, 141.9, 135.7, 135.3, 134.3, 130.0, 129.8, 126.1, 124.5, 123.1, 120.1, 118.5, 116.4, 113.4, 77.1, 72.7, 62.6, 32.7, 30.0, 29.2, 26.4; IR (film, cm^{-1}) 3306, 3044, 2928, 2855, 1652, 1603, 1450, 1217, 1122, 1045, 965, 821, 778; HRMS (ESI+) *m/z* calc'd for $[M+Na]^+$ $C_{24}H_{28}N_2O_6Na$: 463.1840, found 463.1840.

4.5 Cytotoxicity Assay

The human cancer cell lines leukemia (HL-60), breast (MCF-7), melanoma (SK-MEL-28 and SK-MEL-5) were obtained from the NCI and grown in normal RPMI 1640 culture medium containing 10% fetal bovine serum. The cells, in the exponential-phase maintenance culture, were dissociated with 0.25% trypsin and harvested by centrifugation

at 125 × g for 5 min. Trypsin was removed and the cells were resuspended in new culture medium. The cell density was adjusted to 1×10^5 and dispensed in triplicate on 96-well plates in 50 μL volumes. After incubation overnight at 37 °C under 5% CO_2, 50 μL of culture medium containing various concentrations of the tested compounds were added. Paclitaxel (Taxol®) and oximidine II were used as positive controls. After 48 h incubation, the relative cell viability in each well was determined by using the AlamarBlue Assay Kit. Optical densities were then measured photometrically (excitation = 530 nm, emission = 590 nm) on the plate reader. The IC_{50} of each compound was determined by fitting the relative viability of the cells to the drug concentration using a dose-response model.

Bibliography

1. Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45* (12), 2615-2623.

2. Butler, M. S. Natural products to drugs: Natural product-derived compounds in clinical trials. *Nat. Prod. Rep.* **2008**, *25* (3), 475-516.

3. Harvey, A. L. Natural products in drug discovery. *Drug Discov. Today* **2008**, *13* (19-20), 894-901.

4. Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. The exploration of macrocycles for drug discovery — an underexploited structural class. *Nat. Rev. Drug Discov.* **2008**, *7* (7), 608-624.

5. Marsault, E.; Peterson, M. L. Macrocycles are great cycles: Applications, opportunities, and challenges of synthetic macrocycles in drug discovery. *J. Med. Chem.* **2011**, *54* (7), 1961-2004.

6. Mallinson, J.; Collins, I. Macrocycles in new drug discovery. *Future Med. Chem.* **2012**, *4* (11), 1409-1438.

7. Butler, M. S.; Robertson, A. A. B.; Cooper, M. A. Natural product and natural product derived drugs in clinical trials. *Nat. Prod. Rep.* **2014**, *31* (11), 1612-1661.

8. Parenty, A.; Moreau, X.; Campagne, J. M. Macrolactonizations in the total synthesis of natural products. *Chem. Rev.* **2006**, *106* (3), 911-939.

9. Parenty, A.; Moreau, X.; Niel, G.; Campagne, J. M. Update 1 of: Macrolactonizations in the total synthesis of natural products. *Chem. Rev.* **2013**, *113* (1), PR1-40.

10. Hamada, Y.; Shioiri, T. Recent progress of the synthetic studies of biologically active marine cyclic peptides and depsipeptides. *Chem. Rev.* **2005**, *105* (12), 4441-4482.

11. Edmonds, D. J.; Johnston, D.; Procter, D. J. Samarium(II)-iodide-mediated cyclizations in natural product synthesis. *Chem. Rev.* **2004**, *104* (7), 3371-3403.

12. Gradillas, A.; Perez-Castells, J. Macrocyclization by ring-closing metathesis in the total synthesis of natural products: Reaction conditions and limitations. *Angew. Chem. Int. Ed.* **2006**, *45* (37), 6086-6101.

13. Duncton, M. A. J.; Pattenden, G. The intramolecular Stille reaction. *J. Chem. Soc., Perkin Trans. 1* **1999**, (10), 1235-1246.

14. Gallenkamp, D.; Fürstner, A. Stereoselective synthesis of *E*,*Z*-configured 1,3-dienes by ring-closing metathesis. Application to the total synthesis of lactimidomycin. *J. Am. Chem. Soc.* **2011**, *133* (24), 9232-9235.

15. Paquette, L. A.; Basu, K.; Eppich, J. C.; Hofferberth, J. E. Systematic analysis of the intramolecular competition associated with the ring closing metathesis of ene-diene systems of differing chain length with a pair of ruthenium catalysts. *Helv. Chim. Acta* **2002**, *85* (10), 3033-3051.

16. Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y. B.; Tong, W. P.; He, L. F.; Horwitz, S. B.; Danishefsky, S. J. Highly concise routes to epothilones: The total synthesis and evaluation of epothilone 490. *J. Am. Chem. Soc.* **2002**, *124* (33), 9825-9832.

17. Evano, G.; Schaus, J. V.; Panek, J. S. A convergent synthesis of the macrocyclic core of cytotrienins: Application of RCM for macrocyclization. *Org. Lett.* **2004**, *6* (4), 525-528.

18. Lu, K.; Huang, M. W.; Xiang, Z.; Liu, Y. X.; Chen, J. H.; Yang, Z. Development of a concise and diversity-oriented approach for the synthesis of plecomacrolides via the diene–ene RCM. *Org. Lett.* **2006**, *8* (6), 1193-1196.

19. Wagner, J.; Martin Cabrejas, L. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. Synthesis of macrolide analogues of sanglifehrin by RCM: Unique reactivity of a ruthenium carbene complex bearing an imidazol-2-ylidene ligand. *J. Org. Chem.* **2000**, *65* (26), 9255-9260.

20. Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. Stereoselective total synthesis of etnangien and etnangien methyl ester. *J. Org. Chem.* **2010**, *75* (8), 2429-2444.

21. Rössle, M.; Del Valle, D. J.; Krische, M. J. Synthesis of the cytotrienin A core via metal catalyzed C–C coupling. *Org. Lett.* **2011**, *13* (6), 1482-1485.

22. Neeman, I.; Fishelson, L.; Kashman, Y. Isolation of a new toxin from sponge *Latrunculia magnifica* in Gulf of Aquaba (Red Sea). *Mar. Biol.* **1975**, *30* (4), 293-296.

23. Kashman, Y.; Groweiss, A.; Shmueli, J. Latrunculin, a new 2-thiazolidinone macrolide from the marine sponge *Latrunculia magnifica*. *Tetrahedron Lett.* **1980**, *21* (37), 3629-3632.

24. Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. Latrunculins: Novel marine toxins that disrupt microfilament organization in cultured cells. *Science* **1983**, *219* (4584), 493-495.

25. Groweiss, A.; Shmueli, U.; Kashman, Y. Marine toxins of *Latrunculia magnifica*. *J. Org. Chem.* **1983**, *48* (20), 3512-3516.

26. Delmotte, P.; Delmotte-Plaque, J. A new antifungal substance of fungal origin. *Nature* **1953**, *171* (4347), 344-344.

27. Mirrington, R. N. R., E.; Shoppee, C. W.; Taylor, W. C.; Sternhell, S. The constitution of radicicol. *Tetrahedron Lett.* **1964**, *5* (7), 365-370.

28. McCapra, F.; Scott, A. L.; Delmotte, P.; Delmotte-Plaquee, J.; Bhacca, N. S. The constitution of monorden, an antibiotic with tranquilizing action. *Tetrahedron Lett.* **1964**, *5* (15), 869-875.

29. Cutler, H. G.; Arrendale, R. F.; Springer, J. P.; Cole, P. D.; Roberts, R. G.; Hanlin, R. T. Monorden from a novel source, *Neocosmospora tenuicristata*: Stereochemistry and plant growth regulatory properties. *Agric. Biol. Chem.* **1987**, *51* (12), 3331-3338.

30. Sugawara, K.; Nishiyama, Y.; Toda, S.; Komiyama, N.; Hatori, M.; Moriyama, T.; Sawada, Y.; Kamei, H.; Konishi, M.; Oki, T. Lactimidomycin, a new glutarimide group antibiotic. Production, isolation, structure and biological activity. *J. Antibiot.* **1992**, *45* (9), 1433-1441.

31. Ju, J.; Seo, J.-W.; Her, Y.; Lim, S.-K.; Shen, B. New lactimidomycin congeners shed insight into lactimidomycin biosynthesis in *Streptomyces amphibiosporus*. *Org. Lett.* **2007**, *9* (25), 5183-5186.

32. Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. Oximidines I and II: Novel antitumor macrolides from *Pseudomonas* sp. *J. Org. Chem.* **1999**, *64* (1), 153-155.

33. Fürstner, A.; Turet, L. Concise and practical synthesis of latrunculin A by ring-closing enyne–yne metathesis. *Angew. Chem. Int. Ed.* **2005**, *44* (22), 3462-3466.

34. Fürstner, A.; De Souza, D.; Turet, L.; Fenster, M. D. B.; Parra-Rapado, L.; Wirtz, C.; Mynott, R.; Lehmann, C. W. Total syntheses of the actin-binding macrolides latrunculin A, B, C, M, S and 16-*epi*-latrunculin B. *Chem. Eur. J.* **2007**, *13* (1), 115-134.

35. Garbaccio, R. M.; Danishefsky, S. J. Efficient asymmetric synthesis of radicicol dimethyl ether: A novel application of ring-forming olefin metathesis. *Org. Lett.* **2000**, *2* (20), 3127-3129.

36. Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. Concise asymmetric syntheses of radicicol and monocillin I. *J. Am. Chem. Soc.* **2001**, *123* (44), 10903-10908.

37. Barluenga, S.; Moulin, E.; Lopez, P.; Winssinger, N. Solution- and solid-phase synthesis of radicicol (monorden) and pochonin C. *Chem. Eur. J.* **2005**, *11* (17), 4935-4952.

38. Micoine, K.; Fürstner, A. Concise total synthesis of the potent translation and cell migration inhibitor lactimidomycin. *J. Am. Chem. Soc.* **2010**, *132* (40), 14064-14066.

39. Micoine, K.; Persich, P.; Llaveria, J.; Lam, M.-H.; Maderna, A.; Loganzo, F.; Fürstner, A. Total syntheses and biological reassessment of lactimidomycin, isomigrastatin and congener glutarimide antibiotics. *Chem. Eur. J.* **2013**, *19* (23), 7370-7383.

40. Wang, X.; Porco, J. A., Jr. Total synthesis of the salicylate enamide macrolide oximidine II. *J. Am. Chem. Soc.* **2003**, *125* (20), 6040-6041.

41. Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. Total synthesis of the salicylate enamide macrolide oximidine III: Application of relay ring-closing metathesis. *Angew. Chem. Int. Ed.* **2004**, *43* (27), 3601-3605.

42. Molander, G. A.; Dehmel, F. Formal total synthesis of oximidine II via a Suzuki-type cross-coupling macrocyclization employing potassium organotrifluoroborates. *J. Am. Chem. Soc.* **2004**, *126* (33), 10313-10318.

43. Coué, M.; Brenner, S. L.; Spector, I.; Korn, E. D. Inhibition of actin polymerization by latrunculin A. *FEBS Lett.* **1987**, *213* (2), 316-318.

44. Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. Latrunculins—novel marine macrolides that disrupt microfilament organization and affect cell growth: I. Comparison with cytochalasin D. *Cell Motil. Cytoskeleton* **1989**, *13* (3), 127-144.

45. Smith, A. B., III; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. Total synthesis of (+)-latrunculin A. *J. Org. Chem.* **1990**, *55* (13), 3977-3979.

46. Smith, A. B., III; Leahy, J. W.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. Total synthesis of the latrunculins. *J. Am. Chem. Soc.* **1992**, *114* (8), 2995-3007.

47. White, J. D.; Kawasaki, M. Total synthesis of (+)-latrunculin A. *J. Am. Chem. Soc.* **1990**, *112* (12), 4991-4993.

48. White, J. D.; Kawasaki, M. Total synthesis of (+)-latrunculin A, an ichthyotoxic metabolite of the sponge *Latrunculia magnifica*, and its C-15 epimer. *J. Org. Chem.* **1992**, *57* (20), 5292-5300.

49. Fürstner, A.; Kirk, D.; Fenster, M. D. B.; Aissa, C.; De Souza, D.; Muller, O. Diverted total synthesis: Preparation of a focused library of latrunculin analogues and evaluation of their actin-binding properties. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102* (23), 8103-8108.

50. Fürstner, A.; Kirk, D.; Fenster, M. B.; Aissa, C.; De Souza, D.; Nevado, C.; Tuttle, T.; Thiel, W.; Mueller, O. Latrunculin analogues with improved biological profiles by "diverted total synthesis": Preparation, evaluation, and computational analysis. *Chem. Eur. J.* **2007**, *13* (1), 135-149.

51. Schulte, T. W.; Akinaga, S.; Soga, S.; Sullivan, W.; Stensgard, B.; Toft, D.; Neckers, L. M. Antibiotic radicicol binds to the N-terminal domain of Hsp90 and shares important biologic activities with geldanamycin. *Cell Stress Chaperones* **1998**, *3* (2), 100-108.

52. Sharma, S. V.; Agatsuma, T.; Nakano, H. Targeting of the protein chaperone, HSP90, by the transformation suppressing agent, radicicol. *Oncogene* **1998**, *16* (20), 2639-2645.

53. Hayakawa, Y.; Tomikawa, T.; Shin-ya, K.; Arao, N.; Nagai, K.; Suzuki, K. Oximidine III, a new antitumor antibiotic against transformed cells from *Pseudomonas* sp. I. Taxonomy, fermentation, isolation, physico-chemical properties and biological activity. *J. Antibiot.* **2003**, *56* (11), 899-904.

54. Hayakawa, Y.; Tomikawa, T.; Shin-ya, K.; Arao, N.; Nagai, K.; Suzuki, K.; Furihata, K. Oximidine III, a new antitumor antibiotic against transformed cells from *Pseudomonas* sp. II. Structure elucidation. *J. Antibiot.* **2003**, *56* (11), 905-908.

55. Schneider, C. M.; Khownium, K.; Li, W.; Spletstoser, J. T.; Haack, T.; Georg, G. I. Synthesis of oximidine II by a copper-mediated reductive ene–yne macrocyclization. *Angew. Chem. Int. Ed.* **2011**, *50* (34), 7855-7857.

56. Coleman, R. S.; Garg, R. Stereocontrolled synthesis of the diene and triene macrolactones of oximidines I and II: Organometallic coupling versus standard macrolactonization. *Org. Lett.* **2001**, *3* (22), 3487-3490.

57. Scheufler, F.; Maier, M. E. Synthesis of a model system for the macrocyclic subunit of the oximidines. *Synlett* **2001**, (8), 1221-1224.

58. Fürstner, A.; Konetzki, I. Synthesis of 2-hydroxy-6-{[(16*R*)-β-δ-mannopyransyloxy]heptadecyl}benzoic acid, a fungal metabolite with $GABA_A$ ion channel receptor inhibiting properties. *Tetrahedron* **1996**, *52* (48), 15071-15078.

59. Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. Total synthesis of (–)-salicylihalamide. *Chem. Eur. J.* **2001**, *7* (24), 5286-5298.

60. Shen, R.; Porco, J. A., Jr. Synthesis of enamides related to the salicylate antitumor macrolides using copper-mediated vinylic substitution. *Org. Lett.* **2000**, *2* (9), 1333-1336.

61. Denmark, S. E.; Muhuhi, J. M. Development of a general, sequential, ring-closing metathesis/intramolecular cross-coupling reaction for the synthesis of polyunsaturated macrolactones. *J. Am. Chem. Soc.* **2010**, *132* (33), 11768-11778.

62. Haack, T.; Kurtkaya, S.; Snyder, J. P.; Georg, G. I. Studies toward the synthesis of oximidines I and II. *Org. Lett.* **2003**, *5* (26), 5019-5022.

63. Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. Synthesis of arylacetylene and vinylacetylene derivatives by copper-catalyzed reaction of aryl and vinyl iodides with terminal alkynes. *J. Org. Chem.* **1993**, *58* (17), 4716-4721.

64. Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. Simplified, "one-pot" procedure for the synthesis of $[(Ph_3P)CuH]_6$, a stable copper hydride for conjugate reductions. *Tetrahedron Lett.* **1988**, *29* (31), 3749-3752.

65. Stephens, R. D.; Castro, C. E. The substitution of aryl iodides with cuprous acetylides. A synthesis of tolanes and heterocyclics. *J. Org. Chem.* **1963**, *28* (12), 3313-3315.

66. Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. CuI-catalyzed Suzuki-Miyaura and Sonogashira cross-coupling reactions using DABCO as ligand. *J. Org. Chem.* **2007**, *72* (6), 2053-2057.

67. Ma, D.; Liu, F. CuI-catalyzed coupling reaction of aryl halides with terminal alkynes in the absence of palladium and phosphine. *Chem. Commun.* **2004**, (17), 1934-1935.

68. Deng, C.-L.; Xie, Y.-X.; Yin, D.-L.; Li, J.-H. Copper(II) acetate/1,4-diphenyl-1,4-diazabuta-1,3-diene catalyzed Sonogashira cross-coupling of aryl halides with terminal alkynes under aerobic and solvent-free conditions. *Synthesis* **2006**, (20), 3370-3376.

69. Tang, B.-X.; Wang, F.; Li, J.-H.; Xie, Y.-X.; Zhang, M.-B. Reusable Cu_2O/PPh_3/TBAB system for the cross-couplings of aryl halides and heteroaryl halides with terminal alkynes. *J. Org. Chem.* **2007**, *72* (16), 6294-6297.

70. Liu, F.; Ma, D. Assembly of conjugated enynes and substituted indoles via CuI/amino acid-catalyzed coupling of 1-alkynes with vinyl iodides and 2-bromotrifluoroacetanilides. *J. Org. Chem.* **2007**, *72* (13), 4844-4850.

71. Rendler, S.; Oestreich, M. Polishing a diamond in the rough: "Cu–H" catalysis with silanes. *Angew. Chem. Int. Ed.* **2007**, *46* (4), 498-504.

72. Deutsch, C.; Krause, N.; Lipshutz, B. H. CuH-catalyzed reactions. *Chem. Rev.* **2008**, *108* (8), 2916-2927.

73. Lipshutz, B. H. Rediscovering organocopper chemistry through copper hydride. It's all about the ligand. *Synlett* **2009**, (4), 509-524.

74. Churchill, M. R.; Bezman, S. A.; Osborn, J. A.; Wormald, J. Preparation and crystallographic characterization of a hexameric triphenylphosphinecopper hydride cluster. *J. Am. Chem. Soc.* **1971**, *93* (8), 2063-2065.

75. Chiu, P.; Li, Z.; Fung, K. C. M. An expedient preparation of Stryker's reagent. *Tetrahedron Lett.* **2003**, *44* (3), 455-457.

76. Lee, D.-W.; Yun, J. Direct synthesis of Stryker's reagent from a Cu(II) salt. *Tetrahedron Lett.* **2005**, *46* (12), 2037-2039.

77. Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. Selective hydride-mediated conjugate reduction of *α,β*-unsaturated carbonyl compounds using $[(Ph_3P)CuH]_6$. *J. Am. Chem. Soc.* **1988**, *110* (1), 291-293.

78. Brestensky, D. M.; Stryker, J. M. Regioselective conjugate reduction and reductive silylation of α,β-unsaturated aldehydes using $[(Ph_3P)CuH]_6$. *Tetrahedron Lett.* **1989**, *30* (42), 5677-5680.

79. Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. Conjugate reduction of polyfunctional α,β-unsaturated carbonyl compounds using $[(Ph_3P)CuH]_6$. Compatibility with halogen, sulfonate, and γ-oxygen and sulfur substituents. *Tetrahedron Lett.* **1990**, *31* (23), 3237-3240.

80. Mahoney, W. S.; Stryker, J. M. Hydride-mediated homogeneous catalysis. Catalytic reduction of *α,β*-unsaturated ketones using $[(Ph_3P)CuH]_6$ and H_2. *J. Am. Chem. Soc.* **1989**, *111* (24), 8818-8823.

81. Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. Convenient, efficient method for conjugate reductions using catalytic quantities of Cu(I). *Tetrahedron Lett.* **1998**, *39* (26), 4627-4630.

82. Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. Asymmetric conjugate reduction of *α,β*-unsaturated esters using a chiral phosphine-copper catalyst. *J. Am. Chem. Soc.* **1999**, *121* (40), 9473-9474.

83. Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. Synthesis of *β*-alkyl cyclopentanones in high enantiomeric excess via copper-catalyzed asymmetric conjugate reduction. *J. Am. Chem. Soc.* **2000**, *122* (28), 6797-6798.

84. Hughes, G.; Kimura, M.; Buchwald, S. L. Catalytic enantioselective conjugate reduction of lactones and lactams. *J. Am. Chem. Soc.* **2003**, *125* (37), 11253-11258.

85. Lipshutz, B. H.; Servesko, J. M. CuH-catalyzed asymmetric conjugate reductions of acyclic enones. *Angew. Chem. Int. Ed.* **2003**, *42* (39), 4789-4792.

86. Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. Asymmetric 1,4-reductions of hindered β-substituted cycloalkenones using catalytic SEGPHOS−ligated CuH. *Org. Lett.* **2004**, *6* (8), 1273-1275.

87. Daeuble, J. F.; McGettigan, C.; Stryker, J. M. Selective reduction of alkynes to *cis*-alkenes by hydrometallation using $[(Ph_3P)CuH]_6$. *Tetrahedron Lett.* **1990**, *31* (17), 2397-2400.

88. Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. Synthesis, structure, and alkyne reactivity of a dimeric (carbene)copper(I) hydride. *Organometallics* **2004**, *23* (14), 3369-3371.

89. Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. Copper-catalyzed highly selective semihydrogenation of non-polar carbon-carbon multiple bonds using a silane and an alcohol. *Adv. Synth. Catal.* **2012**, *354* (8), 1542-1550.

90. Whittaker, A. M.; Lalic, G. Monophasic catalytic system for the selective semireduction of alkynes. *Org. Lett.* **2013**, *15* (5), 1112-1115.

91. Schneider, C. M. Studies on oximidine II – total synthesis by an unprecedented reductive coupling. Ph.D. Dissertation, The University of Kansas, Lawrence, KS, 2009.

92. Spivey, A. C.; McKendrick, J.; Srikaran, R.; Helm, B. A. Solid-phase synthesis of an A-B loop mimetic of the Cε3 domain of human IgE: Macrocyclization by Sonogashira coupling. *J. Org. Chem.* **2003**, *68* (5), 1843-1851.

93. Balraju, V.; Reddy, D. S.; Periasamy, M.; Iqbal, J. Synthesis of conformationally constrained cyclic peptides using an intramolecular Sonogashira coupling. *J. Org. Chem.* **2005**, *70* (23), 9626-9628.

94. Koyama, Y.; Lear, M. J.; Yoshimura, F.; Ohashi, I.; Mashimo, T.; Hirama, M. Efficient construction of the kedarcidin chromophore ansamacrolide. *Org. Lett.* **2005**, *7* (2), 267-270.

95. Krauss, J.; Unterreitmeier, D.; Neudert, C.; Bracher, F. Short and efficient approach towards macrocyclic lactones based on a Sonogashira reaction. *Arch. Pharm.* **2005**, *338* (12), 605-608.

96. Hussain, A.; Yousuf, S. K.; Kumar, D.; Lambu, M.; Singh, B.; Maity, S.; Mukherjee, D. Intramolecular base-free Sonogashira reaction for the synthesis of benzannulated chiral macrocycles embedded in carbohydrate templates. *Adv. Synth. Catal.* **2012**, *354* (10), 1933-1940.

97. Niu, T. F.; Sun, M.; Lv, M. F.; Yi, W. B.; Cai, C. Synthesis of highly functionalized macrocycles by tandem multicomponent reactions and intramolecular Sonogashira cross-coupling. *Org. Biomol. Chem.* **2013**, *11* (41), 7232-7238.

98. Santandrea, J.; Bédard, A.-C.; Collins, S. K. Cu(I)-catalyzed macrocyclic Sonogashira-type cross-coupling. *Org. Lett.* **2014**, *16* (15), 3892-3895.

99. Lindlar, H. Ein neuer Katalysator für selektive Hydrierungen. *Helv. Chim. Acta* **1952**, *35* (2), 446-450.

100. Lindlar, H.; Dubuis, R. Palladium catalyst for partial reduction of acetylenes. *Org. Synth.* **1966**, *46*, 89-92.

101. Cortese, N. A.; Heck, R. F. Palladium-catalyzed reductions of *α,β*-unsaturated carbonyl compounds, conjugated dienes, and acetylenes with trialkylammonium formates. *J. Org. Chem.* **1978**, *43* (20), 3985-3987.

102. Weir, J. R.; Patel, B. A.; Heck, R. F. Palladium-catalyzed triethylammonium formate reductions. 4. Reduction of acetylenes to *cis*-monoenes and hydrogenolysis of tertiary allylic amines. *J. Org. Chem.* **1980**, *45* (24), 4926-4931.

103. Tani, K.; Ono, N.; Okamoto, S.; Sato, F. Palladiurn(0)-catalysed transfer hydrogenation of alkynes to *cis*-alkenes with HCO_2H–NEt_3. *J. Chem. Soc., Chem. Commun.* **1993**, (4), 386-387.

104. Hauwert, P.; Maestri, G.; Sprengers, J. W.; Catellani, M.; Elsevier, C. J. Transfer semihydrogenation of alkynes catalyzed by a zero-valent palladium N-heterocyclic carbene complex. *Angew. Chem. Int. Ed.* **2008**, *47* (17), 3223-3226.

105. Hauwert, P.; Boerleider, R.; Warsink, S.; Weigand, J. J.; Elsevier, C. J. Mechanism of Pd(NHC)-catalyzed transfer hydrogenation of alkynes. *J. Am. Chem. Soc.* **2010**, *132* (47), 16900-16910.

106. Shen, R.; Chen, T.; Zhao, Y.; Qiu, R.; Zhou, Y.; Yin, S.; Wang, X.; Goto, M.; Han, L.-B. Facile regio- and stereoselective hydrometalation of alkynes with a combination of carboxylic acids and group 10 transition metal complexes:

Selective hydrogenation of alkynes with formic acid. *J. Am. Chem. Soc.* **2011**, *133* (42), 17037-17044.

107. Drost, R. M.; Bouwens, T.; van Leest, N. P.; de Bruin, B.; Elsevier, C. J. Convenient transfer semihydrogenation methodology for alkynes using a Pd^{II}-NHC precatalyst. *Acs Catalysis* **2014**, *4* (5), 1349-1357.

108. Cao, H.; Chen, T.; Zhou, Y.; Han, D.; Yin, S.-F.; Han, L.-B. Copper-catalyzed selective semihydrogenation of terminal alkynes with hypophosphorous acid. *Adv. Synth. Catal.* **2014**, *356* (4), 765-769.

109. Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. Regioselective transformation of alkynes catalyzed by a copper hydride or boryl copper species. *Catal. Sci. Technol.* **2014**, *4* (6), 1699-1709.

110. Wang, G.-H.; Bin, H.-Y.; Sun, M.; Chen, S.-W.; Liu, J.-H.; Zhong, C.-M. Copper-catalyzed *Z*-selective semihydrogenation of alkynes with hydrosilane: a convenient approach to *cis*-alkenes. *Tetrahedron* **2014**, *70* (12), 2175-2179.

111. Semba, K.; Kameyama, R.; Nakao, Y. Copper-catalyzed semihydrogenation of alkynes to *Z*-alkenes. *Synlett* **2015**, *26* (3), 318-322.

112. Ulan, J. G.; Maier, W. F.; Smith, D. A. Rational design of a heterogeneous pd catalyst for the selective hydrogenation of alkynes. *J. Org. Chem.* **1987**, *52* (14), 3132-3142.

113. van Laren, M. W.; Elsevier, C. J. Selective homogeneous palladium(0)-catalyzed hydrogenation of alkynes to (*Z*)-alkenes. *Angew. Chem. Int. Ed.* **1999**, *38* (24), 3715-3717.

114. Molnár, Á.; Sárkány, A.; Varga, M. Hydrogenation of carbon-carbon multiple bonds: chemo-, regio- and stereo-selectivity. *J. Mol. Catal. A: Chem.* **2001**, *173* (1-2), 185-221.

115. Lin, J.; Nikaido, M. M.; Clark, G. Convergence with mutual kinetic resolution. 1. Studies defining methodology for the taxol C/D ring fragment and synthesis of the A ring fragment. *J. Org. Chem.* **1987**, *52* (17), 3745-3752.

116. Ju, J.; Rajski, S. R.; Lim, S.-K.; Seo, J.-W.; Peters, N. R.; Hoffmann, F. M.; Shen, B. Lactimidomycin, iso-migrastatin and related glutarimide-containing 12-membered macrolides are extremely potent inhibitors of cell migration. *J. Am. Chem. Soc.* **2009**, *131* (4), 1370-1371.

117. Schneider-Poetsch, T.; Ju, J.; Eyler, D. E.; Dang, Y.; Bhat, S.; Merrick, W. C.; Green, R.; Shen, B.; Liu, J. O. Inhibition of eukaryotic translation elongation by cycloheximide and lactimidomycin. *Nat. Chem. Biol.* **2010**, *6* (3), 209-217.

118. de Loubresse, N. G.; Prokhorova, I.; Holtkamp, W.; Rodnina, M. V.; Yusupova, G.; Yusupov, M. Structural basis for the inhibition of the eukaryotic ribosome. *Nature* **2014**, *513* (7519), 517-522.

119. Larsen, B. J.; Sun, Z.; Nagorny, P. Synthesis of eukaryotic translation elongation inhibitor lactimidomycin via Zn(II)-mediated Horner–Wadsworth–Emmons macrocyclization. *Org. Lett.* **2013**, *15* (12), 2998-3001.

120. Nagasawa, T.; Kuwahara, S. Formal total synthesis of lactimidomycin. *Org. Lett.* **2013**, *15* (12), 3002-3005.

121. Pilli, R. A.; de Andrade, C. K. Z.; Souto, C. R. O.; de Meijere, A. Total synthesis of 10-deoxymethynolide the aglycon of the macrolide antibiotic 10-deoxymethymycin. *J. Org. Chem.* **1998**, *63* (22), 7811-7819.

122. Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. Oxidative cyclizations in a nonpolar solvent using molecular oxygen and studies on the stereochemistry of oxypalladation. *J. Am. Chem. Soc.* **2005**, *127* (50), 17778-17788.

123. Omura, K.; Swern, D. Oxidation of alcohols by "activated" dimethyl sulfoxide. A preparative, steric and mechanistic study. *Tetrahedron* **1978**, *34* (11), 1651-1660.

124. Schöllkopf, U. Neuere präparative Methoden der organischen Chemie II 13. Carbonyl-Olefinierung mit Triphenyl-phosphin-methylenen Wittig-Reaktion. *Angew. Chem.* **1959**, *71* (8), 260-273.

125. Wu, Y.; Gao, J. Total synthesis of (+)-brefeldin A. *Org. Lett.* **2008**, *10* (8), 1533-1536.

126. Schmauder, A.; Müller, S.; Maier, M. E. Concise route to defined stereoisomers of the hydroxy acid of the chondramides. *Tetrahedron* **2008**, *64* (27), 6263-6269.

127. Jahns, C.; Hoffmann, T.; Müller, S.; Gerth, K.; Washausen, P.; Höfle, G.; Reichenbach, H.; Kalesse, M.; Müller, R. Pellasoren: Structure elucidation, biosynthesis, and total synthesis of a cytotoxic secondary metabolite from *Sorangium cellulosum*. *Angew. Chem. Int. Ed.* **2012**, *51* (21), 5239-5243.

128. Ho, G.-J.; Mathre, D. J. Lithium-initiated imide formation. A simple method for N-acylation of 2-oxazolidinones and bornane-2,10-sultam. *J. Org. Chem.* **1995**, *60* (7), 2271-2273.

129. Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. Remote asymmetric induction with vinyl ketene silyl *N*,*O*-acetal. *J. Am. Chem. Soc.* **2004**, *126* (42), 13604-13605.

130. Shirokawa, S.-i.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. Total synthesis of khafrefungin using highly stereoselective vinylogous mukaiyama aldol reaction. *Org. Lett.* **2007**, *9* (5), 849-852.

131. Marshall, J. A.; Wang, X. J. Synthesis of enantioenriched homopropargylic alcohols through diastereoselective S_E' additions of chiral allenylstannanes to aldehydes. *J. Org. Chem.* **1992**, *57* (4), 1242-1252.

132. Marshall, J. A. Chiral allylic and allenic stannanes as reagents for asymmetric synthesis. *Chem. Rev.* **1996**, *96* (1), 31-47.

133. Marshall, J. A. Synthesis and reactions of allylic, allenic, vinylic, and arylmetal reagents from halides and esters via transient organopalladium intermediates. *Chem. Rev.* **2000**, *100* (8), 3163-3185.

134. Marshall, J. A.; Eidam, P.; Eidam, H. S. (*R*)- and (*S*)-4-TIPS-3-butyn-2-ol. Useful precursors of chiral allenylzinc and indium reagents. *J. Org. Chem.* **2006**, *71* (13), 4840-4844.

135. Marshall, J. A. Chiral allylic and allenic metal reagents for organic synthesis. *J. Org. Chem.* **2007**, *72* (22), 8153-8166.

136. Marshall, J. A.; Grant, C. M. Preparation of chiral allenylmetal reagents from enantioenriched allenyl iodides and propargylic mesylates. A comparison of indium, bismuth, and tin derivatives. *J. Org. Chem.* **1999**, *64* (22), 8214-8219.

137. Marshall, J. A.; Chobanian, H. Lipase-catalyzed resolution of 4-trimethylsilyl-3-butyn-2-ol and conversion of the (*R*)-enantiomer to (*R*)-3-butyn-2-yl mesylate and (*P*)-1-tributylstannyl-1,2-butadiene. *Org. Synth.* **2005**, *82*, 43-54.

138. Tan, Z.; Negishi, E. Selective synthesis of epolactaene featuring efficient construction of methyl (*Z*)-2-iodo-2-butenoate and (2*R*,3*S*,4*S*)-2-trimethylsilyl-2,3-epoxy-4-methyl-*γ*-butyrolactone. *Org. Lett.* **2006**, *8* (13), 2783-2785.

139. Mitsunobu, O.; Yamada, M. Preparation of esters of carboxylic and phosphoric acid *via* quaternary phosphonium salts. *Bull. Chem. Soc. Jpn.* **1967**, *40* (10), 2380-2382.

140. Mitsunobu, O. The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis* **1981**, (1), 1-28.

141. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *N*,*N*,*N*',*N*'-Tetramethylazodicarboxamide (TMAD), a new versatile reagent for mitsunobu reaction. Its application to synthesis of secondary amines. *Chem. Lett.* **1994**, (3), 539-542.

142. Yet, L. Chemistry and biology of salicylihalamide A and related compounds. *Chem. Rev.* **2003**, *103* (11), 4283-4306.

143. Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. Salicylihalamides A and B, novel cytotoxic macrolides from the marine sponge *Haliclona* sp. *J. Org. Chem.* **1997**, *62* (23), 8188-8192.

144. Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. Salicylihalamides A and B, novel cytotoxic macrolides from the marine sponge *Haliclona* sp. (Erratum for Vol. 62, Pg. 8188-8192, 1997). *J. Org. Chem.* **2001**, *66* (4), 1532-1532.

145. Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H.; Boyd, M. R. Lobatamides A and B, novel cytotoxic macrolides from the tunicate *Aplidium lobatum*. *J. Org. Chem.* **1997**, *62* (26), 8968-8969.

146. McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H.; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. The lobatamides, novel cytotoxic macrolides from southwestern Pacific tunicates. *J. Org. Chem.* **1998**, *63* (22), 7805-7810.

147. Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. Novel lactone compounds from *Mortierella verticillata* that induce the human low density lipoprotein receptor gene: Fermentation, isolation, structural elucidation and biological activities. *J. Antibiot.* **1998**, *51* (1), 14-20.

148. Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. Apicularens A and B, new cytostatic macrolides from *Chondromyces* species (Myxobacteria): Production, physico-chemical and biological properties. *J. Antibiot.* **1998**, *51* (12), 1075-1080.

149. Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. Apicularen A and B, cytotoxic 10-membered lactones with a novel mechanism of action from *Chondromyces* species (myxobacteria): Isolation, structure elucidation, and biosynthesis. *Eur. J. Org. Chem.* **2000**, (6), 913-919.

150. Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. W.; Hayakawa, Y.; Beutler, J. A.; McKee, T. C.; Bowman, B. J.; Bowman, E. J. Discovery of a novel antitumor benzolactone enamide class that selectively inhibits mammalian vacuolar-type (H^+)-ATPases. *J. Pharmacol. Exp. Ther.* **2001**, *297* (1), 114-120.

151. Boyd, M. R.; Paull, K. D. Some practical considerations and applications of the National Cancer Institute *in vitro* anticancer drug discovery screen. *Drug Dev. Res.* **1995**, *34* (2), 91-109.

152. Nishi, T.; Forgac, M. The vacuolar (H^+)-ATPases — nature's most versatile proton pumps. *Nat. Rev. Mol. Cell Biol.* **2002**, *3* (2), 94-103.

153. Forgac, M. Vacuolar ATPases: rotary proton pumps in physiology and pathophysiology. *Nat. Rev. Mol. Cell Biol.* **2007**, *8* (11), 917-929.

154. Lafourcade, C.; Sobo, K.; Kieffer-Jaquinod, S.; Garin, J.; van der Goot, F. G. Regulation of the V-ATPase along the endocytic pathway occurs through reversible subunit association and membrane localization. *PLoS One* **2008**, *3* (7), e2758.

155. Wieczorek, H.; Brown, D.; Grinstein, S.; Ehrenfeld, J.; Harvey, W. R. Animal plasma membrane energization by proton-motive V-ATPases. *Bioessays* **1999**, *21* (8), 637-648.

156. Farina, C.; Gagliardi, S. Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents. *Drug Discov. Today* **1999**, *4* (4), 163-172.

157. Hinton, A.; Bond, S.; Forgac, M. V-ATPase functions in normal and disease processes. *Pflugers Arch. - Eur. J. Physiol.* **2009**, *457* (3), 589-598.

158. Pérez-Sayáns, M.; Somoza-Martín, J. M.; Barros-Angueira, F.; Rey, J. M.; García-García, A. V-ATPase inhibitors and implication in cancer treatment. *Cancer Treat. Rev.* **2009**, *35* (8), 707-713.

159. Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. Total synthesis and initial structure−Function analysis of the potent V-ATPase inhibitors salicylihalamide A and related compounds. *J. Am. Chem. Soc.* **2002**, *124* (13), 3245-3253.

160. Xie, X.-S.; Padron, D.; Liao, X.; Wang, J.; Roth, M. G.; De Brabander, J. K. Salicylihalamide A inhibits the V_0 sector of the V-ATPase through a mechanism distinct from bafilomycin A_1. *J. Biol. Chem.* **2004**, *279* (19), 19755-19763.

161. Lebreton, S.; Xie, X.-S.; Ferguson, D.; De Brabander, J. K. Ring-closing metathesis: a powerful tool for the synthesis of simplified salicylihalamide-based V-ATPase inhibitors. *Tetrahedron* **2004**, *60* (43), 9635-9647.

162. Smith, A. B., III; Zheng, J. Total synthesis of (–)-salicylihalamide A and related congeners. *Tetrahedron* **2002**, *58* (32), 6455-6471.

163. Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. Synthesis and V-ATPase inhibition of simplified lobatamide analogues. *Org. Lett.* **2002**, *4* (18), 3103-3106.

164. Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. Lobatamide C: Total synthesis, stereochemical assignment, preparation of simplified analogues, and V-ATPase inhibition studies. *J. Am. Chem. Soc.* **2003**, *125* (26), 7889-7901.

165. Shen, R.; Inoue, T.; Forgac, M.; Porco, J. A., Jr. Synthesis of photoactivatable acyclic analogues of the lobatamides. *J. Org. Chem.* **2005**, *70* (9), 3686-3692.

166. Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. Total synthesis and biological evaluation of apicularen A and synthetic analogs. *Tetrahedron Lett.* **2001**, *42* (7), 1217-1220.

167. Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A.; Giannakakou, P. Total synthesis and biological evaluation of (–)apicularen A and analogues thereof. *Chem. Eur. J.* **2003**, *9* (24), 6177-6191.

168. Petri, A. F.; Sasse, F.; Maier, M. E. Synthesis and biological evaluation of apicularen A analogues. *Eur. J. Org. Chem.* **2005**, (9), 1865-1875.

169. Yang, K. L.; Blackman, B.; Diederich, W.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Ahn, Y. M.; Georg, G. I. Formal total synthesis of (+)-salicylihalamides A and B: A combined chiral pool and RCM strategy. *J. Org. Chem.* **2003**, *68* (26), 10030-10039.

170. Yang, K. L.; Haack, T.; Blackman, B.; Diederich, W. E.; Roy, S.; Pusuluri, S.; Georg, G. I. Enantiospecific formal total syntheses of (–)-salicylihalamides A and B from D-Glucose and L-rhamnose. *Org. Lett.* **2003**, *5* (21), 4007-4009.

171. Haack, T.; Haack, K.; Diederich, W. E.; Blackman, B.; Roy, S.; Pusuluri, S.; Georg, G. I. Formal total syntheses of the (–)-salicylihalamides A and B from D-glucose and L-rhamnose. *J. Org. Chem.* **2005**, *70* (19), 7592-7604.

172. Khownium, K. Synthesis and evaluation of modified oximidine analogues as anticancer agents and of terephthalaldehyde-*bis*-guanylhydrazones as endotoxin sequestering agents. Ph.D. Dissertation, The University of Kansas, Lawrence, KS, 2009.

173. Palmer, J. T.; Rasnick, D.; Klaus, J. L.; Bromme, D. Vinyl sulfones as mechanism-based cysteine protease inhibitors. *J. Med. Chem.* **1995**, *38* (17), 3193-3196.

174. Klebe, G.; Abraham, U.; Mietzner, T. Molecular similarity indexes in a comparative analysis (CoMSIA) of drug molecules to correlate and predict their biological activity. *J. Med. Chem.* **1994**, *37* (24), 4130-4146.

175. Blackman, B.; Georg, G. I.; Lushington, G. H. CoMSIA/QSAR models for vacuolar (H^+) ATPase inhibition by selected benzoate and benzolactone species. *Letters in Drug Design & Discovery* **2006**, *3* (2), 104-107.

176. Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. The use of phosphine ligands to control the regiochemistry of Pd-catalyzed hydrostannations of 1-alkynes: Synthesis of (*E*)-1-tributylstannyl-1-alkenes. *Org. Lett.* **2008**, *10* (5), 861-864.

177. Parikh, J. R.; Doering, W. v. E. Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide. *J. Am. Chem. Soc.* **1967**, *89* (21), 5505-5507.

178. Echavarren, A. M.; Stille, J. K. Palladium-catalyzed coupling of aryl triflates with organostannanes. *J. Am. Chem. Soc.* **1987**, *109* (18), 5478-5486.

179. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and activity of a new generation of ruthenium-based olefin metathesis catalysts coordinated with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligands. *Org. Lett.* **1999**, *1* (6), 953-956.

180. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. Specific removal of O-methoxybenzyl protection by DDQ oxidation. *Tetrahedron Lett.* **1982**, *23* (8), 885-888.

181. Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* **1983**, *48* (22), 4155-4156.

182. Takai, K.; Nitta, K.; Utimoto, K. Simple and selective method for RCHO → (*E*)-RCH=CHX conversion by means of a CHX_3-$CrCl_2$ system. *J. Am. Chem. Soc.* **1986**, *108* (23), 7408-7410.

183. Evans, D. A.; Black, W. C. Total synthesis of (+)-A83543A [(+)-lepicidin A]. *J. Am. Chem. Soc.* **1993**, *115* (11), 4497-4513.

184. Lee, A. S.-Y.; Hu, Y.-J.; Chu, S.-F. A simple and highly efficient deprotecting method for methoxymethyl and methoxyethoxymethyl ethers and methoxyethoxymethyl esters. *Tetrahedron* **2001**, *57* (11), 2121-2126.

185. Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. Copper-catalyzed coupling of amides and carbamates with vinyl halides. *Org. Lett.* **2003**, *5* (20), 3667-3669.

186. Palimkar, S. S.; Uenishi, J. i. Total synthesis of (–)-apicularen A. *Org. Lett.* **2010**, *12* (18), 4160-4163.

187. Grafton, M. W.; Farrugia, L. J.; Senn, H. M.; Sutherland, A. Discovery of a multi-bond forming, four-step tandem process: construction of drug-like polycyclic scaffolds. *Chem. Commun.* **2012**, *48* (64), 7994-7996.

188. Karabelas, K.; Hallberg, A. Synthesis of (*E*)-(2-arylethenyl)silanes by palladium-catalyzed arylation of vinylsilanes in the presence of silver nitrate. *J. Org. Chem.* **1986**, *51* (26), 5286-5290.

189. Rozkiewicz, D. I.; Janczewski, D.; Verboom, W.; Ravoo, B. J.; Reinhoudt, D. N. "Click" chemistry by microcontact printing. *Angew. Chem. Int. Ed.* **2006**, *45* (32), 5292-5296.

190. Iafe, R. G.; Chan, D. G.; Kuo, J. L.; Boon, B. A.; Faizi, D. J.; Saga, T.; Turner, J. W.; Merlic, C. A. Cyclization strategies to polyenes using Pd(II)-catalyzed couplings of pinacol vinylboronates. *Org. Lett.* **2012**, *14* (16), 4282-4285.

191. Darwish, A.; Chong, J. M. Synthesis of *E*-vinyl iodides via Pd-catalyzed hydrostannation of terminal alkynes. *Tetrahedron* **2012**, *68* (2), 654-658.

192. Liu, H.; Wang, L.; Tong, X. Palladium-catalyzed Heck-type reaction of oxime ether bearing a pendant vinyl iodide moiety. *Chem. Commun.* **2011**, *47* (44), 12206-12208.

193. Coleman, R. S.; Liu, P.-H. Divergent and stereocontrolled synthesis of the enamide side chains of oximidines I/II/III, salicylihalamides A/B, lobatamides A/D, and CJ-12,950. *Org. Lett.* **2004**, *6* (4), 577-580.