The Pennsylvania State University

The Graduate School

Department of Chemistry

STUDIES TOWARD THE TOTAL SYNTHESIS OF STREPTORUBIN B

A Dissertation in

Chemistry

by

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ABSTRACT

Streptorubin B is a member of the prodigiosin family of natural products which are receiving considerable attention from academia as well as the pharmaceutical industry for their novel immunosuppressive and cytotoxic properties. Despite this interest, little effort has been shown toward an asymmetric synthesis of streptorubin B or the relationship between its chirality and biological activity. Progress toward the asymmetric synthesis of streptorubin B and its stereoisomers is herein described.

Alkynyliodonium salts are versatile substrates which have been used to form a variety of heterocycles and other ring systems. The alkylidenecarbenes generated from the addition of soft nucleophiles to alkynyliodonium salts can insert intramolecularly into carbon-hydrogen bonds and typically do so with a high degree of regio- and stereoselectivity. The C ring of streptorubin B was made using this branch of hypervalent iodine chemistry, but this route was later abandoned due to failure of subsequent steps and instability of the products formed.

The challenges involved in forming medium sized rings with ring closing metathesis are beginning to be understood and in many cases have been overcome by conformation constraints. The possibility of using ring closing metathesis to close the bridging ten membered D ring of streptorubin B was explored. However, the enthalpy and entropy barriers for this conversion were determined to be too great to surmount. After other ring closing methods were investigated, a Nozaki-Hiyama-Kishi coupling was found to be successful.

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Chapter 1

Streptorubin B and Related Prodigiosins

Streptorubin B is part of the prodigiosin family of natural products that has been isolated from various strains of *Streptomyces* and *Serratia* bacteria. A defining physical characteristic of the prodigiosins is their deep-red color which resembles blood. When colonies of *Streptomyces* or *Serratia* bacteria grow on food and secrete these red pigments, the food appears to bleed. The observations of these "bleeding" foods have had both religious and military implications throughout history.[1-2]

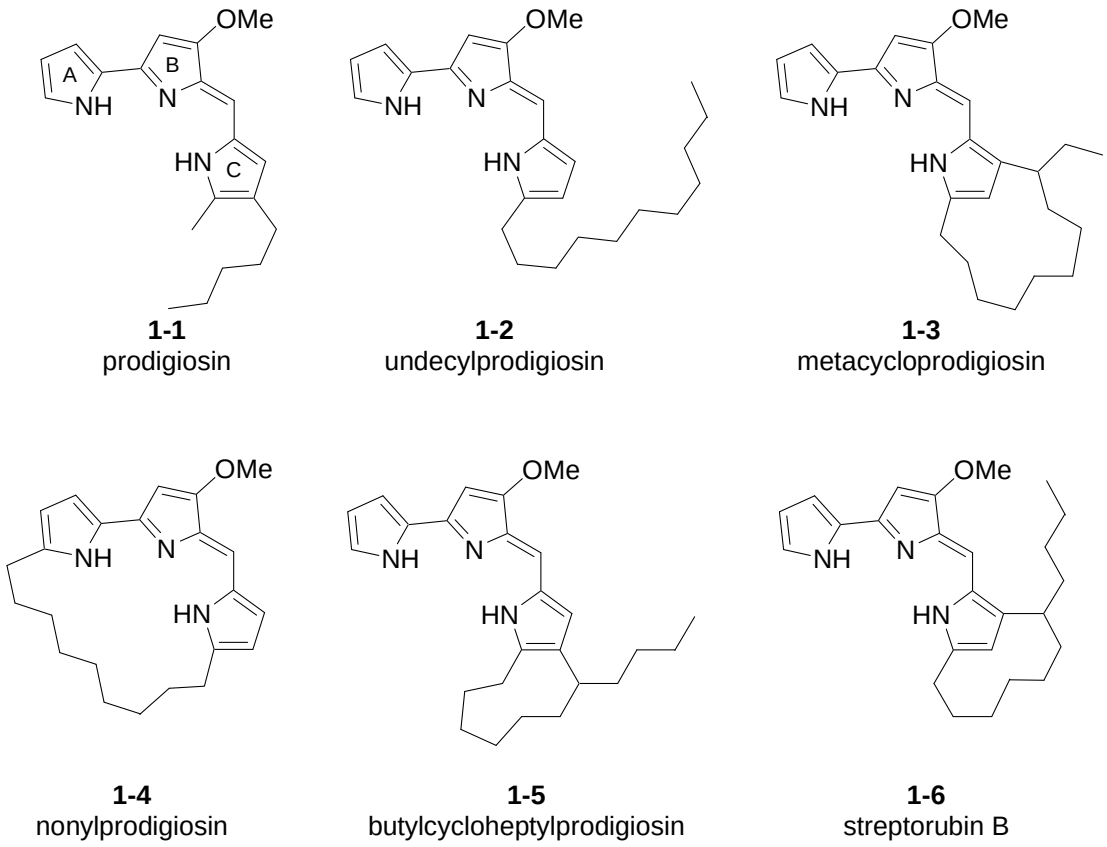


Figure **1.1**: Some examples of naturally occurring prodigiosins.

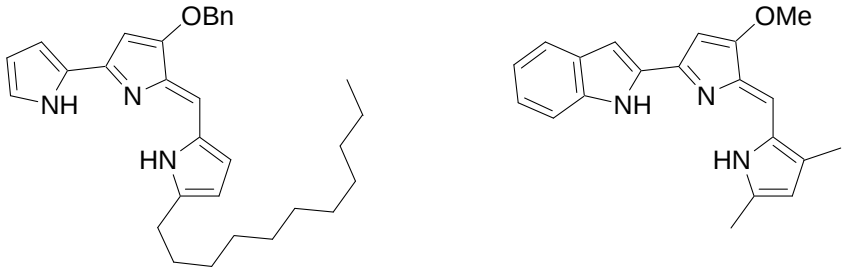
Prodigiosins share a common methoxy-bipyrrolylpyrrolemethane skeleton. Typically, alkyl substitution is confined to the C ring, with the exception of the macrocyclic members of type **1-4**, see Figure **1.1**. The alkyl portion usually possesses an odd number of carbons and can be linear or cyclic with both fused and bridged attachments.

1.1 Biological activity of prodigiosins.

The prodigiosins have been recognized for their potential as anticancer and immunosuppressant therapeutics. Some members of this family have shown immunosuppressive activity at non-toxic doses.[3-5] Certain prodigiosins have shown selective cytotoxicity against tumor cells. For example, streptorubin B has been shown to kill 100% of breast cancer cells at 1 μM doses while causing no increase in the death rate of normal breast cells.[6-7] Selected cytotoxic data of the prodigiosins are shown in Figure **1.2**.[6-7] These reports have prompted the pharmaceutical industry to look to the prodigiosins as lead compounds for potential drug candidates. Pharmacia & UpJohn selected PNU156804 (**1-7**) for further studies in the immunosuppressive area,[13] and the non-natural prodigiosin derivative, GX15-070 (**1-8**), has reached phase II clinical trials as an anticancer drug, see Figure **1.3**.[14]

	IC_{50} (nM)	Cell line
prodigiosin (**1-1**)	62	L1210 (leukemia)
	93	B16 (melanoma)
	1	P388 (leukemia)
	275	SW-620 (colon)
	1550	Swiss-3T3 (nonmalignant)
cycloprodigiosin	460	KPL-1 (breast)
	540	T-47D (breast)
	550	MCF-7 (breast)
	550	MKL-F (breast)
	620	MDA-MB231 (breast)
	300*	HL-60 (leukemia)
streptorubin B (**1-6**)	200	MCF-7 (breast)
	200	MDA-MB231 (breast)
metaprodigiosin (**1-3**)	640	MCF-7 (breast)
taxol	10	MCF-7 (breast)
	1	MDA-MB231 (breast)

Figure **1.2**: IC_{50} values of various prodigiosins and taxol for various cancer cell lines. *IC_{25}



1-7 **1-8**

Figure **1.3**: Stuctures of drug candidates PNU156804 (**1-7**) and GMX15-070 (**1-8**).

1.1.1 pH modulation.

The cytotoxicity of the prodigiosins might stem from one or more of three possible biological pathways: pH modulation, cell cycle inhibition, and DNA cleavage.[15]

Many cellular functions are sensitive to pH, and inhibition of a cell's ability to control the pH of the cytosol and organelles can lead to cell arrest and apoptosis. Prodigiosins uncouple vacuolar H^+-ATPase and show H^+/Cl^- symport activity.[3, 16] This prevents cells from acidifying internal organelles and raising the pH of the cytosol. It has been shown that a variety of cancer cells require this basic environment to maintain cell functions. Fürstner has claimed that the immunosuppressant activity shown by prodigiosins, however, is not related to their ability to inhibit cellular control over pH.[17]

The ability of the prodigiosins to perturb vacuole acidification is highly dependent on the tripyrrole core. Fürstner showed that nonylprodigiosin's (**1-4**) H^+/Cl^- symport activity drops significantly when the A-ring pyrrole is replaced by a non-basic aryl group, such as benzene, furan, or thiophene.[17] Whereas the ability of the prodigiosins to modulate pH is documented, the molecular target, if one exists, is not known; hence, it is hard to speculate exactly why certain structural features are necessary while others are not.

1.1.2 Cell cycle inhibition.

Some members of the prodigiosin family have been shown to inhibit T-cell proliferation at nM concentrations, see Figure **1.4**.[8, 17-19] Once again, whereas the precise molecular targets of the prodigiosins have not yet been identified, the biological pathways and systems they affect have been reported.

	IC_{50} (nM)
prodigiosin (**1-1**)	10
cycloprodigiosin	3
undecylprodigiosin (**1-2**)	0.6
PNU156804 (**1-7**)	5*
nonylprodigiosin (**1-4**)	26
cyclosporin A	2

Figure **1.4**: IC_{50} values of various prodigiosins and cyclosporine A for the inhibition of T-cell proliferation. *lymphocyte inhibition

The activation system of T-cell proliferation consists of three stages, see Figure **1.5**.[20] First, an antigen is detected by specific receptors within the cell. The second stage consists of a series of enzyme activations, including calcineurin (CaN) phosphatases dephosphorylating nuclear factor of activated T-cells (NFAT) and NFAT binding to the interleukin (IL-2) cytokine. In stage three, IL-2 phosphorylates Janus kinase (Jak3), which turns on the signal transducers and activators of transcription (Stat 1, Stat 3, Stat 5a/b, and Stat 6), indispensable proteins in gene replication. Also, IL-2 has been shown to cause the degradation of IκB, an inhibitor protein, thus liberating nuclear factor (NF-κB) to go inside the nucleus and initiate cell proliferation.[21]

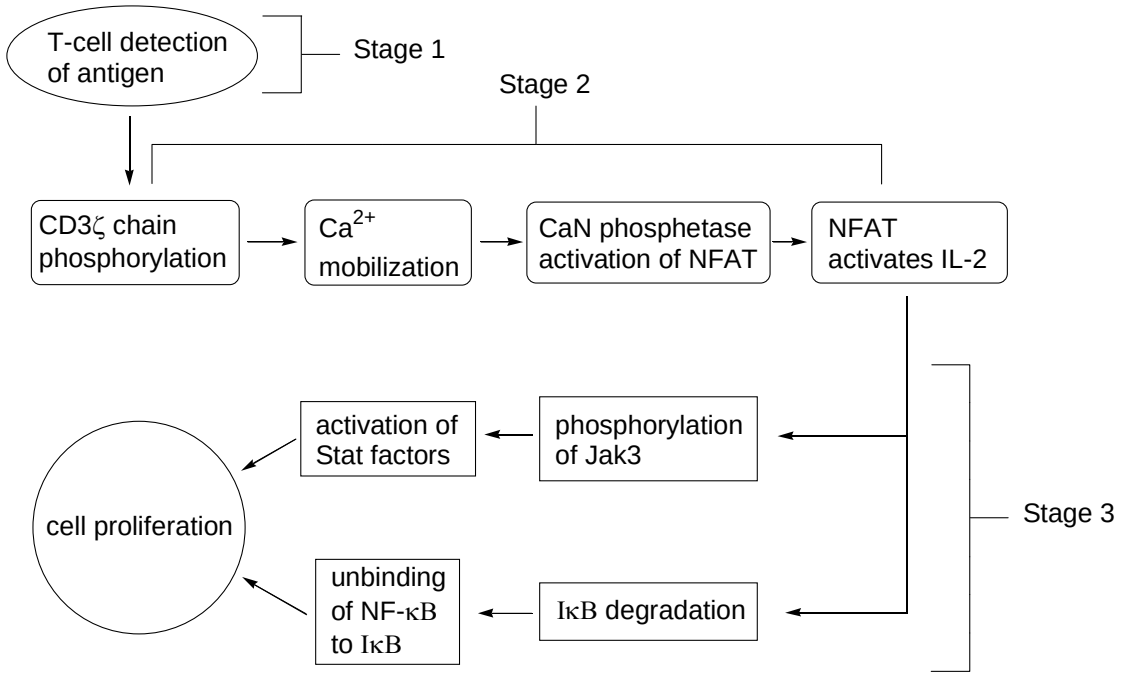


Figure **1.5**: The activation system of T-cell proliferation.

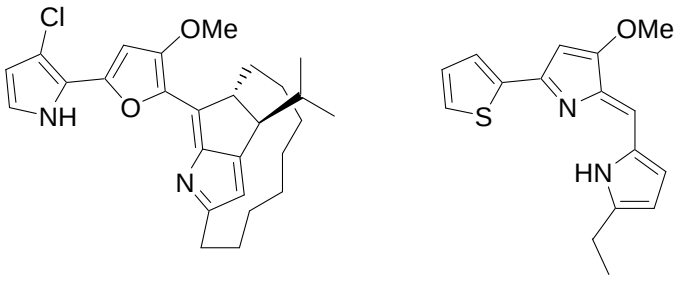
UP156804 (**1-7**) has been shown to prevent T-cell proliferation at several junctions in the activation system. **1-7** blocks the activation of NF-κB by inhibiting the IL-2 mediated degradation of IκB.[21] The same report claims that **1-7** also hinders the IL-2 activation of activator protein-1 (AP-1). In addition, this prodigiosin prevents IL-2 mediated Jak-3 auto-tyrosine phosphorylation. This action interrupts the activation of the Stat factors and inhibits gene transcription.[20] It is important to note that **1-7** only exerts its effects in the third stage of T-cell activation, whereas the standard immunosuppressant drugs (cyclosporine A, rapamycin, and FK506) inhibit CaN in stage two. Because prodigiosins act *via* a pathway independent of current drugs, there is the potential for combined usage. In fact, Stepkowski found that mixtures of PNU156804 with cyclosporin A and with rapamycin both resulted in prolonged survival rates of rats which received allografts.[20]

1.1.3 DNA cleavage.

Prodigiosins can cause cell arrest by facilitating copper-mediated oxidative cleavage of DNA. The flat polyaromatic core of the prodigiosins can become bound to DNA by intercalating into the minor groove. Additional binding interactions include hydrogen bonding between the methoxy group and DNA nucleobases, and an electrostatic pairing of DNA's phosphate anions with the pyrrolylbipyrrole, which is positively charged at physiological pH.[15]

In the presence of Cu(II), prodigiosins and related molecules are believed to form dimeric complexes (prodigiosin·Cu(II))$_2$ and undergo an oxidative electron transfer leading to Cu(I) and π-radical cation prodigiosin derivatives.[22-23] The resulting Cu(I) ions go on to form copper–oxo species in the presence of oxygen, which can cleave DNA at the phosphodiester backbone. Double-stranded DNA cleavage has been observed through this process.[24] Also, it has been postulated that even single stranded DNA cleavage may be hard to repair because of continued prodigiosin-DNA binding which blocks DNA reconstruction.

Similar to the results found for prodigiosin effectiveness as H^+/Cl^- symporters, the presence of the three nitrogen atoms is necessary for efficient DNA cleavage. Substrates without all three nitrogens, such as roseophilin (**1-9**) and thiophene **1-10**, gave inferior results, see Figure **1.6**.[25-27]



1-9
roseophilin

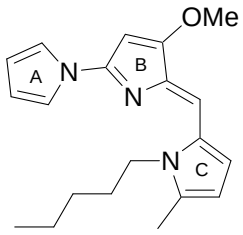
1-10

Figure **1.6**: Prodigiosin-like compounds which are ineffective at Cu(II) mediated DNA cleavage.

1.1.4 Other biological properties.

Other reports of prodigiosin biological activity have been published. The ability of **1-2** to disrupt the pH of microenvironments has been implicated in its inhibition of osteoclastic bone resorption.[28-29] Also, a close derivative of **1-1** has been found to inhibit NADPH oxidase, an enzyme that is associated with immune response, inflammation, and organ/tissue blood supply.[30]

An interesting twist in the relationship between the structures of the prodigiosins and their biological activity recently has emerged. The novel *N*-alkylated prodigiosin derivative MAMPDM (**1-11**) was isolated in 2003, see Figure **1.7**.[31] With tertiary nitrogens in both the A and C rings, the accepted modes of prodigiosin binding to HCl and Cu(II) seem impossible. **1-11** is reported to have similar immunosuppressant activity and has selectively inhibited the proliferation of various cancer cell lines.[32] However, Deorukhkar claims this activity is most likely manifested through different pathways than those used by the traditional prodigiosins. Brown had synthesized various *N*-alkyl prodigiosins almost two decades prior to the isolation of **1-11**, but claimed they were "devoid of the cyctotoxic properties of the natural series."[33]

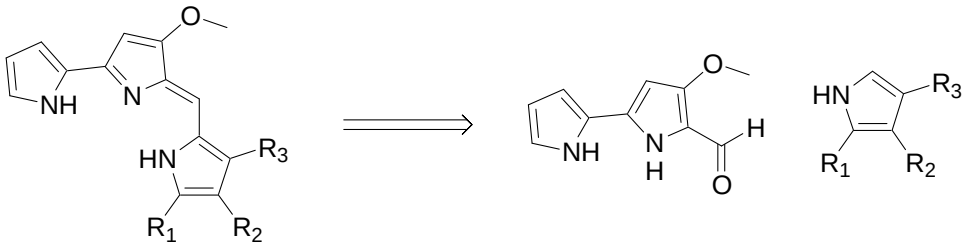


1-11

Figure **1.7**: MAMPDM (**1-11**), a naturally occurring N-alkylated prodigiosin.

1.2 Biosynthesis.

It has become generally accepted that a key step in the biosynthesis of prodigiosins is the non-enzymatic condensation of the bipyrrolyl aldehyde **1-13** with a substituted monopyrrole **1-14**, see Figure **1.8**.[2] Early biosynthetic studies using ^{13}C labeled feeding studies showed that each pyrrole was formed from different amino acid sources and that the alkyl chains originated from repetitive acetyl units, see Figure **1.9**.[1]



1-12 **1-13** **1-14**

Figure **1.8**: Retro biosynthetic coupling of aldehyde **1-13** and pyrrole **1-14**.

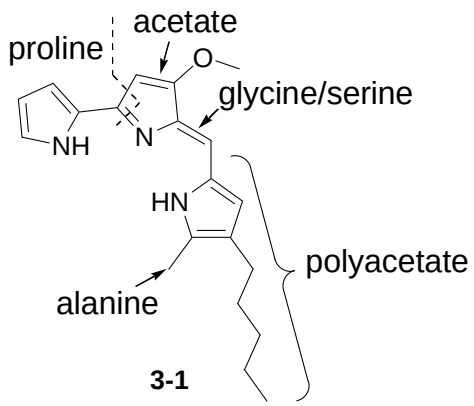


Figure **1.9**: Early proposal for the biosynthesis of prodigiosin.

Recently, various groups have used more advanced biological tools to refine the early biosynthetic proposal and identify the requisite enzymes and feedstock for each step, see Figure **1.10**.[34-37] One of these refinements was the determination that the repeating acetate units incorporated in the alkyl chains actually originate from malonyl derivatives. Similar studies were done for undecylprodigiosin (**1-2**) with parallel results.

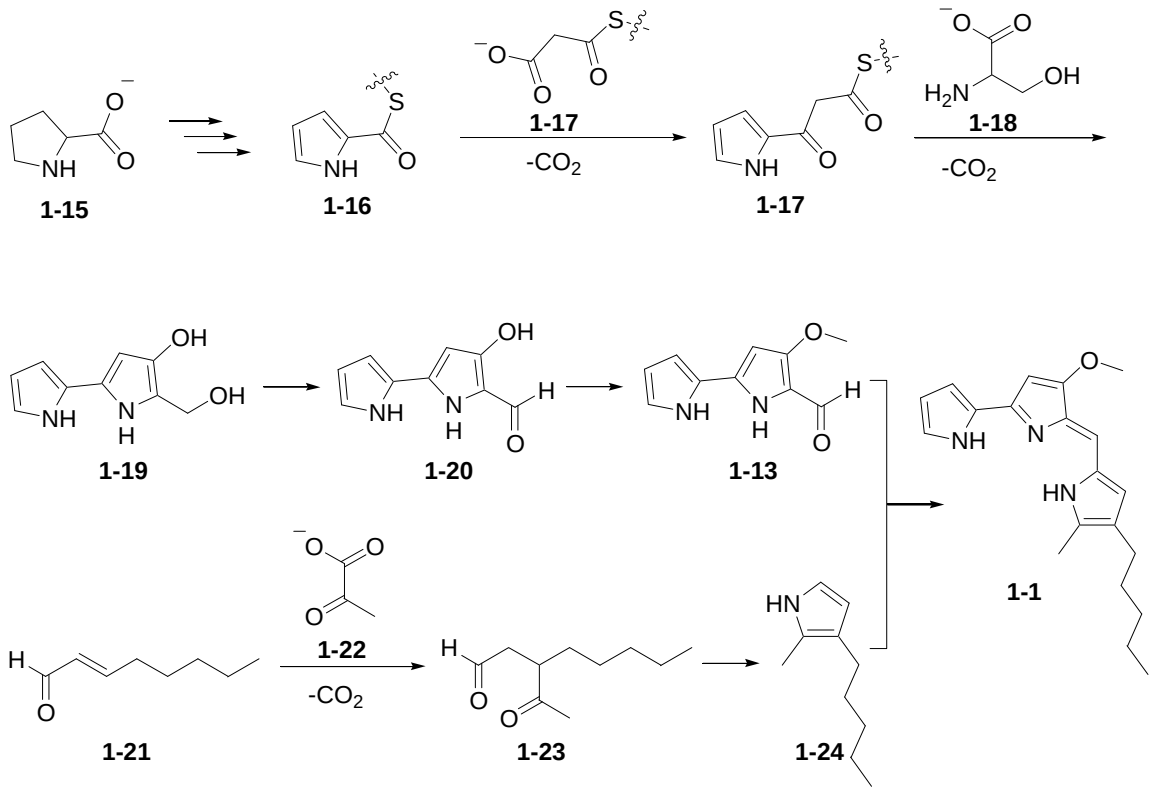


Figure **1.10**: Biosynthetic pathway to prodigiosin.

Many of the macrocyclic prodigiosin derivatives contain alkyl units eleven carbons long. This observation has led to proposals that there is a common intermediate in the biosynthesis of **1-2** , possibly **1-2** itself, that can undergo an oxidative cyclization to the cyclic compounds shown in Figure **1.11**.[35, 38] This hypothesis is strengthened by the fact that **1-2** has been isolated alongside streptorubin B (**1-6**),[35] butylcycloheptylprodigiosin (**1-5**),[39] and metacycloprodigiosin (**1-3**).[40]

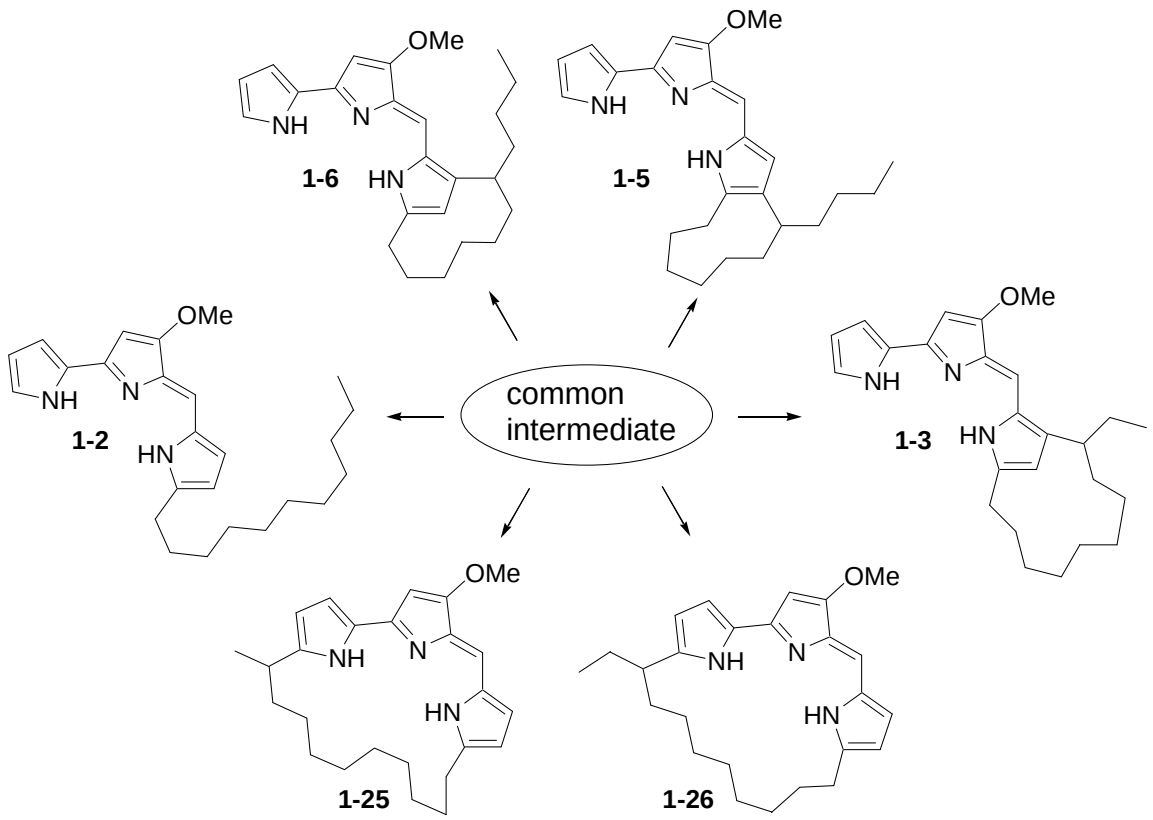


Figure **1.11**: Many of the prodigiosins come from a common intermediate.

1.3 Structure: Confusion between streptorubin B and butylcycloheptylprodigiosin.

The earliest report of streptorubin B dates back to 1964.[41] Thirumalachar isolated two compounds from *Streptomyces caespitosus* found in soil samples in Pimpri, India that he named "streptorubrin" A and B. In 1975, Gerber reported the isolation of a prodigiosin from *Streptomyces* sp. Y-42 which was structurally assigned as **1-5**.[39] Gerber continued to publish this structure using both butylcycloheptylprodigionine and streptorubin B as descriptors for this compound until 1978, [1, 42, see also 43] when she published structure **1-6** "which had hitherto been incorrectly identified as" structure **1-5**.[38] Years later in 1991, Weyland isolated a prodigiosin from the actinomycete strain B 4358.[44] The ^{1}H NMR spectrum of this compound showed a mulitplet at -1.55 ppm, an

unusual feature not mentioned in the previous studies. Using more modern 2D NMR techniques, he assigned this compound as Gerber's structure **1-6** and asserted that the originally assigned structure "must be revised." When Fürstner published his partial synthesis of **1-6** in 1998, he too used both the butylcycloheptylprodigiosin and streptorubin B descriptors as Gerber did.[45] It was not until 2005 that he challenged the structural reassignment of **1-5**.[46] Whereas he admits that the reported NMR data of butylcycloheptylprodiginine was incomplete, no mention of the -1.55 ppm peak was ever made before Weyland's paper. Was it possible that the Gerber and Weyland compounds, while given the same name, were actually separate and distinct? After all, they were isolated from different bacterial sources. In his report of the synthesis of **1-5**, Fürstner puts forward the claim that Weyland's structural reassignment of **1-5** was premature and that **1-5** is a naturally occurring compound. An additional paper from Fürstner in 2007 reaffirms that streptorubin B (**1-6**) and butylcycloheptylprodiginine (**1-5**) are distinct enities.[47]

A comparison of the reported IR data from Thirumalachar's isolation paper with Weyland's isolated streptorubin B and Fürstner's synthesized butylcycloheptylprodigiosin shows that neither of the latter compounds matches well with the originally isolated "streptorubrin B," although all three sets of IR data were taken in different media. NMR instrumentation was not widely available when Thirumalachar's "streptorubrin B" was isolated; hence no such data were acquired. With this context in mind, it is highly possible that streptrubin B as we know it today was not isolated until 1992 by Weyland.

Equal ambiguity surrounds the stereochemical configuration of **1-6**. In addition to the obvious stereocenter at C7', there is another element of stereochemistry which arises from the relatively short seven carbon cyclic chain which must reside either on the top or the bottom face of the pyrrole. Weyland reported that no inversion of this planar chirality is seen below 120 ˚C, see Figure **1.12**.[44] However, Fürstner observed diastereomeric peaks after heating **1-27** (Figure **1.13**) or simply keeping it in solution for prolonged periods of time, though spectral coalescence was never reached.[45] Even though Weyland isolated **1-6**·HCl as a crystalline salt, no X-ray crystal structure was determined, so the relative stereochemistry is not known for certain. However, an nOe correlation was seen between the methoxy protons and those of the butyl side chain, making the stereochemical relationship shown in **1-6** (**1.12**) the most likely naturally occurring diastereomer.[44] No specific rotation of **1-6** was taken either, and thus it is not certain that **1-6** exists in nature as a single enantiomer.

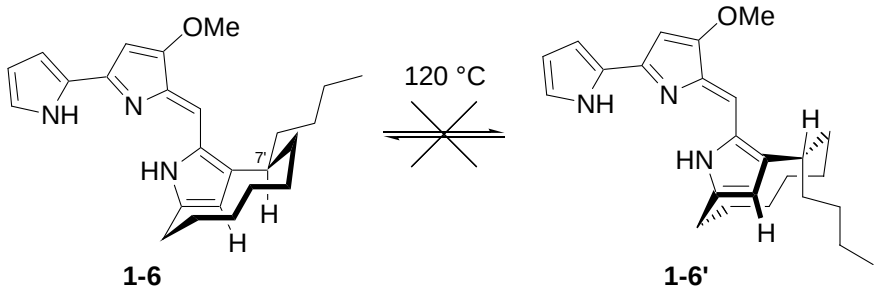


Figure **1.12**: No inversion of planar chirality observed by Weyland.

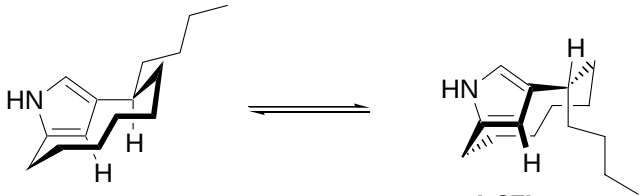


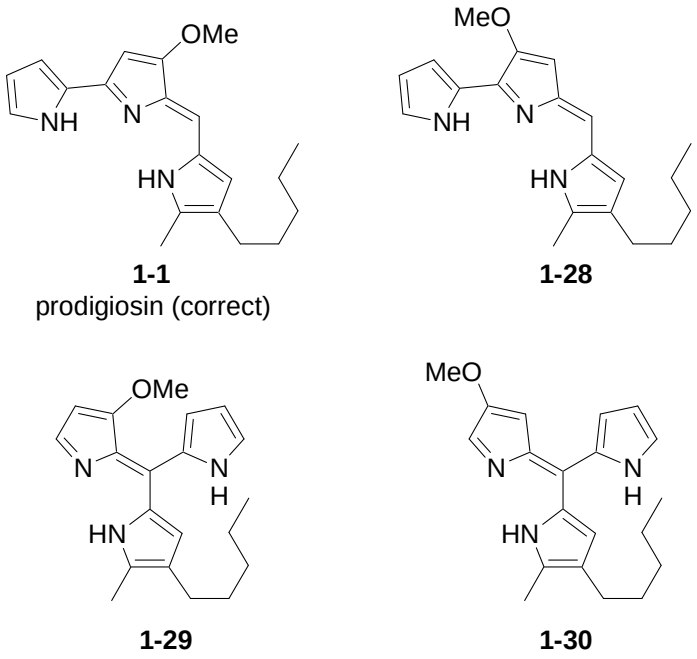
Figure **1.13**: Inversion of planar chirality observed by Fürstner.

1.4 Published syntheses of prodigiosins.

The structurally intriguing tripyrrolomethane backbone of the prodigiosin family of natural products has maintained the interest of organic chemists for over seventy years.[1-2] Rapoport's synthesis of **1-1** in 1962 played a key role in determining the correct structure of the prodigiosins. Many other groups have followed with published reports of total syntheses of various members of this chemical family, in particular Fürstner, who has published five such syntheses. These efforts are usually split into two areas of interest: improving methods of installing the bipyrrole section **1-13** (northern half) and construction of a properly substituted pyrrole **1-14** (southern half).

1.4.1 Rapoport's synthesis of prodigiosin.

The first successful synthesis studies on the prodigiosins was performed by Rapoport.[48] At this point in the history of the prodigiosins, the correct structure was still in doubt. Not only was the regiochemistry of the methoxy group uncertain, but the correct placement of the unsubstituted pyrrole A ring was not yet widely accepted, see Figure **1.14**. Thus, efforts began to ascertain the correct structure of prodigiosin by chemical synthesis.



1-1
prodigiosin (correct)

1-28

1-29

1-30

Figure **1.14**: Early structural possibilities of prodigiosin.

Rapoport's synthesis of the bipyrrolyl northern half of prodigiosin was fairly concise, consisting of only seven steps, see Figure **1.15**. He began with the condensation of the sodium salt of the glycinate derivative **1-31** with methylenemalonate **1-32** to furnish pyrrole **1-33**. Methylation of the alcohol followed by a two-step selective decarboxylation gave methoxypyrrole **1-36**. The key bipyrrole bond was made using a condensation of **1-36** with 1-pyrroline **1-37**.[49] Dehydrogenation of **1-38** followed by a McFadyen-Stevens reaction[50] of ester **1-39** gave aldehyde **1-13**, thus completing the first synthesis of the northern half of all of the naturally occurring prodigiosins.

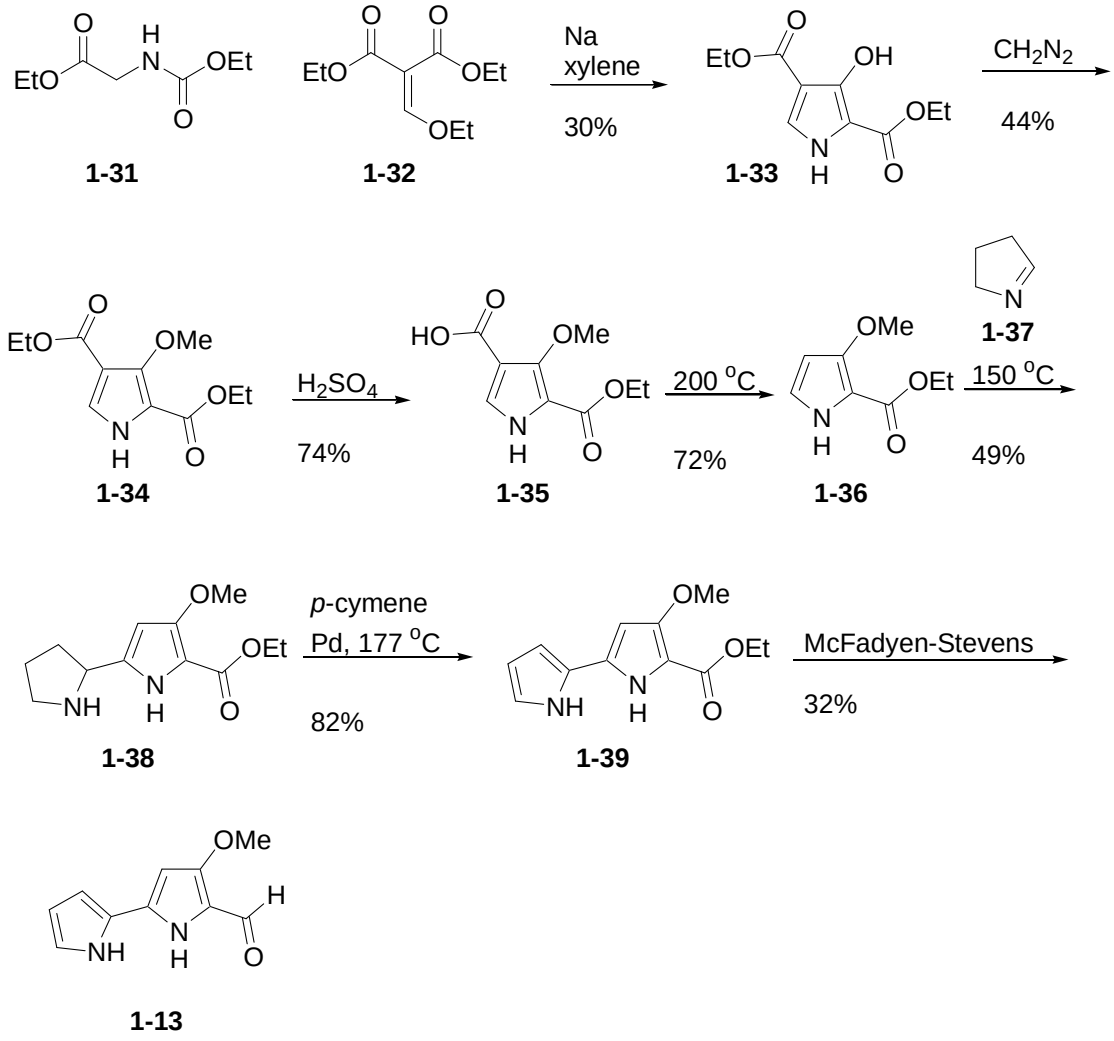


Figure **1.15**: Rappoport's synthesis of the bipyrrolylaldehyde.

The southern half of prodigiosin (**1-1**) was made in five steps from 3-octanone (**1-40**) following the work of Wrede, see Figure **1.16**.[51] Selective α-oximination of **1-40** followed by reduction gave amine **1-41** as a 15:1 mixture of amine regioisomers. Condensation of **1-41** with diethyl oxaloacetate followed by two decarboxylation steps gave 2-methyl-3-amyl-pyrrole (**1-45**). The completed southern half was then condensed with the previously discussed bipyrrolocarboxaldehyde **1-13** in the presence of HCl to

complete the first total synthesis of prodigiosin and definitively confirmed the structural elements of the prodigiosins.

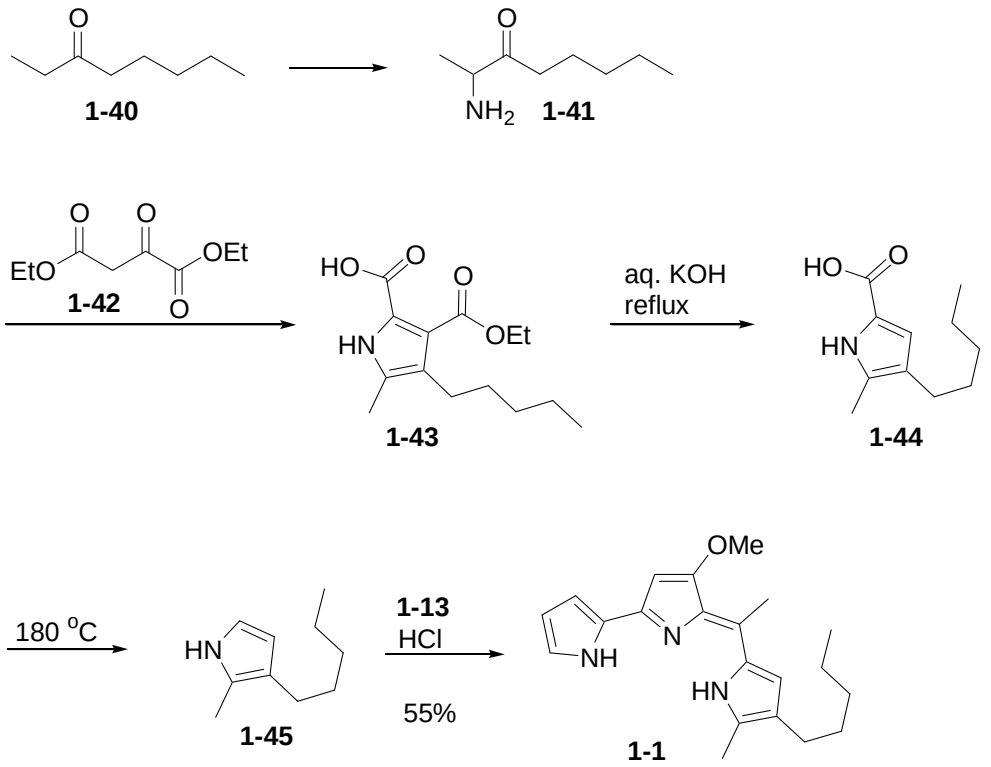


Figure **1.16**: Rapoport's completion of prodigiosin (**1-1**).

1.4.2 Boger's sythesis of prodigiosin.

Many years after the first synthesis of prodigiosin was published, Boger developed a new method of constructing the northern bipyrrole section of **1-1**.[8] This method utilized an intramolecular palladium-mediated coupling to form the biaryl bond.

His strategy started with a dimerization of ethyl diazoacetate (**1-46**) to dihydrotetrazine **1-47**, see Figure **1.17**. Nitrous gases, generated from a mixture of $NaNO_2$, HNO_2, and HCl, oxidized **1-47** to a tetrazine capable of undergoing an inverse electron demand Diels-Alder reaction with 1,1-dimethoxyethene to give diazine **1-48**.

Reduction of **1-48** with an excess of zinc in the presence of acetic acid induced a ring contraction to pyrrole **1-49**. A three step selective decarboxylation sequence gave pyrrole **1-50** as the properly substituted central ring of prodigiosin.

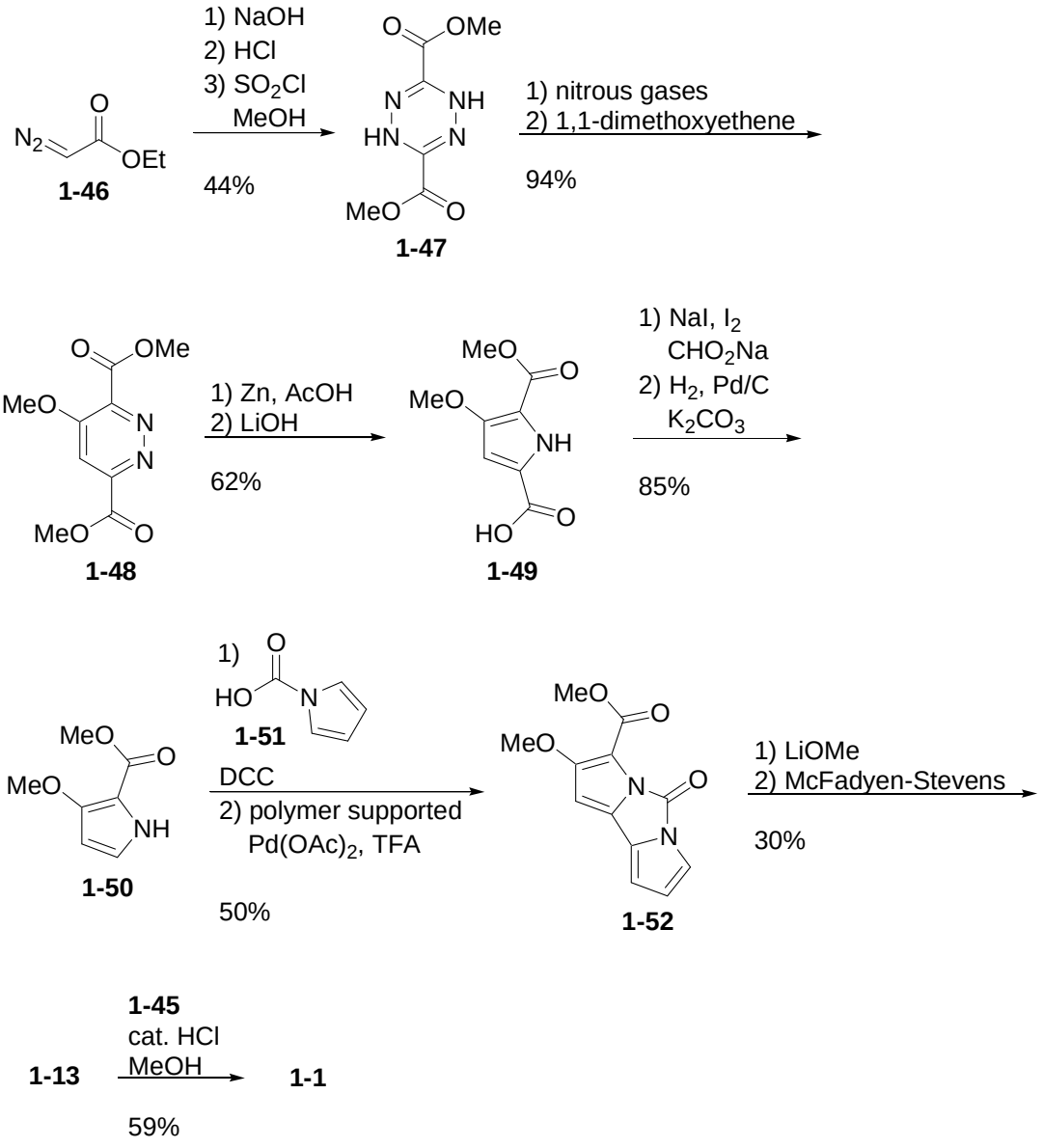


Figure **1.17**: Boger's synthesis of prodigiosin.

The second pyrrole was brought in by a DCC coupling with pyrrole-1-carboxylic acid (**1-51**), and then the key C-C linkage was established with a palladium mediated biaryl coupling to deliver **1-52**. Lithium hydroxide was used to open the urethane, and the methyl ester was reduced to aldehyde **1-13** using the well established McFayden-Stevens protocol. As with Rapoport's original synthesis, Boger's approach was completed *via* condensation of the known pyrrole **1-45** with **1-13** under acidic conditions. Although this approach required more steps and resulted in a lower overall yield than previous reports, it was an important example of using transition metal assisted coupling to form the key biaryl bond.

1.4.3 Wasserman's synthesis of the northern half of the prodigiosins.

Wasserman has found that the addition of singlet oxygen to certain pyrrole compounds generates a reactive imino hydroperoxide intermediate which can be trapped by a variety of nucleophiles including alcohols, amines, 1,3-diketones, pyrroles, and imidazole.[52-54] He showed that this methodology could be used in a shorter and much more efficient pathway to the northern half of the prodigiosins compared to those routes previously reported.

Coupling acid chloride **1-53** with phosphanylidene **1-54** followed by oxidation of **1-55** with singlet oxygen to give the tricarbonyl compound **1-56**, see Figure **1-18**. Cyclization of **1-56** with ammonia gave hydroxypyrrole **1-57** and etherification of this alcohol with dimethylsulfate yielded the key substrate **1-58**. Photooxidation of **1-58** in the presence of methylene blue created the electrophilic imino hydroperoxide **1-59** which was trapped by pyrrole to furnish bipyrrole species **1-60**.

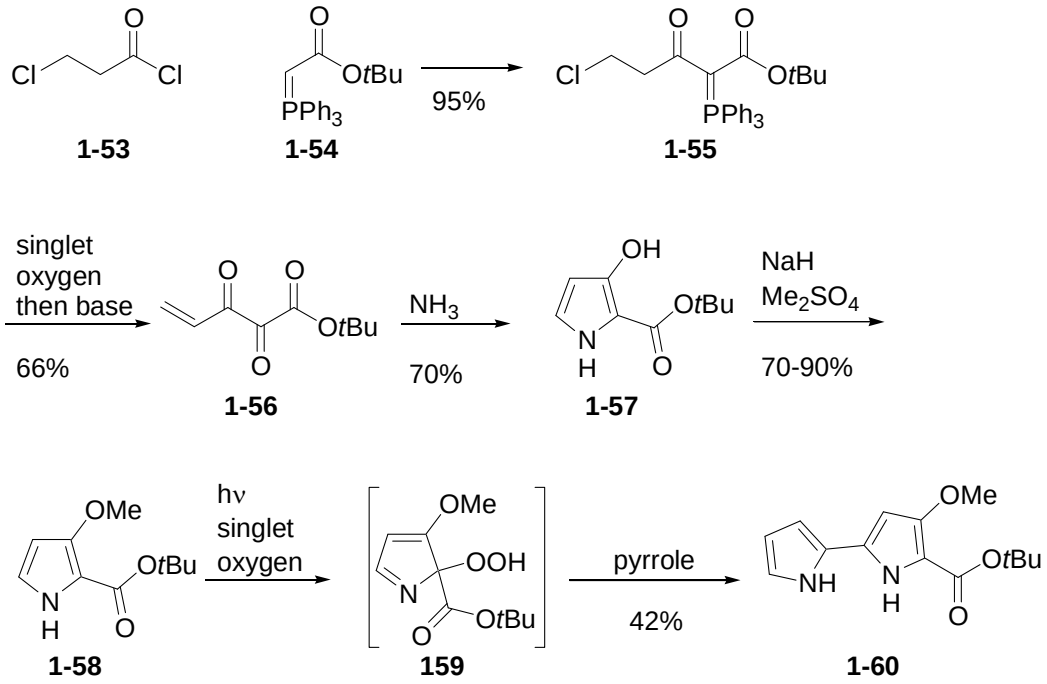


Figure **1.18**: Wasserman's singlet oxygen methodology applied to the prodigiosins.

1.4.4 Undecylprodigiosin.

Because of its simplicity, the lower half of undecylprodigiosin (**1-62**) has received little attention from synthetic organic chemists. In 1976 Wasserman and coworkers made **1-62** as a method of structure determination for **1-2**, see Figure **1.19**.[55] This synthesis consisted of alkylation of pyrrole and condensation with the known bipyrrolealdehyde **1-13**.

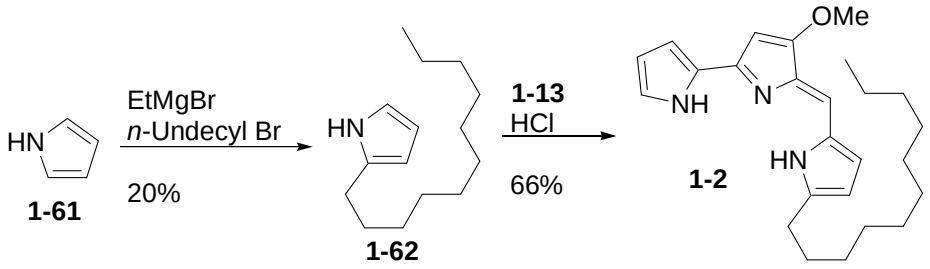


Figure **1.19**: Wasserman's synthesis of undecylprodigiosin.

By contrast, the simplicity of **1-2**, along with its potent biological activity, has attracted the attention of biochemists as well as medicinal chemists. Decades after Wasserman's synthesis, D'Alessio and coworkers at Pharmacia & Upjohn used **1-2** as a lead compound for derivatization studies to optimize the immunosuppressive activity/cytotoxicity ratio of the prodigiosins.[13] To this end, a practical method of installing substituents into each of the pyrroles was developed, see Figure **1.20.**[56] Pyrrole **1-62** and similar compounds can be carbonylated using standard Vilsmeier conditions and the resulting aldehydes can be condensed with 4-alkoxy-3-pyrrolidin-2-ones such as **1-64**. Conversion of lactam **1-65** to aryl triflate **1-66** creates a suitable Suzuki cross coupling partner to construct the biaryl bond with a variety of arylboronic acids. Using this technology, D'Alessio was able to make over thirty-nine variations of **1-2** including PNU-156804 (**1-7**), which showed the best *in vivo* therapeutic index (toxic dose / effective dose) of the analogues tested.[13]

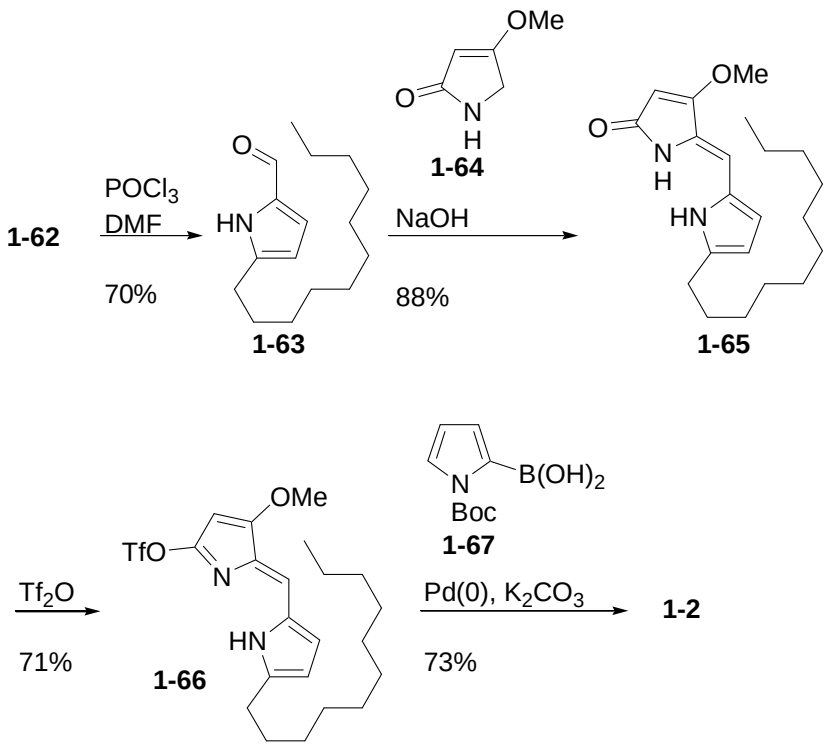


Figure **1.20**: D'Alessio's flexable synthesis of undecylprodigiosin.

1.4.5 Wasserman's synthesis of metacycloprodigiosin.

The first total synthesis of metacycloprodigiosin (**1-3**) was published by Wasserman as an accompanying paper to its isolation and structural determination.[57-58] Efficient methods for closing medium-to-large sized rings were lacking at the time, and so Wasserman opted to buy the twelve membered ring of **1-3** and, after proper derivatization, form the bridging pyrrole with a Paal-Knorr condensation. [59]

Cyclododecanone (**1-68**) was alkylated with ethyl bromide, and the product ketone was protected as the spiroketal **1-69**, see Figure **1.21**. Regioselective bromination of this species followed by elimination of the bromide with DBU gave cyclododecene **1-70**. After deprotection of the ketone and epoxidation of the olefin, the resulting α,β-epoxyketone was rearranged to allylic alcohol **1-71** with acidic hydrazine. Oxidation of

alcohol **1-71** to the ketone allowed the installation of a cyanide at the β-position of ketone **1-72**. Facile transformation of **1-72** to aldehyde **1-73** set up the key Paal-Knorr cyclization with ammonium carbonate to furnish pyrrole **1-74**. This pyrrole was condensed with aldehyde **1-13** to complete the total synthesis of **1-3**.

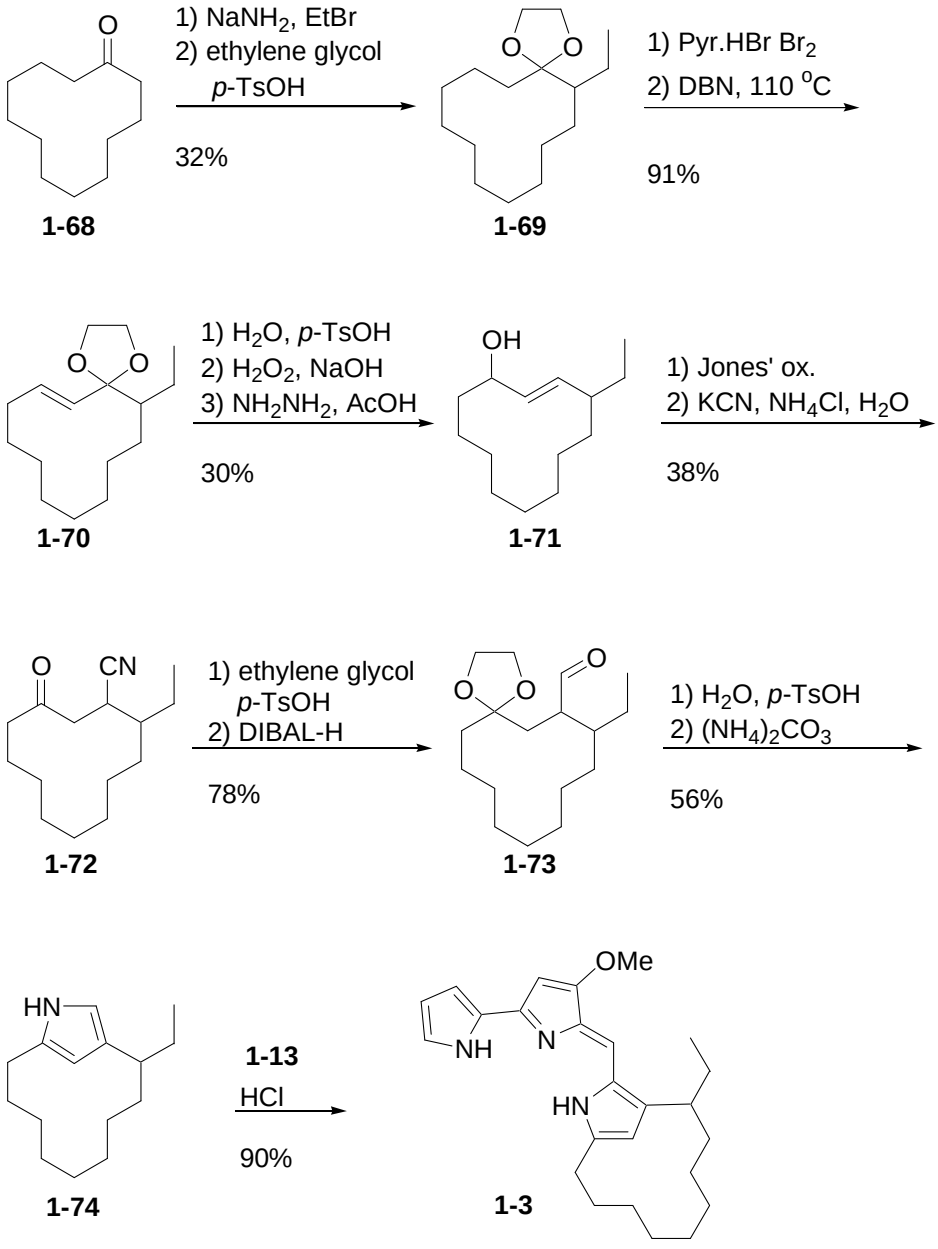


Figure **1.21**: Wasserman's synthesis of metacycloprodigiosin.

1.4.6 Fürstner's synthesis of the core of metacycloprodigiosin.

For the synthesis of metacycloprodiosin (**1-3**), Fürstner elected to construct the macrocycle in lieu of buying it. The synthesis began with the combination of the thionium ylide of **1-75** and 8-bromooctanal to generate epoxide **1-76**, see Figure **1.22**.[45] The bromide was then displaced with methyl (phenylsulfonyl)acetate to give ester **1-78**. The key macrocyclization step passes through a π-allyl palladium species which reacts intramolecularly with the enolate of the α-sulfonylester. Lactonization of **1-79**, oxidation of the remaining alcohol, and elimation of the sulfone yielded α-pyrone **1-81**. Ring opening in basic methanol gave the corresponding ester and aldehyde, and this aldehyde was condensed with benzylamine followed by further condensation with the neighboring ketone to furnish pyrrole **1-82**. Hydrolysis of the unanticipated acetate in **1-82** followed by oxidation of the resulting alcohol and thermal decarboxylation of the methyl ester led to ketone **1-83**, which was easily homolygated to the lower half of metacycloprodigiosin **1-84** *via* Wittig chemistry and hydrogenation.

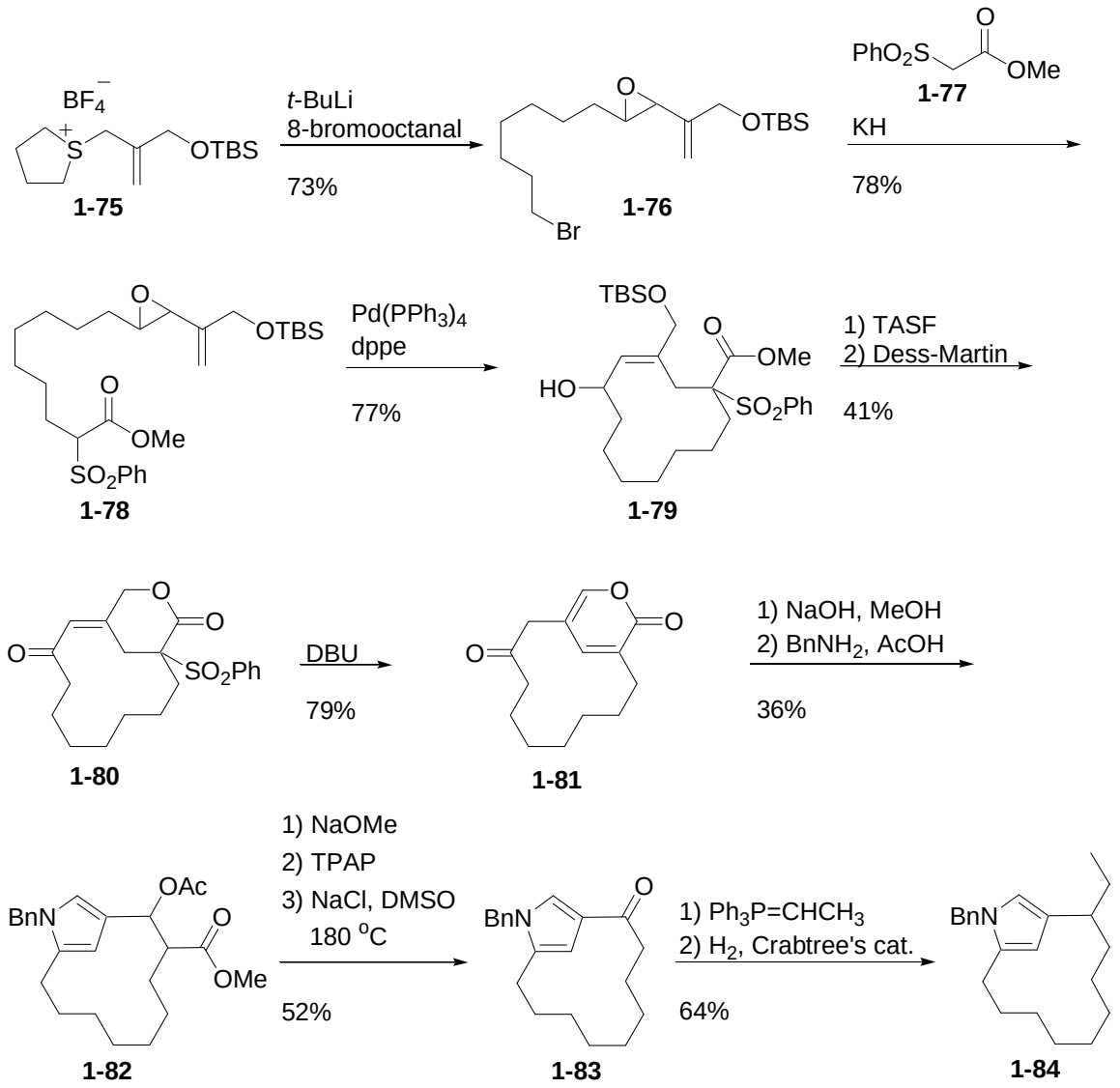


Figure **1.22**: Fürstner's synthesis of the core of metacycloprodigiosin.

1.4.7 Fürstner's synthesis of butylcycloheptylprodigiosin.

Like many of the syntheses of the cyclic prodigiosins, Fürstner began his pursuit of butylcycloheptylprodigiosin (**1-5**) with the alkyl ring preformed. Reduction of ketone **1-85** and acylation of this alcohol gave allylic acetate **1-86**, which underwent a palladium-mediated substitution to β-ketoester **1-87**, see Figure **1.23**.[46] Thermal decarboxylation of **1-87** followed by oximation of ketone **1-88** and acylation of the

resulting oxime led to **1-89** in excellent yield. A Narasaka-Heck cyclization[60] provided dihydropyrrole **1-90**, which required an olefin isomerization to aromatize the pyrrole. Exposure of this pyrrole to Boc anhydride gave the protected bicyclic pyrrole **1-91**, and a hydroboration/oxidation sequence converted cycloalkene **1-91** into ketone **1-92** in 65% overall yield.

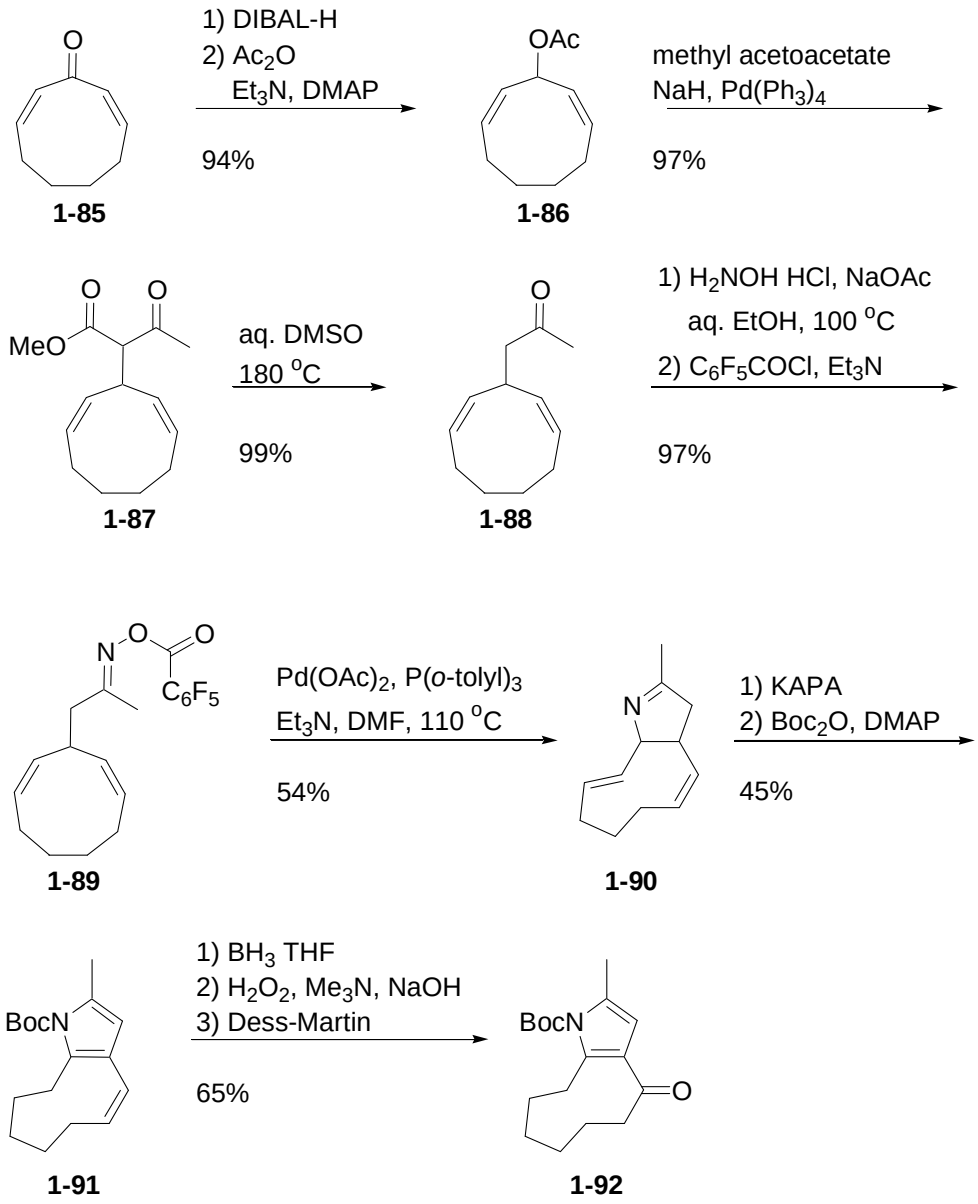


Figure **1.23**: Fürstner's synthesis of the lower half of butylcycloheptylprodigiosin.

A simple Wittig olefination of ketone **1-92** followed by hydrogenation of the olefin gave **1-93**, as seen in Figure **1.24**. The pyrrolylmethyl group was then oxidized with ceric ammonium nitrate to afford aldehyde **1-94**. Fürstner then followed D'Alessio's procedure to construct the bipyrrole northern half and complete the first total synthesis of **1-5**.

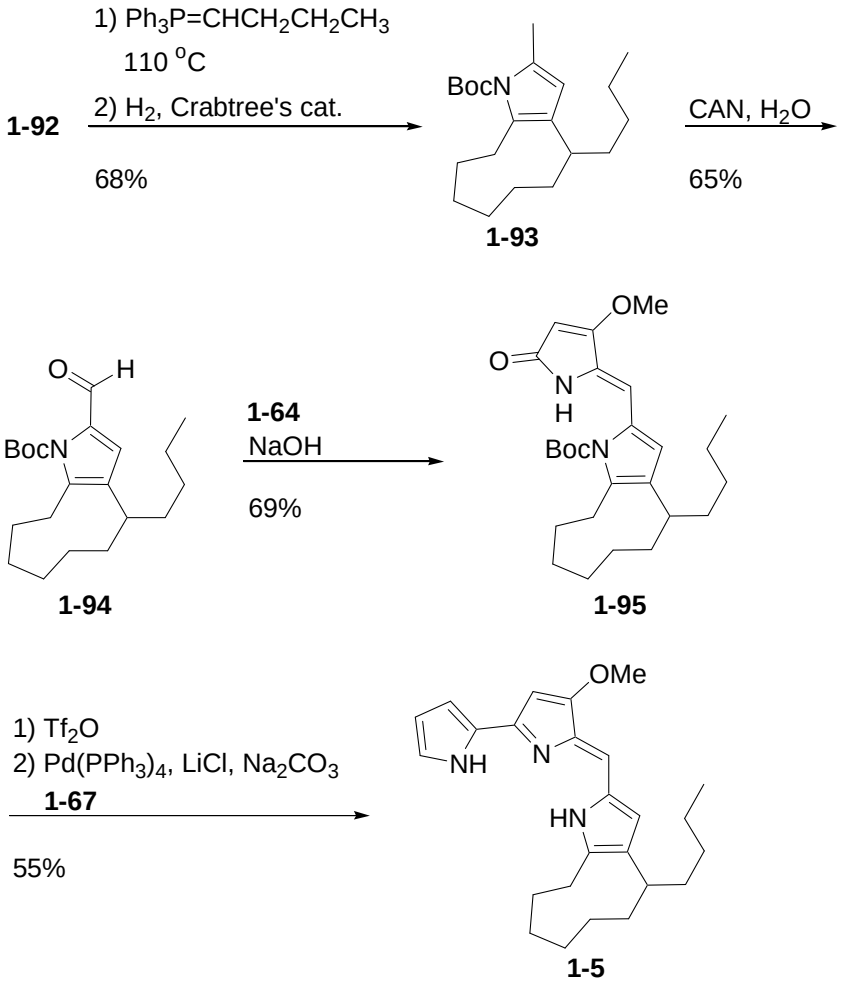


Figure **1.24**: Completion of Fürstner's synthesis of butylcycloheptylprodigiosin.

1.4.8 Reeves' synthesis of butylcycloheptylprodigiosin.

Recently Reeves published a synthesis of butylcycloheptylprodigiosin (**1-5**) which significantly reduced the number of steps required to construct the lower half of this target.[61] Starting from cyclononanone (**1-96**), an IBX oxidation to give α,β-unsaturated ketone **1-97** set up a 1,4-addition of butylcuprate and an aldol reaction with aldehyde **1-98**, see Figure **1.25**. Elimination of the alcohol moiety in **1-99** led to enone **1-100**. Aqueous sodium hydroxide opened the isoxazole in **1-100**, releasing the amine which condensed with the ketone to give carboxypyrrole **1-102** in four steps and 44% yield from commercially available starting materials. This route compares favorably with Fürstner's fourteen step effort to reach the same point (i.e. **1-94** and **1-102**) in 6% yield. Like Fürstner's synthesis, Reeves used D'Alessio's end-game strategy to append the northern half and finish the synthesis.

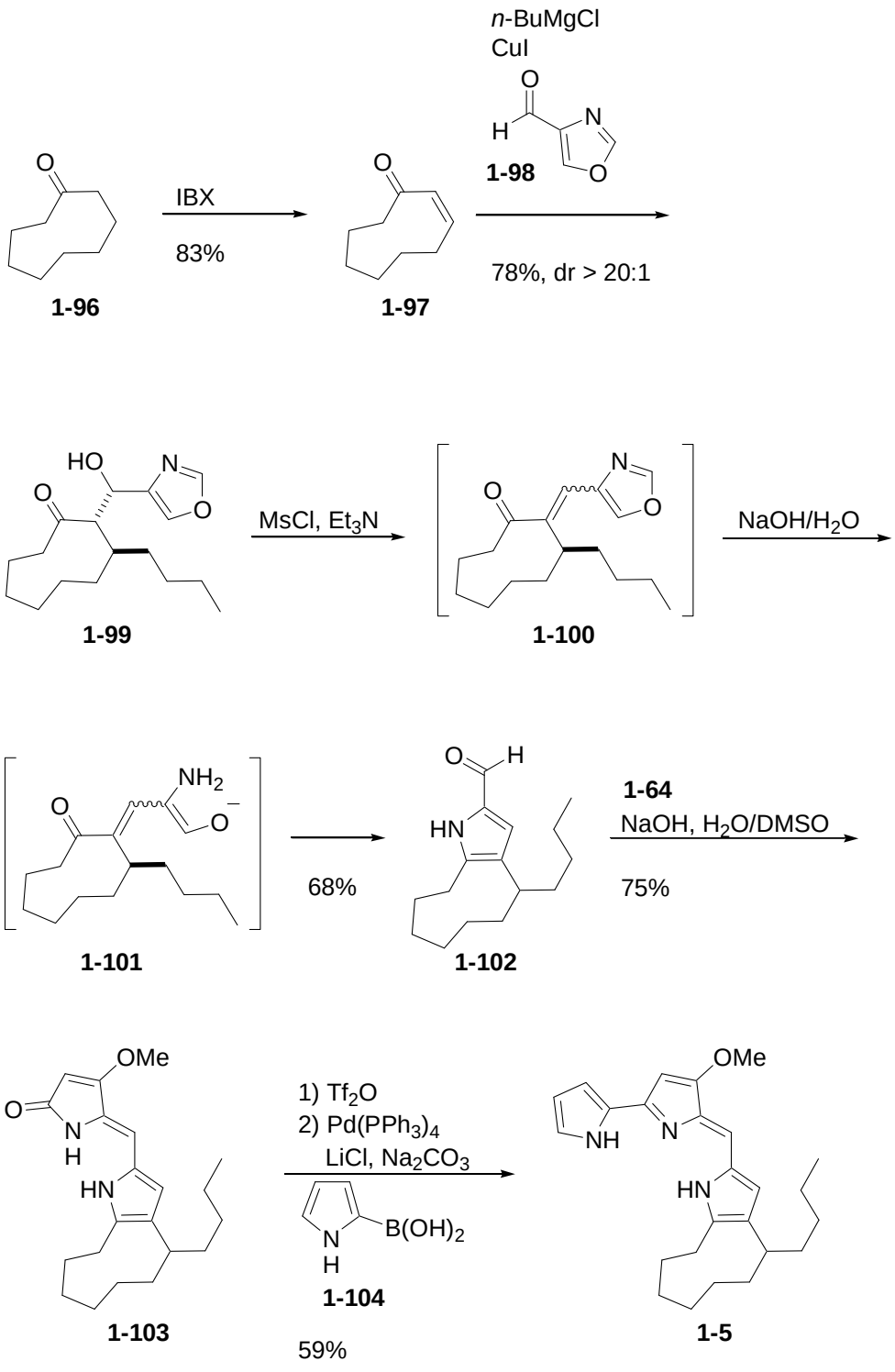


Figure **1.25**: Reeves' synthesis of butylcycloheptylprodigiosin.

1.4.9 Nonylprodigiosin.

Nonylprodigiosin (**1-4**) is one of the more intriguing members of the prodigiosin family. It is one of the only examples in which the A-ring is substituted, and the macrocyclic tether prevents rotation of the exocyclic olefin in the azafulvene B-ring to isomer **1-4'**, see Figure **1.26**.

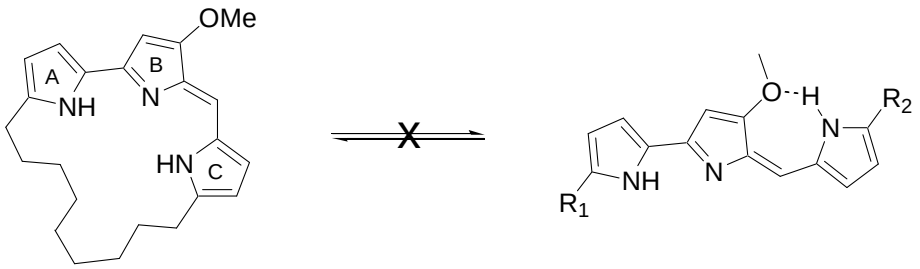


Figure **1.26**: Hindered conformational equilibration.

Fürstner synthesized the tripyrrolyl diene **1-114** following the D'Alessio method starting from alkylpyrroles **1-110** and **1-113**, which were made from the respective pyridylthioesters, see Figure **1.27**.[62] The tripyrrole salt **1-114** was exposed to RCM catalyst **1-115** and the alkene was subsequently reduced with hydrogen and Wilkinson's catalyst to complete the first total synthesis of nonylpropdigiosin (**1-4**).

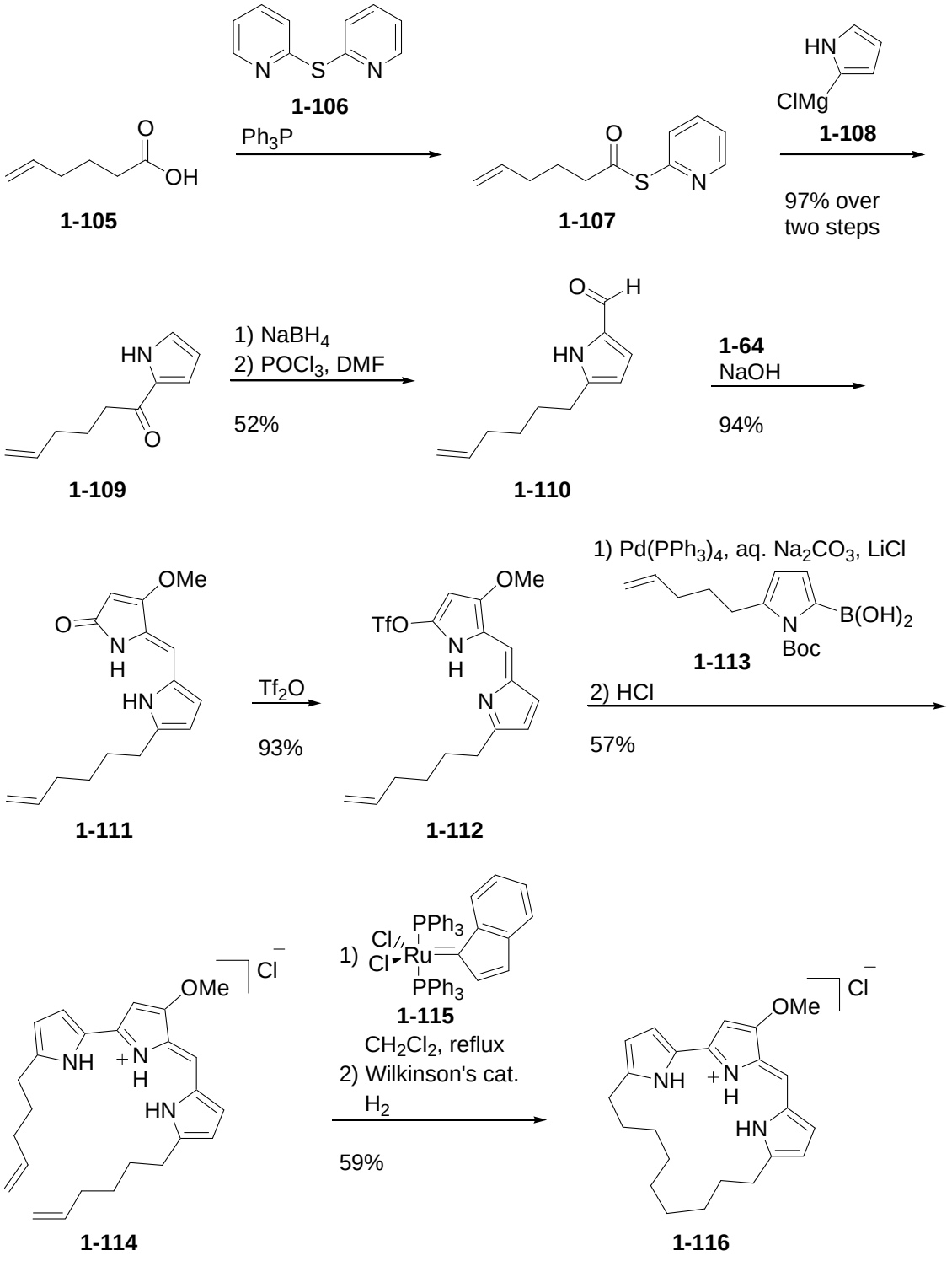


Figure **1.27**: Fürstner's synthesis of nonylprodigiosin.

1.4.10 Lavallée's synthesis of the northern half of the prodigiosins.

Recently Lavallée and Tripathy reported the shortest route of **1-13** to date, see Figure **1.28**.[14] The key step of this approach is the Suzuki coupling of boronic acid **1-67** and bromo pyrrole enamine **1-118**. The use of an enamine to mask the required aldehyde avoids the low yielding McFadyen-Stevens reaction used in previous work. This route consists of only four total steps with an overall yield of 35% in the longest linear sequence; however, lactam **1-64** is quite expensive.

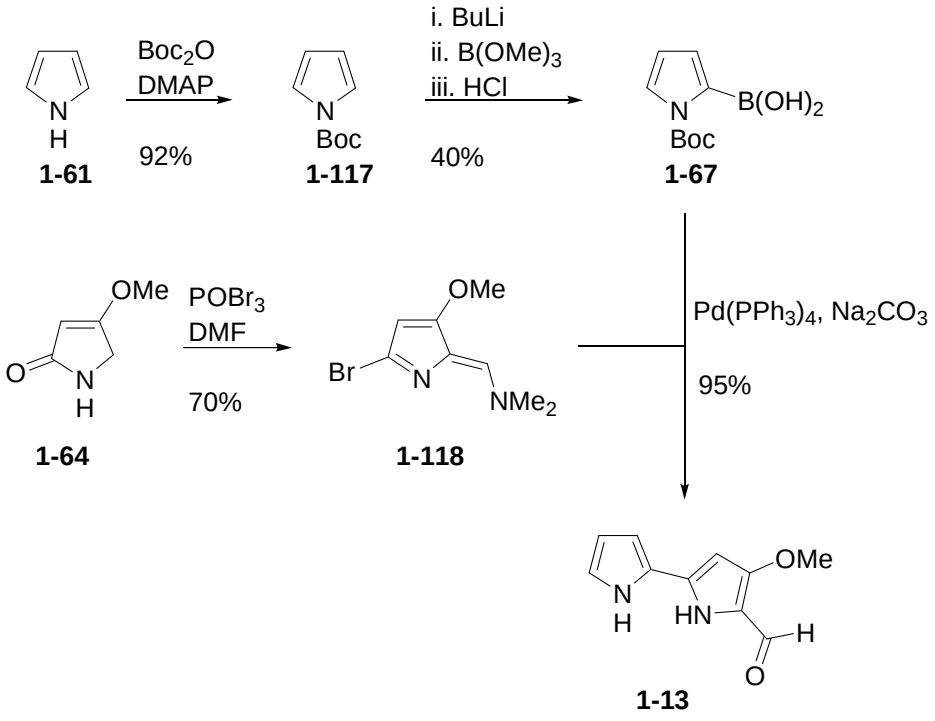


Figure **1.28**: Lavallée's short synthesis of **1-13**.

1.4.11 Fürstner's synthesis of the core of streptorubin B.

There are three published studies concerning the synthesis of streptorubin B. Fürstner completed the first synthesis of the lower half of streptorubin B **1-27** starting

from cyclooctene (**1-119**), see Figure **1.29**.[45] Allylamine **1-120** was generated from an ene-type reaction between **1-119** and a Se/chloramine-T mixture. Alkylation of **1-120** followed by a zinc mediated acylation gave enyne **1-122**. Exposure of **1-122** to catalytic $PtCl_2$ caused a ring expanding enyne metathesis that created the [7.2.1] bicyclic core of **1-6**. Enone **1-123** was reduced to the alkane in a four-step procedure. Strong base-mediated elimination of the tosyl moiety and tautomerization of the resulting diene gave pyrrole **1-27**. A key piece of spectral evidence confirming this successful synthesis is an alkyl chain proton ^{1}H NMR peak shifted upfield to -1.88 ppm due to anisotropy from the pyrrole. This diagnostic signal supports the bridged structure proposed by Weyland, which has a similar peak at -1.55 ppm.[44] Although Fürstner reports that **1-27** was isolated as a single diastereomer, he did not determine which isomer was made, nor did he make any effort to control the absolute or relative stereochemistry. Surprisingly, Fürstner never coupled this lower portion with **1-13**, despite the fact that he used that aldehyde the following year to complete other prodigiosin natural products, *vide supra*.

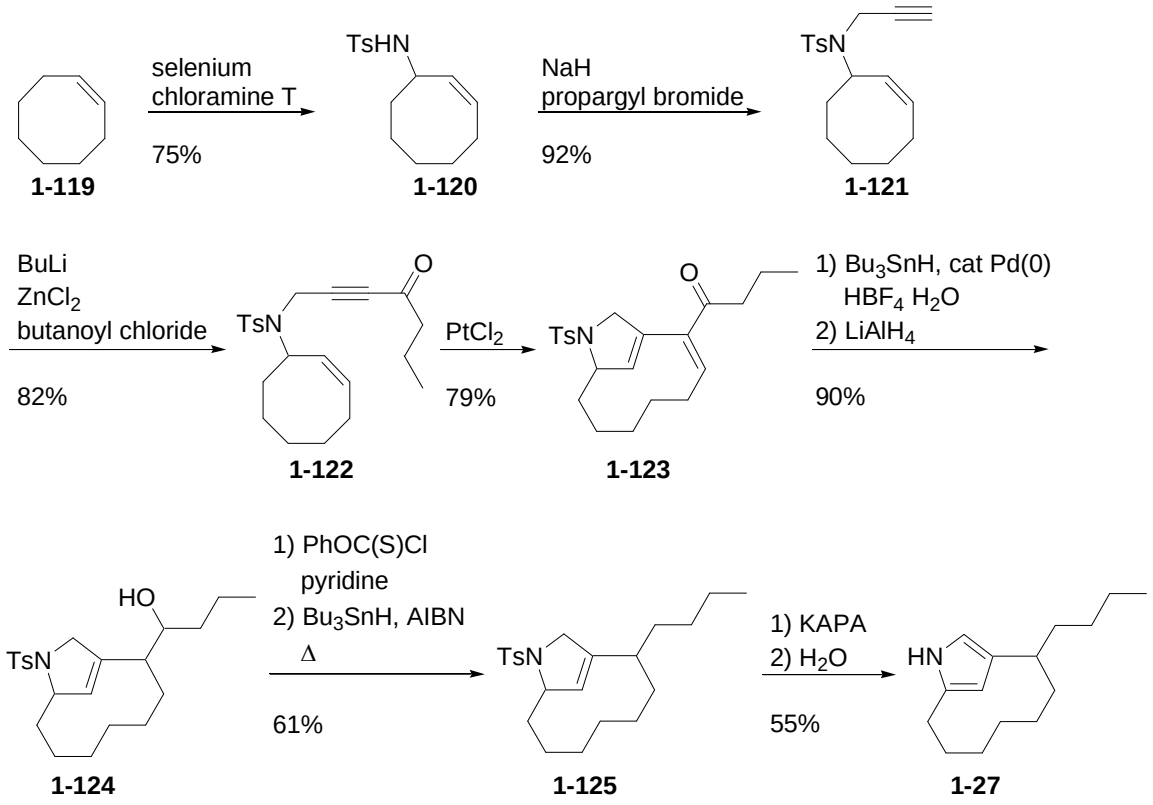


Figure **1.29**: Fürstner's synthesis of the core of streptorubin B.

1.4.12 Murthy's synthesis of streptorubin B.

Murthy and co-workers at Gemin X completed the first total synthesis of **1-6** in 2000 as part of a broader effort to synthesize a library of prodigiosin derivatives for drug candidate screening.[6-7] They followed Fürstner's route with one small variation. In order to gain access to two separate diastereomers, they used $Ru_2Cl_2((S)\text{-BINAP})_2(NEt_3)/H_2$ to reduce ketone **1-126** to the pair of alcohols **1-124a** and **1-124b**, which were separated and carried on independently according to Fürstner's published route, see Figure **1.30**. The final condensation step proceeded without incident and two isomers of **1-6** were isolated. Like Fürstner, they too ignored the planar chirality of **1-6**. Even though Murthy isolated the naturally occurring **1-6** from *Streptoverticillium baldacci*, no comparison of the final

compounds **1-6a** and **1-6b** with the natural product was reported, and thus, the absolute and relative configuration of **1-6** is still unknown.

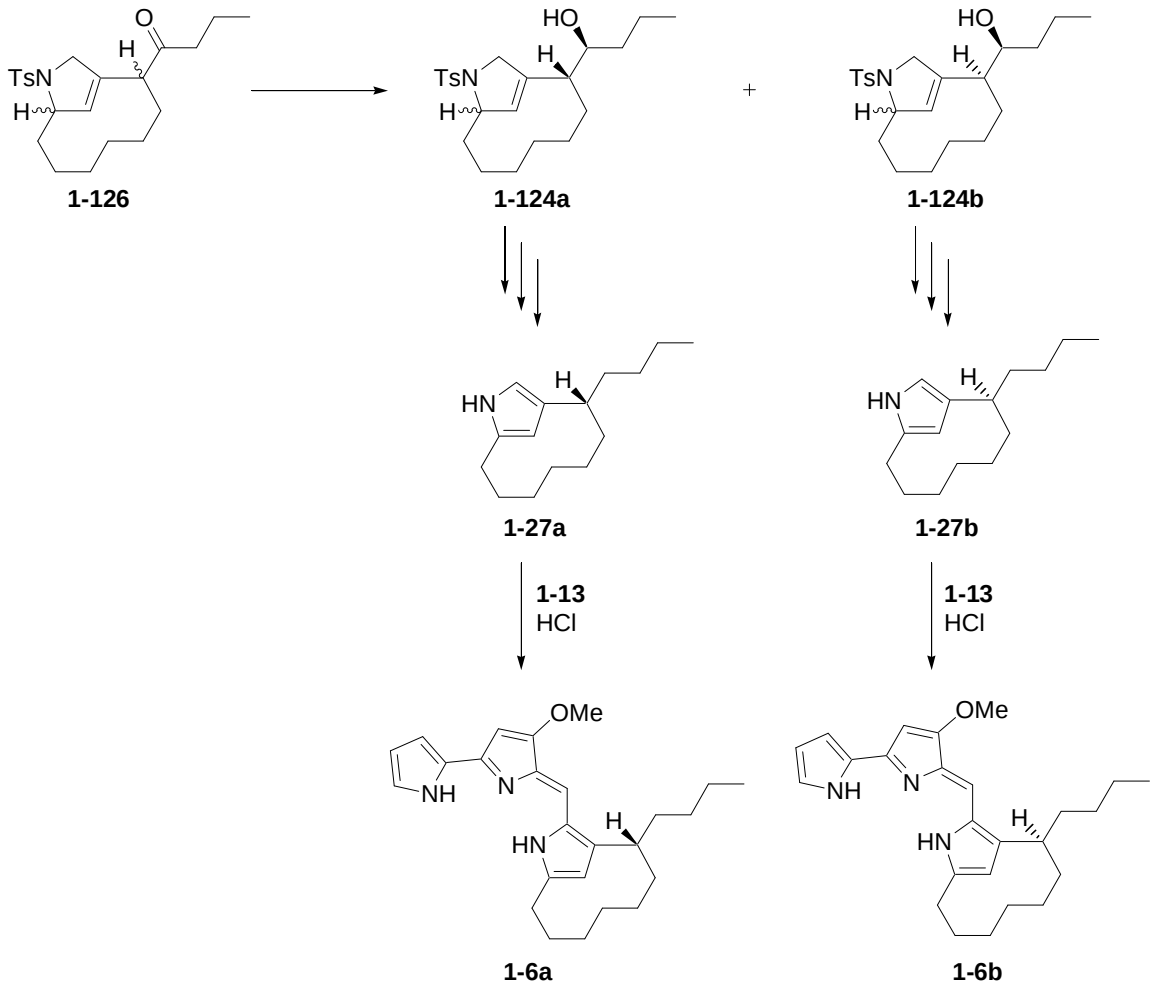


Figure **1.30**: Murthy's asymmetric reduction and the completion of streptorubin B.

Gemin X used this technology to create analogues of **1-6** as well, see Figure **1.31**. They were able to synthesize hundreds of prodigiosin-like compounds. It was during this process that GX15-070 (**1-8**) emerged as a promising oncology drug.

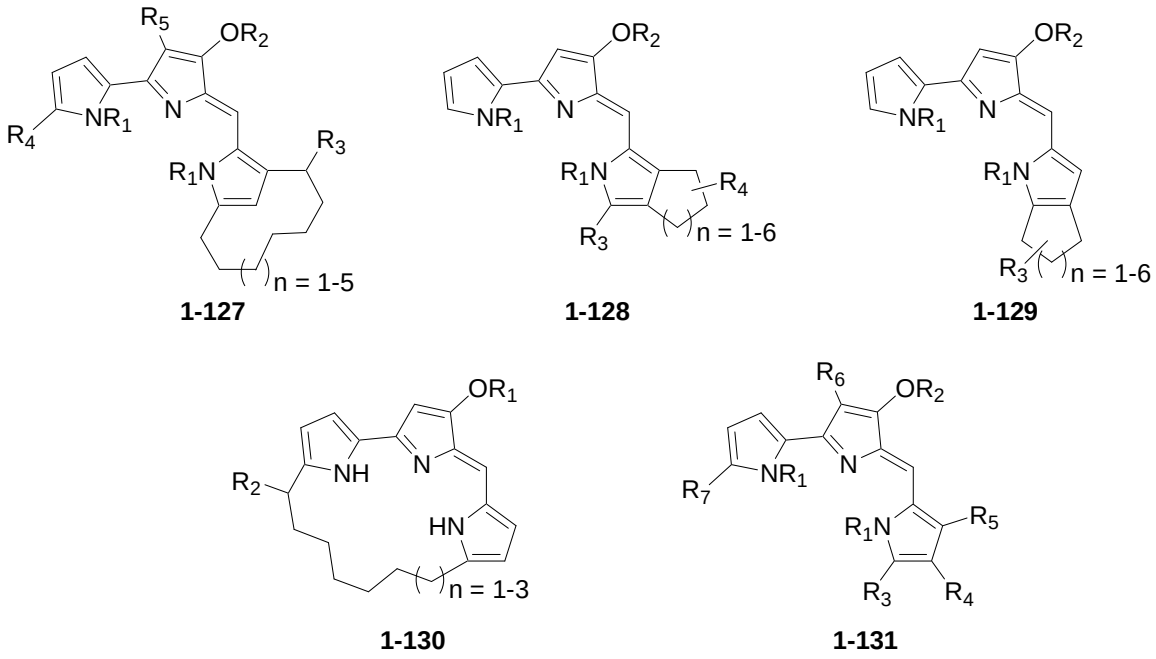


Figure **1.31**: Prodigiosin derivatives made by Gemin X.

1.4.13 Chang's synthesis of the core of streptorubin B.

Recently Chang and coworkers reported a synthesis of Fürstner's intermediate **1-125**, see Figure **1.32**.[63] Esterification and tosylation of amino acid **1-132** followed by TBS protection of the alcohol in **1-133** and reduction of the ester function furnished alcohol **1-134** in good yield over four steps. Alcohol **1-134** was homologated to the α,β-unsaturated ester **1-135**, which was reduced to the corresponding alcohol **1-136**. This alcohol was converted to ketone **1-138** over four simple functional group transformations.

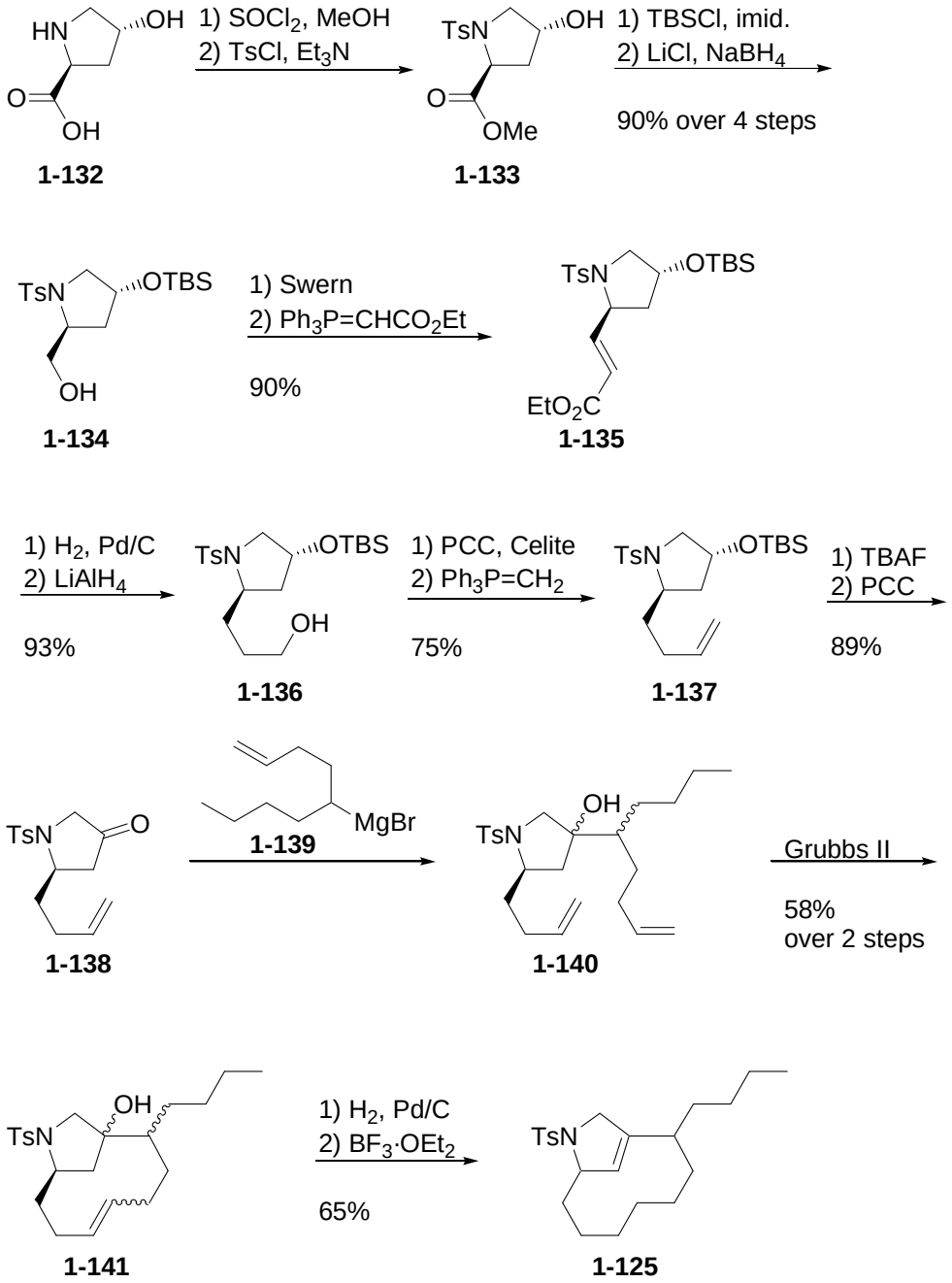


Figure **1.32**: Chang's synthesis of Fürstner's streptorubin B intermediate.

Addition of the Grignard reagent **1-139** to ketone **1-138** gave alcohol **1-140** as a mixture of diastereomers. Chang reports that exposure of this diene to Grubbs second generation catalyst induced a ring closing metathesis to the bicyclic compound **1-141**.

Hydrogenation of the alkene and elimination of the alcohol yielded Fürstner's intermediate **1-125**.

1.5 Conclusions.

As the synthetic efforts toward the prodigiosin family of natural products has spanned several decades, so have the general approaches and reagent choices evolved through the eras. The strategies have improved from Rapoport's straightforward but lengthy route to **1-13** to Lavallée and Tripathy's inventive appraoch to **1-13** requiring only three linear steps. Methods have been developed that allow for facile analogue formation.These efforts have led to screening for enhanced biological properties.

Many uncertainties still surround the prodigiosin known today as streptorubin B (**1-6)**. While the biological systems affected by many of the prodigiosins are well known, the precise molecular targets for streptorubin B have not yet been found. In addition, neither the absolute nor the relative stereochemistry of **1-6** is known. Streptorubin B has been synthesized, but little effort has thus far been put forth to control the relative and absolute stereochemistry. The determination of this stereochemistry by chemical synthesis and the synthesis of its stereoisomers could aid in the search for these targets through biological testing. In particular, the question of selective vs. general membrane transport can be probed by the acquisition of the full set of **1-6** stereoisomers. If there is a difference between the four isomers of **1-6** in their capability to transport HCl through membranes, then it can be concluded that a discrete molecular target does in fact exist. If little difference is observed, then it is probable that the prodigiosins simply transport HCl passively through membranes using their dual hydrophilic/hydrophobic character. It is

also possible that prodigiosins bring Cu(I) species into contact with DNA without enzymatic assistance.

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Chapter 2

Project Plans and Goals

2.1 Retrosynthesis.

The final condensation step in many syntheses of the prodigiosins is well established, and it has been used successfully for streptorubin B (**2-1**), see Figure **2.1**. Therefore, the focus of this work will be the construction of **2-3**, namely the bridged C and D rings. The major challenge yet to be addressed in the syntheses of **2-3** is the control of planar chirality. Our plan was to use conventional chirality in the form of a stereogenic atom to set the planar chirality. With the stereochemistry at C2 set as *S* in **2-4**, the alkyl tether must reside on the top face of the pyrrolidine and should maintain that position during the elimination of TBSOH to give the *P* isomer of **2-3**. Thus, either isomer can be accessed by controlling the stereochemistry at C2.

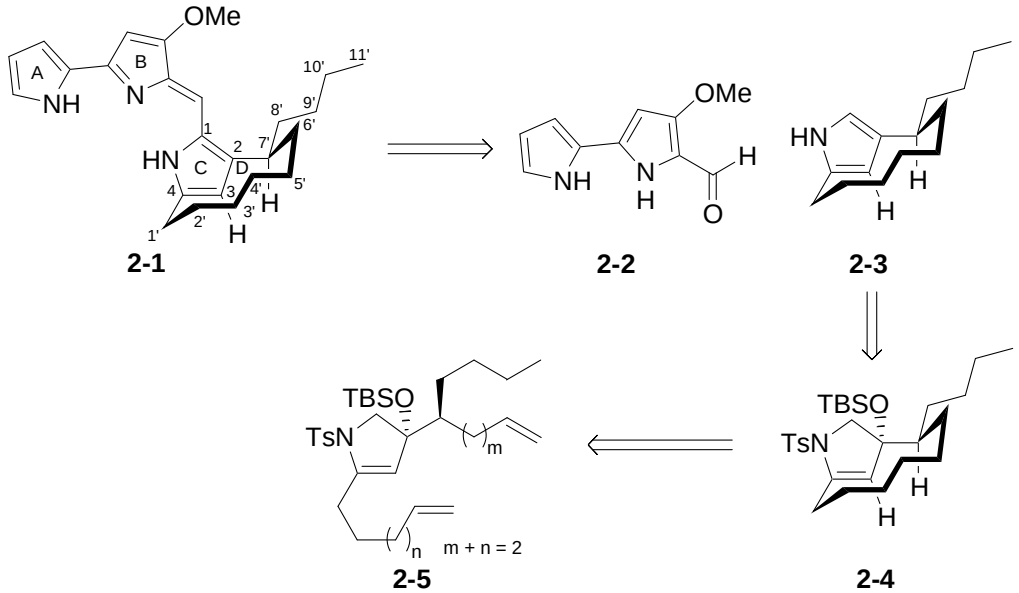

Figure **2.1**: Retrosynthesis of **2-1** with a RCM reaction of dihydropyrrole **2-5**.

The bridged cyclodecenyl D ring could be closed using ring closing metathesis (RCM). The closure of medium sized rings *via* RCM is a difficult task, but many successful examples are known, see Chapter 4. Any engagement of the internal olefin by a Ru catalyst would be discouraged for steric reasons, as that olefin is both trisubstituted and bears a *t*-butyl type substituent.

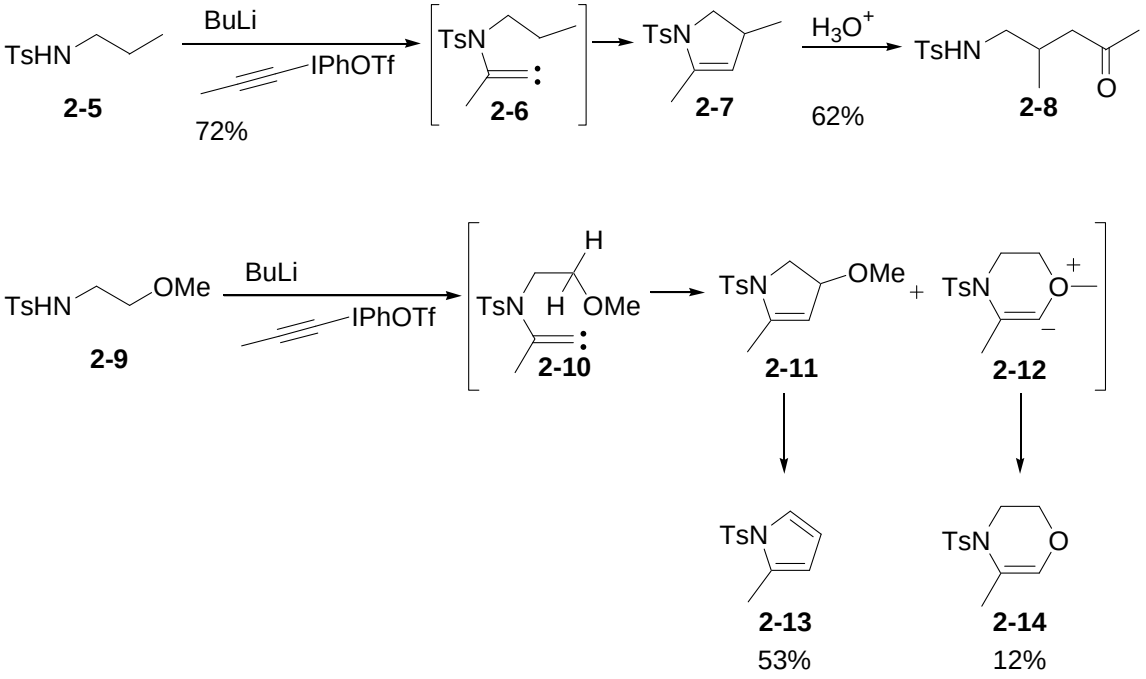

Figure **2.2**: Previous C-H insertion reactions to yield dihydropyrroles and related species.

The C ring can be formed with a C-H insertion of an alkylidenecarbene generated from alkynyliodonium salt chemistry previously developed in our laboratory,[64] see Figure **2.2**. The instability of dihydropyrroles was expected to be impediment. Enamine **2-7** is stable enough to allow for isolation, but exposure of this compound to acid caused it to open to ketone **2-8**. The presence of an alkoxy group creates another problem of stability. The methoxy group in **2-11** is easily eliminated to give pyrrole **2-13**. Also, combination

of the oxygen lone pair with the carbene (e.g., **2-12**) competes with C-H insertion. In an effort to avoid these problems, a TBS group was selected to replace the methyl group, see **2-17** in Figure **2.3**. A silyl ether should be less prone to carbene additions as the oxygen lone pairs participate in pπ-dπ backbonding with the silicon.

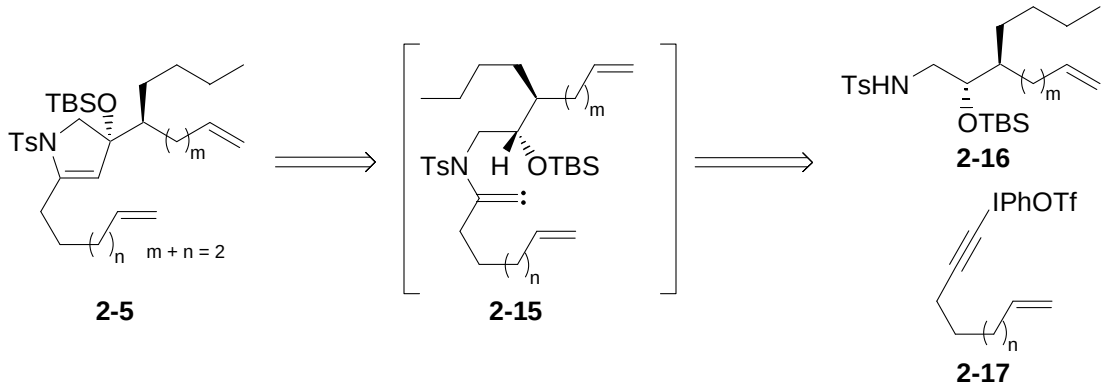

Figure **2.3**: Retrosynthesis of **2-5** using alkynyliodonium salts.

The advantage of using these insertions is that they occur with retention of stereochemistry,[65] and thus stereochemical information from the simple linear molecule **2-16** completely dictates the chirality of a the complex heterocycle **2-5**. The control over regiochemistry will be much less certain. With an alkyl chain attached to both tosylamide **2-16** and alkyne **2-17**, two C-H insertion options are available. Insertion into the lower chain of carbene intermediate **2-15** can be discouraged by introducing an sp^2 hybridized C-H bond sp^2 at that location. In addition, the desired insertion into the upper chain can be encouraged by increasing the level of substitution and appending a heteroatom at the insertion site, see chapter 3.

Using this strategy, the relative and absolute stereochemistry of **2-1** can be derived from the vicinal stereocenters in **2-16**. All four stereoisomers of **2-16** can be readily accessed using standard Evans' oxizolidinone chemistry.

2.2 Backup plans.

If the challenges surrounding the alkynyliodonium chemistry cannot be overcome a backup plan will be pursued. A precursor to the C ring containing a stereocenter can be purchased as lactam **2-21**, see Figure **2.4**. The two key stereocenters would be more difficult to install here than in the original plan. The stereochemistry at C2 can be set by diastereoselective protonation of the enolate of **2-19** using substrate control influenced by the butenyl group at C4. At C7', substrate control may be able to influence the conjugate addition of a butyl fragment to α,β-unsaturated amide **2-20**; however, reagent control might be necessary.

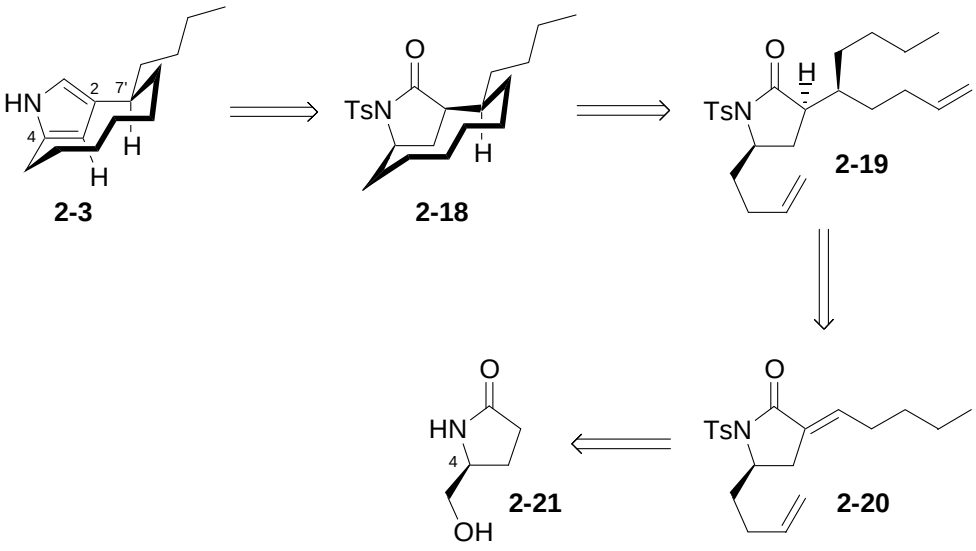

Figure **2.4**: Retrosynthesis of **2-3** using RCM of a lactam.

Diene **2-19** is likely to be a much better RCM substrate than **2-5** because the lactam ring does not suffer from the instability problems of dihydropyrroles. Also, having two sp^3 hydridized carbons at the bridgehead positions should decrease the ring strain in **2-18**. The conformation of the two alkyl appendages in **2-19** is uncertain; on the one hand, the two side chains are expected to be diaxial to prevent an $A^{1,3}$ interaction between the butyl chain and the tosyl group. However, there is also a competing repulsive *syn*-pentane interaction between the two chains, which would push them down toward equatorial positions.

Once again, all four stereoisomers are easily accessed by simple variations in the route. Both enantiomers of **2-21** are commercially available, which takes care of the chirality at C2. Also, by switching the order of incorporation of the butyl and butenyl groups, the stereochemistry at C7' can be manipulated, see Figure **2.5**.

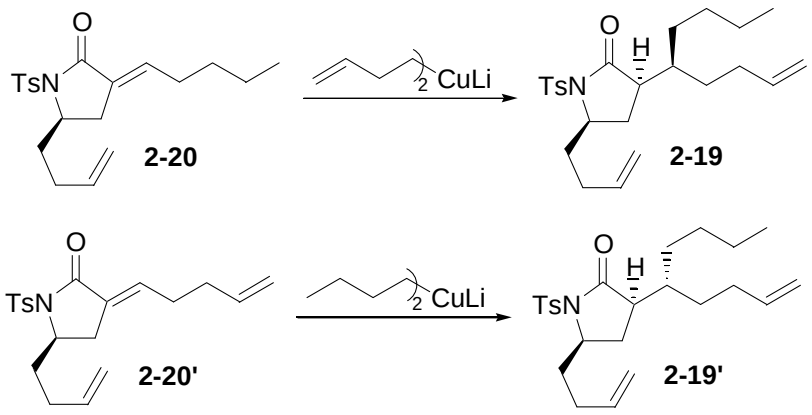

Figure **2.5**: Easy access to both diastereomers of **2-10**.

If the RCM proves to be ineffective, other methodologies will be explored. These routes could include Horner-Wadsworth-Emmons macrocyclization,[66-68] Ramberg-Bäcklund ring contraction,[69-70] McMurry coupling.[71-73]

One attractive methodology would be a Nozaki-Hiyama-Kishi (NHK) coupling of an aldehyde and a vinyl iodide.[74-84] This chemistry has been used to close a variety of strained medium sized rings. A suitable NHK precursor **2-23** could be made following the same general procedure used for **2-19**, see Figure **2.6**.

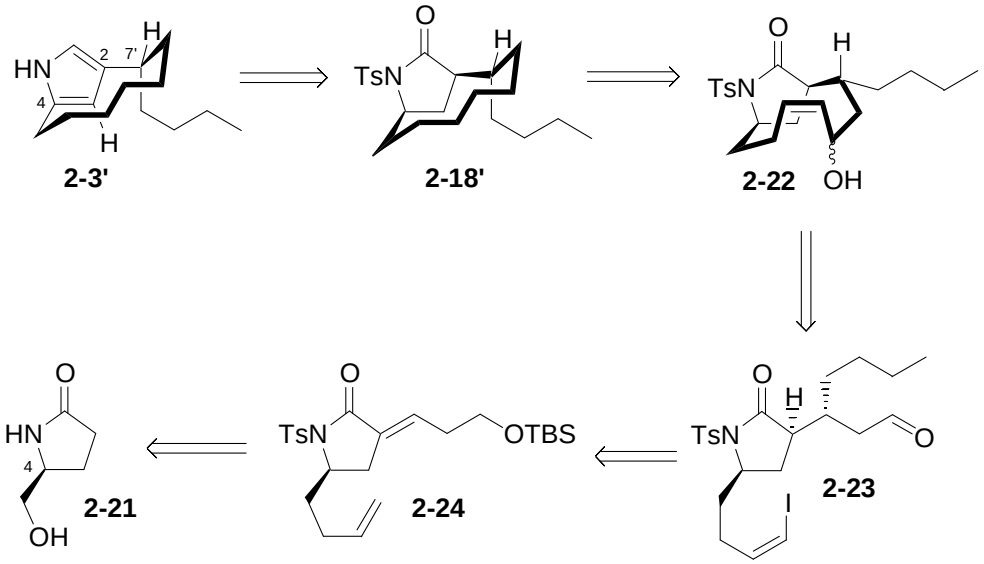

Figure **2.6**: Retrosynthesis of **2-3'** using a Nozaki-Hiyama-Kishi coupling.

2.3 Biology and isolation.

One of the main purposes of this project is to determine the effects of stereochemistry in the biological activity of **2-1**. Once all four stereoisomers have been synthesized, they will be submitted to biological assays to determine if the chirality of **2-1** plays any role in its biological function. The D ring is held rigidly across the C ring,

and thus the wrong enantiomer could prevent proper binding to a chiral receptor and attenuate activity. Also, varying the stereochemistry at C7' could also play a role in disrupting binding if a specific cellular receptor does in fact exist.

Lastly, the absolute configuration of naturally occurring **2-1** will be determined. **2-1** will be isolated from cultures of *Streptomyces*, and the NMR and optical rotation data will be compared to those of the four synthetic streptorubins to unambiguously assign relative and absolute stereochemistry.

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Chapter 3

Alkylidenecarbenes

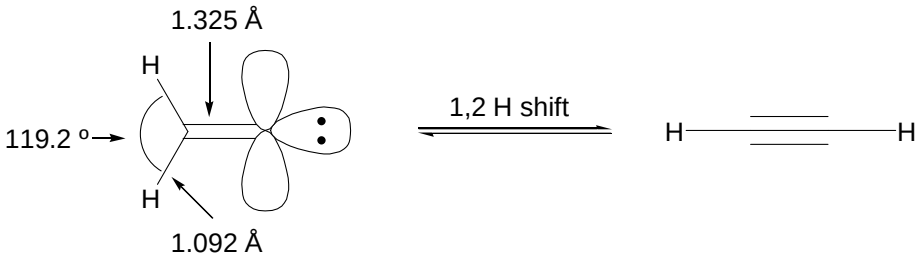
A valuable strategy in the field of synthetic organic chemistry is to create complex molecular systems in a small number of transformations. In many cases these sequences require the use of high-energy reactive intermediates that possess the energy needed to drive a cascade of reaction steps. The key to this strategy is to guide the reactivity of these intermediates toward productive bond formation. Superior methodologies of this type proceed with exceptional chemo-, regio-, and stereoselectivity.

Alkylidenecarbenes have been used to construct novel functionality and complex ring systems for decades.[85-89] In many cases, these moieties were created in a concise manner with complete control of regiochemisty. Historically, the methods for generating members of this class of carbenes have been harsh, but current approaches allow for their formation under milder conditions. Their ease of preparation, coupled with their compatibility with most functional groups, make alkylidenecarbenes excellent entry points to complex, polycyclic functionalized molecules.

3.1 Structure of alkylidenecarbenes.

The simplest alkylidenecarbene, vinylidenecarbene (**3-1**), is a planar molecule possessing both an empty *p* orbital and a filled *sp* orbital, see Figure **3.1**.[90] This hybridization is reflected in the calculated bond lengths and angles, as well as the reactivity. The C-C bond of **3-1** is estimated at 1.325 Å and the C-H bond is 1.092 Å.[91]

When comparing this value with the corresponding bond lengths of 1.317 Å and 1.079 Å for ethylene[92], the C-H bond of **3-1** is slightly longer, possibly due to $\sigma \rightarrow p$ hyperconjugative interactions. Also, the 119.2 ˚ H-C-H bond angle is enlarged compared to the usual 116-117 ˚ observed in ethylene. The C-H bonds in **3-1** are shifted to achieve better overlap with the empty *p* orbital. These calculations are consistent with supporting experimental evidence, which will be discussed later.



3-1 **3-2**

Figure **3.1**: Structure of alkylidenecarbene **3-1** and rearrangement to acetylene.

Vinylidenecarbene (**3-1**) is considered to be an equilibrium structure of acetylene. Both experimental evidence and computational estimations place acetylene ~44 kcal/mol lower in energy than **3-1**. [91, 93-94] This extremely exothermic transform also has been shown to have a very low activation energy barrier, as low as 3 kcal/mol.

3.2 Formation of alkylidenecarbenes.

Alkylidenecarbenes are formed predominantly via several variations of the following general method; an anion on an sp^2 carbon also bearing a good leaving group results in α-elimination to the alkylidenecarbene **3-5**, see Figure **3.2**. These anions are

typically made by deprotonation of vinyl species **3-3**,[95-96] but anions such as **3-4** also have been made *via* lithium halogen exchange of 1,1-dibromides.[86]

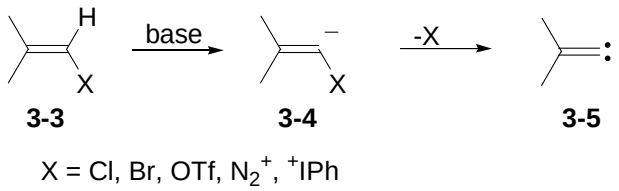


Figure **3.2**: α-elimination method to form alkylidenecarbenes.

As expected, the better the leaving group on **3-4**, the more facile the formation of the alkylidenecarbene. As nitrogen gas is one of the best known leaving groups, vinyl diazonium compounds have been used extensively in the formation of alkylidenecarbenes.[97-99] Therefore, it is no surprise that many methods have been devised to create vinyldiazonium ions, Figure **3.3**. The simplest method is converting a ketone, such as **3-6**, to anion **3-7** using either trimethylsilyldiazomethane or dimethyl diazomethylphosphonate.[100]

Other more elaborate methods to generate diazoalkenes also exist. One reported precursor is the *gem*-dialkyl-*N*-nitrosooxazolidinone **3-8**.[99] Upon exposure to alkoxide bases, the carbamate is cleaved to an alkylcarboxylate and the nitrosoamine is converted to a diazonium salt following a similar pathway as in the reaction of an amine with an alkyl nitrite. The alkylcarboxylate is then eliminated to leave diazoalkene **3-7**.

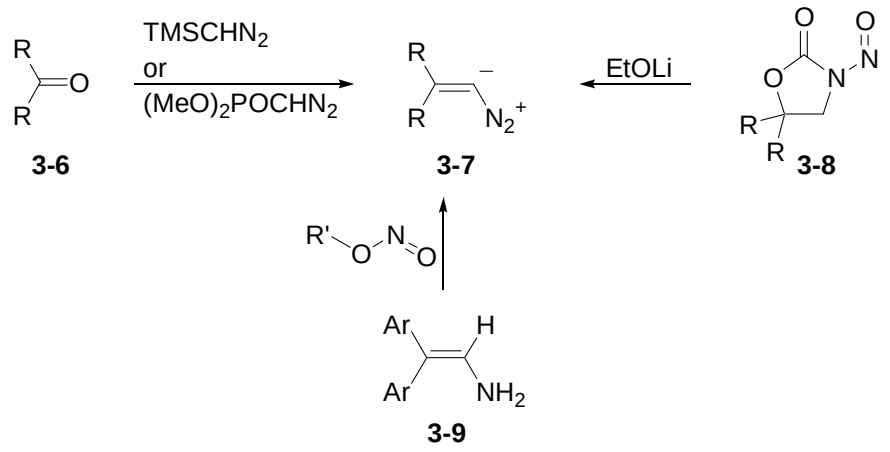


Figure **3.3**: Various methods to form diazoalkenes.

Another interesting example of vinyl diazonium ion synthesis uses α,β-epoxy-*N*-aziridinylimines, see Figure **3.4**.[101] In refluxing toluene, the aziridine **3-10** ejects styrene to leave nitrene **3-11**. The anionic character on the diazo carbon of **3-12**, causes the epoxide to open and subsequently forms the vinyldiazonium species **3-14**.

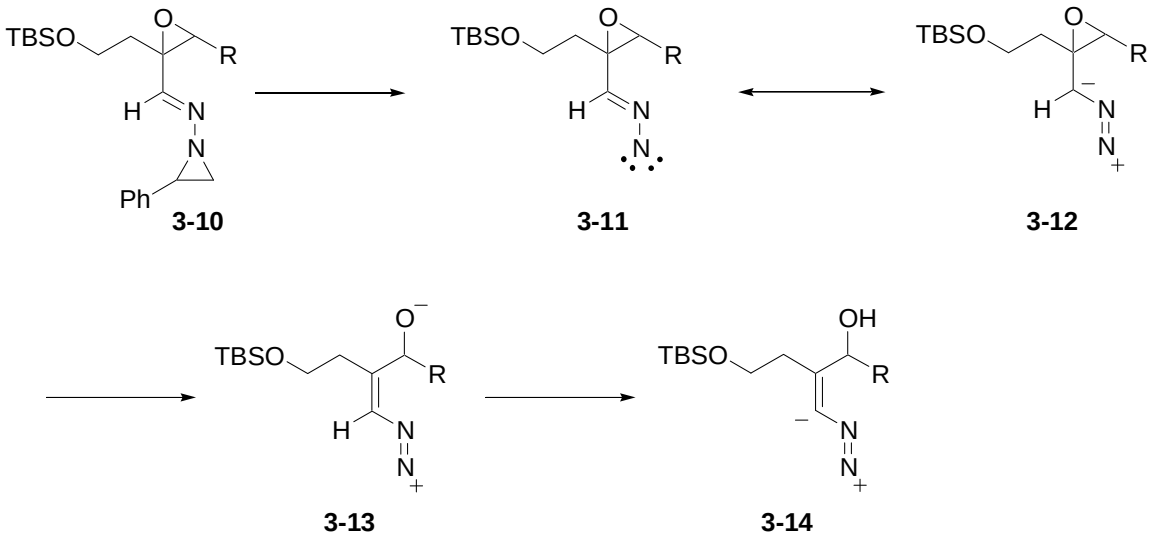


Figure **3.4**: Kim's generation of a diazoalkene.

As early as 1965, alkynyl(aryl)iodonium salts were used to generate alkylidenecarbenes, although this transform was not appreciated at the time.[102] In later years, this branch of hypervalent iodide chemistry evolved into a general method for easy access to alkylidenecarbenes.[103-106] At low temperatures, electron deficient alkynes **3-19** undergo conjugate addition with soft nucleophiles to form zwitterions of type **3-22**, see Figure **3.5**. Loss of iodobenzene then generates the carbene **3-23**. This mild route to accessing alkylidenecarbenes tolerates a wide variety of functional groups. Over the years, methods for creating alkynyl(aryl)iodonium salts have evolved from Koser's reagent **3-16**[107] to Zefirov's reagent **3-20**,[108] and now to Stang's reagent **3-18**.[109] Stang's reagent has become the method of choice because of its stability, versatility, and reliability.

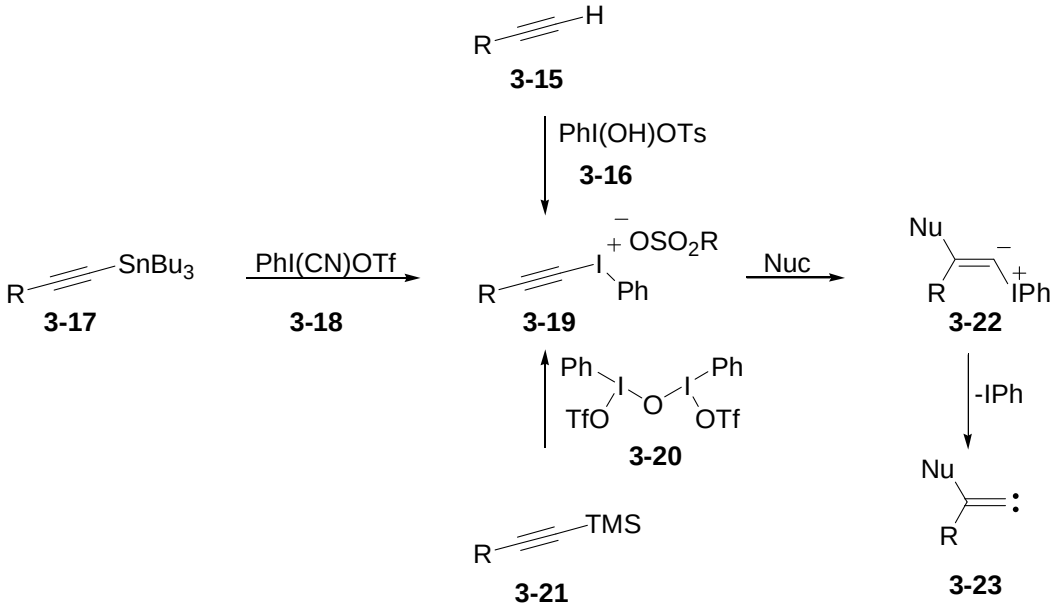


Figure **3.5**: Various methods of forming alkynyliodonium salts en route to alkylidenecarbenes.

Examples of creating alkylidenecarbenes by photochemical methods are rare but have been published. One example of such a method is the photoinduced loss of phenylmercuric chloride from **3-24** to generate 2,2-dichloroethenylidenecarbene **3-25**, see Figure **3.6**.[110]

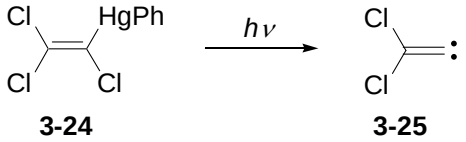


Figure **3.6**: Photochemical method of forming an alkylidenecarbene.

3.3 Reactivity of alkylidenecarbenes.

Alkylidenecarbenes follow three general reaction pathways: (1) additions to olefins, (2) 1,2-shifts, and (3) 1,5-insertions, see Figure **3.7**. The actual pathway taken is dependent upon the nature of the β substituents, usually proceeding with excellent chemoselective control.

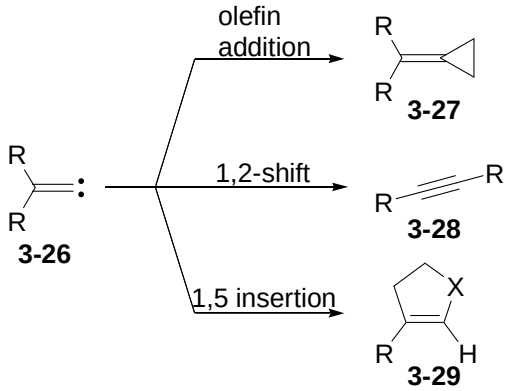


Figure **3.7**: Possible reaction pathways of alkylidenecarbenes.

3.3.1 Additions to double bonds.

Carbenes have long been known to react with olefins to form cyclopropanes.[111] This reaction has been used to probe spin multiplicity of various carbenes. Like all carbenes, alkylidenecarbenes can exist in four spin states, see Figure **3.8**. Of these possibilities, only the singlet states can add to olefins stereospecifically. The triplet (T_1) **3-32** would follow stepwise cyclopropanation mechanisms and thus stereochemical information would be lost.

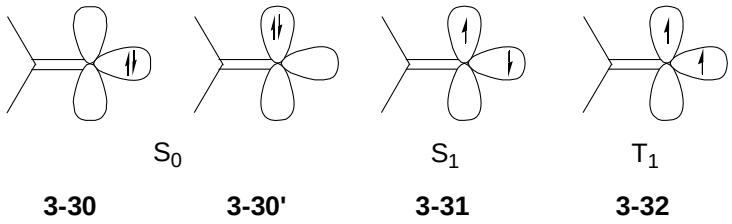


Figure **3.8**: Possible spin states of alkylidenecarbenes.

Stang and Mangum examined the reaction of isopropylidenecarbene **3-5** with both *trans* and *cis* 2-butene, **3-34** and **3-36** respectively, see Figure **3.9**.[96] After correcting for minor amounts of **3-36** impurities in **3-34** and compensating for the relative reaction rates, it was found that **3-34** was converted to *trans* cyclopropane **3-35** with >99.9% stereoselectivity. Similar studies with **3-36** showed >99.4% stereoselectivity. This reactivity data favoring the singlet state was further confirmed with IR data of **3-30** in an Ar matrix.[112] Also, calculations showed that the singlet (S_0) **3-30** state is ~45 kcal/mol lower in energy than the triplet (T_1) state **3-32** due to the empty *p*-orbital that is more available for hyperconjugation.

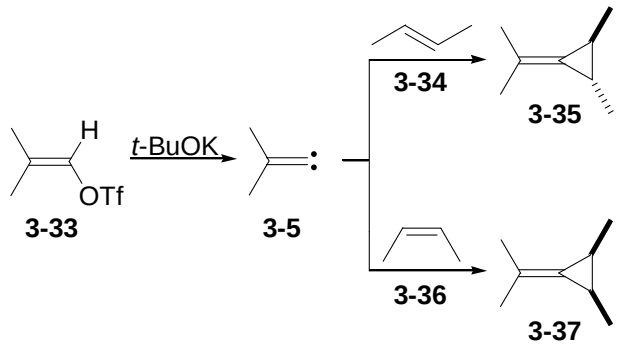


Figure **3.9**: Stereospecefic cyclopropanations of isopropylidenecarbene.

When an olefin addition occurs intramolecularly as in Figure **3.10**,[113] the strain of the derived bicyclo[3.1.0]-alkene is too great to allow for isolation, and further reactions and isomerizations are observed. These pathways include opening to trimethylenemethane diyl (TMM) derivatives,[86, 114-115] dimerization to cyclobutanes,[86, 113] alkene isomerization to vinylcyclopropanes,[113] and electrocyclic ring opening to larger cycloalkenes.[116]

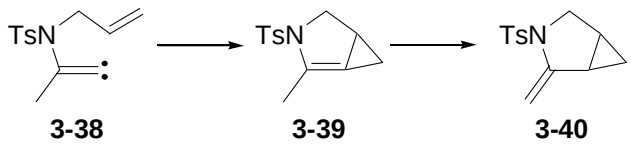


Figure **3.10**: Intramolecular cyclopropanation and rearrangement.

3.3.2 1,2-Shifts.

The Fritsch-Buttenberg-Wiechell rearrangement, or a 1,2-shift within an alkylidenecarbene, has been known since the late 1800's.[117-119] This shift is possible because the empty *p*-orbital of a singlet alkylidenecarbene is co-planar with the σ-bonds of both β substituents. This enforced allignment causes many groups to shift before any

other type of reaction can occur. Groups that have shown a high aptitude for this shift include: sulfinates,[120] sulfides,[85] thiocyanates,[121] phosphates,[122] phosphines,[123] selenides and tellurides,[124] hydrogens,[125] silanes,[126] and arenes.[127] This method has been used by many groups to serve as a formal S_N2 displacement on an sp hybridized center, see Figure **3.11**. Alkyl substituents, however, are poor participants in this rearrangement. Although cases do exist, those shifts occured under constrained conditions.[128-129]

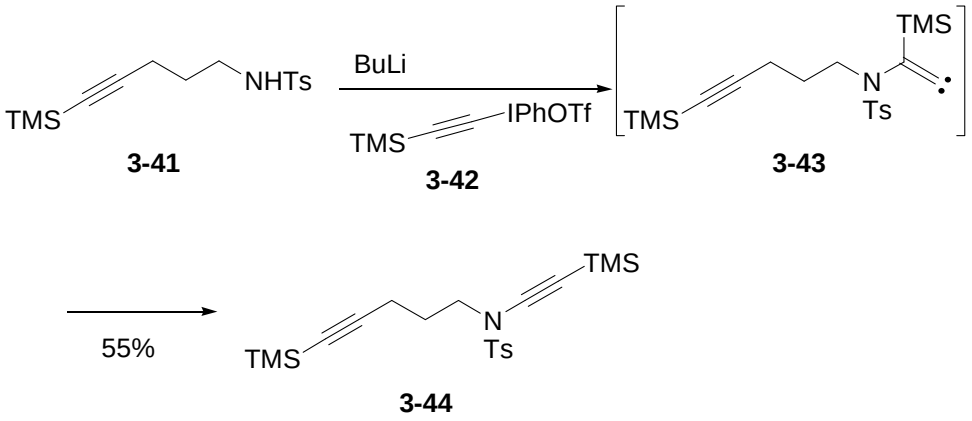


Figure **3.11**: 1,2-shift of a trimethylsilyl group.[126]

3.3.3 1,5-Insertions and additions.

3.3.3.1 Carbon-hydrogen insertions.

The propensity of alkylidenecarbenes to insert into C-H bonds intramolecularly has prompted their use in the formation of various five membered carbocycles and heterocycles.[89, 103-105] This reaction has been shown to tolerate a wide variety of functional groups and can proceed with good yields. One of the great advantages of this methodology is the stereospecific nature by which the insertion occurs, see Figure **3.12**.[65]

This chemistry allows for the facile formation of quaternary stereocenters from relatively easy-to-make tertiary stereocenters.

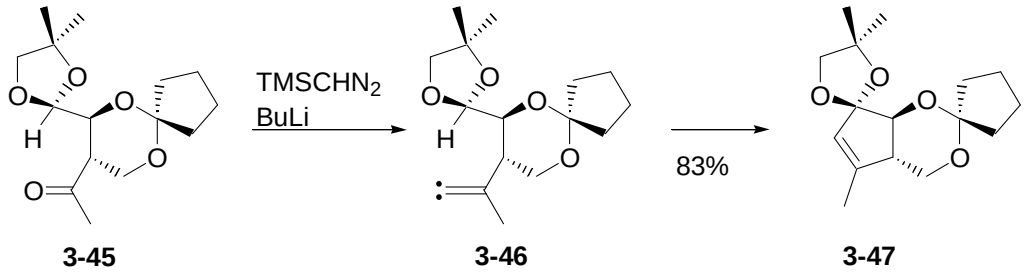


Figure **3.12**: Stereospecific 1,5 C-H insertion.

Carbon-hydrogen insertions by alkylidenecarbenes are very selective for forming five membered rings. This observation can be rationalized by evaluating a putative transition state, see Figure **3.13**.[64, 130] The initial interaction involves the nearly parallel C-H bond and the empty *p*-orbital of the carbene. As the reaction progresses, the lone pair of the carbene interacts with the hydrogen atom, and the C-C bond is formed.

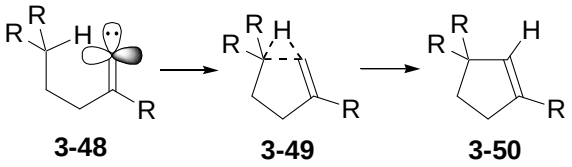


Figure **3.13**: Transition state structures of a 1,5 C-H insertion.

Alkylidenecarbene C-H insertions are sensitive to the nature of the C-H bond. Wolinsky has shown that the rate of insertion follows the trend: tetriary > secondary (benzylic) > secondary >> primary.[95] These measurements were taken by observing the

ratios of 1,5 C-H insertion products to 1,2 shift products. Gilbert later saw similar results when conducting competition experiments such as those shown in Figure **3.14**.[131]

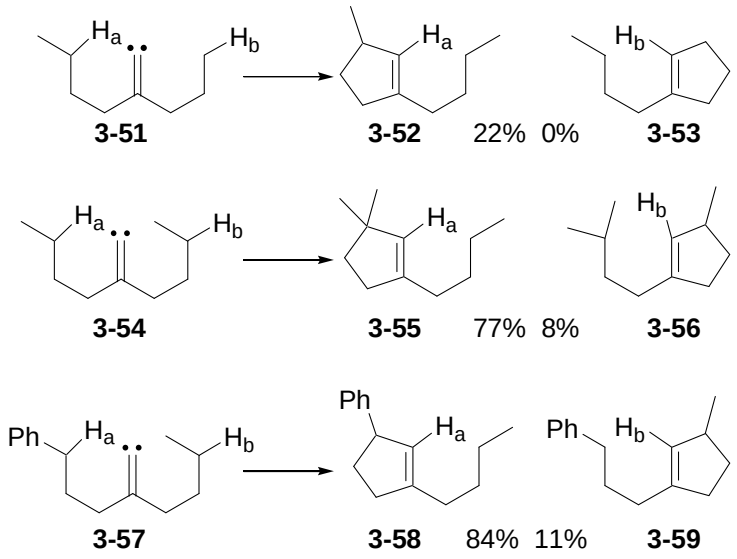


Figure **3.14**: C-H insertion regioselectivity competition experiments.

The presence of adjacent heteroatoms has been reported to increase the rate of C-H insertion relative to the rate of interaction of the carbene with alcoholic solvents.[132] This effect is apparent in the good-to-moderate yields observed in insertion reactions with methyl ethers.[133-134] In one extreme case, insertion into such a primary C-H bond was favored over a tertiary alternative.[135]

To a first approximation, these regioselectivities can be correlated to the corresponding C-H bond dissociation energies, see Figure **3.15**. As the level of alkyl substitution increases down the table, the strength of the C-H bond declines. Also, the presence of oxygen and nitrogen significantly decreases the bond strength. However, this

analysis breaks down with benzyl C-H bonds which have lower BDE's but have been reported to react more slowly than tertiary C-H bonds.

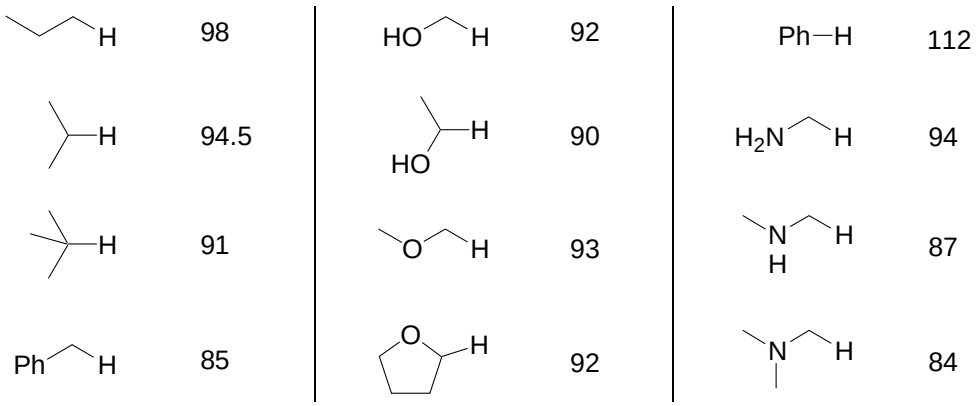


Figure **3.15**: Selected C-H bond dissociation energies (kcal/mol).[136-138]

Interestingly, in the case where C-C-H is pitted against O-C-H, the results do not follow the expected trend, see Figure **3.16**.[139] Ketones **3-60a-b** were converted to alkylidenecarbenes **3-61a-b** which contain two possible sites for insertion. Great selectivity for the oxygen substituted site was seen between the tertiary acetal center and the secondary alkyl C-H bond as in **3-62a** (~12 : 1), but when the substitution of the alkyl site is increased to the tertiary alkyl level in **3-60b**, it is the alkyl insertion site that is slightly favored over the acetal C-H bond.

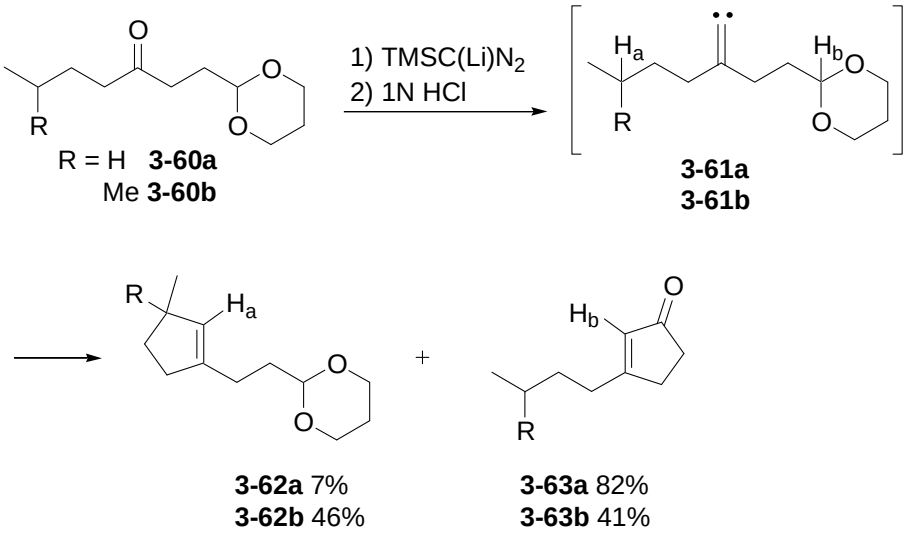


Figure **3.16**: C-H insertion regioselectivity competition experiments between alkyl and acetal sites.

The nature of the C-H bond is not the only factor controlling regioselectivity. Note the example from Ochiai, Figure **3.17**.[140] Using alkynyliodonium salt chemistry, alkylidenecarbene **3-66** was generated and allowed to react at two possible C-H insertion sites which are nearly identical. The results show that the carbene reacted with the α-unsubstituted side chain in a greater than 3 : 1 ratio over the lower chain. It is possible that either the presence of the spirobicycle somehow impeded cyclization at the lower chain, or that there is some inherent geometrical preference resulting from the nucleophilic attack on the alkyne (or during the loss of iodobenzene). This preference might cause the unsubstituted chain to be in closer proximity to the newly formed alkylidenecarbene, and thus that the rate of cyclization in this scenario might be faster than any change in conformation.

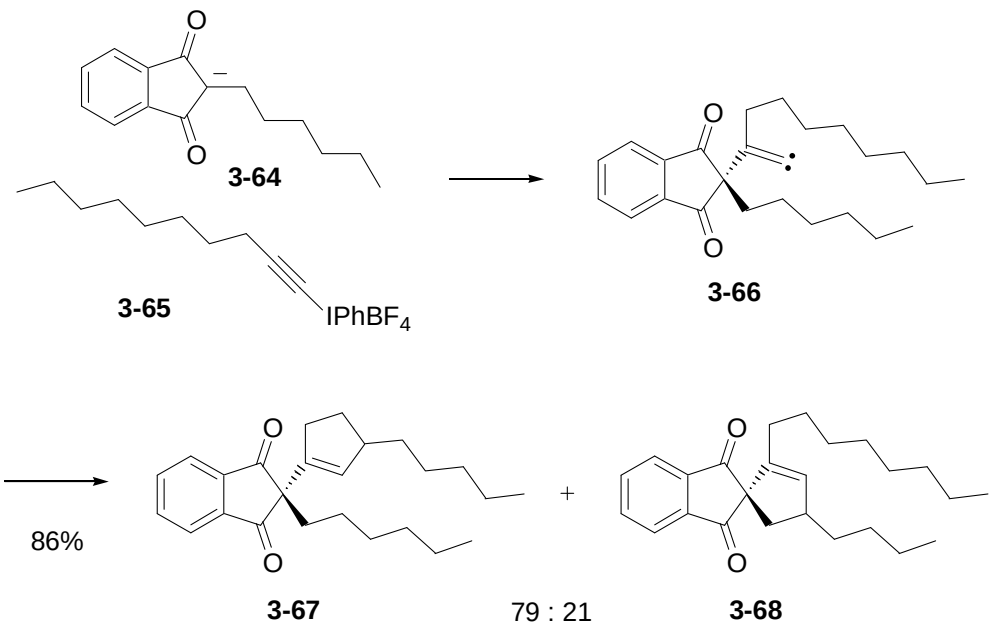


Figure **3.17**: C-H insertion regioselectivity competition experiments with nearly identical chains.

C-H insertions involving sp^2 hybridized carbons, which have BDE's ranging from 108-112 kcal/mol,[137] are much more difficult and thus less common than their sp^3 counterparts. With alkenes, the competing cyclopropanation pathway is too fast to allow for C-H insertion reactions to take place. However, aromatic rings are typically unreactive to cyclopropanation, and thus successful aryl C-H insertions of this type have been achieved. For example, reacting the propynyliodonium salt **3-42** with a deprotonated tosylaniline **3-69** creates alkylidenecarbene **3-70**, see Figure **3.18**.[141] The molecule lacks 1,5 disposed alkyl C-H insertion positions, and so the carbene now is sufficiently long-lived to react with the more refractory aryl C-H bond, forming indole **3-71**.

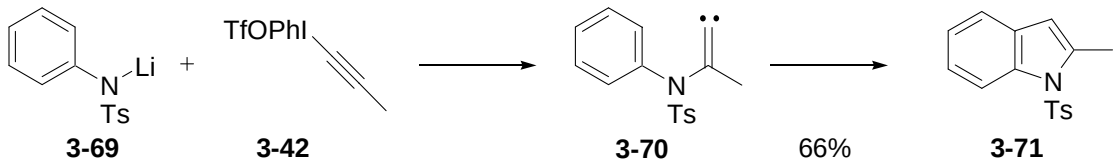


Figure **3.18**: 1,5 insertion to an aryl C-H bond.

Similar work has been reported with naphthol derivatives to form benzofurans.[142] Also, when the 5 position is blocked, as in **3-72** in Figure **3.19**, aryl 1,6 C-H insertions have been observed. No signs of cyclopropane intermediates were found during the studies of naphthol derivatives, but some of the minor side products from the tosylaniline reports were tentatively assigned structures derived from cyclopropanation reactions.

Figure **3.19**: 1,6 insertion into an aryl C-H bond.

One case where cyclopropanation of an aryl ring is predominant is in the total synthesis of pareitropone, see Figure **3.20**.[116] In this instance, the rotated biaryl bond in alkylidenecarbene **3-75** renders the 1,6 C-H bonds inaccessible, but exposes the π system to the reactive carbene. The unstable [4.1.0] bicycle **3-76** undergoes a ring expansion to azafulvene derivative **3-77**.

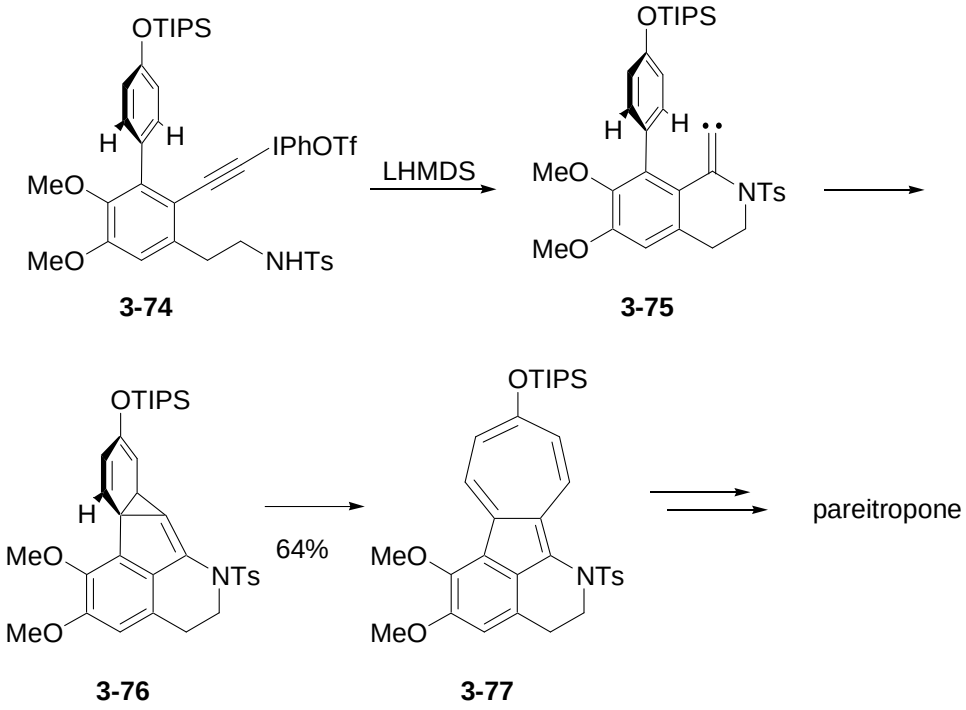


Figure **3.20**: Synthesis of a pareitropone precursor via alkylidenecarbene aryl cyclopropanation.

3.3.3.2 Heteroatom-hydrogen insertions.

Whereas it is well known that alkylidenecarbenes insert intermolecularly into Si-H and O-H bonds, the mechanisms by which these transformations occur are not fully understood. When *N*-nitroso-oxazolidinone **3-78**, Figure **3.21**, is treated with EtOLi and Et_3SiH, vinyl silane **3-82** is isolated as a 10 : 1 mixture of alkene isomers.[99] To explain the predominant formation of the thermodynamically less stable isomer, Newman proposed a stepwise mechanism involving hydride transfer followed by immediate quenching of the vinyl carbanion with TES^+. Whereas this mechanism is fundamentally sound, it does not fully account for the absence of **3-84** in the glpc analysis. Presumably, the TES^+ stays in close proximity, and its subsequent reaction with the carbanion is rapid

enough to exclude a proton quench by either the ethanol or water which are formed during the generation of the carbene.

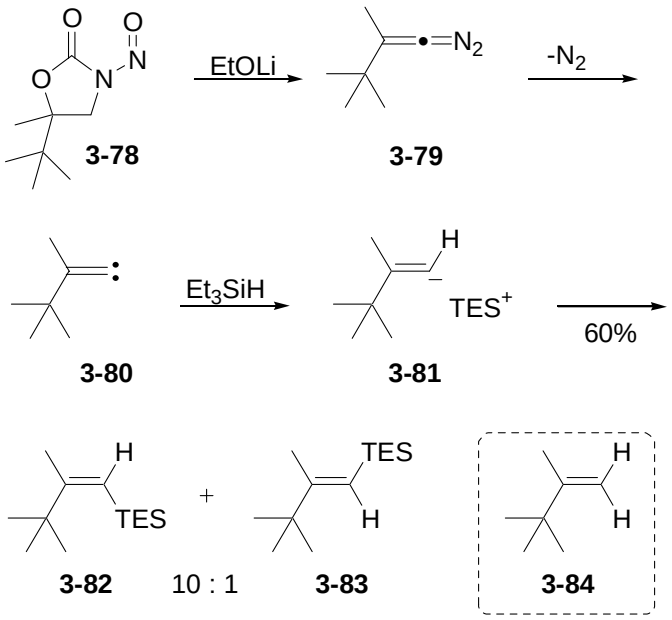
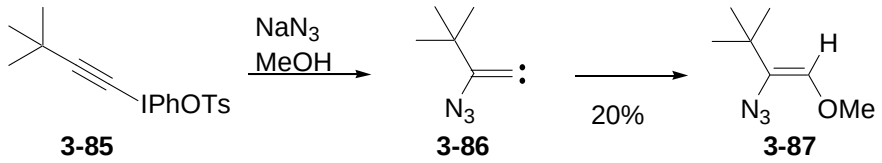


Figure **3.21**: Formal insertion into a Si-H bond.

Some ambiguity also surrounds the interaction of alkylidenecarbenes with alcohols to form vinyl ethers. Newman has shown that various alkylidenecarbenes react with several simple alcohols in good yields.[143] More recently, Stang has seen similar results, see Figure **3.22**.[144] However, it is unclear if these products result from direct insertion into the O-H bond or by a stepwise process. Alternative routes include initial protonation followed by alkoxide attack on a vinyl cation (unlikely), or interaction of the carbene's empty *p*-orbital with an oxygen lone pair of either an alcohol or alkoxide followed by protonation.[89]



3-85 **3-86** **3-87**

Figure **3.22**: Alkylidenecarbene insertion into the O-H bond of methanol.

3.3.3.3 Intermolecular heteroatom-lone pair additions.

Intermolecular alkylidenecarbene combination with into lone pairs of heteroatoms is known, but these processes are typically only seen when the heteroatom-containing species is present in large excess, i.e. the solvent. Ochiai performed competition experiments between THF and various amine bases, see Figure **3.23**.[145] He found that when THF was the solvent, and therefore was present in large excess compared to the amine bases, *N*-lone pair additions were still competitive. At lower temperatures, the equilibrium between alkylidenecarbene **3-5** and ylide **3-89** is slower and favors **3-89**, and the product ratios shift further in favor of O-lone pair reaction.

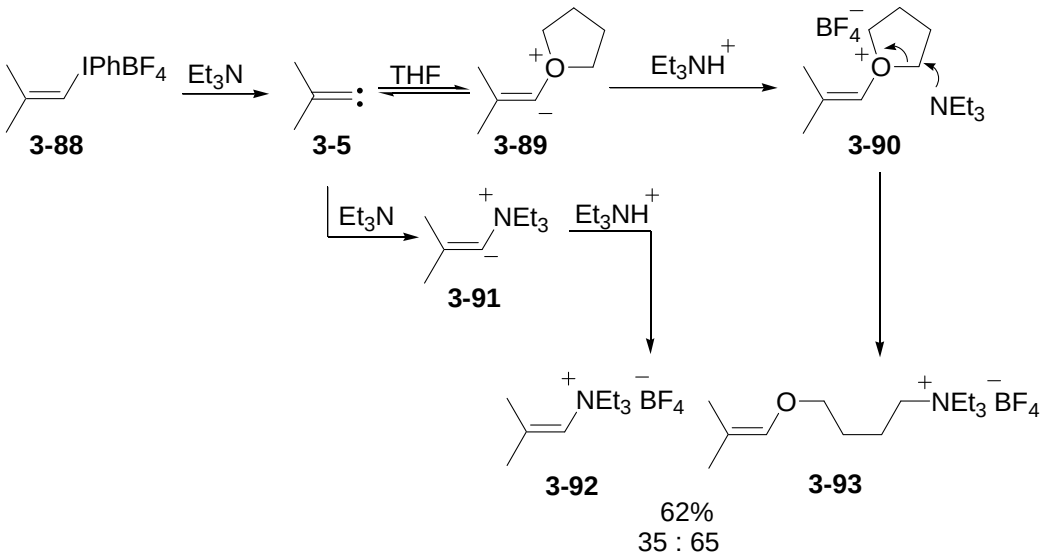


Figure **3.23**: Competition experiments for intermolecular additions to heteroatom lone pairs with amine bases and THF.

When THF is replaced with tetrahydrothiophene (THT), N-lone pair addition is diminished in favor of reaction at sulfur, Figure **3.24**. This bias can be attributed to sulfur's increased nucleophilicity over oxygen and sulfur's enhanced ability to bear a positive charge. In fact, intermolecular addition of sulfur is even faster than intramolecular 1,5 C-H insertion, see Figure **3.25**. When the dibutyl analogue **3-96** is examined in THF solvent, the dominant product is the cyclopentene resulting from a 1,5 C-H insertion, but in THT no evidence of either a 1,5 C-H insertion or a 1,2 alkyl shift is seen.

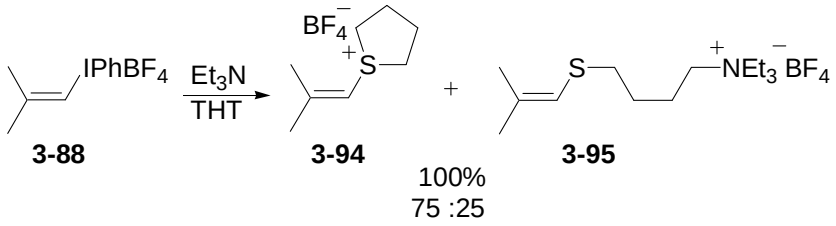


Figure **3.24**: Competition experiments for intermolecular additions to heteroatom lone pairs with amine bases and THT.

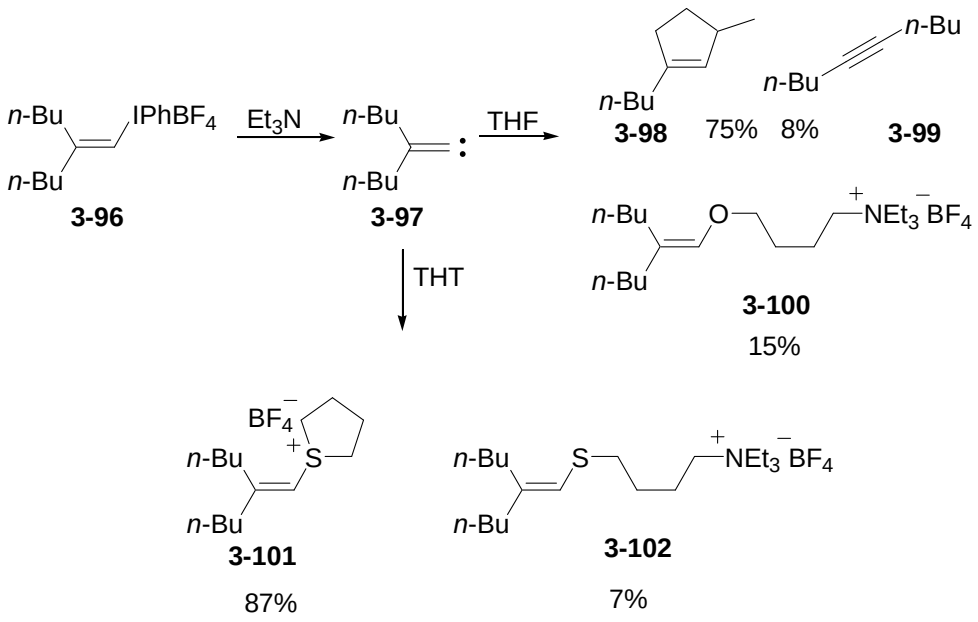


Figure **3.25**: Competition experiments for intermolecular additions to heteroatom lone pairs and 1,5 C-H insertions.

3.3.3.4 Intramolecular heteroatom-lone pair additions.

Shioiri reported that 2,3-dihydrofurans can be made from alkylidenecarbene additions with into oxygen lone pairs as long as the vinyl substituents have a low migratory aptitude.[146] Kim reported similar results, see Figure **3.**26.[101] Kim also observed the products of formal 1,6 and 1,7 O-Si insertions, albeit in lower yields than the accompanying 1,5 C-H insertion products. Although a two step mechanism was

considered, Kim concluded that **3-304a-c** resulted from a concerted alkylidenecarbene insertion into the O-Si bond.

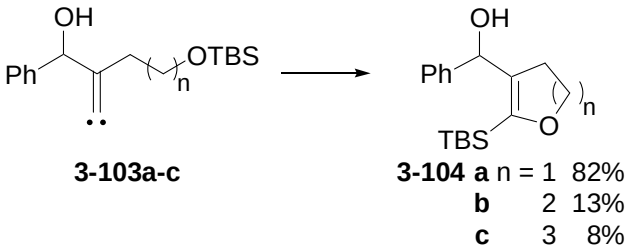


Figure **3.26**: Formal alkylidenecarbene insertions into O-Si bonds.

Later, Feldman did similar studies with variations on the oxygen protecting group.[147-148] While he did not directly dispute the direct O-Si insertion proposal, he did show evidence supporting a two step O-lone pair addition followed by a formal 1,2-shift mechanism, Figure **3.27**. The most compelling proof of an initial O-lone pair alkylidenecarbene interaction is the isolation of significant quantities of **3-108** a byproduct presumably formed from **3-106** and a proton source.

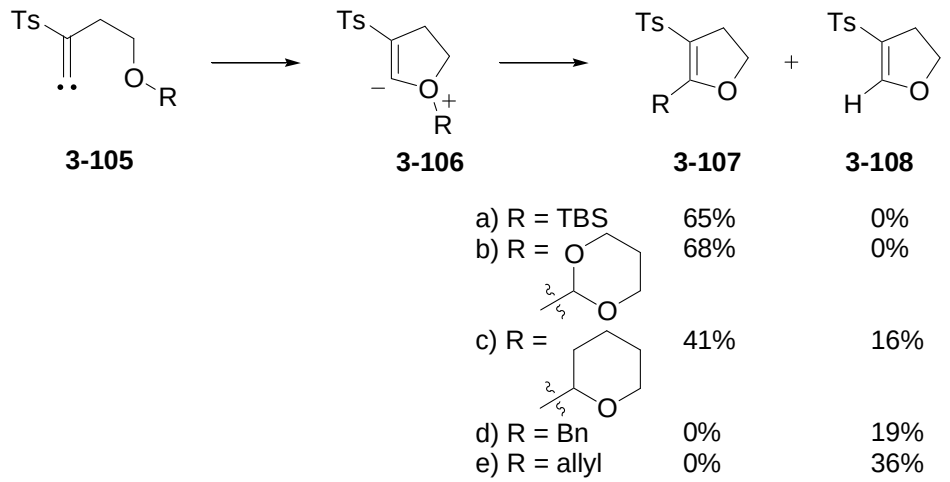
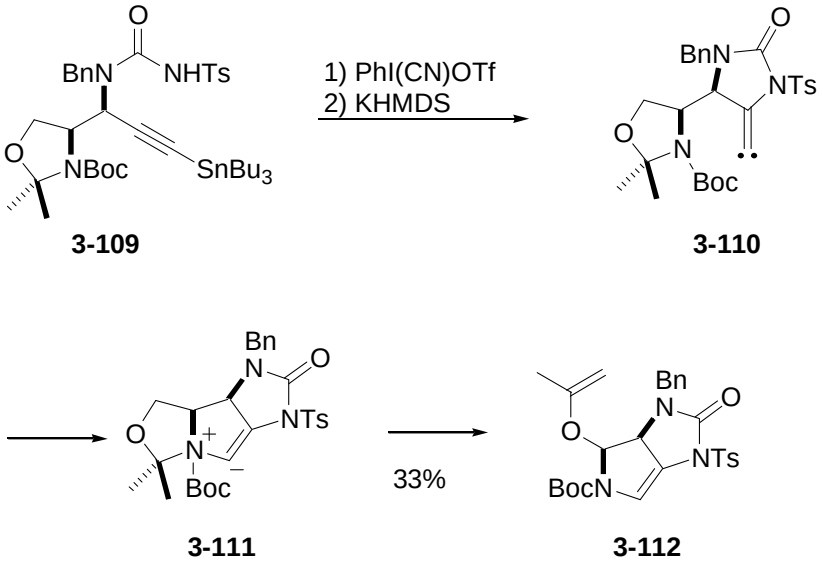


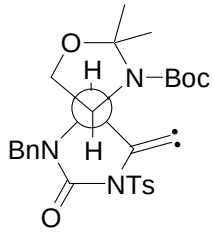
Figure **3.27**: Two step mechanism for formal O-Si and O-C alkylidenecarbene insertion.

An intramolecular *N*-lone pair addition of an alkylidenecarbene has been suggested by Feldman and coworkers, see Figure **3.28**.[149] Conversion of stannane **3-109** to an alkynyliodonium salt followed by conjugate addition of the acyltosylamide anion generated alkylidenecarbene **3-110**. No evidence for the expected 1,5 C-H insertion was seen, but instead the bicyclic compound **3-112** was formed in low yield. Bicycle **3-112** presumably derives from an addition with into the lone pair of the Boc-protected nitrogen, followed by opening of the acetonide in **3-111**. One of two conclusions can be drawn from this example: 1) A lone pair on nitrogen is so prone to such addition reactions that this pathway is faster than a competitive C-H insertion, even when the lone pair is tied up in resonance. 2) The preferred conformation of **3-110'** places the carbene away from the desired C-H bond and in close proximity to the lone pair of the nitrogen, making the *N*-addition faster than the necessary bond rotation that would bring the carbene closer to the C-H bond, see Figure **3.29**.



3-109 **3-110** **3-111** **3-112**

Figure **3.28**: Intramolecular alkylidenecarbene addition of a nitrogen lone pair.



3-110'

Figure **3.29**: Newman projection of the most stable conformation of **3-110'**.

Alkylidenecarbene chemistry has been used to create thiazoles, which are important building blocks of many biologically active molecules.[150] Under basic conditions, thioamides add to alkynyliodonium salts to form carbenes such as **3-117**, see Figure **3.30**. However, the mechanism by which this reaction takes place is distinct from the typical pathway. It is postulated that the more nucleophilic site of **3-114**, the sulfur, first attaches to the iodine itself. Compound **3-115** is then set up to undergo a novel poly-hetero Claisen rearrangement to afford **3-116**. Loss of iodobenzene leads to carbene **3-117**, and cyclization of this reactive intermediate followed by proton transfer affords

thiazole **3-119**. It is interesting to note that no evidence for a 1,5 C-H insertion is reported, despite the proximal saturated butyl side chain. Perhaps it is possible that the alkylidenecarbene is not involved and the cyclization is the result of an electrocyclic ring closure of **3-116** followed by loss of iodobenzene. Or, as seen in Ochiai's experiments with THT, the sulfur's interaction with the carbene is so rapid that no C-H insertion can occur.

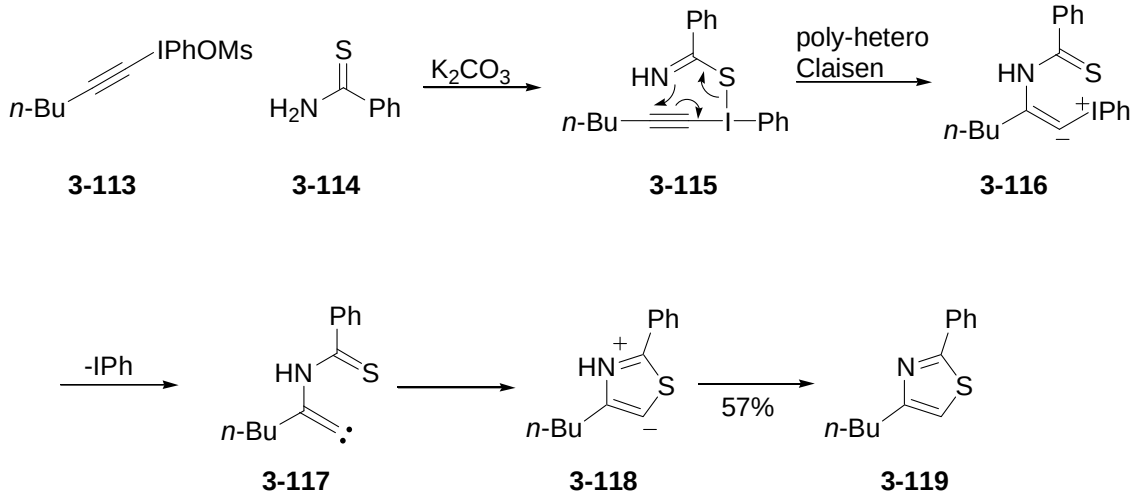


Figure **3.30**: An alkynyliodonium salt route to thiazoles.

3.4 Conclusions and application to streptorubin B.

Alkylidenecarbenes have been utilized in the creation of various ring systems and functional groups. The mild conditions developed to generate alkylidenecarbenes make them easily accessed and widely used. With proper planning, their wide ranging reactivity can be controlled to create interesting functionalities and structurally complex products in good yields.

Alkylidenecarbene chemistry was chosen for streptorubin B because of the stereospecificity of 1,5 C-H insertions. This methodology can be used to form chiral quaternary centers within a dihydropyrrole with complete strereochemical control. The regiochemical control, however, could be problematic. The synthesis of streptorubin B requires two alkyl chains to be present, both of which would be open to reaction with the carbene. Also, the conversion of a dihydropyrrole to a pyrrole is facile. This observation is important in the case of streptorubin B, as the planned conversion from sp^3 to sp^2 hybridization at C2 will cause an increase in ring strain, which may prevent pyrrole formation. This benefit comes with the challenge of preventing the pyrrole formation from occurring while necessary chemistry is taking place elsewhere in the molecule. If the regiochemistry of C-H insertion can be controlled and elimination to the pyrrole can be stalled, the use of alkylidenecarbenes can be an excellent means to create the strained pyrrole core of streptorubin B with stereochemical control.

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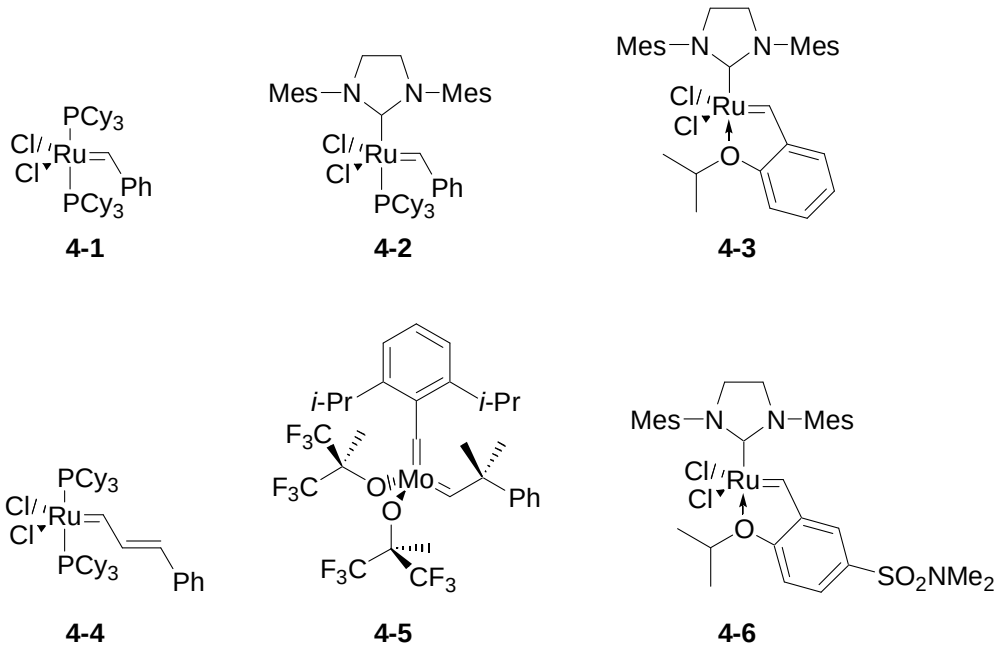
Chapter 4

Ring Closing Metathesis involving Medium Sized Rings

The importance of ring closing metathesis (RCM) chemistry in synthesis cannot be overstated. It has become a standard component of the tool box for synthetic organic chemists.[151-154] The improved stability of ruthenium catalysts such as **4-2** and **4-3**, Figure **4.1**, has increased the popularity and practicality of olefin metathesis. Modifications of the catalysts have made it possible to carry out RCM in the presence of almost all types of functionalities, as well as with a wide variety of olefin partners. The efficiency at which RCM can effect the closure of large rings has made it the reaction of choice for constructing macrocyclic products.



4-1 **4-2** **4-3**

4-4 **4-5** **4-6**

Figure **4.1**: Examples of RCM catalysts.

Although RCM has proven to be effective for the construction of small and large rings, medium sized rings (9-11 carbons) have remained elusive targets. Ring strain caused by transannular interactions in medium sized rings can push the equilibrium away from the closed alkene in favor of the open diene, dimers, or other oligomers. Medium sized ring closures also must overcome the entropic barrier of bringing both alkenes into close proximity. In many cases, these hurdles can be overcome through conformational constraints and elimination of transannular steric problems.

4.1. Difficulties in ring closing metathesis reactions involving medium sized rings.

Any closure of a medium sized ring must address two important reaction components: enthalpy and entropy. The enthalpy component of the energy barrier consists mostly of the ring strain inherent in these rings. Ring strain is a composite of three types of individual strain: transannular repulsion caused by Van der Waals interactions, torsional strain caused by eclipsing atoms, and angle strain caused by distortions away from the ideal angles for a given hybridization. For all rings, there exists a balance such that any action to decrease the strain of one type will increase the strain of another. Figure **4.2** shows measured experimental values for ring strain of cycloalkanes.[155-156] The rings with the highest recorded strain (exempting the smallest rings, 3-4) are the 9-11 membered cycloalkanes. Strain energies for cycloalkenes are not as readily available, but from the data that are known, it is clear that medium sized cycloalkenes also suffer from an increase in strain energy, see Figure **4.3**. [157-158]

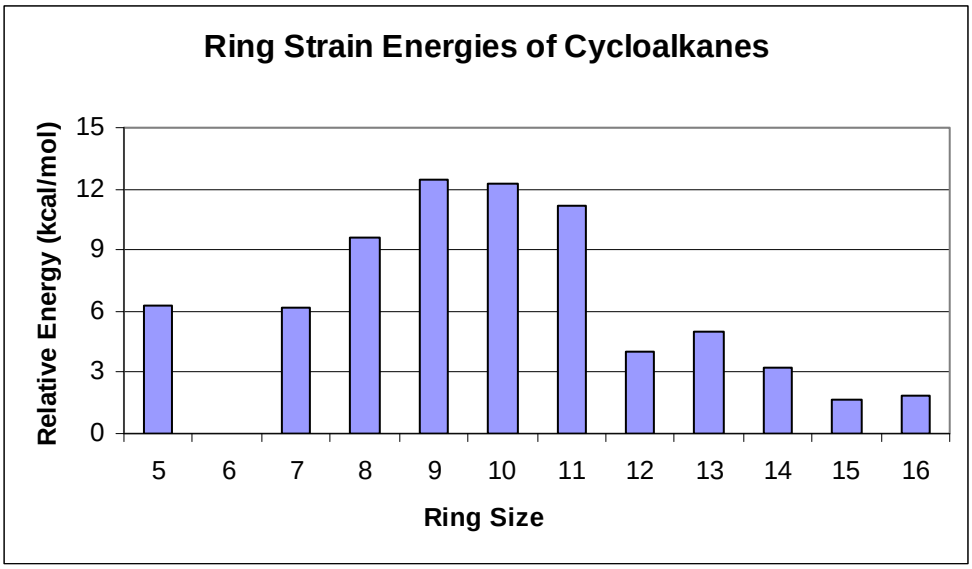


Figure **4.2**: Ring strain energies of cycloalkanes.

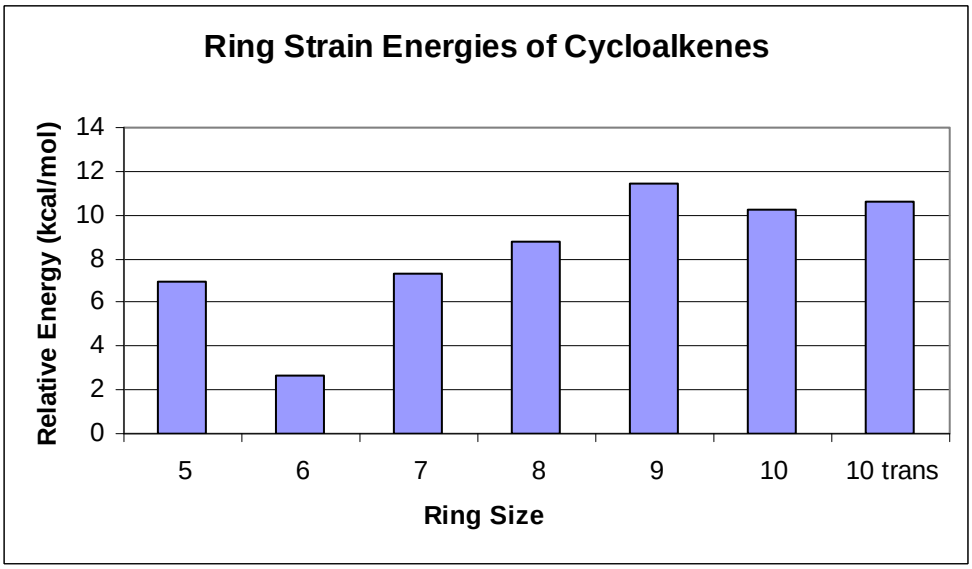


Figure **4.3**: Ring strain energies of cycloalkenes.

The manifestation of these data is seen in the sudden drop in yields in the cyclizations of **4-7**, see Figure **4.4**. Both the seven and eight membered rings cyclize in excellent yields, but cyclononene **4-8c** is formed in a modest 40% yield.[159]

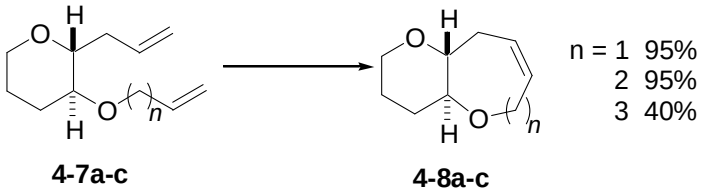


Figure **4.4**: Example of ring size diminishing yield.

There is also an entropy component to the cyclization of medium and large rings. Bringing the ends of a chain within reaction proximity requires the freezing of rotors along the chain. Freezing each rotor requires approximately 0.5 kcal/mol at 25 °C.[160] As the size of the desired ring increases, so does the number of rotors that must be restricted to bring the termini together, and thus more energy will be required to achieve cyclization.

One common result that occurs when these enthalpy and entropy barriers are not overcome is an intermolecular reaction instead of an intramolecular one. This competition results in dimerization and even polymerization. The dominant strategy employed to avoid intermolecular reactions is high dilution. Whereas dilution does lower the likelihood of two individual molecules coming together, it does nothing to lower the enthalpic barrier of an intramolecular reaction. To address this problem, higher temperatures often are used. However, these tactics can lead to long reaction times, and with excess energy present in the system, they can result in a greater chance of undesired side reactions occurring, i.e. eliminations, isomerizations, etc.[161]

RCM is reversible, sort of. That is to say, most of the steps are reversible. However, the reaction is driven by an irreversible loss of ethylene gas, so the original diene can never be remade. With the remaining steps being reversible, the

thermodynamically most favorable product should predominate given sufficient time. This happenstance is the case in Overman's synthesis of sarain A.[162] He observed that regardless of whether he started with the open diene **4-9**, the closed dimer **4-10**, or the closed monomer **4-11**, the same product distribution was produced with catalyst **4-2,** see Figure **4.5**.

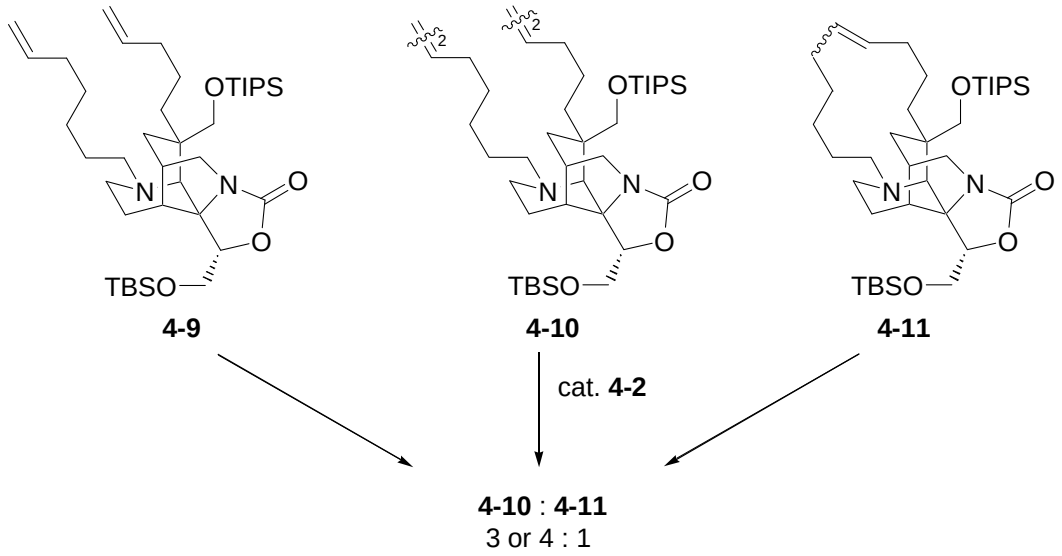


Figure **4.5**: RCM gives the thermodynamic ratio of products in Overman's synthesis of sarain A.

In metathesis reactions, there is a competition taking place between inter- and intramolecular reactions, see Figure **4.6**. Once the active catalyst has interacted with the open α,ω-diene **4-12** and released ethylene gas, the resulting ruthenium carbene **4-13** can either react with the attached alkene and close the ring leading to monomer **4-14**, or it can react with another α,ω-diene **4-12** to form an open dimer of type **4-15**. This dimer can react further and form the metalated species **4-16** which, once again, can react intermolecularly to form oligomers. Carbene **4-16** can also react intramolecularly to

furnish the closed monomer **4-14** and metalated **4-13**, or to the closed dimer **4-17** depending on whether the ruthenium reacts with the internal or terminal double bond. Theorectically, this backbiting event can occur with any oligomer and evidence for it has been seen by Fogg [163] as well as Gibson.[164] Secondary reactions can also work against monomer formation. An active ruthenium catalyst can, in principle, react with the closed monomer **4-14** and reopen it back to **4-13**, where it once again must choose to react in either an inter- or intramolecular sense.

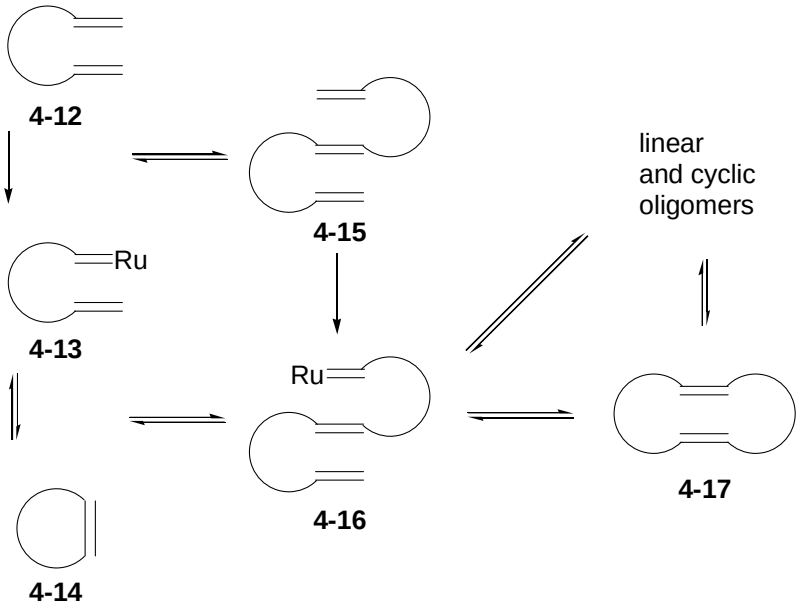


Figure **4.6**: Mechanistic possibilities for RCM.

4.2 Conformational consequences in ring closing metathesis reactions.

The structure and conformations of linear dienes have large consequences on the ability of these molecules to undergo RCM reactions. Some substituents or inherent geometrical constraints predispose the termini to be in close proximity one with another,

thus increasing the rate of ring closure. Other conformational constraints can hinder cyclization reactions, often leading to dimeric products.

4.2.1 Substitution Effects.

Most relatively unsubstituted 1,9-dienes are unsuitable for RCM reactions, see Figure **4.7**.[165-166] With no substituent or constraint favoring cyclization, these molecules simply polymerize. A number of studies have been published describing the importance of proper substitution.[161, 167-168] While most of these studies deal with cyclizations to form cyclooctenes, the same principles apply to the formation of the slightly larger cyclononenes, cyclodecenes, and cycloundecenes.

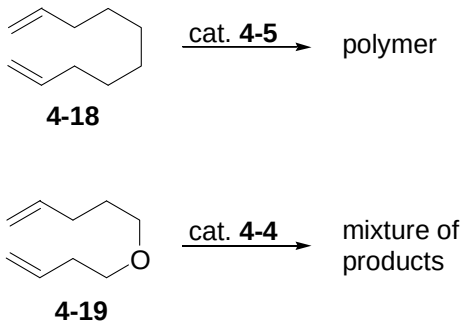


Figure **4.7**: Failed cyclization of unsubstituted dienes.

One of the more famous examples of substitution favoring ring closure is the Thorpe-Ingold effect.[169-170] A *gem*-dialkyl moiety in a chain is known to accelerate ring closing events. As alkyl groups are larger than hydrogens, the dialkyl arrangement causes a slight angle compression and thus brings the two termini closer together. An example of this effect is shown in Figure **4.8**.[165] While ketodiene **4-20** gave only oligomers when subjected to the Schrock catalyst **4-5**, the tetramethyl variant **4-21** cyclized in excellent

yield. However, when the desired ring size is increased from seven to eleven as in **4-23**, the Thorpe-Ingold effect is not enough to overcome the other difficulties associated with closing rings of this size.

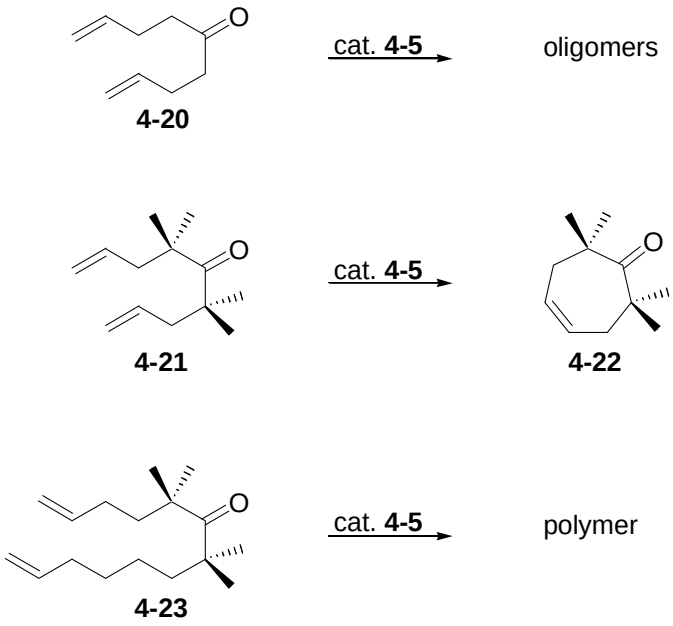


Figure **4.8**: Thorpe-Ingold effect in RCM reactions.

Another benefit of substitution along the chain is the "reactive rotomer effect". [171] As illustrated by the Newman projections in Figure **4.9**, increasing the substitution on an atom in the chain increases the relative populations of *syn* rotomers and likewise increases the likelihood of the termini finding one another. In the unsubstituted case the lowest energy conformation places the alkenes *anti* to one another. With one substituent, half of the lower energy conformers have the alkenes in a *syn* arrangement, while in the *gem*-disubstituted case two-thirds are *syn*.

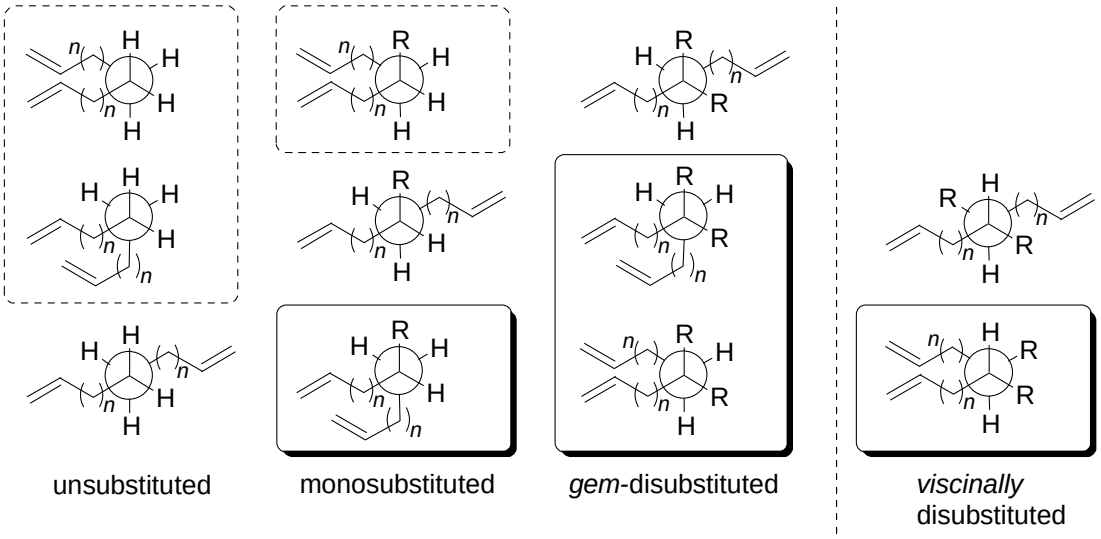


Figure **4.9**: Newman projections of α,ω-dienes depicting the "reactive rotomer effect." Higher energy conformations are outlined with dashes and reactive conformations are outlined with boxes.

Taylor and coworkers explored some of these ideas in their efforts toward the laureatin natural products, see Figure **4.10**.[172] They observed a dramatic effect as the size of the O-subsitituent was increased from H to TMS, and again to the larger TES and TBS groups. This strategy is not always successful; for example diene **4-26** failed to cyclize.[173] This failure shows that seemingly small and insignificant changes in structure can cause a large divergence in results for reasons yet to be understood.

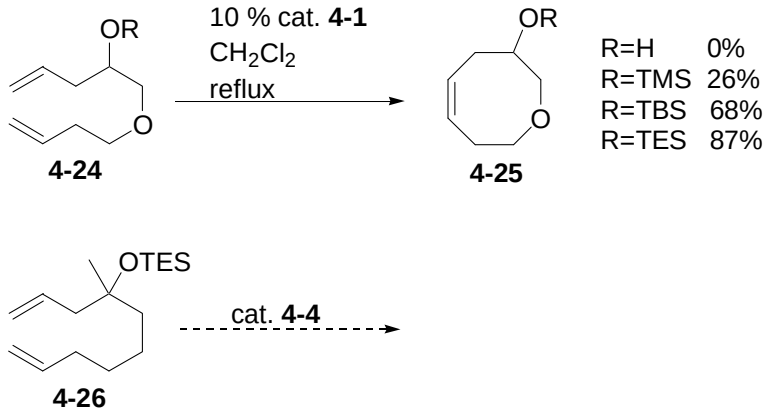


Figure **4.10**: Effects of the size of a silyl ether on RCM reactions.

Perhaps the best example of substituent effects on RCM outcome is in Fuchs' synthesis of the core of roseophilin, see Figure **4.11**.[174] Cyclization of **4-27c** proceeded smoothly, while all attempts to cyclize the simpler dienes **4-27a** and **4-27b** failed.

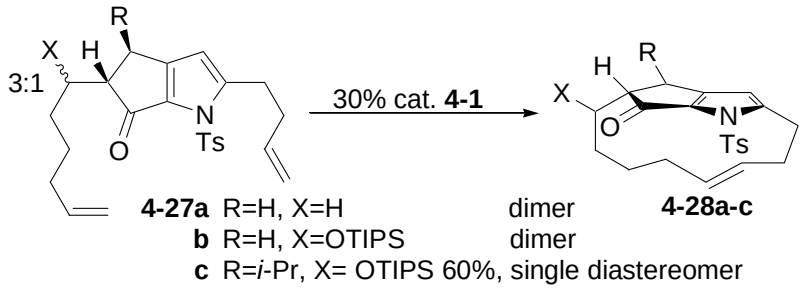


Figure **4.11**: Fuchs' synthesis of the core of roseophilin.

4.2.2 Fused polycycles.

Vicinally dialkenylsubstituted rings offer an advantageous conformational constaint for RCM reactions. Regardless of the relative stereochemistry, this arrangement usually favors the two olefin substituents to be either gauche or eclipsed, thus lowering the entropy barrier. Figure **4.12** shows two examples of efficient ring closures which

form bicyclic alkenes. Sniekus and co-workers were able to take advantage of this principle to close an otherwise difficult ten membered ring in tricyclic indole **4-34**, see Figure **4.13**.[175]

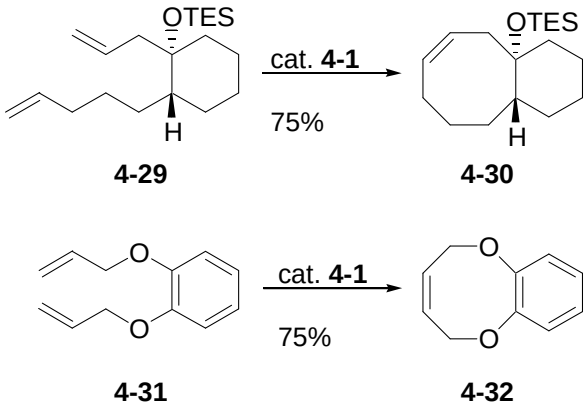


Figure **4.12**: RCM reactions to fused bicycles.

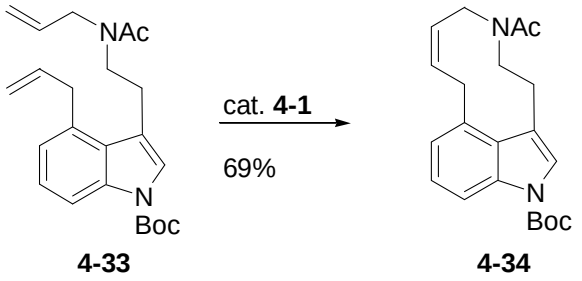


Figure **4.13**: Closure of a ten membered ring with RCM to form a fused polycyle.

Using a cyclic scaffold is not always enough to drive a RCM reaction to clean monomer formation. Bermejo and co-workers were unable to suppress dimer formation despite having two fused rings present, see Figure **4.14**.[176] As with all chemical principles, these conformational constraints play only a part of the complex dynamics that control reactivity preferences.

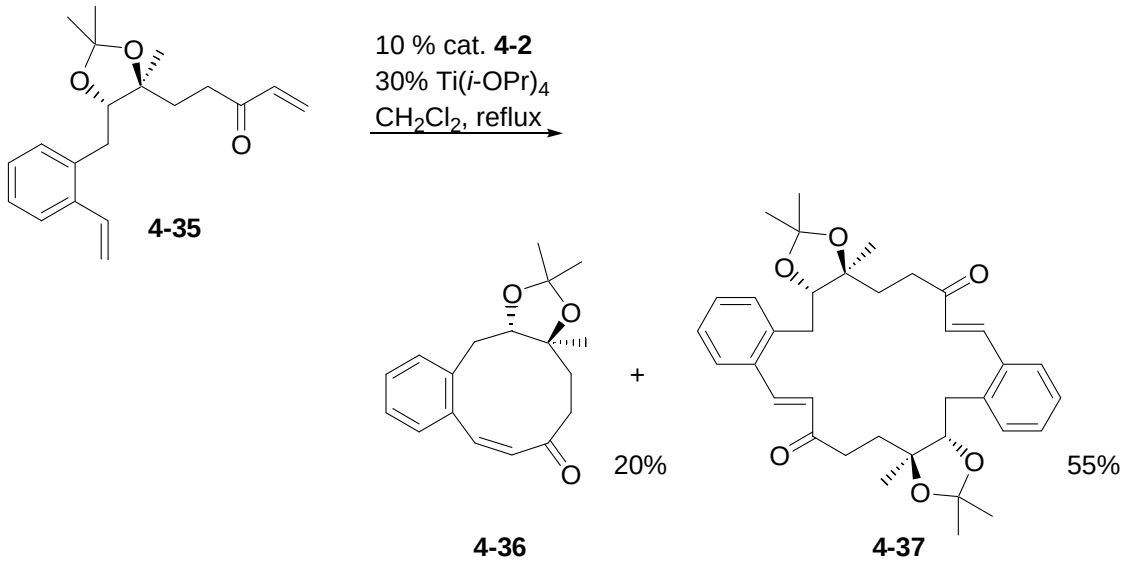


Figure **4.14**: Failed attempt at RCM leading to a fused polycycle.

4.2.3 Bridged polycycles.

The formation of bridged polycycles has presented many challenges to the field of synthesis, in part because of the increased ring strain they possess.[177] Bridged polycycles containing small and medium sized rings have been used as polymer precursors in the presence of RCM catalysts.[178] Despite the significant challenges in closing bridged rings *via* metathesis, some groups have had success with both small and medium sized systems.

Grubbs and co-workers reported the first systematic study of the formation of bridged bicyclic compounds using ruthenium carbenes.[179] In this study, they made a variety of bis-alkenyl-cyclohexanes and cyclopentanes and submitted them to RCM conditions at high dilution, see Figure **4.15**. They found that whereas many of these dienes did close in excellent yields, all attempts to form eight membered rings failed

completely. A correlation was found between the ΔH_{rxn} and the success of the reaction. In both cases, when *n* is increased from 2 to 3, there is a large jump in the calculated enthalpy of the reaction. Grubbs postulated that there exists a maximum at which cyclization can compete with oligomerization, which is somewhere around 10 kcal/mol. However, this maximum energy is dependent on ring size as seen with **4-41a,** which has an enthalpy of reaction of 13.3 kcal/mol. That value is higher than that for **4-39c**, which failed. Presumably, the proximity of the alkenes in **4-40a** causes cyclization to occur before any dimerization can take place, and the reaction proceeds in good yield.

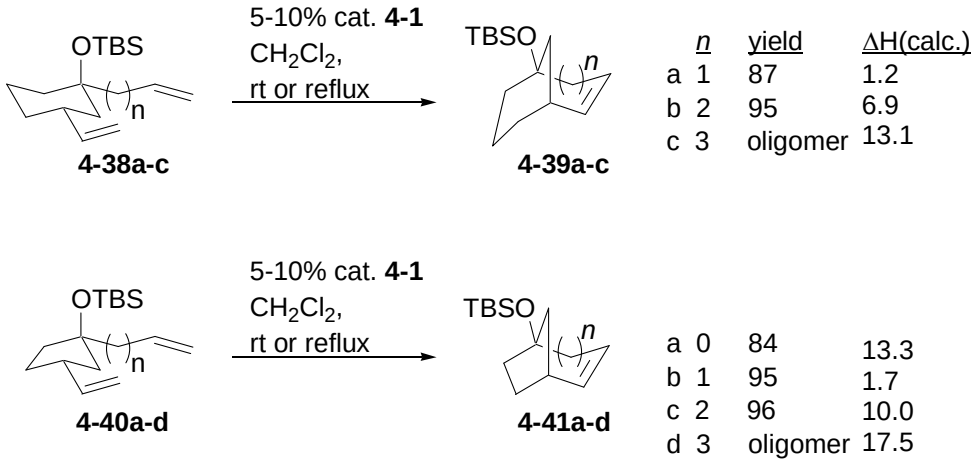


Figure **4.15**: Grubbs' thermodynamic analysis of bridged RCM reactions.

Proper orientation of the alkenes also plays a crucial role in the outcome of metathesis reactions. Despite the reported success by Grubbs with small bridged systems, Kibayashi was unable to effect cyclization with ammonium salt **4-42**, see Figure **4.16**.[180] The suggested reason for this failure is that the preferred conformation of **4-42** puts both alkenes in equatorial orientations. Formylation of the amine to **4-43** causes the alkenes to

move to a diaxial disposition to avoid $A^{1,3}$ strain. With the two alkenes in the proper conformation, ring closure generates **4-44** in 92% yield.

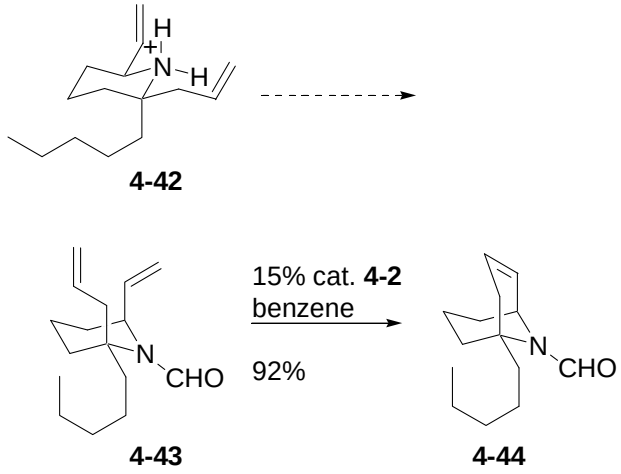
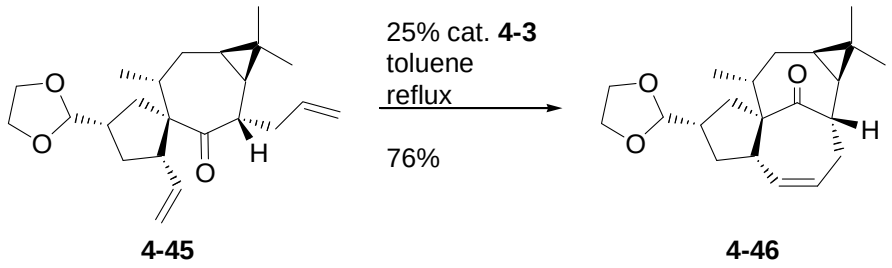


Figure **4.16**: A diaxial conformation is required for bridged RCM reactions.

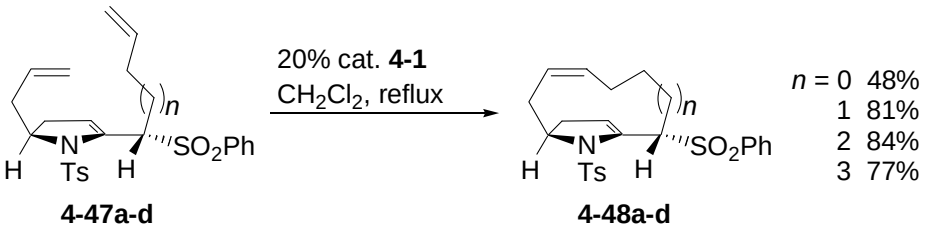
Although the proper conformation of two *syn* alkenes is of great importance for the success of RCM, Wood showed that in some cases RCM is possible even when the substituents are in a *trans* orientation, see Figure **4.17**.[181] This rare example is made possible by other conformational factors which bring the two alkenes into close enough proximity for cyclization. Wood reports that a computational conformational search showed that the spirocyclic cyclopentane in **4-45** causes a decrease in the dihedral angle of the two chains and reduces the distance between the internal olefinic carbons to 3.8 Å. This predisposition results in lower enthalpy and entropy barriers than might be estimated at first glance.



4-45 **4-46**

Figure **4.17**: Wood's synthesis of ingenol precursor **4-46**.

Another impressive example of RCM forming bridged rings is the closure of dihydropyrroles **4-47** to form macrocycles **4-48**, Figure **4.18**.[182] Even with the internal alkene preventing the olefinic side chains from adopting a diaxial conformation, Bamford was able to close rings ranging in size from nine to twelve atoms in moderate to good yields. It is likely that the sulfone bearing stereocenter is the key to this success. Because a hydrogen substituent has the lowest $A^{1,3}$ strain energy in **4-47**, the preferred orientation of the longer alkene chain places the two olefins on the same face of the dihydropyrrole.



4-47a-d **4-48a-d**

Figure **4.18**: Bicyclic RCM of a dihydropyrrole.

Accompanying the exemplary successes of bridged RCM shown above are many examples of unrealized cyclizations. One such example is found in Jacobsen's pursuit of a combinatorial library based on diketopiperazines (DKPs), when he attempted a bridged RCM reaction to form the ten membered cycloalkene **4-50**, Figure **4.19**.[183] When the

reaction was carried out at 0.04 M, only dimer was isolated in 79% yield. When the concentration was dropped to 0.0002 M, **4-50** was successfully isolated in 21% yield, along with 43% of the dimer. It was concluded that a more appealing option would be to leave the DKP ring open until after the RCM reaction. Hence, diene **4-51** was subjected to Grubbs second generation catalyst at 0.001 M, and macrocycle **4-52** was obtained in 60% yield with no mention of dimerization. The strategy was completed by cyclizing the DKP with piperidine to **4-50**.

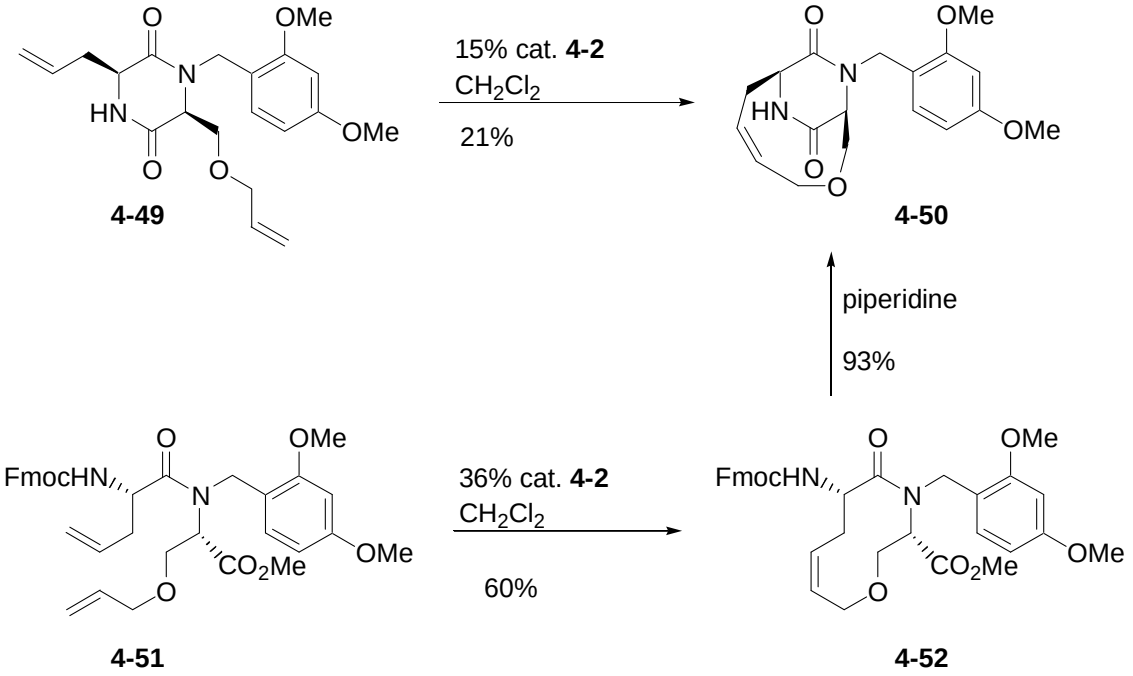


Figure **4.19**: Unsatisfactory RCM of a bridged DKP and the successful alternative.

Arguably the most structurally complex examples of attempted RCM to form medium sized rings are the endeavors to close the nine membered ring of pestaltiopsin using metathesis. While diene **4-53** possesses no RCM-incompatible functional groups, the presumably high enthalpy barrier along with the steric interactions from the *gem*

disubstituted alkene and allylic substitution impede RCM and only olefin isomerization was observed, see Figure **4.20**.[184] Extensive experimentation was carried out with **2-53** and several derivatives, but no evidence of cyclization or even dimerization was seen.

4-53 **4-54**

Figure **4.20**: A metathesis attempt toward pestaltiopsin.

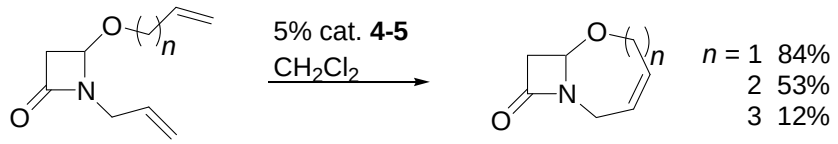
4.3 Examples of ring closing metathesis reactions forming medium sized rings.

Many research groups have succeeded in forming medium sized rings using RCM on a variety of substrates despite the difficulties and challenges involved. The following is a collection of the successful RCM examples found in the literature. Many have taken advantage of the conformational constraints already present in the diene substrates.

4.3.1 Nine membered rings.

The first group to report a successful closure of a nine membered ring was Barret and co-workers in 1996.[185] In his efforts to construct a diverse library of β-lactams for antibiotic purposes, he constructed fused bicyclic lactams **4-55** using Schrock's molybdenum based catalyst **4-5**, see Figure **4.21**. Whereas the seven membered ring closed in good yield, the effectiveness of this strategy decreased with increasing ring size,

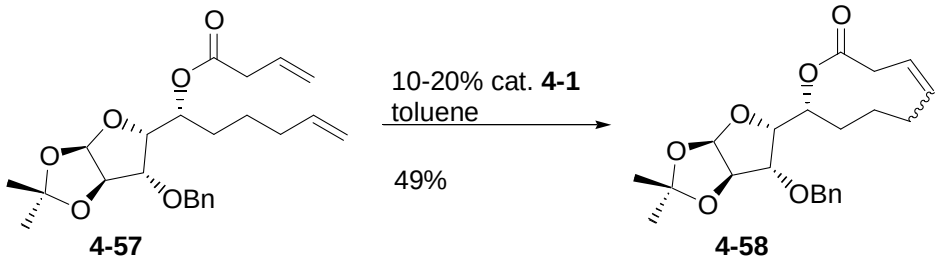
culminating in a poor 12% yield for the nine membered ring, accompanied by 17% of the corresponding dimer.



4-55a-c **4-56a-c**

Figure **4.21**: First example of a nine membered ring synthesized by RCM.

In one of the first examples of RCM involving carbohydrate substrates, Gesson and co-workers constructed various ring sizes required for their work toward annonaceous acetogenins, see Figure **4.22**.[186] These transformations required long reaction times and suffered from low conversion rates. Slow addition of the ester and the catalyst *via* a syringe pump showed only moderate improvements in both rates of conversion and suppressing dimer formation.



4-57 **4-58**

Figure **4.22**: Gesson's successful RCM toward annonaceous acetogenins.

Crimmins has published several papers on the synthesis of marine natural products containing medium sized rings.[187-190] Figure **4.23** shows the cyclononenyl ethers he successfully made *via* RCM while pursuing isolaurallene and obtusenyne.

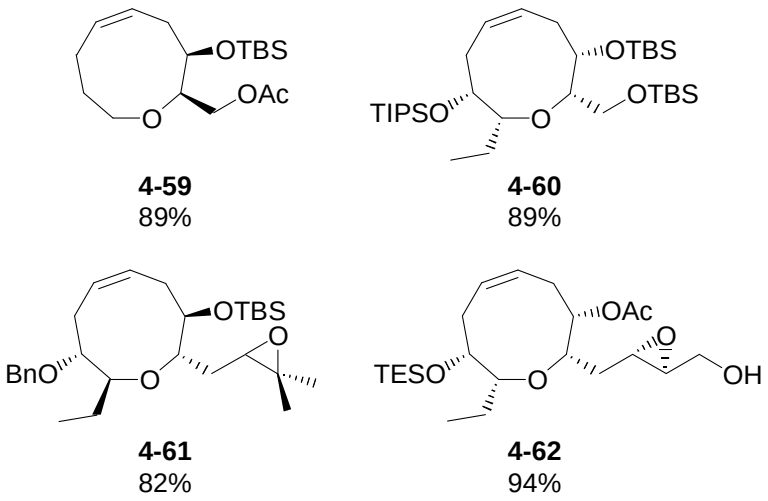
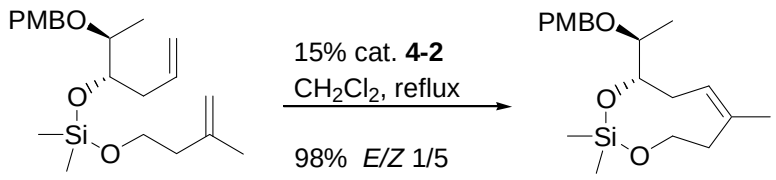


Figure **4.23**: Examples of cyclononenyl ethers made *via* RCM.

Mulzer used RCM as a method of forming a trisubstitued linear alkene with controlled geometry. He hypothesized that if an alkene is formed in a sufficiently small ring, it will preferentially exist as the *Z* isomer. Then, the ring can be opened while maintaining the stereochemistry of the alkene. After attempts to close an eight membered ring with an ester tether failed, Mulzer turned toward a successful silylether tethered nine membered ring, see Figure **4.24**.[191-192] Other groups who have closed nine membered rings successfully include Liskamp,[193] Takemoto,[194-195] Lee,[196] and Lubell.[197-198]



4-63 **4-64**

Figure **4.24**: RCM of a nine membered ring with a silicon tether.

4.3.2 Ten membered rings.

The first published example of a ten membered ring formed *via* RCM was reported by Fürstner in 1997 in his total synthesis of jasmine ketolactone **4-66**, Figure **4.25**.[199] The vicinal substitution of the cyclopentanone lowers the dihedral angle of the two substituents from the natural 180˚ to 60˚, thus helping to overcome the entropic impediment. Over a dozen other ten-membered lactones followed in syntheses of the herbarumins and related nonelide natural products; one example is shown in Figure **4.26**.[200-213] One fortuitous conformational detail of these macrolides is their lack of transannular steric interactions. As illustrated in Figure **4.27**, the newly formed alkene is aligned with the lactone.[210] This model shows the predisposition of such macrolides to align the four sp^2 hybridized atoms of the alkene and ester moieties, thus reducing detrimental transannular interactions. In fact, Paquette has found that 1,6-decadiene is ~ 4.4 kcal/mol more stable than cyclodecene.[214]

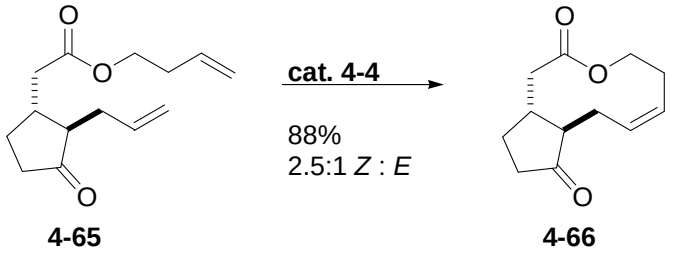


Figure **4.25**: Fürstner's synthesis of jasmine ketolactone (**4-66**).

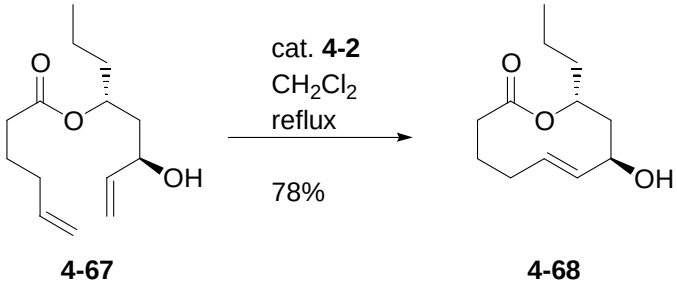


Figure **4.26**: Gurjar's synthesis of herbarumin III (**4-68**).

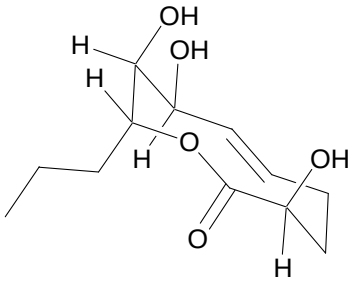


Figure **4.27**: Ley's calculated conformation of herbarumin II.[210]

As in the above example, most ten membered rings created by RCM have sp^2 hybridized atoms on the opposite side of the ring from the desired alkene. The simplest case is shown in Figure **4.28**.[163] Even though ester **4-69** is relatively unfunctionalized and has no conformational constraints, the lack of transannular interactions lowers the

enthalpy barrier enough to allow for successful cyclization to occur. The RCM of the symmetric diene **4-71** is another example illustrating this principle.

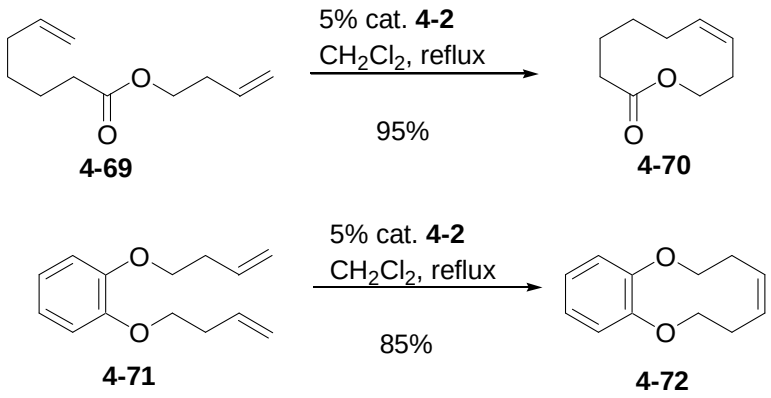
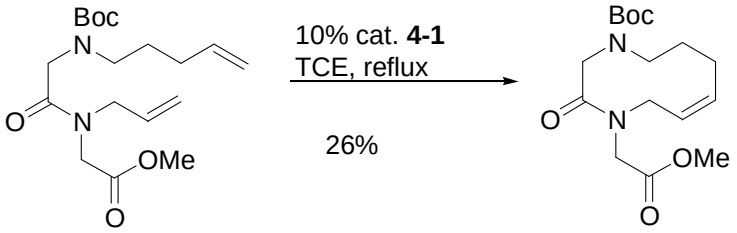


Figure **4.28**: RCM of simple 1,11-dienes aided by a transannular double bond.

The drawback of having an ester or amide inside a medium sized ring is the *trans* conformation of the partial C-O or C-N double bond. A *trans* double bond arrangement can exist in a ten membered ring without significantly raising the relative energy of the molecule (enthalpy barrier), but in the open diene the termini are held further apart, thus decreasing the likelihood of the alkenes coming into proximity (entropy barrier). However, slightly elevated temperatures are apparently adequate to overcome these challenges in the case of esters.

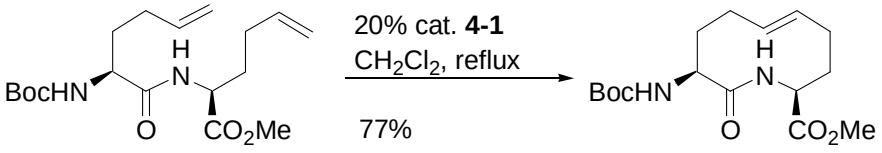
The effects of the *trans* conformational barrier should be more pronounced with amides than with esters. This effect is seen in Figure **4.29** with the poor yield in the cyclization of **4-73**.[193] Liskamp found that increasing the temperature from 80ºC to 100ºC caused coalescence of the amide substituent's ^{1}H NMR signals. Thus, changing solvents from 1,2-dichloroethane (DCE) to the higher boiling 1,1,2-trichloroethane (TCE) ensures that all rotational isomers are available for RCM. Whereas he does not report any RCM

attempts with **4-73** in DCE, in the case of his eight-membered ring examples, changing the solvent from DCE to TCE doubled the observed yield. Liskamp's difficulty in cyclizing tertiary amide **4-73** might simply be an isolated example. Both Lubell[197-198] and Rojo[215] have reported cyclizations of secondary amides in acceptable yields, see Figures **4.30** and **4.31**.



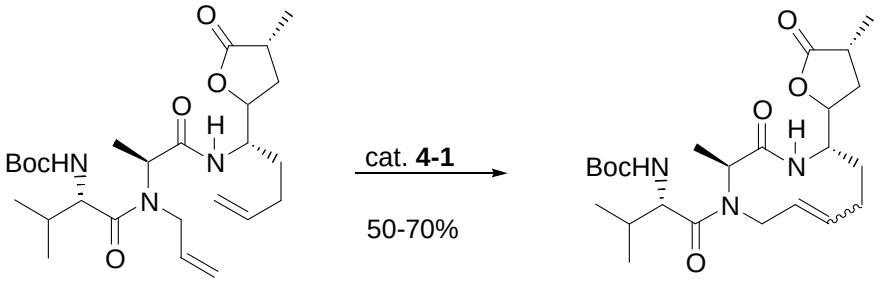
4-73 **4-74**

Figure **4.29**: Unsatisfactory RCM involving an amide.



4-75 **4-76**

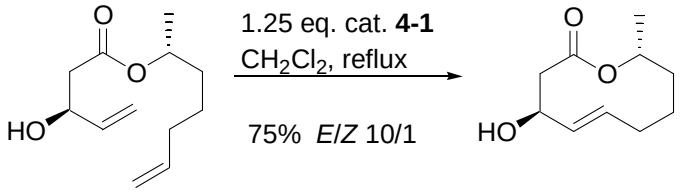
Figure **4.30**: Lubell's metathesis with an amide.



4-77 **4-78**

Figure **4.31**: Rojo's metathesis with an amide.

One interesting example of substituent effects on the efficiency of RCM reactions for closing ten membered lactones is Reddy's approach to the diplodialides, see Figure **4.32**.[216] Diene **4-79** cyclized in good yield, although this transformation required 1.25 equivalents of catalyst **4-1**. In contrast, when the alcohol in **4-79** was protected with a TBS group, no cyclization took place and a linear dimer was isolated in 70% yield. This example goes against the observed trend that larger protecting groups favor cyclization, *vide supra*.



4-79 **4-80**

Figure **4.32**: Reddy's's RCM of ten membered lactone without a bulky alcohol protecting group.

Curran used RCM to form a ten-membered lactone as a means to control olefin geometry in his efforts toward dictyostatin.[217] Wittig olefinations in related linear systems failed to provide *cis* alkenes with acceptable selectivity. It was postulated that the cyclic constraint in lactone **4-82** could favor the *Z* configuration over the *E*, although RCM to form ten-membered rings is capable of producing both olefin geometries depending on the substrate. This strategy was bold, given the historical difficulties inherent in forming medium sized rings, and the two allylic substituents providing steric encumbrance further hindering cyclization. Nevertheless, Curran was successful in forming the *Z*-alkene in both simplified models and in the more highly functionalized case of **4-93**, see Figure **4-33**.

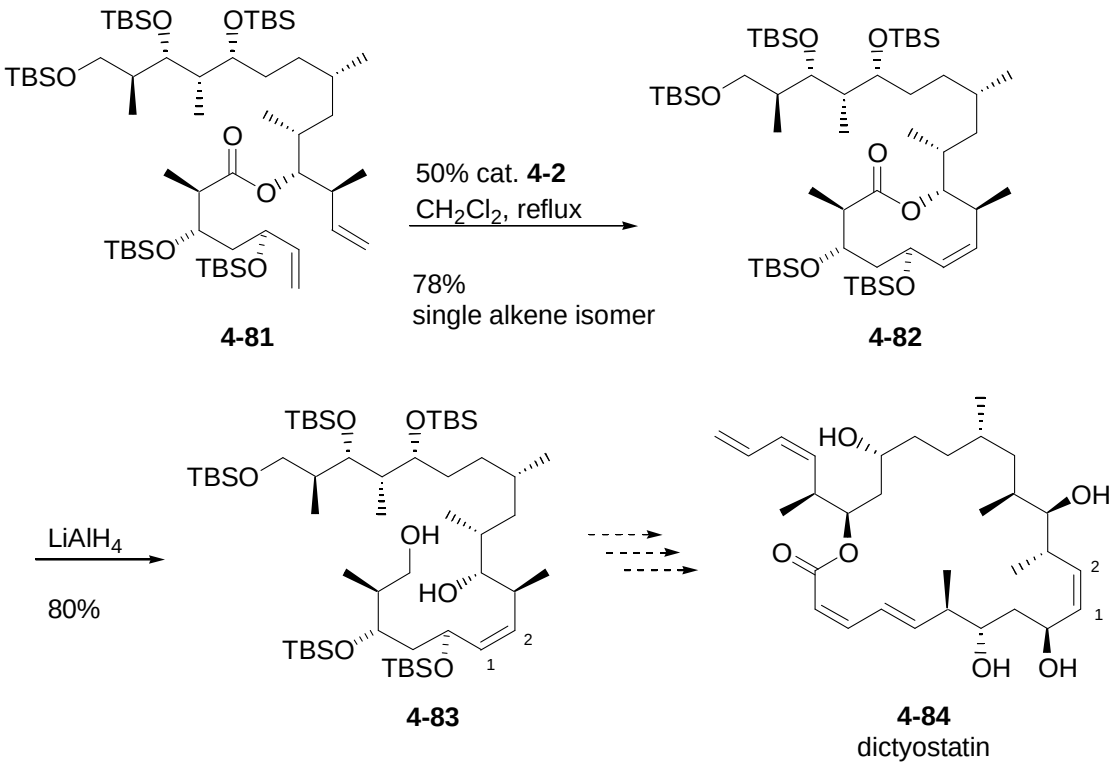


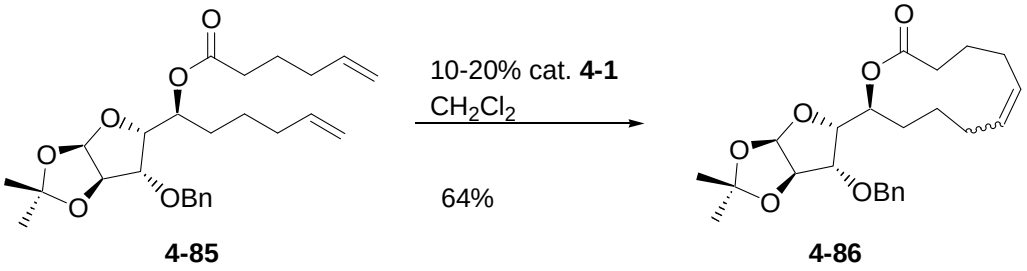
Figure **4.33**: Curran's *Z* selective RCM.

Ten membered ring formation *via* metathesis is tolerant of a wide range of functionality, from relatively simple dienes to substrates possessing dense and uncommon functional groups. Such examples are found in the reports of Koshkinen,[218] Steglich,[219] Lee,[196] and Dougherty.[220]

4.3.3 Eleven membered rings.

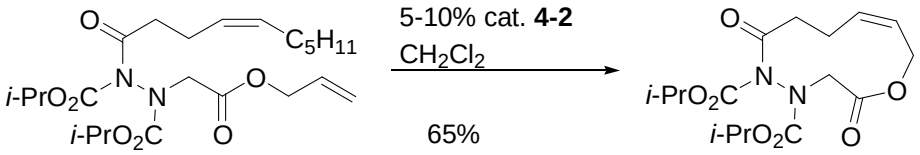
Eleven-membered rings found in nature and accordingly in the literature are much scarcer compared to the other ring sizes previously discussed. In fact, two of the examples shown here are simply analogues of examples already discussed, see Figures **4.34** and **4.35**.[186, 196] However, the next example does reiterate quite nicely how small, seemingly insignificant changes in structure can have dramatic effects on the outcomes of

RCM reactions. Nakagawa demonstrated the successful use of RCM in the synthesis of a relatively unsubstituted azacycloundecene **4-90** as a manzamine C analogue, see Figure **4.36**.[221] In an attempt to make these analogues more water soluble for biological studies, Nakagawa also wanted to make bis-ether macrocycle **4-92**. Whereas the introduction of the oxygens in **4-91** vs. **4-100** produced the monomer as a single alkene isomer, it also made the substrate much more prone to dimerization.



4-85 **4-86**

Figure **4.34**: Gesson's RCM of an eleven membered lactone.



4-87 **4-88**

Figure **4.35**: Lee's closure to of an eleven membered lactam.

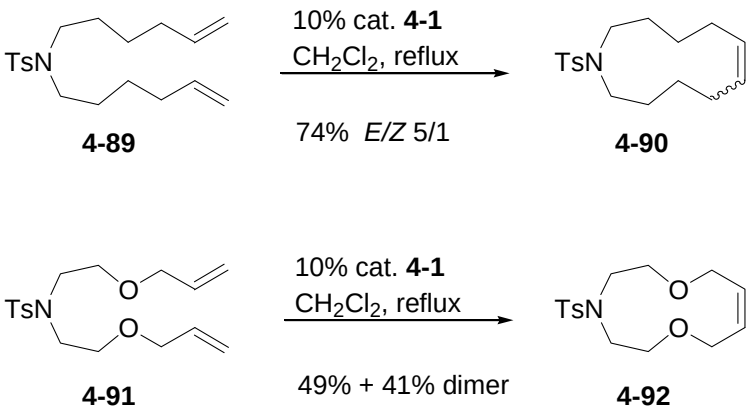


Figure **4.36**: A small structural change exerted a substantial effect in RCM.

Recently RCM has been used to form eleven membered rings in complex natural product synthesis. Nicolaou and co-workers cyclized **4-93** as well as a variety of derivatives in good yields en route to the syntheses of coleophomone B and C, see Figure **4.37**.[222-223] Later Fürstner was successful in the metathesis of **4-95** to **4-96** as part of his synthesis of aspercyclide C.[224] Both of these examples benefited from conformational constraints as well as a lack of transannular interactions, but they are great successes in the field of metathesis as the first applications of RCM toward the total synthesis of complex medium sized rings in natural products.

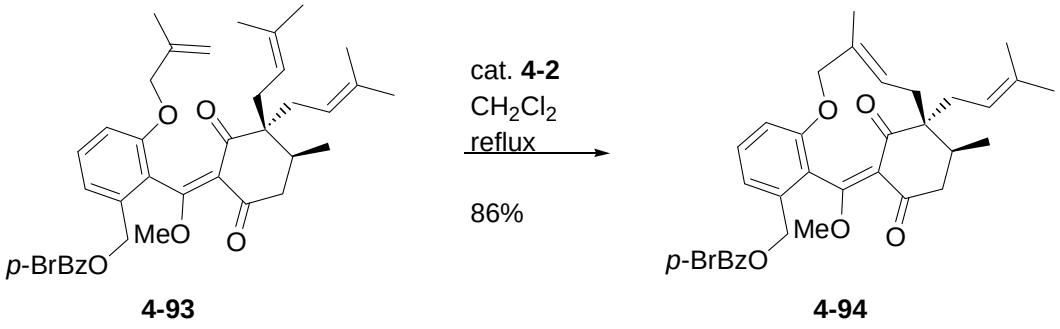
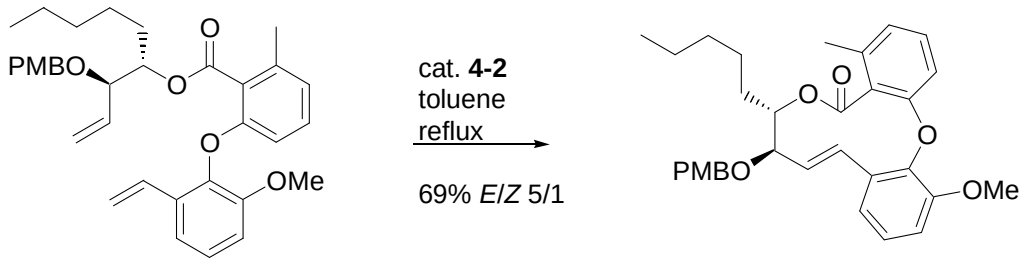


Figure **4.37**: Nicolau's RCM step in the total synthesis of coleophomone B and C.



4-95 **4-96**

Figure **4.38**: Successful metathesis toward aspercyclide C.

The formation of the eleven membered ring in okilactomycin is one of the few examples of closing a bridged polycycle containing a medium sized ring, see Figure **4.39**.[225] This transformation required an excess of the Hoveyda-Grubbs catalyst (**4-3**) and suffered from dimerization problems. To overcome these challenges, the reaction was run at high dilution (60 μM) and the catalyst had to be destroyed by exposure to air for 24 h before concentrating at room temperature. The crude material was immediately hydrogenated to remove any opportunity for ring opening/dimerization by residual active catalyst. Similar to the ingenol example (Figure **4.17**), the tricyclic arrangement of **4-97** brings the termini into proximity, thus eliminating some of the entropic barrier.

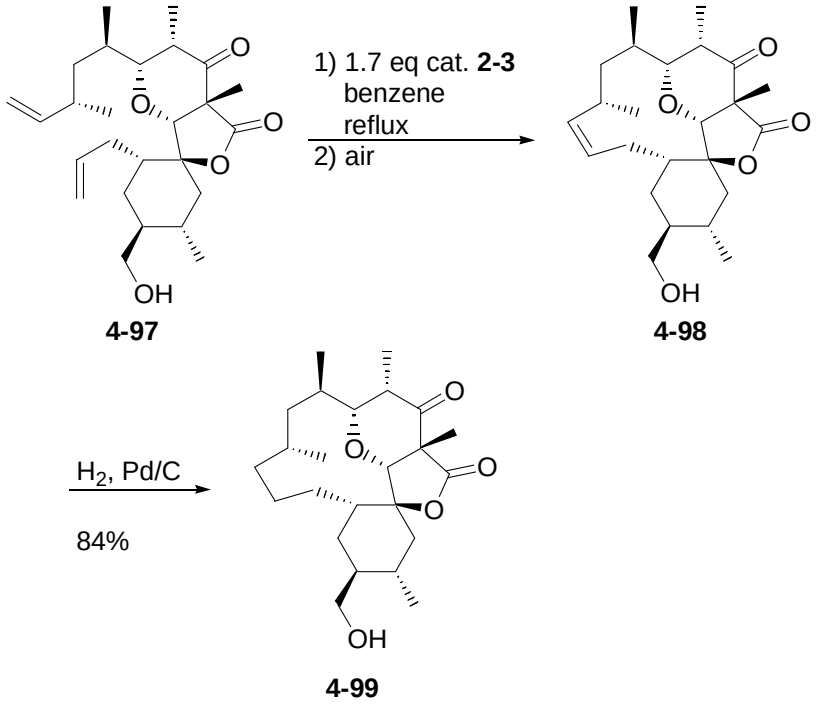


Figure **4.39**: Smith's use of RCM in the synthesis of okilactomycin.

4.4 Conclusions and application to streptorubin B.

RCM of medium sized rings remains a daunting challenge for organic chemists. Despite the common result of dimer formation, an increasing understanding of the substitutional and conformational effects is widening the use of this chemistry. Many complex and interesting compounds have been constructed, but for each success story there are many untold examples of failed attempts. This area is still an open field where greater comprehension of the scope and limitations is needed, and additional insight will yield new methods of closing difficult rings.

The application of this chemistry to the synthesis of streptorubin B will be a difficult test for RCM. Aside from the butyl group, the seven carbon tether is unsubstituted. However, as Kibayashi observed, a benefit may be gained by proper

substitution of the nitrogen, which might cause the two olefinic chains to be diaxial. Also, it is possible to incorporate sp^2 hybridized atoms into the C ring to reduce transanular steric interactions. The cyclization of various bicyclic dihydropyrroles, as seen in Figure **4.18**, instills the greatest hope for a successful closure of a streptorubin B precursor.

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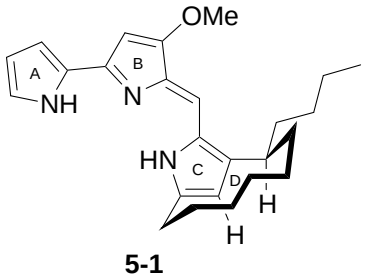
Chapter 5

Efforts toward a stereoselective synthesis of Streptorubin B

5.1 Overview.

As explained in Chapter 1, a synthesis of streptorubin B **5-1** (Figure **5.1**) must be robust enough to produce adequate quantities of material for biological testing, and must be flexible enough to allow for the formation of all four stereoisomers. Because the synthesis of the A/ B ring fragment is already well precedented, the primary focus of this work is the stereochemically controlled formation of rings C and D. Originally it was believed that the D ring, although strained, could be constructed *via* a ring closing metathesis reaction with the planar stereochemistry predetermined by the stereochemical information at C2 in dihydropyrrole **5-5**, see Figure **5.2**. This stereocenter could be made with a stereospecific alkylidenecarbene C-H insertion using alkynyliodonium chemistry starting from tosylamide **5-6** and alkynyliodonium salt **5-7**. In this approach, the difficult to control planar chirality is derived from vicinal stereocenters within a simple linear fragment.



5-1

Figure **5.1**: Streptorubin B (stereochemistry arbitrarily assigned).

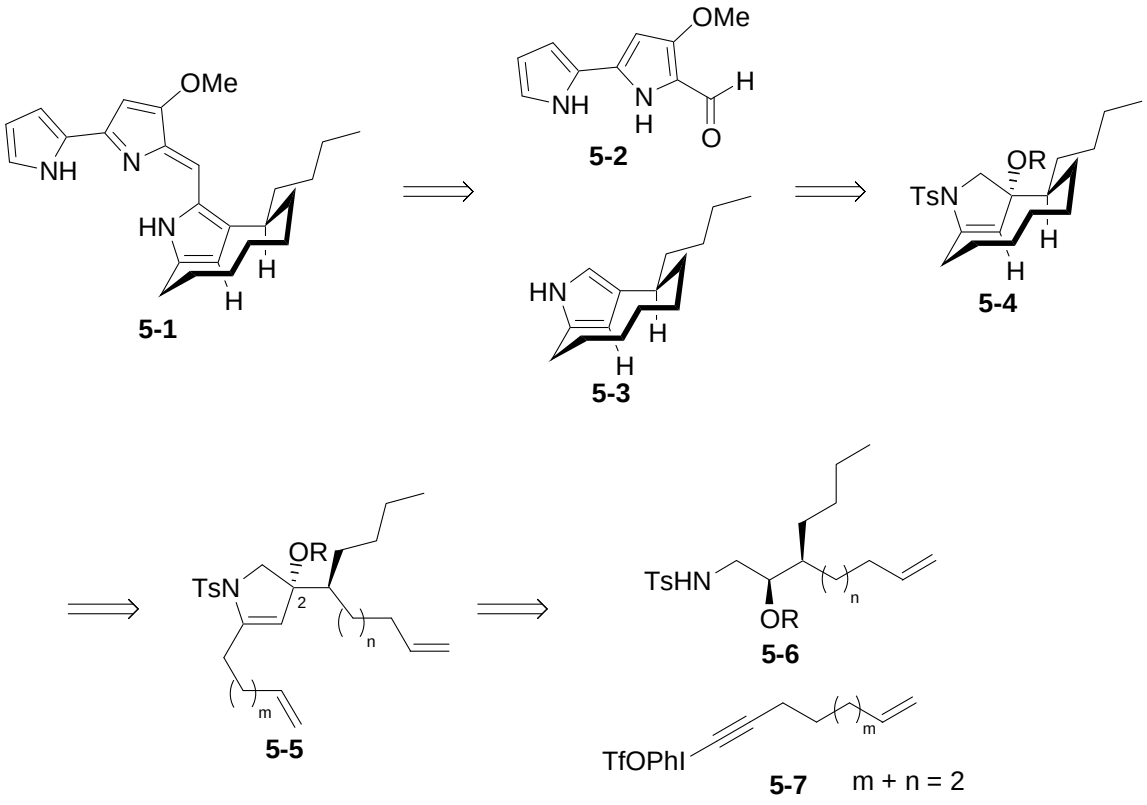


Figure **5.2**: Retrosynthetic analysis of streptorubin B.

5.2 Synthetic methods.

5.2.1 Attempts with alkynyliodonium salts.

5.2.1.1 Intermolecular strategy.

The major hurdle in constructing pyrrolidine **5-5** via alkylidenecarbene chemistry is devising a way to effect C-H insertion on one carbon chain selectively over the other. As discussed in Chapter 3, hydrogens bonded to sp^2 hybridized carbons are less likely to react with alkylidenecarbenes than hydrogens bonded to sp^3 hybridized carbons. Proper

placement of an olefin on one chain should discourage insertion, favoring insertion on the other chain. Thus, a competition experiment was set up between these two types of C-H bonds, see Figure **5.3**.

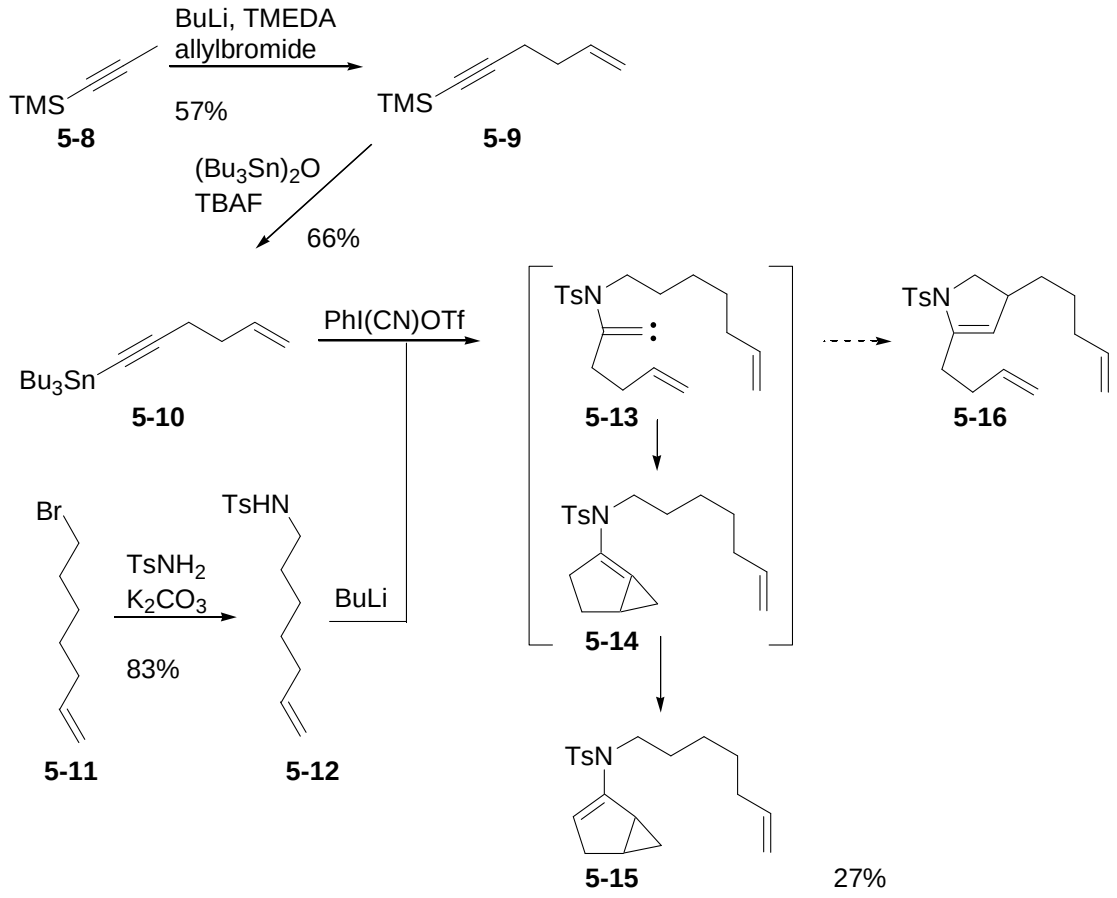


Figure **5.3**: Cyclopropanation is favored over 1,5 C-H-insertion.

The alkynyliodonium salt required to test this premise was made in a three step procedure consisting of (1) allylation of TMS propyne (**5-8**), (2) replacing the silicon in **5-9** with a tributyltin, (3) and treatment with Stang's reagent. The tosylamide was generated by a nucleophilic displacement of bromine in **5-11** to form **5-12**. When the lithium anion of **5-12** was slowly added to the iodonium salt to form alkylidenecarbene **5-**

13, no evidence of the desired dihydropyrrole **5-16** was observed. Insertion into the olefinic C-H bond was not seen either. The sole identifiable product of this reaction was cyclopropane **5-15,** which presumably arose from carbene addition into the double bond followed by an olefin migration to relieve strain. This result is unsurprising, as cyclopropanation reactions are well known in the field of carbene chemistry.[86, 96, 113-115]

Attention was next turned away from discouraging insertion on one chain to encouraging insertion on the other. Adding a vicinal siloxy group to the sulfonamide should increase the rate of insertion on the upper chain both by increasing the substitution level and by lowering the C-H bond strength. Also, the inclusion of a non-hydrogen substituent at this position would later become necessary as a means to control the absolute stereochemistry in the synthesis route. Thus, tosylamide **5-21** was prepared in four steps by the following method, see Figure **5.4**. Epichlorohydrin (**5-17**) was opened with vinylcuprate to give the alcohol **5-18**, which upon heating with strong base closed to epoxide **5-19**. This epoxide was again opened in the presence of tosylamide to alcohol **5-20**, and TBS protection gave **5-21**.

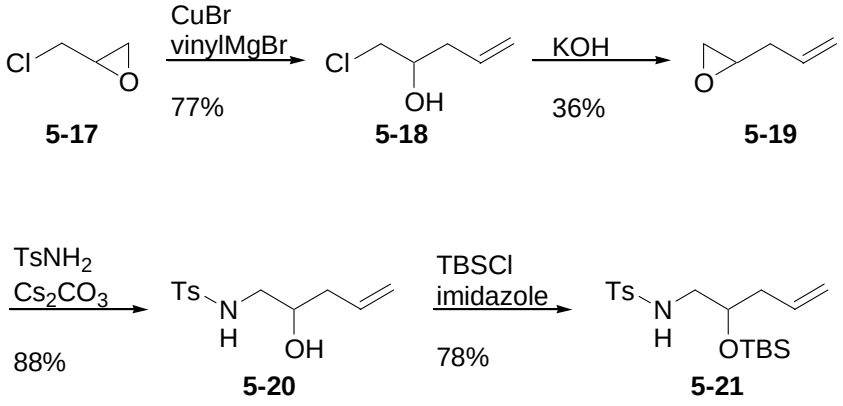


Figure **5.4**: Synthesis of tosylamide **5-21**.

Alkynylstannane **5-23** was made using similar procedures to those used in the synthesis of **5-10**, see Figure **5.5**. It was considered necessary to extend the chain length to eight carbons to ensure that no alkene addition of the carbene would occur. When the lithium anion of **5-21** was added to the alkynyliodonium salt derived from stannane **5-23**, none of the desired C-H insertion product **5-24** was detected. Instead, a small amount of the enamine **5-25**, which resulted from the undesired C-H insertion regiochemistry, was isolated. As this observation went against the general trend for relative C-H insertion rates, it may be that the reaction regiochemistry is under kinetic control where rotamer populations influence the outcome of the insertion. It is possible that the newly formed alkylidenecarbene has the alkyl chain juxtaposed closer than the OTBS-bearing chain, and that C-H insertion occurs faster than conformational equilibrium (i.e. non Curtin-Hammet conditions).

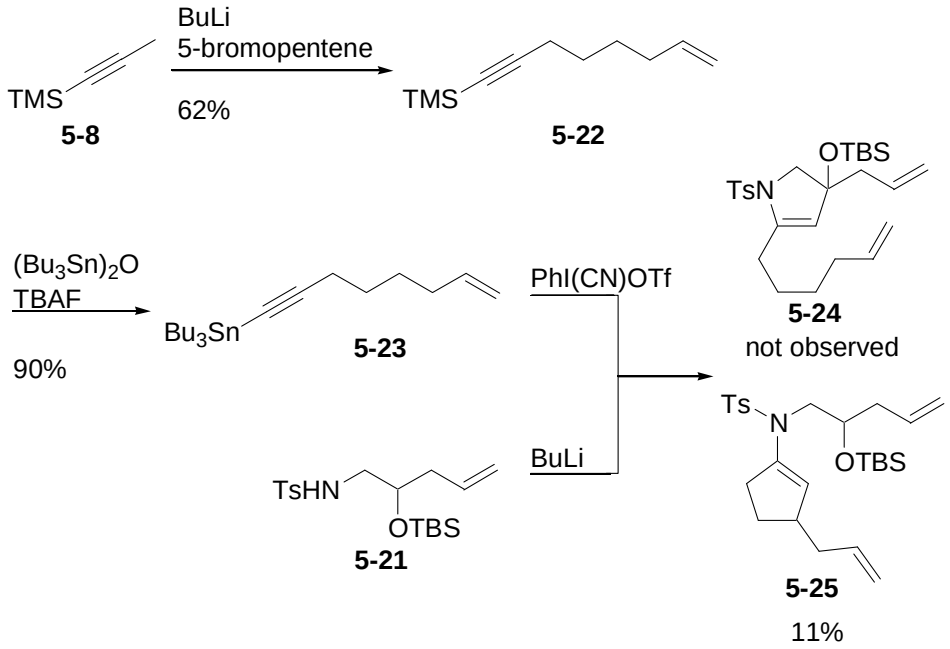


Figure **5.5**: Observation of C-H insertion on the wrong chain.

5.2.1.2 Intramolecular strategy.

It was then deemed necessary to constrain the lower side chain in such a way that only the upper chain is available for C-H insertion. This plan would require a method of releasing the alkene on the lower chain for the forthcoming RCM reaction to later close the macrocycle. Any reagents used in this transformation would also have to be compatible with the sensitive dihydropyrrole functionality, which is prone to aromatization. It was decided that the best way to keep the lower chain from interacting with the alkylidenecarbene would be to incorporate it into a cyclic sulfonamide that could be opened later to an alkene.

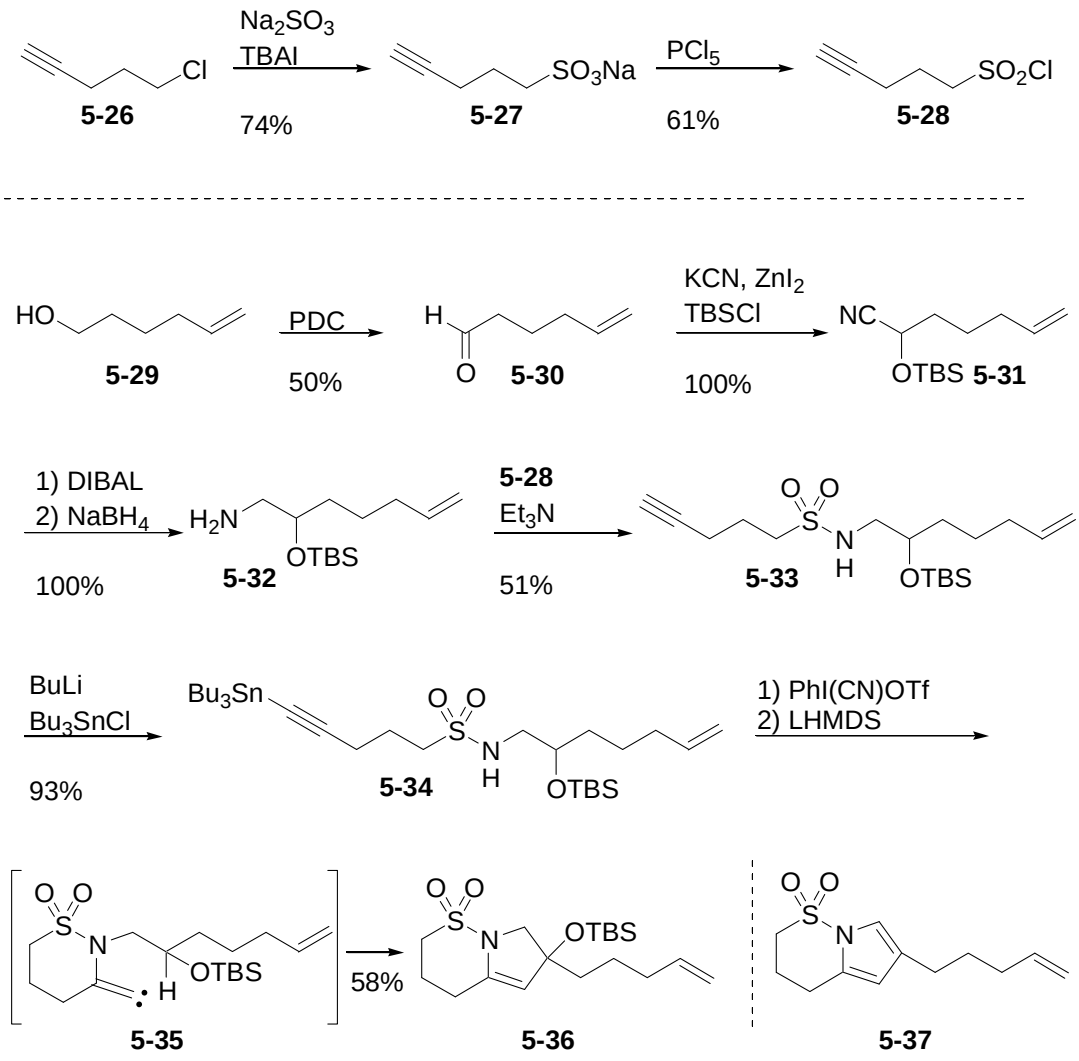


Figure **5.6**: Successful C-H insertion to bicyclic tosylamide **5-36**.

5-Chloropentyne (**5-26**) was converted to the sulfonate salt facilitated by tetrabutylammonium iodide, see Figure **5.6**. Chlorination of **5-27** gave sulfonyl chloride **5-28** in moderate yield. The other half of the molecule was made starting from 5-hexenol (**5-29**). Oxidation with PDC gave aldehyde **5-30**, which was converted to the cyanohydrin **5-31** with ZnI_2 as a Lewis acid catalyst.[207] The cyanide was reduced to amine **4-32** through a two step procedure in quantitative yield.[208] This amine was coupled with sulfonyl chloride **5-28**, and the alkyne was deprotonated and exposed to tributyltin

chloride to form the alkynylstannane **5-34**. Upon treatment of **5-34** with Stang's reagent followed by LHMDS, the tosylamide nitrogen anion added into the alkynyliodonium salt and generated carbene **5-35**. With only one viable insertion option available, the pyrrolidine **5-36** was formed in 58% yield from the alkynylstannane. Dihydropyrrole **5-36** was found to be a sensitive compound that readily lost HOTBS to form pyrrole **5-37** in the presence of acid, silica gel, or when left at room temperature for extended periods of time.

With the pyrrolidine successfully prepared, attention was turned towards opening the sulfonamide and unmasking the alkene. Using an adaptation of Julia's electrophillic Grignard methodology,[209-212] **5-36** was deprotonated and then anion **5-38** was alkylated with CH_2IMgX. The resulting lone pair of the new Grignard compound **5-39** eliminated sulfur dioxide, leaving behind imine **5-41**, see Figure **5.7**. Unfortunately, this imine was too unstable for effective ring closing metathesis experiments.

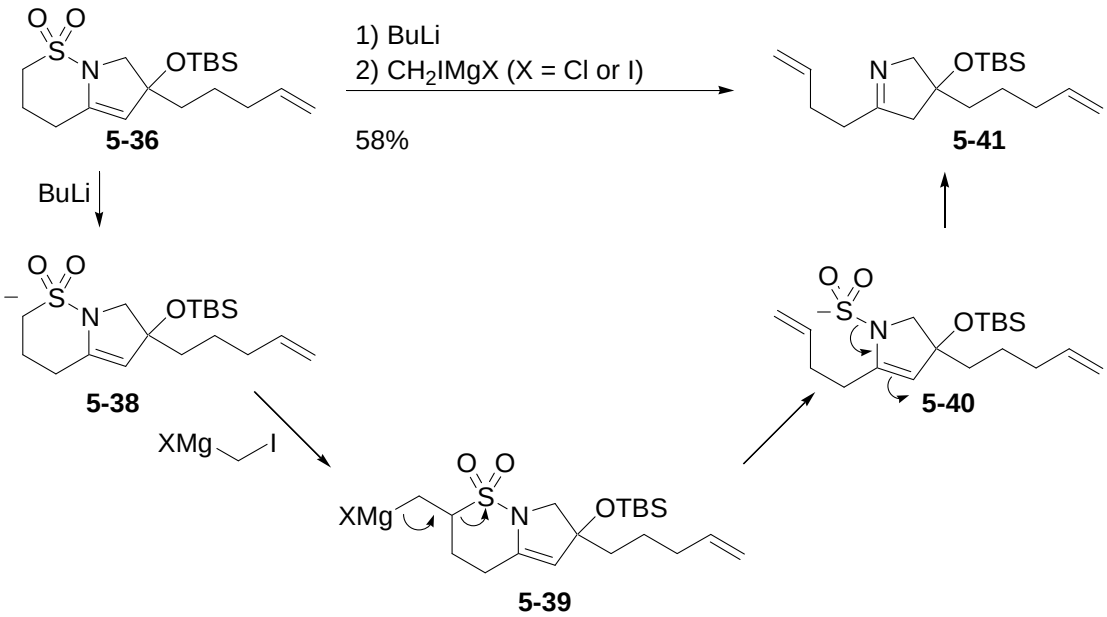


Figure **5.7**: Electrophilic Grignard methodology to open sulfonamides to imines.

Imine **5-41** was converted to the Boc protected enamine **5-42** to increase its stability for metathesis experiments, see Figure **5.8**. However, all attempts to close the macrocycle resulted in decomposition, dimerization, or elimination of OTBS to the pyrrole.

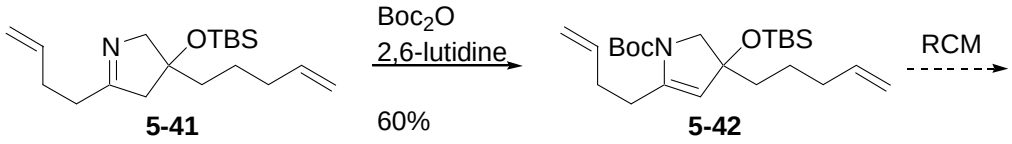


Figure **5.8**: Protection of the imine and attempted RCM.

Reduction of imine **5-41** would result in a stable pyrrolidine, but a *cis* orientation of the two alkenyl chains is necessary for successful RCM. Unfortunately, reduction of **5-41** with lithium aluminum hydride gave only a small percentage of the desired pyrrolidine **5-44** along with a larger portion of the *trans* diasteromer **5-43**, see Figure **5.9**. As this reduction method would never yield any significant amount of usable diene **5-44**, an alternative was sought.

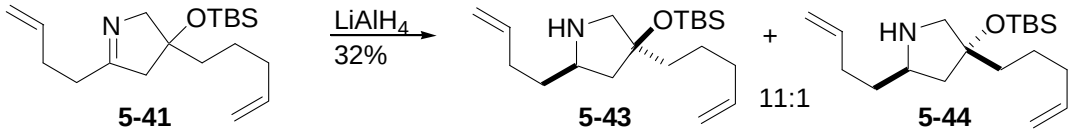


Figure **5.9**: Reduction of imine **5-41**.

Benzyl ethers chelate to Lewis acidic metals and can be used to assist in delivery of nucleophiles.[213-214] With this in mind, the synthesis of the benzyloxy substrate **5-53** was undertaken, see Figure **5.10**. N-BocGlycine was converted to ketone **5-47** in 73%

yield *via* Weinreb amide **5-46** and subsequent addition of pentenyl MgBr. Reduction of the ketone in **5-47**, protection of the alcohol in **5-48** with benzylbromide, and removal of the Boc group with TFA gave the primary amine **5-50**. Following procedures used for the synthesis of **5-36**, benzyloxypyrrolidine **5-53** was successfully prepared in 34% yield over three steps from the alkyne. Attempts to open the sulfonamide using Julia's method resulted in elimination of benzylalcohol to furnish the pyrrole.

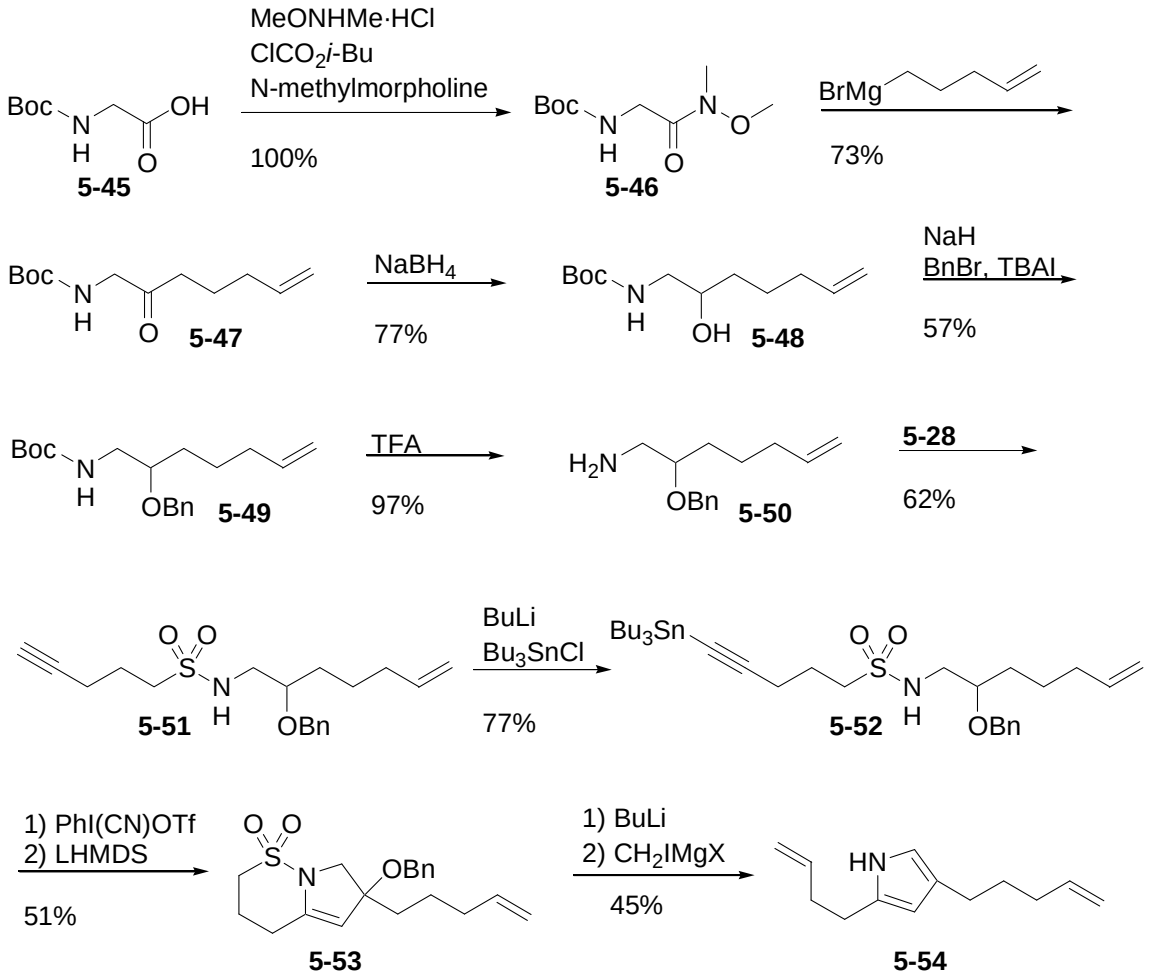


Figure **5.10**: Synthesis of bicyclic sulfonamide **5-53**.

One last attempt was made at a **5-36** derivative with a suitable chelating group was explored. The naked alkoxide of imine **5-56** should be an excellent chelating group with a low propensity towards elimination. Thus, silylether **5-36** was treated with TBAF to give alcohol **5-55** in 92% yield, see Figure **5.11**. The sulfonamide was opened as before in acceptable yields. However treatment of **5-55** with lithium aluminum hydride led to aromatization. It is possible that the alkoxide coordinated with an aluminum species, creating a suitable leaving group.

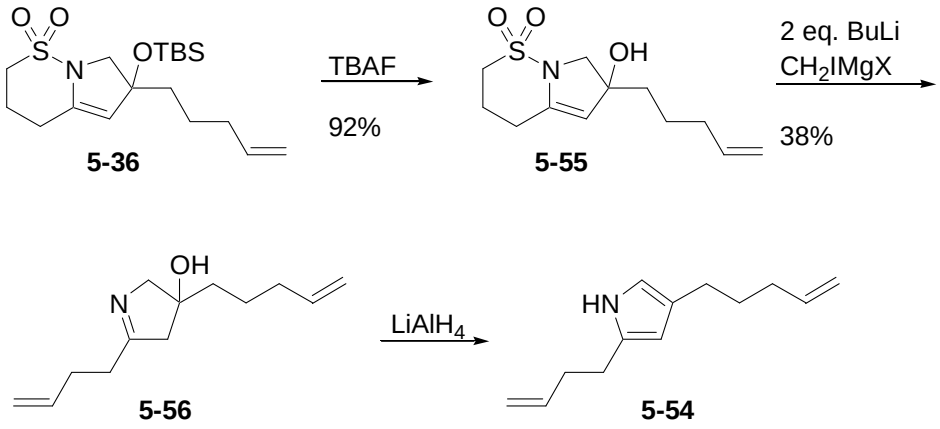


Figure **5.11**: Removal of the silyl protecting group and attempted reduction.

The persistent problems of aromatization led to the discontinuation of all efforts linked to alkynyliodonium salt chemistry. The challenges of C-H insertion selectivity brought forth a novel method of synthesizing bicyclic pyrroles and pyrrolidines. Also, an opportunity was given to explore intriguing electrophilic Grignard chemistry. However, these methods proved to be unfruitful in the quest to make **5-1**, and the pressing need to complete the synthesis outweighed the benefits of further investigation into this methodology.

5.2.2 Attempts with Horner-Wadsworth-Emmons.

It was envisioned that the bridging ten membered ring of **5-1** could be closed using Horner-Wadsorth-Emmons (HWE) chemistry, see Figure **5.12**. This approach has been successful in the construction of various eleven membered rings,[66-68] as well as simple small bicyclic compounds with bridgehead olefins.[215-217] Is it possible to combine these two ideas and close a medium sized ring with a bridgehead olefin? If the α,β-unsaturated amide **5-58** could be isolated, both diastereomers of **5-57** could be reached by either the addition of butylcuprate or hydrogenation, depending on the identity of R. The diastereoselectivity would arise from peripheral attack on the alkene in **5-58**.

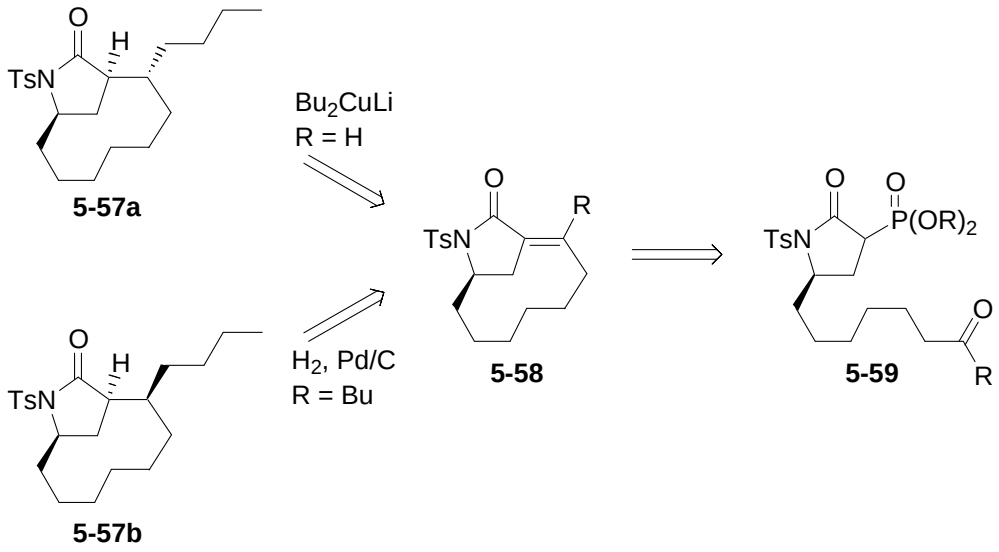


Figure **5.12**: Retrosynthesis involving Horner-Wadsworth-Emmons macrocyclization chemistry.

The first attempts at attaching the properly substituted alkyl chain to **5-60** met with complete failure. It is well precedented that Grignard and lithium reagents add to tosylate **5-60** *via* a two step process to give substituted lactams **5-62**, see Figure **5.13**.[218-221] However, alkyl halides and sulfide **5-63** were found to be unreactive under these

conditions, see Figure **5.14**. In most cases, **5-63** was isolated unchanged. It is possible that complexation with the acetal rendered the metalation process ineffective.

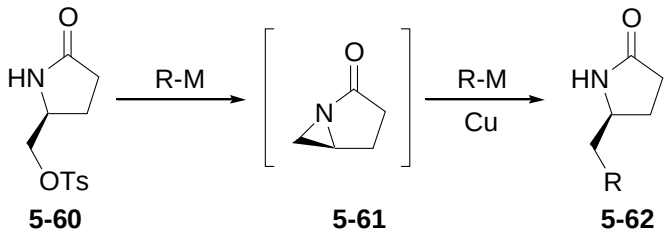


Figure **5.13**: Two step mechanism for the displacement of tosylate from **5-60**.

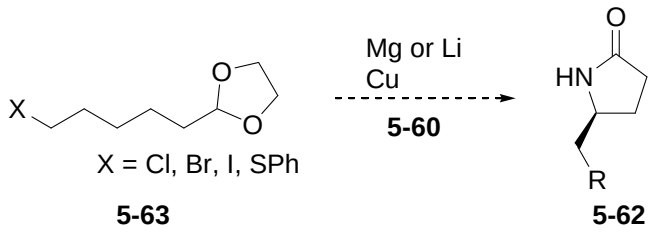


Figure **5.14**: Inertness of halo/acetal derivatives **5-63**.

Successful addition was finally achieved by replacing the acetal with an alkene, see Figure **5.15**. The addition of heptenyl magnesium bromide to **5-60** in the presence of catalytic lithium tetrachlorocuprate gave the alkene substituted lactam **5-65** in good yields without incident. The amide of **5-65** was tosylated, and tosyl lactam **5-66** was isolated in 57% over two steps. The phosphate was installed by quenching the enolate of **5-66** with diethyl chlorophosphite followed by an acid mediated air oxidation to deliver **5-67**.[222] This method overcomes phosphorous's natural affinity for oxygen and selectively places the phosphorous on the α-carbon. Ozonolysis of the olefin unmasked the aldehyde in **5-59**, and the stage was set for the key HWE ring closure. Unfortunately, no desired

cyclization was observed under any conditions when **5-59** was exposed to a variety of bases. Only dimers and unreacted aldehyde were observed.

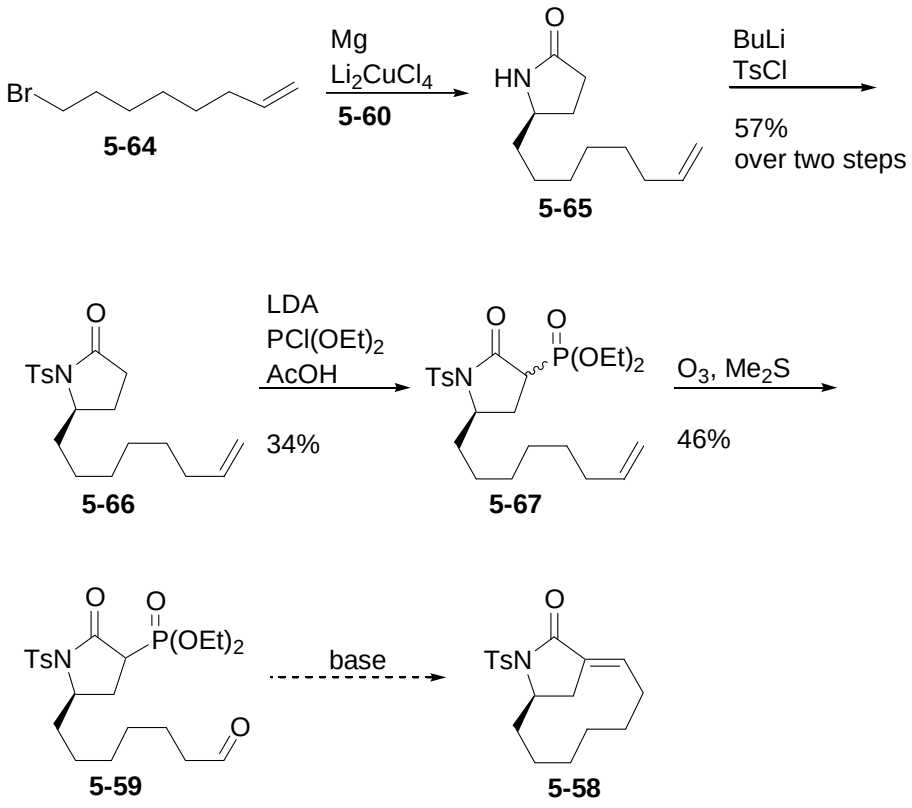


Figure **5.15**: Synthesis of Horner-Wadsworth-Emmons reagent **5-59**.

5.2.3 Attempts with ring closing metathesis.

Interest was shifted back to ring closing metathesis as a means to form the bicyclic pyrrole **5-3**. For this strategy to be a worthwhile endeavor, three conditions had to be met. First, the open diene had to be a stable substrate so that extensive RCM experimentation could be carried out. Second, all four stereoisomers must be readily accessible. Third, the synthesis of the diene must be concise. Diene **5-68** was selected for

its stability and because it could be made by adapting chemistry used in the construction of the HWE substrate, see Figure **5.16**.

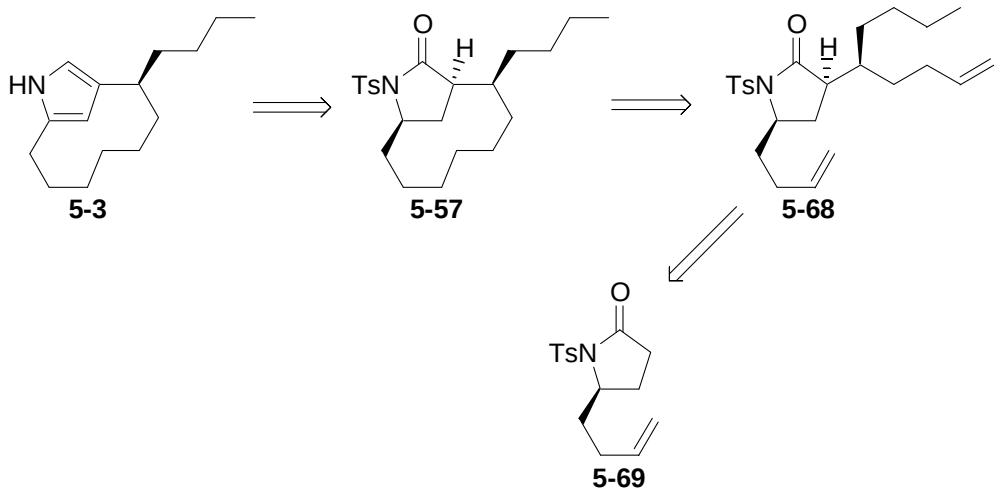


Figure **5.16**: Retrosynthesis involving RCM of a lactam.

Tosylamide **5-69** was synthesized following the general method for **5-66**. The lactam then underwent an aldol/elimination process to give unsaturated amide **5-71**. The butenyl chain of **5-71** provides some steric bulk to influence the stereochemistry of the conjugate addition at C7' (2 : 1). Protonation at C2 with a sterically encumbered acid occurred with a 24 : 1 preference away from the butenyl group. These ratios were derived from comparison of ^{1}H NMR peak integrations. The ratio at the C7' can be discerned by a comparison of diastereomeric peaks in the aromatic region. It was determined that the ratio of epimers at C2 could be observed in the relative integrations of the diastereomeric peaks at both 4.1(H4) and 2.6 (H2) ppm. When the enolate is quenched with aqueous ammonium chloride, the ratios at these peaks drop to ~1 : 1. An nOe correlation is seen between H2 and H4, indicating that the alkenyl chains reside on the same side of the

lactam. Unfortunately, the configuration at C7' cannot be determined at this stage by the nOe data, but it was assumed that major direction of the cuprate attack was from the back face away from the C4 butenyl substituent.

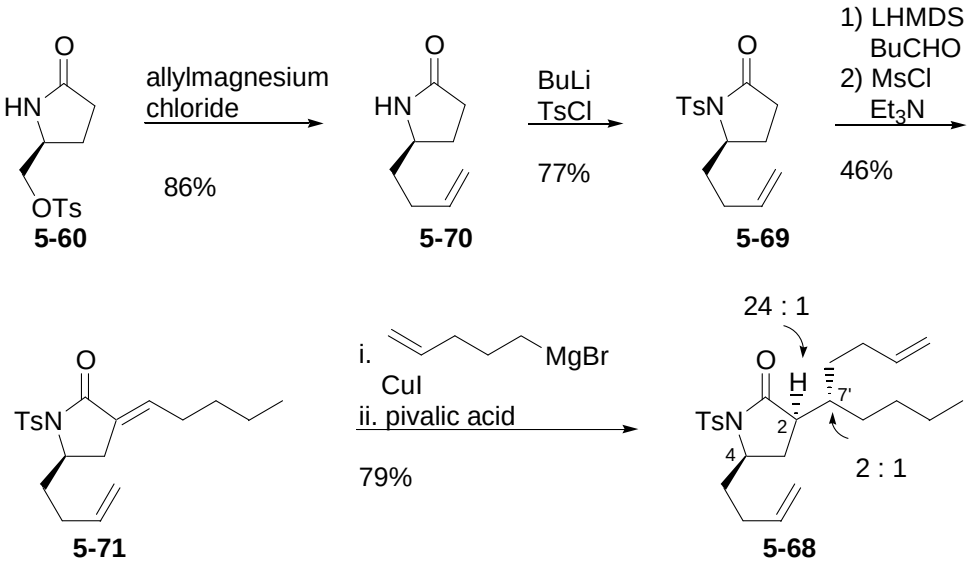


Figure **5.17**: Synthesis of diene **5-68**.

With diene **5-68** in hand, studies toward RCM were undertaken. It was assumed that a tosyl substituent on sp^2 hybridized nitrogen would encourage the butenyl side chain to adopt an axial conformation to avoid $A^{1,3}$ strain. This cyclopentene-like envelope conformation should also put the C2 side chain in an axial position. However, calculations showed that these two groups, while not in equatorial positions, were not fully axial either, probably due to the syn pentane interaction involving the butenyl side chain and the isopropyl like substituent.

Diene **5-68** was subjected to a variety of RCM conditions utilizing Schrock, Hoveyda-Grubbs, and Grubbs first and second generation catalysts. Unfortunately, no

conclusive evidence for cyclized monomer ever was observed. The usual outcome for most attempts was a mixture of dimeric and oligomeric products even at very low concentrations (0.4 μM). Reactions carried out at higher temperatures (150˚C) or under 1 atm of ethylene gas resulted in alkene migration products as well as dimer formation.

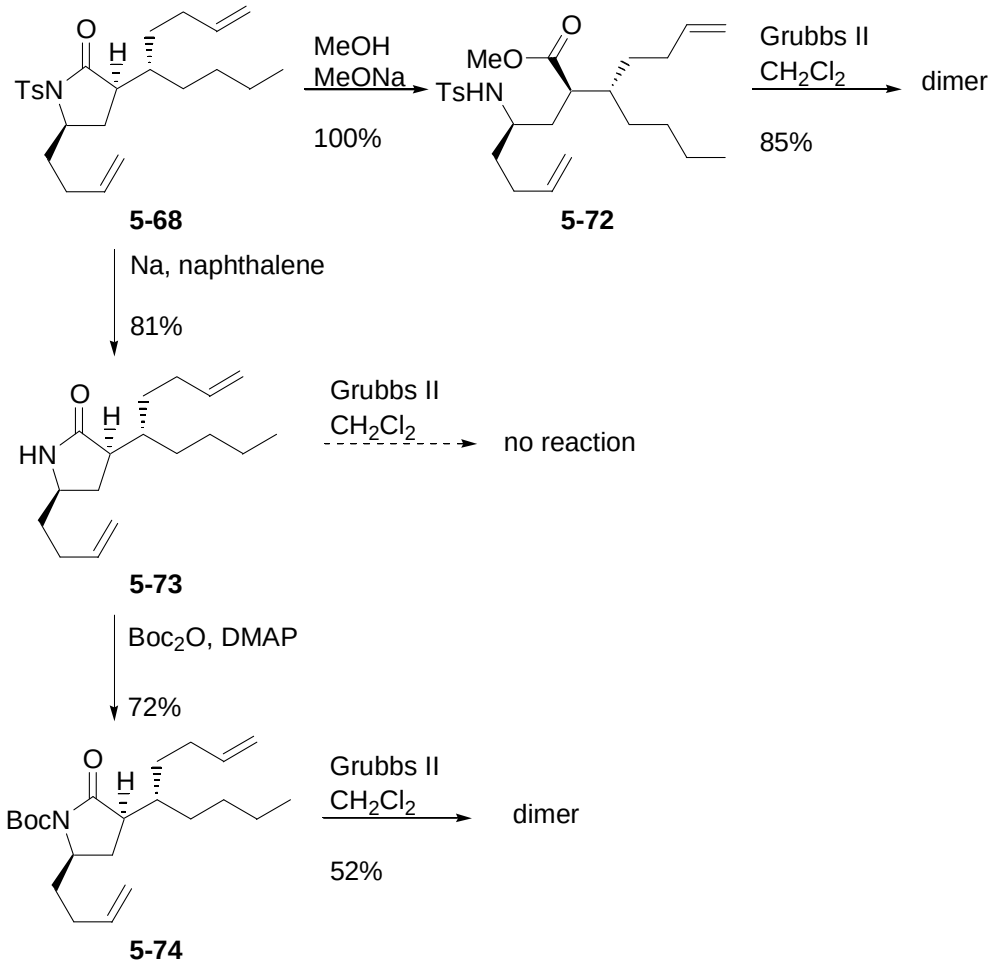


Figure **5.18**: Attempted RCM of **5-68** derivatives.

As the literature is full of examples where small changes to the structure caused big changes in reactivity (cf. Chapter 4) a few derivatives of **5-68** were made, see Figure **5.18**. Regrettably, changing the nature of the lactam was not enough to suppress dimer

formation. Even ester **5-72**, which would have resulted in an unbridged cyclodecene, failed to provide the desired monomer.

At this point it was still unclear if the dimeric products owed their origin to ring opening of a strained closed monomer or if they were formed directly from open dienes. It is known that medium ring monocyclic alkenes can be converted into their respective dimers by exposure to RCM catalysts.[162] Recently, Fogg and coworkers challenged the current understanding of dimer formation by suggesting that it is the dimer that is formed first, not the monomer.[163] The monomers are the result of "back-biting" reactions of dimers and oligomers. Fogg monitored several RCM reactions using MALDI/MS and GC analysis. In the early stages of the reaction, the diene starting material was almost completely consumed, and the relative amounts of dimers and oligomers present were much higher than that of the monocyclic product. As the reaction progressed, the amount of oligomeric material decreased as the amount of monomer increased. These data clearly show that individual monomers were breaking away from larger dimers and oligomers.

A similar experiment was carried out with diene **5-68**, see Figure **5.19**. Similar to the results seen by Fogg, the starting diene **5-68** rapidly cyclized to dimeric products in the first few minutes of the reaction. A small amount of a compound which was assumed to be the closed monomer was also seen. The MS data for this "monomer" did in fact show the correct mass peak at 390 amu, but the major peak was at 554 amu. It is possible that the peak at 390 amu is simply a fragment of a larger compound, and no true monomer was ever detected. The true identity of this "monomer" was never discovered.

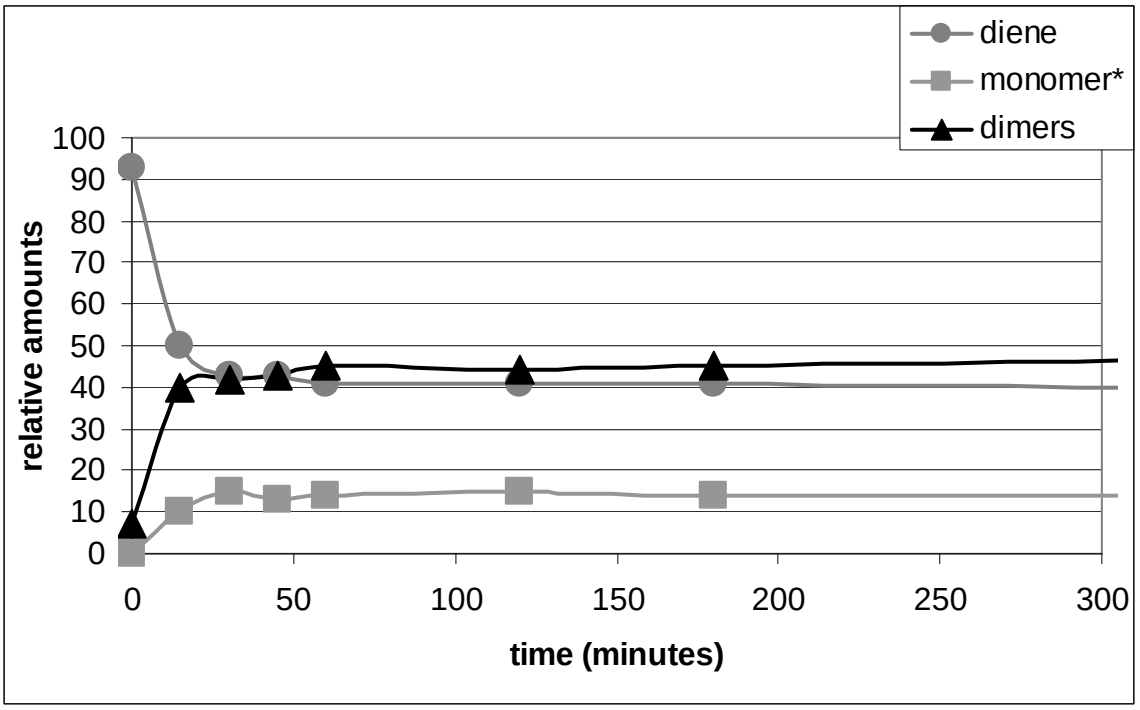


Figure **5.19**: Dimer vs. monomer mass spectrometry analysis for the reaction of **5-68** with Grubbs second generation catalyst.

It is clear that even at high dilution, dimer formation is kinetically favored. Attention was turned toward the possibility of the monomer being the thermodynamically favored product. Molecular mechanics calculations using the Merck force field were carried out for the open diene, closed monomer, and closed dimer. The closed monomer is ~11 kcal/mol uphill in energy compared to the dimer, so it is unlikely that under thermodynamic conditions the monomer can be formed. Also, the ΔH_{rxn} for monomer formation was found to be 15.6 kcal/mol, well over the limit of 10 kcal/mol described by Grubbs.[179] The knowledge of these unfavorable thermodynamic approximations, coupled with the lack of derivatization sites on the relatively unfunctionalized **5-68**, caused the

RCM methodology to be abandoned. As Schrock once said, “not every ring is supposed to be closed by metathesis”.[223]

5.2.4 Success with Nozaki-Hiyama-Kishi macrocyclization chemistry.

Another ring closing method that has been widely used to close medium sized rings is the Nozaki-Hiyama-Kishi (NHK) coupling of a vinyl iodide with an aldehyde.[74-76] NHK reactions have been shown to tolerate a wide variety of functional groups and have been used as the method of choice for ring closure in a variety of natural product syntheses,[77-82] most recently for pestaltiopsin where RCM failed (see Figure **4.20**).[83-84]

To test the viability of an NHK reaction in this synthesis, aldehyde/vinyliodide **5-80** was made in a similar route to **5-68**. The enolate of **5-69** was added to aldehyde **5-75** to form alcohol **5-76**, see Figure **5.20**. Elimination of this alcohol proved to be problematic. The $MsCl/Et_3N$ protocol, which worked well previously, now stopped at the mesylate and did not proceed to elimination until after the addition of LHMDS. Also, this method caused a considerable amount of OTBS elimination to occur; thus, an alternative procedure was sought. Treatment of alcohol **5-76** with iodine, imidazole, and triphenylphosphine resulted in clean single elimination to α,β-unsaturated amide **5-77** with an 8 : 1 E : Z ratio.

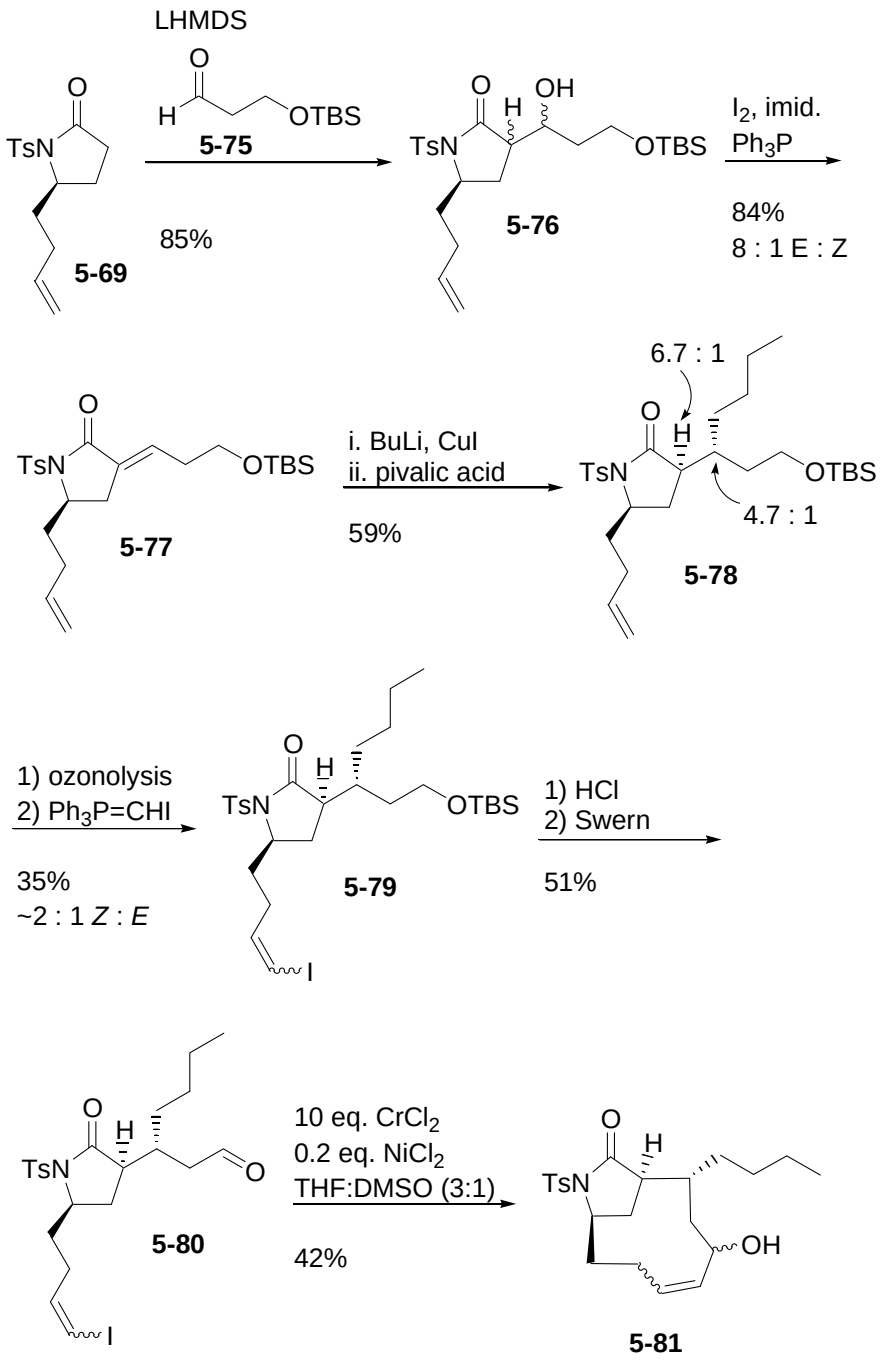


Figure **5.20**: Successful ring closure using an NHK coupling.

The addition of butylcuprate to **5-77** proceeded easily, but the diastereoselectivity was an issue. A similar spectral analysis as with **5-68** was performed for **5-78**. The ratio of epimers at C7' was found to be 4.6 : 1, but the ratio at C2 dropped to 6.7 : 1, compared

to 24 : 1 for **5-68** in the metathesis route. Preliminary work using chiral phosphine ligands improved the selectivity at C7' to 9-12:1, but the ratio at C2 remains an unsolved problem. Once again, the stereochemistry at C7' could not be determined at this point.

Alkene **5-78** was homologated to vinyliodide **5-79** through ozonolysis to the aldehyde and an iodomethyl Wittig reaction. The TBS protecting group was removed with HCl, and the resulting alcohol was oxidized to aldehyde **5-80** under Swern conditions. In the presence of catalytic $NiCl_2$ and an excess of $CrCl_2$, aldehyde **5-80** was successfully closed to the monomeric cyclic allylic alcohol **5-81**, albeit in modest yields and as a complex mixture of stereoisomers. Both *E* and *Z* alkene isomers were observed in these products.

5.3 Conclusions and future work.

The quest to make all possible stereoisomers of streptorubin B has taken many paths through several different fields of organic chemistry. A novel alkynyliodonium chemistry methodology was developed, and various ring closing methods were explored. The chromium-mediated NHK coupling has once again proven to be an effective cyclization methodology for closing strained medium sized rings.

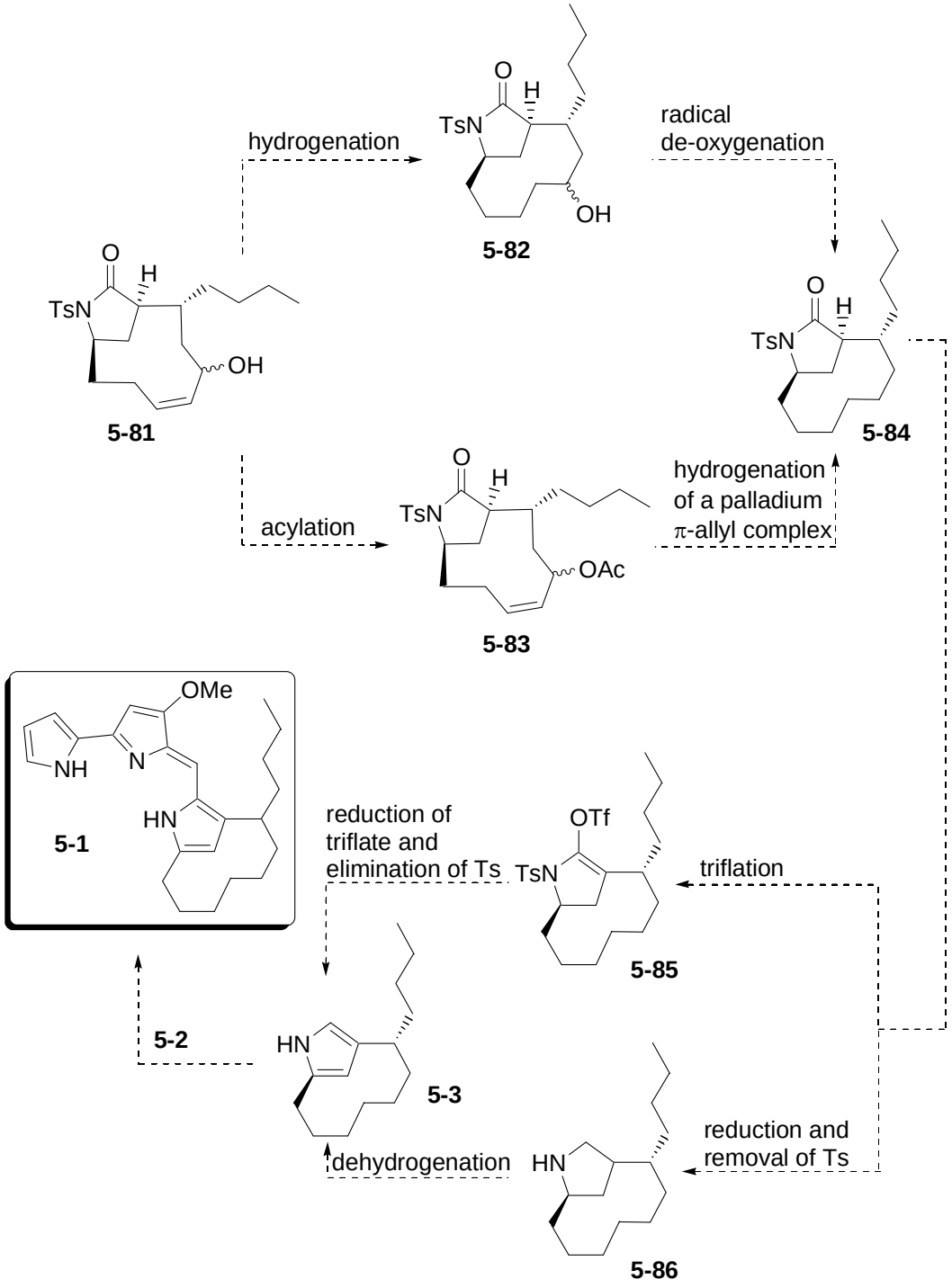


Figure **5.21**: Endgame options for finishing the synthesis of **5-1**.

Before this project can be considered complete, the allylic alcohol must be reduced to an alkane, and the lactam must be converted to a pyrrole. At least two options

are available for both transformations, see Figure **5.21**. The allylic alcohol **5-81** could be reduced either by hydrogenation of the olefin and radical deoxygenation, or by hydrogenation of a palladium π-allyl complex from **5-83**. Lactam **5-84** could be converted to the vinyl triflate and reduced with tributyl tin hydride, and the tosyl group could be eliminated with a strong base following Fürstner's procedure to yield **5-3**. Alternatively, **5-84** could be reduced to amine **5-86**, but this otherwise facile reaction runs the risk of irreversible ring opening to the amino alcohol. If **5-86** were formed, it could be dehydrogenated with MnO_2.[224-225] Once pyrrole **5-3** is obtained, the synthesis will be completed by the well precedented coupling with the bipyrrolyl aldehyde **5-2**.

5.4 References.

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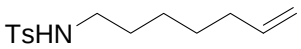
Chapter 6

Experimentals

6.1 General Experimental.

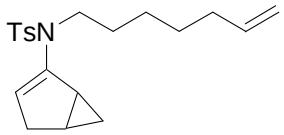
All reactions involving air and moisture sensitive reagents were performed in flame-dried Schlenk glassware under a nitrogen atmosphere. Solvents used for reactions (THF, Et_2O, CH_2Cl_2, DME, hexanes, benzene, toluene, MeOH, DMF, CH_3CN, and Et_3N) were obtained from a purification column filled with conditioned alumina resin available from Glass Countours (http://www.glasscontour.com/). Tosyl chloride was recrystalized from CH_3Cl/pet ether before use. Diiodomethane was washed with sat. aq. $Na_2S_2O_3$ and dried with sodium sulfate. All other reagents were used as purchased. Crude reaction products were purified *via* chromatography on 32-63 μm silica gel with solvents used as purchased. Low- and high-resolution mass spectra were obtained from the Proteomics and Mass Spectrometry Core Facility, University Park at Pennsylvania State University.

6.2 Alkynyliodonium routes.



6-Heptenyl-toluenesulfonamide (**5-12**): A solution of 1-bromo-6-heptene (**5-11**) (1.19 g, 6.69 mmol), $TsNH_2$ (3.44 g, 20.1 mmol), and K_2CO_3 (9.25 g, 66.9 mmol) in acetone (35 mL) was heated to reflux and stirred for 20 h. The solvent was removed *in vacuo*. Water (50 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. Purification by column chromatography on silica gel (1:1 hexanes:Et_2O) yielded the title

compound as a colorless oil (1.48 g, 83%). IR (neat): 3282, 1640 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 5.75 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 4.94 (m, 2H), 4.37 (t, *J* = 6.0 Hz, 1H), 2.93 (td, *J* = 7.0, 6.4 Hz, 2H), 2.43 (s, 3H), 1.99 (dt, *J* = 7.2, 6.8 Hz, 2H), 1.46 (pent, *J* = 7.1 Hz, 2H), 1.37-1.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 138.5, 136.9, 129.6, 127.0, 114.5, 43.1, 33.4, 29.3, 28.2, 25.9, 21.4; TOFESMS m/*z* relative intensity 268 (MH^+ 100), HRMS (+ES) calculated for $C_{14}H_{22}NO_2S$: 268.1371, found 268,1346.



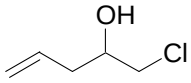
N-Bicyclo[3.1.0]hex-2-en-2-yl-N-hept-6-enyl-toluenesulfonamide (**5-15**): A solution of 1-trimethylsilyl propyne (**5-8**) (9.00 mL, 60.8 mmol) and TMEDA (10.1 mL, 66.9) in Et_2O (45 mL) was cooled to -5 °C (measured with an internal thermometer). *n*-BuLi (26.7 mL, 2.5M hexanes, 66.8 mmol) was added dropwise, never allowing the internal temperature to rise above 0 °C. To this white slurry was added allylbromide (1.75 mL, 20.3 mmol) in Et_2O (10 mL) dropwise keeping the internal temperature below 0 °C. As the reaction progresses the white solids dissolve and the solution becomes wine red. The reaction mixture was stirred for 15 min and then poured over ice and pentane (50 mL). The aqueous portion was removed and the remaining pentane was washed with 1M H_3PO_4 (3 × 50 mL). The crude mixture was dried over Na_2SO_4 and fractionally distilled to give 1-trimethylsilyl-hex-5-en-1-yne (**5-9**) as a colorless liquid (1.76 g, 57%, b.p. 55 °C/ 13 torr). ^1H NMR (300 MHz, C_6D_6) δ 5.82 (m, 1H), 5.02 (m, 2H), 2.29-2.17 (m, 4H), 0.11 (s, 9H).

A solution of **5-9** (313 mg, 2.06 mmol) in THF (5 mL) was degassed by bubbling with nitrogen gas. Bistributyltin oxide (0.491 mL, 0.925 mmol) and *n*-Bu_4NF (41 μL, 1M THF, 0.411 mmol) were added, and the reaction solution was heated to reflux for 2.5 h. At this time, the mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography on silica gel (hexanes) to give 1-(tributyltin)-hex-5-en-1-yne (**5-10**) as a yellow oil (450 mg, 66%). ^1H NMR (360 MHz, C_6D_6) δ 5.82 (ddt, *J* = 16.9, 10.3, 6.3 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.96 (m, 1H), 2.24-2.10 (m, 4H), 1.80-1.52 (m, 6H), 1.38 (sext, *J* = 7.3 Hz, 6H), 1.00 (dd, *J* = 8.1, 7.9 Hz, 6H), 0.92 (t, *J* = 7.3 Hz, 12H).

To a solution of PhI(CN)OTf (511 mg, 1.35 mmol) in CH_2Cl_2 (8.5 mL) was added alkynylstannane **5-10** (498 mg, 1.35 mmol) in CH_2Cl_2 (5 mL) at -42 ºC. The reaction solution was stirred at this temperature for 1.5 h. The solvent was removed *in vacuo* while keeping the temperature below 0 ºC. The yellow oil was washed with dry hexanes (3 × 10 mL) *via* syringe below 0 ºC and the residual solvent was removed *in vacuo* to leave the alkynyliodonium salt as a white solid (184 mg).

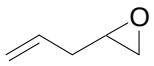
A solution of 6-heptenyl-toluenesulfonamide (**5-12**) (110 mg, 0.409 mmol) in THF (40 mL) was cooled to -78 °C, and *n*-BuLi (0.186 mL, 2.2M hexanes, 0.41 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 5 min and then allowed to warm to room temperature. The alkynyliodonium salt was added in THF (10 mL) over 30 min and the reaction mixture was stirred for an additional 30 min. The reaction solution was poured over a mixture of ice, brine (25 mL), Et_2O (25 mL), and hexanes (25 mL). The aqueous portion was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. One

drop of Et_3N was added to sequester any adventitious acid, and the solvent was removed *in vacuo*. Purification of the residue through column chromatography on silica gel (4:1:0.05 hexanes:Et_2O:Et_3N) gave tosylenamine **5-15** as a yellow oil (38 mg, 27%). IR (neat): 1640 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.78 (d, *J* = 6.5 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 5.74 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.99 (m, 2H), 4.93 (m, 1H), 3.66 (ddd, *J* = 13.5, 8.0, 7.0 Hz, 1H), 3.26 (ddd, *J* = 13.5, 7.8, 5.8 Hz, 1H), 2.35 (ddd, *J* = 17.5, 7.4, 2.1 Hz, 1H), 3.66 (dt, *J* = 17.6, 2.6 Hz, 1H), 1.93 (m, 2H), 1.87 (s, 3H), 1.76 (tt, *J* = 6.8, 3.1 Hz, 1H), 1.54 (m, 2H), 1.32-1.20 (m, 5H), 0.62 (td, *J* = 7.6, 4.0 Hz, 1H), -0.12 (td, *J* = 3.9, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.2, 143.3, 139.6, 138.7, 130.0, 129.0, 115.6, 115.3, 50.0, 34.6, 33.9, 29.4 (2C), 27.0, 24.1, 21.7, 16.7, 15.6; $APCI^+$ m/z relative intensity 346 (MH^+ 100).

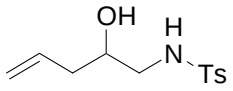


1-Chloro-pent-4-en-2-ol (**5-18**): Vinylmagnesium bromide (122 mL, 1M in THF, 122 mmol) was added to a slurry of CuBr (1.75 g, 12.2 mmol) in Et_2O (320 mL) at -78°C. This yellow solution was stirred at -78°C for 5 min, and then epichlorohydrin (**5-17**) (10.0 mL, 128 mmol) was added. The reaction mixture was stirred at -78°C for 5 h and then slowly warmed to room temperature overnight. The reaction solution was poured into ice water (200 mL) and 1M H_3PO_4 (100 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 300 mL) and the combined organics were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the yellow residue was distilled to give the alcohol as a colorless liquid (11.4 g, 77%, b.p. 73-75 °C/ 50 torr). IR (neat): 3387 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, *J* =

17.1, 11.2, 7.1 Hz, 1H), 5.17 (m, 2H), 3.98 (m, 1H), 3.63 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.51 (dd, *J* = 11.2, 6.5 Hz, 1H), 2.63 (s, 1H), 2.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3, 118.6, 70.6, 49.4, 38.7; TOFEIMS m/z relative intensity 79 (M^+–$CH_2CH{=}CH_2$ 100), 120 (M^+ 5), HRMS (+EI) calculated for $C_5H_9O^{35}Cl$: 120.0342, found 120.0336.

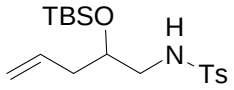


2-Allyl-oxirane (**5-19**): 1-Chloro-pent-4-en-2-ol (**5-18**) (4.00 g, 33.2 mmol) was added to crushed KOH (2.23g, 39.8 mmol). The slurry was stirred vigorously and heated until the epoxide distilled over as a colorless liquid (1.02 g, 36%, 65-66°C/ 760 torr). IR (neat): 1642, 1257, 833 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.14 (m, 2H), 3.00 (tdd, *J* = 5.4, 3.9, 2.7 Hz, 1H), 2.77 (dd, *J* = 4.9, 4.0 Hz, 1H), 2.52 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 117.6, 51.2, 46.5, 36.5; TOFEIMS m/z relative intensity 83 (M^+–H 100), 84.1 (M^+ 16), HRMS (+EI) calculated for $C_{12}H_7O$: 83.0497, found 83.0493.



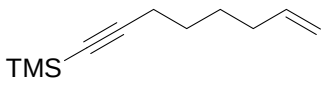
***N*-(Toluenesulfonyl)-1amino-pent-4-en-2-ol** (**5-20**): Toluenesulfonamide (2.64 g, 15.5 mmol) was added to a solution of oxirane **5-19** (650 mg, 7.73 mmol), Cs_2CO_3 (2.52 g, 7.73 mmol), and DMF (16 mL). The reaction mixture was heated at 80°C for 18 h. The solution was poured into water (15 mL) and neutralized with 1M H_3PO_4. The crude mixture was extracted with Et_2O (5 × 15 mL) and the organics were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude

material was purified through column chromatography on silica gel (9:1, Et_2O:hexanes) to give alcohol **5-20** (1.63 g, 88%) as a colorless oil. IR (neat): 3498, 1324, 1159, 1092 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.75 (d, *J* = 6.9 Hz, 2H), 7.31 (d, *J* = 6.6 Hz, 2H), 5.74 (ddt, *J* = 16.5, 10.7, 6.8 Hz, 1H), 5.24 (m, 1H), 5.15 (m, 2H), 3.76 (m, 2H), 3.08 (ddd, *J* = 12.9, 7.3, 3.2 Hz, 1H), 2.82 (ddd, *J* = 13.0, 7.9, 5.2 Hz, 1H), 2.44-2.41 (m, 4H), 2.20 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.6, 136.6, 133.4, 129.8, 127.1, 118.8, 69.4, 48.1, 39.1, 21.5; TOFESMS m/z relative intensity 256 (MH^+ 95), 278 (MNa^+ 100), HRMS (+ES)calculated for $C_{12}H_{17}NO_3Si$: 256.1007 found 256.1012.

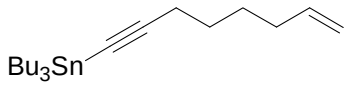


N-Toluenesulfonyl-2-(tert-Butyl-dimethyl-silanyloxy)pent-4-enylamine (**5-21**): A solution of alcohol **5-20** (1.50 g, 6.22 mmol) and DMF (20 mL) was cooled to 0°C. TBSCl (2.34 g, 15.5 mmol) and imidazole (2.12 g, 31.1 mmol) were added and the reaction solution was stirred at room temperature for 24 h. The reaction mixture was poured into water (40 mL) and extracted with hexanes (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. Purification through column chromatography on silica gel (4:1 hexanes:Et_2O) gave **5-21** (1.80 g, 78%) as a colorless oil. IR (neat): 3292, 1472, 1331, 1256, 1163, 1094 cm^{-1}; ^1H NMR (360 MHz, C_6D_6) δ 7.83 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 5.66 (m, 1H), 4.97 (m, 2H), 4.94 (t, *J* = 1.0 Hz, 1H), 3.69 (tt, *J* = 5.7, 5.6, 1H), 2.90 (m, 2H), 2.13 (m, 2H), 1.90 (s, 3H), 0.87 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.3, 136.7, 133.5, 129.6, 127.0, 118.1, 70.3, 47.6, 39.6, 25.7, 21.4, 17.9, -4.6,

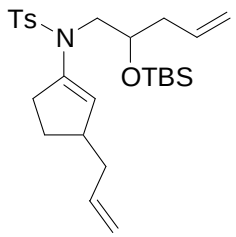
-4.9; TOFESMS m/z relative intensity 370 (MH^+ 100), HRMS (+ES) calculated for $C_{18}H_{32}NO_3SiS$: 370.1872, found 370.1856.



Trimethyl-oct-7-en-1-ynyl-silane (**5-22**): TMEDA (1.28 mL, 8.45 mmol) was added to a solution of 1-trimethylsilyl-propyne (**5-8**) (1.87 mL, 12.7 mmol) in Et_2O (10 mL) and the reaction solution was cooled to 0 °C. *n*-BuLi (3.71 mL, 2.5M hexanes, 9.3 mmol) was added dropwise and the reaction solution was stirred at 0 °C for 30 min. 5-Bromo-1-pentene (1.00 mL, 8.45 mmol) in Et_2O (3 mL) was added over a period of 90 min *via* syringe pump while maintaining the reaction temperature at 0°C. After two additional hours, the reaction mixture was poured into 1M H_3PO_4 (10 mL), and the aqueous portions were extracted with pentane (3 × 10 mL). The solvent was removed by distillation using a Vigreux column, and then the title compound was distilled as a colorless oil (943 mg, 62%, 66-68°C/ 5.8 torr). IR (neat): 2175, 1642, 1430 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.66 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 4.95 (m, 2H), 2.04 (m, 2H), 1.85 (m, 2H), 1.40-1.26 (m, 4H), 0.22 (s, 9H); (75 MHz, C_6D_6) δ 138.6, 114.7, 107.8, 84.6, 33.5, 28.3, 28.3, 20.0, 0.3; TOFEIMS *m/z* (relative intensity) 180 (M^+ 0.1), 165 (M^+-CH_3 30), 73 (TMS^+ 100), HRMS (+EI) calculated for $C_{10}H_{17}Si$: 165.1100, found 165.1096.



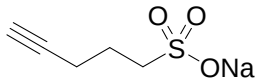
Tributyl-oct-7-en-1-ynyl-stannane (**5-23**): To a solution of alkynylsilane **5-22** (0.700 g, 3.88 mmol) in THF (40 mL) was added bis tributyltinoxide (0.854 mL, 1.75 mmol) and *n*-Bu_4NF (0.194 mL, 1M THF, 0.194 mmol). The reaction solution was heated to reflux and stirred for 3.5 h. The solvent was removed *in vacuo*, and the reddish brown oil was filtered through Celite with hexanes. The solvent was once again removed *in vacuo* and alkynylstannane **5-23** was isolated as a colorless oil which was used without further purification (1.26 g, 90%). IR neat 2150, 1641, 1463 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.73 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 4.97 (m, 2H), 2.17 (m, 2H), 1.90 (m, 2H), 1.77-1.60 (m, 6H), 1.48-1.32 (m, 10H), 1.01 (m, 6H), 0.93 (m, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 138.8, 114.6, 111.8, 81.6, 33.5, 29.4 ($J_{^{13}C\text{-}Sn}$ = 11.5 Hz), 28.8, 28.2, 27.4 ($J_{^{13}C\text{-}Sn}$ = 29.5 Hz), 20.4, 13.9, 11.2 ($J_{^{13}C\text{-}^{119}Sn}$ = 191.8 Hz, $J_{^{13}C\text{-}^{117}Sn}$ = 183.2 Hz).



N-(3-Allyl-cyclopent-1-enyl)-N-[2-(tert-butyl-dimethyl-silanyloxy)-pent-4-enyl]-4-methyl-benzenesulfonamide (**5-25**): To a solution of PhI(CN)OTf (286 mg, 0.755 mmol) in CH_2Cl_2 (3 mL) was added alkynylstannane **5-23** (300 mg, 0.755 mmol) in CH_2Cl_2 (5 mL) at -42 ºC. The reaction solution was stirred at this temperature for 3 h. The solvent was removed *in vacuo* while keeping the temperature below 0 ºC. The yellow

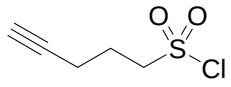
oil was washed with dry hexanes (3x10 mL) *via* syringe at 0 ºC and the residual solvent was pumped off leaving the alkynyliodonium salt as a white solid.

A solution of tosylamide **5-21** (254 mg, 0.686 mmol) in THF (65 mL) was cooled to -78 ºC, and *n*-BuLi (0.275 mL, 2.5M hexanes, 0.69 mmol) was added dropwise. The solution was then warmed to room temperature and a solution of the alkynyliodonium salt in THF (10 mL) was added over 30 min. The reaction solution was poured over a mixture of ice, brine (25 mL), Et_2O (25 mL), and hexanes (25 mL). The aqueous portions were extracted with Et_2O (25 mL), washed with brine and dried over Na_2SO_4. Purification through column chromatography on silica gel (4:1:1% hexanes:Et_2O:Et_3N) gave enamine **5-25** as a yellow oil (36 mg, 11%). IR neat 1639, 1406, 1355, 1166 cm^{-1}; ^1H NMR (360 MHz, C_6D_6) δ 7.69 (d, *J* = 6.75 Hz, 2H), 6.73 (d, *J* = 6.33 Hz, 2H), 5.95 (m, 1H), 5.63 (m, 1H), 5.47 (d, *J* = 12.4 Hz, 1H), 5.10, (m, 2H), 4.96 (m, 2H), 4.17 (m, 1H), 3.55 (m, 2H), 2.31-2.58 (m, 5H), 1.90 (m, 2H), 1.81 (s, 3H), 1.35 (m, 2H), 1.01 (s, 9 H), 0.23 (s, 3H), 0.12 (s, 3H); (90 MHz, C_6D_6) δ 143.0, 141.7, 137.3, 137.2, 134.8, 129.5, 128.0, 124.2, 117.8, 116.0, 71.4, 54.8, 43.3, 40.5, 40.2, 33.2, 28.8, 26.1, 21.1, 18.3, -4.2, -4.4; TOFESMS m/z relative intensity 476 (MH^+ 100), HRMS (+ES) calculated for $C_{26}H_{42}NO_3SiS$: 476.2655, found 476.2647.

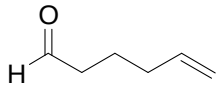


Pent-4-yne-1-sulfonic Acid, Sodium Salt (**5-27**): Sodium sulfite (94.5 g, 750 mmol) was added to a solution of 5-chloropent-1-yne (**5-26**) (55.1 g, 537 mmol) and *n*-Bu_4NI (13.9 g, 37.6 mmol) in EtOH (500 mL) and water (500 mL). The reaction mixture was refluxed for 3 days and then concentrated *in vacuo* to a white solid. The solid was

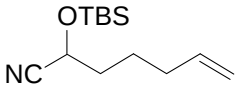
extracted with hot THF (3 × 500 mL) and the combined extracts were concentrated *in vacuo*. The white solid residue was recrystallized with hot ethanol and the supernatant was removed. The sulfonate salt was dried over P_2O_5 under reduced pressure leaving a white solid (67.4 g, 74 %). mp : (dec) 250 ºC; IR (KBr): 3278, 2114, 1447, 1221 cm^{-1}; ^1H NMR (300 MHz, MeOD) 2.90 (m, 2H), 2.34 (td, *J* = 7.1, 2.6 Hz, 2H), 2.25 (t, *J* = 2.6 Hz, 1H), 1.94 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 84.3, 71.3, 50.1, 24.3, 17.0; TOFESMS m/*z* relative intensity 147 (M^- 100), TOFHRMS (-ES) calculated for $C_5H_7O_3S$: 147.0116, found 147.0113.



Pent-4-ynesulfonyl Chloride (**5-28**): Phosphorus pentachloride (19.3 g, 92.6 mmol) was added in portions to a solution of sulfonate salt **5-27** (6.30 g, 37.0 mmol) in CH_2Cl_2 (74 mL) at 0 ºC. After 15 min the ice bath was removed and the solution was stirred at room temperature for 1 h. The reaction mixture was again cooled to 0 ºC, and ice was slowly added, which resulted in vigorous bubbling. The organic phase was washed with sat. aq. $NaHCO_3$ (2 × 200 mL) and brine (100 mL). The pink solution was dried with Na_2SO_4 and concentrated *in vacuo*. The red oil residue was purified through column chromatography on silica gel (3:1 hexane:Et_2O) to yield a colorless oil (3.75 g, 61%) which was used immediately. IR (neat): 3298, 2122, 1375, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (m, 2H), 2.48 (td, *J* = 6.5, 2.7 Hz, 2H), 2.27 (m, 2H), 2.10 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.9, 71.0, 63.7, 23.1, 16.5.

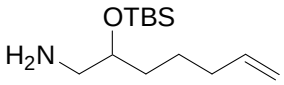


5-Hexenal (**5-30**): Pyridinium chlorochromate (72.9 g, 338 mmol) was added in portions to a solution of 5-hexenol (**5-29**) (24.9 g, 249 mmol) and 4Å molecular sieves in CH_2Cl_2 (1.25 L) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After diluting with Et_2O (1 L), the crude mixture was filtered through a pad of Celite and silica gel. The brown solution was concentrated *in vacuo* to approximately 50 mL, and filtered again to provide a green liquid. This residue was fractionally distilled to yield 5-hexenal (**5-30**) (12.2 g, 50%) as a colorless oil: at 42-44 ºC/ 30 torr; IR (neat): 1723, 1641, 1441, 1413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.6 Hz, 1H), 5.77 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.03 (m, 2H), 2.45 (td, *J* = 7.3, 1.7 Hz, 2H), 2.11 (m, 2H), 1.7 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 137.5, 115.5, 43.1, 32.9, 21.1; TOFESMS m/z relative intensity 54 (M^+- H_2CCHOH 100), 80 (M^+- H_2O 90), 97 (M^+- H 5), 98 (M^+ 4), HRMS (+ES) calculated for C_6H_9O: 97.0653, found 97.0653.



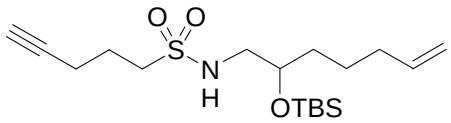
2-(tert-Butyl-dimethyl-silanyloxy)-hept-6-enenitrile (**5-31**): To a solution of 5-hexenal (**5-30**) (12.1 g, 123 mmol) in CH_3CN (616 mL) was added KCN (32.1 g, 493 mmol), ZnI_2 (787 mg, 2.47 mmol), and TBSCl (22.3 g, 148 mmol) in rapid succession. The reaction mixture was stirred overnight at room temperature. The solution was concentrated *in vacuo* and the residue was mixed with Et_2O (200 mL). The white precipitate was removed by filtration and washed twice with Et_2O. The filtrate was

concentrated *in vacuo* to a colorless oil (29.5 g, 100%), which was used without further purification. IR (neat): 1642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.18 (m, 2H), 4.43 (t, *J* = 6.3 Hz, 1H), 2.1 (m, 2H), 1.8 (m, 2H), 1.6 (m, 2H), 0.9 (s, 9H), 0.2 (s, 3H), 0.1 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 120.0, 115.3, 61.8, 35.6, 32.9, 25.5, 23.7, 18.0, -5.2, -5.4; $APCI^+$ m/*z* relative intensity 240 (MH^+ 85), HRMS (+AP) calculated for $C_{13}H_{26}NOSi$: 240.1784, found 240.1798.

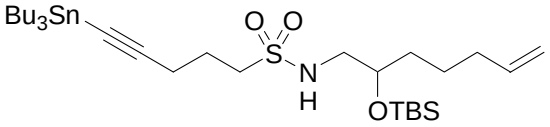


2-(tert-Butyl-dimethyl-silanyloxy)-hept-6-enylamine (**5-32**): Diisobutylaluminum hydride (216 mL, 1M hexane, 216 mmol) was added *via* addition funnel to a solution of cyanohydrin **5-31** (29.5 g, 123 mmol) in Et_2O (493 mL) at -78 ºC over a 20 min period. This solution was allowed to stir at -78 ºC for 4 h. MeOH (246 mL) was added *via* addition funnel over 20 min, quickly followed by $NaBH_4$ (9.32 g, 246 mmol). The reaction mixture was stirred overnight while slowly warming to room temperature. Water (1 L) was added and the mixture was extracted with Et_2O (3 × 300 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a colorless oil (29.9 g, 100%) which was used without further purification. IR (neat): 3383, 3298, 1641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 4.95 (ddt, *J* = 17.1, 1.8, 1.7 Hz, 1H), 4.90 (m, 1H), 3.57 (ddt, *J* = 5.7, 4.2, 1.5 Hz, 1H), 2.66 (dd, *J* = 13.0, 4.1 Hz, 1H), 2.57 (dd, *J* = 13.0, 5.6 Hz, 1H), 2.00 (m, 2H), 1.48-1.30 (m, 4H), 1.04 (s, 2H), 0.85 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 114.5, 73.8, 47.6, 34.2, 33.8, 25.9, 24.7, 18.1, -4.4, -4.5; TOFESMS m/z

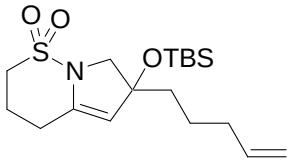
relative intensity 244 (MH^+ 100), HRMS (+ES) calculated for $C_{13}H_{30}NOSi$: 244.2097, found 244.2083.



Pent-4-yne-1-sulfonic Acid [2-(tert-Butyl-dimethyl-silanyloxy)-hept-6-enyl]-amide (**5-33**): Pent-4-ynesulfonyl chloride (1.23 g, 7.39 mmol) in DMF (5 mL) was added to a solution of amine **5-32** (1.80 g, 7.39 mmol) in DMF (10 mL) at 0 ºC, followed by the addition of Et_3N (1.03 mL, 7.39 mmol). The reaction mixture was stirred at room temperature for 3 h and then poured into ice water (20 mL) and Et_2O (20 mL). The organic layer was washed with water (3 × 10 mL) and brine (10 mL), and dried over $MgSO_4$. After the solvent was removed *in vacuo*, the crude material was purified through column chromatography on silica gel (3:1 hexanes:Et_2O) yielding sulfonamide **5-33** as a colorless oil (1.42 g, 51%). IR (neat): 3310, 1322, 1153 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.99 (m, 2H), 4.46 (t, 5.9 Hz, 1H), 3.81 (dddd, *J* = 11.3, 5.6, 5.4, 1.6 Hz, 1H), 3.22-3.13 (m, 3H), 3.05 (m, 1H), 2.38 (td, *J* = 6.9, 2.5 Hz, 2H), 2.10-1.98 (m, 5H), 1.53 (m, 2H), 1.40 (m, 2H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 114.9, 82.1, 71.1, 70.0, 51.1, 48.1, 34.1, 33.6, 25.8, 24.3, 22.6, 18.0, 17.2, -4.5, -4.6; TOFESMS m/z relative intensity 374 (MH^+ 100), HRMS (+ES) calculated for $C_{18}H_{36}NO_3SiS$: 374.2185, found 374.2169.



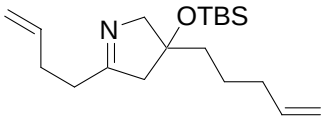
5-Tributylstannanyl-pent-4-yne-1-sulfonic Acid [2-(tert-Butyl-dimethyl-silanyloxy)-hept-6-enyl]-amide (**5-34**): *n*-BuLi (13.0 mL, 2.5 M in hexanes, 32.6 mmol) was added dropwise to a solution of alkyne **5-33** (5.80 g, 15.5 mmol) in THF (78 mL) at -78 ºC. After 20 min, tributyltin chloride (4.61 mL, 16.3 mmol) was added dropwise to the reaction mixture. The cold bath was removed and the reaction solution was allowed to stir for 2 h. The crude mixture was poured over ice, brine (30 mL), Et_2O (30 mL), and hexane (30 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic extracts were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (4:1:0.1 hexanes:Et_2O:Et_3N) with deactivated silica gel (20% water by weight) to give alkynylstannane **5-34** (9,60 g, 93%) as a yellow oil which was used immediately. IR (neat): 3312, 2149, 1463, 1256, 1152 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.1, 10.2, 6.7 Hz, 1H), 4.99 (m, 2H), 4.39 (t, J = 5.9 Hz, 1H), 3.82 (dtd, J = 6.0, 5.9, 3.9 Hz, 1H), 3.21-3.13 (m, 3H), 3.03 (m, 1H), 2.42 (t, J =6.8 Hz, 2H), 2.09-1.94 (m, 4H), 1.64-1.47 (m, 8H), 1.45-1.26 (m, 9H), 0.99-0.87 (m, 23H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.2, 114.9, 108.7, 84.0, 71.2, 51.4, 48.1, 34.2, 33.6, 28.9 ($J_{^{13}C\text{-}Sn}$ = 11.2 Hz), 27.0 ($J_{^{13}C\text{-}Sn}$ = 29.7 Hz), 25.8, 24.4, 23.3, 19.0, 18.0, 13.7, 11.0 ($J_{^{13}C\text{-}^{119}Sn}$ = 191.9 Hz, $J_{^{13}C\text{-}^{117}Sn}$ = 183.3 Hz)., -4.4, -4.5; TOFESMS m/*z* relative intensity 374 (MH^+ - Bu_3Sn, 70), 396 (100), 664 (MH^+, 68), 686 (MNa^+, 100), HRMS (+ES) calculated for $C_{30}H_{62}NO_3SiSSn$: 664.3242, found 664.3276.



6-(tert-Butyl-dimethyl-silanyloxy)-6-pent-4-enyl-3,4,6,7-tetrahydro-2H-pyrrolo[1,2-b][1,2]thiazine 1,1-dioxide (**5-36**): A solution of alkynylstannane **5-34** (120 mg, 0.181 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of PhI(CN)OTf (69 mg, 0.18 mmol) in CH_2Cl_2 (0.4 mL) at -42 ºC. The reaction solution was stirred at -42 ºC for 45 min by which time all the solid had dissolved. The solvent was removed with a high vacuum pump while maintaining the temperature below 0 ºC. The solid residue was dissolved in cold Et_2O (1 mL) at -42 ºC and the alkynyliodonium salt was precipitated with cold hexanes (5 mL). This sticky solid was washed with cold hexanes (2 × 5 mL) and the residual solvent was removed *in vacuo* below 0 ºC.

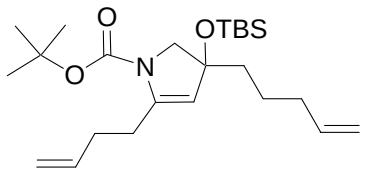
The iodonium salt was dissolved in DME (0.9 mL) at -42 ºC, and LHMDS (181 μL, 1M THF, 0.181 mmol) was added. The cold bath was removed and the reaction solution was stirred at room temperature for 30 min. At that time the solution was poured over ice, brine (5 mL), Et_2O (5 mL), and hexanes (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified through column chromatography on silica gel (3:1:0.1 hexanes:Et_2O:Et_3N) with a jacketed column at -78 ºC, and deactivated silica gel (20% water) to afford bicycle **5-36** as a white solid (37 mg, 58%), mp = 80–83ºC. Dihydropyrrole **5-36** decomposed to pyrrole **5-37** upon exposure to silca gel under normal conditions. **5-36**: IR (neat): 1641, 1316, 1117 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H),

5.06 (s, 1H), 4.98 (m, 2H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.53 (d, *J* = 11.6 Hz, 1H), 3.22 (m, 2H), 2.54 (dt, *J* = 9.7, 5.5 Hz, 1H), 2.40 (m, 1H), 2.21 (m, 2H), 2.05 (td, *J* = 7.1, 6.9 Hz, 2H), 1.65 (m, 2H), 1.48 (m, 2H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 139.0, 115.7, 115.1, 83.1, 56.3, 49.3, 42.1, 34.3, 26.2, 24.8, 23.8, 21.8, 18.4, -5.8, -6.6; TOFESMS m/*z* relative intensity 240 (M – OTBS 54), 394 (MNa^+ 100), HRMS (+ES) calculated for $C_{18}H_{33}NO_3SiSNa$: 394.1848, found 394.1817. **5-37**: IR (neat): 1640, 1442, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 5.93 (s, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 4.99 (m, 2H), 3.44 (m, 2H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.52-2.36 (m, 4H), 2.08 (td, *J* = 7.4, 6.7 Hz, 2H), 1.64 (pent, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 132.2, 128.5, 114.7, 112.7, 111.6, 50.2, 33.2, 29.2, 26.1, 22.6, 21.9; TOFESMS m/*z* relative intensity 240 (MH^+ 40), 262 (MNa^+ 100), HRMS (+ES) calculated for $C_{18}H_{33}NO_3SiSNa$: 394.1848, found 394.1817.



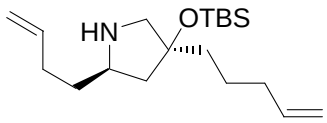
5-But-3-enyl-3-(tert-butyl-dimethyl-silanyloxy)-3-pent-4-enyl-3,4-dihydro-2H-pyrrole (**5-41**): A solution of diiodomethane (401 μL, 4.97 mmol) in THF (1 mL) was added to isopropylmagnesium chloride (11.6 mL, 0.43M THF, 5.0 mmol) at -78 ºC over 5 min and the reaction solution was stirred at -78 ºC for 40 min. *n*-BuLi (365 μL, 2.5 M hexanes, 0.92 mmol) was added dropwise *via* cannula to a solution of sulfonamide **5-36** (308 mg, 0.829 mmol) and THF (4 mL) at -78 ºC. This solution was stirred at -78 ºC for 40 min and then added dropwise to the Grignard solution over 5 min at -78 ºC. The cold bath was removed and the reaction mixture was stirred at room temperature for 3 h.

This solution was poured over ice, brine (15 mL) and hexanes (15 mL), and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (2:1:0.1 hexanes:Et_2O:Et_3N) with a jacketed column at -78 ºC to afford imine **5-41** as a colorless oil (154 mg, 58%) IR (neat): 1641 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 5.87 (ddt, *J* = 17.2, 10.2, 6.5 Hz, 1H), 5.77 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.09-4.96 (m, 4H), 4.00 (d, *J* = 16.1 Hz, 1H), 3.60 (d, *J* = 16.1 Hz, 1H), 2.40 (m, 2H), 2.33 (d, *J* = 17.5 Hz, 1H), 2.26 (m, 2H), 2.08 (d, *J* = 17.4 Hz, 1H), 1.95 (m, 2H), 1.50-1.35 (m, 4H), 0.94 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 138.6, 137.6, 115.1, 114.7, 83.2, 72.8, 51.5, 40.7, 34.0, 33.5, 30.1, 25.7, 24.2, 18.1, -2.8, -2.9; TOFESMS m/z relative intensity 322 (MH^+ 100), HRMS (+ES) calculated for $C_{19}H_{36}NOSi$: 322.2566, found 322.2556.



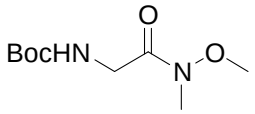
5-But-3-enyl-3-(tert-butyl-dimethyl-silanyloxy)-3-pent-4-enyl-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (**5-42**): Imine **5-41** (243 mg, 0.756 mmol) in THF (10 mL) was added to a solution of Boc_2O (275 mg, 1.26 mmol) in THF (3 mL) at 0 ºC. 2,6-Lutidine (147 μL, 1.26 mmol) was then added. The reaction mixture was stirred overnight while slowly warming to room temperature. The reaction mixture was poured into brine (10 mL) and hexanes (10 mL). The organic layer was dried over Na_2SO_4 and

the solvent was removed *in vacuo*. Purification through column chromatography on silica gel in a jacketed column at -78ºC (9:1 hexanes:Et_2O) yielded the pyrrolidine as an orange oil (189 mg, 60%). IR (neat): 1715, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 16.9, 10.3, 6.4 Hz, 1H), 5.79 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H), 5.00 (m, 4H), 4.83 (s, 1H), 3.66 (d, *J* = 12.6 Hz, 1H), 3.57 (d, *J* = 12.5 Hz, 1H), 2.64 (m, 2H), 2.27 (m, 2H), 2.06 (m, 2H), 1.63-1.41 (m, 13H), 0.84 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 139.3, 139.3, 138.2, 115.4, 115.2, 114.9, 80.7, 77.6, 62.1, 42.1, 34.4., 32.2, 28.8, 28.5, 26.2, 23.9, 18.6, -1.8, -3.0; TOFESMS m/z relative intensity 290 (M^+–OTBS 100), 422 (M^+ 31), 444 (MNa^+ 50), HRMS (+ES) calculated for $C_{24}H_{44}NO_3Si$: 422.3090, found 422.3125.

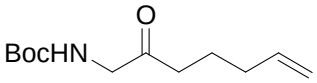


2-But-3-enyl-4-(tert-butyl-dimethyl-silanyloxy)-4-pent-4-enyl-pyrrolidine. (**5-43**): Lithium aluminum hydride (1.43 mL, 1M THF, 1.43 mmol) was added to imine **5-41** (153 mg, 0.476) in THF (1 mL) at -78ºC. This solution was warmed to room temperature and stirred for 2 h. Ice was added to the reaction solution and the crude mixture was extracted with CH_2Cl_2 (5 × 1 mL). The organics were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the residue through column chromatography on silica gel (1:1 hexanes:Et_2O) gave **5-43** (45 mg, 29%) and **5-44** (4 mg, 3%). IR (neat): 3077, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 2H), 4.98 (m, 4H), 3.00 (m, 1H), 2.91 (d, *J* = 11.8 Hz, 1H), 2.63 (d, *J* = 11.7 Hz, 1H), 2.21-1.98 (m, 5H), 1.93 (dd, *J* = 13.1, 7.8 Hz, 1H), 1.75-1.41 (m, 7H), 0.87 (s, 9H), 0.09 (s, 6H);^{13}C NMR (75 MHz,

$CDCl_3$) δ 138.6, 138.4, 114.6, 114.5, 84.8, 59.7, 58.7, 46.6, 39.7, 35.9, 34.1, 31.5, 25.9, 23.8, 18.1, -2.3, -2.3; TOFESMS m/*z* relative intensity 324 (MH^+ 100), HRMS (+ES) calculated for $C_{19}H_{38}NOSi$: 324.2723, found 324.2711.

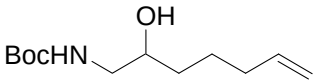


[(Methoxy-methyl-carbamoyl)-methyl]-carbamic Acid tert-Butyl Ester (**5-46**): To a -15 ºC solution of N-Bocglycine (**5-45**) (25.0 g, 143 mmol) and N-methylmorpholine (34.5 mL, 314 mmol) in CH_2Cl_2 (1 L) was added isobutyl chloroformate (21.0 mL, 162 mmol) and this reaction solution was stirred at -15 ºC for 15 min. N,O-Dimethylhydroxylamine·HCl (13.9 g, 143 mmol) was added and the reaction mixture was stirred for 15 min at -15 ºC then warmed to room temperature and stirred overnight. The reaction mixture was poured into aq. $KHSO_4$ (1 L, 0.2 M) and the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the solid was recrystallized from CH_2Cl_2 and hexanes to give white needle crystals (31.0 g, 100%). IR (neat): 3287, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.25 (s, 1H), 4.08 (d, *J* = 4.7 Hz, 2H), 3.81 (s, 3H), 3.19 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 155.9, 79.6, 61.5, 41.8, 32.4, 28.4; TOFESMS m/*z* relative intensity 219 (MH^+ 25), 241 (MNa^+ 100), HRMS (+ES) calculated for $C_9H_{19}N_2O_4$: 219.1345, found 219.1331.



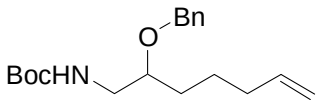
(2-Oxo-hept-6-enyl)-carbamic Acid tert-Butyl Ester (**5-47**): A solution of 4-pentenylmagnesium bromide was prepared by the addition of magnesium turnings (3.42 g, 141 mmol) to 5-bromo-pent-1-ene (12.0 mL, 96.3 mmol) in Et_2O (96 mL) at -5 ºC.

i-PrMgCl (36.3 mL, 1M THF, 36.3 mmol) was added to Weinreb amide **5-46** (16.2 g, 74.0 mmol) in THF (378 mL) at 0 ºC. After this solution was stirred for 5 min, the 4-pentenylmagnesium bromide solution was added and the reaction mixture was allowed to warm to room temperature and stir for 3 h. The reaction mixture was cooled again to 0 ºC and ice water was added. The crude mixture was neutralized with 1M H_3PO_4. The aqueous layer was extracted CH_2Cl_2 (3 × 200 mL) and the combined organic extracts were washed with brine (200 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to leave the ketone as a colorless oil (12.1 g, 74%) IR (neat): 3370, 1712, 1504 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (ddt, J = 17.1, 11.0, 6.7 Hz, 1H), 5.26 (s, 1H), 4.99 (m, 2H), 4.00 (d, J = 4.2 Hz, 2H), 2.44 (m, 2H), 2.07 (m, 2H), 1.72 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 155.6, 137.5, 115.5, 79.8, 50.3, 39.1, 32.9, 28.3, 22.5; TOFESMS m/z relative intensity 128 (MH^+– Boc 100), 228 (MH^+ 8), 250 (MNa^+ 78), HRMS (+ES) calculated for $C_{12}H_{22}NO_3$: 228.1600, found 228.1597.



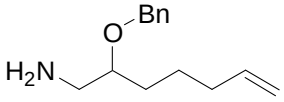
(2-Hydroxy-hept-6-enyl)-carbamic Acid tert-Butyl Ester (**5-48**): $NaBH_4$ (1.75 g, 46.2 mmol) was added to ketone **5-47** (10.5 g, 46.2 mmol) in MeOH (460 mL) at 0 ºC.

This solution was stirred at 0 ºC for 45 min. At that time the reaction solution was poured into ice water (500 mL) and neutralized with 1M H_3PO_4. The crude mixture was extracted with Et_2O (4 × 200 mL) and the combined extracts were washed with brine (200 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, leaving the alcohol (8.11 g, 77%) as a colorless oil. IR (neat): 3371, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.1, 11.0, 6.7, 1H), 5.06-4.86 (m, 3H), 3.69 (m, 1H), 3.30 (m, 1H), 3.01 (ddd, *J* = 14.0, 7.6, 5.7, 1H), 2.38 (s, 1H), 2.06 (m, 2H), 1.59-1.41 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 138.4, 114.7, 79.6, 71.4, 46.6, 34.1, 33.6, 28.3, 24.7; TOFESMS m/z relative intensity 130 (MH^+– Boc 100), 174 (MH^+– *t*Bu 72), 230 (MH^+ 8), 252 (MNa^+ 72), HRMS (+ES) calculated for $C_{12}H_{24}NO_3$: 230.1756, found 230.1769.

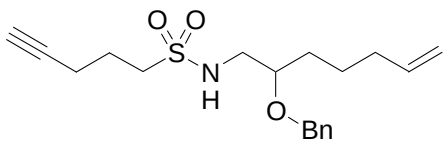


(2-Benzyloxy-hept-6-enyl)-carbamic Acid tert-Butyl Ester. (**5-49**): Alcohol **5-48** (6.72 g, 29.3 mmol) in THF (93 mL) was added to a suspension of NaH (1.29 g, 32.2 mmol, 60% in mineral oil) in THF (200 mL) at 0 ºC. The resulting solution was stirred for 5 min at 0 ºC and benzyl bromide (4.27 mL, 35.2 mmol) was added, followed by *n*-Bu_4NI (2.16 g, 5.86 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h. The crude mixture was poured into ice water (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (300 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude material was purified by column

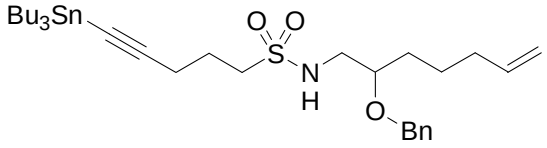
chromatography on silica gel (2:1, hexanes: Et_2O) to provide the title compound (5.36 g, 57%) as a colorless oil. IR (neat): 3357, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 5.77 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 4.98 (m, 2H), 4.84 (s, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6, 1H), 3.48 (m, 1H), 3.37 (m, 1H), 3.12 (dt, *J* = 13.9, 5.9 Hz, 1H), 2.04 (m, 2H), 1.64-1.46 (m, 4H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 138.3, 128.3 (2C), 127.7, 127.6, 114.7, 79.0, 77.8, 71.1, 43.1, 33.6, 31.2, 28.3, 24.4; TOFESMS m/*z* relative intensity 264.2 (MH^+-*t*Bu 46), 320.2 (MH^+ 100), 342.2 (MNa^+ 72), HRMS (+ES) calculated for $C_{19}H_{30}NO_3S$: 320.2226, found 320.2213.



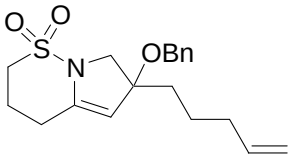
2-Benzyloxy-hept-6-enylamine (**5-50**): A solution of carbamate **5-49** (5.32 g, 16.7 mmol) in CH_2Cl_2 (167 mL) was cooled to 0 ºC. Trifluoroacetic acid (13.1 mL, 167 mmol) was added and the reaction solution was stirred for 5 min. The reaction mixture was then warmed to room temperature and stirred for 3 h. The solution was poured into ice and sat. aq. Na_2HCO_3 (150 mL) and the aqueous portion was extracted with CH_2Cl_2 (3 × 150 mL). The solvent was removed *in vacuo* to give amine **5-50** (3.54 g, 97%) as a colorless oil. IR (neat): 3066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 6.80 (s, 2H), 5.74 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 4.97 (m, 2H), 4.51 (d, *J* = 11.3Hz, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 3.57 (m, 1H), 2.89 (m, 1H), 2.74 (m, 1H), 2.01 (m, 2H), 1.58 (m, 1H), 1.46 (m, 1H), 1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.7, 128.4, 127.9, 127.8, 115.0, 76.1, 71.2, 42.7, 33.5, 30.6, 23.7; TOFESMS m/*z* relative intensity 220 (MH^+ 100), HRMS (+ES) calculated for $C_{14}H_{22}NO$: 220.1701, found 220.1683.



Pent-4-yne-1-sulfonic Acid (2-Benzyloxy-hept-6-enyl)-amide (**5-51**): Pentynesulfonyl chloride (**5-28**) (3.38 g, 20.3 mmol) was added to a solution of amine **5-50** (3.44 g, 15.7 mmol) in DMF (26 mL) at 0 ºC. Et_3N (3.06 mL, 22.0 mmol) was added slowly, forming a white slurry. The reaction solution was stirred at room temperature for 2 h before the addition of 1M H_3PO_4 (30 mL). The organics were washed with water (2 × 30 mL) and the combined aqueous fractions were extracted with Et_2O (1 × 30 mL). The crude organic mixture was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification through column chromatography on silica gel (3:1 hexanes:Et_2O) gave sulfonamide **5-51** (3.41 g, 62%) as a colorless oil. IR (neat): 3294, 2118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.00 (m, 2H), 4.72 (t, *J* = 6.0 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 3.54 (m, 1H), 3.31 (ddd, *J* = 13.2, 6.9, 3.6 Hz, 1H), 3.13-3.02 (m, 3H), 2.29 (td, *J* = 6.8, 2.61 Hz, 2H), 2.06 (m, 2H), 2.00 (t, *J* = 2.6 Hz, 1H), 1.94 (m, 2H), 1.66 (m, 1H), 1.59-1.38 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 128.4, 127.8 (2C), 114.9, 82.1, 77.7, 71.3, 69.9, 51.2, 45.7, 33.5, 30.8, 24.2, 22.5, 17.1; TOFESMS m/z relative intensity 350 (MH^+ 58), 367 (MNH_4^+ 100), 372 (MNa^+ 80), HRMS (+ES) calculated for $C_{14}H_{28}NO_3S$: 350.1790, found 350.1784.



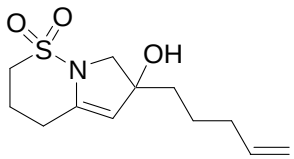
5-Tributylstannanyl-pent-4-yne-1-sulfonic acid (2-benzyloxy-hept-6-enyl)-amide (**5-52**): *n*-BuLi (1.38 mL, 2.4M hexanes, 3.3 mmol) was added to a solution of alkyne **5-51** (550 mg, 1.57 mmol) in THF (8 mL) at -78ºC. After stirring this solution for 10 min, Bu_3SnCl (467 μL, 1.65 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured into ice and brine (10 mL), and the aqueous layer was extracted with Et_2O (3 × 10 mL). The crude organic phases was washed with brine (10 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo*. Purification through column chromatography on silica gel (3:1:.05 hexanes: Et_2O:Et_3N) on deactivated silica gel (20% water) yielded the alkynylstannane **5-52** (772 mg, 77%) as a colorless oil. IR (neat) 3290, 2149 cm^{-1};^{1}H NMR (300 MHz, C_6D_6) δ 7.31-7.07 (m, 5H), 5.73 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 5.01 (m, 2H), 4.72 (dd, *J* = 6.2, 6.1 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 4.30 (d, *J* = 11.7 Hz, 1H), 3.27 (m, 1H), 3.14 (ddd, *J* = 13.4, 6.6, 3.9 Hz, 1H), 3.00-2.82 (m, 3H), 2.10 (t, *J* = 6.8 Hz, 2H), 1.98-1.79 (m, 4H), 1.70-1.57 (m, 6H), 1.43-1.27 (m, 10H), 0.90 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 139.1 138.9, 128.8, 128.3, 128.1, 115.2, 110.0, 83.6, 78.4, 71.7, 52.0, 46.2, 34.2, 31.5, 29.5 ($J_{^{13}C\text{-}Sn}$ = 11.6 Hz), 27.6 ($J_{^{13}C\text{-}Sn}$ = 29.5 Hz), 24.8, 24.0, 19.4, 14.1, 11.4 ($J_{^{13}C\text{-}^{119}Sn}$ = 191.6 Hz, $J_{^{13}C\text{-}^{117}Sn}$ = 183.1 Hz); TOFESMS m/z relative intensity 640 (MH^+ 81), 662 (MNa^+ 100), HRMS (+ES) calculated for $C_{31}H_{54}NO_3SSn$: 640.2846, found 640.2892.



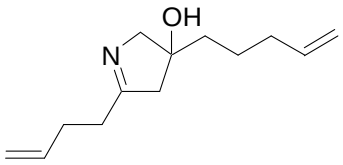
6-Benzyloxy-6-pent-4-enyl-3,4,6,7-tetrahydro-2H-pyrrolo[1,2-b][1,2]thiazine 1,1-Dioxide (**5-53**): A solution of alkynylstannane **5-52** (2.00 g, 3.13 mmol) in CH_2Cl_2 (16 mL) was added to a slurry of PhI(CN)OTf in CH_2Cl_2 (15 mL) at -42ºC. The reaction solution was stirred for 45 min, at which point all the solid dissolved. The solvent was evaporated *in vacuo* while maintaining the temperature below 0 ºC. The residue was dissolved in cold Et_2O (5 mL) at -42 ºC and the alkynyliodonium salt was precipitated with cold hexanes (20 mL) at -42 ºC. This sticky solid was washed with cold hexanes (2 × 20 mL) and the residual solvent was removed *in vacuo* below 0 ºC.

The iodonium salt was dissolved in DME (31 mL) and LHMDS (3.13 mL, 1.0 M THF, 3.1 mmol) was added at -42 ºC. The cold bath was removed and the reaction solution was stirred at room temperature for 30 min. The solution was poured into ice, brine (30 mL), Et_2O (30 mL), and hexanes (30 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (3:1:0.1 hexanes: Et_2O:Et_3N) with a jacketed column at -78 ºC, and deactivated silica gel (20% water) to afford bicycle **5-53** as a sticky white solid (560 mg, 51%). IR (neat): 1662, 1454 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.34-7.03 (m, 5H), 5.71 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 4.98 (m, 2H), 4.62 (t, *J* = 1.2 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 3.62 (d, *J* = 12.5 Hz, 1H), 2.47 (m, 2H), 1.90 (m, 2H), 1.74-1.61 (m, 4H), 1.51-1.32 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 146.4, 140.2, 138.7, 128.4, 127.5, 127.5, 114.9,

111.8, 86.1, 65.2, 51.5, 48.8, 39.9, 34.2, 24.1, 23.6, 21.5; TOFESMS m/z relative intensity 240 (MH^+–BnOH 54), 370 (MNa^+ 100), HRMS (+ES) calculated for $C_{19}H_{25}NNaO_3S$: 370.1453, found 370.1452.

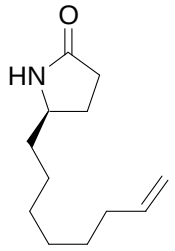


6-Hydroxy-6-pent-4-enyl-3,4,6,7-tetrahydro-2H-pyrrolo[1,2-b][1,2]thiazine 1,1-dioxide (**5-55**): A solution of silyl ether **5-36** (1.20 g, 3.23 mmol) and THF (32 mL) was cooled to 0 ºC. *n*-Bu_4NF (42.0 mL, 1.0 M THF, 42.0 mmol) was added slowly over 15 min, and the solution was warmed to room temperature and stirred for 3 h. The mixture was filtered through Celite and silica gel, and the solvent was removed *in vacuo*. The crude material was purified through column chromatography on silica gel (4:1 hexanes:EtOAc) with a jacketed column at -78 ºC, and deactivated silica gel (20% water) to afford alcohol **5-55** as a yellow oil (768 mg, 92%). IR (neat): 3502 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.73 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.01 (m, 2H), 4.92 (s, 1H), 3.84 (d, *J* = 12.7 Hz, 1H), 3.41 (d, *J* = 12.7 Hz, 1H), 2.76 (s, 1H), 2.59 (m, 2H), 1.93 (m, 2H), 1.85 (m, 1H), 1.70 (m, 1H), 1.62-1.25 (m, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 144.9, 138.8, 117.5, 114.8, 80.8, 56.6, 48.7, 38.4, 34.2, 24.4, 24.0, 22.0; TOFESMS m/z relative intensity 240 (MH^+–OH 100), 258 (MH^+ 10), HRMS (+ES) calculated for $C_{12}H_{20}NO_3S$: 258.1164, found 258.1175.

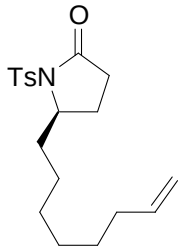


5-But-3-enyl-3-pent-4-enyl-3,4-dihydro-2H-pyrrol-3-ol (**5-56**): To a solution of diiodomethane (492 μL, 6.11 mmol) in THF (1 mL) was added to isopropylmagnesium chloride (8.05 mL, 0.87 M THF, 6.1 mmol) at -78 ºC over 5 min, and and this reaction solution was stirred at this temperature for 1 h. *n*-BuLi (855 μL, 2.5 M hexanes, 2.1 mmol) was added dropwise to a solution of sulfonamide **5-55** (262 mg, 1.02 mmol) in THF (12 mL) at -78 ºC. This solution was stirred at -78 ºC for 1 h and then added dropwise *via* cannula to the Grignard solution over 5 min at -78 ºC. The cold bath was removed and the reaction mixture was stirred at room temperature for 3 h. This solution was poured into ice, brine (15 mL), and hexanes (15 mL) and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (1:0.1 Et_2O:Et_3N) with a jacketed column at -78 ºC to afford imine **5-56** (80 mg, 38%) as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6) δ 5.83 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.12-4.94 (m, 4H), 4.28 (s, 1H), 2.82 (d, *J* = 10.8 Hz, 1H), 2.45 (d, *J* = 10.8 Hz, 1H), 2.40-2.08 (m, 4H), 2.08-1.90 (m, 4H), 1.68-1.54 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 183.5, 139.1, 139.0, 114.8, 114.7, 54.7, 51.3, 47.8, 40.1, 34.8, 34.6, 31.2, 23.4; TOFESMS m/*z* relative intensity 208 (MH^+ 22).

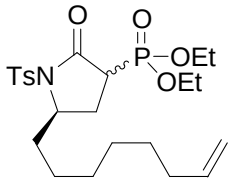
6.3 Horner-Wadsorth-Emmons route.



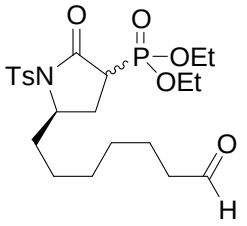
5-Oct-7-enyl-pyrrolidin-2-one (**5-65**): Magnesium turnings (650 mg, 26.7 mmol) were flame dried and 1-bromo-6-heptene (**5-64**) (3.06 mL, 20.1 mmol) was added to the magnesium suspended in THF (60 mL). This mixture was stirred at room temperature for 30 min and added *via* cannula to a solution of (*S*)-5-(hydroxymethyl)-2-pyrrolidinone *p*-toluenesulfonate (**5-60**) (1.80 g, 6.68 mmol) in THF (60 mL) at -78°C. Dilithium tetrachlorocuprate (3.34 mL, 0.1 M THF, 0.3 mmol) was added and the solution was kept at -78°C for 3 h and then allowed to warm to room temperature while stirring overnight. To the reaction mixture was added sat. aq. NH_4Cl and the aqueous portion was extracted with EtOAc (3 × 100 mL). The crude organic phases were washed with brine (100 mL) and dried over Na_2SO_4 to give alkyated lactam **5-65** (1.16 g), which was used without further purification. $[\alpha]^{20}_D$ = 7.8 (c = 2.54, MeOH). IR (neat): 3205, 1697 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.97 (s, 1H), 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.97 (m, 2H), 3.62 (tt, *J* = 6.7, 6.6 Hz, 1H), 2.34 (m, 2H), 2.22 (m, 1H), 2.04 (m, 2H), 1.69 (m, 1H), 1.58–1.25 (m, 10H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.4, 138.9, 114.2, 54.6, 36.7, 33.6, 30.3, 29.3, 28.9, 28.7, 27.2, 25.7; TOFESMS m/z relative intensity 196 (MH^+ 83), 218 (MNa^+ 100), HRMS (+ES) calculated for $C_{12}H_{22}NO$: 196.1701, found 196.1695.



5-Oct-7-enyl-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**5-66**): Lactam **5-65** (1.11 g, 5.69 mmol) was cooled to -78°C in THF (40 mL). *n*-BuLi (2.61 mL, 2.4 M hexane, 6.3 mmol) was added and the solution was stirred for 1 h. Tosyl chloride (2.71 g, 14.2 mmol) was added in THF (17 mL) and the reaction mixture was warmed to room temperature and stirred overnight. Sat. aq. NH_4Cl was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The crude organic phases was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (2:1 hexanes:Et_2O) to yield tosylated lactam **5-66** (1.14 g, 57% over two steps) as a yellow oil. $[\alpha]^{20}_D$ = -48.7 (c = 0.78, MeOH). IR (neat): 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 5.81 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H), 4.98 (m, 2H), 4.39 (m, 1H), 2.52 (ddd, *J* = 17.6, 11.2, 9.1 Hz, 1H), 2.43 (s, 3H), 2.34 (ddd, *J* = 17.6, 9.4, 2.3 Hz, 1H), 2.18 (m, 1H), 2.04 (m, 2H), 1.95 (m, 1H), 1.85 (ddt, *J* = 12.8, 8.9, 1.9 Hz, 1H), 1.65 (m, 1H), 1.43–1.21 (m, 8H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.5, 144.8, 138.4, 136.0, 129.4, 128.2, 114.3, 60.4, 34.5, 33.6, 30.8, 29.1, 28.9, 28.7, 25.0, 23.5, 21.6; TOFESMS m/*z* relative intensity 350 (MH^+ 78), 372 (MNa^+ 100), HRMS (+ES) calculated for $C_{19}H_{28}NO_3S$: 350.1790, found 350.1795.

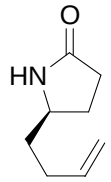


[5-Oct-7-enyl-2-oxo-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-phosphonic Acid Diethyl Ester (**5-67**): A solution of diisopropylamine (0.633 mL, 4.50 mmol) and Et_2O (10 mL) was cooled to -78°C and *n*-BuLi (1.80 mL, 2.5 M hexane, 4.5 mmol) was added dropwise to this mixture. This solution was stirred at -78°C for 45 min. Lactam **5-66** (1.43 g, 4.09 mmol) was added in Et_2O (1 mL) and the solution was kept at -78°C for 1 h. Diethyl chlorophosphite (0.491 mL, 4.50 mmol) was added and the reaction mixture was allowed to warm to 0°C and stirred for an additional 2 h. AcOH (16.4 mL, 1.0 M Et_2O, 16.4 mmol) was added and the mixture was filtered through Celite. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (9:1 EtOAc:CH_3CN) to yield a yellow oil, phosphate **5-67** (670 mg, 34%), as an inseparable mixture of diastereomers. The spectral data given for **5-67** corresponds to the major diastereomer. IR (neat): 1730, 1362 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.80 (m, 1H), 4.94 (m, 2H), 4.40 (tt, J = 5.7, 2.8 Hz, 1H), 4.16-4.00 (m, 4H), 3.06 (m, 1H), 2.50 (m, 1H), 2.42 (s, 3H), 2.10-2.00 (m, 4H), 1.60 (m, 1H), 1.39-1.21 (m, 14H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.1 ($J_{^{13}C\text{-}P}$ = 2.7 Hz), 144.9, 138.7, 135.5, 129.3, 128.4, 114.2, 63.0 ($J_{^{13}C\text{-}P}$ = 6.3 Hz), 62.8 ($J_{^{13}C\text{-}P}$ = 5.9 Hz), 58.9, 40.3 ($J_{^{13}C\text{-}P}$ = 146.4 Hz), 34.7, 33.5, 29.0, 28.8, 28.6, 26.0, 24.6, 21.5, 16.1 (2C); ^{31}P NMR (147 MHz, $CDCl_3$) δ 21.1; TOFESMS m/z relative intensity 486 (MH^+ 27), 503 (MNH_4^+ 100), 508 (MNa^+ 80), HRMS (+ES) calculated for $C_{23}H_{37}NO_6PS$: 486.2079, found 486.2082.

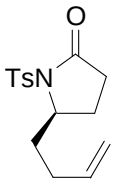


[2-Oxo-5-(7-oxo-heptyl)-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-phosphonic Acid Diethyl Ester (**5-59**): A solution of phosphate **5-67** (200 mg, 0.412 mmol) and CH_2Cl_2 (4 mL) was cooled to -78°C. Ozone was bubbled through this solution for 30 min until a blue color persisted. The reaction mixture was stirred for an additional 30 min and the reaction vessel was purged with nitrogen. Dimethylsulfide (0.303 mL, 4.12 mmol) was added and the solution was slowly warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and purification of the crude material through column chromatography on silica gel (EtOAc) yielded aldehyde **5-59** (93 mg, 46%) as a colorless oil. IR (neat): 1728, 1361 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (td, J = 1.7, 0.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 4.50 (m, 1H), 4.18-3.95 (m, 4H), 3.08 (dt, J = 23.1, 9.5 Hz, 1H), 2.55-2.44 (m, 3H), 2.43 (s, 3H), 2.20 (m, 1H), 2.05 (m, 2H), 1.64 (m, 2H), 1.35-1.29 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 168.2 ($J_{^{13}C\text{-}P}$ = 2.7 Hz), 145.1, 135.5, 129.4, 128.5, 63.2 ($J_{^{13}C\text{-}P}$ = 6.7 Hz), 62.9 ($J_{^{13}C\text{-}P}$ = 6.6 Hz), 58.9, 43.8 ($J_{^{13}C\text{-}P}$ = 146.5 Hz), 34.8, 29.0, 26.1, 25.0, 24.6, 21.8, 21.6, 16.3 ($J_{^{13}C\text{-}P}$ = 2.6 Hz), 16.3 ($J_{^{13}C\text{-}P}$ = 2.6 Hz); TOFESMS m/*z* relative intensity 488 (MH^+ 21), 352 (MH_2^+-$PO(OEt)_2$ 93), 279 (M+-$PO(OEt)_2$-$(CH_2)_3CHO$ 100), HRMS (+ES) calculated for $C_{22}H_{35}NO_7PS$: 488.1872, found 488.1847.

6.4 Ring closing metathesis route.

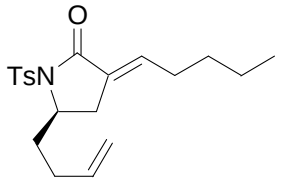


5-But-3-enyl-pyrrolidin-2-one (**5-70**): A solution of tosylate **5-60** (18.4 g, 68.3 mmol) in THF (134 mL) was cooled to 0°C. AllylMgBr (150 mL, 1.0M Et_2O, 15 mmol) was added and the reaction solution was heated to reflux and stirred for 4 h. The crude mixture was then cooled to 0°C and sat. aq. NH_4Cl was added. The aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organics were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave the title compound as a brown oil (8.15 g, 86%) which was used without further purification. $[\alpha]^{20}_D$ = 26.0 (c = 1.00, MeOH). IR (neat): 3207, 1694, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 5.80 (ddt, *J* = 17.1, 11.0, 6.6 Hz, 1H), 5.06 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 4.99 (m, 1H), 3.66 (pent, *J* = 6.7 Hz, 1H), 2.34 (m, 2H), 2.25 (m, 1H), 2.13 (m, 2H), 1.75–1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 137.6, 115.3, 54.3, 35.9, 30.4, 30.2, 27.2; TOFESMS m/z relative intensity 140 (MH^+ 53), 162 (MNa^+ 100), HRMS (+ES) calculated for $C_8H_{14}NO$: 140.1075, found 140.1078.



N-Tosyl-5-but-3-enyl-pyrrolidin-2-one (**5-69**): *n*-BuLi (1.38 mL, 2.4M hexanes, 3.3 mmol) was added to a solution of lactam **5-70** (420 mg, 3.02 mmol) in THF (20 mL)

at -78°C. After this solution was stirred at -78°C for 45 min, a solution of TsCl (863 mg, 4.53 mmol) in THF (10 mL) was added. The reaction solution was allowed to warm to room temperature and was stirred for 6 h. The reaction mixture was poured into sat. aq. NH_4Cl and the aqueous portion was extracted with EtOAc (3 × 30 mL). After these extracts were washed with brine (30 mL) and dried over Na_2SO_4, the solvent was removed *in vacuo*. The crude mixture was purified through column chromatography on silica gel (1:1 hexanes:Et_2O) yielding the tosylamide as a white solid (578 mg, 65%), mp = 78-80˚C. $[\alpha]^{20}_D$ = -53.8 (c = 1.04, MeOH). IR (neat): 1734, 1357 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.80 (ddt, *J* = 17.1, 10.8, 6.3 Hz, 1H), 5.05 (m, 2H), 4.42 (m, 1H), 2.53 (ddd, *J* = 17.6, 11.1, 9.1 Hz, 1H), 2.43 (s, 3H), 2.34 (ddd, *J* = 17.6, 9.4, 2.4 Hz, 1H), 2.25–2.03 (m, 4H), 1.87 (dddd, *J* = 12.9, 9.1, 2.4, 1.8 Hz, 1H), 1.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 145.0, 136.8, 136.0, 129.5, 128.3, 115.6, 59.9, 33.5, 30.7, 29.4, 23.4, 21.7; TOFESMS m/z relative intensity 294 (MH^+ 52), 316 (MNa^+ 100), HRMS (+ES) calculated for $C_{15}H_{20}NO_3S$: 294.1164, found 294.1185.

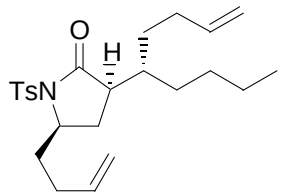


5-But-3-enyl-3-pentylidene-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**5-71**): LHMDS (20.6 mL, 1.0M THF, 20.6 mmol) was added to a cooled solution of lactam **5-69** (5.26 g, 17.9 mmol) in THF (180 mL) at -78°C. This solution was stirred at -78°C for 1 h. $BF_3{\cdot}Et_2O$ (2.59 mL, 20.6 mmol) was added to the solution followed by valeraldehyde

(2.19 g, 20.6 mmol) in THF (60 mL). The reaction mixture was warmed to room temperature and stirred for 2 h. Et_2O (250 mL) was added and the crude mixture was washed with sat. aq. NH_4Cl (2 × 200 mL), water (200 mL), 1M H_3PO_4 (2 × 200 mL), water (200 mL), and brine (200 mL). The remaining organic layer was dried over Na_2SO_4 and then the solvent was removed *in vacuo* to yield the crude alcohol (6.95 g) as a yellow oil.

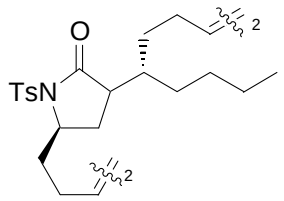
This alcohol was cooled to 0°C in CH_2Cl_2 (180 mL), and MsCl (2.49 mL, 32.3 mmol) and Et_3N (45.0 mL, 323 mmol) was added sequentially. This mixture was stirred overnight while slowly warming to room temperature. Ice was added to the reaction mixture and the organic portion was washed with 1M H_3PO_4 (2 × 200 mL) and brine (200 mL). The crude organic solution was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified through column chromatography on silica gel (2:1 hexanes:Et_2O) to yield the Z-enamide (0.550 g) and E-enamide (3.74 g, 66% combined). *E*-enamide: $[\alpha]^{20}_D$ = -14.2 (c = 0.28, MeOH); IR (neat): 1722, 1673, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.59 (tdd, *J* = 7.5, 2.7, 2.6 Hz, 1H), 5.76 (ddt, *J* = 16.7, 10.5, 6.1 Hz, 1H), 4.98 (m, 2H), 4.47 (tdd, *J* = 8.6, 2.1, 1.9 Hz, 1H), 2.81 (m, 1H), 2.48 (d, *J* = 16.8 Hz, 1H), 2.41 (s, 3H), 2.10 (m, 2H), 2.07-1.93 (m, 3H), 1.76 (m, 1H), 1.45-1.22 (m, 4H) 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 144.9, 139.6, 136.9, 136.1, 129.5, 129.0, 128.4, 115.4, 56.7, 34.9, 30.2, 29.1, 28.3, 28.3, 22.3, 21.6, 13.8; TOFESMS m/z relative intensity 362 (MH^+ 100), HRMS (+ES) calculated for $C_{20}H_{28}NO_3S$: 362.1790, found 362.1795. *Z*-enamide: IR (neat): 1720, 1666, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 6.02 (tdd, *J* = 7.7, 2.8, 1.5 Hz, 1H),

5.76 (ddt, *J* = 17.1, 10.3, 6.3 Hz, 1H), 5.01 (m, 2H), 4.37 (tdd, *J* = 8.9, 2.5, 1.6 Hz, 1H), 2.88 (dddd, *J* = 15.7, 8.9, 5.3, 2.7 Hz,1H), 2.63 (m, 2H), 2.48-2.38 (m, 4H), 2.12-1.97 (m, 3H), 1.74 (m, 1H), 1.39-1.21 (m, 4H) 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 144.7, 144.3, 136.9, 136.2, 129.5, 128.4, 126.8, 115.4, 56.7, 34.5, 32.1, 31.3, 28.8, 27.2, 22.3, 21.7, 13.9.

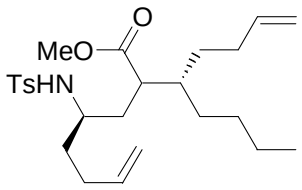


5-But-3-enyl-3-(1-butyl-pent-4-enyl)-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**5-68**): To a solution of copper iodide (316 mg, 1.66 mmol) in Et_2O (4 mL) at 0°C was added butenylMgBr (6.64 mL, 0.5M THF, 3.3 mmol) and the resulting blue-gray solution was stirred for 5 min. The cuprate mixture was cooled to -15°C and a solution of enamide **5-71** (500 mg, 1.38 mmol) in Et_2O (10 mL) was added dropwise. The reaction mixture was cooled to -78°C and a solution of pivalic acid (353 mg, 3.46 mmol) in Et_2O (1 mL) was slowly added. After the mixture was warmed to room temperature, the crude mixture was washed with sat. aq. NH_4Cl (15 mL) and 14% NH_4OH (2 × 15 mL) to remove any remaining copper salts. After washing with brine and drying over Na_2SO_4, the diene was purified through column chromatography on silica gel (4:1 hexanes:Et_2O) to provide a mixture of isomers (422 mg, 73%). A small sample of one diastereomer for characterization pruposes was isolated after purification through column chromatography with silver nitrate coated silica gel (10% silver nitrate by weight). $[\alpha]^{20}_D$ = -5.7 (c = 1.04, MeOH). IR (neat): 1732, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz,

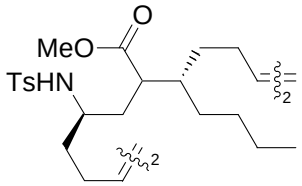
2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.84 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.07 (m, 2H), 4.94 (m, 2H), 4.16 (dtd, *J* = 9.7, 7.8, 2.6 Hz, 1H), 2.54 (m, 2H), 2.43 (s, 3H), 2.18 (m, 2H), 2.09 (m, 1H), 1.97 (m, 2H), 1.86 (m, 1H), 1.64 (m, 1H), 1.50 (m, 2H), 1.29-1.08 (m, 7H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 144.8, 138.2, 137.1, 136.1, 129.5, 128.2, 115.5, 114.7, 58.0, 44.8, 36.7, 35.2, 31.4, 31.0, 30.6, 29.6, 28.9, 25.8, 22.8, 21.7, 14.0; TOFESMS m/z relative intensity 418 (MH^+ 90), HRMS (+ES) calculated for $C_{24}H_{36}NO_3S$: 418.2416, found 418.2411.



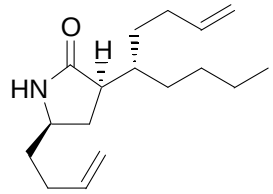
Dimer of 5-But-3-enyl-3-(1-butyl-pent-4-enyl)-1-(toluene-4-sulfonyl)-pyrrolidin-2-one: To a solution of diene **5-68** (20 mg, 0.048 mmol) in benzene (120 mL) was added Grubbs second generation catalyst (41 mg, 0.048 mmol) and the solution was heated at reflux for 2 hours. At this time, the reaction was cooled to room temperature and the solvent was removed *in vacuo*, and the crude material was purified through column chromatography on silica gel (4:1 hexanes:Et_2O) to give the dimer as a brown oil (11 mg, 58%). IR (neat): 1730, 1597, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 4H), 7.31 (m, 4H), 5.40-5.15 (m, 4H), 4.36 (m, 2H), 2.62 (m, 2H), 2.52 (m, 2H), 2.43 (s, 6H), 2.08 (m, 4H), 2.02-1.73 (m, 8H), 1.71-1.59 (m, 6H), 1.36-0.93 (m, 14H), 0.92-0.72 (m, 6H); TOFESMS m/z relative intensity 801 (MNa^+ 25), 307 (50), 281 (100).



2-(1-Butyl-pent-4-enyl)-4-(toluene-4-sulfonylamino)-oct-7-enoic Acid Methyl Ester (**5-72**): To a solution of lactam **5-68** (100 mg, 0.239 mmol) in MeOH (0.5 mL) was added MeONa (65 mg, 1.2 mmol). This mixture was stirred at room temperature for 2 h. Water (1 mL) was added to the reaction mixture and the solution was neutralized with 1M H_3PO_4. Extraction of the aqueous portion with EtOAc (3 × 1 mL) followed by washing the organics with brine and drying with Na_2SO_4 left ester **5-72** as a colorless oil (108 mg, 100%). IR (neat): 3279, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.81-5.55 (m, 2H), 5.02-4.86 (m, 4H), 4.57 (m, 1H), 3.66 (s, 3H), 3.23 (td, *J* = 14.0, 6.1 Hz, 1H), 2.41 (s, 3H), 2.27 (m, 1H), 1.96 (q, *J* = 7.4 Hz, 4H), 1.80 (ddd, *J* = 14.1, 9.7, 8.8 Hz, 1H), 1.59 (m, 1H), 1.54-1.35 (m, 3H), 1.30-1.22 (m, 3H), 1.22-1.11 (m, 5H), 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 143.1, 138.5, 138.4, 137.5, 129.5, 126.9, 115.2, 114.6, 51.7, 44.5, 40.1, 34.7, 31.9, 31.4, 31.2, 30.7, 30.2, 29.4, 22.7, 21.5, 14.0; TOFESMS m/z relative intensity 450 (60 MH^+), 418 (100 M^+-OMe), HRMS (+ES) calculated for $C_{25}H_{40}NO_4S$: 450.2678, found 450.2691.

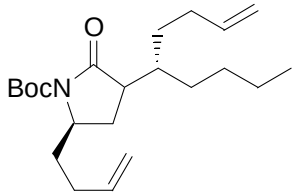


Dimer of 2-(1-Butyl-pent-4-enyl)-4-(toluene-4-sulfonylamino)-oct-7-enoic Acid Methyl Ester: Ester **5-72** (50 mg, 0.11 mmol) was stirred for 2 h in refluxing CH_2Cl_2 (111 mL) in the presence of Grubbs second generation catalyst (19 mg, 0.022 mmol). The crude mixture was filtered through Celite and the solvent was removed *in vacuo*. Purification through column chromatography on silica gel (2:1 hexanes:Et_2O) gave the dimer as a orange oil (40 mg, 85%). IR (neat): 3492, 1729, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.31 (m, 4H), 5.50-5.00 (m, 4H), 3.64 (m, 6H), 3.21 (m, 2H), 2.57 (s, 2H), 2.41 (s, 6H), 2.10-1.50 (m, 12H), 1.50-1.00 (m, 24H), 0.81 (m, 6H); TOFESMS m/z relative intensity 865 (100 M_2Na^+), 307 (80), HRMS (+ES) calculated for $C_{46}H_{74}N_3O_8S_2$ ($M + NH_4^+$): 860.4917, found 860.4866.



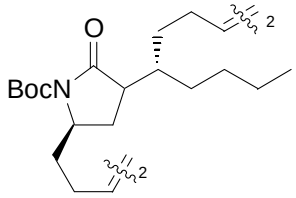
5-But-3-enyl-3-(1-butyl-pent-4-enyl)-pyrrolidin-2-one (**5-73**): To a solution of naphthalene (369 mg, 2.87 mmol) in DME (4 mL) was added finely cut sodium metal (66 mg, 2.9 gm-atoms). This mixture was sonicated for 15 min and the solution turned brown and then dark green. This solution was stirred for an additional 2 h and cooled to 0 °C. Tosylamide **5-68** (200 mg, 0.479 mmol) was added in DME (1 mL), and the solution was stirred at 0 °C for 20 min. After sat. aq. NH_4Cl (5 mL) was added, the crude mixture was

extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4. Purification of the crude material through column chromatography on silica gel (1:1 hexanes:EtOAc) gave amide **5-73** as a colorless oil (101 mg, 81%). IR (neat): 3215, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 1H), 5.80 (m, 2H), 5.10-4.89 (m, 4H), 3.52 (m, 1H), 2.64 (ddd, *J* = 9.2, 7.9, 3.6, 1H), 2.17-1.98 (m, 5H), 1.88 (m, 1H), 1.73 (ddd, *J* = 13.3, 9.7, 3.6, 1H), 1.68-1.52 (m, 3H), 1.27-1.15 (m, 7H), 0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 139.1, 137.9, 115.8, 114.9, 52.6, 43.1, 38.0, 36.7, 32.0, 31.7, 30.7, 30.6, 30.2, 28.4, 23.4, 14.4; TOFESMS m/z relative intensity 264 (100 MH^+), HRMS (+ES) calculated for $C_{17}H_{30}NO$: 264.2327, found 264.2341.



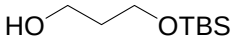
5-But-3-enyl-3-(1-butyl-pent-4-enyl)-2-oxo-pyrrolidine-1-carboxylic Acid tert-Butyl Ester (**5-74**): To a solution of lactam **5-73** (50 mg, 0.19 mmol) in CH_3CN (0.4 mL) was added Boc_2O (46 mg, 0.21 mmol) and DMAP (2 mg, 0.019 mmol) at 0 °C. The solution was allowed to warm to room temperature and was stirred overnight. $0.1MH_3PO_4$ (2 mL) was added, the crude mixture was extracted with EtOAc (3 × 1 mL). The combined organic portions were washed with brine (1 mL) followed by drying over Na_2SO_4. The solvent was removed *in vacuo* to give Boc lactam **5-74** as an orange oil (50 mg, 72%). IR (neat): 1783, 1747, 1714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.81 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.6 Hz,

1H), 5.03 (dq, *J* = 9.4, 1.4 Hz, 1H), 4.97 (m, 2H), 4.05 (td, *J* = 9.1, 2.3 Hz, 1H), 2.75 (ddd, *J* = 11.9, 8.7, 3.7 Hz, 1H), 2.16 (m, 1H), 2.10-2.01 (m, 3H), 1.97 (m, 1H), 1.87 (m, 2H), 1.73 (dd, *J* = 12.7, 8.8 Hz, 1H), 1.58 (m, 2H), 1.53 (s, 9H), 1.38-1.19 (m, 7H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 150.0, 138.5, 137.3, 115.4, 114.7, 82.6, 55.2, 44.1, 36.7, 32.6, 31.6, 31.0, 30.6, 30.2, 29.9, 28.1, 23.9, 23.0, 14.0; TOFESMS m/z relative intensity 364 (MH^+ 100), HRMS (+ES) calculated for $C_{22}H_{37}NO_3SNa$: 386.2671, found 386.2689.

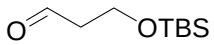


Dimer of 5-But-3-enyl-3-(1-butyl-pent-4-enyl)-2-oxo-pyrrolidine-1-carboxylic Acid tert-Butyl Ester: Boc lactam **5-74** (25 mg, 0.069 mmol) was stirred for 24 h in refluxing CH_2Cl_2 (275 mL) in the presence of Grubbs second generation catalyst (18 mg, 0.021 mmol). At this time the crude mixture was filtered through Celite and the solvent was removed *in vacuo*. Purification of the residue through column chromatography on silica gel (4:1 hexanes:Et_2O) gave the dimer as a brown oil (12 mg, 52%). IR (neat): 1778, 1745, 1713 cm^{-1}; TOFESMS m/z relative intensity 693 (MNa^+ 100), HRMS (+ES) calculated for $C_{40}H_{66}N_2O_6S_2Na$: 693.4819, found 693.4818.

6.5 Nozaki-Hiyama-Kishi route.

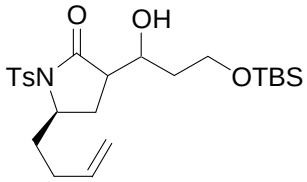


3-(tert-Butyl-dimethyl-silanyloxy)-propan-1-ol. To a solution of 1,3-propanediol (5.00 mL, 69.2 mmol) in THF (154 mL) at 0°C was added *n*-BuLi (27.7 mL, 2.5 M hexanes, 69.2 mmol) over 20 min *via* an addition funnel. The resulting slurry was stirred at 0°C for 1 h. A solution of TBSCl (9.48 g, 62.9 mmol) in THF (18 mL) was added to this slurry and the reaction mixture was allowed to warm to room temperature and was stirred overnight. Water (25 mL) was added and the organic solvent was removed *in vacuo*. The remaining aqueous portion was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The crude alcohol was purified through column chromatography on silica gel (4:1 hexanes:Et_2O) to give the title compound (10.2 g, 85%) as a yellow oil. IR (neat): 3356 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (t, *J* = 5.6 Hz, 2H), 3.80 (q, *J* = 5.5 Hz, 2H), 2.61 (t, *J* = 5.4 Hz, 1H), 1.78 (pent, *J* = 5.6 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.9, 62.4, 34.2, 25.8, 18.2, -5.5; TOFESMS m/z relative intensity 191 (MH^+ 100), HRMS (+ES) calculated for $C_9H_{23}O_2Si$: 191.1467, found 191.1485.



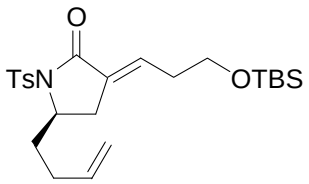
3-(tert-Butyl-dimethyl-silanyloxy)-propionaldehyde (**5-75**): A solution of DMSO (12.1 mL, 170 mmol) in CH_2Cl_2 (15 mL) was added to a solution of oxalyl chloride (6.73 mL, 79.6 mmol) and CH_2Cl_2 (25 mL) at -78°C *via* an addition funnel over 20 min. After stirring for an additional 20 min, a solution of 3-(tert-butyl-dimethyl-

silanyloxy)-propan-1-ol (10.1 g, 53.1 mmol) in CH_2Cl_2 (40 mL) was added *via* an addition funnel over 20 min. After stirring for another 20 min, Et_3N (37.0 mL, 265 mmol) was added *via* an addition funnel over 20 min. The reaction solution was warmed to 0°C and stirred for 3 h. 50% Aq. $NaHCO_3$ (2 × 25 mL) was added to the reaction mixture and the layers were separated. The organic portion was evaporated to ~1/2 volume. Meanwhile, the aqueous layer was extracted with Et_2O (3 × 25 mL) and the organic layers were combined with the previously concentrated organic portion. The combined organics were washed with 1M $NaHSO_4$ (2 × 25 mL) and 50% aq. $NaHCO_3$ (25 mL). The mixture was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (9:1 hexanes:Et_2O) to give the aldehyde (6.00 g, 60%) as a yellow oil. IR (neat): 1729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.1 Hz, 1H), 3.99 (td, *J* = 4.8, 0.5 Hz, 1H), 2.60 (td, *J* = 6.0, 2.1 Hz, 2H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 57.3, 46.5, 25.8, 18.2, -5.5.



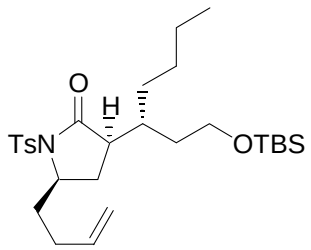
5-But-3-enyl-3-[3-(tert-butyl-dimethyl-silanyloxy)-1-hydroxy-propyl]-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**5-76**): LHMDS (3.75 mL, 1M THF, 3.75 mmol) was added to a solution of lactam **5-69** (1.00 g, 3.41 mmol) in THF (17 mL) at -78°C. The solution was stirred at -78°C for 1 h. A mixture of aldehyde **5-75** (0.835 g, 4.43 mmol) and $BF_3{\cdot}Et_2O$ (0.428 mL, 3.41 mmol) in THF (10 mL) was then added and the

reaction mixture was stirred at -78°C for 45 min. Sat. aq. NH_4Cl (30 mL) was added to the reaction mixture, and the aqueous portion was extracted with EtOAc (3 × 30 mL). The crude mixture was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified through column chromatography on silica gel (3:1 hexanes:Et_2O). Alcohol **5-76** was isolated as a colorless oil (1.40 g, 85%). IR (neat): 3505, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.80 (ddt, *J* = 17.0, 10.3, 6.3 Hz, 1H), 5.05 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.03 (dd, *J* = 10.0, 1.4 Hz, 1H), 4.37 (td *J* = 6.5, 3.1 Hz, 1H), 3.98 (s, 1H), 3.90 (m, 1H), 3.77 (t, *J* = 5.7 Hz, 2H), 2.71 (ddd, *J* = 12.7, 9.2, 7.3 Hz, 1H), 2.44 (s, 3H), 2.16-2.01 (m, 3H), 1.98 (m, 2H) 1.66 (m, 2H), 1.50 (m, 1H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 145.1, 136.6, 135.5, 129.5, 128.3, 115.7, 70.4, 60.3, 58.0, 46.2, 35.8, 33.3, 29.6, 26.8, 25.8, 21.6, 18.2, -5.5; TOFESMS m/z relative intensity 482 (MH^+ 100), HRMS (+ES) calculated for $C_{24}H_{40}NO_5SSi$: 482.2396, found 482.2408.



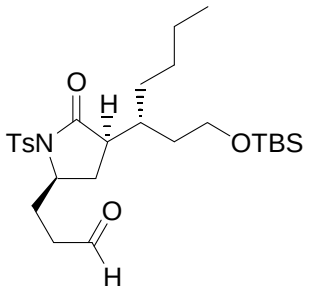
5-But-3-enyl-3-[3-(tert-butyl-dimethyl-silanyloxy)-propylidene]-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**5-77**): A solution of alcohol **5-76** (1.23 g, 2.54 mmol) in THF (13 mL) was cooled to 0°C and imdazole (519 mg, 7.63 mmol) was added followed by triphenylphosphine (734 mg, 2.80 mmol) and iodine (710 mg, 2.80 mmol). The mixture was warmed to room temperature and stirred for 8 h. Sat. aq. $Na_2S_2O_3$ (25 mL) was added and the mixture was diluted with water (25 mL). The aqueous portion was

then extracted with CH_2Cl_2 (3 × 25). The crude organic phases was washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification through column chromatography on silica gel (3:1 hexanes:Et_2O) gave amide **5-77** as a yellow oil (994 mg, 84%). $[\alpha]^{20}_D$ = 2.0 (c = 1.00, MeOH). IR (neat): 1724, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.62 (ttd, *J* = 7.6, 2.8, 0.8 Hz, 1H), 5.76 (m, 1H), 4.98 (m, 2H), 4.46 (tt, *J* = 8.8, 2.1 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.82 (dddt, *J* = 16.8, 9.0, 3.3, 1.7 Hz, 1H), 2.50 (d, *J* = 16.8 Hz, 1H), 2.42 (s, 3H), 2.33 (m, 2H), 2.08 (m, 1H), 2.00 (m, 2H), 1.70 (m, 1H), 0.85 (s, 9H), -0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 144.8, 136.7, 136.0, 136.0, 130.5, 129.4, 128.3, 115.4, 61.2, 56.6, 34.9, 33.1, 28.4, 28.3, 25.8, 21.6, 18.1, -5.5; TOFESMS m/z relative intensity 464 (MH^+ 95), HRMS (+ES) calculated for $C_{24}H_{38}NO_4SiS$: 464.2291, found 464.2296.

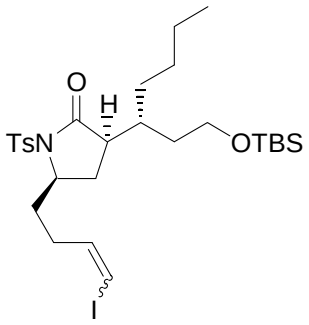


5-But-3-enyl-3-{1-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-pentyl}-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (**5-78**): To a solution of CuI (838 mg, 4.40 mmol) in Et_2O (25 mL) at 0°C was added *n*-BuLi (3.99 mL, 2.3M hexane, 9.2 mmol). This brown solution was cooled to -78°C and enamide **5-77** (1.70 g, 3.67 mmol) was added in Et_2O (12 mL). The reaction mixture was stirred at this temperature for 20 min at which point the cold bath was removed and stirring continued for 1 h. After recooling to -78°C,

a solution of pivalic acid (936 mg, 9.17 mmol) in Et_2O (2 mL) was added, and the mixture was allowed to warm to room temperature. The crude mixture was washed with 14% aq. NH_4OH (2 × 40 mL), and the aqueous portions were extracted with Et_2O (3 × 40 mL). The combined organic portions were washed with brine (2 × 40 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*. Purification through column chromatography on silica gel (3:1 hexanes: Et_2O) yielded lactam **5-78** as a colorless oil (1.55 g, 81%). Lactam was isolated as an inseparable mixture of diastereomers. IR (neat): 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.84 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.08 (dd, 17.1, 1.3 Hz, 1H), 5.03 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.11 (dtd, *J* = 9.8, 7.8, 2.6 Hz, 1H), 3.57 (m, 2H) 2.63 (td, *J* = 10.5, 3.7 Hz, 1H), 2.55 (m, 1H), 2.41 (s, 3H), 2.24 (ddd, *J* = 12.9, 10.1, 7.7 Hz, 1H), 2.15 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H), 1.63 (m, 2H), 1.50 (ddd, *J* = 12.8, 11.0, 8.1 Hz, 1H), 1.36 (m, 1H), 1.30-1.08 (m, 6H) 0.84 (m, 12H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 144.7, 137.1, 136.1, 129.4, 128.1, 115.5, 61.7, 58.0, 45.3, 35.2, 34.9, 34.6, 31.0, 29.8, 28.9, 26.2, 25.8, 22.7, 21.6, 18.1, 13.9, -5.5, -5.5; TOFESMS m/z relative intensity 522 (MH^+ 100), HRMS (+ES) calculated for $C_{28}H_{48}NO_4SSi$: 522.3073, found 522.3069.

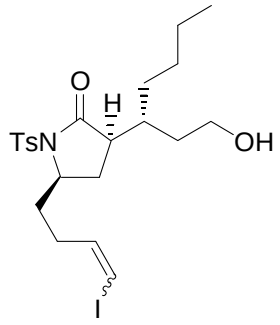


3-[4-{1-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-pentyl}-5-oxo-1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-propionaldehyde. A solution of alkene **5-78** (1.31 g, 2.50 mmol) in CH_2Cl_2 (25 mL) was cooled to -78°C and ozone was bubbled through this solution for 45 min until a blue color persisted. The flask was purged with nitrogen gas and Me_2S (9.20 mL, 125 mmol) was added. The cold bath was removed and the reaction mixture was stirred at room temperature overnight. The solvent was removed by rotary evaporation and the crude material was purified through column chromatography on silica gel (1:1 hexanes:Et_2O) to give the aldehyde as a colorless oil (871 mg, 66%). IR (neat): 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.14 (dtd, *J* = 8.0, 7.2, 2.5 Hz, 1H), 3.56 (m, 2H), 2.63 (m, 3H), 2.51 (m, 1H), 2.43 (s, 3H), 2.21 (ddd, *J* = 12.9, 9.8, 7.8 Hz, 1H), 2.04 (m, 1H), 1.94 (m, 1H), 1.60 (m, 1H), 1.46 (ddd, *J* = 12.5, 11.4, 8.6 Hz, 1H), 1.32 (hex, *J* = 7.2 Hz, 1H), 1.24 (m, 3H), 1.15 (m, 3H), 0.87-0.78 (m, 12H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 176.1, 145.0, 135.6, 129.5, 128.2, 61.7, 57.5, 45.3, 39.0, 34.8, 34.4, 31.0, 29.7, 28.2, 26.1, 25.8, 22.7, 21.6, 18.1, 13.9, -5.5, -5.5; TOFESMS m/z relative intensity 524 (MH^+ 25), 579 (MNa^++MeOH 100), HRMS (+ES) calculated for $C_{27}H_{46}NO_5SSi$: 524.2866, found 524.2842.



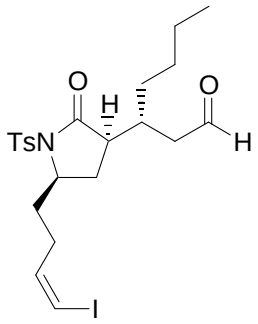
3-{1-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-pentyl}-5-(4-iodo-but-3-enyl)-1-(toluene-4-sulfonyl)-pyrrolidin-2-one. (**5-79**): LHMDS (0.968 mL, 1M THF, 0.968 mmol) was added to a solution of (iodomethyl)triphenylphosphonium iodide (493 mg, 0.931 mmol) and THF (1.9 mL) in the absence of light. While stirring for 10 min, the white slurry became cloudy orange and finally turned into a clear red solution. This solution was cooled to -78°C and 3-[4-{1-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-pentyl}-5-oxo-1-(toluene-4-sulfonyl)-pyrrolidin-2-yl]-propionaldehyde (390 mg, 0.745 mmol) was added in THF (1.9 mL). The solution was stirred at -78°C for 30 min and the cold bath was removed. Stirring was continued at room temperature for 1 additional hour, at which point, hexanes (20 mL) were added and the slurry was filtered through Celite. After concentration *in vacuo*, the crude material was purified through column chromatography on silica gel (4:1 hexanes: Et_2O) to give a yellow oil. Vinyl iodide **5-79** (286 mg, 59%) was isolated as an inseparable mixture of alkene isomers (2:1, *Z*:*E*). The spectral data given correspond to the major isomer (*Z*-alkene). IR (neat): 1734, 1598 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.29 (d, *J* = 7.3 Hz, 1H), 6.24 (dt, *J* = 7.3, 6.5 Hz, 1H), 4.10 (dtd, *J* = 9.7, 7.8, 2.6 Hz, 1H), 3.58 (m, 2H), 2.64 (td, *J* = 10.4, 3.8 Hz, 1H), 2.53 (m, 1H), 2.42 (s, 3H), 2.31 (ddd, *J* = 12.9, 9.8, 7.8 Hz, 1H), 2.23 (m, 2H), 1.95 (m, 1H), 1.72 (m, 1H), 1.61 (m, 2H), 1.36 (m, 1H), 1.38-1.21 (m, 3H), 1.21-1.04 (m, 3H), 0.95-0.78 (m, 12H), 0.01 (m, 6H); ^{13}C NMR

(90 MHz, $CDCl_3$) δ 176.1, 144.8, 139.6, 135.6, 129.5, 128.1, 83.8, 61.7, 57.6, 45.3, 34.9, 34.5, 34.3, 31.0, 30.2, 29.7, 26.2, 25.9, 22.7, 21.6, 18.1, 14.0, -5.5; TOFESMS m/z relative intensity 648 (MH^+ 100), HRMS (+ES) calculated for $C_{28}H_{47}INO_4SSi$: 648.2040, found 648.1990.



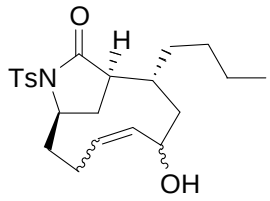
3-[1-(2-Hydroxy-ethyl)-pentyl]-5-(4-iodo-but-3-enyl)-1-(toluene-4-sulfonyl)-pyrrolidin-2-one. To a solution of siloxane **5-79** (45 mg, 0.070 mmol) in EtOH (0.70 mL) was added one drop of conc. HCl in the absence of light. The reaction mixture was stirred for 3 h and the solvent was removed *in vacuo*. Purification of the crude material through column chromatography on silica gel (1:1 hexanes:Et_2O) gave the alcohol (27 mg, 73%) as a colorless oil. The title compound was isolated as an inseparable mixture of isomers. The spectral data given correspond to the major isomer. IR (neat): 3428, 1730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.30 (dt, *J* = 7.3, 1.1 Hz, 1H), 6.25 (dt, *J* = 7.3, 6.5 Hz, 1H), 4.14 (dtd, *J* = 9.9, 7.6, 2.6 Hz, 1H), 3.63 (d, *J* = 4.6 Hz, 2H), 2.59 (td, *J* = 10.1, 4.7 Hz, 1H), 2.53 (m, 1H), 2.43 (s, 3H), 2.35 (ddd, *J* = 13.0, 10.3, 7.9 Hz, 1H), 2.22 (m, 2H), 1.94 (m, 1H), 1.70 (m, 2H), 1.62 (ddd, *J* = 12.3, 9.6, 6.7 Hz, 1H), 1.48 (m, 2H), 1.31-1.08 (m, 6H), 0.83 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.2, 144.9, 139.5, 135.8, 129.5, 128.1, 83.8,

60.8, 57.7, 45.2, 34.8, 34.3, 31.1, 31.0, 30.2, 29.4, 26.6, 22.8, 21.6, 13.9; TOFESMS m/z relative intensity 534 (MH^+ 100), HRMS (+ES) calculated for $C_{22}H_{33}INO_4S$: 534.1175, found 534.1161.



3-[5-(4-Iodo-but-3-enyl)-2-oxo-1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-heptanal (**5-80**): To a solution of oxalyl chloride (19 μL, 0.23 mmol) in CH_2Cl_2 (0.75 mL) at -78°C was added a solution of DMSO (33 μL, 0.47 mmol) in CH_2Cl_2 (0.75 mL) in the absence of light. After stirring for 10 min, a solution of 3-[1-(2-hydroxy-ethyl)-pentyl]-5-(4-iodo-but-3-enyl)-1-(toluene-4-sulfonyl)-pyrrolidin-2-one (80 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) was added, and the reaction mixture was stirred for an additional 10 min. Triethylamine (105 μL, 0.750 mmol) was added, and the solution was warmed to room temperature and stirred for an additional 1.5 h. Water (3 mL) was added and the mixture was extracted with Et_2O (3 × 3 mL). The combined organic portions were washed with brine (3 mL) and dried over Na_2SO_4. Purification through column chromatography on silica gel (2:1 hexanes:Et_2O) gave aldehyde **5-80** (56 mg, 70%) as a colorless oil. Aldehyde **5-80** was isolated as an inseparable mixture of isomers. The spectral data given correspond to the major isomer. IR (neat): 1724, 1597 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.69 (t, J = 1.7 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 7.9

Hz, 2H), 6.30 (d, *J* = 7.3, Hz, 1H), 6.24 (dt, *J* = 7.2, 6.6 Hz, 1H), 4.13 (m, 1H), 2.54 (m, 2H), 2.48 (m, 1H), 2.43 (s, 3H), 2.38 (m, 2H), 2.22 (m, 2H), 1.73 (m, 1H), 1.60 (ddd, *J* = 12.7, 9.2, 7.4 Hz, 1H), 1.40-1.10 (m, 7H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.3, 175.1, 145.0, 139.4, 135.7, 129.5, 128.1, 83.9, 57.6, 45.6, 44.9, 34.1, 33.0, 31.1, 30.2, 28.9, 27.5, 22.6, 21.6, 13.9; TOFESMS m/z relative intensity 532 (MH^+ 35), 586 (MNa^++MeOH 100), HRMS (+ES) calculated for $C_{22}H_{31}INO_4S$: 532.1019, found 532.1000.



2-Butyl-4-hydroxy-10-(toluene-4-sulfonyl)-10-aza-bicyclo[7.2.1]dodec-5-en-11-one (**5-81**): DMSO (83 mL) was degassed by bubbling with nitrogen for 30 min and was then was added to a mixture of $CrCl_2$ (102 mg, 0.828 mmol) and $NiCl_2$ (2 mg, 0.02 mmol). In the absence of light a similarly degassed solution of aldehyde **5-80** (44 mg, 0.083 mmol) in THF (21 mL) was added at 0°C. The reaction solution was allowed to warm to room temperature and stirred in the dark for 36 h. Water (100 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined ether extracts were dried washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified through column chromatography on (1:1 hexanes:Et_2O) to give macrocyclic alcohol **5-81** (14 mg, 42%) as a colorless oil. Allylic alcohol **5-81** was isolated as a complex mixture of diastereomers and olefin isomers. One diastereomer containing a *trans* alkene was purified for characterization purposes. IR

(neat): 3534, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 5.82 (t, *J* = 14.5 Hz, 1H), 5.55 (d, *J* = 14.5 Hz, 1H), 4.42-4.33 (m, 2H), 2.67-2.54 (m, 3H), 2.52 (m, 1H), 2.44 (s, 3H), 2.34 (m, 1H), 2.20 (dd, *J* = 8.1, 1.6 Hz, 1H), 1.92 (ddd, *J* = 13.4, 7.8, 6.2 Hz, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.64 (td, *J* = 13.6, 4.5 Hz, 1H), 1.42 (d, *J* = 2.5 Hz, 1H), 1.32 (m, 2H), 1.26-1.1.18 (m, 4H), 0.84 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.4, 144.8, 135.8, 135.8, 129.5, 128.4, 127.2, 68.5, 57.4, 43.2, 39.6, 37.6, 36.6, 34.7, 33.2, 20.4, 28.7, 22.7, 21.7, 14.1; TOFESMS m/z relative intensity 406 (MH^+ 75), 428 (MNa^+ 100), HRMS (+ES) calculated for $C_{22}H_{32}NO_4S$: 406.2052, found 406.2040.

VITA

W. Brent Clayton

Brent Clayton was born in Idaho Falls, ID on May 7, 1978. After growing up in Salt Lake City, UT, he completed high school Corinth, MS in 1996. The following year he began his undergraduate studies at Brigham Young University in Provo, UT. After one year he took two years off from his schooling to work as a missionary in southwestern France. In 1999, he returned to BYU and became involved in undergraduate research in the chemistry department. He studied both thermodynamics with Dr. Earl Woolley and organic photochemistry with Dr. Steve Fleming. In 2002, Brent moved to Penn State and joined Dr. Ken Feldman's research lab. There his research efforts involved carbene methodology studies and natural product synthesis. After graduating from Penn State, he will join AMRI in Albany, NY as a medicinal chemist.