TOTAL SYNTHESIS OF POLYENE NATURAL PRODUCTS LUCILACTAENE AND GYMNOCONJUGATIN: DEVELOPMENT OF A BORON-TIN LINCHPIN

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
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By

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*****

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ABSTRACT

Natural products possessing multiple carbon-carbon double bonds, known as polyenes, are widely distributed among plant, animal, bacterial and fungal species. Many of these compounds possess potentially useful biological activity. Polyenes from fungi of the genus *Fusarium* sp. have been a rich source of biologically active natural products, including the polyene lucilactaene.

In this thesis, the development of a hetero-*bis*-metalated 1,3-butadiene is described for the use in the linchpin coupling of synthetic fragments of the polyene side chain of the antitumor agent, lucilactaene. Sequential Stille and Suzuki-Miyaura couplings interpolate this unique boron/tin diene into the pentaene chain.

Using this strategy, the total synthesis of lucilactaene was accomplished efficiently, in just eight linear steps. This strategy was also made use of in the synthesis of two polyenylfurans, gymnoconjugatin A and B.
Dedicated to Dr. Minaz and Father Leopold.
ACKNOWLEDGMENTS

I wish to thank Robert S. Coleman, my adviser, for his intellectual support, encouragement, and enthusiasm for the work that made this thesis possible. This gratitude is further extended to the members of the Coleman group, past and present, who contributed time, experience, and advice in my research.
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PUBLICATIONS

Research Publications

   Coupling Reactions of a Hetero bis-Metallated 1,3-Butadiene. Rapid, One-Pot

2. Robert S. Coleman, Matthew C. Walczak, and Erica L. Campbell, “Total Synthesis
   of Lucilactaene, A Cell Cycle Inhibitor Active in p53-Inactive Cells,” *Journal of the


4. Matthew C. Walczak, Robert S. Coleman, “Tributyl ((1E,3E)-4-(4,4,5,5)-
tetramethyl)-1,2,3-dioxaborolan-2-yl)buta-1,3-dienyl)stannane,” in *Encyclopedia of

FIELDS OF STUDY

Major Field: Chemistry
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α  alpha
[α]  specific rotation
Ac  acetyl
br  broad (IR and NMR)
β  beta
n-Bu  normal-butyl
t-Bu  tert-butyl
Bz  benzoyl
°C  degrees Celsius
calc  calculated
COSY  correlation spectroscopy
CSA  (1S)-(+)10-camphorsulfonic acid
δ  chemical shift in parts per million downfield from tetramethylsilane
d  doublet (spectra); day(s)
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ  2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT  distortionless enhancement by polarization transfer
DIBAL  diisobutylaluminum hydride
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</tr>
<tr>
<td>DMD</td>
<td>dimethyldioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
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<tr>
<td>equiv.</td>
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<tr>
<td>Et</td>
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<td>γ</td>
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<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz (NMR)</td>
</tr>
<tr>
<td>k</td>
<td>kilo</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>milli; multiplet (NMR)</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>M</td>
<td>moles per liter</td>
</tr>
<tr>
<td>Mc</td>
<td>chloromethylsulfonyl</td>
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<tr>
<td>Me</td>
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<td>MHz</td>
<td>megahertz</td>
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<td>min</td>
<td>minute(s)</td>
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<tr>
<td>mol</td>
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</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry; molecular sieves</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio (MS)</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium hexamethyldisilazide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidinone</td>
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<tr>
<td>NMR</td>
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</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
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<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
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<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>p-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
</tbody>
</table>
s  singlet (NMR); second(s)
SEM  2-(trimethylsilyl)ethoxymethyl
t  tertiary (tert)
t  triplet (NMR)
TBAF  tetrabutylammonium fluoride
TBAI  tetrabutylammonium iodide
TBDPS  tert-butyldiphenylsilyl
TBS  t-butyldimethylsilyl
TES  triethylsilyl
Tf  trifluoromethanesulfonyl
TFP  tris(o-furyl)phosphine
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
Tr  triphenylmethyl
Ts  tosyl, p-toluenesulfonyl
CHAPTER 1

INTRODUCTION TO POLYENES

1.1 Polyene natural products

Natural products possessing multiple carbon-carbon double bonds are widely distributed among plant, animal, bacterial and fungal species.\(^1\) Biologically active polyenes from bacterial sources, most typically *Streptomyces*, include such well-studied compounds as amphotericin B (1), among many other oxopolyene macrolides (Figure 1.1).\(^2\) These compounds are usually of polyketide origin and have been well studied synthetically. In contrast, polyenes from fungi are more often produced by the isoprenoid pathway, and include compounds such as fumigillin (2)\(^3\) and rhizoxin (3).\(^4\)

Slime molds produce cytotoxic polyene chromophores such as fuligrobin A, likely as a chemical defense mechanism or to function as photoreceptors, although compounds from these organisms are not well studied.\(^5\) Plants species produce a diverse array of polyene compounds, including what is arguably the most widely known group of polyenes, the carotenoids.\(^6\)
Marine organisms also produce a variety of polyene natural products, many of which are vividly colored and often possess potent toxicity as a means of chemical defense against larger marine species. The class of highly evolved sea-slugs known as opisthobranchia secretes a highly toxic polyenic ketone navanone (6) as an alarm pheromone in the absence of the hard shell possessed by many other gastropods (Figure 1.2). Marine dinoflagellates, such as *Amphidinium*, produce powerful nerve toxins that led to “red tides” or harmful algae blooms, and have been a rich source of secondary
metabolites. The antifungal polyene amphidinol 3 (8) is a prominent example that has been the target of many synthetic studies.

Polyene metabolites of animal origin fall into two major classes: retinoids such as retinol (7), from the isoprenoid pathway, and eicosanoids such as prostaglandin F$_{2\alpha}$ (9), from the polyketide pathway. The retinoids possess a variety of biological activities depending on the functional group appended to the tail and the geometry of the polyene chain. Over 3000 tons of retinol or vitamin A, is produced annually and sales world-wide exceed $360 million (US).

Figure 1.2 Polyene natural products
1.2 Lucilactaene and *Fusarium* metabolites

Over the past few decades, a variety of biologically active natural products possessing a $\gamma$-lactam nucleus with a polyunsaturated side-chain have been isolated from the genus *Fusarium*. In 2001, Osada and co-workers reported the isolation of lucilactaene (10) (along with NG-391 (17) and NG-393, a $Z$ stereoisomer of 17 at the C-8 position) from the fungal strain *Fusarium* sp. RK97-94, which was obtained from the leaf of an unidentified plant collected at Mt. Inasa, Nagaski Prefecture, Japan (Figure 1.3). Lucilactaene (10) is related to other *Fusarium* natural products, including epolactaene (11), fusarins A (12), D (13), C (14), and F (15), L-755,807 (16),17 and NG-391 (17), all of which possess a $\gamma$-lactam nucleus with a polyunsaturated side-chain.
The structure and relative stereochemistry of lucilactaene (10) was elucidated by NMR spectral analysis, including a variety of two-dimensional techniques (COSY, HMBC and NOESY). The molecular formula was established by high-resolution FABMS. The E configuration of the five olefinic bonds was established through the high-field carbon shifts for the three allylic methyls and large vicinal coupling constants ($J_{6,7} = 15.1$ Hz and $J_{8,9} = 14.7$ Hz) along with NOEs between C1-H and C4-H, C4-H and C6-H, C6-H and C8-H, C8-H and C10-H, and C7-H and C10-H. The relative stereochemistry of
was established as C13S*, C14R*, C15S* based on NOEs between C13-H and C10-H, C14-H and C15-OH and N16-H, and C16-H and C15-OH and C18-H. Hayashi and co-workers later demonstrated that lucilactaene occurs naturally as the racemate.\textsuperscript{19}

It was demonstrated that lucilactaene induces cell cycle arrest in a p53-independent manner in H1299/tsp53 cells possessing a temperature sensitive p53 protein.\textsuperscript{20} The tumor suppressor gene p53, which controls important cellular processes such as apoptosis and DNA repair,\textsuperscript{21} is often mutated and therefore inactive in many human tumors.\textsuperscript{22} In cells lacking function p53, control of cell division is lost, and such cells are often resistant to chemotherapy because of defects in the damage-induced apoptotic pathway due to lack of p53 function.\textsuperscript{23} Small molecules that could reestablish or mimic p53 function could be useful in cancer therapy by restoring the normal apoptotic p53 response to DNA damage.\textsuperscript{24}

The reported biological activities for the other *Fusarium* metabolites is exceptionally varied, ranging from neurotrophic (NG-391), mutagenic (fusarin C), and neuritogenic (epolactaene), as well as being reported to be potent mycotoxins. Considering the similarity of structures amongst this family of compounds raises questions as to the mechanism(s) of action responsible for the observed biological activities.

Studies involving epolactaene demonstrated two possible mechanisms of action. Osada and co-workers found that the tertiary butyl ester derivative of epolactaene covalently binds to Hsp60 Cys\textsuperscript{442}.\textsuperscript{25} Hsp60 is a member of the heat-shock protein family that mediates protein folding (chaperone activity), and that has been shown to play a role in apoptosis. This same group performed a structure-activity study, finding that the
lactam moiety, alkyl side chain length, and α,β- unsaturated ketone are important for the Hsp60 activity.\textsuperscript{26} Kobayashi and co-workers demonstrated that epolactaene inhibits DNA polymerases α and β,\textsuperscript{27} although the basis of inhibition is unclear.\textsuperscript{28} This group also confirmed the importance of the alkyl side chain length.\textsuperscript{29}

1.3 Gymnoconjugatin

In early 2006, a report from Capon and co-workers detailed the isolation and structure determination of two polynylfurans, named gymnoconjugatins A (18) and B (19), from the soil microbe \textit{Gymnoascus reessii} (Figure 1.4).\textsuperscript{30} These new compounds were isolated along with several known polynylpyrroles, including rumbrin (22),\textsuperscript{31} 12\textit{E}-isorumbrin (21) and auxarconjugatin A (20).\textsuperscript{32} The structure of these natural products are characterized by tetraene flanked at either end by a furan/pyrrole and a pyrone. This same species produces the structurally unrelated prenylated diketopiperazine, roquefortine E (23)\textsuperscript{33} and the butenolides gymnoascolides A-C.\textsuperscript{34} In addition to the interesting structures of the gymnoconjugatins, structure determination and bioassays were hampered by the small quantities of compounds that were isolated, and gymnoconjugatin B was not fully characterized. Auxarconjugatin A and 12\textit{E}-isorumbrin, which possesses the chloropyrrole, showed significant cytotoxic properties against an NS-1 cell line (LD\textsubscript{99} 2.3 and 0.41 μg/mL respectively) while gymnoconjugatin A was far less potent (LD\textsubscript{99} 50 μg/mL). These results may suggest that the chloropyrrole substituent plays an important role in the biological activity.
1.4 Synthesis of polyenes: general strategies

Conjugated dienes and polyenes represent an important functionality among organic compounds and a significant part of modern synthetic chemistry has focused on their synthesis. The most common strategies for the synthesis of polyenes include elimination, the Wittig and the Horner-Wadsworth-Emmons (HWE) reactions, and the cross-coupling method (Figure 1.5). Strategic considerations for their synthesis must focus on difficulty that most commonly arises during the assembly of dienes and polyenes, the stereoselective construction of the alkene, as separation of the cis and trans
isomers by flash chromatography can often be extremely tedious and yield lowering, if separating the isomers is even possible. Methods to synthesize dienes and polyenes that allow access to either isomer in high geometric purity, but yet possess conditions that are mild and functional group tolerant are highly desired. Additionally, methods that allow for convergent and modular preparation of polyenes are sought-after. In the next few pages, some representative examples of polyene syntheses will be presented.

![Synthetic strategies for polyene synthesis](image)

**Figure 1.5 Synthetic strategies for polyene synthesis**

The BASF synthesis of vitamin A (7), which is produced on an industrial scale annually (>3000 tons), utilizes Wittig chemistry to produce the precursor retinyl acetate (Scheme 1.1).¹⁰
Nicolaou and co-workers applied a series of HWE olefinations in their synthesis of amphotericin B (1) (Scheme 1.2). The all-trans acyclic heptaene was assembled through two iterative HWE reactions with the functionalized phosphonate 27, which after condensation with polyhydroxylated top-piece 28 was subjected to a final intramolecular HWE, arriving at heptaene 29.

Transition metal based strategies, such as palladium catalyzed cross-coupling, has become a prominent method for assembling sp–sp carbon-carbon bond formation due to the ability to synthesize a diverse array of polyenes under mild conditions and with excellent stereocontrol, often tolerant of many functional groups. In the synthesis of rapamycin (32), a 31-member macrolide with potent immunosuppressive activity, Nicolaou and co-workers made use of the bis-stannyl alkene 30 developed by Corey, to “stitch” together the triene chain though a tandem inter-/intramolecular Stille coupling.
Scheme 1.2 Nicolau’s synthesis of amphotericin B (1)

The reaction proceeded smoothly under dilute conditions affording (−)-rapamycin (32) in 27% yield, along with unchanged starting material (ca. 30% yield) and the intermolecular coupled vinyl iodide/vinylstannane (ca. 30% yield), both of which could be recycled.
Lipshutz and Lindsley have developed a linchpin that allows for the bidirectional synthesis of \textit{all-}E tetra- and pentaenes (Figure 1.6).\textsuperscript{38} The stannyldienyne linchpin 33 was envisioned as a metalated triene equivalent, which could be first cross-coupled at the vinylstannane terminus, followed by subsequent hydrometalation at the desilylated alkyne terminus, then further cross-coupled to afford a variety of polyene products (Scheme 1.4). This method was applied to the synthesis of the polyene chain common to many of the oxopolyene macrolides such as the mycoticins, roxatcins, and RK-397.
In 2007, de Lera and co-workers reported the synthesis of perdinin\textsuperscript{39} (39), a
carotenoid isolated from planktonic dinoflagelates, such as \textit{Amphidinium carterae}.
Perdinin (39) possesses a highly functionalized C\textsubscript{37}-norcarotenoid structure with a \(\gamma\)-
alkyldienebutenolide as a part of the polyene chain, making the synthesis a formidable
exercise in polyene synthesis. de Lera’s strategy relied on a convergent and sequential
cross-coupling between the differentially halogenated butadiene linchpin 37 and
alkenylstannane fragments 36 and 38 (Scheme 1.5). Selective cross-coupling at the more
reactive vinyl iodide terminus of the linchpin and 36, followed by a final cross-coupling with 38 and concomitant Pd(0) catalyzed isomerisation completed the synthesis.

Scheme 1.5 de Lera’s synthesis of peridinin (39)
CHAPTER 2

REVIEW OF SYNTHETIC STRATEGIES FOR THE SYNTHESIS OF 
FUSARIUM NATURAL PRODUCTS

2.1 Introduction

The therapeutic potential combined with the synthetic challenge associated with epolactaene, NG-391, and lucilactaene has sparked interest in this area from the synthetic community (Figure 2.1). To date, epolactaene has been synthesized by four groups,\textsuperscript{40,41,42,43} NG-391 was synthesized in 2002 by Hayashi and co-workers,\textsuperscript{44} and most recently there have been two reported syntheses of lucilactaene, including ours.\textsuperscript{45,46}

![Figure 2.1 Synthesized Fusarium metabolites]

Figure 2.1 Synthesized *Fusarium* metabolites

2.2 Epolactaene

In 1998, Kogen and co-workers reported the synthesis of epolactaene (11), making use of a Wittig strategy to construct the side chain. The heterocyclic fragment was constructed through a diastereoselective aldol condensation with aldehyde 40,
derived from D-lactic acid and di-tert-butyl malonate, which set the required stereocenter as a 9:1 mixture (Scheme 2.1). The resulting alcohol was then further transformed in a few steps to epoxide 41. Lactonization of expoxide 41 with formic acid, followed by conversion of the corresponding acid into the Weinreb amide and lactone opening with ammonia in methanol provided amide 42. Addition of vinyllithium 43 to the weinreb amide 42, followed by Dess–Martin periodinane oxidation of the primary alcohol afforded aldehyde 44, completing the synthesis of the heterocyclic fragment.

Scheme 2.1 Kogen’s epolactaene heterocyclic fragment synthesis

Synthesis of the polyene fragment embarked with a cross-coupling between vinyl stannane 45 derived from (E)-3-ido-2-methyl-2-propen-1-ol and methyl (Z)-2-bromobut-2-enoate 46 under Stille coupling conditions to provide the desired diene in 47% yield (Scheme 2.2). Deprotection and conversion of the alcohol to the tributylphosphonium salt 47 provided the precursor for the Wittig olefination. Generation
of the ylide from phosphonium salt 47 using potassium tert-butoxide in the presence of 18-crown-6 in CH$_3$CN provided triene 48 in 69% yield with high stereoselectivity (E/Z = 10:1). Final deprotection and oxidation with Dess–Martin periodinane effected spontaneous cyclization afforded (+)-epolactaene (11), which was completed in 14 linear steps and 24 total synthetic operations in an overall yield of 4.3%.

Scheme 2.2 Kogen’s epolactaene synthesis

In 2003, Kobayashi and co-workers reported a synthesis of (+)-epolactaene that utilized an aldol-type reaction of a bridgehead oxiranyl anion derived from trimethylsilyl epoxylactone 56 with a tetraene aldehyde as the key step. The required enantiomerically pure silylated epoxylactone 56 could be obtained in large quantities in five steps from β-
angelica lactone epoxide. Synthesis of the side-chain of epolactaene began with a Wittig reaction of 49, prepared from 1,4-butanediol, with phosphonium salt 50 affording a mixture of isomers (E/Z = 5.7:1), which was carried into the next step (Scheme 2.3). After desilylation, the enyne was carbometaled to afford dienyl iodide 51, once again as a mixture of isomers (E/Z = 5.7:1). Stille coupling between dienyl iodide 51 and known vinyl stannane 52 assembled the triene 53, which after removal of the PMB group and oxidation afforded aldehyde 54. A final Wittig olefination with the ylide derived from propionaldehyde afforded the polyene fragment 55 required for the critical coupling.

Treatment of the trimethylsilyl epoxylactone 56 and aldehyde 55 with TBAF in the presence of 4Å MS afforded the aldol product 57 in 39% yield (78% yield based on recovered 55). Alcohol 57 was transformed into epolactaene via known procedures in three steps.
In 2006, Negishi and Tan used an organometallic approach towards the side chain synthesis of epolactaene. A stereocontrolled synthesis of diene 58 was achieved in seven steps through a series of Zr-catalyzed carboalumination reaction of alkynes, Pd-catalyzed cross-coupling with organozinc reagents, and hydrozirconation with HZrCp₂Cl (Scheme 2.4). The fully elaborated side chain 60 was completed through the cross-coupling of the zinc derivative of 58 and methyl ester 59 in the presence of Pd₂dba₃ and tris(o-furyl)phosphine (TFP) in 76% yield. After desilylation and oxidation, completion of epolactaene (11) was achieved following the protocol developed by Kobayashi.
2.3 NG-391 and lucilactaene

Hayashi and co-workers relied on a sequence of olefinations to construct the pentaene side-chain of NG-391 (17) and lucilactaene (10). Wittig olefination of tetrahydropyran-2-ol with (ethoxycarbonylthethylidene)triphenylphosporane followed by reduction of the resulting ester and oxidation provided aldehyde 61 in 89% yield over 4 steps (Scheme 2.5). HWE reaction of 61 with tert-butyl dimethylphosphonoacetate afforded diene 62 with greater than 95:5 E/Z selectivity. Aldol condensation of the lithium enolate of 62 with acetaldehyde followed by conversion to the mesylate and subsequent elimination afforded a mixture of trienoate isomers (E/Z = 15:1) in 83% over
three steps. Isomerization of the Z-isomer to the E-isomer proceeded gradually (2 days) under the reaction conditions. Further elongation of the polyene chain continued after deprotection of the silyl ether and IBX oxidation to the aldehyde. A final HWE olefination with methyl diethylphosphonopropionate afforded the \((E,E,E,E,E)\)-pentaene 65 in 92% yield, an advanced intermediate \textit{en route} to NG-391 and lucilactaene.

![Scheme 2.5 Hayashi's NG-391 and lucilactaene polyene synthesis](image)

Pentaene methyl ester 65 was converted to the corresponding \(\beta\)-ketonitrile 66, which was then subjected to a Knoevenagel condensation with \((S)\)-4-(\(t\)-butyldiphenylsiloxy)-2-triethylsiloxybutanal (67), affording the E-Knoevenagal adduct stereoselectively (Scheme 2.6). Epoxidation with the lithium anion of tritylperoxide gave epoxide 68, with delivery opposite to the TES group, without affecting the polyene. After removal of TES protecting group, stirring a solution of 68 in silicia gel effected
hydrolysis of the nitrile to the amide, which under the same conditions spontaneously lactonized affording 69 in 60% yield from 66. Conversion of the lactone into the lactam, using previously developed procedures, and final removal of the TBDPS group afforded NG-391 (17).

![Scheme 2.6 Hayashi’s NG-391 synthesis](image)

In 2005, Hayashi and co-workers reported the synthesis of (+)-lucilactaene (10) (Scheme 2.7). Embarking from NG-391 (17), stereoselective formation of methyl ether 71 was achieved through treatment with catalytic amount of TsOH·H2O and trapping the acyliminium ion 70 from the side opposite to the epoxide with methanol. It was found that protection of the amide greatly facilitated reductive removal of the epoxide, thus 71 was protected as the bis-Boc derivative, which could then be treated SmI2 to effect removal of the epoxide.
Scheme 2.7 Hayashi’s lucilactaene synthesis
Treatment of 73 with TFA resulted in removal of the two Boc protecting groups with spontaneous conjugate addition to form the tetrahydrofuran and conversion of the methyl ether into the hydroxyl affording lucilactaene (10), along with significant amounts of methyl ether 76. Not surprisingly, facile racemization of 73 occurred upon treatment with TFA, likely proceeding through a retro-Michael or acyliminium ion like intermediate. Thus, a protecting group was sought that could be removed under conditions that would avoid racemization of the labile hemiaminal.

After considerable experimentation, it was found that protection of the hemiaminal as the phenylselenylethyl allowed for deprotection to lucilactaene without racemization (Scheme 2.8). After treatment with PhSeCH₂CH₂OH in the presence of a catalytic amount of TsOH·H₂O, the previous sequence (Boc protection, reductive epoxide removal, Boc deprotection, and conjugate addition) proceeded in a similar fashion as the methyl ether. A final deprotection of the phenylselenylethyl ether 78 was achieved in three steps (oxidation to the selenoxide with dimethyldioxirane, elimination to the vinyl ether with DABCO, and oxidative removal of the vinyl ether with dimethyldioxirane) afforded (+)-lucilactaene (79).
Scheme 2.8 Hayashi’s (+)-lucilactaene synthesis

Hayashi also determined that isolable lucilactaene is likely itself produced as the racemate. Examination of a variety of conditions that could effect racemization of lucilactaene revealed that while both basic and acidic conditions will racemize 80, the conditions in that isolation and purification is performed do not (Table 2.1).
Table 2.1 Racemization of the lucilactaene model 80

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>ee [%]</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>none</td>
<td>23</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>AcOH/CH₂Cl₂ (1:20)</td>
<td>23</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>PPTS in MeOH (0.005 M)</td>
<td>23</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>DMD in acetone (0.07 M)</td>
<td>−78</td>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Et₂N/CH₂Cl₂ (1:4)</td>
<td>23</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>TFA/CH₂Cl₂ (1:100)</td>
<td>0</td>
<td>0.1</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>TFA/CH₂Cl₂ (1:20)</td>
<td>0</td>
<td>0.25</td>
<td>57</td>
</tr>
<tr>
<td>8</td>
<td>TsOH·H₂OinCH₂Cl₂ (0.013 M)</td>
<td>23</td>
<td>3</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>K₂CO₃ in MeOH (0.15 M)</td>
<td>23</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>TFA/CH₂Cl₂ (1:4)</td>
<td>0</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>culture medium</td>
<td>28</td>
<td>48</td>
<td>100</td>
</tr>
</tbody>
</table>
These results suggest that lucilactaene may be biosynthesized through an intermediate such as 83, where Michael addition and oxidation to form the hemiaminal are the remaining biosynthetic steps (Scheme 2.9). If Michael addition where to occur first, then racemization is likely to happen during the oxidation to the hemiaminal. In this pathway, an acidic moiety in the enzyme responsible for the oxidation is likely to be the cause of racemization. While if oxidation proceeds first, then intermediate 83 would undergo tautomerization to an achiral 2-hydroxypyrrole derivative, which would then undergo epoxidation, isomerization, and conjugate addition to afford lucilactaene (10).

Scheme 2.9 Possible racemization mechanism for lucilactaene
CHAPTER 3

HETERO-BIS-METALATED ALKENE SYSTEMS

3.1 Development

As can be noted in the previous chapters describing the synthesis of polyene natural products, strategies have classically relied on phosphorous-based methods such as the Wittig or the HWE. Although reliable, from a synthetic design standpoint these methods possess a number of distinct disadvantages. The principal one being that they invariably lead to a mixture of geometric isomers, necessitating separation, or isomerization of the unwanted isomer. Additionally, this method often leads to a route that is linear and iterative, relying on a reduction-oxidation-olefination procedure, disparagingly known as the “DIBAL-Swern-Wittig” strategy. Development of a divergent strategy\textsuperscript{47} that would allow for the stereospecific synthesis of a variety of both E and Z polyenes could greatly improve upon on existing methods.

Palladium-catalyzed cross-coupling reactions are a tremendously effectual tool in organic chemistry; it is difficult to imagine the design and execution of complex molecule syntheses in their absence. The Stille\textsuperscript{48} and Suzuki-Miyaura\textsuperscript{49} reactions are preeminent due to their compatibility with a diverse range of functional groups and because of the ease with which tin and boron can be incorporated into organic molecules and the stability of organotin and boron compounds. As part of an interest in the efficient
and stereodefined production of polyene systems,\textsuperscript{50} we have developed a novel linchpin system useful for the construction of biologically relevant polyenes.\textsuperscript{51}

![Hetero-bis-metalated butadiene](image.png)

**Figure 3.1 Hetero-*bis*-metalated butadiene**

The key recognition in the development of our own work in this area was the retrosynthetic excision of a 1,3-butadiene fragment from a polyene-containing synthetic target (Figure 3.1). In this strategy, the 1,3-butadiene is differentially metalated with tin and boron at its termini, with the expectation that reaction conditions could be developed for orthogonal palladium-catalyzed cross-coupling with electrophiles. Selective Stille coupling at the vinyl stannane terminus in the presence of a vinyl boronate is possible due to the difference in mechanistic pathways between the Stille and Suzuki-Miyaura couplings (Figure 3.2). In the Suzuki-Miyaura coupling, a suitable base must be present in order form the tetravalent borate species to effect transmetalation. Thus, the hetero-*bis*-metalated butadiene could be interpolated within the polyene chain via a linchpin coupling by sequential Stille and Suzuki-Miyaura cross-coupling reactions. In addition, it was anticipated that conditions could be found that would allow for a one-pot tandem Stille/Suzuki-Miyaura cross-coupling reaction, using a single palladium-catalyst system. We were also curious if the linchpin could be used in the opposite direction, performing
the Suzuki-Miyaura coupling first leaving the vinyl stannane intact. This reagent represents the prototypical orthogonal Stille/Suzuki-Miyaura linchpin system.

**Figure 3.2 Stille and Suzuki-Miyaura mechanisms**

In synthetic organic chemistry, a linchpin can be described as a central structural component that holds two or more larger, complex components together, and can be as simple as a single atom. In terms of synthetic strategy, use of a linchpin would serve to sequentially couple, in a convergent fashion, complex fragments of a target molecule. Recent examples include Smith’s dithiane linchpin strategy (1), 52 Evans’ rhodium-catalyzed allylic cross-coupling protocol (2), 53 and Taber’s use of 1,4-dichloro-2-butene for unsaturated fatty acid synthesis (3) (Figure 3.3). 54 Schlessinger appears to be the first to use the term “linchpin” in the context of complex molecule synthesis for his synthesis of dihydrojasmine. 55 These examples are strategically differentiated from examples where structural fragments are incorporated in a bi-directional manner using a series of
transformations.\textsuperscript{56} The key issue here is not simply one of fragment couplings, as exemplified in many total syntheses, but one of interpolation of a functionalized reagent between more complex fragments.

![Figure 3.3 Linchpins](image)

On the onset of developing this methodology, there were limited reports of other hetero-\textit{bis}-metalated alkene systems used in organic transformations. Examples included a well-known tin/silicon alkene \textsuperscript{84}\textsuperscript{57} and a few reported boron/tin systems \textsuperscript{85}\textsuperscript{58}. Several homo-\textit{bis}-metalated olefins where also known, including those of tin \textsuperscript{30}\textsuperscript{59}, boron \textsuperscript{86}\textsuperscript{60}, and silicon \textsuperscript{87} (Figure 3.4).\textsuperscript{61} It should be noted, however, that in some applications of these systems, subsequent transformation of the second metal is required for reaction at the opposite terminus. Shortly after publication of our methodology, a homo-\textit{bis}-metalated diene \textsuperscript{88} was reported for the cross-coupling of polyene systems and was used in the total synthesis of RK-397.\textsuperscript{62} In late 2007, Burke and co-workers reported a
protected boron (as the pyramidalized \(N\)-methyliminodiacetic acid) haloalkenylboronic acid 89 building block for iterative cross-coupling\(^{63}\) This building block was transformed into a number of bis-metalated alkenes including a boron/tin system.

![Figure 3.4 Metaled linchpins](image)

### 3.2 Synthesis and application

Butadiene 93 was effectively synthesized from propargaldehyde diethyl acetal (90) by stannylcupration\(^{64}\) followed directly by acetal hydrolysis to afford \(\beta\) -stannylacrolein 91. A more cost effective route to 91 involving hydrostannylation of propargyl alcohol was less advantageous because a poor and variable E/Z ratio was obtained requiring an extremely tedious chromatographic separation of a poorly UV-active compound. Takai olefination\(^{65}\) with dichloromethylboronate 92 afforded butadiene 93 in yields routinely above 75% with high geometric purity (E/Z \(\geq\) 90:10) (Scheme 3.1). The linchpin can be easily prepared on a multigram scale, requiring minimal purification, and the product is stable for extended periods at 0 °C.
Selective Stille coupling at the tin-bearing terminus of 93 was possible because of the need for basic reaction conditions to affect transmetalation at the boron-bearing end. Bromides, iodides, and triflates all effectively participated in Stille coupling reactions with 93 (Table 3.1).
There was little difference in yield between the electron deficient aryl bromide 94 (entry 1) and iodide 95 (entry 2) [Pd$_2$dba$_3$ (1.5 mol %), P(furyl)$_3$ (3.5 mol %), NMP, 23-50 °C] although aryl triflate 96 (entry 3) [Pd$_2$dba$_3$ (1.5 mol %), P(furyl)$_3$ (3.5 mol %), LiCl, NMP, 23-50 °C] provided modest yields of coupled product 104. Electron-rich aryl iodides 97 (entry 4) and 98 (entry 5), and sterically crowded 2,6-dimethyl substituted iodide 99 (entry 6) both provided excellent yields of products 105, 106, and 107, respectively. Iodoacrylic acid 100 (entry 7) [PdCl$_2$(CH$_3$CN)$_2$, DMF, rt] was an effective partner, as were cis- and trans-1-iodo-1-hexene 101 (entry 8). In comparison to aryl triflate 96 (entry 3), enol triflate 102 (entry 9) could be coupled with 93 in excellent yield. Aryl chlorides were found not to be suitable coupling partners using the standard reaction conditions (entry 10). However, it is likely that reaction conditions developed for Stille coupling of aryl chlorides could be successful. Reactions generally proceeded quantitatively, with no evidence of competing reaction of the vinyl boronate.

Subsequent Suzuki-Miyaura coupling with boronate 105 was effectively achieved with various partners (Table 3.2). Aryl iodide 111 (entry 1) [Pd(PPh$_3$)$_4$, 2M Aq K$_2$CO$_3$ Tol, EtOH] provided the highest yield of coupled product 114, significantly higher than the comparable bromide 112 (entry 2). Yields were also lower for sterically crowded iodide 99 (entry 3) [Pd$_2$dba$_3$ (1.5 mol %), P(furyl)$_3$ (3.5 mol %) NMP, CsF, 23-50 °C] and electron rich system 97 (entry 4). Phenyl triflate (113) coupled effectively (entry 5) [Pd(PPh$_3$)$_4$, K$_3$PO$_4$, dioxane, 85 °C], but enol triflate 102 was not an effective partner (entry 6). Stereoisomeric vinyl iodides 101 participated effectively (entry 7).
One of the goals of this project was to streamline the assembly of polyene systems. Thus, it was imagined that a single catalyst system could be found that would allow for the tandem Stille and Suzuki-Miyaura coupling with the butadiene linchpin. Examination of the reactions conditions revealed that the catalyst system \( \text{Pd}_2\text{dba}_3/\text{P(furyl)}_3 \) would be a suitable catalyst to attempt the tandem cross-coupling. Tandem coupling of 93 was implemented in a sequential one-pot sequence, performing the Stille coupling with one partner followed by direct addition of CsF and the second coupling partner to the reaction flask to effect Suzuki-Miyaura coupling, without the addition of a different catalyst. This one-pot, sequential Stille/Suzuki-Miyaura coupling could be achieved in excellent overall yield in the formation of 121 and 122 (Scheme 3.2).
Scheme 3.2 Tandem Stille/Suzuki-Miyaura coupling with butadiene 93

Three additional hetero-*bis*-metalated linchpins were developed by Coleman and Lu for the total synthesis of polyene natural products strobilurin B (125), 2′-*O*-methylmyxalamide (126) and (6E)-2′-*O*-methylmyxalamide (127) (Figure 3.5). 67
Figure 3.5 Hetero-bis-metalated linchpins

The prominent qualities of this methodology were exemplified in the use of these linchpins. In the total synthesis of 2'-O-methylmyxalamide (126), attempts to isolate and purify the Stille coupling product led to isomerization and degradation of the intermediate tetraene species. Therefore, the sequence was performed in one-pot fashion: palladium-promoted Stille coupling between triene 124 and right-hand vinyl iodide 128 followed by the addition of left-hand vinyl iodide 129 and base to promote Suzuki-Miyaura coupling (Scheme 3.3). This directly afforded 126 in excellent yield without isomerization of the sensitive cis double bond.
In the synthesis of strobilurin B (125), the Stille coupling of vinylstannane 123 and vinyl iodide 131 occurred extremely slowly under a variety of conditions, and the coupled product 132 was isolated in low yield (<10%) (Scheme 3.4). Attempts to force the reaction to completion resulted in the isomerization and deboronation of coupled product 132. It was reasoned that the steric crowding of the vinyl stannane 123 and the low reactivity of the vinyl iodide 131, in combination with the instability of the boronate of product 132 lead to this unsuccessful Stille coupling. In light of these findings, attempts were made to perform the Suzuki-Miyaura coupling first. Under aqueous coupling conditions, chemoselective arylation of the vinyl boronate terminus of diene 123 occurred and 133 could be isolated from the reaction as the only coupling product observed (74%). Subsequent Stille coupling of the vinyl stannane of 133 with vinyl
iodide 131 now occurred and strobilurin B (125) was produced as a single stereoisomer in 45% yield.

Scheme 3.4 Total synthesis of strobilurin (125)
CHAPTER 4

TOTAL SYNTHESIS OF LUCILACTAENE

4.1 Retrosynthetic analysis

Our strategy for the total synthesis of lucilactaene was formulated as a convergent synthesis that would allow for the modular preparation of related analogs for structure-activity studies. Our retrosynthetic plan is detailed in Scheme 4.1. Global deprotection and late-stage conjugate addition of the primary alcohol of 134 would form the tetrahydrofuran ring. Under thermodynamic control, this reaction should provide the more stable cis-fused ring system with the pentaenone side chain in the pseudoequatorial position. This reaction has been previously shown to give the cis-fused product in the Hayashi total synthesis. The 2-hydroxyethyl side chain of 134 would arise from the alkene of 135, the product of a regioselective allylation of N-protected iodomaleimide. Making use of our linchpin methodology, assembly and introduction of the polyene side chain would rely on a convergent series of cross-coupling reactions between olefin partners 136, 137 and the hetero-bis-metalated linchpin 93 previously developed. Cuprate-coupling between C12 of acid chloride 136 and C13 of iodide 135 would effect ketone installation. Stille coupling of dienyl iodide 137 with the C6 vinyl stannane of hetero-bis-metalated linchpin 93 would install the terminal tetraene fragment of 134. Suzuki-Miyuara coupling of the C9 vinyl boronate of 93 with C10 of vinyl bromide 136
will accomplish construction of the pentaene side chain. Should a particular cross-coupling prove difficult, an advantage to the modularity of this strategy is that the order of coupling could be changed to achieve the best route towards this highly labile pentaene side chain.

Scheme 4.1 Retrosynthetic analysis of lucilactaene
The synthesis of lucilactaene (10) would result from an orchestrated series of sp\(^2\)-sp\(^2\) bond formation events within a triply convergent synthetic strategy \([(93 + 137) + (136 + 135)]\).

### 4.2 C1–C5 Terminal diene fragment

Synthesis of the highly substituted terminal dienoate fragment 137 was initially envisioned to be synthesized through a series of consecutive cuprate additions (Scheme 4.2). Although, preliminary studies found that the intermediate vinyl cuprate 138 formed after the first conjugate addition (Me\(_2\)CuLi, THF, –78 °C) was not sufficiently nucleophilic to add to a second alkyne, despite prolonged reaction times and varied conditions. After considerable effort towards this method, without success, we decided to abandon this route.

![Scheme 4.2 Failed cuprate route towards terminal diene fragment 137](image)

A second generation synthesis of diene fragment 137 relied on a stereoselective cuprate addition to a functionalized enyne. Regioselective anti-hydrostannylation\(^69\) of 2-butyn-1-ol (141), followed by iododestannylation (I\(_2\), CCl\(_4\), –10 °C) of the resulting
vinylstannane provided allylic alcohol 142 in 85% yield with high Z selectivity (Z:E = 96:4) (Scheme 4.3). Kumada coupling of propynylmagnesium bromide and vinyl iodide 142 [PdCl₂(PPh₃)₂, THF, 50 °C, 80%] afforded enyne 143 required for the critical cupration.⁷⁰ Stannylcupration⁷¹ using the higher order cuprate (Bu₃Sn)₂CuCNLi₂, in the presence of MeOH or water as an proton source resulted in a complex mixture of distal cis- and trans- addition and along with the proximal addition product. In contrast, silylcupration⁷² with water (8 equiv.) as an additive, afforded primarily the distal cis-addition product, silyl diene 144 in good yield (85%) as a separable mixture of isomers (E:Z = 85:15). The addition of a proton source in the form of MeOH or H₂O to the cuprate solution allows for the trapping of the intermediate vinylcuprate as the kinetic product, resulting in an increase of overall yield and purity. Attempts to streamline the synthesis of dienoate 145 using the ester derivate of 143 and avoid oxidation were problematic. Using the ester derivate of 143, resulted in a non-selective addition, presumably due to changes in electronics of the enyne.

Corey-Gilman Ganem oxidation of 144 afforded the methyl ester 145.⁷³ Alternatively, IBX could be used as in place of MnO₂ for oxidation to the aldehyde on a smaller scale. Iododesilylation of 145 in several different solvents (CH₂Cl₂, CH₃CN, Et₂O) resulted in stereoisomeric mixtures at the C5 position, presumably due to solvent participation. However, making use of 1,1,1,3,3,3-hexafluoro-2-propanol, a polar solvent with low nucleophilicity, iododesilylation (2,6-lutidine, NIS, –10 °C, 90 s) afforded the C5 iodide 137 without isomerization.⁷⁴ The C1-C5 terminal dienoate fragment 137 was synthesized in five steps (36% overall) from 2-butyn-1-ol.
Scheme 4.3 C1–C5 Synthesis of terminal diene fragment

4.3 Synthesis of pyrroline core

The heterocyclic fragment 150 was synthesized in high yield from bromomaleimide (146).\(^7^5\) Protection of the imide nitrogen with the trimethylsilylethoxymethyl (SEM) group\(^7^6\) (\(i\)-Pr\(_2\)NEt, DMF, \(-45^\circ\)C, 3 h) afforded 147 (Scheme 4.4). Bromide to iodide conversion (5 equiv of NaI, acetone, reflux, 12 h) quantitatively afforded protected iodomaleimide 148. Regioselective allylation of the carbonyl distal to the iodine was achieved using allylindium in DMF (\(-15^\circ\)C, 3 days)\(^7^7\) to afford 149 as a separable 8:1 mixture of regioisomers. Ozonolysis of the terminal alkene (O\(_3\), CH\(_2\)Cl\(_2\), \(-78^\circ\)C) and reduction of the ozonide with sodium borohydride (CH\(_2\)Cl\(_2\)/MeOH, 0 \(^\circ\)C, 2 h) afforded the corresponding diol, which was protected as the \(bis\)-triethylsilyl ether (2,6-lutidine, CH\(_2\)Cl\(_2\), \(-45\) to 25 \(^\circ\)C, 2 h) to provide 150 in five steps (55% overall) from bromomaleimide.
Scheme 4.4 Synthesis of heterocyclic fragment

Completion of the pyrrolidine core involved connection with the C12 acyl group. Palladium-catalyzed carbonylative coupling between vinyl iodide 150 and vinylstannane 151 (CO, Pd(PPh₃)₄, THF) afforded β-silylenone 152 (Scheme 4.5). Attempts to effect iododesilylation of vinyl silane 152 under various conditions inevitably proved unsuccessful, returning unreacted starting material. It seems that the C10-C11 olefin is not sufficiently nucleophilic to form the intermediate iodonium ion required for transformation. Accordingly, a route towards 153 that did not necessitate an iododesilylation was required.

Scheme 4.5 Failed synthesis of β-iodocene
Successful installation of C12 acyl group of 136 was achieved using a cuprate/acid chloride coupling developed by Knochel (Scheme 4.6).\textsuperscript{78} Formation of Grignard reagent 154 occurred upon treatment of iodide 150 with isopropylmagnesium chloride (THF, \(-60\) °C, 20 min); transmetalation to the corresponding cuprate 155 occurred upon treatment with cuprous cyanide (\(-40\) °C, 30 min). Reaction of cuprate 155 with acid chloride 136\textsuperscript{79} (\(-40\) °C, 1 min) achieved formation of the C12-C13 bond and provided β-bromoenone 156 in good yield (65%). Compound 156 was the result of six synthetic transformations (36% overall) from bromomaleimide.

![Scheme 4.6 Synthesis of β-bromoenone]

**Scheme 4.6 Synthesis of β-bromoenone**

**4.4 Assembly of polyene and completion of lucilactaene**

Two reasonable options existed for the ordering of the final alkene couplings as a consequence of the necessary connections between both C5-C6 and C9-C10: Stille coupling between diene 93 and diene 137 followed by Suzuki coupling with enone 156 or the reverse [enone 156 + diene 93] + diene 137. We first attempted the former connection. Chemoselective Stille coupling of the vinylstannane of 93 with the vinyl
iodide of 137 was achieved using Pd$_2$dba$_3$ and triphenylarsine (DMF, 25 °C, 18 h), and tetraene 157 was obtained in good yield (Scheme 4.7). Tetraene 157 is six steps from 2-butyn-1-ol (29% overall). A later attempt to assemble the polyene in the opposition direction [enone 156 + diene 93] found the resulting tetraene vinyl boronate to be significantly less stable and not a viable route.

Scheme 4.7 Assembly of tetraene

Final assembly of the polyene side chain required formation of the C9–C10 bond through a Suzuki-Miyaura coupling between vinyl boronate 157 and pyrroline core 156. Merger of these two fragments using traditional Suzuki-Miyaura coupling conditions [Pd(OAc)$_2$/Ph$_3$P, aq. Na$_2$CO$_3$, THF/MeOH] afforded pentaene 158 in good yield, completing construction of the lucilactaene framework (Scheme 4.8).
Scheme 4.8 Final assembly of polyene side chain

Completion of lucilactaene required removal of the two silyl ethers and SEM protecting groups, followed by conjugate addition of the primary alcohol to form the tetrahydrofuran ring. Treatment of 158 with trifluoroacetic acid (0 °C to 25 °C, 5h) effected removal of the silyl ethers with concomitant conjugate addition of the primary alcohol and partial deprotection of SEM to afford hydroxymethyl adduct 159 (Scheme 4.9). Removal of the hydroxymethyl proved to be especially capricious and a similar difficulty has been previously reported.80 Workup of the hydroxymethyl adduct with aqueous ammonia afforded lucilactaene (10), which was fully identical with that reported for the natural product.
The synthesis of the *Fusarium* metabolite lucilactaene was achieved using a synthetic approach that is a significant departure from existing work in the field with respect to methodology, strategy, and synthetic efficiency. The synthesis of 10 was achieved in eight linear steps and 17 total synthetic operations in 19% overall yield from commercially available compounds.

4.5 Structure activity-studies

The *Fusarium* metabolites, including lucilactaene, epolactaene, fusarin C, and NG-391 possess exceptionally diverse biological activities, ranging from cell cycle inhibition (lucilactaene), neurotrophic (NG-391), mutagenic (fusarin C), and neuritogenic (epolactaene). Given the similarity of these structures, it seems appropriate to investigate
the mechanism of action amongst these natural products through structure-activity relationship studies.

A commonality amongst the structures include the pyrrolidinone ring system and the polyene side chain bearing a carbomethoxy group near the terminus. Methylation patterns of the side chain differ, and epolactaene is saturated at the C8/C9 position. Epolactaene possesses an epoxide and lacks the tetrahydrofuran ring system. Given these differences we wished to investigate the following key structural features:

1. What features of the polyene side chain are relevant, if any?
2. Is the hemiaminal functionality critical for biological activity?
3. Is the tetrahydrofuran ring important?

Investigation into these questions relied on the synthesis of the following compounds shown in figure 4.1. The synthesis of these structurally and functionally related compounds would make use of existing, modular synthetic technology used in the successful synthesis of lucilactaene.
Syntheses of side chain analogs 162 and 163, made use of the previously developed Knochel cuprate-coupling (Scheme 4.10). Reaction of cuprate 154 with the corresponding acid chloride (−40 to 25 °C, 5 min) afforded the side chain analogs 160 and 161 in good yields. The clean removal of the SEM protecting group proved extremely difficult, and the deprotection of analogs 160 and 161 afforded complicated mixtures of products. Only small quantities (1mg) of 162 were isolated, while 163 could not be synthesized.
Scheme 4.10 Synthesis of side chain analogs

Synthesis of heterocyclic analog 170 began with SEM protection of maleimide (i-Pr₂NEt, DMF, –45 °C, 3 h) followed by allylation (allyl indium, DMF, rt) afforded allylic alcohol 166 (Scheme 4.11). The alcohol was protected as the TES ether (2,6-lutidine, CH₂Cl₂, –45 to 25 °C, 2 h) to afford 167. Ozonolysis of the terminal alkene (O₃, CH₂Cl₂, –78 °C) and reduction of the ozonide with sodium borohydride (CH₂Cl₂/MeOH, 0 °C, 2 h) afforded the primary alcohol 168. Treatment of the alcohol with sodium methoxide (MeOH, 0 to 25 °C) effected cyclization and removal of the TES ether to afford alcohol 169. Treatment of 169 with trifluoroacetic acid (CH₂Cl₂, 0 °C) afforded heterocyclic analog 170.
Synthesis of analog 172 lacking the hemiaminal functionality began with intermediate 168, which was alkylated with methyl triflate (2,6-di-t-Bu-pyridine, CH₂Cl₂, 0 °C) (Scheme 4.11). Treatment of 171 with trifluoroacetic acid (CH₂Cl₂, 0 °C) effected elimination of the hemiaminal affording analog 172. Synthesis of analog 173 was achieved by addition of methyl magnesium bromide (Et₂O, –78 °C) to maleimide (Scheme 4.12). Testing of these successfully synthesized analogs is currently underway.
Scheme 4.13 Synthesis of analog 173
CHAPTER 5

TOTAL SYNTHESIS OF GYMNOCONJUGATINS A AND B

5.1 Retrosynthetic analysis

Our synthetic approach to the gymnoconjugatins (Figure 5.1) relied on disconnection of the central tetraene of 18/19 at the C7/C8 and C11/C12 sp²–sp² single bonds to give the vinyl halide fragments 174 and 175 and the central butadiene connector 93 (Scheme 5.1). The hypothesis that hetero-bis-metalated reagent 93 could be incorporated within a polyene chain via sequential Stille and Suzuki-Miyaura cross-coupling reactions was previously demonstrated in the total synthesis of the antitumor agent lucilactaene. A related pentadiene system was used in a total synthesis of the antifungal agent strobilurin B, where Suzuki-Miyaura cross-coupling was chemoselective in the presence of the vinyl stannane. We now report the implementation of this synthetic strategy with boron/tin diene 93 in a brief total synthesis of gymnoconjugatins A and B. In addition, we provide preliminary biological evaluation of these two natural products.
Figure 5.1 Structures of *Gymnoascus reessii* natural products

Scheme 5.1 Retrosynthetic analysis of gymnoconjugatins
5.2 Synthesis of gymnoconjugatin A and B

Vinyl iodide 174 was synthesized in two steps from pyrone 176 by oxidation with selenium dioxide \(^{81}\) (190 °C, 3 h) followed by Takai olefination \(^{82}\) (Scheme 5.2). Attempts to use IBX \(^{83}\) rather than SeO\(_2\) for oxidation of the methyl group of 176 were less successful, and although aldehyde 177 was present as the major product of this reaction, it was accompanied by the over- and underreduction products (e.g., the corresponding acid and alcohol). Pyrone 176 is synthesized from dehydroacetic acid by known protocols. \(^{84}\)

The second coupling partner, 2-(2-bromovinyl)furan 175, was prepared in two steps from furfural (178) by Corey-Fuchs olefination to afford 179 \(^{85}\) followed by selective reduction of the cis-bromide to afford 175 (Scheme 5.3). \(^{86}\)

![Scheme 5.2 Synthesis of pyrone fragment](image)

Vinyl bromide 175 was produced as a 70:30 mixture of E- and Z-stereoisomers, which proved inconsequential due to subsequent isomerization (Scheme 5.4). Stille coupling of vinyl iodide 174 with the vinyl stannane of hetero-\(bis\)-metalated diene 93 afforded the triene 180.
Subsequent Suzuki-Miyaura coupling of the vinyl boronate of 180 with the bromovinyl furan 175 afforded gymnoconjugatin B (19). Isomerization of stereoisomers about the furan vinyl group occurred during Suzuki-Miyaura cross-coupling, and 19 was produced as a single stereoisomer. Spectroscopic data of synthetic 19, including the UV spectrum, were identical with those published for natural 19 and provided confirmation of the structure of gymnoconjugatin B. The synthesis of 19 was accomplished from pyrone 176, furan 175, and hetero-*bis*-metalated diene 93, in four linear steps without the use of protecting groups.

Scheme 5.3 Synthesis of furan fragment
The synthesis of gymnoconjugatin A (18) presented an additional challenge in the form of the C13-methyl group (Scheme 5.5). Methyl ketone 182 was synthesized from pyrone 181 by two-step oxidation with SeO₂ and MnO₂, in good overall yield. In this system, Takai olefination of 182 produced an inseparable mixture of vinyl iodide stereoisomers. Attempts to increase amounts of the desired E-isomer by changing the solvent system (dioxane, dioxane/THF) were found to be ineffective. This stereoisomeric mixture was propagated through the subsequent Stille coupling of 183 with 93 to afford vinyl boronate 184. Final Suzuki-Miyaura coupling between 184 and 175, with subsequent iodine-promoted isomerization, afforded gymnoconjugatin A (18), which provided spectral data identical with natural 18.
Scheme 5.5 Completion of gymnoconjugatin A

In vitro cytotoxicity assays of gymnoconjugatin A (18) and B (19) were performed against two breast cancer cell lines: hormone-dependent MCF-7 cells and hormone-independent MDA-MB-231 cells (Figure 5.2). Disappointingly, preliminary cell antiproliferation assays\(^89,90\) showed no significant activity for 18 or 19 after exposure of cells to agent for 48 h at 25 μM.\(^91\) Although gymnoconjugatin B (19) was never isolated in sufficient quantities to permit full characterization, in the present cytotoxicity assay this compound was also without significant activity under the same conditions. These results point to the important role that the 3-chloropyrrole of auxarconjugatin and 12\(^E\)-isorumbrin must play in effecting cytotoxic activity, as these compounds were reported to be significantly more active than 19 against murine myeloma NS-1 cells, despite sharing such close structural homology.
In a recent study into the effects of the chloro substituent, Capon and co-workers synthesized bromoisorumbrin and dechloroisorumbrin (Figure 5.3). Tests against the NS-1 cell line determined that bromoisorumbrin was slightly less active than isorumbrin, and dechloroisorumbrin was not cytotoxic at 15 μM. These findings suggest the chloro substituent is the key pharmacophore in this family of compounds.

**Figure 5.2 Biological activities of gymnoconjugatins**
Figure 5.3 Effects of chloro substituent
CHAPTER 6

EXPERIMENTAL PROCEDURES

All melting points were taken with a Thomas-Hoover capillary point apparatus and are uncorrected as are all boiling points. Proton nuclear magnetic resonance spectra were recorded on a Bruker AM-250, Bruker DPX-400 or Bruker AM-500 spectrometers and recorded in parts per million from internal chloroform or dimethyl sulfoxide on the $\delta$ scale. The $^1$H NMR spectra are reported as follows: chemical shift [multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz, integration, interpretation]. $^{13}$C NMR data were obtained with Bruker DPX-400 and Bruker DRX-500 spectrometers. Multiplicities were determined using DEPT experiments. Infrared spectra were taken with Perkin-Elmer 1600 and 2000 instruments. Mass spectra were obtained on Micromass Q-Tof II instrument and were performed by the Campus Chemical Instrument Center (CCIC) Spectrometry Facility at OSU. Compounds for which an exact mass is reported exhibited no significant peaks at $m/z$ greater than that of the parent.

Solvents and reagents were dried and purified prior to use as necessary: diethyl ether and tetrahydrofuran were dried over sodium/benzophenone ketyl; triethylamine, acetonitrile, chlorobenzene, 2-butanol and dichloromethane were dried over
calciumhydride. Reactions requiring an inert atmosphere were run under argon or nitrogen. Analytical thin-layer chromatography was conducted using EM Laboratories 0.25 mm thick precoated silica gel 60F-254 plates. Column chromatography was performed over EM laboraties, ICN, and Whatman silica gel (70-250 or 230-400 mesh). Organolithium reagents were titrated prior to use with menthol using 1,10-phenanthroline as an indicator. Grignard reagents were titrated prior to use by the addition of excess standard HCl, followed by back titration with standard NaOH using 1,10-phenolphthalein as an indicator.

The order of the selected experimental procedures follow the order of appearance in the text:

\[ \text{SnBu}_3 \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{2-((1E,3E)-4-(Tributylstannyl)buta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (93). Stannylaldehyde 91 (2.01 g, 5.83 mmol) and borolane 92} \]

\[ \text{93 (2.46 g, 11.7 mmol) in THF (29 mL) were added by syringe to a solution of anhydrous CrCl}_2 \]

\[ \text{(5.73 g, 46.6 mmol) in THF (58 mL) at 23 °C under argon. Lithium iodide (3.12 g, 23.3 mmol) in THF (29 mL) was added by syringe and the reaction mixture was stirred for 3 h at 23 °C. The reaction mixture was poured onto a large excess of water and was extracted with ether (2x). The combined organic extracts were dried (MgSO}_4 \]

\[ \text{and evaporated in vacuo. The residue was dissolved in 5%EtOAc/hexane (25 mL) and passed through a short plug of Florisil}\]

\[ \text{®, eluting with 5% EtOAc/hexane (250 mL) to afford diene 93 (2.15 g, 79%) as a yellow oil: } \]

\[ \text{^1H NMR (400 MHz, CDCl}_3 \]

\[ \text{)} \]

\[ \delta 6.95 \]

\[ \text{(dd, 1H, } J = 17.6, 6.4 \text{ Hz), 6.61 (dd, 1H, } J = 9.6, 18 \text{ Hz), 6.45 (d, 1H, } J = 15.2 \text{ Hz), 6.47} \]

\[ \text{dd, 1H, } J = 17.6, 6.4 \text{ Hz), 6.61 (dd, 1H, } J = 9.6, 18 \text{ Hz), 6.45 (d, 1H, } J = 15.2 \text{ Hz), 6.47} \]
(d, 1H, J = 17.6) 1.60-1.40 (m, 6H), 1.38-1.22 (m, 9H), 1.27 (s, 12H), 0.93-0.85 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.2, 148.5, 140.3, 83.1, 29.1, 27.2, 21.8, 13.7, 9.5; IR (KBr) $\nu_{\text{max}}$ 3464, 2957, 2897, 2871, 1616, 1557, 1345, 1120 cm$^{-1}$; HRMS (ESI) $m/z$ 493.2255 (calc for C$_{22}$H$_{43}$BO$_2$SnNa: 493.2276).

**Stille Cross-Coupling Reactions**

**Procedure A.** In a dry box, Pd$_2$dba$_3$ (1.5 mol%), and P(furyl)$_3$ (3.5 mol %), and LiCl (for triflates) were added to a reaction vessel equipped with a stir bar, which was capped with a septum and removed from the dry box. Diene 93 and the halide in NMP were added by syringe. The flask was wrapped with foil and stirred at the indicated temperature under argon until TLC indicated starting halide had been consumed. The reaction mixture was diluted with ether and poured onto saturated aqueous NH$_4$Cl. The aqueous layer was extracted with ether (3x) and the combined organic extracts were dried (MgSO$_4$), and evaporated *in vacuo*. The crude product was purified by flash chromatography (Florisil®).

**Procedure B.** In a dry box, PdCl$_2$·(CH$_3$CN)$_2$ (5 mol%) was added to a reaction vessel equipped with a stir bar, which was capped with a septum and removed from the dry box. Diene 93 and the halide in DMF were added by syringe. The flask was wrapped with foil and stirred at the indicated temperature under argon until TLC indicated starting halide had been consumed. The reaction mixture was diluted with ether and poured onto
saturated aqueous NH₄Cl. The aqueous layer was extracted with ether (3x) and the combined organic extracts were dried (MgSO₄), and evaporated in vacuo. The crude product was purified by flash chromatography (Florisil®).

**1-(4-((1E,3E)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dienyl)phenyl)ethanone (104) (Table 3.1, entry 1).** Procedure A was followed using 4-bromoacetophenone (56.0 mg, 0.281 mmol), 93 (145 mg, 0.309 mmol), Pd₂dba₃ (3.9 mg, 4.0 μmol), P(furyl)₃ (2.4 mg, 10 μmol), and NMP (1.5 mL). After stirring 24 h at 50 °C, workup and purification by column chromatography (10% EtOAc/hexane) afforded **104** (72.0 mg, 86 %) as a yellow-orange solid: ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, 2H, J = 8.4 Hz), 7.50 (d, 2H, J = 8.0 Hz), 7.18 (dd, 1H, J = 17.6, 17.6 Hz), 6.94 (dd, 1H, J = 10.8, 15.2 Hz), 6.71 (d, 1H, J = 15.6 Hz), 6.76 (d, 1H, J = 17.6 Hz), 2.59 (s, 1H), 1.3 (s, 12H); ¹³C NMR (100 MHz, CDCl₃) δ 197.3, 149.2, 141.4, 136.3, 134.7, 133.1, 130.5, 126.8, 83.34, 26.5, 24.8; IR (KBr) ν max 3649, 2977, 2927, 1682, 1601, 1360 cm⁻¹; HRMS (ESI) m/z 321.1646 (calc for C₁₈H₂₃BO₃Na: 321.1632).

**1-(4-((1E,3E)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dienyl)phenyl)ethanone (104) (Table 3.1, entry 2).** Procedure A was
followed, using 4-iodoacetophenone (58.0 mg, 0.234 mmol), 93 (121 mg, 0.257 mmol), Pd$_2$dba$_3$ (3.1 mg, 4.0 μmol), P(furyl)$_3$ (2.1 mg, 9.0 μmol), and NMP (1.5 mL). After 24 h at 23 °C, workup and purification by column chromatography (10% EtOAc/hexane) afforded 104 (62.3 mg, 89%) as a yellow-orange solid.

![Image of 1-(4-((1E,3E)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dienyl)phenyl)ethanone (104) (Table 3.1, entry 3). Procedure A was followed, using 4-acetylphenyl trifluoromethanesulfonate (63.0 mg, 0.234 mmol), 93 (121 mg, 0.257 mmol), Pd$_2$dba$_3$ (3.1 mg, 4.0 μmol), P(furyl)$_3$ (2.1 mg, 9.0 μmol), LiCl (30.0 mg, 0.702 mmol) and NMP (1.5 mL). After 24 h at 23 °C, workup and purification by column chromatography (10% EtOAc/hexane) afforded 104 (40.1 mg, 58%) as a yellow-orange solid.

![Image of 2-((1E,3E)-4-(4-Methoxyphenyl)buta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (105) (Table 3.1, entry 4). Procedure A was followed, using 4-iodoanisole (55.0 mg, 0.234 mmol), 93 (121 mg, 0.257 mmol), Pd$_2$dba$_3$ (3.1 mg, 4.0 μmol), P(furyl)$_3$ (2.1 mg, 9.0 μmol), and NMP (1.5 mL). After 24 h at 23 °C, workup and purification by column chromatography (10% EtOAc/hexane) afforded 105 (61.2 mg, 91%) as a light yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, 2H, $J = 8.8$ Hz),
7.17 (dd, 1H, J = 9.6, 17.8 Hz), 6.87 (d, 2H, J = 8.8 Hz). 6.74 (dd, 1H, J = 10.0, 15.6 Hz), 6.66 (d, 1H, J = 15.6 Hz) 6.62 (d, 1H, J = 18.0 Hz), 3.82 (s, 3H), 1.3 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.8, 150.2, 135.8, 129.6, 128.6, 128.2, 114.1, 83.2, 55.3, 24.8; IR (KBr) $\nu_{\text{max}}$ 3398, 2976, 2930, 2871, 1676, 1598, 1511, 1463, 1361, 1259, 1144, 1008, 970, 849 cm$^{-1}$; HRMS (ESI) $m/z$ 309.1632 (calc for C$_{17}$H$_{23}$BO$_3$Na: 309.1632).

2-((1$E$,3$E$)-4-(2,4-Dimethoxyphenyl)buta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (106) (Table 3.1, entry 5). Procedure A was followed, using 1-iodo-2,4-dimethoxybenzene (62.0 mg, 0.234 mmol), 93 (121 mg, 0.257 mmol), Pd$_2$dba$_3$ (3.1 mg, 4.0 $\mu$mol), P(furyl)$_3$ (2.1 mg, 9.0 $\mu$mol), and NMP (1.5 mL). After 24 h at 23 °C, workup and column chromatography (0-10% EtOAc/hexane) afforded 106 (64.4 mg, 87%) as a light yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 (d, 1H, J = 8.4 Hz), 7.20 (dd, 1H, J = 10.8, 17.4 Hz), 7.00 (d, 1H, J = 16.0 Hz). 6.79 (dd, 1H, J = 10.4, 15.8 Hz), 6.48 (dd, 1H, J = 2.4, 8.4 Hz) 6.43 (d, 1H, J = 2.4 Hz), 6.58 (d, 1H, J = 17.2 Hz), 3.83 (s, 3H), 3.82 (s, 3H), 1.29 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.0, 158.4, 151.2, 131.2, 129.0, 127.8, 119.0, 105.1, 98.5, 83.1, 55.5, 55.4, 24.8; IR (KBr) $\nu_{\text{max}}$ 3399, 2976, 2930, 2854, 1676, 1600, 1463, 1364, 1321, 1209, 1144, 970, 849 cm$^{-1}$; HRMS (ESI) $m/z$ 339.1738 (calc for C$_{18}$H$_{25}$BO$_4$Na: 339.1751).
4,4,5,5-Tetramethyl-2-((1E,3E)-4-(2,6-dimethylphenyl)buta-1,3-dienyl)-1,3,2-dioxaborolane (107) (Table 3.1, entry 6). Procedure A was followed, using 2-iodo-\textit{m}-xylene (54.0 mg, 0.234 mmol), 93 (121 mg, 0.257 mmol), Pd\textsubscript{2}dba\textsubscript{3} (3.1 mg, 4.0 \textmu mol), P(furyl)\textsubscript{3} (2.1 mg, 9.0 \textmu mol), and NMP (1.5 mL). After 24 h at 50 °C, workup and column chromatography (0-10% EtOAc/hexane) afforded 107 (64.0 mg, 96%) as a light yellow oil: \textit{^1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.25 (dd, 1H, $J = 10.4, 17.6$ Hz), 7.07 (m, 3H), 6.81 (d, 1H, $J = 16.0$ Hz), 6.42 (dd, 1H, $J = 10.4, 16.0$ Hz), 5.65 (d, 1H, $J = 17.6$ Hz) 2.4 (s, 6H), 1.32 (s, 12H); \textit{^{13}}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 150.2, 136.2, 136.1, 136.1, 134.7, 128.0, 127.0, 83.3, 24.8, 21.1; IR (KBr) $\nu_{\text{max}}$ 2977, 2927, 2854, 1629, 1603, 1466, 1356, 1323, 1260, 1145, 1010, 970, 850, 769 cm\textsuperscript{-1}; HRMS (ESI) $m/z$ 284.1946 (calc for C\textsubscript{18}H\textsubscript{25}BO\textsubscript{2}Na: 284.1942).

(2\textit{E},4\textit{E},6\textit{E})-7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trienoic acid (108) (Table 3.1, entry 7). Procedure B was followed using (\textit{E})-3-idoacrylic acid (60.0 mg, 0.214 mmol), 93 (111 mg, 0.236 mmol), PdCl\textsubscript{2}(CH\textsubscript{3}CN)\textsubscript{2} (3.0 mg, 0.011 mmol), and DMF (0.7 mL). After 5 h at 23 °C, workup and column chromatography (0-25% EtOAc/hexane) afforded 108 (48.0 mg, 90%) as a white-yellow solid: \textit{^1}H NMR (400 MHz, acetone-D\textsubscript{6}) $\delta$ 10.65 (br s, 1H), 7.32 (dd, 1H, $J = 10.8, 15.4$ Hz), 7.05 (dd, 1H, $J = 10.4, 14.8$ Hz), 6.74 (dd, 1H, $J = 10.4, 15.2$ Hz), 6.63 (dd, 1H, $J = 10.8, 15.0$ Hz), 6.02 (d, 1H, $J = 15.2$ Hz), 5.74 (d, 1H, $J = 17.6$ Hz), 1.25 (s,
12H); $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 179.0, 149.1, 144.8, 142.1, 134.2, 124.0, 84.0, 25.1; IR (KBr) $\nu_{\text{max}}$ 3424, 2980, 2925, 1675, 1621, 1361, 1323, 1144, 1014, 848 cm$^{-1}$; HRMS (ESI) $m/z$ 273.1265 (calc for C$_{13}$H$_{19}$BO$_4$Na: 273.1274).

2-((1$E$,3$E$,5$E$)-Deca-1,3,5-trienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (($E$)-109) (Table 3.1, entry 8). Procedure B was followed using ($E$)-1-iodo-1-hexene (49 mg, 0.234 mmol), 93 (121 mg, 0.236 mmol), PdCl$_2$(CH$_3$CN)$_2$ (3 mg, 0.011 mmol), and DMF (0.7 mL). After 5 h at 23 °C, workup and column chromatography (0-5% EtOAc/hexane) afforded ($E$)-109 (51.0 mg, 83%) as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.02 (dd, 1H, $J = 10.4, 17.8$ Hz), 6.39-6.3 (m, 1H), 6.19 (dd, 1H, $J = 10.4, 15.0$ Hz), 6.09 (dd, 1H, $J = 10.4, 15.0$ Hz), 5.50 (d, 1H, $J = 12.8$ Hz), 2.13 (m, 2H), 1.4-1.2 (m, 4H), 1.3 (s, 12H) 0.9 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.0, 138.1, 136.9, 132.1, 130.1, 83.1, 32.6, 31.3, 24.9, 22.2, 13.9; IR (KBr) $\nu_{\text{max}}$ 3424, 2958, 2928, 2858, 1614, 1464, 1377, 1346, 1323, 1145, 1008, 970, 849 cm$^{-1}$; HRMS (ESI) $m/z$ 285.1999 (calc for C$_{16}$H$_{27}$BO$_2$Na: 285.2002).

2-((1$E$,3$E$,5$Z$)-Deca-1,3,5-trienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (($Z$)-109) (Table 1, entry 8). Procedure B was followed, using ($Z$)-1-iodo-1-hexene (49 mg, 0.234 mmol), 93 (121 mg, 0.236 mmol), PdCl$_2$(CH$_3$CN)$_2$ (3 mg, 0.011 mmol), and DMF (0.7 mL). After 5 h at 23 °C, workup and column chromatography (0-5% EtOAc/hexane) afforded ($Z$)-109 (42.3 mg, 69%) as a yellow oil:
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.09 (dd, 1H, $J = 10.4, 16.4$ Hz), 6.67 (dd, 1H, $J = 11.6, 14.8$), 6.27 (dd, 1H, $J = 10.8, 14.8$ Hz), 6.05 (t, 1H, $J = 11.2$ Hz), 5.57 (dd, 1H, $J = 7.6, 17.6$ Hz), 5.45 (d, 1H, $J = 17.6$ Hz), 2.21 (m, 2H), 1.58-1.22 (m, 4H), 1.3 (s, 12H) 0.9 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.0, 135.4, 133.8, 131.9, 127.8, 83.1, 31.7, 27.6, 25.0, 22.3, 13.9; IR (KBr) $\nu_{max}$ 3424, 2958, 2928, 2858, 1614, 1464, 1377, 1346, 1323, 1145, 1008, 970, 849 cm$^{-1}$; HRMS (ESI) $m/z$ 285.2005 (calc for C$_{16}$H$_{27}$BO$_2$Na: 285.2002).

2-((1E,3E)-4-Cyclohexenylbuta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (110) (Table 1, entry 9). Procedure B was followed, using 1-cyclohexen-1-yl trifluoromethanesulfonate (55.0 mg, 0.240 mmol), 93 (124 mg, 0.264 mmol), PdCl$_2$(CH$_3$CN)$_2$ (3.0 mg, 0.012 mmol), LiCl (31 mg, 0.72 mmol), and DMF (1.3 mL). After 4 h at 23 $^\circ$C, workup and column chromatography (0-5% EtOAc/hexane) afforded 110 (55 mg, 88%) as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.06 (dd, 1H, $J = 10.4, 17.6$ Hz), 6.36 (d, 1H, $J = 15.6$ Hz), 6.20 (dd, 1H, $J = 10.4, 15.4$ Hz), 5.86 (bs, 1H), 5.51 (d, 1H, $J = 17.6$ Hz), 2.17 (m, 4H), 1.66-1.56 (m, 4H), 1.32 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.7, 140.2, 135.9, 127.1, 83.1, 24.8, 24.4, 22.4, 10.2; IR (KBr) $\nu_{max}$ 3424, 2977, 2929, 2860, 1615, 1589, 1360, 1259, 1146, 1006, 970, 848 cm$^{-1}$; HRMS (ESI) $m/z$ 283.1830 (calc for C$_{16}$H$_{25}$BO$_2$Na: 283.1845).
Suzuki-Miyaura Cross-Coupling Reactions

Procedure A. Tetrakis(triphenylphosine)palladium (0) (5 mol %) and halide (if solid) were added to reaction vessel equipped with a stir bar under argon. Boronate 105 and halide (if liquid) in toluene then 2M aqueous K$_2$CO$_3$ and ethanol were added by syringe. The flask was wrapped with foil and stirred at the indicated temperature under argon until TLC indicated starting halide had been consumed. The reaction mixture was diluted with ether and poured onto saturated aqueous NH$_4$Cl and extracted with ether. The combined organic extracts were dried (MgSO$_4$) and concentrated in vacuo and the residue was purified by flash chromatography (silica doped with 2% Et$_3$N).

Procedure B. In a dry box, Pd$_2$dba$_3$ (1.5 mol %), and P(furyl)$_3$ (3.5 mol %), and CsF were added to the reaction vessel with a stir bar, and the flask was capped with a septum and removed from the dry box. Boronate 105 and the halide in NMP were added by syringe. The flask was wrapped with foil and stirred at the indicated temperature under argon until TLC indicated starting halide had been consumed. The reaction mixture was diluted with ether and poured onto saturated aqueous NH$_4$Cl. The aqueous layer was extracted with ether (3x) and the combined organic extracts were dried (MgSO$_4$), and evaporated in vacuo. The crude product was purified by flash chromatography (silica doped with 2% Et$_3$N).

Procedure C. Tetrakis(triphenylphosine)palladium (0) (5 mol %), K$_3$PO$_4$, and halide (if solid) were added to reaction vessel equipped with a stir bar under argon. Boronate 105
and halide (if liquid) in dioxane were added by syringe. The flask was wrapped with foil and stirred at the indicated temperature under argon until TLC indicated starting halide had been consumed. The reaction mixture was diluted with ether and poured onto saturated aqueous NH₄Cl and extracted with ether. The combined organic extracts were dried (MgSO₄) and concentrated in vacuo, and the residue was purified by flash chromatography (silica doped with 2% Et₃N).

1-tert-Butyl-4-((1E,3E)-4-(4-methoxyphenyl)buta-1,3-dienyl)benzene (114) (Table 3.2, entry 1). Procedure A was followed, using 1-tert-butyl-4-iodobenzene (37.0 mg, 0.159 mmol), boronate 105 (50.0 mg, 0.175 mmol), Pd(PPh₃)₄ (9 mg, 9.0 μmol), 2M aqueous K₂CO₃ (0.18 mL), EtOH (0.16 mL), and toluene (1.7 mL). After 16 h at 50 °C, workup and column chromatography (0-5% EtOAc/hexane) afforded 114 (44.0 mg, 94%) as a brown solid: ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.35 (m, 6 H), 6.95-6.81 (m, 4H), 6.62 (d, 2H, 16 Hz), 1.36 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 150.5, 131.9, 131.6, 130.4, 128.8, 127.6, 127.5, 126.0, 125.6, 114.2, 55.3, 34.6, 31.3; IR (KBr) ν max 3488, 3001, 2959, 2930, 2857, 1579, 1462, 1408, 1304, 1280, 1209, 1161, 1115, 1033, 989, 833 cm⁻¹; HRMS (ESI) m/z 315.1725 (calc for C₂₁H₂₄ONa: 315.1726).
1-Butyl-4-((1E,3E)-4-(4-methoxyphenyl)buta-1,3-dienyl)benzene (115) (Table 3.2, entry 2). Procedure A was followed, using 1-bromo-4-butylbenzene (34 mg, 0.159 mmol), boronate 105 (50 mg, 0.175 mmol), Pd(PPh₃)₄ (8 mg, 8.0 μmol), 2M aqueous K₂CO₃ (0.18 mL), EtOH (0.16 mL), and toluene (1.7 mL). After 24 h at 50 °C, workup and column chromatography (0-5% EtOAc/hexane) afforded 115 (28.0 mg, 60%) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.38 (m, 4 H), 7.15 (d, 2H, 8 Hz), 6.94-6.80 (m, 4H), 6.61 (d, 2H, 15.6 Hz), 3.83 (s, 3H), 2.61 (m, 2H), 1.37 (m, 2H), 1.37 (m, 2H), 0.97, (t, 3H, 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 159.2, 142.3, 135.0, 131.8, 131.7, 130.4, 128.7, 128.6, 127.5, 127.49, 126.2, 55.3, 35.4, 22.3, 13.9; IR (KBr) νₘₐₓ 3018, 2958, 2930, 2857, 1722, 1602, 1509, 1465, 1253, 1176, 1032, 987, 908, 733 cm⁻¹; HRMS (ESI) m/z 315.1725 (calc for C₂₁H₂₄ONa: 315.1731).

2-((1E,3E)-4-(4-Methoxyphenyl)buta-1,3-dienyl)-1,3-dimethylbenzene (116) (Table 2, entry 3). Procedure B was followed, using 2-iodo-ₘ-xylene (37 mg, 0.159 mmol), boronate 105 (50.0 mg, 0.157 mmol), Pd₂dba₃ (2.2 mg, 2.0 μmol), P(furyl)₃ (1.1 mg, 5.0 μmol), CsF (48.0 mg, 0.318 mmol), and NMP (1.0 mL). After 24 h at 55 °C, workup and column chromatography (0-10% EtOAc/hexane) afforded 116 (35.1 mg, 83%) as a bright yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, 2H, J = 11.6 Hz), 7.07 (bs, 3H), 6.89 (d, 1H, J = 8.8 Hz), 6.88 (dd, 1H, J = 10.4, 14.8 Hz), 6.67 (d, 1H, J = 16 Hz), 6.57 (d, 1H, J = 15.6 Hz), 6.46 (dd, 1H, J = 10.4, 15.8 Hz),
3.84 (s, 3H), 2.37 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.2, 136.8, 134.9, 131.7, 130.2, 129.9, 127.9, 127.7, 127.6, 126.5, 114.1, 55.3, 21.2; IR (KBr) $\nu_{\text{max}}$ 3399, 2976, 2918, 2850, 1602, 1510, 1174, 1034, 990, 831, 764 cm$^{-1}$; HRMS (ESI) $m/z$ 287.1404 (calc for C$_{18}$H$_{25}$ONa: 287.1412).

(1$E$,3$E$)-1,4-bis(4-Methoxyphenyl)buta-1,3-diene (117)

(Table 2, entry 4). Procedure A was followed, using 4-iodoanisole (37 mg, 0.159 mmol), boronate 105 (50 mg, 0.175 mmol), Pd(PPh$_3$)$_4$ (9 mg, 9.0 $\mu$mol), 2M aqueous K$_2$CO$_3$ (0.18 mL), EtOH (0.16 mL), and toluene (1.7 mL). After 16 h at 50 °C, workup and column chromatography (0-10% EtOAc/hexane) afforded 118 (34.0 mg, 81%) as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 (d, 4H, $J = 8.8$ Hz), 6.88 (d, 4H, $J = 8.8$ Hz) 6.82 (dd, 2H, $J = 2.8$, 5.8 Hz), 6.59 (dd, 2H, $J = 2.8$, 5.8 Hz), 3.85 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.1, 131.3, 130.4, 127.6, 127.5, 114.0, 55.3; IR (KBr) $\nu_{\text{max}}$ 3488, 3001, 2959, 2921, 2857, 1659, 1499, 1453, 1288, 1246, 1199, 1157, 1111, 1029, 985 cm$^{-1}$; HRMS (ESI) $m/z$ 266.1316 (calc for C$_{18}$H$_{18}$O$_2$Na: 266.1301).

1-Methoxy-4-((1$E$,3$E$)-4-phenylbuta-1,3-dienyl)benzene (118) (Table 3.2, entry 5). Procedure C was followed, using phenyl trifluoromethanesulfonate (32 mg, 0.143 mmol), boronate 105 (45 mg, 0.157 mmol), Pd(PPh$_3$)$_4$ (8 mg, 7.0 $\mu$mol), K$_3$PO$_4$ (61 mg, 0.286 mmol), and dioxane (1.0 mL). After
24 h at 85 °C, workup and column chromatography (0-5% EtOAc/hexane) afforded 118 (25.0 mg, 74%) as a white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 (d, 2H, $J = 7.6$ Hz), 7.40 (d, 2H, $J = 5.2$ Hz), 7.34 (t, 2H, $J = 7.6$), 7.23 (t, 1H, $J = 7.2$ Hz), 6.99-6.82 (m, 4H), 6.64 (d, 2H, $J = 15.2$), 3.84 (s, 3H), 1.36 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.3, 137.6, 132.5, 131.7, 130.2, 129.5, 128.6, 127.31, 127.28, 126.25, 114.2, 55.3; IR (KBr) $\nu_{max}$ 3488, 3001, 2959, 2930, 2857, 1598, 1509, 1444, 1252, 1030, 990, 840, 747 cm$^{-1}$; HRMS (ESI) m/z 206.1195 (calc for C$_{17}$H$_{16}$ONa: 206.1201).

![Image of 1-((1E,3E)-4-Cyclohexenylbuta-1,3-dienyl)-4-methoxybenzene (119)](Table 3.2, entry 6). Procedure A was followed using 1-cyclohexen-1-yl trifluoromethanesulfonate (37 mg, 0.159 mmol), boronate 105 (50 mg, 0.175 mmol), Pd(PPh$_3$)$_4$ (9 mg, 9.0 $\mu$mol), 2M aqueous K$_2$CO$_3$ (0.18 mL), EtOH (0.16 mL), and toluene (1.7 mL). After 16 h at 50 °C, workup and column chromatography (0-5% EtOAc/hexane) afforded 119 (9.1 mg, 26%) as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34 (d, 2 H, $J = 8.8$ Hz), 6.86 (d, 2H, $J = 8.8$ Hz), 6.75-6.69 (m, 1H), 6.50 (d, 1H, $J = 7.6$ Hz), 6.31 (m, 2H), 5.82 (t, 1H, $J = 4$ Hz), 3.82 (s, 3H), 2.86-2.18 (m, 4H), 1.75-1.60 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.0, 136.1, 136.0, 130.6, 130.1, 127.9, 127.3, 125.8, 114.1, 113.7, 55.3, 26.1, 24.6, 22.5; IR (KBr) $\nu_{max}$ 3430, 2934, 2859, 1720, 1674, 1605, 1512, 1462, 1408, 1302, 1251, 1175, 1032, 832, 735 cm$^{-1}$; HRMS (ESI) m/z 259.1008 (calc for C$_{17}$H$_{16}$ONa: 259.1098).
1-((1E,3E,5E)-Deca-1,3,5-trienyl)-4-methoxybenzene

((E)-120) (Table 3.2, entry 7). Procedure A was followed, using (E)-1-iodo-1-hexene (33 mg, 0.159 mmol), boronate 105 (50 mg, 0.175 mmol), Pd(PPh₃)₄ (9 mg, 0.009 mmol), 2M aqueous K₂CO₃ (0.18 mL), EtOH (0.16 mL), and toluene (1.7 mL). After 24 h at 23 °C, workup and column chromatography (hexane) afforded (E)-120 (27.1 mg, 70%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, 2 H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 6.75 (dd, 1H, J = 10.8, 14.8 Hz), 6.60 (dd, 1H, J = 11.6, 13.6 Hz), 7.40-7.31 (m, 2H), 6.89-6.85 (m, 2H), 6.75-6.27 (m, 3H), 6.03 (m, 1H), 5.76 (m, 1H), 3.82 (s, 3H), 2.29-2.11 (m, 2H), 1.54-1.47 (m, 4H), 0.92 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.4, 131.9, 130.4, 129.3, 127.6, 127.4, 125.9, 122.5, 115.3, 114.1, 55.3, 32.7, 22.3, 13.9; IR (KBr) νₘₐₓ 3425, 2977, 2928, 2872, 1616, 1585, 1367, 1340, 1145, 1010, 971, 849 cm⁻¹; HRMS (ESI) m/z 285.2005 (calc for C₁₇H₂₂ONa: 285.2002).

1-((1E,3E,5Z)-Deca-1,3,5-trienyl)-4-methoxybenzene

((Z)-120) (Table 3.2, entry 7). Procedure A was followed, using (Z)-1-iodo-1-hexene (33 mg, 0.159 mmol), boronate 105 (50 mg, 0.175 mmol), Pd(PPh₃)₄ (9 mg, 9.0 μmol), 2M aqueous K₂CO₃ (0.18 mL), EtOH (0.16 mL), and toluene (1.7 mL). After 24 h at 23 °C, workup and column chromatography (hexane) afforded (Z)-120 (25.0 mg, 65%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.35 (d, 2 H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 6.75 (dd, 1H, J = 10.8, 14.8 Hz), 6.60 (dd, 1H, J = 11.6, 13.6 Hz), 6.51 (d, 1H, J = 15.6 Hz), 6.35 (dd, 1H, J = 10.4, 14.8 Hz) 6.09 (t, 1H, J = 10.8 Hz), 5.48 (dd, 1H, J = 8.0,
18.4 Hz), 3.84 (s, 3H), 2.29-2.17 (m, 2H), 1.54-1.29 (m, 4H), 0.92 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.2, 132.9, 132.8, 130.4, 128.7, 127.9, 127.5, 127.4, 114.1, 55.3, 30.33, 27.67, 22.37, 13.97; IR (KBr) $\nu_{\text{max}}$ 3425, 2977, 2928, 2872, 1600, 1508, 1250, 1174, 1036, 990 cm$^{-1}$; HRMS (ESI) $m/z$ 285.2005 (calc for C$_{17}$H$_{22}$ONa: 285.2002).

One-pot Sequential Stille/Suzuki-Miyaura Coupling

In a dry box, Pd$_2$dba$_3$ (6.4 mg, 7.0 μmol) and P(furyl)$_3$ (3.8 0.016 mmol) were added to a Schlenk flask equipped with a stir bar. The flask was capped with a septum and removed from the dry box. Diene 93 (121 mg, 0.257 mmol) and 4-iodoanisole (55 mg, 0.234 mmol) in NMP (1.3 mL) were added by syringe. The flask was wrapped with foil and stirred at 23 °C under argon until TLC indicated starting halide had been consumed (4 h). Cesium fluoride (110 mg, 0.725 mmol) was added to the flask in one portion and 1-iodo-2,4-dimethoxybenzene (62 mg, 0.234 mmol) in NMP (0.5 mL) was added by syringe and stirred at 23 °C under argon until TLC indicated the halide had been consumed (16 h). The reaction mixture was diluted with ether and poured onto saturated aqueous NH$_4$Cl. The aqueous layer was extracted with ether (3 x) and the combined organic extracts were dried (MgSO$_4$), and evaporated in vacuo. The crude product was purified by flash chromatography (0-5% EtOAc/hexane) (silica doped with 2% Et$_3$N) to afford 121 (48.0 mg, 70%) as a yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) δ
7.43 (d, 1H, J = 8.4 Hz), 7.37 (d, 2H, J = 11.6 Hz), 6.9-6.84 (m, 5H) 6.57 (d, 1H, J = 14.8 Hz), 6.51 (dd, 1H, J = 2.4, 8.4 Hz), 6.46 (d, 1H, J = 2.4 Hz) 3.87 (s, 6H), 3.84 (s, 3H), 3.83 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 160.3, 159.0, 157.8, 130.6, 128.5, 128.1, 127.4, 127.1, 126.4, 119.7, 114.0, 105.0, 98.5, 55.5, 55.4, 55.3; IR (KBr) \(\nu_{\max}\) 3488, 3001, 2959, 2921, 2857, 1659, 1499, 1453, 1288, 1246, 1199, 1157, 1111, 1029, 985 cm\(^{-1}\); HRMS (ESI) \(m/z\) 319.1310 (calc for C\(_{19}\)H\(_{20}\)O\(_3\)Na: 319.1323).

\[
1-((1E,3E)-4-(4-tert-Butylphenyl)buta-1,3-dienyl)-2,4-dimethoxybenzene (122).
\]

In a dry box, Pd\(_2\)dba\(_3\) (6.4 mg, 0.007 mmol), and P(furyl)\(_3\) (3.8 mg, 0.016 mmol), were added to a Schlenk flask with a stir bar. The flask was capped with a septum and removed from the dry box. Diene 93 (121 mg, 0.257 mmol) and 1-iodo-2,4-dimethoxybenzene (62.0 mg, 0.234 mmol) in NMP (1.3 mL) were added by syringe. The flask was wrapped with foil and stirred at 23 ºC under argon until TLC indicated starting halide had been consumed (6 h). Cesium fluoride (110 mg, 0.725 mmol) was added to the flask in one portion and 1-tert-butyl-4-iodobenzene (61 mg, 0.234 mmol) in NMP (0.5 mL) was added by syringe. The reaction mixture was stirred at 23 ºC under argon until TLC indicated the halide had been consumed (16 h). The reaction mixture was diluted with ether and poured onto saturated aqueous NH\(_4\)Cl. The aqueous layer was extracted with ether (3x) and the combined organic extracts were dried (MgSO\(_4\)), and evaporated \(\text{in vacuo}\). The crude product was purified by flash chromatography (0-5% EtOAc/hexane) (silica doped with 2% Et\(_3\)N) to afford 122 (66.0
mg, 87%) as a yellow oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 (d, 1H, $J = 8.4$ Hz), 7.64/7.44 (d, 1H, $J = 8.4$ Hz), 7.37 (m, 4H), 6.97-6.92 (m, 3H) 6.60 (d, 1H, $J = 14.8$ Hz), 6.51/6.46 (dd, 1H, $J = 2.4, 8.6$ Hz), 6.34 (dd, 1H, $J = 2.4, 8.6$ Hz) 3.87/3.86 (s, 3H), 3.84 (s, 3H), 1.34 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.4/160.4, 158.9/157.9, 150.2, 139.2, 135.0, 130.9/129.73, 128.0, 127.2, 127.0, 125.5, 119.6, 107.0/105.0, 99.2/98.5, 56.2, 55.5/55.4, 34.6, 31.3; IR (KBr) $\nu_{\text{max}}$ 3488, 3001, 2926, 2853, 1578, 1462, 1408, 1304, 1279, 1209, 1161, 1033, 989, 834 cm$^{-1}$; HRMS (ESI) $m/z$ 345.1824 (calc for C$_{22}$H$_{26}$O$_2$Na: 345.1830).

(Z)-2-(Tributylstannyl)but-2-en-1-ol. 2,2'-Azobis(2-methylpropionitrile) (135 mg) was added in one portion to a neat mixture of tributyltin hydride (8.5 g, 29 mmol) and 2-butyn-1-ol (5.5 g, 80 mmol). The reaction mixture was warmed to 80 °C over 30 min and was stirred at this temperature for 3 h. Distillation afforded (Z)-2-(tributylstannyl)but-2-en-1-ol (7.8 g, 74%) as a colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.28 (q, 1H, $J = 7.1$ Hz), 4.08 (d, 2H, $J = 6.1$ Hz), 2.98 (s, 1H), 1.71 (d, 3H, $J = 7.1$ Hz), 1.60-1.08 (m, 18H), 0.86 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.4, 136.0, 70.5, 29.2, 27.7, 19.5, 13.6, 10.2; IR (KBr) $\nu_{\text{max}}$ 3320, 1630 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{16}$H$_{34}$OSnNa: 385.1532; found: 385.1532.
(Z)-2-Iodobut-2-en-1-ol (142). Iodine (6.3 g, 25 mmol) was added in a single portion to a solution of (Z)-2-(tributylstannyl)but-2-en-1-ol (5.0 g, 14 mmol) in CCl₄ (175 mL) at 0 °C. The reaction mixture was stirred for 10 min at this temperature and was poured onto an excess of 10% aqueous NaHSO₃. The aqueous phase was extracted with Et₂O, and the organic extracts were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (0-50% EtOAc/hexane) to afford 142 (2.6 g, 95%) as an orange oil: ¹H NMR (400 MHz, CDCl₃) δ 5.98 (q, 1H, J = 6.5 Hz), 4.26 (d, 2H, J = 6.0 Hz), 2.12 (t, 1H, J = 6.0 Hz), 1.79 (d, 3H, J = 6.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 131.1, 109.5, 71.4, 21.4; IR (KBr) νmax 3330, 1650 cm⁻¹; HRMS (ESI), m/z calc for C₄H₇IO: 197.9536; found: 197.9527.

(E)-2-Ethylidenepent-3-yn-1-ol (143). A reaction vessel was charged with PdCl₂(PPh₃)₂ (381 mg, 0.330 mmol) and flushed with argon. A solution of vinyl iodide 142 (1.30 g, 6.57 mmol) in THF (33 mL) at 23 °C was added to the flask in one portion by syringe. The reaction mixture was stirred for 5 min when a solution of propynylmagnesium bromide (0.5 M in THF, 26.3 mL, 13.1 mmol) was added dropwise over 10 min by syringe. The reaction mixture was warmed at 50 °C and was stirred 12-18 h at this temperature. The reaction mixture was cooled and poured onto saturated aqueous NH₄Cl and extracted with Et₂O. The organic extract was dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (silica doped with
2% Et₃N, 0-20% EtOAc/hexane) to afford enyne **143** (622 mg, 86%) as an orange oil: \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 5.87 (q, 1H, \(J = 6.8\) Hz), 4.00 (s, 2H), 2.24 (br s, 1H), 1.97 (s, 3H), 1.79 (d, \(J = 6.8\) Hz); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 131.6, 124.2, 91.5, 76.1, 66.2, 15.6, 4.3; IR (KBr) \(\nu_{max}\) 3376, 2916, 2853 cm\(^{-1}\); HRMS (ESI), \(m/z\) calc for C\(_7\)H\(_{10}\)ONa: 133.0629; found: 133.0631.

![Chemical Structure](image)

**\(2E,3E\)-2-Ethylidene-4-(phenyldimethylsilyl)pent-3-en-1-ol (144).**

A solution of PhMe₂SiLi (1 M in THF, 5.9 mL, 5.9 mmol) was added dropwise by syringe to a solution of dry CuCN (227 mg, 2.54 mmol) in THF (2 mL) at –50 °C. The reaction mixture was warmed to –10 °C and stirred at this temperature for 45 min. The reaction mixture was re-cooled to –50 °C and water (128 µL, 7.12 mmol) was added by syringe in a single portion. The reaction mixture was warmed to –10 °C and was stirred for 30 min. The flask was re-cooled to –50 °C and a solution of enyne **143** (112 mg, 1.02 mmol) in THF (2 mL) was added dropwise by syringe. The reaction mixture was warmed to –10 °C and was stirred for 2 h. The reaction mixture was poured onto saturated aqueous NH₄Cl/conc. NH₄OH (90:10) and stirred for 30 min. The aqueous phase was extracted with Et₂O and the combined organic extracts were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (silica doped with 2% Et₃N, 0-15% EtOAc/hexane) to afford diene **144** (244 mg, 85%) as a colorless oil: \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.64 (m, 2H), 7.59 (m, 3H), 6.26 (s, 1H), 5.67 (dd, \(J = 6.8, 0.8\) Hz), 4.08 (s, 2H), 1.72 (d, 3H, \(J = 1.6\) Hz), 1.61 (dd, 3H, \(J = 0.8, 6.8\) Hz), 0.44 (s,
(2E,3E)-2-Ethylidene-4-(phenyldimethylsilyl)pent-3-enoic acid methyl ester (145). Manganese dioxide (2.61 g, 30.0 mmol) was added in one portion to a solution of alcohol 144 (370 mg, 1.50 mmol) in CH₂Cl₂ (5 mL) at 25 °C and the reaction mixture was stirred for 3 d or until complete by TLC. The mixture was filtered through a pad of Celite® and the solids were washed several times with THF. The filtrate was concentrated in vacuo. The residue was dissolved in MeOH (1.7 mL) and acetic acid (214 µL, 3.75 mmol) was added by syringe followed by NaCN (368 mg, 7.50 mmol) in one portion. The reaction mixture was stirred for 1 h at 25 °C when additional MnO₂ (2.61 g, 30 mmol) was added in one portion. The reaction mixture was stirred for 18 h at 25 °C. The reaction mixture was filtered through a pad of Celite® and the solids were washed several times with THF. The filtrate was concentrated and the residue was suspended in Et₂O, poured onto H₂O, and extracted with Et₂O. The combined organic extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (silica doped with 2% Et₃N, 0-5% EtOAc/hexane) to afford dienoate 145 (370 mg, 90%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.58 (m, 2H), 7.38 (m, 3H) 6.92 (dq, 1H, J = 7.1, 1.2 Hz), 6.35 (d, 1H, J = 1.2 Hz), 3.74 (s, 3H), 1.57 (d, 3H, J = 1.6 Hz), 0.42 (s, 3H), 0.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.7,
141.1, 139.2, 139.1, 137.9, 133.9, 128.9, 127.7, 51.7, 16.9, 15.6, −0.1; IR (KBr) v max 3068, 2954, 1719, 1636, 1605, 1431, 1378, 1248, 1132, 1113, 834, 815 cm −1; HRMS (ESI), m/z calc for C16H24OSiNa: 297.1287; found: 297.1270.

(2E,3E)-2-Ethylidene-4-iodopent-3-enoic Acid Methyl Ester (137). A solution of vinylsilane 145 (0.82 g, 3.0 mmol) in hexafluoroisopropanol (9 mL) was treated with 2,6-lutidine (0.14 mL, 4.5 mmol) at 25 °C. The reaction mixture was cooled to 0 °C and N-iodosuccinimide (4.5 g, 4.5 mmol) was added in one portion. After stirring for 90 sec at 0 °C, the reaction mixture was poured onto a mixture of saturated aqueous Na2SO3 and CH2Cl2. The organic layer was washed with saturated aqueous NaHCO3 and NaCl. The combined organic layers were dried (Na2SO4) and concentrated. The residue was purified by flash chromatography (hexane) to afford vinyl iodide 137 (0.71 g, 89%) as an orange oil: 1H NMR (400 MHz, CDCl3) δ 6.94 (qd, 1H, J = 7.1, 1.2 Hz), 6.69 (dd, 1H, J = 1.4, 2.8), 3.73 (s, 3H), 2.27 (d, 3H, J = 1.4 Hz), 1.74 (dd, 3H, J = 1.4, 7.1 Hz); 13C NMR (100 MHz, CDCl3) δ 177.7, 140.6, 134.1, 130.3, 99.2, 52.0, 29.6, 15.8; IR (KBr) v max 2952, 1720, 1637, 1434, 1377, 1251, 1196, 1072, 832 cm −1; HRMS (ESI), m/z calc for C8H11O2INa: 288.9702; found: 288.9711.

3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrole-2,5-dione (147). A solution of bromomaleimide (5.15 g, 27.0 mmol) in DMF (1 L) at −40 °C
was treated with diisopropylethylamine (5.60 mL, 32.3 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (3.60 mL, 20.4 mmol) dropwise. The reaction mixture was stirred for 2 h at –40 °C, and was allowed to warm to 25 °C. The reaction was quenched by the addition of saturated aqueous NH₄Cl (200 mL) and was concentrated to 200 mL. The mixture was diluted with H₂O and was extracted with Et₂O (5 x 300 mL). The combined organic extracts were washed with saturated aqueous NaCl (400 mL), dried (Na₂SO₄), and concentrated to afford 147 as an oil (6.7 g, 81%), which was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 6.93 (s, 1H), 4.94 (s, 2H), 3.56 (dd, 2H, J = 8.4, 7.6 Hz), 0.90 (dd, 2H, J = 8.4, 8.0 Hz), 0.03 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 168.0, 165.0, 132.1, 131.9, 67.2, 67.1, 17.8, –1.5; IR (neat) ν max 2954, 2889, 1780, 1725, 1585, 1332 cm⁻¹.

![Structure](image)

3-Iodo-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrole-2,5-dione (148). A solution of NaI (18.3 g, 122 mmol) and maleimide 147 (6.20 g, 20.3 mmol) in acetone (20 mL) was warmed at reflux for 12 h. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated to afford a brown solid. Purification by flash chromatography (5% EtOAc/hexane) provided iodomaleimide 148 (7.17 g, 100%): ¹H NMR (400 MHz, CDCl₃) δ 7.23 (s, 1H), 4.97 (s, 2H), 3.58 (dd, 2H, J = 8.4, 8.0 Hz), 2.93 (dd, 2H, J = 8.4, 8.4 Hz), 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 169.4, 166.4, 140.8, 108.1, 67.4, 67.3, 17.9, –1.5; IR (neat) ν max 3074, 2948, 2894, 1769, 1714, 1562, 1338 cm⁻¹.
5-Allyl-5-hydroxy-3-iodo-1-((2-trimethylsilyl)ethoxy)methyl)-1,5-dihydropyrrol-2-one (149). A solution of allyl indium was generated from allyl iodide (0.92 g, 1.0 mmol) and indium (0.72 g, 6.3 mmol) in DMF (10 mL), and was added to a solution of iodomaleimide 148 (2.65 g, 4.70 mmol) in 56 mL DMF dropwise at –10 °C over 30 min. After stirring at –10 °C for 3 d, the reaction was quenched by the addition of saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O (4 x 100 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄) and concentrated to afford a yellow oil. Purification by flash chromatography (10-40% EtOAc/hexane) afforded alcohol 149 (1.6 g, 81%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.38 (s, 1H), 5.65 (m, 1H), 5.16 (dd, 1H, J = 11.6, 2.1), 5.10 (s, 1H), 4.89 (ABq, 2H, J = 11.2 Hz, Δυ = 28.0 Hz), 3.58 (m, 2H), 3.28 (br s, 1H) 2.55 (ABX, 2H, JAB = 14.2 Hz, JAX =7.2 Hz, JBX = 6.8 Hz, Δυ = 90.2 Hz), 0.91 (m, 2H), 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 155.5, 130.8, 120.2, 94.8, 92.7, 68.9, 66.6, 41.1, 18.1, −1.4; IR (neat) νmax 3363, 2933, 2905, 1710, 1691, 1247, 1078, 855 cm⁻¹; HRMS (ESI), m/z calc for C₁₃H₂₂NO₅SiNa: 418.0311; found: 418.0311.

5-Hydroxy-5-(2-hydroxyethyl)-3-iodo-1-((2-trimethylsilyl)ethoxy)methyl)-1,5-dihydropyrrol-2-one. A solution of alkene 149 (260
mg, 0.66 mmol) in CH₂Cl₂/MeOH (1:1, 66 mL) was cooled to −78 °C and a solution of ozone in oxygen was bubbled into the reaction mixture until a blue color developed. Nitrogen was bubbled into the reaction for 30 min to purge excess ozone, and was followed by the addition of sodium borohydride (27.4 mg, 0.73 mmol). The reaction was warmed to 0 °C and was stirred for 2 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl and concentrated to remove 80 percent of the CH₂Cl₂ and MeOH. The mixture was extracted with CH₂Cl₂ (4 x 50 mL) and the combined organics were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated to afford a colorless oil. Purification by flash chromatography (10-40% EtOAc/hexane) afforded the diol (220 mg, 92%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.53 (s, 1H), 4.89 (ABq, 2H, J = 11.2 Hz, Δν = 28.0 Hz), 4.54 (br s, 1H), 3.78 (m, 2H), 3.57 (m, 2H), 2.88 (br s, 1H) 2.38, (m, 1H), 1.95 (m, 1H), 0.89 (m, 2H), 0.0 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.6, 155.8, 94.1, 92.9, 68.7, 66.5, 58.5, 38.6, 18.1, −1.4; IR (neat) ν max 3546, 3465, 2959, 1731, 1437, 1234, 1048 cm⁻¹; HRMS (ESI), m/z calc for C₁₂H₂₂NO₄SiINa: 422.0261; found: 422.0261.

3-Iodo-5-(triethylsilanyloxy)-5-(2-(triethylsilanyloxy)ethyl)-1((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydropyrrol-2-one (150). 2,6-Lutidine (1.3 mL, 11.5 mmol) and Et₃SiOTf (1.2 mL, 5.7 mmol) were added sequentially to a solution of the above diol (575 mg, 2.6 mmol) in CH₂Cl₂ (16 mL) at −40 °C. The reaction mixture was allowed to warm to room temperature over 3 h and
was quenched by the addition of saturated aqueous NaCl. The aqueous layer was extracted with CH₂Cl₂ (4 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford a yellow oil. Purification by flash chromatography (5% EtOAc/hexane) afforded vinyl iodide 150 (900 mg, 91%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.54 (s, 1H), 4.80 (ABq, 2H, J = 11.2 Hz, Δν = 120 Hz), 3.75 (m, 2H), 3.57 (m, 2H), 2.27 (m, 1H), 1.93 (m, 1H), 1.95 (m, 1H), 0.90 (m, 20H), 0.58 (q, 6H, J = 5.3 Hz) 0.49 (q, 6H, J = 5.3 Hz) 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 156.8, 93.4, 93.1, 68.4, 66.4, 58.1, 42.8, 18.1, 6.8, 6.6, 5.6, 4.4, –1.4; IR (neat) ν max 2958, 2916, 2870, 2342, 1734, 1234, 1100 cm⁻¹; HRMS (ESI), m/z calc for C₂₄H₅₀NO₄SiINa: 650.1990; found: 650.1989.

(E)-3-(3-Bromo-2-methylacryloyl)-5-(triethylsilanyloxy)-5-(2(triethylsilanyloxyethyl)-1-(2-(trimethylsilanyl)ethoxy)methyl)-1,5-dihydropyrrol-2-one. (156). A solution of isopropylmagnesium chloride in Et₂O (2.0 M, 25 µL, 0.05 mmol) was added to a solution of vinyl iodide 150 (27 mg, 0.04 mmol) at –60 °C. The reaction was allowed to warm to –50 °C and a solution of CuCN·2LiCl (1 M, 50 µL, 0.05 mmol) was added. The reaction was allowed to warm to –40 °C and (E)-3-bromo-2-methylacryloyl chloride (8.5 µL, 0.07 mmol) was added in one portion. After 1 min, the reaction was quenched by the addition of pH 7.0 buffer and was extracted with Et₂O (4 x 4 mL). The combined organic extracts
were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated to provide a colorless residue. Purification by preparative TLC (10% EtOAc/hexane) afforded vinyl bromide 156 (18 mg, 65%): ¹H NMR (400 MHz, CDCl₃) δ 7.49 (s, 1H), 7.40 (s, 1H), 4.79 (ABq, 2H, J = 11.2 Hz, Δν = 138 Hz), 3.81 (m, 1H), 3.59 (m, 3H), 2.35 (m, 1H), 2.05 (s, 3H), 1.99 (m, 1H), 0.90 (m, 20H), 0.58 (q, 6H, J = 5.3 Hz) 0.49 (q, 6H, J = 5.3 Hz) 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 187.2, 166.3, 152.4, 142.9, 134.4, 128.8, 90.3, 67.9, 66.5, 58.2, 43.4, 18.2, 14.8, 6.8, 6.7, 5.8, 4.4, –1.4; IR (neat) νmax 2938, 2883, 2343, 1739, 1720, 1074, 743 cm⁻¹; HRMS (ESI), m/z calc for C₂₈H₅₄BrNO₅SiNa: 670.2391; found: 670.2391.

(2E,3E,5E,7E)-2-Ethylidene-4-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-3,5,7-trienoate methyl ester (157). In a dry box, Pd₂dba₃ (3 mg, 3.0 µmol) and Ph₃As (2 mg, 6.0 µmol) were added to a Schlenk flask equipped with a stir bar, which was capped with a septum and removed from the dry box. A solution of diene 93 (106 mg, 0.226 mmol) and vinyl iodide 137 (50.0 mg, 0.188 mmol) in DMF (1.3 mL) was added by syringe at 23 °C. The flask was wrapped with foil and stirred at 23 °C for 24 h. The reaction mixture was diluted with Et₂O and poured onto saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O, and the combined organic extracts were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (Florisil®, 0-5% EtOAc/hexane) to afford 157 (48.2 mg, 81%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.09 (dd, 1H, J = 17.2, 10.4...
Hz), 6.91 (q, 1H, J = 14.4 Hz), 6.53 (d, 1H, J = 15.2 Hz), 6.35 (dd, 1H, J = 15.6, 10.4 Hz), 6.13 (s, 1H), 5.60 (d, 1H, J = 17.6 Hz), 3.74 (s, 3H), 1.74 (dd, 3H, J = 7.4, 0.8 Hz), 1.69 (d, 3H, J = 1.2 Hz), 1.29 (s, 12H); 13C NMR (100 MHz, CDCl₃) δ 167.7, 149.9, 140.2, 138.1, 133.2, 130.6, 130.5, 128.4, 126.6, 83.2, 51.9, 24.8, 15.9, 14.3; IR (KBr) ν max 2979, 2933, 1722, 1620, 1452, 1358, 1263, 1145, 1009, 982, 850 cm⁻¹; HRMS (ESI), m/z calc for C₁₈H₂₇BO₂NO₂SiEt₃CO₂CH₃: 341.1900; found: 341.1899.

A reaction vessel was charged with Pd(OAc)₂ (1.6 mg, 7.0 µmol) and Ph₃P (3.7 mg, 14 µmol) and was flushed with argon. A solution of boronate 157 (22 mg, 70 µmol) and vinyl bromide 156 (30 mg, 46 µmol) in MeOH (130 µL) and THF (130 µL) was added by syringe, followed by aqueous Na₂CO₃ (1 M, 97 µL, 97 µmol) in one portion. The flask was wrapped with foil and stirred at 23 °C until TLC indicated starting halide was consumed. The reaction mixture was concentrated and the residue was purified by preparative TLC (10% EtOAc/hexane containing 2% Et₃N) to afford 158 (30 mg, 85%) as a yellow oil: 1H NMR (400 MHz, CDCl₃) δ 7.31 (s, 1H), 7.0-6.96 (m, 2H), 6.71-6.40 (m, 4H), 6.18 (s, 1H), 4.99 (d, 1H, J = 8.8 Hz), 4.65 (d, 1H, J = 10.8 Hz) 3.85 (m, 1H), 3.77 (s, 3H), 3.70-3.56 (m, 3H), 2.40 (m, 1H), 2.01 (s, 3H), 1.99
(m, 1H), 1.75 (dd, 3H, J = 0.8, 7.4 Hz), 1.71 (d, 3H, J = 1.2 Hz), 0.90 (m, 20H), 0.58 (m, 12H), 0.00 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 168.9, 167.6, 149.9, 140.2, 140.0, 139.7, 138.4, 138.0, 130.6, 130.4, 128.6, 127.9, 126.7, 126.6, 126.55, 90.2, 68.2, 65.8, 58.3, 51.9, 45.7, 29.3, 23.8, 18.2, 15.3, 8.8, 6.8, 5.8, 4.4, –1.4; IR (KBr) \(\nu_{\text{max}}\) 3248, 2940, 1714, 1632, 1431, 1251, 994, 728 cm\(^{-1}\); HRMS (ESI), m/z calc for C\(_{40}\)H\(_{69}\)NO\(_7\)Si\(_3\)Na: 783.2246; found: 783.2281.

![Lucilactaene (10)](image)

Lucilactaene (10). Trifluoroacetic acid (0.25 mL) was added slowly by syringe to a solution of 158 (2.5 mg, 5.4 µmol) in CH\(_2\)Cl\(_2\) (2.5 mL) at 0 °C and the reaction mixture was stirred at 23 °C for 5 h. The reaction mixture was concentrated and the residue was purified by preparative TLC (Et\(_2\)O, 2% Et\(_3\)N) to afford 10 (1.4 mg, 64%) as a yellow solid: \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.49 (d, 1H, J = 11.5 Hz), 7.01 (qd, 1H, J = 7.2, 0.8 Hz), 6.85 (dd, 1H, J = 14.4, 10.8 Hz), 6.68 (dd, 1H, J = 14.4, 10.8 Hz), 6.62 (d, 1H, J = 15.2 Hz), 6.47 (dd, 1H, J = 15.4, 10.8 Hz), 6.24 (s, 1H), 5.06 (br s, 1H), 4.40 (br s, 1H), 4.22 (br s, 1H), 4.12 (dd, 1H, J = 8.7, 8.6, 3.6 Hz), 4.00 (ddd, 1H, J = 8.8, 8.8, 6.3 Hz), 3.76 (s, 3H), 2.40 (ddd, 1H, J = 12.9, 8.7, 8.7 Hz), 2.28 (ddd, 1H, J = 12.9, 8.7, 3.6 Hz), 1.95 (s, 3H), 1.75 (dd, 3H, J = 7.2, 1.2 Hz), 1.72 (d, 3H, J = 0.8 Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 197.0, 170.5, 167.5, 145.6, 143.6, 142.3, 140.5, 138.0, 134.2, 130.4, 128.3, 128.1, 94.5, 85.7, 68.5, 56.6, 51.9, 37.5, 15.9, 14.3,
11.6; IR (neat) $\nu_{\max}$ 3448, 2940, 1714, 1650, 1583, 1431, 1252, 996, 725 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{22}$H$_{27}$NO$_6$Na: 424.1736; found: 424.1739.

![Chemical structure](image)

3-(Dodecanoyl)-5-(triethylsilanyloxy)-5-(2-(triethylsilanyloxyethyl)-1-(2-(trimethylsilanyl)ethoxymethyl)-1,5-dihydropyrrol-2-one. (160). A solution of isopropylmagnesium chloride in THF (1.9 M, 92 µL, 0.175 mmol) was added to a solution of vinyl iodide 150 (100 mg, 0.159 mmol) in THF (0.8 mL) at –60 °C. The reaction was allowed to warm to –50 °C and a solution of CuCN·2LiCl (0.5 M, 0.35 mL, 0.175 mmol) was added. The reaction was allowed to warm to –40 °C and dodecanoyl chloride (67 µL, 0.199 mmol) was added in one portion and was allowed to warm to 25 °C. After 30 min, the reaction was quenched by the addition of pH 7.0 buffer and was extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na$_2$SO$_4$), and concentrated to provide a colorless residue. Purification by flash chromatography (5% EtOAc/hexane) afforded maleimide 160 (75 mg, 69%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.78 (s, 1H), 4.78 (ABq, 2H, $J = 11.2$ Hz, $\Delta\nu = 152$ Hz), 3.79 (m, 1H), 3.59 (m, 3H), 2.92 (q, 2H, $J = 7.2$ Hz), 2.35 (m, 1H), 2.05 (s, 3H), 1.93 (m, 1H), 1.63 (m, 2H), 1.25 (br s, 16H), 0.91 (m, 23H), 0.59 (q, 6H, $J = 3.6$ Hz), 0.53 (q, 6H, $J = 3.6$ Hz), 0.00 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 196.5, 166.8, 155.5, 133.8, 89.6, 67.8, 66.3, 58.1, 43.1, 41.9, 31.9, 29.6, 29.5, 29.5, 29.3, 29.2, 23.5, 22.7, 18.1, 14.1, 6.8, 6.6, 5.83, 4.3, −1.4; IR (neat) $\nu_{\max}$ 2954,
3-(Isobutyryl)-5-(triethylsilanyloxy)-5-(2(triethylsilanyloxyethyl)-1-(2-(trimethylsilanyl)ethoxymethyl)-1,5-dihydropyrrol-2-one. A solution of isopropylmagnesium chloride in THF (1.9 M, 0.1 mL, 0.202 mmol) was added to a solution of vinyl iodide 150 (115 mg, 0.183 mmol) in THF (1 mL) at –60 °C. The reaction was allowed to warm to –50 °C and a solution of CuCN·2LiCl (0.5 M, 0.4 mL, 0.20 mmol) was added. The reaction was allowed to warm to –40 °C and isobutyryl chloride (23 µL, 0.22 mmol) was added in one portion and was allowed to warm to 25 °C. After 30 min, the reaction was quenched by the addition of pH 7.0 buffer and was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and concentrated to provide a colorless residue. Purification by flash chromatography (5% EtOAc/hexane) afforded maleimide 160 (78 mg, 78%): ¹H NMR (400 MHz, CDCl₃) δ 7.81 (s, 1H), 4.78 (ABq, 2H, J = 11.2 Hz, Δν = 140 Hz), 3.77 (m, 1H), 3.56 (m, 4H), 2.35 (m, 1H), 1.92 (m, 1H), 1.12 (d, 3H, J = 2.8 Hz), 1.10 (d, 3H, J = 2.8 Hz), 0.90 (m, 20H), 0.55 (q, 6H, J = 3.6 Hz), 0.48 (q, 6H, J = 3.6 Hz), –0.01 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ, 200.1, 166.7, 156.11, 133.6, 125, 89.5, 67.8, 66.3, 58.1, 43.2, 38.5, 18.1, 17.7, 6.6, 5.8, 4.4, –1.5; IR (neat) ν max 2955, 2917, 2849, 2359, 1772, 1469, 1457, 1249, 1100, 1003, 836, 728 cm⁻¹; HRMS (ESI), m/z calc for C₃₆H₇₃NO₅Si₃Na: 706.4694; found: 706.4694.
2916, 2877, 2359, 2340, 1714, 1692, 1462, 1366, 1249, 1078, 1007, 971, 860, 836 cm⁻¹; HRMS (ESI), m/z calc for C_{28}H_{57}NO_{5}Si_{3}Na: 594.3442; found: 594.3441.

6-Dodecanoyl-hexahydro-3a-hydroxyfuro[3,2-b]pyrrol-5-one

(162). Trifluoroacetic acid (0.5 mL) was added slowly by syringe to a solution of 160 (100 mg, 0.146 mmol) in CH₂Cl₂ (2 mL) at 0 °C and the reaction mixture was stirred at 23 °C for 5 h. The reaction mixture was concentrated and the residue was treated with NH₄OH (1 mL) and was stirred at 23 °C for 5 h. The aqueous layer was extracted with CH₂Cl₂ (4 x 2 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford a white solid. Purification by flash chromatography (15% MeOH/CHCl₃, 1% NH₄OH) afforded furan 162 (<1 mg, 2%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 5.56 (br s, 1H), 4.72 (s, 1H), 3.93 (m, 1H), 3.87 (m, 1H), 3.65 (s, 1H), 2.29 (m, 3H), 2.08 (m, 1H), 1.54 (m, 2H), 1.25 (br s, 16H) 0.89 (m, 3H).

1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-pyrrole-2,5-dione

(165). A solution of maleimide (0.500 g, 5.15 mmol) in CH₂Cl₂ (20 mL) at –60 °C was treated with diisopropylethylamine (1.07 mL, 6.18 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (1.1 mL, 6.18 mmol) dropwise. The reaction
mixture was stirred for 2 h at –40 °C, and was allowed to warm to 25 °C. The reaction was quenched by the addition of saturated aqueous NH₄Cl (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (4 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford a white solid. Purification by flash chromatography (15% EtOAc/hexane) afforded maleimide 165 (1.10 g, 94%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.77 (s, 2H), 4.94 (s, 2H), 3.58 (dd, 2H, J = 8.4, 7.6 Hz), 0.93 (dd, 2H, J = 9.2, 7.2 Hz), 0.04 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 134.5, 67.1, 66.4, 17.9, –1.5; IR (neat) ν max 2954, 2889, 1780, 1725, 1585, 1332 cm⁻¹.

A solution of allyl indium was generated from allyl iodide (0.4 mL, 4.35 mmol) and indium (0.33 g, 2.86 mmol) in DMF (5 mL), and was added to a solution of maleimide 165 (500 mg, 2.29 mmol) in 5 mL DMF dropwise at –10 °C over 30 min. After stirring at 25 °C for 1 d, the reaction was quenched by the addition of saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O (4 x 100 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄) and concentrated to afford a yellow oil. Purification by flash chromatography (10-40% EtOAc/hexane) afforded alcohol 166 (0.50 g, 82%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.91 (d, 1H, J = 6 Hz), 5.98 (d, 1H, J = 6 Hz), 5.61 (m, 1H), 5.11

1-((2-(Trimethylsilyl)ethoxy)methyl)-5-allyl-5-hydroxy-1H-pyrrol-2(5H)-one (166). A solution of allyl indium was generated from allyl iodide (0.4 mL, 4.35 mmol) and indium (0.33 g, 2.86 mmol) in DMF (5 mL), and was added to a solution of maleimide 165 (500 mg, 2.29 mmol) in 5 mL DMF dropwise at –10 °C over 30 min. After stirring at 25 °C for 1 d, the reaction was quenched by the addition of saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O (4 x 100 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄) and concentrated to afford a yellow oil. Purification by flash chromatography (10-40% EtOAc/hexane) afforded alcohol 166 (0.50 g, 82%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 6.91 (d, 1H, J = 6 Hz), 5.98 (d, 1H, J = 6 Hz), 5.61 (m, 1H), 5.11
(dd, 1H, $J = 10.4, 1.6$ Hz), 5.07 (s, 1H), 4.76 (s, 2H), 3.99 (s, 1H), 3.52 (m, 2H), 2.67 (ABX, 2H, $J_{AB} = 14.2$ Hz, $J_{AX} = 7.2$ Hz, $J_{BX} = 6.8$ Hz, $\Delta \nu = 90.2$ Hz), 0.89 (m, 2H), $\text{--}0.02$ (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.3, 150.1, 131.5, 125.9, 119.3, 91.2, 67.7, 66.1, 41.1, 17.9, $\text{--}1.5$; IR (neat) $\nu_{\text{max}}$ 3363, 2933, 2905, 1710, 1691, 1247, 1078, 855 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{13}$H$_{23}$NO$_3$SiNa: 292.1345; found: 292.1342.

![Chemical Structure](image_url)

1-((2-(Trimethylsilyl)ethoxy)methyl)-5-allyl-5-(triethylsilanyloxy)-1H-pyrrol-2(5H)-one (167). 2,6-Lutidine (0.53 mL, 4.56 mmol) and Et$_3$SiOTf (0.93 mL, 4.11 mmol) were added sequentially to a solution of alcohol 166 (615 mg, 2.28 mmol) in CH$_2$Cl$_2$ (5 mL) at $-40$ $^\circ$C. The reaction mixture was allowed to warm to room temperature over 3 h and was quenched by the addition of saturated aqueous NaCl. The aqueous layer was extracted with CH$_2$Cl$_2$ (4 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na$_2$SO$_4$), and were concentrated to afford a yellow oil. Purification by flash chromatography (5% EtOAc/hexane) afforded silyl ether 167 (814 mg, 93%) as a colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.92 (d, 1H, $J = 6$ Hz), 6.11 (d, 1H, $J = 6$ Hz), 5.68 (m, 1H), 5.10 (dd, 1H, $J = 4, 1.2$ Hz), 5.07 (s, 1H), 4.80 (ABq, 2H, $J = 11.2$ Hz, $\Delta \nu = 116$ Hz), 3.72 (dd, 1H, $J = 9.2, 6.8$ Hz), 3.56 (m, 2H), 2.67 (ABX, 2H, $J_{AB} = 14$ Hz, $J_{AX} = 7.6$ Hz, $J_{BX} = 6.4$ Hz, $\Delta \nu = 116$ Hz), 0.91 (m, 11H), 0.50 (m, 6H), $\text{--}0.02$ (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.4, 149.5, 132.5, 126.8, 118.8, 67.6, 66.2, 59.9, 44.2, 18.1, 6.8, 6.7, 5.8, 4.5, $\text{--}1.4$; IR
(neat) $\nu_{\text{max}}$ 2954, 2916, 2877, 2342, 1719, 1366, 1248, 1122, 1073 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{19}$H$_{37}$NO$_3$Si$_2$Na: 406.2210; found: 406.2208.

1-((2-(Trimethylsilyl)ethoxy)methyl)-5-(2-hydroxyethyl)-5-(triethylsilanyloxy)-1H-pyrrol-2(5H)-one (168). A solution of alkene 167 (500 mg, 1.30 mmol) in CH$_2$Cl$_2$/MeOH (1:1, 16 mL) was cooled to $-78$ °C and a solution of ozone in oxygen was bubbled into the reaction mixture until a blue color developed. Nitrogen was bubbled into the reaction for 30 min to purge excess ozone, and was followed by the addition of sodium borohydride (345 mg, 9.12 mmol). The reaction was warmed to 0 °C and was stirred for 2 h. The reaction was quenched by the addition of saturated aqueous NH$_4$Cl and concentrated to remove 80 percent of the CH$_2$Cl$_2$ and MeOH. The mixture was extracted with CH$_2$Cl$_2$ (4 x 15 mL) and the combined organics were washed with saturated aqueous NaCl, dried (Na$_2$SO$_4$), and concentrated to afford a colorless oil. Purification by flash chromatography (10-40% EtOAc/hexane) afforded alcohol 168 (402 mg, 83%) as a colorless oil: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.08 (d, 1H, $J = 6$ Hz), 6.14 (d, 1H, $J = 6$ Hz), 4.78 (ABq, 2H, $J = 10.8$ Hz, $\Delta\nu = 96.4$ Hz), 3.63 (m, 4H), 2.36 (m, 1H), 2.31 (br s, 1H), 2.05 (m, 1H), 0.92 (m, 11H), 0.52 (dd, 6H, $J = 15.6, 7.6$ Hz), 0.0 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.6, 149.9, 126.5, 94.1, 92.2, 67.6, 66.5, 58.5, 41.9, 18.2, 6.7, 5.7, $-1.5$; IR (neat) $\nu_{\text{max}}$ 3422, 2954, 2858, 1714, 1472, 1409, 1368, 1250, 1073 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{18}$H$_{37}$NO$_4$Si$_2$Na: 410.2153; found: 410.2204.
4-((2-(Trimethylsilyl)ethoxy)methyl)-hexahydro-3a-hydroxyfuro[3,2-b]pyrrol-5-one (169). Sodium methoxide (13 mg, 0.25 mmol) was added in a single portion to a solution of alcohol 168 (80 mg, 0.21 mmol) in methanol (1 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 0.5 h and was quenched by the addition of saturated aqueous NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ (3 x 1 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford furan 169 (54 mg, 95%) as a white solid, which was used without further purification: ¹H NMR (400 MHz, CDCl₃) δ 4.9 (ABq, 2H, J = 10.8 Hz, Δν = 140 Hz), 4.18 (d, 1H, J = 6 Hz), 4.01 (m, 1H), 3.92 (m, 1H), 3.80 (br s, 1H), 3.60 (m, 2H), 2.80 (dd, 1H, J = 18, 6.8 Hz), 2.47 (d, 1H, J = 18 Hz), 2.37 (m, 1H), 2.28 (m, 1H), 0.93 (m, 2H), 0.0 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 80.6, 69.9, 67.8, 66.7, 37.2, 36.5, 18.2, –1.5.

Hexahydro-3a-hydroxyfuro[3,2-b]pyrrol-5-one (170). Trifluoroacetic acid (0.9 mL) was added slowly by syringe to a solution of 169 (15 mg, 55 µmol) in CH₂Cl₂ (3.5 mL) at 0 °C and the reaction mixture was stirred at 23 °C for 5 h. The reaction mixture was concentrated and the residue was treated with NH₄OH (1 mL) and was stirred at 23 °C for 5 h. The aqueous layer was extracted with CH₂Cl₂ (4 x 2 mL) and the
combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford a white solid. Purification by flash chromatography (15% MeOH/CHCl₃, 1% NH₄OH) afforded furan 170 (4 mg, 55%) as a white solid: ¹H NMR (400 MHz, MeOD) δ 4.1 (dd, 1H, J = 6.4, 0.8 Hz), 3.89 (m, 2H), 2.72 (dd, 1H, J = 18, 6 Hz), 2.47 (d, 1H, J = 18 Hz), 2.18 (m, 1H), 2.11 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 82.7, 67.0, 39.2, 36.5; IR (neat) ν max 3363, 3187, 2923, 1667, 1395, 1147, 1061 cm⁻¹; HRMS (ESI), m/z calc for C₆H₉NO₃Na: 166.0480; found: 166.0480.

![Chemical structure of compound 170]

1-((2-(Trimethylsilyl)ethoxy)methyl)-5-(2-methoxyethyl)-5-(triethylsilanyloxy)-1H-pyrrol-2(5H)-one  (171). 2,6-di-tert-butylpyridine (0.23 mL, 1.01 mmol) and MeOTf (0.11 mL, 1.01 mmol) were added sequentially to a solution of alcohol 168 (300 mg, 0.774 mmol) in CH₂Cl₂ (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 3 h and was quenched by the addition of saturated aqueous NH₄Cl. The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford a yellow oil. Purification by flash chromatography (10% EtOAc/hexane) afforded methyl ether 171 (200 mg, 64%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, 1H, J = 6 Hz), 6.06 (d, 1H, J = 6 Hz), 4.78 (ABq, 2H, J = 11.2 Hz, Δν = 138 Hz), 3.54 (m, 3H), 3.27 (s, 3H), 2.33 (m, 1H), 2.01 (m, 1H), 0.92 (m, 11H), 0.50 (m, 6H), −0.01 (s, 9H); ¹³C NMR (100 MHz,
CDCl₃) δ 169.5, 150.6, 125.3, 68.2, 67.5, 66.0, 58.4, 39.7, 16.2, 6.6, 5.7, –1.45; IR (neat) νₘᵢₓ 2945, 2913, 2858, 2343, 1711, 1357, 1245, 1119, 1075 cm⁻¹; HRMS (ESI), m/z calc for C₁₉H₃₉NO₄Si₂Na: 424.2310; found: 424.2301.

(5E)-5-(2-Methoxyethylidene)-1H-pyrrol-2(5H)-one (172). Trifluoroacetic acid (0.1 mL) was added slowly by syringe to a solution of 171 (10 mg, 25 µmol) in CH₂Cl₂ (0.1 mL) at 0 °C and the reaction mixture was stirred at 23 °C for 5 h. The reaction mixture was concentrated and the residue was treated with NH₄OH (1 mL) and was stirred at 23 °C for 5 h. The aqueous layer was extracted with CH₂Cl₂ (4 x 2 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄), and were concentrated to afford a white solid. Purification by flash chromatography (15% MeOH/CHCl₃, 1% NH₄OH) afforded furan 172 (0.8 mg, 23%) as a orange solid: ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, 1H, J = 1.2 Hz), 6.23 (d, 1H, J = 9.2 Hz) 5.55 (t, 1H, J = 8.8 Hz) 4.18 (d, 2H, J = 7.2 Hz), 3.37 (s. 3H); IR (neat) νₘᵢₓ 3410, 2922, 2851, 2360, 1699, 1457, 1376, 1264, 1202, 744 cm⁻¹; HRMS (ESI), m/z calc for C₇H₉NO₂Na: 162.0526; found: 162.0533.
5-Hydroxy-5-methyl-1H-pyrrol-2(5H)-one (173). A solution of methyl magnesium bromide in Et₂O (3M, 0.8 mL, 2.47 mmol) was added to a solution of maleimide 164 (200 mg, 2.06 mmol) in Et₂O (8 mL) dropwise at −78 °C over 30 min. After stirring at 25 °C for 1 h, the reaction was quenched by the addition of saturated aqueous NH₄Cl. The aqueous layer was extracted with Et₂O (3 x 5 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried (Na₂SO₄) and concentrated to afford a yellow solid. Purification by flash chromatography (10-40% EtOAc/hexane) afforded alcohol 173 (100 mg, 43%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.59 (br s, 1H), 6.91 (d, 1H, J = 7.2 Hz), 5.88 (d, 1H, J = 7.2 Hz), 1.56 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.6, 152.8, 125.1, 87.8, 24.3; IR (neat) νmax 3363, 2933, 2905, 1710, 1691, 1078, 855 cm⁻¹; HRMS (ESI), m/z calc for C₅H₇NO₂Na: 136.0374; found: 136.0372.

4-Methoxy-5-methyl-6-oxo-6H-pyran-2-carbaldehyde (177). Selenium dioxide (1.03 g, 9.34 mmol) was added in a single portion to a solution of pyrone 176 (240 mg, 1.56 mmol) in dioxane (8 mL) in a sealed tube. The reaction mixture was warmed at 180 °C and was stirred rapidly at this temperature for 3 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (silica, 5% acetone/chloroform) to afford
aldehyde 177 (171 mg, 65%) as an light yellow solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.56 (s, 1H), 7.00 (s, 1H), 3.97 (s, 3H), 2.03 (s, 3H); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 183.4, 163.3, 162.4, 152.3, 111.2, 101.6, 56.8, 9.6; IR (KBr) $\nu$$_{max}$ 3080, 2957, 1682, 1636, 1553, 1451, 1340, 1256, 1132, 1017, 857, 747 cm$^{-1}$; HRMS (ESI), $m$/z calc for C$_8$H$_8$O$_4$Na: 191.0320; found: 191.0319.

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\begin{align*}
\text{OMe} & \quad \text{O} \\
\text{I} & \quad \text{I} \\
\text{O} & \quad \text{O} \\
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6-((E)-2-Iodovinyl)-4-methoxy-3-methyl-2H-pyran-2-one (174). A solution of aldehyde 177 (25 mg, 0.15 mmol) and CH$_3$I (117 mg, 0.30 mmol) in dioxane (1 mL) were added by syringe to a solution of anhydrous CrCl$_2$ (110 mg, 0.89 mmol) in THF (1 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 3 h and poured onto a large excess of water and was extracted with Et$_2$O. The combined organic extracts were washed with brine and dried (MgSO$_4$) and concentrated. The residue was purified by flash chromatography (2% acetone/chloroform) to afford vinyl iodide 174 (28 mg, 64%) as an off white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J$ = 14.8 Hz, 1H), 7.83 (d, $J$ = 14.8 Hz, 1H), 4.90 (s, 1H), 3.88 (s, 3H), 1.91 (s, 3H); $^{13}$C NMR (63 MHz, CDCl$_3$) $\delta$ 164.9, 164.1, 155.9, 135.8, 104.2, 95.7, 86.6, 56.3, 8.9; IR (KBr) $\nu$$_{max}$ 3463, 3089, 2919, 1684, 1552, 1465, 1374, 1348, 1289, 1254 cm$^{-1}$; HRMS (ESI), $m$/z calc for C$_9$H$_9$IO$_3$Na: 314.9494; found: 314.9496.
4-Methoxy-3-methyl-6-((1E,3E,5E)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-1,3,5-trienyl)-2H-pyran-2-one (180). In a dry box, Pd$_2$dba$_3$ (1.2 mg, 1.3 μmol) and Ph$_3$As (0.8 mg, 2.6 μmol) were added to a Schlenk flask equipped with a stir bar, which was capped with a septum and removed from the dry box. A solution of diene 93 (44 mg, 94 μmol) and vinyl iodide 174 (25 mg, 86 μmol) in NMP (0.9 mL) was added by syringe at 23 °C. The flask was wrapped with foil and stirred at 23 °C for 24 h. The reaction mixture was diluted with Et$_2$O and poured onto saturated aqueous NH$_4$Cl. The aqueous layer was extracted with Et$_2$O, and the combined organic extracts were dried (MgSO$_4$) and concentrated. The residue was purified by flash chromatography (2% acetone/chloroform) to afford 180 (26 mg, 88%) as an orange-red solid: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.18 (dd, $J = 15.2$, 10.8 Hz, 1H), 7.05 (dd, $J = 17.2$, 10.4 Hz, 1H), 6.53 (dd, $J = 14.8$, 10.4 Hz, 1H), 6.42 (dd, $J = 14.8$, 10.2 Hz, 1H), 6.13 (d, $J = 15.2$, 1H), 6.07 (s, 1H), 5.71 (d, $J = 17.6$ Hz, 1H), 3.88 (s, 3H), 1.95 (s, 3H), 1.29 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.2, 164.7, 157.0, 148.5, 139.3, 135.9, 134.1, 123.9, 117.0, 96.2, 83.4, 56.2, 24.8; IR (KBr) $\nu_{\text{max}}$ 3425, 3143, 2990, 2896, 2249, 1813, 1790, 1649, 1561, 1472, 1378, 1096, 914, 750 cm$^{-1}$; HRMS (ESI), m/z calc for C$_{19}$H$_{25}$BO$_3$Na: 367.1693; found: 367.1692.
Gymnoconjugatin B (19). A reaction vessel was charged with Pd(OAc)$_2$ (1.7 mg, 7.6 μmol) and Ph$_3$P (4.0 mg, 15 μmol) and was flushed with argon. A solution of boronate 180 (26 mg, 70 μmol) and vinyl bromide 175 (14 mg, 83 μmol) in THF (1 mL) was added by syringe, followed by aqueous Na$_2$CO$_3$ (1 M, 0.15 mL, 0.15 mmol) in one portion. The flask was wrapped with foil and the reaction mixture was stirred at 23 °C until TLC indicated starting halide was consumed. The reaction mixture was concentrated and the residue was purified by preparative TLC (7% acetone/chloroform) to afford gymnoconjugatin B (19) (18 mg, 77%) as a red solid: $^1$H NMR (400 MHz, $d_6$-DMSO) δ 7.68 (br s, 1H), 7.06 (dd, $J = 15.2$, 11.5 Hz, 1H), 6.76 (dd, $J = 15.6$, 10.0 Hz, 1H), 6.74 (dd, $J = 15.1$, 9.6 Hz, 1H), 6.67 (s, 1H), 6.59 (d, $J = 15.2$ Hz, 1H), 6.59 (dd, $J = 14.6$, 10.0 Hz, 1H), 6.55 (dd, $J = 14.6$, 10.0 Hz, 1H), 6.54 (br s, 1H), 6.53 (br s, 1H), 6.51 (dd, $J = 14.6$, 11.5 Hz, 1H), 6.36 (d, $J = 15.2$ Hz, 1H), 3.89 (s, 3H), 1.81 (s, 3H); $^{13}$C NMR (100 MHz, $d_6$-DMSO) δ 165.9, 163.4, 156.9, 152.7, 143.5, 138.3, 135.6, 133.2, 131.6, 128.7, 127.2, 122.6, 121.3, 112.4, 110.1, 100.7, 96.8, 56.8, 8.9; UV (MeOH) $\lambda_{\text{max}}$ 442.5, 423.5, 330.5, 319.5, 264.0, 224.0 nm; IR (KBr) $\nu_{\text{max}}$ 3154, 2990, 2896, 2249, 1813, 1790, 1649, 1561, 1467, 1384, 1167, 1091, 908, 744 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{19}$H$_{18}$O$_4$Na: 333.1103; found: 333.1109.
6-Acetyl-4-methoxy-3-methyl-2H-pyran-2-one (182). Selenium dioxide (219 mg, 1.99 mmol) was added in a single portion to a solution of pyrone 181 (51 mg, 0.33 mmol) in dioxane (1.3 mL) in a sealed tube. The reaction mixture was warmed at 190 °C and was stirred rapidly at this temperature for 3 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated. The crude product was treated with MnO₂ (720 mg, 8.3 mmol) in CHCl₃ (2 ml) and the reaction mixture was stirred for 24 h. The reaction mixture was filtered, concentrated and the residue was purified by flash chromatography (3% acetone/chloroform) to afford ketone 182 (40 mg, 67%) as an off yellow solid: ¹H NMR (250 MHz, CDCl₃) δ 7.05 (s, 1H), 3.95 (s, 3H), 2.54 (s, 3H), 2.01 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.7, 164.1, 163.3, 153.0, 109.7, 98.1, 56.7, 25.9, 9.4.; IR (KBr) νmax 3460, 2955, 2849, 1684, 1619, 1396, 1343, 1261, 1161 cm⁻¹; HRMS (ESI), m/z calc for C₉H₁₀O₄Na: 205.0477; found: 205.0477.

6-(1-Iodoprop-1-en-2-yl)-4-methoxy-3-methyl-2H-pyran-2-one (183). A solution of ketone 182 (40 mg, 0.22 mmol) and CHI₃ (173 mg, 0.44 mmol) in dioxane (1 mL) were added by syringe to a solution of anhydrous CrCl₂ (162 mg, 1.32 mmol) in THF (1 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 3 h and poured onto a large excess of water and was extracted with Et₂O. The combined organic extracts were washed with brine and dried (MgSO₄) and concentrated. The residue was
purified by flash chromatography (2% acetone/chloroform) to afford a 50:50 $E/Z$ mixture of vinyl iodide 183 (48 mg, 71%) as an off white solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 (s, 1H), 6.68 (s, 1H), 6.60 (dd, $J$ = 4.8, 2.4 Hz, 1H) 6.25 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 2.18 (d, $J$ = 2.4 Hz, 3H), 2.13 (d, $J$ = 1.6 Hz, 3H), 1.95 (s, 3H), 1.92 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.2, 164.0, 139.4, 136.9, 98.0, 97.5, 93.4, 89.9, 78.8, 56.4, 56.2, 23.2, 20.6, 8.8, 8.8; IR (KBr) $\nu_{\text{max}}$ 3472, 2943, 2907, 2849, 1713, 1666, 1631, 1543, 1455, 1384, 1349, 1243, 1149 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_9$H$_9$IO$_3$Na: 328.9651; found: 328.9652.

4-Methoxy-3-methyl-6-((6E)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,4,6-trien-2-yl)-2H-pyran-2-one (184). In a dry box, Pd$_2$dba$_3$ (1.6 mg, 2.0 $\mu$mol) and Ph$_3$As (1.3 mg, 4.0 $\mu$mol) were added to a Schlenk flask equipped with a stir bar, which was capped with a septum and removed from the dry box. A solution of diene 93 (61 mg, 0.13 mmol) and vinyl iodide 183 (32 mg, 0.11 mmol) in NMP (1.5 mL) was added by syringe at 23 °C. The flask was wrapped with foil and stirred at 23 °C for 24 h. The reaction mixture was diluted with Et$_2$O and poured onto saturated aqueous NH$_4$Cl. The aqueous layer was extracted with Et$_2$O, and the combined organic extracts were dried (MgSO$_4$) and concentrated. The residue was purified by flash chromatography (2% acetone/chloroform) to afford a 50:50 $E/Z$ mixture of triene 184 (24 mg, 65%) as a orange-red solid: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.20 (d, $J$ = 2.4 Hz, 1H), 7.16 (s, 1H), 7.12–7.15 (m, 1H), 7.08–7.10 (m, 1H), 6.69 (dd, $J$ = 14.8, 11.6 Hz, 1H), 7.16 (s, 1H), 7.12–7.15 (m, 1H), 7.08–7.10 (m, 1H), 6.69 (dd, $J$ = 14.8, 11.6 Hz, 1H),
6.58 (dd, J = 14.4, 10.4 Hz, 1H), 6.39 (dd, J = 14.8, 10.8 Hz, 1H), 6.31 (d, J = 12 Hz, 1H), 6.20 (s, 1H), 6.15 (s, 1H), 5.71 (d, J = 17.6 Hz, 1H), 5.64 (d, J = 17.6 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.28 (s, 12H), 1.27 (s, 12H); 13C NMR (100 MHz, CDCl3) δ 165.6, 164.7, 159.3, 159.3, 149.4, 149.0, 139.4, 138.6, 134.2, 132.6, 131.3, 131.1, 128.4, 127.5, 103.1, 96.1, 93.1, 83.4, 83.3, 56.2, 56.1, 29.7, 27.8, 24.9, 24.8, 21.8, 17.5, 13.6, 12.6, 8.8, 8.7; IR (KBr) νmax 3425, 3143, 2990, 2896, 2249, 1631, 1531, 1384, 995 cm⁻¹; HRMS (ESI), m/z calc for C20H27BO5Na: 381.1853; found: 381.1849.

Gymnoconjugatin A (18). A reaction vessel was charged with Pd(OAc)2 (1.0 mg, 4.6 μmol) and Ph₃P (2.4 mg, 9.2 μmol) and was flushed with argon. A solution of boronate 184 (17 mg, 46 μmol) and vinyl bromide 175 (8.8 mg, 51 μmol) in THF (1 mL) was added by syringe, followed by aqueous Na₂CO₃ (1 M, 0.1 mL, 0.09 mmol) in one portion. The flask was wrapped with foil and stirred at 23 °C until TLC indicated starting halide was consumed. The reaction mixture was concentrated and the residue was purified by preparative TLC (7% acetone/chloroform) to afford a 50:50 E/Z mixture of gymnoconjugatin A (18). This mixture was treated with a catalytic amount of I₂ in benzene (1 ml) at 25 °C. After 24h, the mixture was concentrated and purified by preparative TLC (7% acetone/chloroform) to afford stereoisomerically pure gymnoconjugatin A (18) (10 mg, 61%) as a red solid: ¹H NMR (400 MHz, d₆-DMSO) δ 7.67 (br s, 1H), 7.05 (d, J = 10.0 Hz, 1H), 6.72–6.78 (m, 3H), 6.59 (d, J = 11.2 Hz, 1H), 6.56–6.59 (m, 2H), 6.50–6.53 (m, 1H), 6.54 (br s, 1H), 6.53 (br s, 1H), 3.95 (s, 3H), 2.05
(s, 3H), 1.81 (s, 3H); $^{13}$C NMR (100 MHz, $d_6$-DMSO) $\delta$ 166.0, 163.3, 158.7, 152.7, 143.4, 138.3, 135.2, 133.6, 130.9, 128.8, 126.5, 121.1, 112.3, 100.5, 94.0, 56.8, 12.4, 8.7; IR (KBr) $\nu_{\text{max}}$ 3154, 2990, 2896, 2364, 1813, 1772, 1653, 1560, 1465, 1374, 1142, 744 cm$^{-1}$; HRMS (ESI), $m/z$ calc for C$_{19}$H$_{18}$O$_4$Na: 333.1103; found: 333.1109.
REFERENCES


62 (a) Denmark, S. E.; Tymonko, S. A. “Sequential Cross-Coupling of 1,4-
Bissilylbutadienes: Synthesis of


68 For example: (Ph3P)4Pd, CuI, CsF, DMF; PdCl2 (CH3CN)2, DMF; Pd2dba3, P(furyl)3, NMP; (Ph3P)4Pd, CuTC, DMF.


APPENDIX A

SELECTED SPECTRUM
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Et₃SiO

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N-O
NO
OSiEt₃
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N-CH₂OCH₂CH₂SiMe₃
OSiEt₃
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\[
\text{NO} \quad \text{OSiEt}_3 \\
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SpinWorks 2.5:

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number of scans: 12

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processed size: 32768 complex points

LB: 0.300 G B: 0.0000

OMe

I
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- Time domain size: 65536 points
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- Number of scans: 256
- Frequency of 0 ppm: 400.130005 MHz
- Processed size: 32768 complex points

Chemical structure and spectra for compounds with respective PPM values.
SpinWorks 2.5

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[Chemical structure image]
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Structure:

Me

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O

Me

I

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