The Pennsylvania State University

The Graduate School

Department of Chemistry

ALKYNYLIODONIUM SALTS IN ORGANIC SYNTHESIS. APPLICATION TOWARDS THE SYNTHESIS OF THE CORE OF (±)-HALICHLORNIE.

and

ATTEMPTS TOWARDS THE SYNTHESIS OF KINAMYCIN F.

A Thesis in

Chemistry

by

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ABSTRACT

Alkynyliodonium salts are synthetically useful intermediates that serve as electrophilic acetylene equivalents due to the electron withdrawing nature of the hypervalent iodine. In one example, reaction of an alkynyliodonium salt with soft nucleophiles via conjugate addition, followed by loss of iodobenzene, generates alkylidenecarbenes. Alkylidenecarbenes are divalent, short lived intermediates capable of participating in a various bond-forming processes depending upon the functionality present within the molecule. Due to the wide variety of possible reactions, alkylidenecarbenes are useful reactive intermediates in natural product synthesis.

The application of alkynyliodonium salts to generate alkylidenecarbenes is described in the first part of this thesis. Chapter 1 discusses the formation of alkynyliodonium salts and their application towards the generation of alkylidenecarbenes. The total synthesis of radermachol, a natural product target, was examined utilizing an alkylidenecarbene addition to a double bond as a key step. However, preliminary results shifted the focus away from this synthesis. Instead, aryl C-H insertion was examined by the reaction of phenoxide anions of naphthol derivatives with an alkynyliodonium salt. A variety of naphthol derivatives were used to study the preference for C-H insertion in these aromatic systems.

Halichlorine is a natural product target to which alkynyliodonium chemistry was applied in chapter 2. Halichlorine is a structurally unique marine alkaloid, which has interesting biological activity, in that it is a selective inhibitor of VCAM-1. The focus of the synthesis of halichlorine centers on the formation of a key quaternary center of the spirocyclic ring system. This bond can be formed using an alkynyliodonium salt to generate an alkylidenecarbene, which can undergo a 1,5-C-H insertion to generate the quaternary center with retention of stereochemistry. This synthesis highlights the use of alkynyliodonium salt chemistry for increasing molecular complexity in a single operation.

The final project discussed in this thesis is the progress made towards the total synthesis of kinamycin F. Kinamycin F is a compound in a class of potent antibiotics, whose members have also exhibited interesting cytotoxicity to a variety of tumor cell lines via cleavage of double stranded DNA. The proposed mechanism of action of these kinamycin compounds is thought to be through a bio-reductive process, generating a radical species which interacts with DNA leading to strand scission. Completion of the total synthesis of kinamycin F will permit a more thorough evaluation of the hypothesized biological mechanism of action.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

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For my friends who always gave me something to laugh about and who always knew how a good story could brighten up the day. Rachel and Paula, you are my best friends and I am privileged to have been allowed to spend these last

six years with you. Rachel, there is no one else with whom I would rather run home from the bar or watch really, really bad movies. You were a great roommate and I am thankful that we got placed together for visitation weekend. Paula, my other remarkable roommate, we got through P-Chem together, though I am not sure that we actually learned anything. Ladies, you are outstanding and you have made the last six years bearable, and I will never forget you.

Last, but certainly not least, Daniel, without you I would have most certainly been hit by a bus!!! I appreciate all that you have done for me these last few years. Thank you for volunteering to work the crazy hours with me in the beginning, and in the end for motivating me to go back to work when I really didn't want to. I most definitely could not have done this alone. Though you are not told this often enough, you have the patience of a saint, even when it wasn't deserved. I have enjoyed completing this chapter of my life with you and I am excited to see what the future hold for us next.

Chapter 1

ALKYNYLIODONIUM SALT CHEMISTRY FOR THE GENERATION OF ALKYLIDENECARBENES FOR 1,6-ARYL C-H INSERTIONS

1.1 Overview

Alkylidenecarbenes **2** (Figure **1-1**) are short lived intermediates capable of participating in various bond-forming processes depending upon the functionality present within the molecule. While there are different ways to generate an alkylidenecarbene, the focus of this discussion will be their formation from highly electron deficient alkynyliodonium salts **1**. Alkynyliodonium salts have been utilized in the synthesis of natural products,[1-4] taking advantage of the variety of bond formations that can be achieved with alkylidenecarbenes. Chapter 1 discusses the application of alkynyliodonium salts to the synthesis of radermachol **(3)** (Section **1.6**). The synthesis of the core of halichlorine **(152)** utilizing an alkylidenecarbene C-H insertion to generate the quaternary spirocyclic center (Figure **2-2**) is discussed in chapter 2.

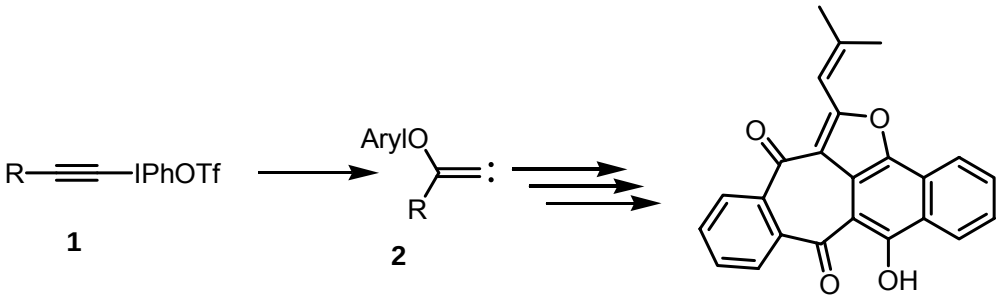
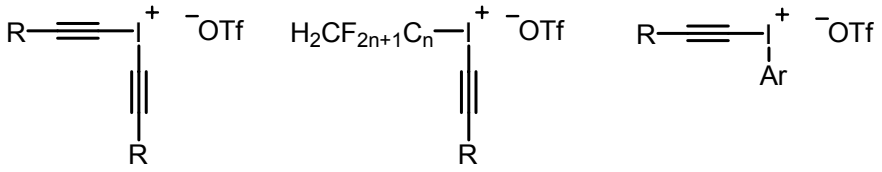


Figure **1-1**: Alkynyliodonium salt chemistry to generate an alkylidenecarbene used for the synthesis of radermachol.

1.2 Alkynyl(aryl)iodonium Salts

The ever expanding synthetic utility of alkynyliodonium salts is due to the continuing advances in their synthesis and their ability to serve as alkylidenecarbene precursors under mild experimental conditions. Alkynyliodonium salts have been prepared as bis(alkynyl)iodonium triflates **4**,[5] alkynyl(polyfluoroalkyl)iodonium triflates **5**,[6] and alkynyl(aryl)iodonium salts **6** (Figure **1-2**). While iodonium salts **4** and **5** lacked stability and did not receive practical application, the alkynyl(aryl)iodonium salt **6** was far more widely applied in synthetic transformations due to its stability and tolerance to a variety of R groups bonded to the alkyne.



4 **5** **6**

Figure **1-2**: Examples of alkynyliodonium salts.[5,6]

The first stable class of alkynyl(aryl)iodonium salts were the tosylates **9** developed by Koser and coworkers in 1981 (Figure **1-3**).[7-9] These tosylates **9** are formed from the reaction of terminal alkynes **7** with [hydroxyl(tosyloxy)iodo]benzene **(8)** in refluxing chloroform. Unfortunately, this method suffers from a lack of generality in that either phenyl[β-(tosyloxy)vinyl]iodonium tosylates **10** or alkynylphenyliodonium tosylates **9** or a mixture of both could be formed depending upon the R group on the alkyne. When R was *n*-propyl, the vinyliodonium tosylate **10** was exclusively generated; however, when R was a *tert*-butyl group the alkynyliodonium tosylate **9** was the

only product observed.[8] Nevertheless, the discovery of this relatively simple process led to rapid developments in the synthesis of other alkynyl(aryl)iodonium species.

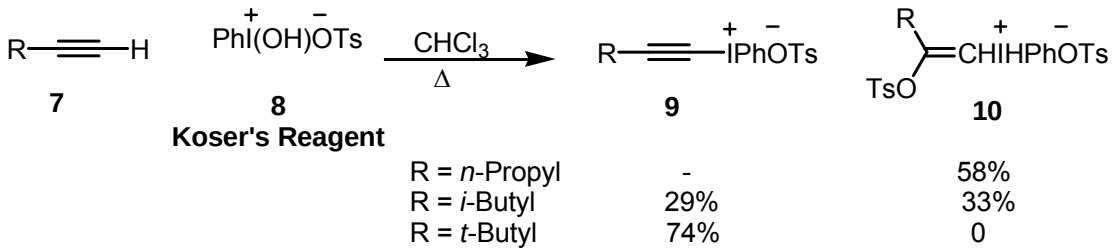


Figure **1-3**: Koser's alkynylphenyliodonium tosylates.[8]

Further developments led to the formation of alkynyl(aryl)iodonium salts using iodosylbenzene, PhIO (not shown), complexed with a Lewis acid (Figure **1-4**).[10,11] While iodosylbenzene does not react with alkynylsilanes by itself, when complexed with either triethyloxonium tetrafluoroborate or boron trifluoride etherate, it generates complexes **12** and **14**, respectively. These relatively unstable complexes react with the alkynylsilane **11** to generate alkynyl(phenyl)iodonium tetrafluoroborate **13**.

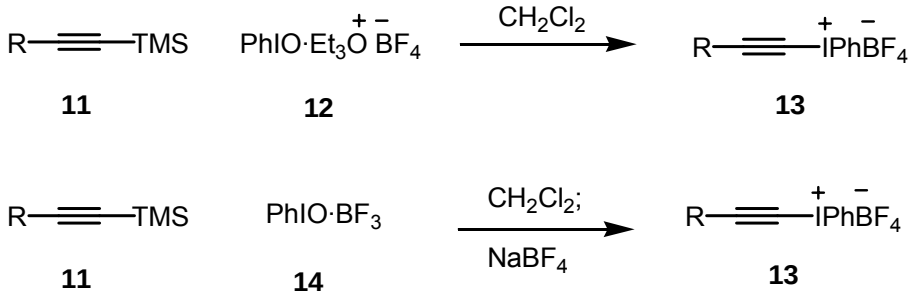


Figure **1-4**: Preparation of alkynyl(phenyl)iodonium salts from PhIO and Lewis acid complexes.[10,11]

Alkynyl(aryl)iodonium salts were also generated with triflate counterions (Figure **1-5**).[12,13] Either silylated alkynes **11** or stannylated alkynes **16** could be reacted with Zefirov's reagent **(15)**,[14] which is generated in situ from

iodosylbenzene and triflic anhydride, to afford alkynylphenyliodonium triflates **1**. This complexation of PhIO with a Lewis acid was shown to be a more efficient way to afford alkynyliodonium salts due to the fact the process occurred in better yields compared to the reactions of Koser's reagent **8**. However, the major disadvantage is that they still lack generality since only a limited number of functional groups (R) can survive these conditions.

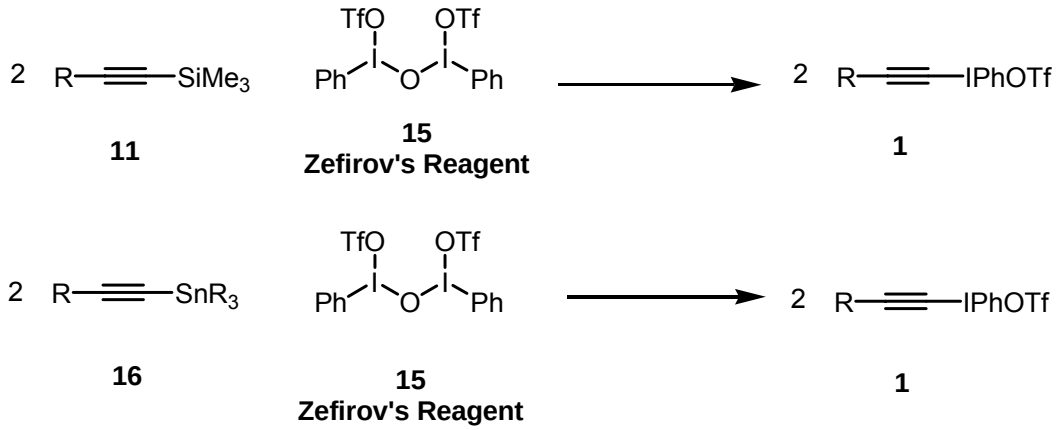


Figure **1-5**: The generation of alkynyl(phenyl)iodonium triflates from Zefirov's reagent.[12,13]

A new synthesis of alkynyl(phenyl)iodonium triflates **1** was developed by Stang and coworkers in 1991, using cyano(phenyl)iodonium triflate (Stang's Reagent) **(19)**. This reagent is generated by the reaction of iodosylbenzene **(17)** and trimethylsilyl triflate to generate the intermediate **18**, which upon addition of trimethylsilyl cyanide affords **19** (Figure **1-6**).[15,16] This triflate salt **19** can then be reacted with a variety of alkynylstannanes **16** to generate alkynyl(phenyl)iodonium triflates **1** (Figure **1-7**). Unlike previous syntheses of these iodonium salts, the triflate salts generated via Stang's reagent are compatible with a wide variety of functional groups, permitting the synthesis of a broad range of alkynyliodonium triflates.

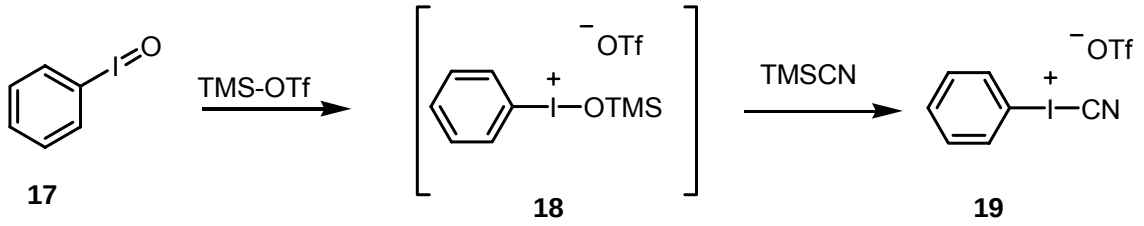
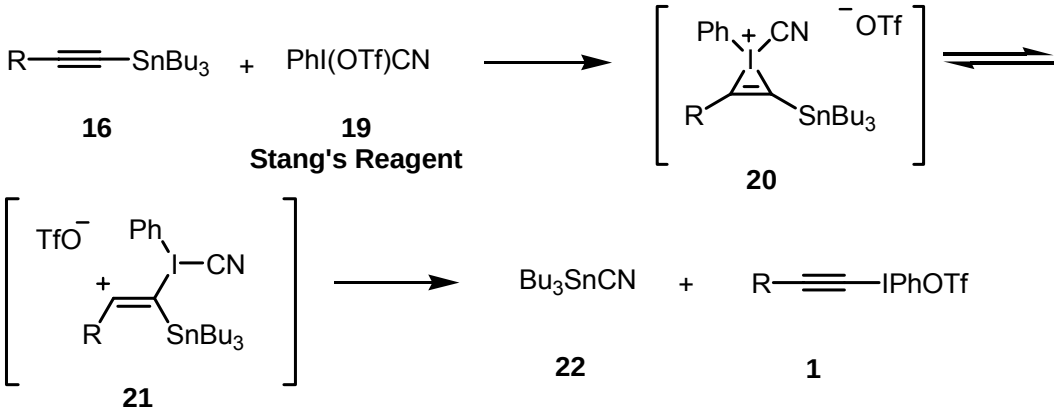


Figure **1-6**: Generation of cyano(phenyl)iodonium triflate (Stang's Reagent).[15,16]



Tolerated Functionalities R = H, Me, *n*-Bu, 1-cyclohexenyl, $MeOCH_2$, $ClCH_2$ $BrCH_2$, CN, Cl, MeC(OH)Ph, Ts, *t*-BuC(O), PhC(O), MeOC(O), $Me_2NC(O)$, 1-adamantyl-C(O), 2-furyl-C(O), 2-thienyl-C(O), cyclopropyl-C(O), $(CH_2)_4N$-C(O)

Figure **1-7**: Generation of alkynyl(phenyl)iodonium triflate via cyano(phenyl)iodonium triflate (Stang's reagent).[17]

1.3 The Generation of Alkylidenecarbenes from Alkynyliodonium Salts

Alkynyliodonium salts are useful synthetic reagents because they serve as electrophilic acetylene equivalents, a change from the usual nucleophilic characteristics of acetylene, due to the electron withdrawing nature of the hypervalent iodine. Alkynyliodonium salts can react with a wide variety of nucleophiles, due to the good leaving ability of the iodobenzene moiety, and can

be used for cycloaddition chemistry by reaction with dipolar compounds (1,3-dipolar cycloadditions) or electron-rich dienes (Diels-Alder).

Alkynyliodonium salts are highly reactive and are formally tetraphilic, containing four sites (Cα, Cα', Cβ, and I) available for nucleophilic attack due to the electron withdrawing nature of the hypervalent iodine (Figure **1-8**).[18] The selectivity of nucleophilic attack is generally governed by the nature of the nucleophile. For example, hard nucleophiles (Nu_H) tend to react at the iodine center generating a new iodonium salt **25** and the corresponding terminal alkyne **24**, which is believed to occur via displacement of the acetylide from the iodine center (Figure **1-9**).

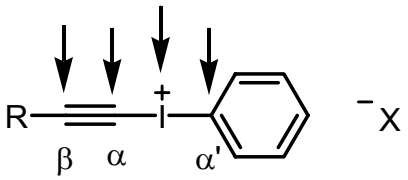
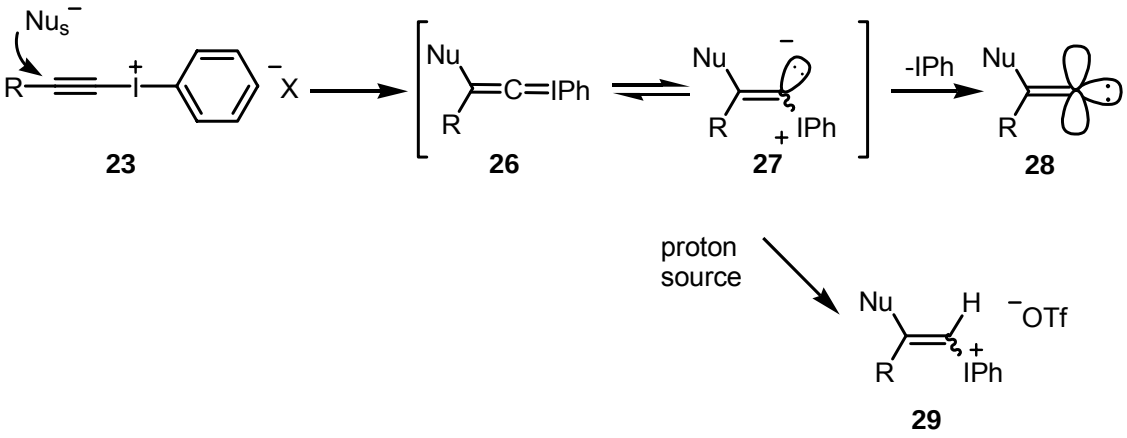


Figure **1-8**: Potential sites for nucleophilic attack.[18]

Figure **1-9**: Reaction of alkynyliodonium salt with a hard nucleophile.

Soft nucleophiles (Nu_S), however, often react at the β-alkynyl carbon of the iodonium salt **23** via conjugate addition (Figure **1-10**). The conjugate addition of a soft nucleophile, results in the ylide **27** and allene **26** equilibrium structures, which can undergo loss of iodobenzene to generate the alkylidenecarbene **28**. In the presence of a proton source, intermediate **27** can be protonated to generate

the alkenyliodonium salt **29**. Nucleophiles that typically trigger this conjugate addition reaction pathway are those whose anionic charge is well diffused. Carbon nucleophiles of this type include β-di-ketones, β-ketoesters, diesters, nitro-containing compounds, and malonates.[19] Many other non-carbon nucleophiles also undergo conjugate additions, including nitrogen nucleophiles (arylamines, sulfonylamides, and azides), oxygen nucleophile (phenoxide), sulfur nucleophiles (thiocyanate, arylsulfinates, sulfides, and sulfonates) and phosphorous nucleophiles (phosphonates, and phosphines).



23 **26** **27** **28** **29**

Figure **1-10**: Conjugate addition of a soft nucleophile to an alkynyl(phenyl)iodonium salt.

Ochiai and coworkers (1986) reported the utility of these alkynyliodonium salts in the generation of alkylidenecarbenes (Figure **1-11**).[20] Using dicarbonyl compounds **30**, the salt enolate (not shown) was generated using sodium *tert*-butoxide (NaO*t*Bu), which was then reacted with alkynyliodonium salt **31** via conjugate addition to generate ylide **32**. Loss of iodobenzene afforded alkylidenecarbene **33**, which was aligned for a 1,5 carbon-hydrogen insertion into the alkyl chain to generate cyclopentene compound **34** in good yield. Since this initial report, many others have used alkynyliodonium salts to generate alkylidenecarbenes via conjugate addition of soft nucleophiles.

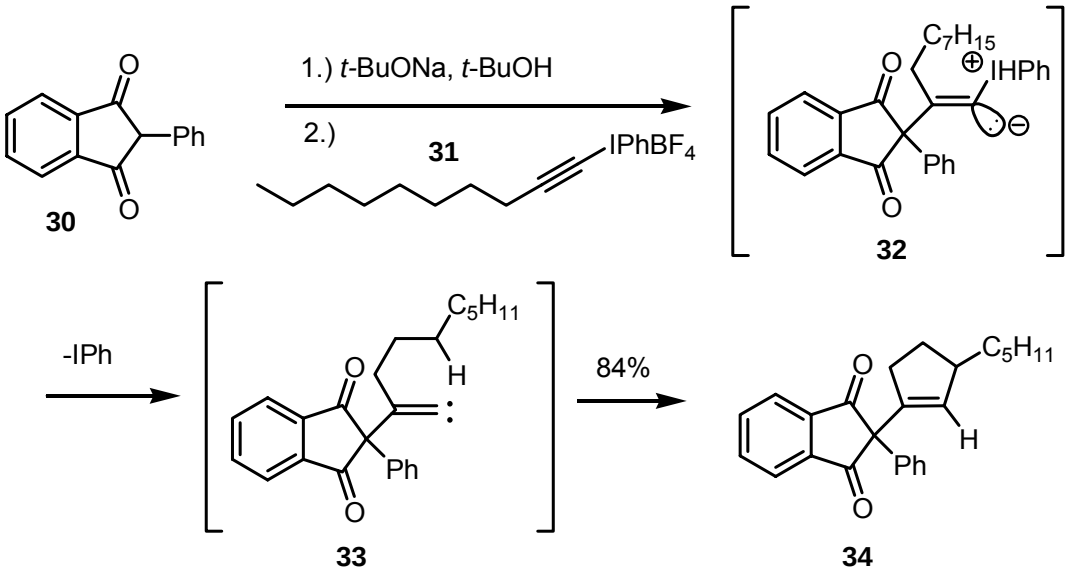
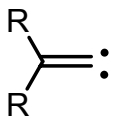


Figure **1-11**: Ochiai's generation of an alkylidenecarbene from an alkynyliodonium salt.[20]

1.4 Alkylidenecarbenes

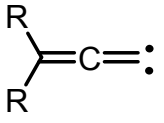
1.4.1 Structure and Electronic Properties of an Alkylidenecarbene

Unsaturated carbenes are members of a large series of reactive intermediates characterized by a terminal divalent, highly reactive sp carbon atom (Figure **1-12**).[21,22] Alkylidenecarbene **35** is the shortest member of this class, containing only one double bond and has the most potential for application due to its ease of preparation and versatility in bond forming processes. Alkylidenecarbenes, with a few exceptions [vinylidenecarbene (R = H)[23-25] and isopropylidene carbene (R = CH_3)[26]], have not been able to be studied spectroscopically due to their high reactivity. However, their existence is clearly demonstrated by their chemical behavior and the products formed from their reactions.[21]



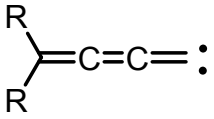
alkylidenecarbene

35



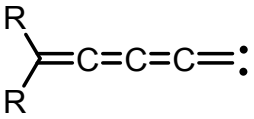
alkenylidenecarbene

36



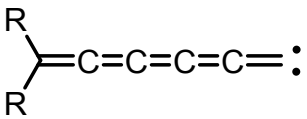
alkadienylidenecarbene

37



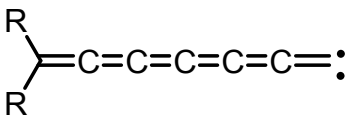
alkatrienylidenecarbene

38



alkatetraenylidenecarbene

39

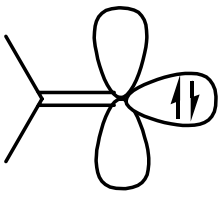


alkaoctaenylidenecarbene

40

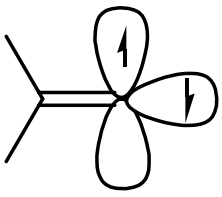
Figure **1-12**: Unsaturated carbenes.

An alkylidenecarbene may be in one of three low-energy states: the singlet state (S_0) **41**, in which one orbital contains two paired electrons; the singlet state (S_1) **42**, with two singly occupied orbitals with opposite electron spin; and the triplet state (T_1) **43**, with two singly occupied orbitals with parallel electron spin (Figure **1-13**).[21,27] While the bond lengths and geometries of alkylidenecarbenes are unknown, quantum mechanics calculations have predicted a bond angle of 119.2 ^{o} and bond lengths for vinylidenecarbene to be 1.352 Å for C=C, and 1.092 Å for C-H (Figure **1-14**).[28]



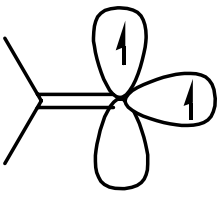
S_0 (singlet)

41



S_1 (singlet)

42



T_1 (triplet)

43

Figure **1-13**: Three low-energy spin states of an isopropylidenecarbene.[21,27]

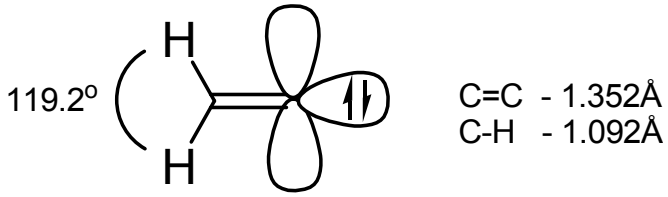


Figure **1-14**: Calculated structure of singlet vinylidenecarbene.[28]

The reactive electronic configuration of an alkylidenecarbene was examined by Stang and Mangum (1975) via the stereoselective cyclopropanation reactions of *cis*- and *trans*-2-butene (Figure **1-15**).[27] Isopropylidenecarbene **(44)** was generated *in situ* and reacted with either *cis*- or *trans*-2-butene **(45 or 47)** and the relative stereochemistry of the products was examined by gas chromatography to determine the ratio of *cis*- and *trans*-cyclopropane isomers **(46 and 48)**. It was found that these reactions proceed with great stereoselectivity, where *cis*-2-butene **(45)** produces the *cis*-cyclopropane compound **46**, and *trans*-2-butene **(47)** affords the *trans*-cyclopropane **48**. Because of this conservation of stereochemical information, it can be determined that the electronic configuration of the reactive alkylidenecarbene is in its singlet state (S_0). If the reactive alkylidenecarbene was in its triplet form **49**, this reaction would proceed as a diradical. Upon reaction with the olefin **45**, diradical **50** would form, which could undergo bond rotation, and the stereochemical information would be lost, generating a mix of *cis* and *trans* cyclopropane isomers **51** (Figure **1-16**). More recently Modarelli and coworkers confirmed the original work by Stang, studing the isopropylidenecarbene **(42)** spectroscopically using an argon matrix.[26] As originally proposed by Stang, the singlet carbene **41** is the reactive ground state, with the singlet isopropylidenecarbene ~45 kcal/mol more stable than the corresponding triplet alkylidenecarbene **43**.

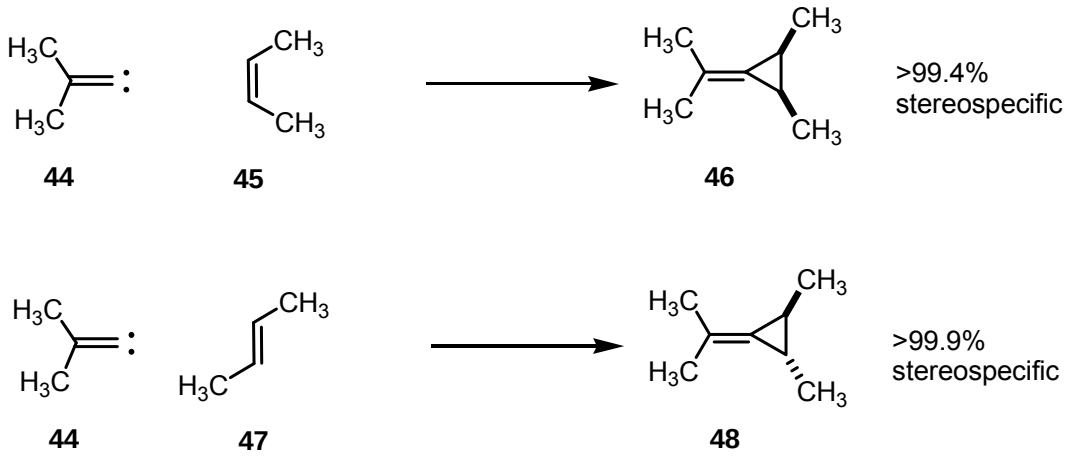


Figure **1-15**: Stereoselective cyclopropanation reactions with isopropylidenecarbene **(44)**.[27]

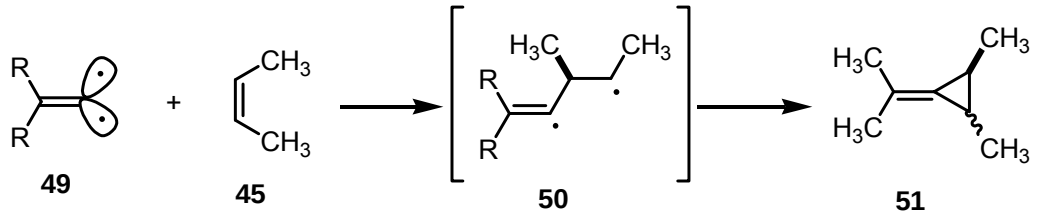


Figure **1-16**: Reaction of a triplet alkylidenecarbene.

1.4.2 Reactive Pathways of Alkylidenecarbenes

Alkylidenecarbenes can participate in a range of bond forming processes, creating a wide variety of structurally diverse compounds. Due to its empty p orbital, an alkylidenecarbene reacts as an electrophilic species with nucleophiles either inter- or intra-molecularly. Typical reactions are rearrangements, carbon-hydrogen insertions, additions to double bonds, H-X insertions, and heteroatom lone pair additions (Figure **1-17**).

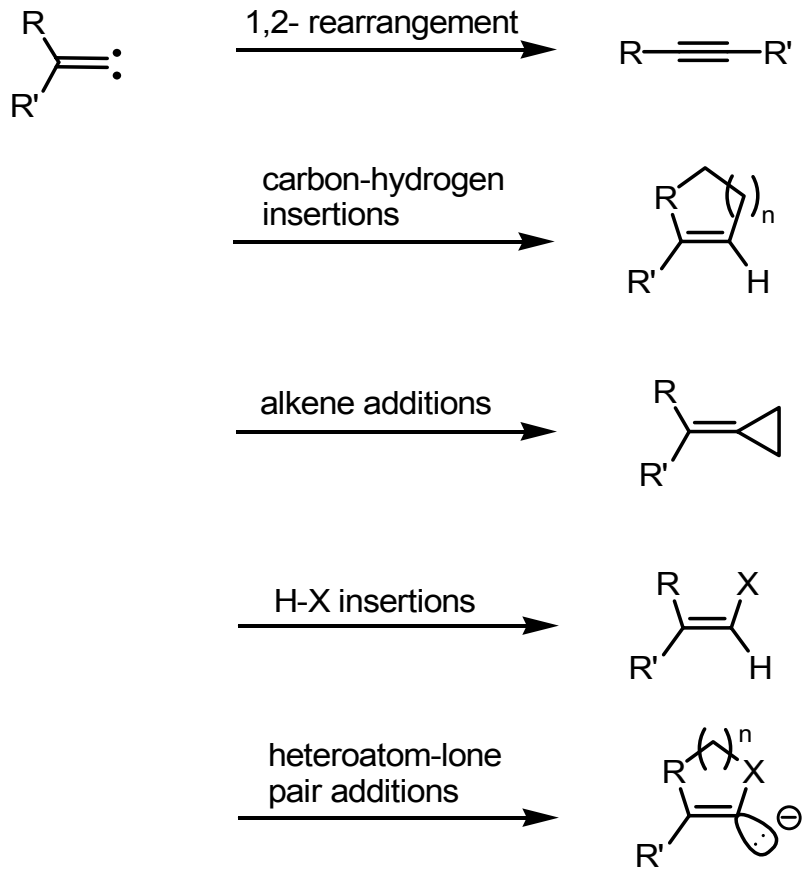
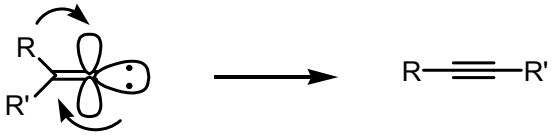


Figure **1-17**: Typical reactions of an alkylidenecarbene.

1.4.2.1 1,2 – Rearrangements

A common reaction of alkylidenecarbenes is a 1,2 rearrangement to form an acetylene product. This facile process occurs because the β-substituents in an alkylidenecarbene lie in the same plane as the empty p-orbital of the carbenic carbon (Figure **1-18**).[21] This orientation causes certain groups to migrate before any other course of reaction can take place. For example, when R is an aryl, alkylsilane or hydrogen, this 1,2-rearrangement dominates the chemistry of the carbene. Alkyl substituents, however, do not migrate as easily, and in these instances other reactivity pathways can be expressed.

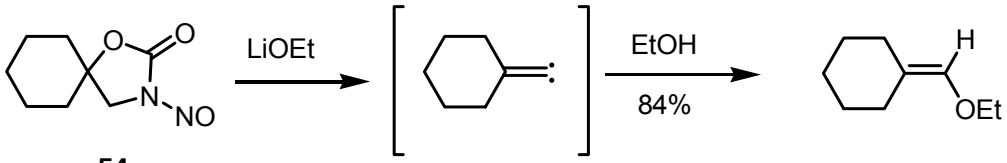


52 **53**

Figure **1-18**: 1,2-Rearrangement of an alkylidenecarbene.[21]

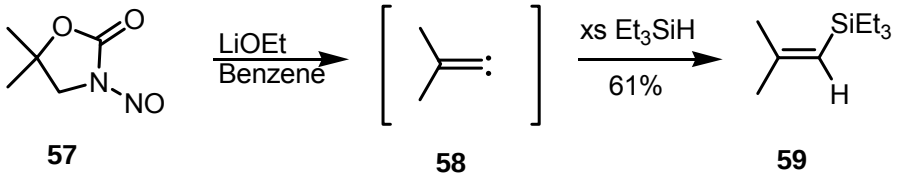
1.4.2.2 Intermolecular H-X Insertions

Alkylidenecarbenes can also undergo insertion into an electron rich covalent bond when migration is not a facile process. These carbenes readily insert into silicon-hydrogen (Si-H) and oxygen-hydrogen (O-H) bonds. In 1969, Newman and coworkers reported the use of cyclohexyl-*N*-nitrosooxazolidone **(54)** to generate the alkylidenecarbene **55** upon addition of lithium ethoxide. The alkylidenecarbene **55** underwent an insertion into the O-H bond of ethanol to generate the vinyl ether **56** (Figure **1-19**).[29] The following year, they reported the use of the dimethyl-*N*-nitrosooxazolidone **(57)** in the presence of lithium ethoxide to generate alkylidenecarbene **58**. When **58** is generated in the presence of excess triethylsilanes, the reaction affords the vinylsilane **59** in good yield via a Si-H bond insertion (Figure **1-20**).[30]



54 **55** **56**

Figure **1-19**: Alkylidenecarbene insertion into an O-H bond.[29]

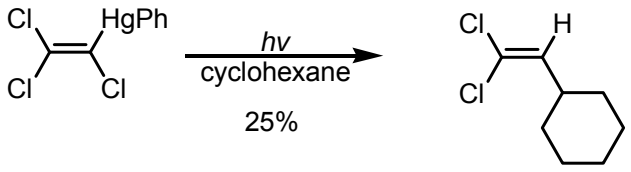


57 **58** **59**

Figure **1-20**: Insertion of an alkylidenecarbene into a Si-H bond.[30]

1.4.2.3 Carbon-Hydrogen Insertions

Unlike insertion into a Si-H bond and O-H bond, intermolecular insertion into a C-H bond occurs much less readily.[21] Intermolecular C-H insertions have only been observed with photogenerated carbenes and proceed in low yields (Figure **1-21**). It has been proposed that the C-H bond does not contain the necessary electron density to interact with the electron deficient carbene in an intermolecular process.

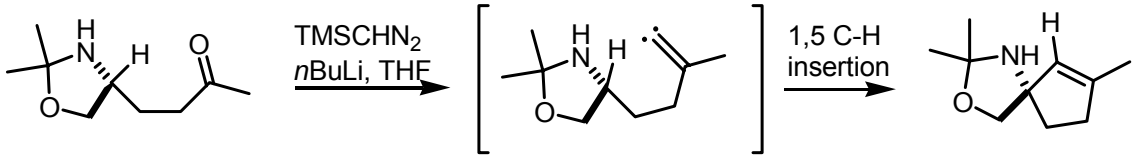


60 **61**

Figure **1-21**: Intermolecular C-H insertion.[21]

Intramolecular C-H insertions to generate unsaturated rings are very prominent in the use of alkylidenecarbenes in organic (Figure **1-22**). Alkylidenecarbenes have shown preference for 1,5 C-H insertion to generate 5-membered ring products, with the exclusion of 1,4 and 1,6 insertions. A few examples of 1,3 insertions have been observed as well.[31] Alkylidenecarbene insertion proceeds with retention of stereochemistry when reaction occurs at a stereogenic center. They also display selectivity in the C-H bonds they react

with, showing preference for more electron-rich bonds. The preference for insertion has been shown to be tertiary > secondary benzylic > secondary >> primary alkyl bonds.[31,32]



62 **63** **64**

Figure **1-22**: Intramolecular 1,5 Carbon-Hydrogen insertion reaction of an alkylidenecarbene.[33]

Gilbert and coworkers, in examining the stereochemical outcome of a 1,5 C-H insertion, investigated the possible trajectories of transfer of the hydrogen to the carbenic center (Figure **1-23**).[34] An "in plane" transfer of hydrogen has a linear orientation of the carbenic carbon atom and C-H bond as compared to the "out of plane" alternative, which has a non-linear relationship between the carbenic atom and the C-H bond. After studying temperature independent isotope effects for the 1,5 insertions, it was hypothesized that insertions occur through a non-planar, 6-membered transition state. The transfer of hydrogen proceeds via the formation of a complex between the σ bond and the carbenic carbon, followed by the development of the new C-H and C-C bonds.[34]

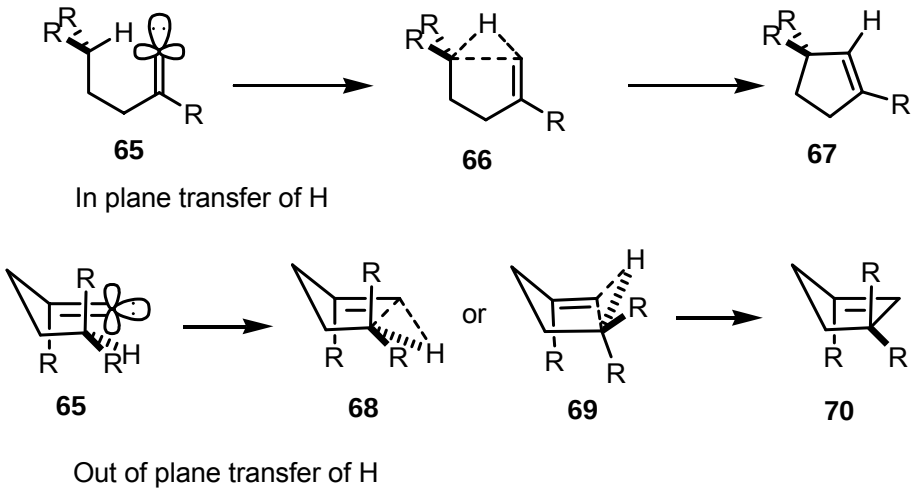


Figure **1-23**: Possible trajectories for the 1,5 C-H insertion.[34]

This non-planar transition state proposed by Gilbert could proceed through either a chair-like or boat-like architecture. However, experimental results have supported a dominance of the chair-like transition state in these C-H insertions.[35,36] Taber and coworkers, in 1994, reported a 1,5 C-H insertion which proceeded with modest diastereoselectivity (Figure **1-24**). The alkylidenecarbene **74** can proceed through two different nonlinear transition states, a chair-like transition state **75**, leading to *trans* product **72**, or a boat-like transition state **76**, leading to *cis* product **73**. The *trans* product **72** was found to be the favored product by a 4.4 : 1 ratio over the *cis* product **73**, thus showing preference for a chair-like transition state.

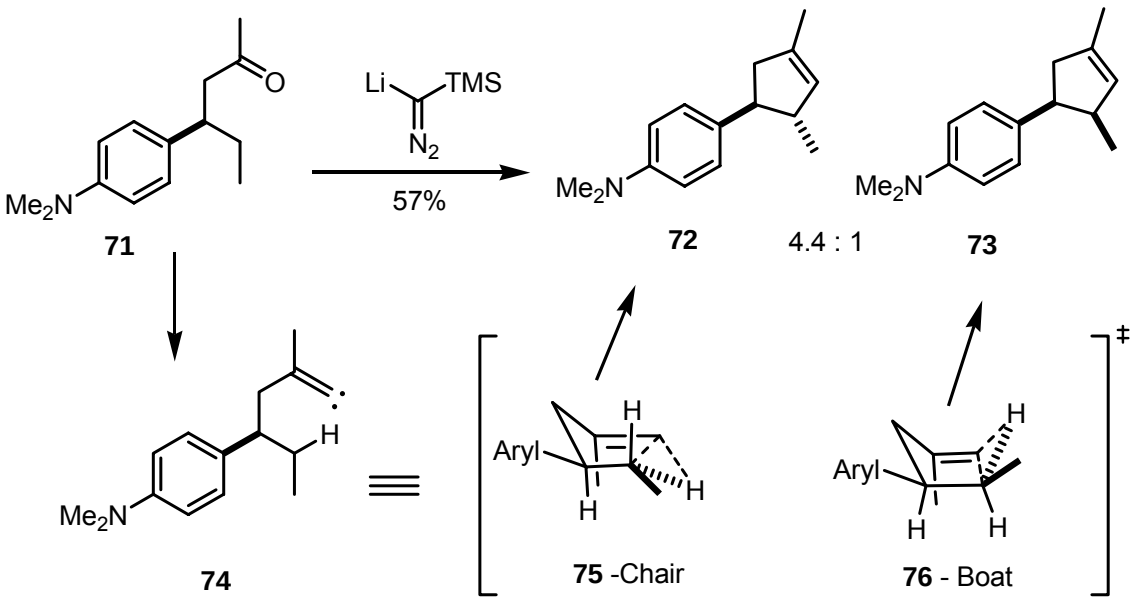


Figure **1-24**: Examination of the transition state of a 1,5 C-H insertion of an alkylidenecarbene to generate substituted cyclopentene diastereomers.[36]

1.4.2.4 Heteroatom-Lone Pair Additions

Alkylidenecarbenes have also been shown to add to a heteroatom (nitrogen, oxygen) lone pair in a reaction that can out-compete C-H insertion.[37-41] In this reaction, the lone pair on the heteroatom adds to the empty *p* orbital, creating ylide **78** (Figure **1-25**). A formal Steven's rearrangement[42] of the R' group then occurs to generate the heterocycle **79**. When the heteroatom is an oxygen, dihydrofurans can be generated as in Figure **1-26**,[38,39] where the alkylidenecarbene **81** inserts into the lone pair on oxygen, forming ylide **82**. A shift of the alkyl group generates the dihydrofuran product **83**. Another example by Feldman and coworkers demonstrates the additions of a nitrogen lone pair, to the exclusion of 1,5 C-H insertion, to generate a dihydropyrrole (Figure **1-27**).[37] The rotational isomers of alkylidenecarbene **85**, generated from alkynyliodonium salt **84**, have two options for reaction: a 1,5 C-H insertion to generate the

cyclopentene **88**, or combination with the lone pair on nitrogen leading to ylide **86**. The ylide **86** can then lose a proton from the acetonide, followed by ring opening and protonation of the vinyl anion to afford the cyclized compound **87**. The cyclopentene product was not observed and instead the dihydropyrrole product **87** was isolated in modest yield revealing the preference for lone-pair addition over C-H insertion.

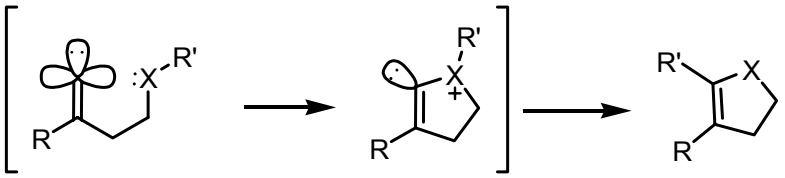


Figure **1-25**: Combination of an alkylidenecarbene with a heteroatom lone pair.[37]

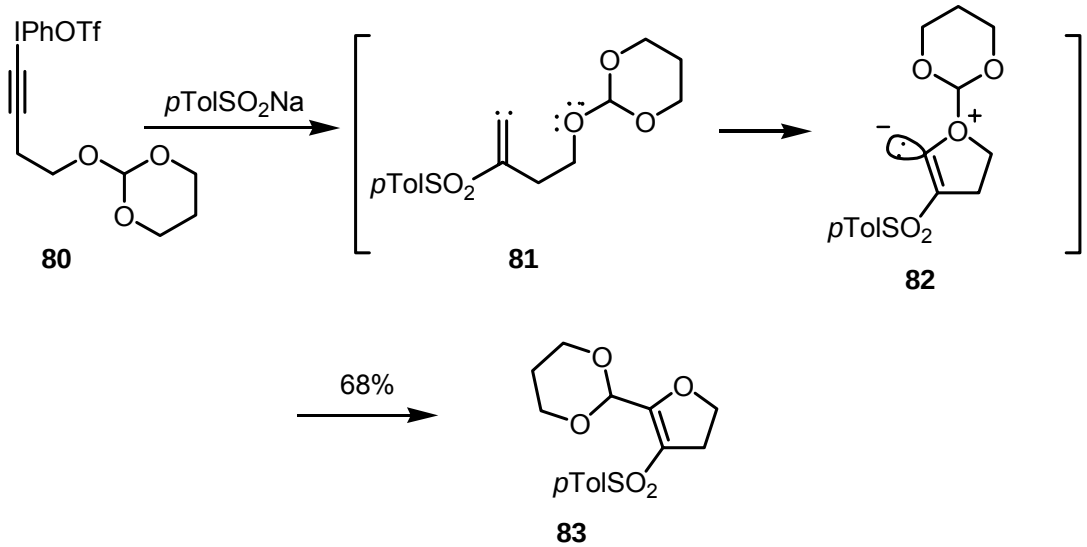


Figure **1-26**: Formation of 2-substituted dihydrofuran via lone pair addition of an alkylidenecarbene.[38,39]

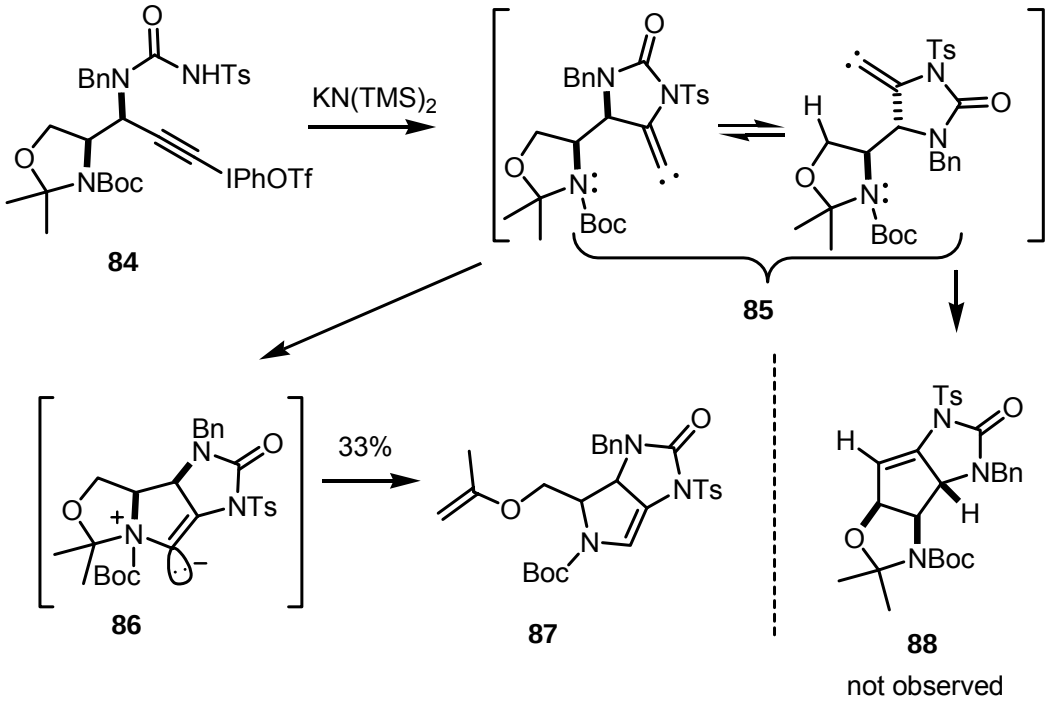


Figure **1-27**: Nitrogen lone pair addition of an alkylidenecarbene.[37]

1.4.2.5 Alkene Additions – Cyclopropanations

When more facile pathways are not available, alkylidenecarbenes can also add to sources of unsaturation to generate three-membered ring-containing systems. As shown previously in the determination of the nature of an alkylidenecarbene, section 4.1.4, alkylidenecarbenes can add to olefins to generate methylenecyclopropane rings.[43-46] They can also add to other unsaturated bonds (i.e. allenes,[21] C=O,[47] N=O,[48] and C=S[49]) to generate three-membered rings, which can further react. The addition of alkylidenecarbenes to olefins has been exploited in synthesis to generate bicyclic ring systems that can undergo ring expansion (Figure **1-28**).[43] In 1986, Gilbert and coworkers reported the synthesis of cyclohepta[*b*]pyrrol-2-one **(91)** via the intramolecular addition of the alkylidenecarbene **89** to a double bond of the aromatic ring, generating the

unisolated tricyclic intermediate **90**. Ring opening of the cyclopropane afforded the bicyclic compound **91** in good yield.

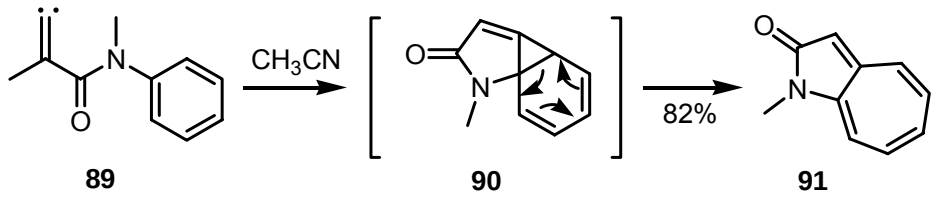


Figure **1-28**: Alkylidenecarbene addition to an olefin followed by ring expansion of methylenecyclopropane to generate cyclohepta[*b*]pyrrole-2-ones.[43]

The synthesis of 1,3-dioxalane compound **95** was reported in 1973 by Kuo and coworkers. This chemistry involved addition of an alkylidenecarbene to a C-O double bond (Figure **1-29**).[47] The alkylidenecarbene **92** was combined with 4-methylbenzaldehyde **(93)** to generate the allene oxide intermediate **94**. This highly reactive species then reacts with another equivalent of aldehyde **93** to afford the 1,3-dioxalane **95** in low yield.

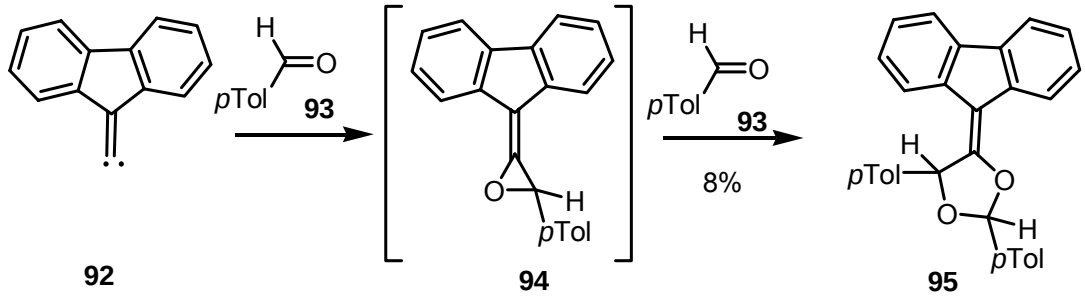


Figure **1-29**: Alkylidenecarbene addition to a carbonyl to generate a 1,3-dioxalane.[47]

Alkylidenecarbenes can also react with C-S and N-O double bonds to generate three-membered ring structures. Addition of alkylidenecarbene **96** to *p*-tosylisothiocyanate **(97)** generates thiiranimine **98** in good yield (Figure **1-30**).[48,49] Addition could occur at either double bond of the isothiocyanate **(97)**. However, the C=S bond strength is only about 130 kcal/mol compared to 143 kcal/mol for

the C=N bond, which provides a rational for the preferential formation of the thiiranimine product **98**.[48] A similar structure is generated upon addition across the N=O bond as seen in Figure **1-31**.[48] In this example, isopropylidenecarbene **(99)** is added to the nitroso compound **100** to generate initially the alkylideneoxazoline **101**, which undergoes a rearrangement to generate the α-lactam **102**.

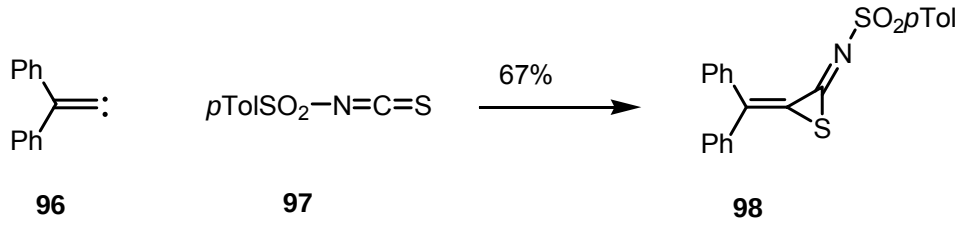


Figure **1-30**: Generation of a Thiiraminime via Addition to an Isothiocyanate.[48,49]

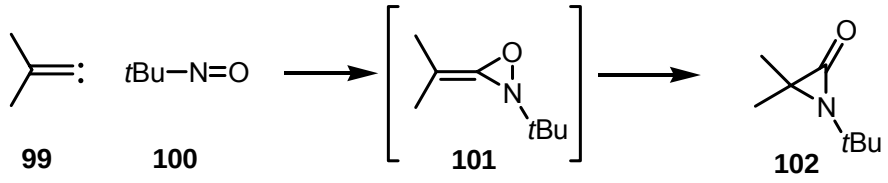


Figure **1-31**: α-Lactam Formation from Alkylidenecarbene Addition to a Nitroso Compound.[48]

1.5 Alkylidenecarbene Aromatic C-H Insertions

While it has been shown that carbenes can insert into saturated benzylic, tertiary, secondary and primary C-H bonds, insertion into aromatic and vinylic C-H bonds is much less common. This observation is presumably due to the stronger bond strength of a C_{sp}^2-H compared to a C_{sp}^3-H bond.[50] Some of these aromatic C-H insertions have been reported only under pyrolysis conditions.[21,51]

However, a few examples of aromatic 1,5 C-H insertions have been reported. These transformations have been shown to occur under mild conditions.

Stang and coworkers, in 1993, reported an aromatic 1,5 C-H insertion that occurs in solution at room temperature (Figure **1-32**).[50] Starting with the alkynyliodonium salt **103**, the alkylidenecarbene **105** was generated by nucleophilic attack of sodium *p*-toluenesulfinate **(104)**. This carbene **105** then underwent an aromatic insertion into the C-H bond to generate the indene compounds **106**. Yields were seen to vary due to the nature of the aryl ring. When an activating group (OMe) was on the ring, the reaction proceeded in better yield then when a deactivating group (CF_3) was present.

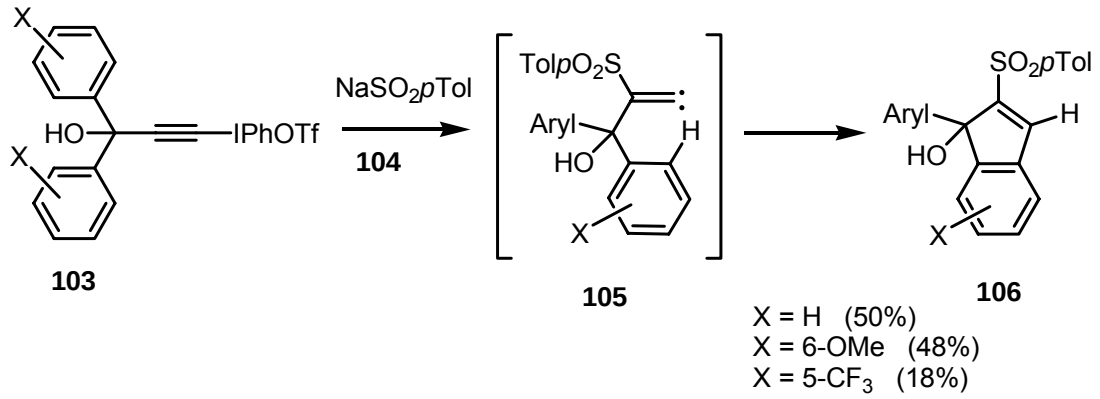
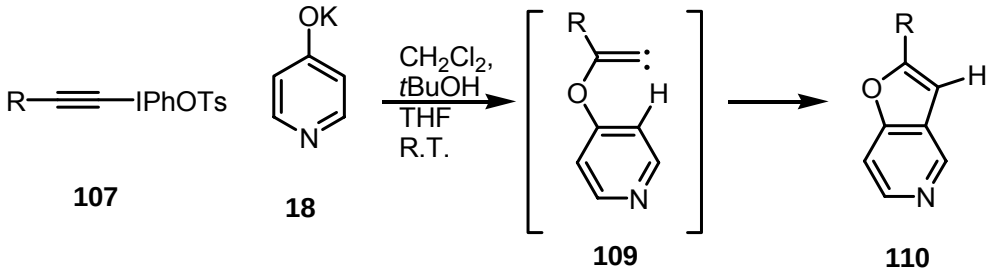


Figure **1-32**: Aromatic 1,5 C-H insertion of an alkylidenecarbene.[50]

A second example of an aromatic C-H insertion was reported by Kitamura and coworkers for the generation of furopyridine structures.[52,53] Figure **1-33** shows the generation of 2-substituted furo[3,2-*c*]pyridine derivatives **(110)** from the reaction of the potassium salt of 4-hydroxypyridine **(108)** with the tosyl iodonium salt **107**. The alkylidenecarbene **109** actually has two choices for C-H insertion, the aromatic C-H bond, and the alkyl C-H bond of the R group on the starting tosyl salt. However, no (4-pyridyloxy)cyclopentenes (not shown) are derived from aliphatic C-H insertions, leading to the conclusion that the C-H insertion at the heteroaromatic ring is more favorable than C-H insertion at the alkyl group. Additional examples shown by Kitamura suggests that the

preference for 1,5 insertions over 1,6 insertions in aromatic C-H bonds is general (Figure **1-34**).[52] Using the potassium salt of the 4-hydroxyquinoline **(111)**, the furo[3,2-*c*]quinoline system **113** was formed exclusively with no evidence of alkyl C-H insertion or aromatic 1,6 C-H insertion at the *peri* position.



R =
*n*Pr (65%), *n*Bu (86%), *n*Hex (49%), *n*Oct (58%), *n*Dec (44%)

Figure **1-33**: Synthesis of 2-substituted furo[3,2-*c*]pyridine derivatives via alkylidenecarbene insertion into an aromatic C-H bond.[53]

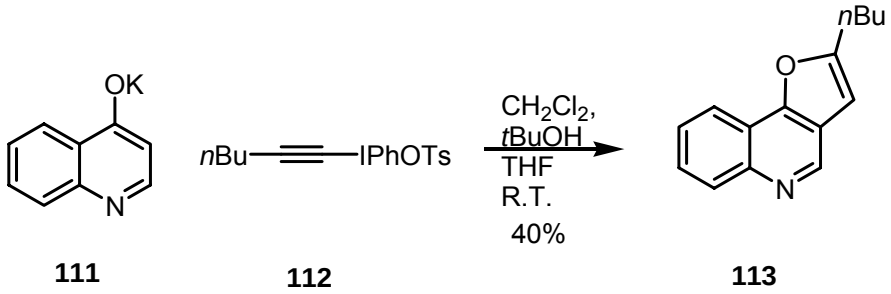


Figure **1-34**: Synthesis of furo[3,2-*c*]quinoline system via aromatic C-H insertion.[52]

Gilbert and coworkers reported an example of aromatic 1,6 C-H insertion and compared it to the rate of other reactions that could occur within their system.[54] Using the same alkylidenecarbene **89** as Figure **1-28**, it was discovered that by changing the reaction solvent to methanol, three additional products could be generated (Figure **1-35**). In acetonitrile, the reaction proceeds to generate only the cyclohepta[*b*]pyrrol-2-one **(91)** via addition to the aryl ring, in

82% yield (see Section 1.4.2.5). However, when the solvent is switched to methanol, compound **91** still dominates the product mixture, but also formed are the products of 1,5 C-H insertion **114**, 1,2 migration **115**, and an aromatic 1,6 C-H insertion **116**, albeit in low yields.

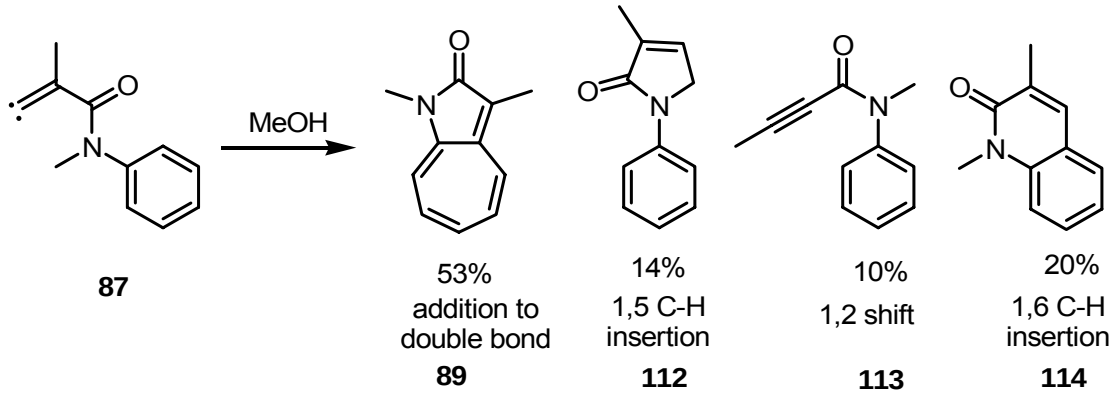


Figure **1-35**: Four different products formed from the alkylidenecarbene in methanol.[54]

This chemistry was the first example of a 1,6 C-H insertion into an aromatic C-H bond. A stepwise mechanism was proposed for the formation of the 1,3-dimethylquinol-2-one **(116)**, which was hypothesized to pass through the zwitterionic intermediate **118** (Figure **1-36**). Deuterium labeling studies were performed to determine if 1,6 C-H insertion was a concerted process, a situation that would yield a deuterium atom at the 4-position of the quinol-2-one ring. However, if the reaction proceeds through a stepwise mechanism, the deuterium could be lost to the protic solvent via protonation/deprotonation of the zwitterionic intermediate **118**, leading to a hydrogen atom at the 4-position. The results showed the complete loss of the deuterium atom in the conversion to **116**, an observation consistant with a stepwise mechanism featuring protonation from the solvent.

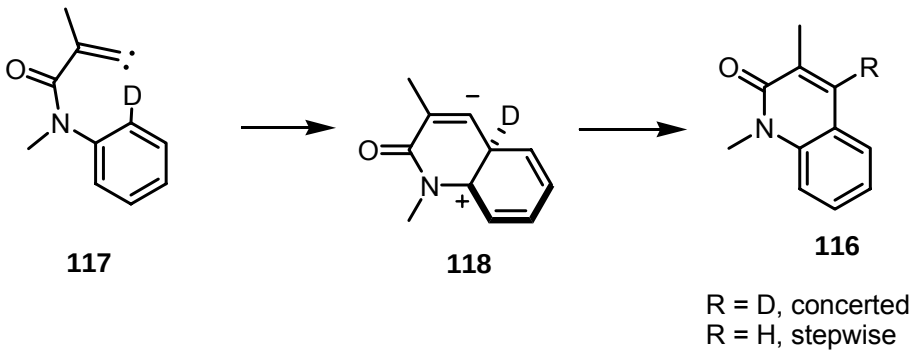
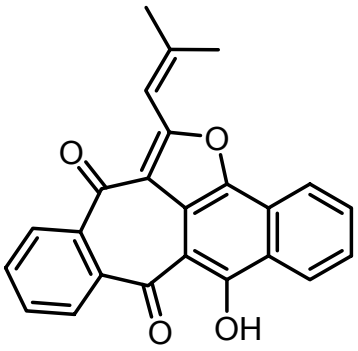


Figure **1-36**: Stepwise mechanism of C-H insertion.

1.6 Radermachol

1.6.1 Isolation and Previous Total Syntheses

Radermachol **(3)**, a red pigment, was isolated in 1984 by Joshi *et al.* from the roots of the plant *Radermachera xylocarpa* (Figure **1-37**).[55] This compound contains three six-membered, one five membered, and one seven-membered ring. This fused aromatic ring system is unique and has not been encountered previously in any other natural product. The first total synthesis of **(3)** was competed in 1991 by Pelletier *et al.* using 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane **(119)** as a key intermediate (Figure **1-38**).[56,57] This first total synthesis of radermachol was completed in 14 steps with an overall yield of 7%. A second synthesis was complete in 2000 by Hauser *et al.*, which also used precursor **119** as a key intermediate.[58]



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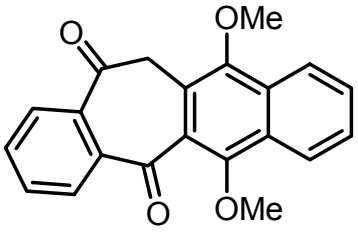


119

Figure **1-37**: Radermachol and 6,7-benzo-3,4-(1,4-dimethoxy-2,3-naphtho)-1,5-dioxosuberane key intermediate.[55]

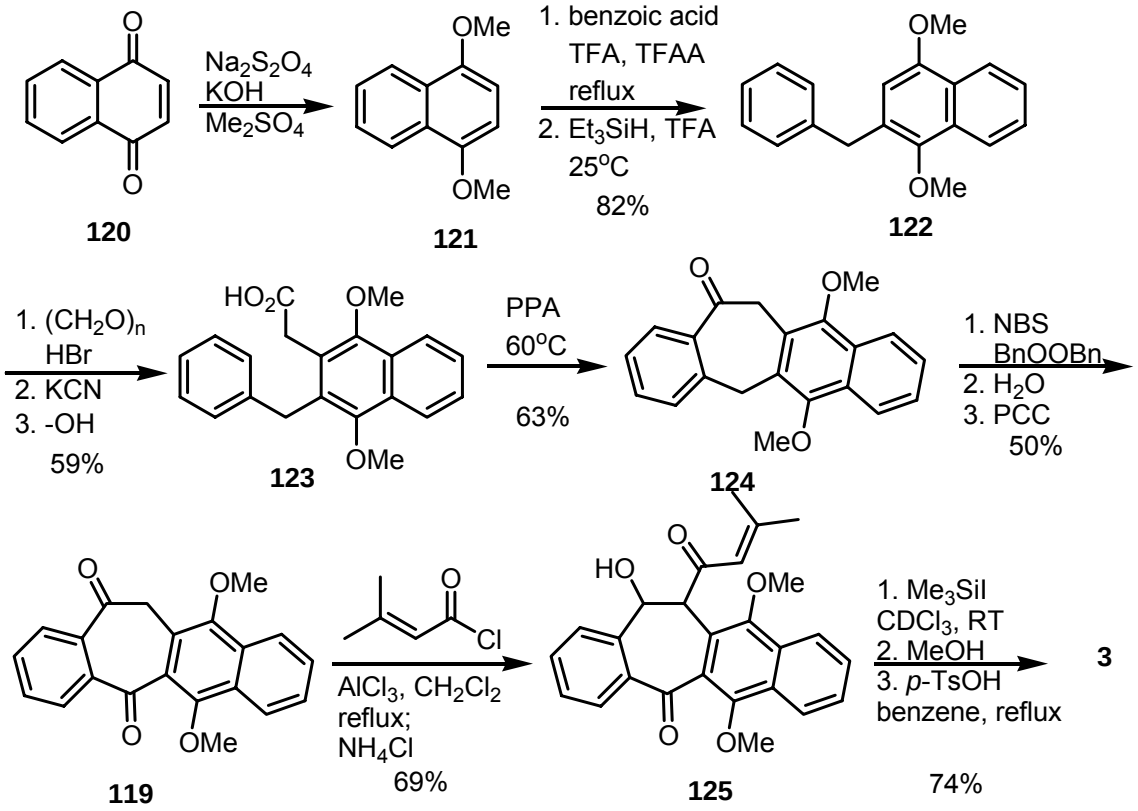


Figure **1-38**: The first synthesis of radermachol.[56,57]

1.6.2 Proposed Total Synthesis

The proposed synthesis to radermachol is different from those previously completed in that it would involve a ring expansion to generate the seven-membered ring. A retrosynthetic proposal is shown in figure **1-39** , where the key transformation involves the reaction of the phenoxide anion **131** with the alkynyliodonium species **130** to generate the alkylidenecarbene **129**. The alkylidenecarbene can then undergo addition to the double bond to form the methylene cyclopropane compound **128**, which can undergo a ring expansion to generate the seven-membered ring of **127**. Further synthetic manipulations can be accomplished to complete the synthesis of radermachol **(3)**. Model systems for the synthesis of radermachol **(3)** looked at the reaction of alkylidenecarbenes that were derived from phenoxide anions of naphthol derivatives.

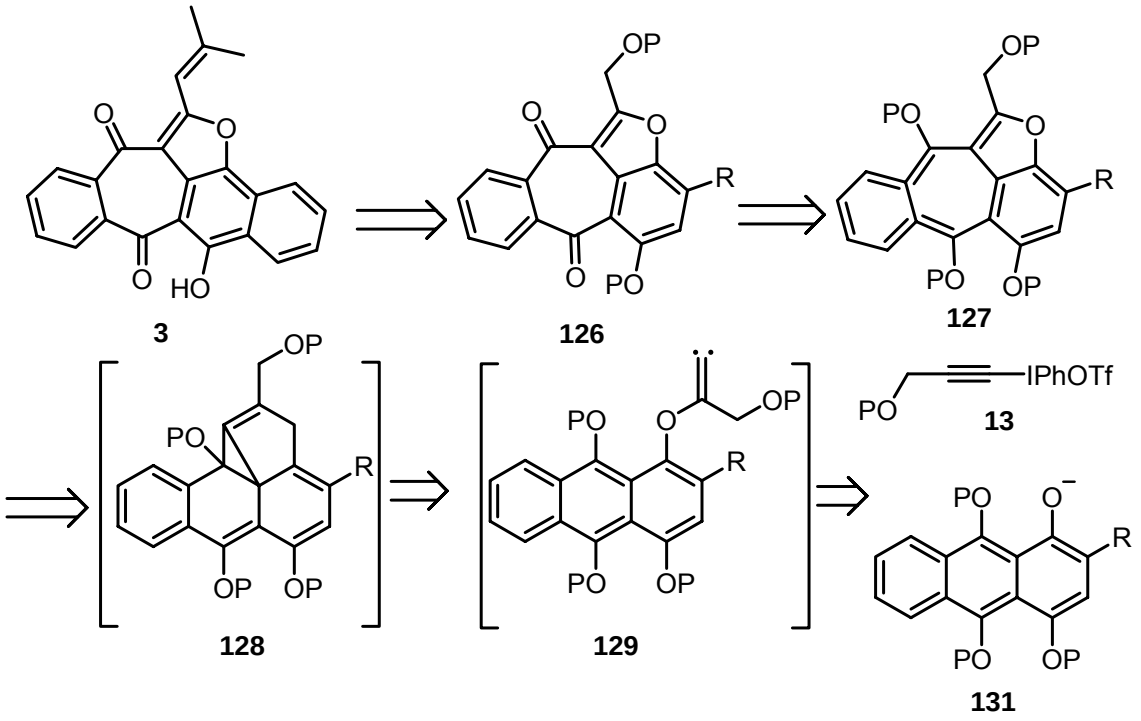


Figure **1-39**: Retrosynthetic analysis of radermachol.

1.7 Naphthol Derivatives

The work reported by Gilbert and Kitmura led to the examination alkylidenecarbenes derived from naphthol derivatives to determine a preference for reaction. This examination of phenoxy-substituted alkylidenecarbenes commenced with the reaction of 1-naphthol **(132)** and the propynyliodonium(phenyl) triflate salt **(133)**, which was used as a baseline of comparison between aryl 1,5 and 1,6 insertion and addition to the double bond. 1-Naphthol **(132)** was deprotonated with *n*-butyllithium, followed by addition of propynyliodonium salt **133**, which generated alkylidenecarbene **134** (Figure **1-40**). The alkylidenecarbene **134** underwent exclusively 1,5 C-H insertion into the aryl C-H bond to generate the furan containing product **135**, in modest yield. There was no evidence of a 1,6 C-H insertion product, alkene addition product or a 1,2- rearrangement product. However due to the lability of the alkynyl ether product, it could not be assumed that the 1,2- rearrangement species was not formed, since isolation may not be feasible. These results parallel the results by Kitmura (Figure **1-34**), with preference shown towards the formation of the 1,5 C-H insertion product with the exclusion of the 1,6 C-H product and alkene addition product.

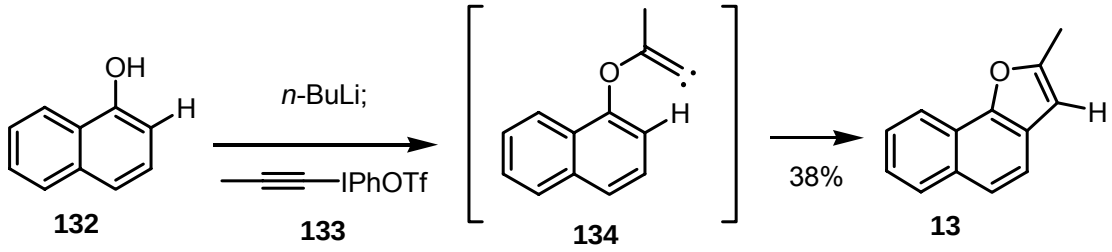
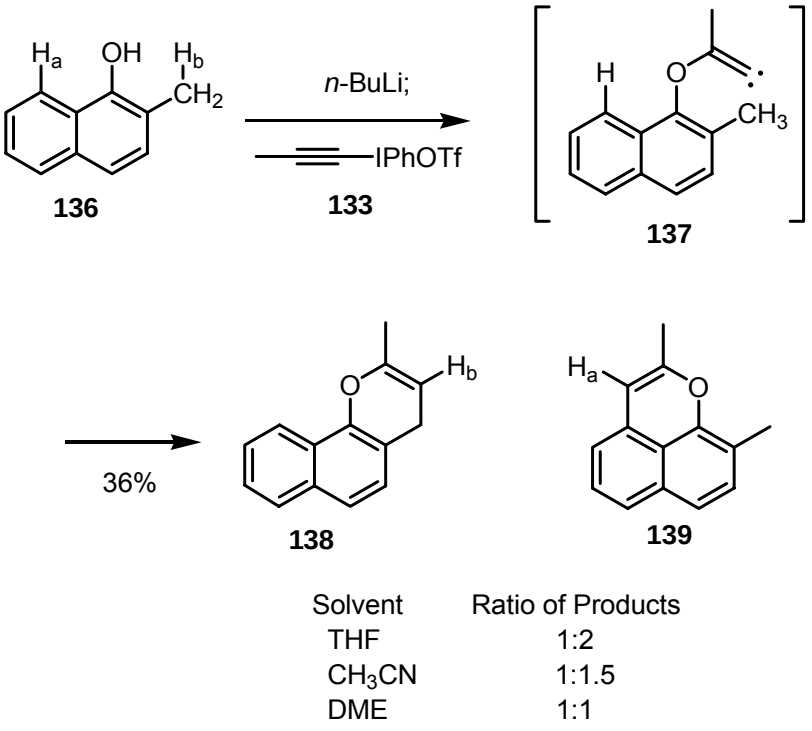


Figure **1-40**: The use of 1-naphthol to examine an aromatic C-H insertion.

The next progression in this study focused on the blocking of the *ortho* position in an attempt to force a 1,6 aryl insertion or addition to the double bond. Using 2-methyl-1-naphthol **(136)**, which had a methyl group at the *ortho* position, the possibility of 1,5 C-H insertion was eliminated. In a similar fashion, 2-methyl-1-naphthol **(136)** was treated with *n*-butyllithium, followed by addition of the propynyliodonium salt **133** to generate alkylidenecarbene **137** (Figure **1-41**). Examination of the product mixture showed the generation of two compounds of 1,6 C-H insertion, an expected product **138** resulting from insertion in the aryl C-H_a bond, but also an unanticipated product **139** from insertion into the alkyl C-H_b bond, there was also no evidence of addition to the double bond. Both insertion products were formed in a combined 36% yield with an approximate 2 : 1 to 1 : 1 ratio (depending on solvent) favoring the formation of aryl C-H_a insertion. While there are examples of aromatic 1,6 C-H insertion, this case was the first example of aliphatic 1,6 C-H insertion.



Solvent	Ratio of Products
THF	1:2
CH_3CN	1:1.5
DME	1:1

Figure **1-41**: 2-Methyl-1-naphthol reacted with propynyliodoium(phenyl)triflate to study aromatic 1,6 C-H insertion.

Further modification of the substrate led to the use of 2,4-dichloro-1-naphthol **(140)** and salt **133** to probe the scope of aryl C-H insertion vs alkene addition (Figure **1-42**). Upon generation of the alkylidenecarbene **141** from the lithium salt of **140** and the propynyliodonium salt **133**, aromatic 1,6 C-H insertion occurred in good yield to give **142** as the only product.

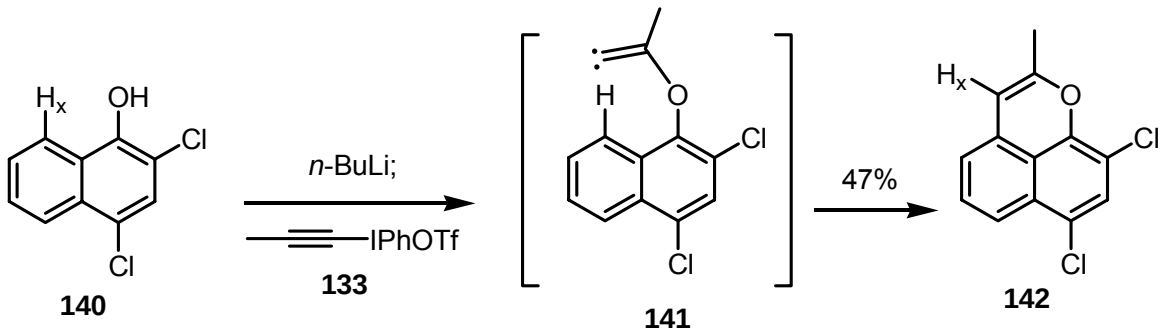


Figure **1-42**: Examination of aryl 1,6 C-H insertion with 2,4-dichloro-1-naphthol.

Further examination of this reaction established the origin of the H_x proton. This information can in turn, be used to determine if the reaction proceeds through a stepwise mechanism, like that proposed by Gilbert, or a concerted process. Gilbert proposed the protonation of the zwitterionic intermediate **118** (Figure **1-36**) with the solvent. By repeating this reaction in a deuterated protic solvent (CD_3OD), one could test the theory of a stepwise mechanism. When the experiment was run again in CD_3OD, there was no deuterium incorporation seen at H_x (^{1}H NMR or CI MS). This negative result rules out any mechanism that involves exchange of H_x with the solvent.

One last naphthol derivative containing a blocking group at the *ortho* position was examined, 2-phenyl-3-trimethylsilyl-1-naphthol **(145)**, which could be synthesized in one step from terephthaldehyde **(143)** (Figure **1-43**).[59,60] This new naphthol derivative has an additional site for reactivity of the carbene with a phenyl group six atoms away. However, when the lithium salt of **145** was combined with propynyliodonium salt **133**, the only product seen was C-H insertion at the *peri* position, with no reaction occurring at the phenyl groups *ortho* position, as well as no alkene addition seen.

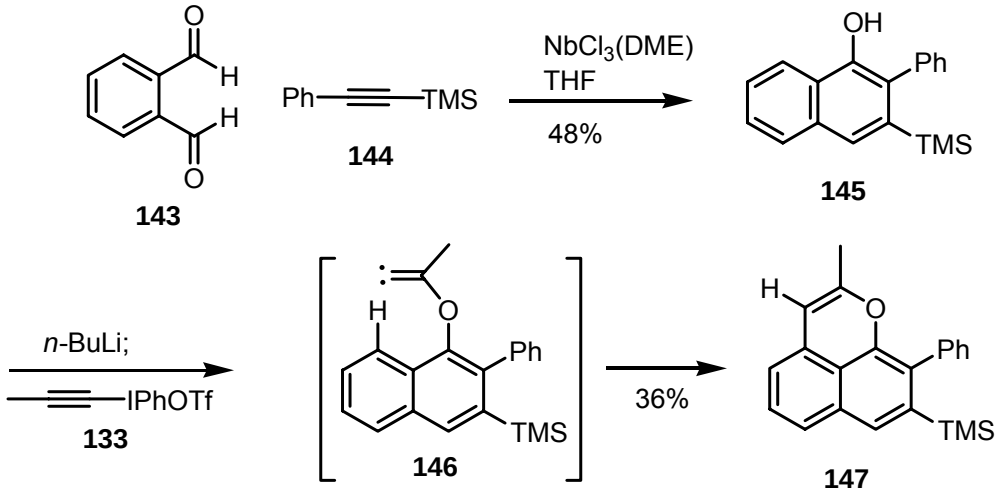


Figure **1-43**: Insertion of the alkylidenecarbene of 2-phenyl-3-trimethylsilyl-1-naphthol.

1.8 Anthroxy-Substituted Alkylidenecarbene

A final examination of the phenoxy-substituted alkylidenecarbene chemistry was completed with 2-phenyl-3-trimethylsilyl-1-anthrol **(139)**,[59,60] which was synthesized by a procedure similar to that used for the naphthol derivative **145** (Figure **1-44**). Alkylidenecarbene reaction occurred at the *peri* position of the anthrol ring, leading to a C-H insertion to afford **151** in modest yield. There was no reaction seen at the *ipso* position of the phenyl group.

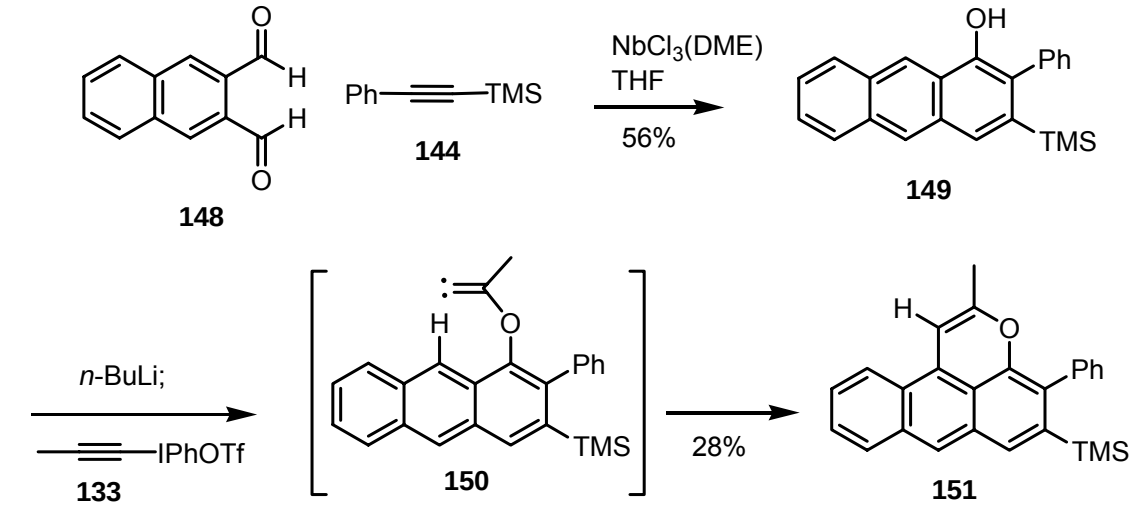


Figure **1-44**: Aromatic C-H insertion of the anthroxy-substituted alkylidenecarbene.

1.9 Conclusions

In summary, the value of alkynyliodonium salts in organic synthesis is due to their ability to serve as alkylidenecarbene precursors under mild experimental conditions (Figure **1-1**). Alkylidenecarbenes are highly reactive species containing a divalent carbon atom that can participate in a variety of bond forming processes including 1,2 migrations, C-H insertions, heteroatom-H insertions, heteroatom-lone pair additions, and additions to double bonds. The

insertion of these alkylidenecarbenes into C_{sp}^2-H bonds of naphthol and anthrol systems was examined. It was determined that insertion into an aromatic 1,5 C-H bond was the preferred course of the reaction. However, when this position was blocked, 1,6 C-H insertion into the *peri* position occurred almost exclusively. The only other competitive reaction was the 1,6 aliphatic C-H insertion, which occurred when the *ortho* substituted group was a methyl. These reaction all occurred at the expense of addition to the double bond, as would be desired for the synthesis of radermachol.

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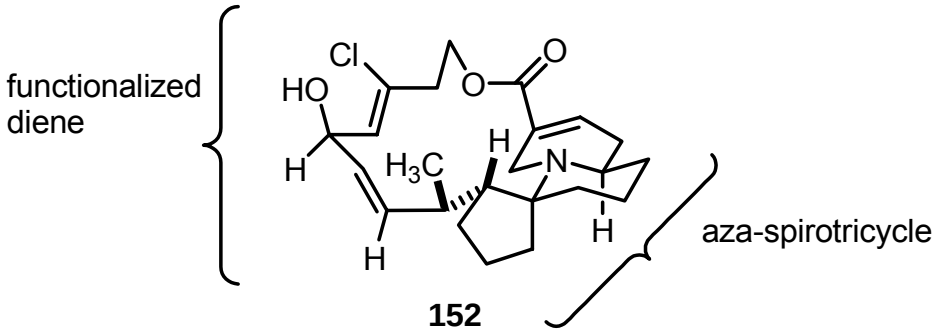
Chapter 2

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF THE SPIROCYCLIC CORE OF HALICHLORINE

2.1 Overview

Halichlorine (**152**, Figure **2-1**) is a structurally unique marine alkaloid which was isolated from the sponge *Halichondria okadai Kadota* in 1996.[61,62] Biological evaluation indicated that halichlorine inhibited the induction of VCAM-1 (vascular cell adhesion molecule-1) with an IC_{50} of 7 μg/mL. The selective inhibition of VCAM-1 makes halichlorine a worthwhile target for chemical synthesis, as drugs that specifically block the induced expression of VCAM-1 may be useful for treating atherosclerosis, coronary artery disease, angina, and non-cardiovascular inflammatory diseases. Structurally, halichlorine features an aza-spirotricycle core and a functionalized diene macrolactone.



152

Figure **2-1**: (+) – Halichlorine.

The synthesis of the aza-spirotricyclic core is discussed herein. The focus of this synthesis was the generation of the quaternary center of the spirocyclic system (Figure **2-1**). It was hypothesized that the key quaternary center could be

formed utilizing the series of reactions shown in Figure **2-2**. Alkynyliodonium salt **153** would be used to generate alkylidenecarbene **154** upon reaction with an appropriate nucleophile. The generated alkylidenecarbene **154** could then undergo a 1,5-C-H insertion to generate the quaternary center of the spirocyclic ring system precursor **155** with retention of stereochemistry at the quaternary center. Efforts to develop this methodology are described below.

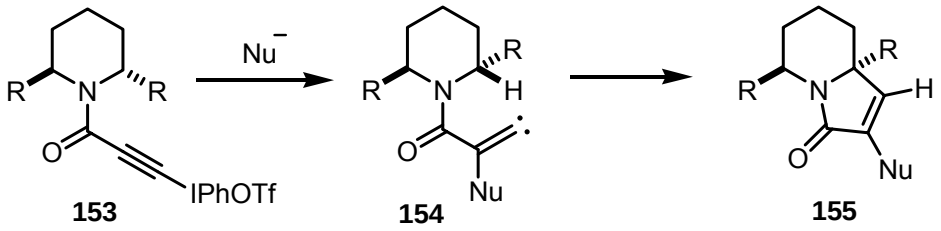
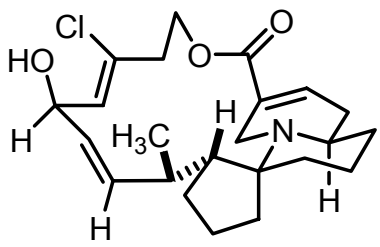


Figure **2-2**: Utilization of an alkynyliodonium salt to generate the quaternary center of halichlorine.

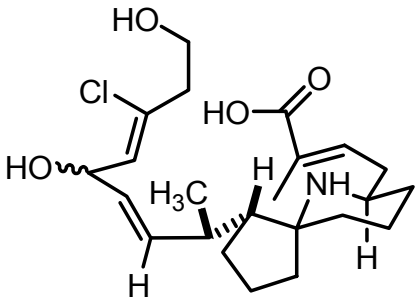
2.2 Isolation and Biological Activity

2.2.1 Isolation of Halichlorine

Two related alkaloids were isolated in 1996 by Uemura and coworkers from Okinawan waters, halichlorine **(152)** from the sponge *Halichondria okadai Kadota*,[61,62] and pinnaic acid **(156)** from the Okinawan bivalve *Pinna muricata*[63] (Figure **2-3**). Both compounds were found to contain a similar spirocyclic ring system and analogous functionality about the olefinic portion. The more complex halichlorine **(152)** alkaloid contains an additional fused ring and a 15-membered macrolactone.



Halichlorine
152



Pinnaic Acid
156

Figure **2-3**: (+) - Halichlorine and Pinnaic Acid.

2.2.2 Biological Activity of Halichlorine

Both halichlorine **(152)** and pinnaic acid **(156)** were found to exhibit anti-inflammatory activity. Halichlorine **(152)** was found to selectively inhibit the induced expression of VCAM-1 at IC_{50} = 7 μg/mL. The synthetic interest in halichlorine **(152)** is attributed to this ability to selectively inhibit VCAM-1, which makes it a potential lead target for the development of drugs to treat atherosclerosis, coronary artery disease, angina, and non-cardiovascular inflammatory diseases. Current pharmaceutical therapeutics for these conditions do not selectively inhibit VCAM-1, but inhibit other cellular adhesion molecules (CAM's) as well, yielding undesired immune inflammatory responses. The identification and development of selective VCAM-1 inhibitors would be of great therapeutic interest.

The cascade of events leading to inflammation begins with an initial stimulus or injury that causes leukocytes to slow and roll along the endothelial lining of the blood vessels (Figure **2-4**).[64-69] This initiation event is followed by an adhesion to the surface of the endothelial cells via a cell adhesion molecule (CAM). Once attached to the cell surface, the leukocytes migrate along the

surface to an intercellular junction, which allows the leukocyte to pass through the vessel wall and into the affected tissue. This localized attachment and recruitment of leukocytes is recognized as a central aspect of the inflammatory response. When the inflammatory response does not effectively neutralize the inflammatory stimulus chronic inflammation and related problems result.

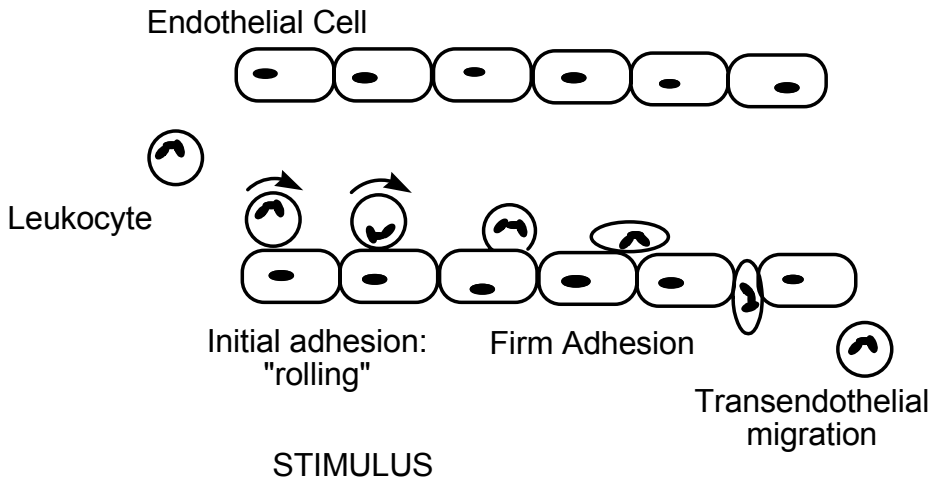


Figure **2-4**: Cellular events that occur during inflammation.

The key adhesion receptors belong to three molecular families: the selectins, the immunoglobulin supergene family and the integrins. It is the members of the immunoglobulin supergene family that are found on endothelial cell walls and that participate in the recruitment of leukocytes in inflammation. The three main endothelial CAM's include ELAM-1 (endothelial adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and VCAM-1 (vascular cell adhesions molecule-1). These CAM's are expressed on the surface of endothelial cells upon stimulation by the inflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). ELAM-1 mediates early and reversible events of leukocyte binding, while both ICAM-1 and VCAM-1 regulate later and irreversible binding events leading to the attachment and recruitment of the leukocytes into endothelial cells. The development of therapeutics that would

inhibit these two cell adhesion molecules could be possible targets in the treatment of inflammation.

2.3 Previous Studies Directed Towards the Synthesis of Halichlorine

Many studies towards the synthesis of the aza-spirocyclic core of halichlorine and pinnaic acid have emerged since the isolation of these alkaloids in 1996. The general focus of these syntheses is the construction of the core spirocyclic structure. Danishefsky and coworkers provided the first and only asymmetric total synthesis of halichlorine, while others have provided syntheses of the spirocyclic core.

2.3.1 The First Asymmetric Total Synthesis of Halichlorine

The first and only asymmetric total synthesis of halichlorine **(152)** was completed in 1999 by Danishefsky and coworkers (Figure **2-5** and Figure **2-6**).[70,71] Their route started with readily prepared Meyer's lactam **159**, which upon further functionalization of the β-lactam system, afforded compound **160** containing the appropriate stereochemistry at the quaternary center. Stereoselective methylation, followed by ring opening, and protection led to the formation of compound **161**, which contains all the stereochemical information for the spirocyclic core of halichlorine. This unit was then coupled with olefin **147** to yield the functionalized cyclopentane **163**. Removal of the Boc protecting group set up an intramolecular Michael reaction, affording spirocycle **164**. Claisen condensation, followed by a Mannich reaction, yielded the construction of the fused tetrahydropyridine moiety of **165**, which is the core tricycle of halichlorine.

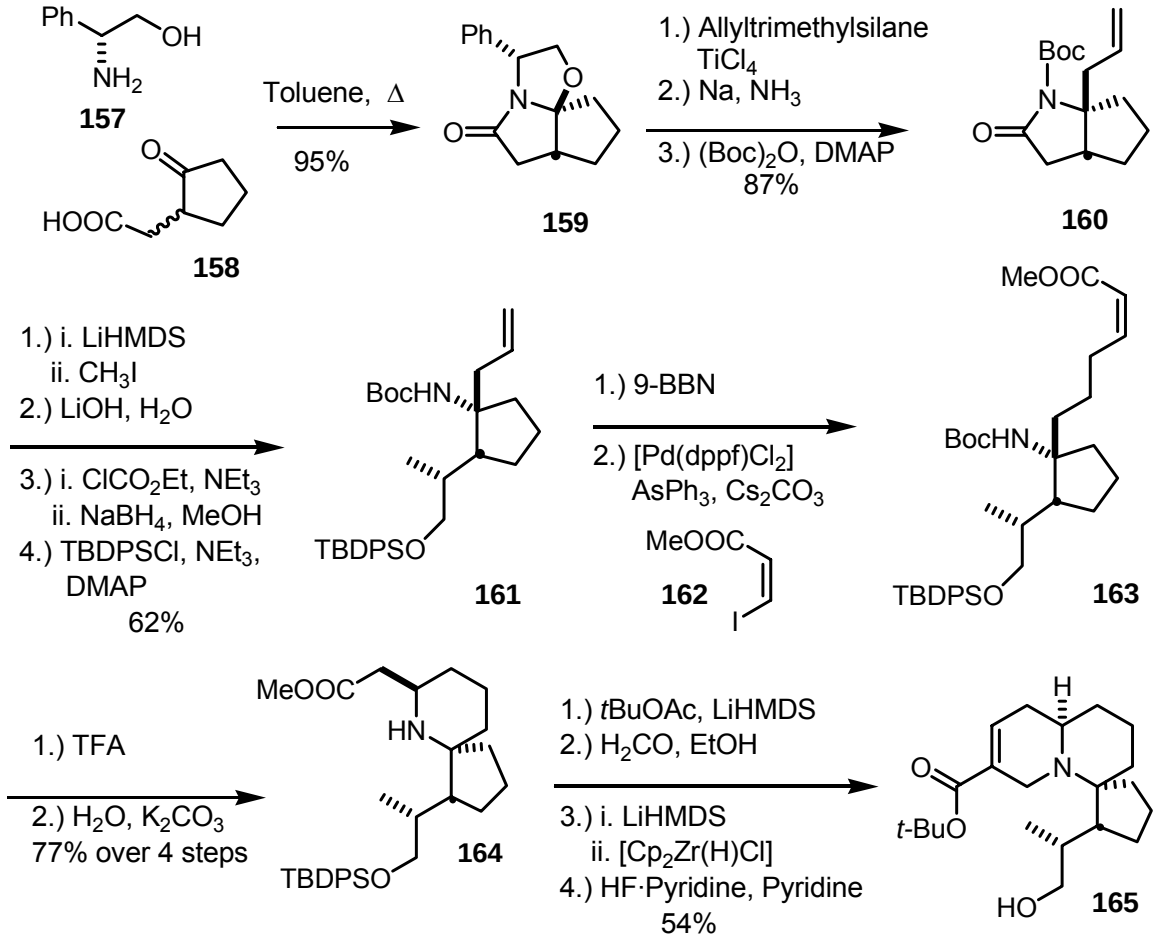


Figure **2-5**: Danishefsky's synthesis of the core of halichlorine.[70,71]

The route continues with further manipulation of **165** resulting in alkyne **167** (Figure **2-6**). Hydrozirconation followed by coupling of the resultant vinyl zinc intermediate with aldehyde **168**[72] in the presence of Soai's chiral amino alcohol furnished **169** in a 4:1 mixture of diastereomers favoring the desired product. Finally, macrolactonization and deprotection yielded halichlorine **(152)** in 3% overall yield in 22 steps.

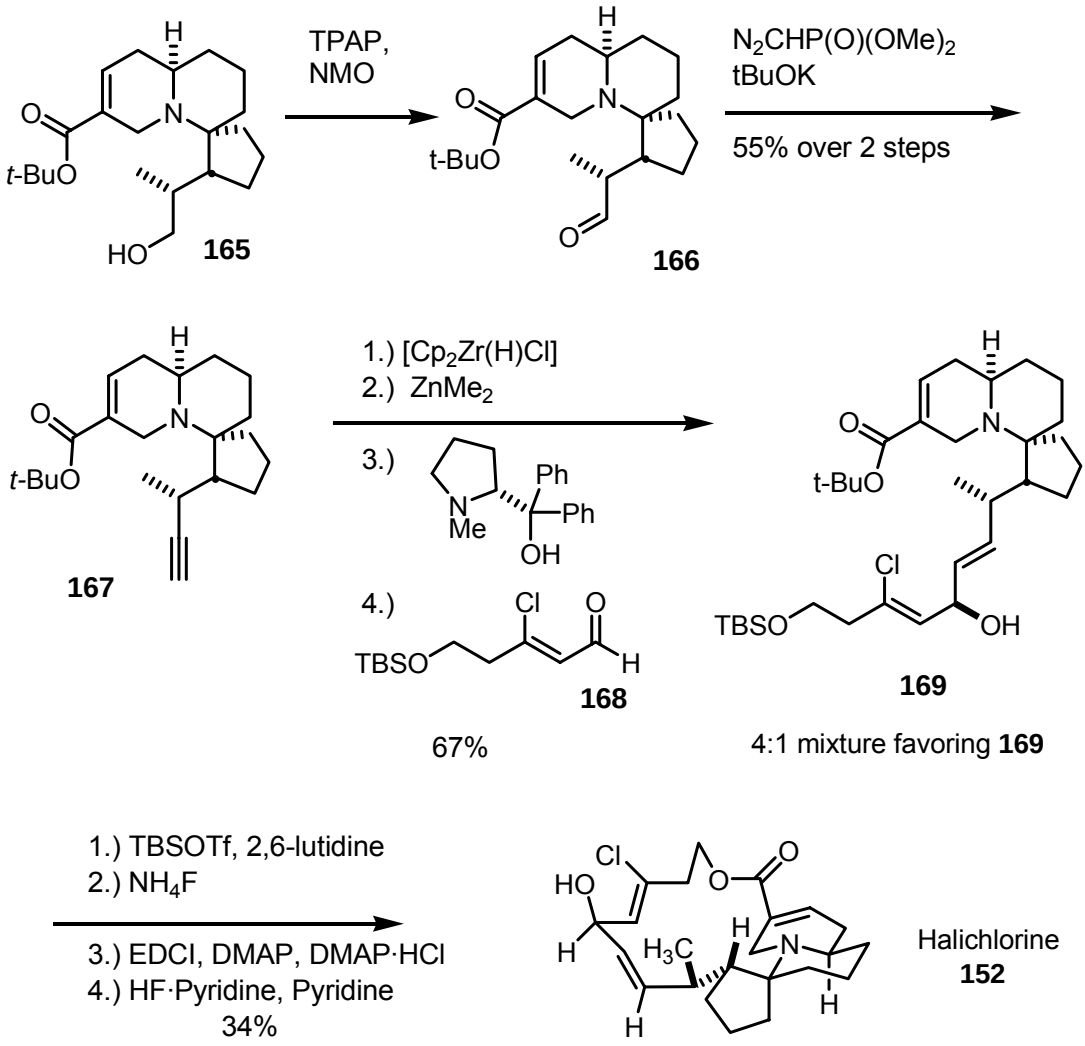


Figure **2-6**: Danishefsky's completion of the synthesis of halichlorine.[70,71]

2.3.2 Synthesis of the Spirocyclic Core of Halichlorine

Many syntheses of the spirocyclic core have followed since Danishefsky's total synthesis. These routes all focus on the formation of the spirocyclic quaternary center with the appropriate stereochemistry. Many different types of reactions have been used to generate the spirocycle including: imine formation,

radical cyclization, [3 + 2] cyclizations, and ene reactions. Presented here are these approaches focusing on the key reactions used to form the aza-spirocyclic core.

2.3.2.1 Uemura's Asymmetric Synthesis of the Core

In 1999, Uemura reported an asymmetric synthesis of the spirocyclic core designed for the synthesis of pinnaic acid, which was used to probe the stereochemistry of the then unknown C14 methyl group (Figure **2-7**).[73] The synthetic strategy was based on an imine cyclization and selective reduction to form the spirocyclic core. The scheme started with the SAMP hydrazone **170**, which was converted to the Cbz protected amine **171** in 10 steps. Palladium catalyzed hydrogenation of the alkene, deprotection of the Cbz group, and reduction of the imine all proceeded in one step in excellent yield to produce the spirocyclic ring system **173**. Hydrogenation of the imine proceeded exclusively from the desired face of **172**. The selectivity can be rationalized by noting the presence of the substituents at C13, which hinder the approach of the palladium catalyst from the opposite face. Overall, this synthesis was completed in 11 steps with a yield of 17%. When the stereochemistry of the C14 methyl group was found to be inverted in this system, Uemura and coworkers published additional syntheses towards halichlorine[74] and pinnaic acid[75] utilizing this same key step. However, both syntheses were completed using racemic versions of **171**.

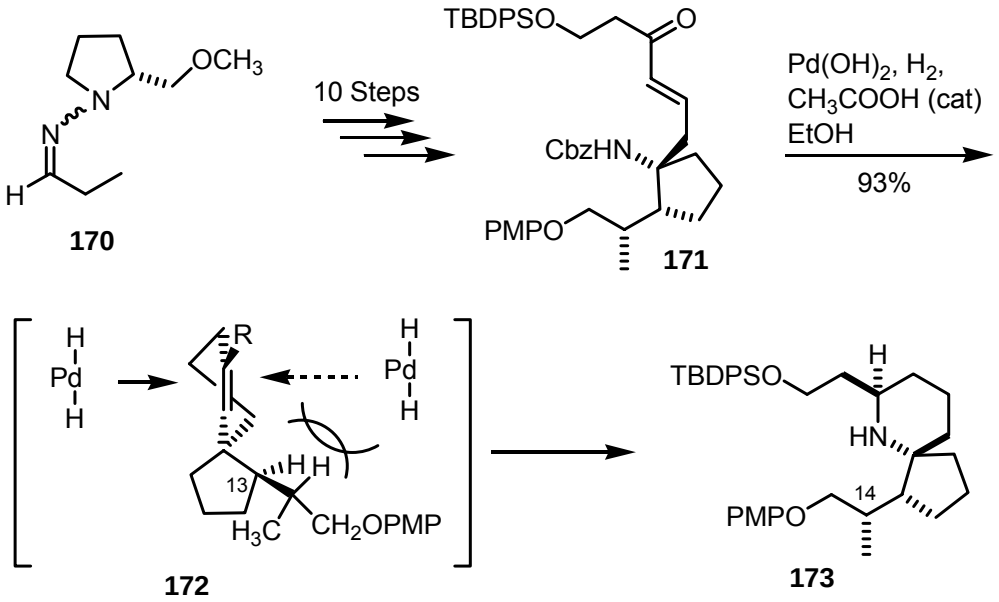


Figure **2-7**: Uemura's asymmetric synthesis of the spirocyclic core.[73]

2.3.2.2 Imine Formation to Generate Spirocycle

Three other independent approaches have explored similar imine formation reactions to generate the core spirocyclic ring system. The first, published by Forsyth in 1999 (Figure **2-8**),[76] which utilized the Cbz protected amine **174**. Spontaneous cyclization to the desired spirocycle did not occur upon oxidation of the alcohol to aldehyde **175** as first predicted. However, the treatment of aldehyde **175** with TFA led to iminium ion formation (not shown), which was quenched with allyltrimethyl silane, to afford **176** as a single diastereomer in good yield.

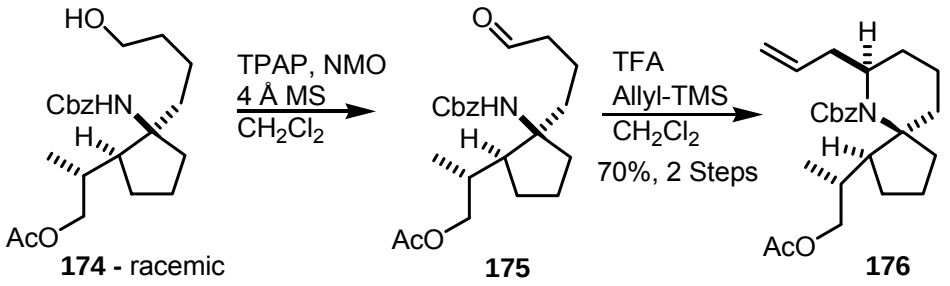


Figure **2-8**: Forsyth's spirocyclic core synthesis.[76]

Wright and coworkers (2000) also used an imine formation reaction, which was then followed by ring closing metathesis. in their approach towards the spirocyclic core **180** (Figure **2-9**)**.**[77] Coupling of cyclopentanone **(178)** with chiral amine **177** generates the iminium ion (not shown), which is quenched with allylmagnesium bromide to give the diolefinic compound **179**. Protection of the secondary amine, followed by olefin metathesis using Grubb's second generation catalyst[78] afforded spirocyclic compound **180**.

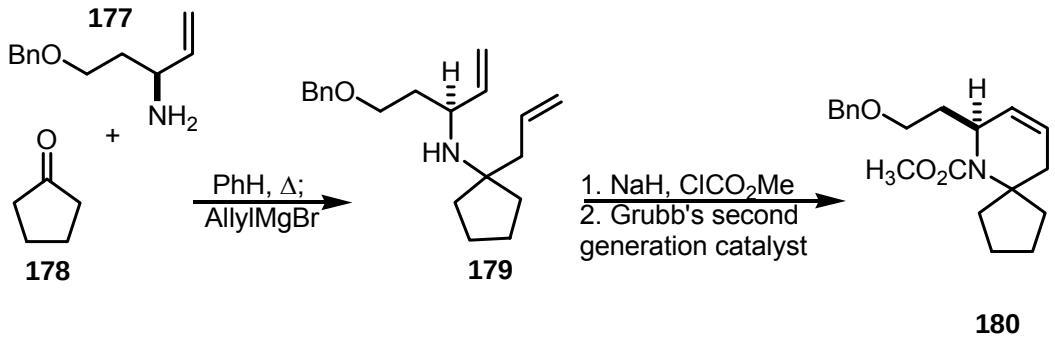
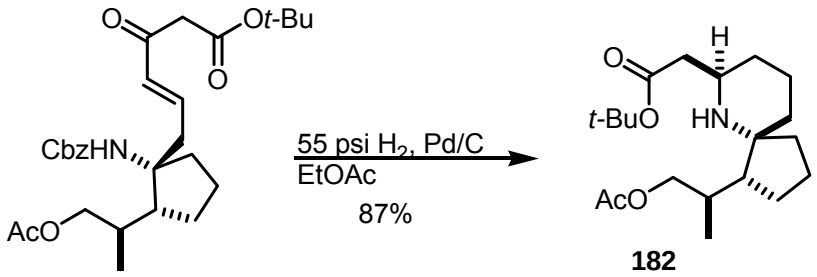


Figure **2-9**: Wright's attempt towards the spirocyclic core.[77]

The final published route utilizing similar imine chemistry was put forth in 2004 by Heathcock (Figure **2-10**).[79] In a strikingly similar route to that previously published by Uemura[73], Cbz protected amine **181** was subjected to hydrogenation conditions, which simultaneously reduced the alkene and removed the Cbz protecting group, allowing spontaneous cyclization of the

ketone. The imine is then reduced stereoselectively in situ to afford spirocycle **182**.



181 - racemic

182

Figure **2-10**: Heathcock's Attempt Towards the Spirocyclic Core.[79]

2.3.2.3 Radical Cyclization to Generate the Spirocyclic Core

Two independent laboratories have utilized radical cyclization methodologies to generate the spirocyclic ring system of halichlorine and pinnaic acid. Clive and coworkers[80,81] reported two separate syntheses of the core of halichlorine, which both utilized a radical cyclization as the key reaction to form the spirocycle (Figure **2-11**). In their 1999 report, D-glutamic acid was employed to generate the enantiopure diester **183**, which could be transformed into bromide **184** in 12 steps.[80] Treatment of this compound with tributyltin hydride and AIBN generated the primary radical which cyclized into the olefin, generating spirocycle **185**. Their second synthesis was presented in 2004 and commenced with racemic **186**, which could be converted to bicyclic compound **172** in 18 steps.[81] Treatment of phenylselenide **187** with tribulyltin hydride afforded the primary radical, which cyclized to yield the tricycle **188**.

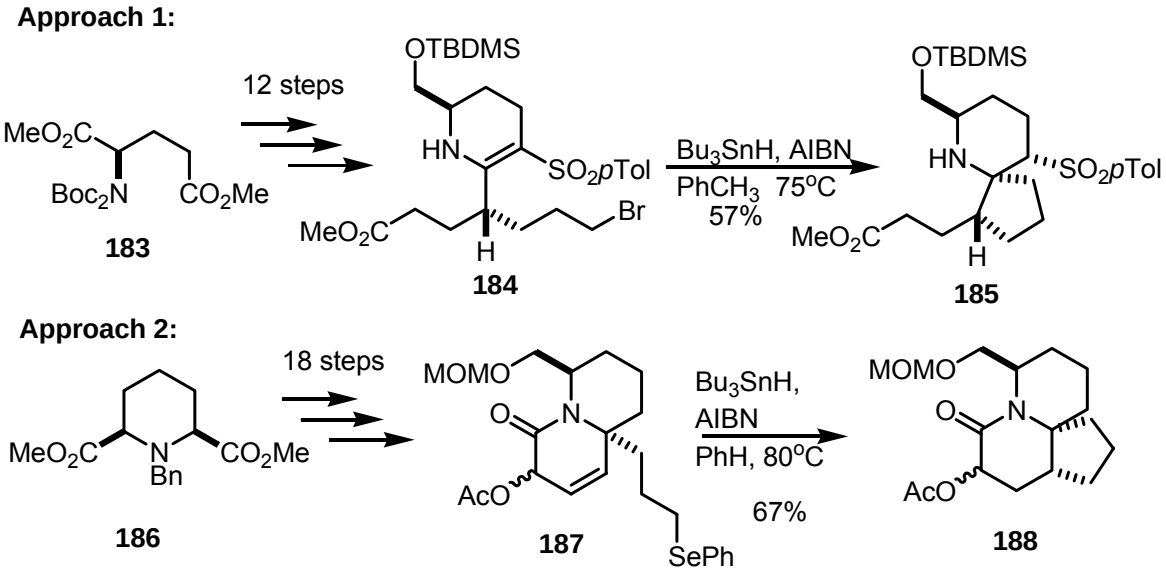


Figure **2-11**: Clive's two spirocyclic core syntheses.[80,81]

In 2003, Ihara demonstrated another radical cyclization to generate the aza-spirocycle (Figure **2-12**).[82] His synthesis commenced with aryl bromide **190**. An aryl radical was generated using tributyltin hydride, which translocated to a tertiary radical via hydrogen (H) abstraction of the hydrogen adjacent to the nitrogen. The tertiary radical is then cyclized into the double bond to generate spirocycle **191**. All of these routes by Clive and Ihara show formation of the aza-spirocyclic via radical cyclization with good diastereoselectivity.

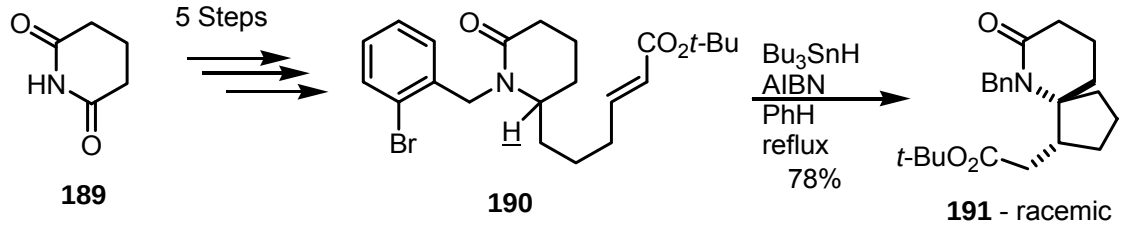


Figure **2-12**: Ihara's radical translocation/cyclization reaction.[82]

2.3.2.4 Intramolecular [3 + 2] Cycloaddition

Intramolecular [3 + 2] cycloaddition was another route explored to generate the spirocyclic core of halichlorine. Zhao, in 1999, reported the first synthesis of the core using a cycloaddition (Figure **2-13**).[83] Heating oxime **192** with benzyl acrylate in xylene afforded cyclized product **193** as a sole diastereomer via an intramolecular [3 + 2] cycloaddition. The stereochemistry of the exocyclic methyl group was determined by the *cis* olefin geometry in the starting material. Further elaboration of bicycle **193** generated **194**, which when heated in dichlorobenzene, underwent an intramolecular Michael addition. This process was followed by an in situ isomerization with loss of benzyl acrylate to generate aza-spirocycle **195**. This synthesis provided the racemic spirobicyclic core **195** in 10 steps with 40% overall yields.

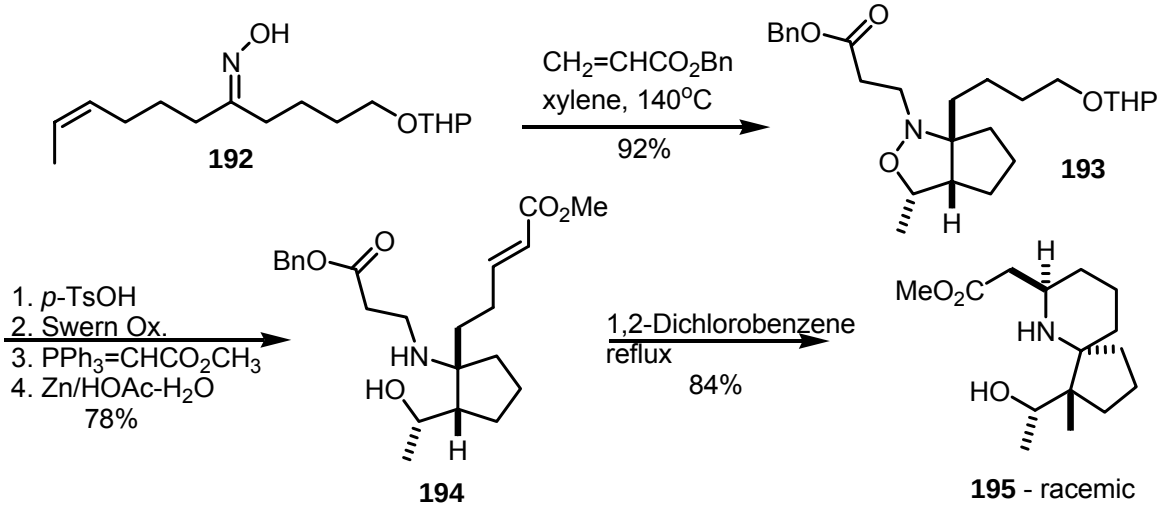


Figure **2-13**: Zhao's spirocyclic core via cycloaddition.[83]

The following year, Shishido and coworkers published a similar route to the core using cycloaddition chemistry (Figure **2-14**).[84] Starting with ketone **196,** the oxime (not shown) was prepared, which underwent an intramolecular Michael addition, followed by a [3 + 2] dipolar cycloaddition of the resulting 6-membered

cyclic nitrone, generating spirocycle **197**. However, **197** contained the wrong stereochemistry at C5, which had to be inverted chemically. Compound **197** was converted to the unsaturated ester **198**, followed by ring opening to afford **199**. Finally, hydrogenation of **199** afforded the azaspirocyclic core **200** in quantitative yield with the appropriate stereochemistry at C5. A few years later Stockman and coworkers put forth a similar route using a more functionalized starting material **201** for a tandem Michael addition and cyclization (Figure **2-15**).[85] Again, the wrong stereochemistry at C5 was obtained in compound **204** and epimerization was achieved in refluxing ethanol to obtain **205** with the appropriate C5 stereochemistry.

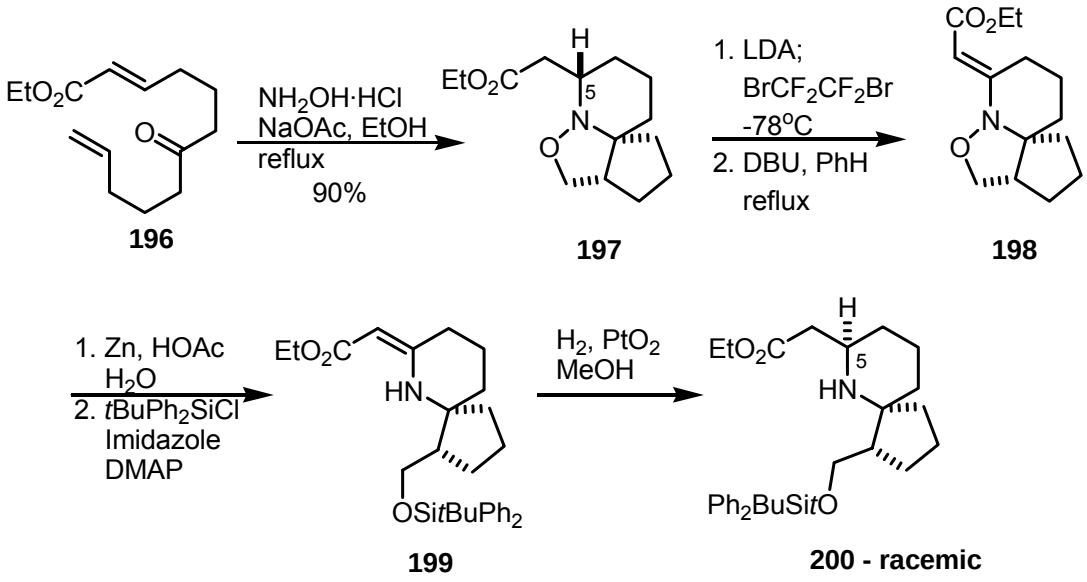


Figure **2-14**: Shishido's synthesis of the aza-spirocyclic core.[84]

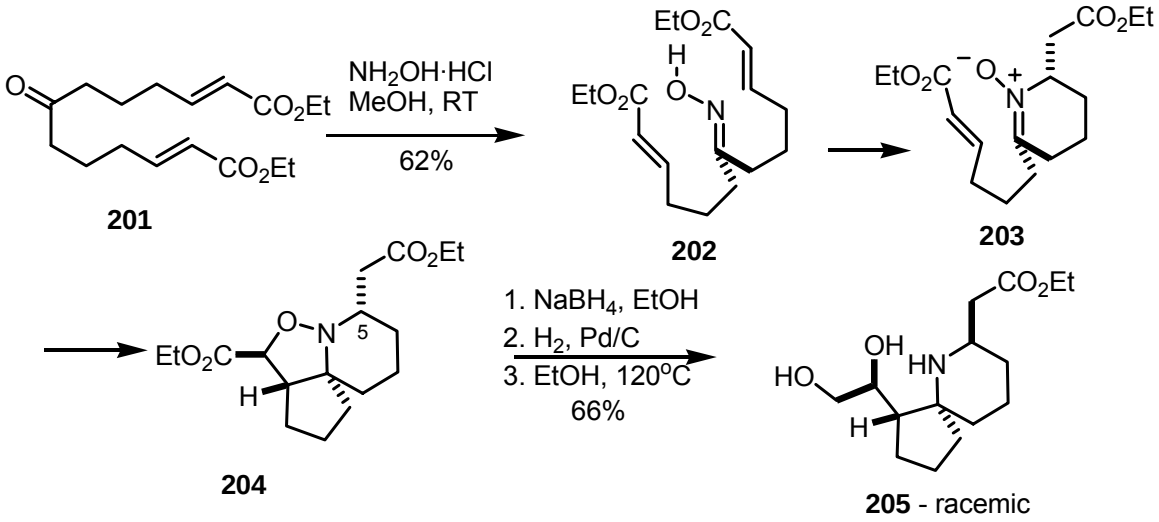


Figure **2-15**: Stockman's tandem reaction synthesis of the core.[85]

A final approach which utilized this nitrone-olefin [3 + 2] cyclization was put forth by White in 2001 (Figure **2-16**).[86] White's route commences with the macrocyclic oxaziridine **206**. Using hydrolysis conditions, the hydroxylamine **207** was formed, which underwent an intramolecular condensation to produce nitrone **208** as a 4:1 mixture of *E* and *Z* isomers. Nitrone **208** was then heated to initiate a stereospecific transannular nitrone-olefin cycloaddition to generate **209**. Finally, base catalyzed opening of the lactone, followed by reductive cleavage of the isoxazolidine, affords the racemic aza-spirocycle **210**.

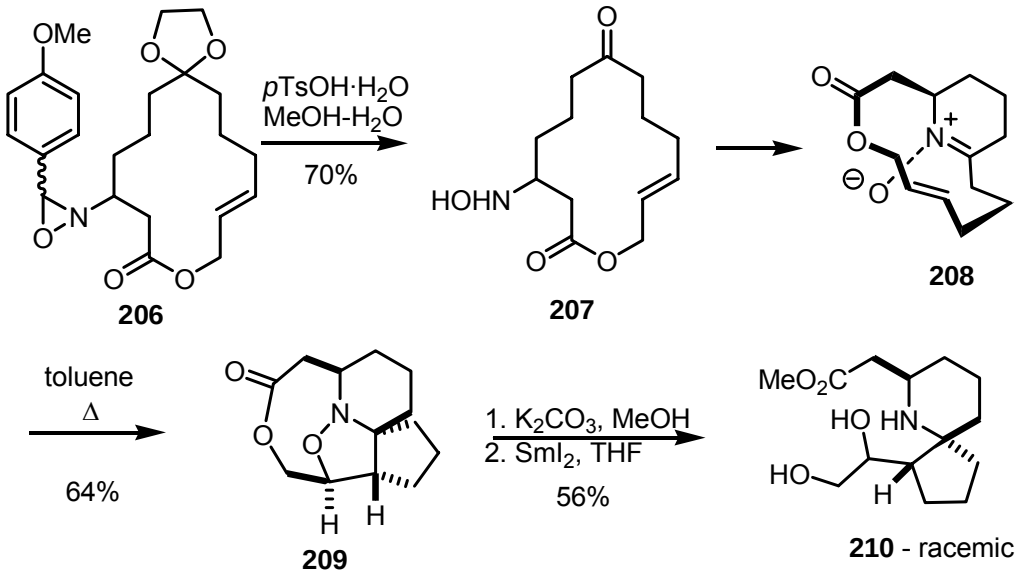


Figure **2-16**: White's cyclization to generate the azaspirocycle.[86]

2.3.2.5 Kibayashi's Generation of the Core via an Ene Reaction

In 2003, Kibayashi and coworkers utilized an ene reaction to generate the aza-spirocyclic core of (±)-halichlorine and (±)-pinnaic acid.[87,88] Hydroxamic acid **211**, which was synthesized in 5 steps, was oxidized to acylnitroso compound **212,** setting up an intramolecular ene reaction to generate the spirocyclic lactam **213** as a single diastereomer (Figure **2-17**). The stereochemistry of this reaction was conferred by the approach of the nitroso moiety to the less hindered face of the cyclopentene ring (opposite of the MOM-oxy group).

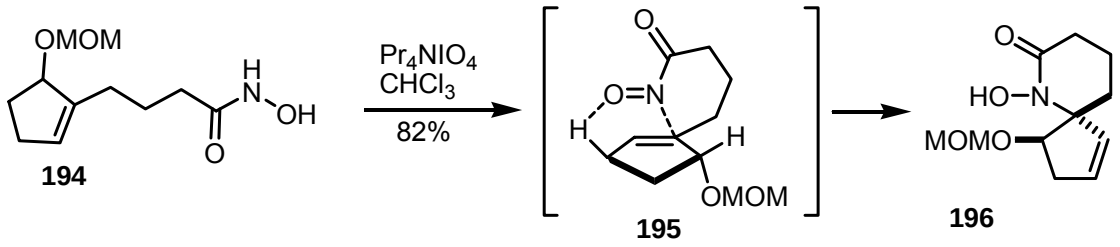


Figure **2-17**: Kibayashi's Ene Reaction Towards the Spirocyclic Core

2.4 A New Synthesis of Halichlorine Based upon Alkylidenecarbene Chemistry

2.4.1 Retrosynthetic Analysis of Halichlorine

The following synthesis of the spirocyclic core of halichlorine **152** utilizes a different approach in comparison to the other previous synthesis. Retrosynthetically, the macrolactone portion of halichlorine might be closed using a Kishi-Nozaki-Hiyama reaction involving the intramolecular coupling of the aldehyde moiety within **214** with the vinyl iodide (Figure **2-18**). A dienol similar to that previously prepared by Weinreb,[72] coupled with the acid of **215**, appends the β-chloro-unsaturated aldehyde moiety.

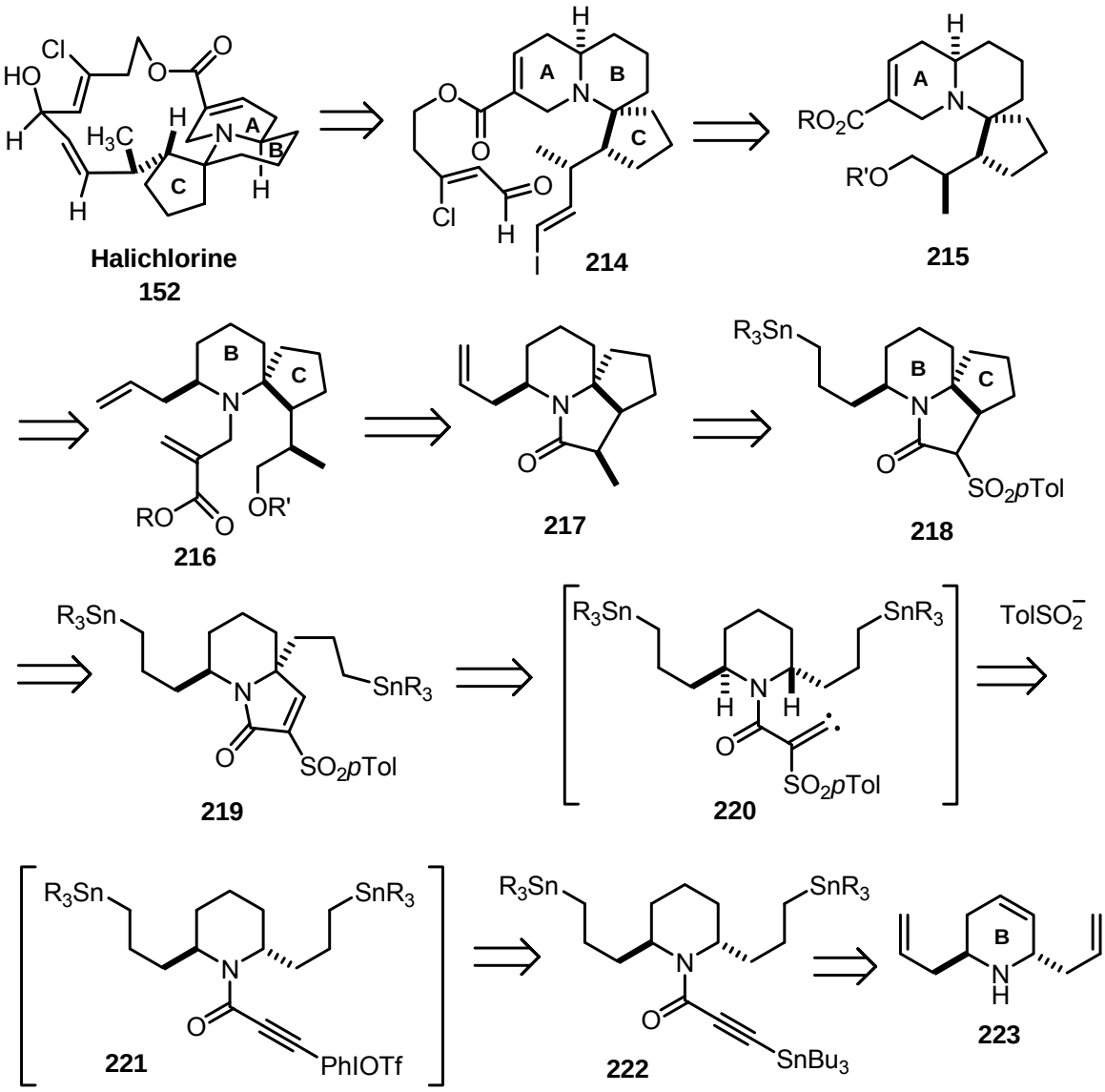


Figure **2-18**: Retrosynthetic analysis.

The tricyclic core A ring of **215** could be formed from a Grubb's olefin metathesis closure of compound **216**, which could be obtained from the ring opening of lactam **217** followed by allylation of the amine. The C ring could be closed using chemistry developed by Macdonald,[89,90] involving an intramolecular conjugate addition of an alkylstannane into the α,β-unsaturated amide within **219**. The key step in this synthesis could be the generation of the quaternary center of the spirocyclic system via a 1,5-C-H insertion of alkylidenecarbene **220**, which

could be generated from the alkynyliodonium salt **221** upon addition of a nucleophile. The alkynyliodonium salt could be generated from the *pseudo* C-2 symmetrical alkynylstannane **222**, which could be generated from racemic *trans*-2,6-diallyl-1,2,5,6-tetrahydropyridine **(223)**.[91]

2.4.2 Precedent for the Key Step

Stang, in 1994, reported the synthesis of γ-lactams utilizing alkynyliodonium salt chemistry to generate an alkylidenecarbene for an intramolecular carbon-hydrogen insertion affording a 5-membered ring.[92] The most relevant example towards the synthesis of halichlorine **(152)** is shown in Figure **2-19**, where conjugate addition of sodium *p*-toluenesulfinate to the β-amidoethynyl(phenyl)iodonium triflate **224** generated alkylidenecarbene **225**. Carbene insertion into the secondary C-H bond afforded α,β-unsaturated-γ-lactam **226** in good yield. Stang also concluded that the sodium *p*-toluenesulfinate nucleophile was highly beneficial for two reasons: (1) it has a low migratory aptitude, thus eliminating the usual 1,2 rearrangement leading to alkyne **227,** and (2) it can be easily removed allowing for further synthetic manipulations and regio-controlled elaboration of the products.

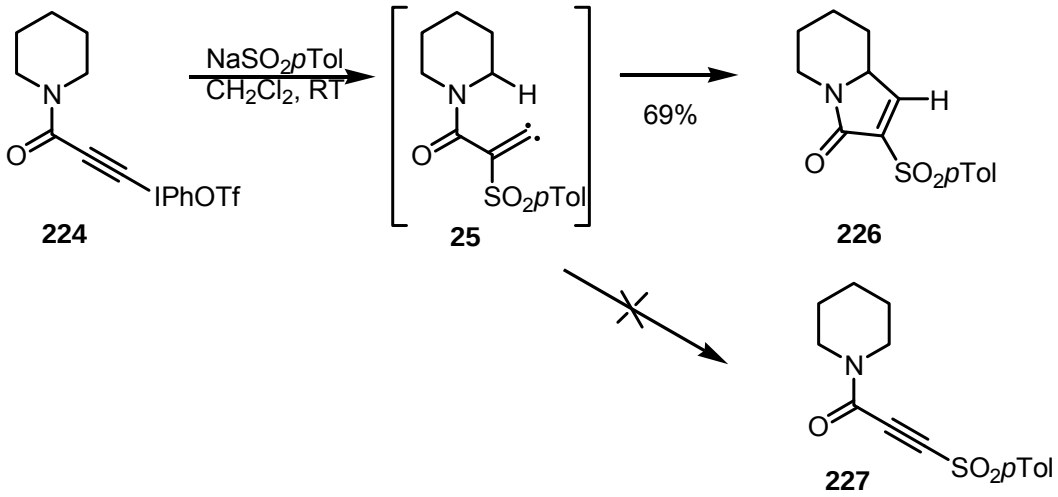


Figure **2-19**: Stang's synthesis of γ-lactams Via alkynyliodonium chemistry.[92]

2.5 Racemic Synthesis of the Core of Halichlorine

Reported here is the racemic synthesis of the aza-spirobicyclic core of halichlorine. A 1,5-carbon-hydrogen insertion of an alkylidenecarbene was thought to be an effective method to generate the quaternary center of the spirocyclic ring system based upon Stang's[92] work to generate unsaturated butyrolactams. Further transformation will complete the spirocyclic system using chemistry introduced by Macdonald[89,90] and ring closing metathesis[78] to generate the tricyclic core of halichlorine.

2.5.1 Synthesis of the Alkynylstannane Precursor

The synthesis of (±)-halichlorine commenced with the formation of known *trans*-2,6-diallyl-1,2,5,6-tetrahydropyridine **(223)**.[91] This species was formed using chemistry developed by Bubnov, who reacted pyridine with triallylborane

(228) in the presence of isopropanol to generate the tetrahydropyridine **223** (Figure **2-20**). Radical stannylation using tributyltin hydride and AIBN at 100 ^{o}C afforded the stannylated product **229**, which was then hydrogenated to afford the functionalized piperidine **231**. This secondary amine was then acylated with the acid chloride of 3-trimethylsilylpropionic acid **(230)**[93,94] to generate the amide, which was deprotected with tetrabutylammonium fluoride in one pot to give the alkynylamide **233**. Bis(tributyltin)oxide and magnesium sulfate were then used to form the alkynylstannane **234**, the precursor for alkynyliodonium chemistry.

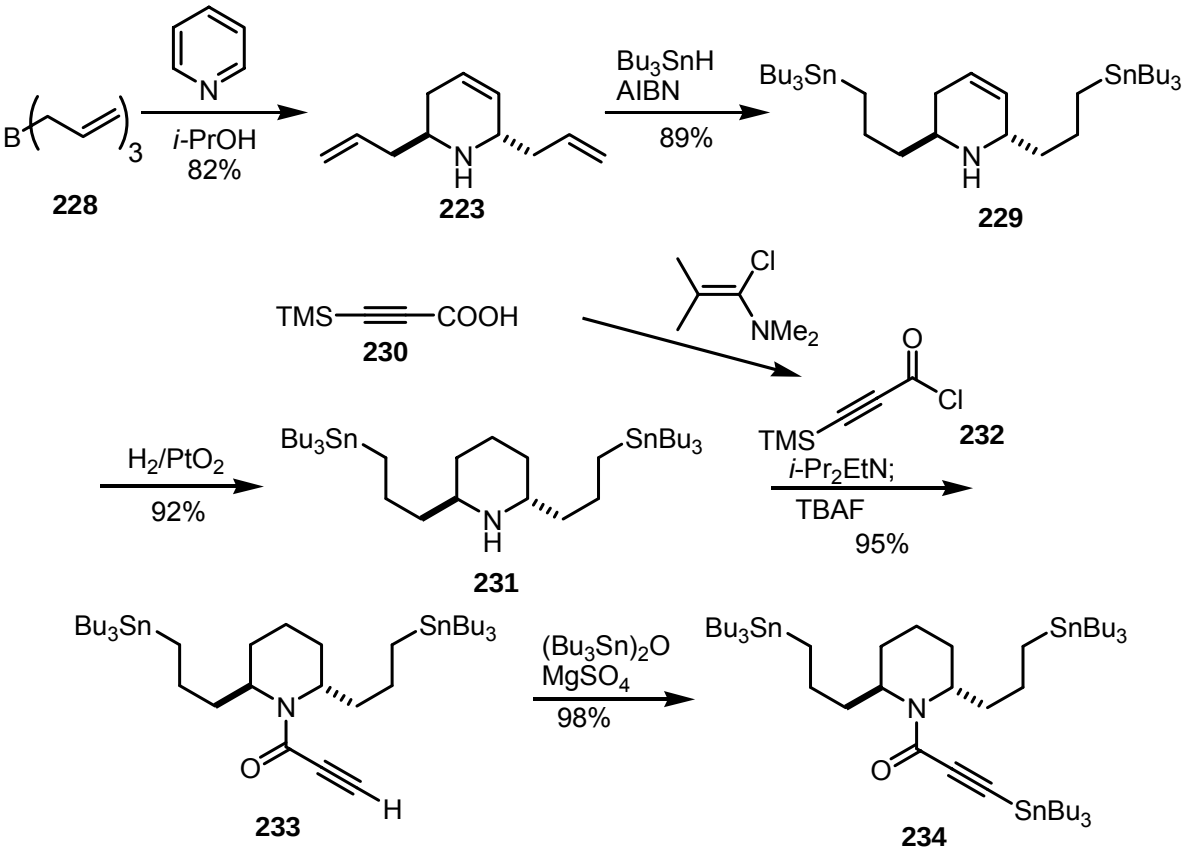


Figure **2-20**: Synthesis of the alkynylstannane precursor.

2.5.2 Alkynyliodonium Salt Chemistry

Following the preparation of precursor **234**, our adaptation of Stang's alkynyliodonium salt methodology was evaluated. Alkynylstannane **234** was reacted at -45 °C with cyano(phenyl)iodonium triflate (Stang's Reagent)[95] to generate the β-ketoethynyl(phenyl)iodonium salt **(235)** (Figure **2-21**). This intermediate was isolated at low temperatures by removal of the solvent in vacuo. Warming this sample above -10 °C leads to decomposition of the iodonium salt after a few minutes. Dissolution of this intermediate was performed in prechilled dimethoxyethane (DME) and cannulated into a refluxing solution of sodium *p*-toluenesulfinate in DME **(236)** to generate the alkylidenecarbene **237**. This species immediately underwent a 1,5-C-H insertion to generate the quaternary center of **238**. Alkylidenecarbene insertion into either of the tertiary C-H bonds generates the same product due to the C_2-symmetrical nature of the piperdine moiety, and insertion occurs with retention of stereochemistry. There was also no evidence for the undesired 1,2-rearrangement alkyne product.

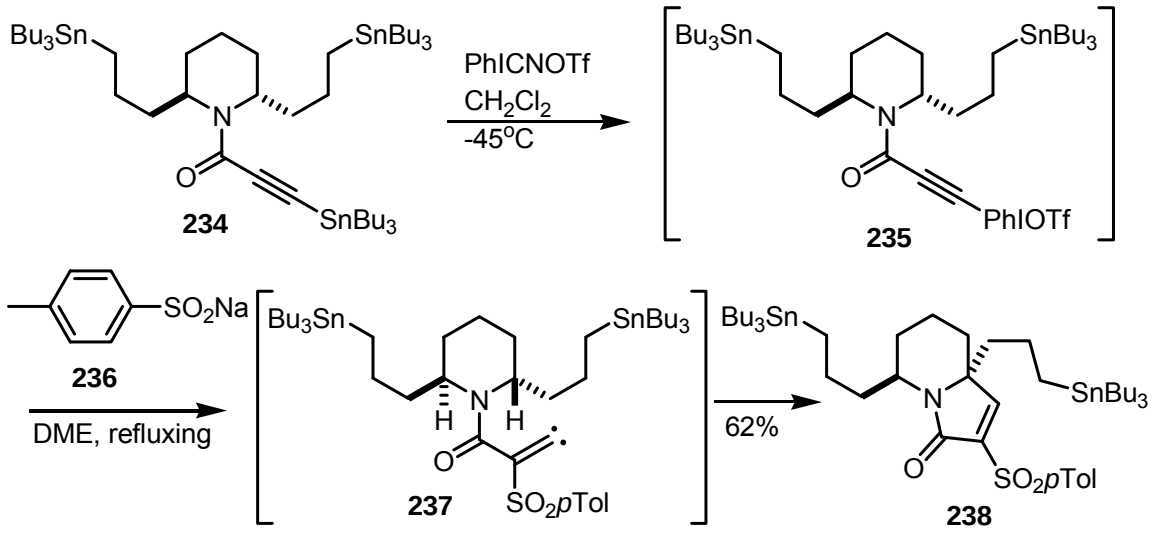


Figure **2-21**: Alkynyliodonium salt chemistry to generate an alkylidenecarbene.

2.5.3 Macdonald Chemistry to Generate the C Ring of the Spirocyclic Core

With the quaternary center of **238** in place, enone **239** served as a template for the cyclization of the C-Ring using chemistry developed by Macdonald. An example of this transformation involves an intramolecular conjugate addition of an alkylstannane into the α,β-unsaturated ketone of **239** (Figure **2-22**).[89,90] A Lewis acid [either titanium (IV) chloride ($TiCl_4$) or tin (IV) chloride ($SnCl_4$)] was added to the enone **239**, generating intermediate **240**. The polarized nature of the carbon-tin bond allows for addition of the slightly negatively charged carbon to the β-electrophilic site of the enone affording bicycle **241**.

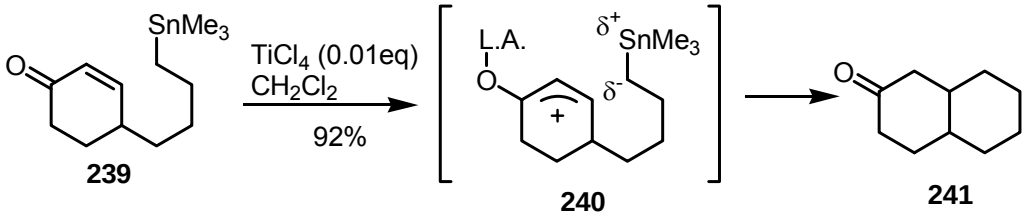


Figure **2-22**: Macdonald chemistry.[89,90]

This chemistry was applied to the synthesis of the C-Ring of halichlorine utilizing the cyclopentenone functionality of **238** where only one of the alkyltin bonds is in proximity for cyclization into the enone to generate a 5-membered ring (Figure **2-23**). Starting with identical conditions to those used by Macdonald (Figure **2-22**) (0.01 eq of $TiCl_4$ in CH_2Cl_2), no cyclized product was obtained. Increasing the temperature of the reaction by changing the solvent to benzene as well as increasing the amount of $TiCl_4$ to one equivalent, yielded cyclized product **242**; however, the Lewis acid also interacted with the other tin moiety to obtain byproduct **243**. It is hypothesized that the chloride ions from the Lewis acid displaces one of the butyl ligands on the tin leading to a chlorostannane intermediate **244**, which is converted to the hydroxyl tin compound **243** via hydrolysis upon SiO_2 chromatography. To optimize this transformation for

yielding only product **242**, a variety of Lewis acids were screened, along with a variety of solvents and temperature conditions (Table **2-1**). From these efforts, magnesium bromide was found to be the ideal Lewis acid catalyst as it produced cyclized product **242** in a relatively good yield with no by-product **243** observed, provided the reaction is stopped immediately after consumption of the starting material.

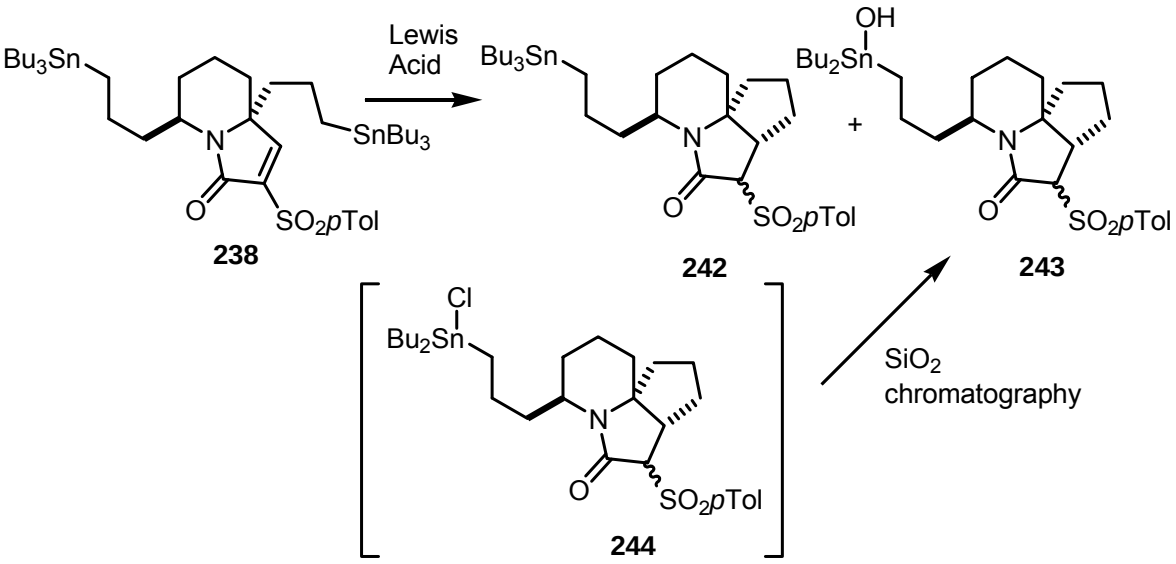


Figure **2-23**: Lewis acid mediated cyclization.

Table **2-1**: Lewis acids examined for cyclization.

Lewis Acid (eq)	Solvent (refluxing)	Time (h)	Yield of **242** (%)	Yield of **243** (%)	Notes
$TiCl_4$ (0.01)	CH_2Cl_2	24	-	-	no reaction
$TiCl_4$ (1.0)	Benzene	24	24	36	30% starting material recovered
$TiCl_4$ (1.0) di-*t*-butylpyridine	Benzene	24	-	-	no reaction
$Eu(OTf)_3$ (1.0)	Benzene	24	-	-	no reaction
$Eu(OTf)_3$ (1.0)	Toluene	18	44	28	
$Eu(OTf)_3$ (1.0) di-*t*-butylpyridine	Toluene	48	19	26	38% starting material recovered
$Yb(OTf)_3$ (1.0)	Benzene	48	-	-	no reaction
$Yb(OTf)_3$ (1.0)	Toluene	18	45	28	
$AlBr_3$:$AlMe_3$ (1.0:0.1)	Toluene	3	43	18	
CF_3COOH (1.0)	Toluene	4	-	-	decomposition
MgI_2 (1.0)	Toluene	44	58	30	
$Mg(OTf_3)$ (1.0)	Toluene	24	-	-	no reaction
$MgCl_2$ (1.0)	Toluene	24	-	-	no reaction
$MgBr_2$ (1.2)	Toluene	14	69	-	
ZnI_2 (1.0)	Toluene	3	-	-	decomposition
$ZnBr_2$ (1.6)	Toluene	10	24	-	9% starting material recovered

2.5.4 Removal of the Tributyltin Moiety

The next step towards the synthesis of the tricyclic core **215** was the removal of the tributyltin moiety to regenerate an olefin for subsequent use in the functionalization of the propyl chain (Figure **2-24**). A variety of conditions were screened as shown in Table **2-2**. Electrophilic bromination utilizing both bromine and dioxane-dibromide[96,97] yielded a mixture of both the brominated product **245** along with a greater amount of dihydroxyl tin compound **246**. Generation of this by-product likely was accomplished in the same manor as in the Lewis acid

chemistry where a butyl group is removed and replaced by a bromine. Upon chromatography, this intermediate stannyl bromide was converted to the tin hydroxyl compound **246**. Additional conditions, such as iron (III) bromide and bromine, and bromine and diisopropylethylamine were used for electrophilic bromination. However, the same mix of products **245** and **246** was obtained. Electrophilic iodination reagents were also examined for tin removal but were found to be unsuccessful at generating exclusively the destannylated product.

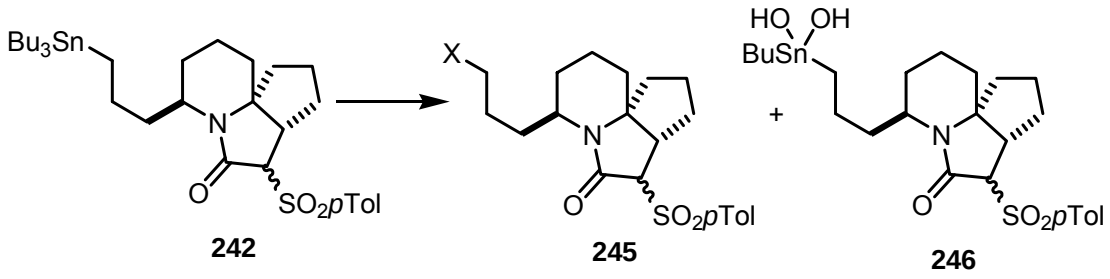


Figure **2-24**: Removal of the tributyltin moiety.

Table **2-2**: Attempts toward the cleavage of the tributyltin moiety.

Reagents	X=	Solvent	Yield of **245** (%)	Yield of **246** (%)	Notes
Br_2	Br	CH_2Cl_2	25	66	
Dioxane : dibromide	Br	CH_2Cl_2	10	27	10% starting material recovered
$FeBr_3$, Br_2	Br	CH_2Cl_2	18	59	
I_2	I	CH_2Cl_2	5	60	
N-iodosuccimide	I	CH_2Cl_2	11	20	34% iodination at α–position only
Br_2, iPr$_2$NEt	Br	MeOH	23	25	32% starting material recovered

Direct elimination of the tin moiety to generate the olefin in one step also was explored (Figure **2-25**). Using lead (IV) acetate according to conditions used by Fuchs[98] resulted in no reaction after 24 hours. When triphenylcarbenium

tetrafluoroborate[99] was employed, only a small amount of olefin product **247** was formed (12%), with the remainder comprising starting material and the dihydroxytin compound **246**. There was concern that the ability of the amide to enolize, due to the presence of the sulfone, was causing some of the problem with removal of the tin moiety. To circumvent this problem, removal of the sulfone first was explored.

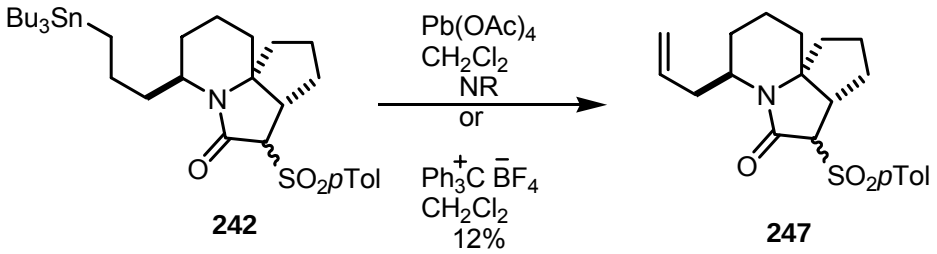


Figure **2-25**: Direct cleavage of tin to generate olefin.

2.5.5 Reductive Methylation

Initial attempts at desulfonylation and subsequent methylation followed a one-pot procedure put forth by Kurth and coworkers (Figure **2-26**).[100] Lithium-ammonia was used to desulfonate compound **248**, followed by trapping of the enolate with tributyltin chloride to generate intermediate **249** Allylbromide was then added (with HMPA) to give alkylation product **250**. When this one-pot procedure was used to desulfonate/methylate **242**, the desulfonylated product **251** was not detected, and instead yielded only the methylated compound **252** (Figure **2-27**).

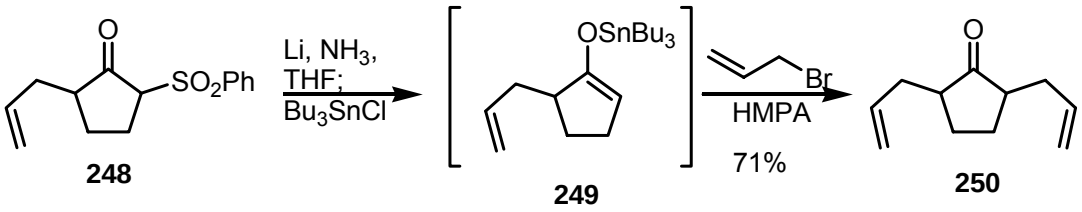


Figure **2-26**: Kurth's desulfurization/α-alkylation of β-keto sulfones.[100]

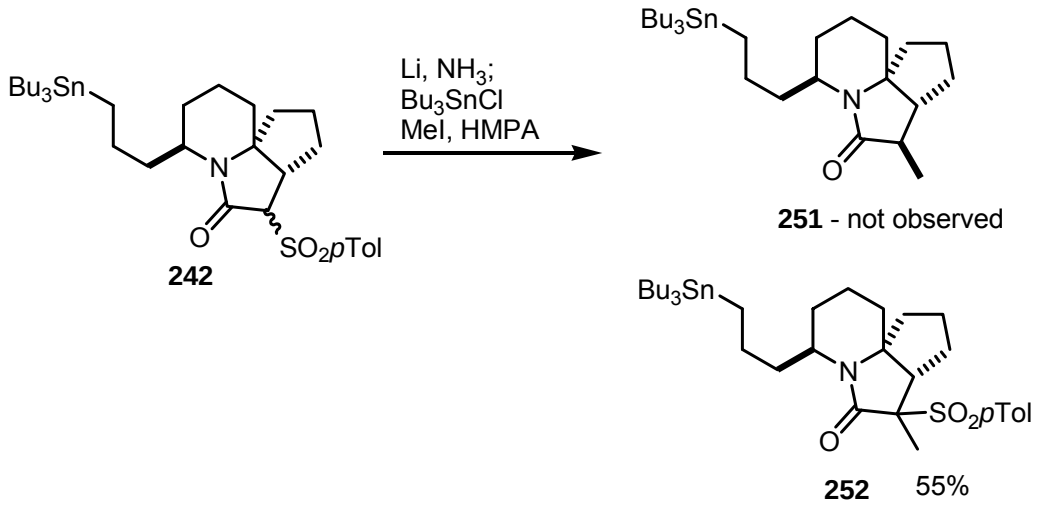


Figure **2-27**: Desulfonylation/α-methylation using Kurth's procedure.

A two-step procedure for desulfonylation/methylation was also examined. In this protocol, sulfone reduction and then deprotonation of the α-position of the amide, followed by quenching of the resultant enolate with a methyl source was explored (Figure **2-28**). Many different reduction conditions were examined including sodium-mercury amalgam,[101,102] lithium naphthalene,[103] and samarium diiodide[86,104] (Table **2-3**). However, while all these reductions proceeded in good yields, the methylated product was not obtained, although a combination of different bases (LDA, LiHMDS) and methylating agents (methyl iodide, methyl triflate, dimethylsulfate) were examined. Due to this problem, the one pot procedure for desulfonation/methylation was again revisited.

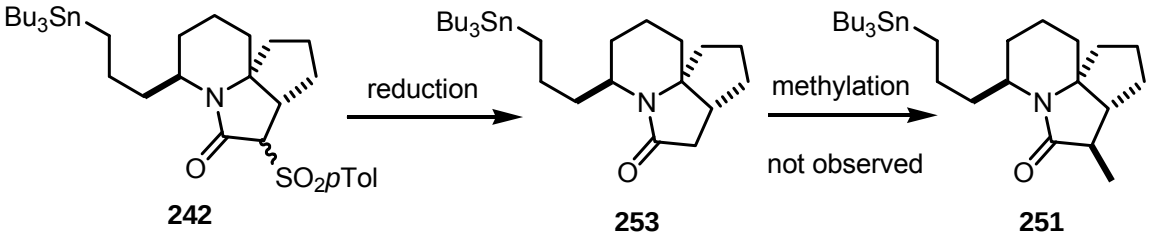


Figure **2-28**: Two step procedure for sulfone reduction and methylation.

Table **2-3**: Reduction of sulfone **242**.

Reducing Reagent	Yield of **253** (%)	Recovery of Starting Material (%)
Na(Hg), Na_2HPO_4, MeOH, THF	69	9
Li, naphthalene, THF	75	-
Sm, ICH_2CH_2I, THF	67	-

Following a one-pot procedure for reduction then methylation reported by Danishefsky,[105] sulfone **242** was treated with lithium naphthalenide in THF, followed by a methyl iodide quench of the resulting enolate **254**, to generate the desired methylated compound **251** (Figure **2-29**). However, two other products were isolated as well, compound **255**, which was methylated but the sulfone was not reduced, and compound **256**, which was not methylated but the sulfone was reduced. One can envision the formation of the later two products by a proton transfer from the sulfone **242** to the enolate **254**, which generates compound **253** and the enolate of compound **242** (not shown). This enolate cannot be reduced by lithium naphthalenide, but it can be methylated to generate compound **255**. Further attempts using these conditions, but varying the amount of lithium naphthalenide, the rate of addition, and the concentration of the reactants, eventually eliminated the formation of the two by products and yielded product **251** in a 57% yield. This product was obtained in greater than 10:1 diastereomeric ratio of methyl configuration, favoring the methyl at C(14) in the

desired orientation. These diastereomers were separated via careful silica gel chromatography.

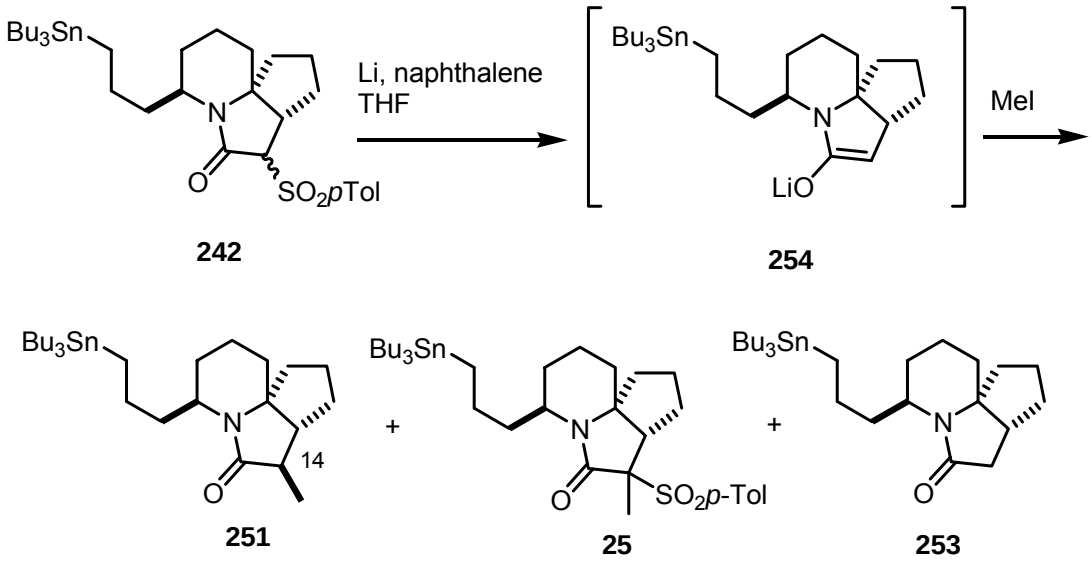
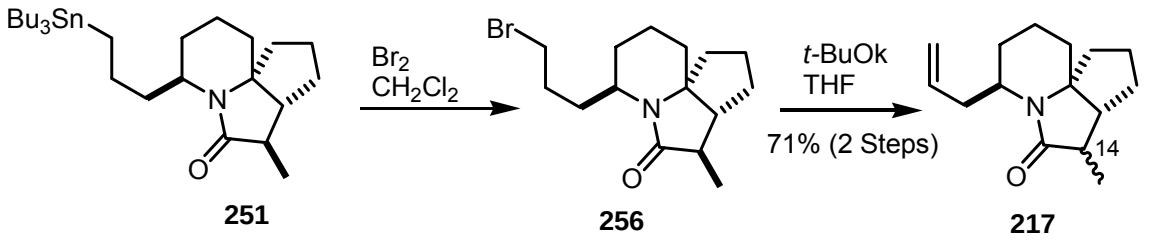


Figure **2-29**: Reductive methylation for removal of the sulfone.

2.5.6 Removal of the Tributyltin Moiety Revisited

The removal of the tributyltin moiety was revisited following the preparation of compound **251**. Initially, it was found that removal of the tin functionality using excess bromine generated bromide **256**, which could then be subjected to elimination conditions using potassium *t*-butoxide to generate olefin **217** in decent yield (Figure **2-30**). Unfortunately, while the tin moiety is removed, the *t*-BuOK required for the elimination process generated an approximately 2:1 mixture of diastereomers of **217** at the C(14) stereocenter. A variety of milder bases [triethylamine (NEt_3), 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), diazabicyclo[2.2.2]octane (DABCO), phosphazene base P_4-*t*-Bu] were tested to avoid racemizing the stereochemistry at C(14) while eliminating the bromide to

provide the olefin. However, none of the bases examined generated the desired olefin containing product **217**.



251 **256** **217**

Figure **2-30**: Tin removal using bromine followed by E_2 elimination.

The difficulty in generating the olefin without effecting the stereochemistry at C(14) was overcome with a Tamao-Fleming-type oxidation sequence to replace the tributyltin moiety of **242** with an alcohol (Figure **2-31**).[106-110] Tributyltin compound **242** was reacted with iodosylbenzene and boron trifluoride-diethyl ether ($BF_3{\cdot}OEt_2$), followed by a quench with ammonium chloride to generate chlorodibutyltin compound **257**. The chlorotin compound **257** was then oxidized with peroxide to cleanly generate alcohol **258**. Indirect elimination of water from alcohol **258** was achieved using Greico's selenoxide elimination chemistry.[111-113] This elimination occurred under mild enough conditions to retain the stereochemistry at C(14)of the olefin **217**.

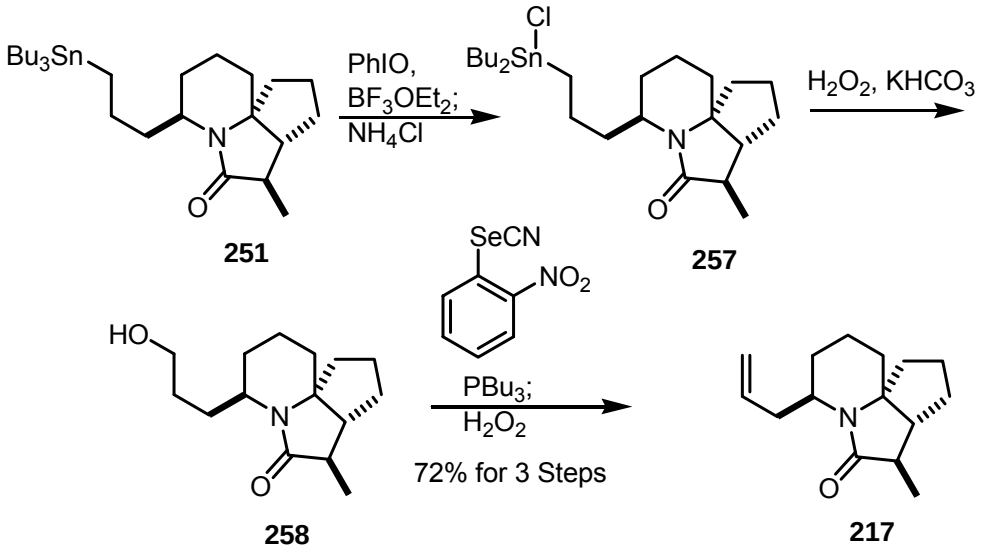


Figure **2-31**: Tamao-Fleming oxidation followed by Greico's selenoxide chemistry to generate olefin.

2.5.7 Cleavage of the Amide

Reductive cleavage of the lactam of **217** to generate the bicyclic amino alcohol **265** was the next planned transformation in this synthesis. Unfortunately, there are few reagents that will transform a tertiary amide into its corresponding primary alcohol and secondary amine. Most highly nucleophilic reagents will add to the tertiary amide **259** to form the tetrahedral intermediate **260**, which can then undergo two different cleavage pathways (Figure **2-32**).[114] In the first pathway, the C-O bond is cleaved giving rise to the tertiary amine **261**, whereas the second pathway results in the cleavage of the C-N bond followed by reduction of the resulting aldehyde **262** to generate the desired primary alcohol **263**. Most metal hydrides [lithium aluminum hydride, ($LiAlH_4$), diborane] undergo the first process. However, some hydride sources [lithium triethylborohydride 'superhydride',[115] lithium aminoborohydrides (LiR_2NBH_3)[114,116-120]] have been

found to proceed through the second route generating a primary alcohol. In applying this reaction to the olefin **217**, Figure **2-33** shows the two possible products from cleavage with a metal hydride.

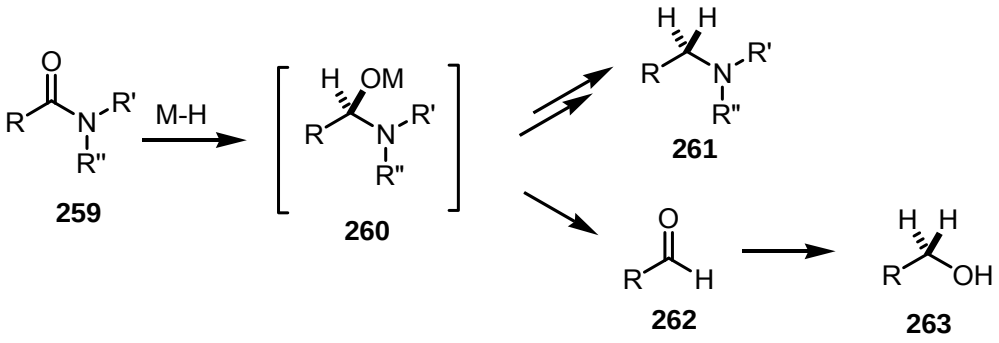


Figure **2-32**: Reaction of a metal-hydride reagent with a tertiary amide

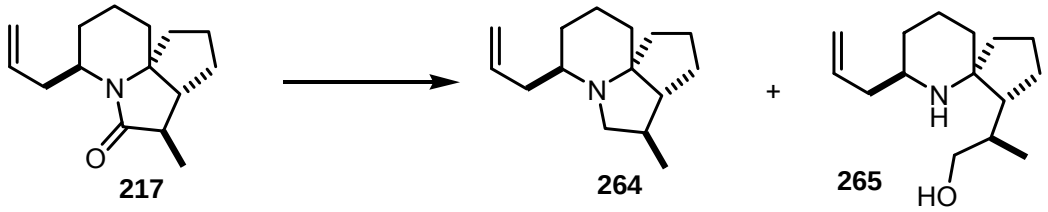
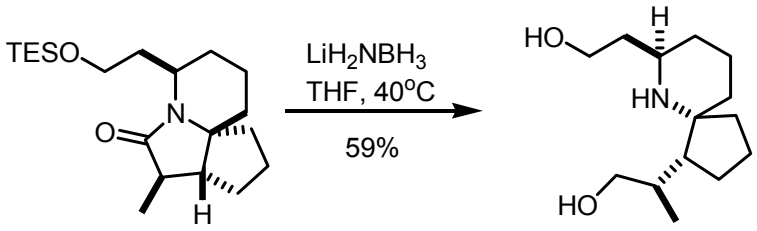


Figure **2-33**: Reductive cleavage of the lactam to generate a pyrrolidine or an amino-alcohol.

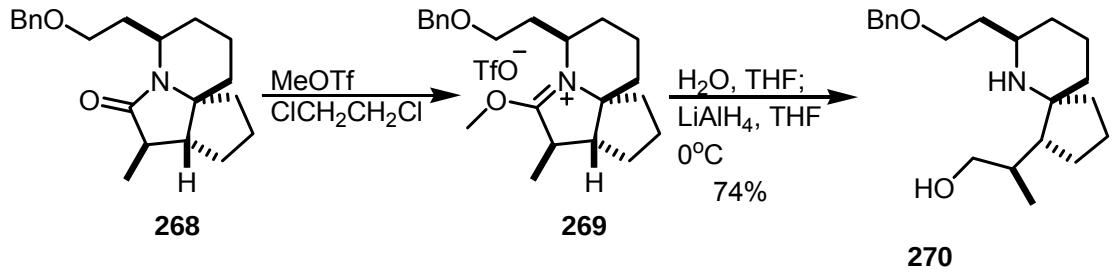
Initial attempts at the cleavage of the tertiary amide **217**, were performed using lithium amidotrihydroborate (LiH_2NBH_3), as previous studies have shown that it cleaves the amide bond of a similar halichlorine tricyclic structure (Figure **2-34**).[82] However, when this reagent was used to cleave the amide bond of **217**, a mixture of primary alcohol **265** and tertiary amine **264** were obtained favoring the tertiary amine **264**. A variety of different conditions yielded the same results using LiH_2NBH_3, with the tertiary amine formation dominating in most cases.



266 **267**

Figure **2-34**: Ihara's cleavage of the amide bond via lithium amidotrihydroborate.[82]

While the feasibility of this transformation was being explored, a second paper by Kibayashi was published on the core of halichlorine, revealing a new route to the cleavage of the tertiary amide **268** via hydrolysis of its methyl imidate **269** (Figure **2-35**).[88] Applying his methodology to our system, tertiary amide **217** was reacted with methyl triflate to generate imidate **271** (Figure **2-36**). Hydrolysis of this product cleaved the desired C-N bond, leading to the triflate salt **272**. The methyl ester is then reduced with $LiAlH_4$, generating amino-alcohol **265** in a 68% yield over the three steps.



268 **269** **270**

Figure **2-35**: Kibayashi's amide cleavage.[88]

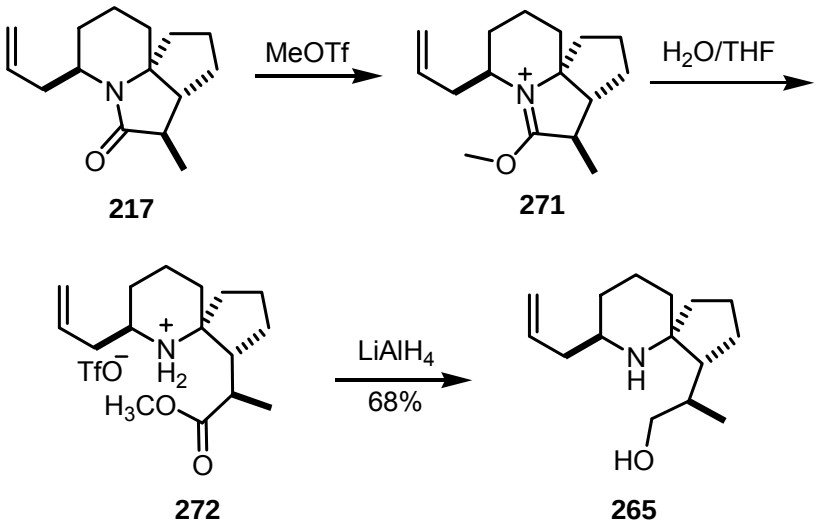


Figure **2-36**: Cleavage of the β-lactam.

2.5.8 Completion of the Core Tricycle

From the amino-alcohol **265**, the completion of the tricyclic core of halichlorine **(152)** was accomplished using the sequence described by Kibayashi[88] (Figure **2-37**). Silylation of the primary alcohol of **265** afforded compound **273**, which allowed for allylation of the secondary amine with 2-(bromomethyl)acrylic acid ethyl ester **(274)** to furnish the bis olefin **275**. Grubb's olefin metathesis of the bis-olefin, using the second-generation olefin metathesis reagent **276,**[78,121,122] provided the tricyclic compound **277**. Upon deprotection of the silyl ether in **277** the tricyclic core of halichlorine **278** was formed.

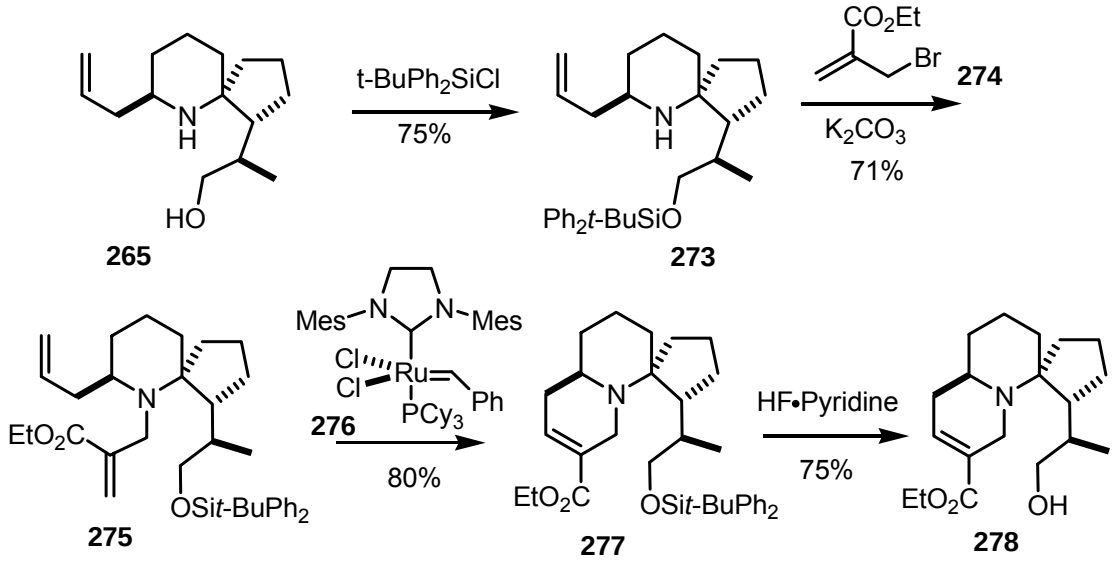


Figure **2-37**: Completion of the spirocyclic core of halichlorine.

2.6 Conclusions

In, summary the completion of the core of halichlorine **(152)** has been reported in 17 steps from pyridine. The synthesis uses alkynyliodonium salt chemistry to generate the key quaternary center of the spiro-bicyclic ring system via generation of an alkylidenecarbene, followed by 1,5-C-H insertion (Figure **2-2**). The spiro-bicyclic ring system was then completed with the Lewis acid mediated cyclization of the C-Sn bond into the enone of **238**, followed by further functionalization to finish the spirocyclic core **278**. For comparison, only three syntheses have progessed to afford tricycle **278**. Danishefsky completed the asymmetric core in 14 steps starting from chiral starting materials **157** and **158** (Figure **2-5**)[70,123]. A racemic synthesis was reported by Kibayashi, which completed the core in 37 steps from cyclopentanone (Figure **2-17**).[87,88]

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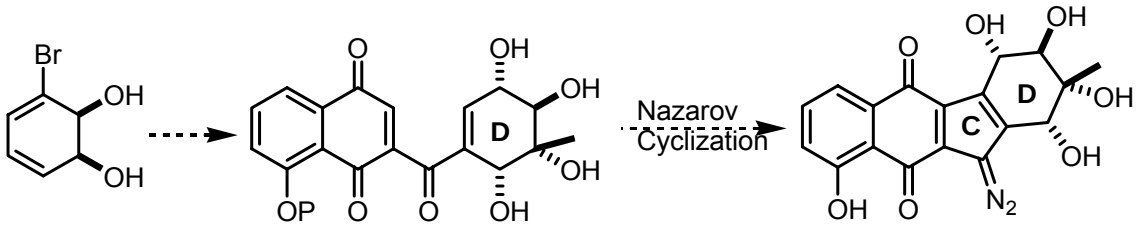
Chapter 3

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF KINAMYCIN F

3.1 Overview

Kinamycin F **(281)** which was isolated in 1989, is a member of a class of potent antibiotics whose first compounds were isolated in 1970 from *Streptomyces murayamaensis* (Figure **3-1**).[124,125] Kinamycin F possess a diazobenzo[*b*]fluorene framework composed of a 6 – 6 – 5 – 6 ring system with a highly oxygenated cyclohexene D-ring. A dimer related to these diazobenzo[*b*]fluorene compounds, lomaiviticin A **(298)**, has been isolated and found to exhibit interesting cytotoxicity against a variety of tumor cell lines via cleavage of double stranded DNA under reducing conditions[126,127] This proposed mechanism of action of these kinamycin compounds is thought to be through a bio-reductive process, generating a radical species which interacts with DNA causing strand scission. Completion of the total synthesis of kinamycin F (efforts discussed within) will permit a more thorough evaluation of its biological mechanism of action.



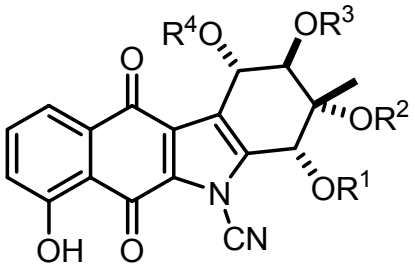
279 **280** **281**

Figure **3-1**: Utilization of a Nazarov cyclization to generate the C-ring of kinamycin F.

The attempt towards the synthesis of kinamycin F is discussed herein. The two key focal points of this synthesis were on the formation of the D-ring stereoselectively and the cyclization closure of the C-ring. It was hypothesized that the D-ring could be generated from (1*S*-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol **(279)**. The C-ring closure could then be carried out using a Nazarov cyclization to afford the 6 – 6 – 5 – 6 ring system of kinamycin F.

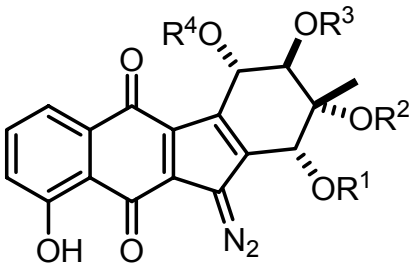
3.2 Isolation

The first series of the kinamycin antibiotics were isolated in 1970 from the fermentation broth of *Streptomyces murayamaensis sp. nov.* Hata *et* Otani.[124]. Structural elucidations on the bases of chemical, spectroscopic, and X-ray crystallographic data of these compounds initially reported them to be N-cyanobenzo[*b*]carbazoles **282** - **285** as shown in Figure **3-2**.[128,129] However, results from synthetic studies led to the reexamination of these structures and twenty-four years later, Gould and coworkers reported a revised structure of the kinamycins as diazobenzo[*b*]fluorene compounds **286** - **289** (Figure **3-3**).[130-132] Kinamycins E **(290)** and F **(281)** were subsequently isolated in 1989, and their structural revisions are shown in Figure **3-3**.[125] Since the initial isolation of the kinamycin antibiotics in 1970, a variety of different compounds have been isolated that resemble the benzo[*b*]fluorene core and are thought to be possible intermediates in the biosynthesis of the kinamycins (Figure **3-4**).[126,133-141]



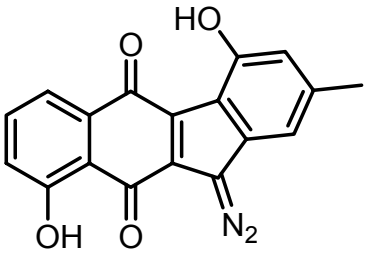
282 - Kinamycin A R^1 = H, R^2 = R^3 = R^4 = Ac
283 - Kinamycin B R^1 = R^3 = R^4 = H, R^2 = Ac
284 - Kinamycin C R^1 = R^3 = R^4 = Ac, R^2 = H
285 - Kinamycin D R^1 = R^3 = Ac, R^2 = R^4 = H

Figure **3-2**: Initial structural assignment of the kinamycin antiobiotics A-D.[128,129]

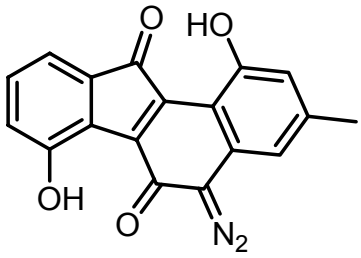


286 - Kinamycin A R^1 = H, R^2 = R^3 = R^4 = Ac
287 - Kinamycin B R^1 = R^3 = R^4 = H, R^2 = Ac
288 - Kinamycin C R^1 = R^3 = R^4 = Ac, R^2 = H
289 - Kinamycin D R^1 = R^3 = Ac, R^2 = R^4 = H
290 - Kinamycin E R^1 = Ac, R^2 = R^3 = R^4 = H
281 - Kinamycin F R^1 = R^2 = R^3 = R^4 = H

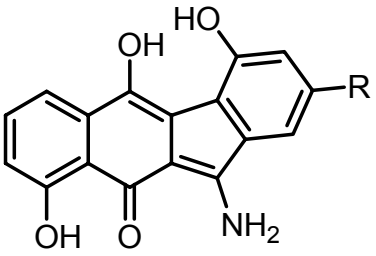
Figure **3-3**: Revised structural assignment of the kinamycins A-F.[125,130-132]



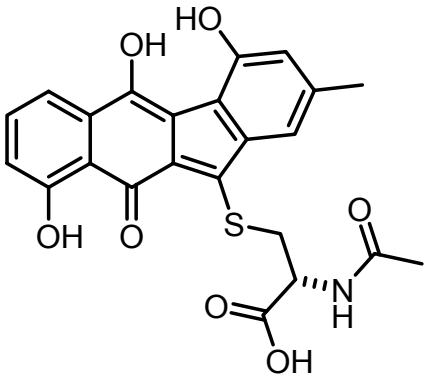
291 - Prekinamycin



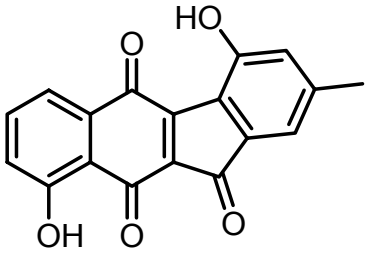
292 - Isoprekinamycin



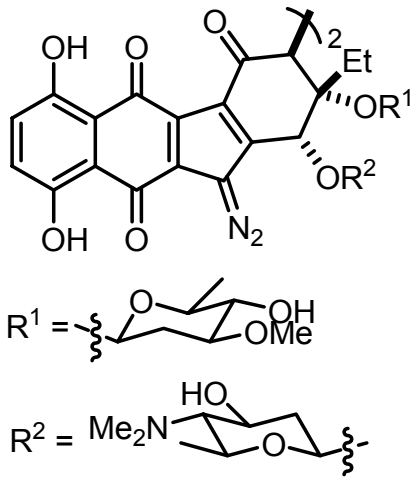
293 - Stealthin A R = CH_2OH
294 - Stealthin B R = CHO
295 - Stealthin C R = CH_3



296 - Seongomycin



297 - Kinobscurinone



298 - Lomaiviticin A

Figure **3-4**: Examples of other isolated kinamycin antibiotics.[126,133-141]

3.3 Biology

Kinamycins A-D are potent antimicrobial agents. They have strong activity against gram-positive bacteria, but are less active against gram-negative (Table **3-1**).[129] Among kinamycin A-D **(286 - 289)**, B **(287)** and D **(289)** are more active than A **(286)** and C **(288)**. This evidence suggests that there is a clear structure-activity relationship, as the anti-microbial activity increases as the number of acetates on the D-ring decreases. However, no biological activity studies have been performed for kinamycins E **(290)** and F **(281)**. Kinamycin C was also reported to have weak antitumor activity against Ehrlich ascites carcinoma cells at 0.1 mg / kg.[133] Lomaiviticin A **(298)**, which is a dimeric diazobenzofluroene glycoside, was also reported to exhibit promising cytotoxicity against a variety of tumor cell lines.[127] Their intriguing structures as well as interesting biological activities has made the kinamycins worthwhile structures for chemical synthesis.

Table **3-1**: Inhibitory concentration of kinamycins A-D towards gram negative and gram positive bacteria.[129]

	Minimium Inhibitory Concentration (μg/mL)			
Test Organism	A - **286**	B - **287**	C - **288**	D - **289**
Bacillus subtilis PCI-219	0.024	0.012	0.19	0.012
Bacillus anthracis	0.19	0.012	0.19	0.024
Staphylococcus aureus FDA 209F	0.78	0.012	0.78	0.024
Staphylococcus albus	0.024	0.012	0.39	0.024
Mycobacterium ATCC 607	25	6.25	6.25	6.25
Escherichia coli NIHJ	> 100	3.12	> 100	12.5
Klebsiella pneumonia	>100	12.5	> 100	25
Pseudomonas aeruginosa P-2	> 100	> 100	> 100	> 100
Salmonella typhosa 901W	> 100	6.25	> 100	12.5

3.3.1 Previous Biological Mechanism of Action

3.3.1.1 Proposed Oxidation of the Diazo Compound to Induce DNA Cleavage

Jebaratnam and Arya, in 1995, reported their initial efforts to probe the biological mechanism of action of these diazofluorene antitumor antibiotics, focusing on the diazofluorene model structure **299** (Figure **3-5**).[142] It was shown that copper mediated oxidation of the diazofluorene **299** in the presence of DNA induced strand cleavage. It was proposed that in the presence of cupric acetate, oxidation generated radical **300**. This radical can then further react with DNA in the presence of some active oxygen species, possibly generated from the oxidation by the cupric acetate, to achieve DNA cleavage. The problem with this mechanism is that it requires an oxidation to generate the delocalized radical, which is inconsistent with observations later made by He that the diazo compound lomaiviticin A cleaves double stranded DNA under reducing conditions.[126]

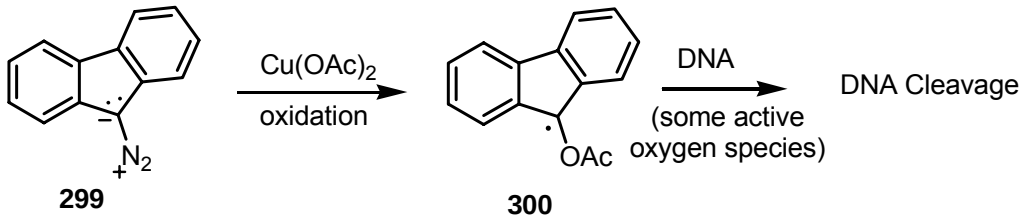


Figure **3-5**: Proposed mechanism of oxidation of diazofluorene leading to DNA cleavage.[142]

3.3.1.2 Nucleophilic Addition to the Electrophilic Diazonium Ion to Induce DNA Cleavage

Another possible mechanism of action was proposed by Dmitreinko using isoprekinamycin **(301)** (Figure **3-6**).[143] In this model the diazofluorene is actually quite diazonium-ion-like due to the hydrogen bonding ability of the alkoxide and the neighboring hydroxyl. Due to this enhanced electrophilicity, nucleophiles (like naphthol) can react with the diazonium ion to generate adduct **302**, which upon loss of nitrogen will generate two radicals, a radical of the nucleophile, and an aryl radical **303**. It was hypothesized that these aryl radicals could undergo further reaction leading to chemical modifications of the nucleic acids in DNA.

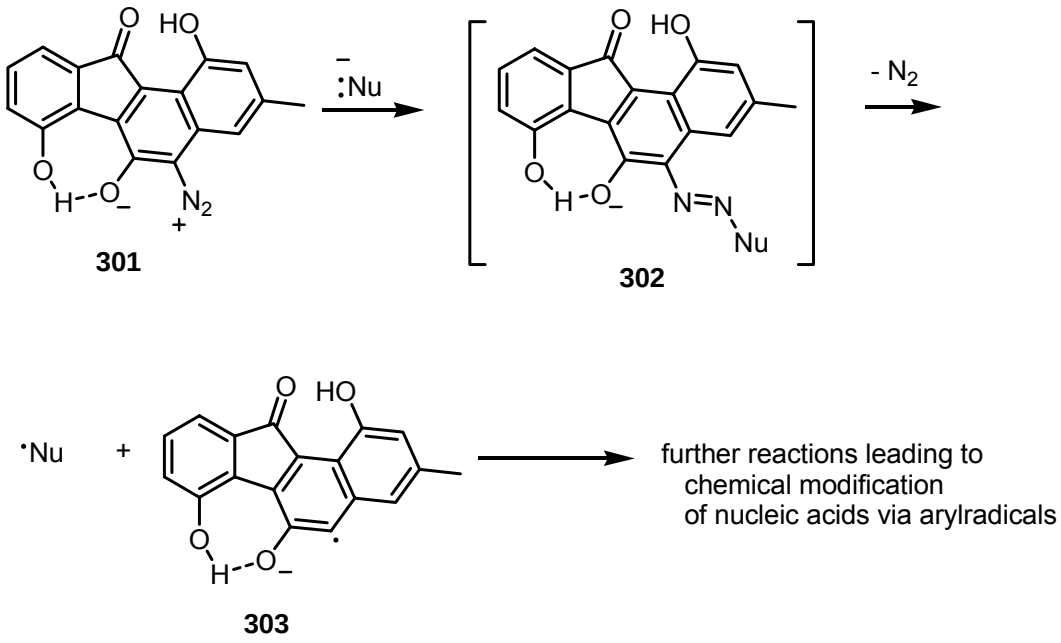


Figure **3-6**: Nucleophilic addition to the diazonium electrophile.[143]

3.3.2 Hypothesized Mechanism of Action

Another postulated mechanism of action (shown in Figure **3-7**) proceeds through a bio-reductive process, similar to which the antitumor activity of many quinone containing compounds are expressed. Thus, a one electron reduction of the quinone **304** generates the radical anion **305**. The radical anion **305** can be drawn as resonance form **306**, due to the hydrogen bonding ability of the hydroxyl group. The loss of nitrogen from **306** generates a new radical species **307**. In the proximity of DNA, this radical **307** can abstract a hydrogen from DNA, generating compound **308** and a DNA radical.

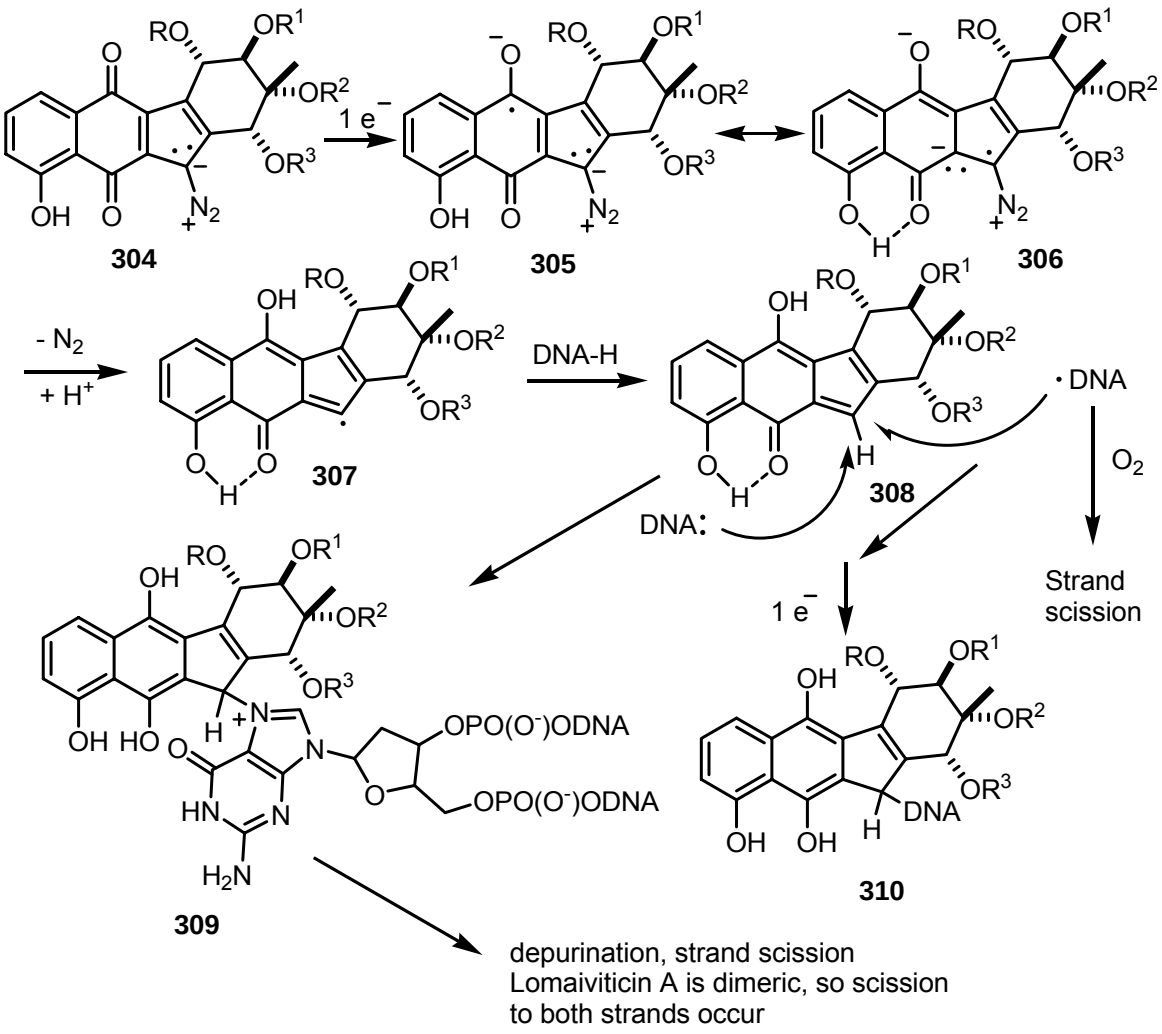


Figure **3-7**: New proposed mechanism of action of the kinamycin diazobenzo[*b*]fluorenes.

The possibility exists that the generation of this DNA radical could result in DNA strand scission in the presence of O_2; however, DNA could also add back into the enone moiety of **308** leading to strand scisson. The generated DNA radical also could add into the enone **308**, followed by another one electron reduction to generate the hydroquinone-DNA adduct **310**, which could further lead to DNA scission. Another possibility exists where addition of another strand of DNA into the enone **308**, via a guanosine moiety, would generate **309**. This alkylation would then lead to depurination and strand scission. The dimeric

structure of lomaiviticin A **(298)** could enhance DNA cleavage by tandem reaction to both strands of DNA.

3.4 Previous Total Syntheses

Numerous studies towards the synthesis of the kinamycins have emerged since their isolation in 1970. However, many of these syntheses were directed towards the synthesis of the carbazoloquinone cyanamide structures, that were initially thought to be the kinamycins.[144-150] It was these syntheses that helped to correct the structural identification of the kinamycins as diazobenzo[*b*]fluroenes. There are multiple new syntheses of the revised diazo structure of the kinamycins, a few of which pass through a common benzo[*b*]fluroene ketone core. The reported synthesis and synthesis attemps of the kinamycins include: prekinamycin **(291)**, kinobscurinone **(297)**, isoprekinamycin**(292)**, stealthin A **(293)** and C**(295)**, and the kinamycins A-F **(296 – 290, 281)**

3.4.1 Synthesis of Prekinamycin

The first synthesis of the revised kinamycin structure was of prekinamycin **(291)** by Hauser and Zhou in 1996 (Figure **3-8**).[151] This synthesis commenced with dihydrocoumarin **(311)**, which underwent and intramolecular Friedel-Crafts rearrangement followed by methylation to furnish **312**. The silylation of the ketone **312**, followed by oxidation, afforded the indenone compound **313**, which was then condensed with the anion of the phthalide sulfone **314** to furnish the ketone **315** in good yield. The removal of the methyl ethers, followed by conversion to the hydrazone and oxidation yielded the diazo compound prekinamycin **(391)** in 8 steps.

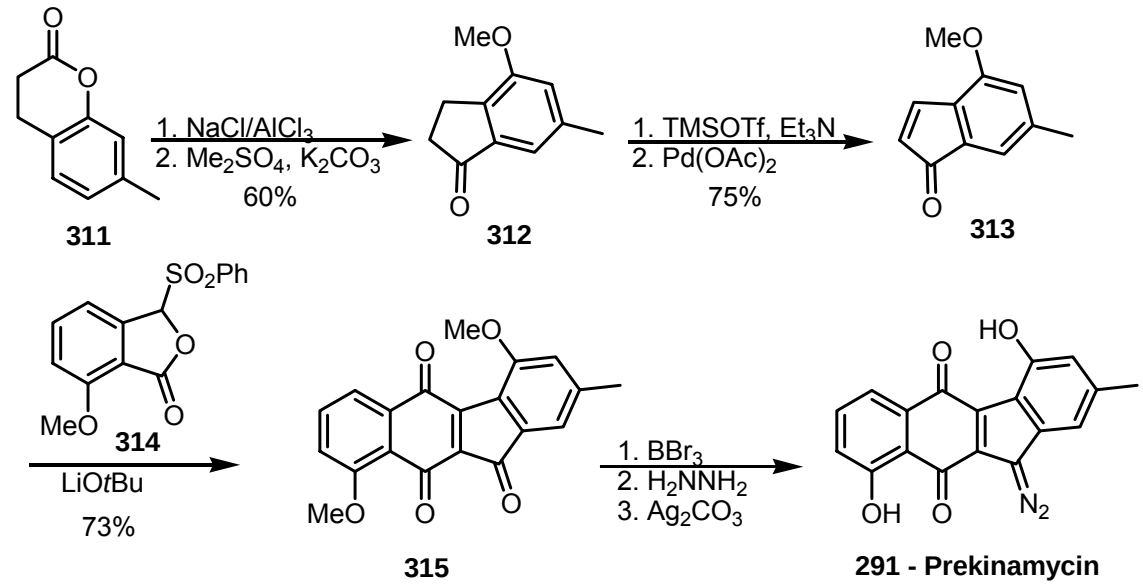


Figure **3-8**: Synthesis of prekinamycin reported by Hauser[151]

3.4.2 Gould's Synthesis of Stealthin C and Kinobscurinone

Gould and coworkers, in 1997, reported the syntheses of two additional members of the kinamycin family, stealthin C **(295)** and kinobscurinone **(297)**, which diverge at the benzo[*b*]fluorene ketone **(321)** (Figure **3-9**).[152] The synthesis of the key intermediate **321** started with the formation of aldehyde **317**, which could undergo a Knoevenagle condensation, followed by methylation to generate cinnamate **318**.[146] The condensation of **318** with the lithium salt of the cyanophthalide **319**, followed by methylation afforded the methylated hydroquinone **320**. Polyphosphoric acid cyclized the ester to generate the hydroquinone which was again methyl protected to afford benzo[*b*]fluorene ketone **(321)**. At this point, the synthetic route diverges and treatment of the fluorene core **321** with boron tribromide affords kinobscurinone **(297)** in 8 steps with a 31% yield from **316**.[153] Alternatively, hydroxyl amine can be used to generate the oxime **322**, which can then be treated with boron tribromide,

followed by reduction of the oxime to generate stealthin C **(295)**, in 10 steps in a 28% yield.

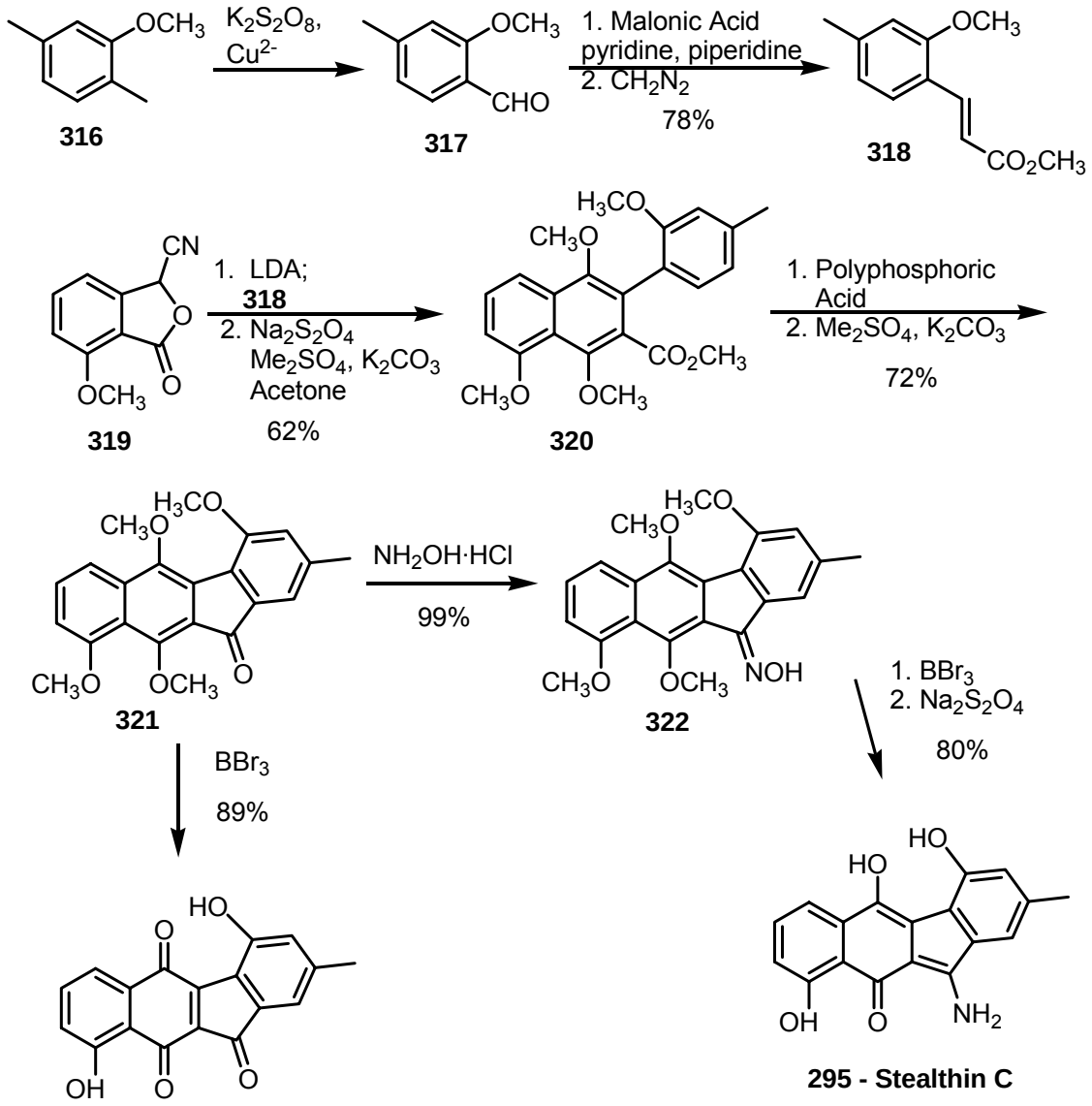


Figure **3-9**: Synthesis of kinobscurinone and stealthin C reported by Gould.[146,152,153]

3.4.3 Synthesis of O^4, O^9- Dimethylstealthins A and C

Kamikawa and coworkers in 1997 reported syntheses of the O^4, O^9-dimethylstealthins A **(332)** and C **(330)** from a divergent pathway through intermediate **328** (Figure **3-10**)[154,155] The syntheses commenced with a palladium catalyzed Suzuki coupling of boronic acid **324** and the aromatic bromide **326** to afford biaryl compound **327**. Compound **327** was then oxidized using alkaline hydrogen peroxide, followed by Friedel-Crafts cyclization with titanium (IV) chloride as a catalyst generated the benzo[*b*]fluoren-11-one **328**, which is the key intermediate for both compounds. The benzo[*b*]fluoren-11-one **328** was converted to the benzyl oxime **329**. Demethylation of **329** using cerium (IV) ammonium nitrate (CAN) followed by reduction of the oxime using zinc in acetic acid afforded the O^4,O^9-dimethylstealthin C **(330)**. Benzo[*b*]fluoren-11-one **328** was also further reacted to form the methylated stealthin A **332**. Compound **328** underwent radical bromination using NBS. Alkaline hydrolysis of the resulting bromide (not shown) gave the benzyl alcohol **331**. The benzyl alcohol **331** was then acylated and converted to the benzyl oxime (not shown). Further reaction with CAN for demethylation, followed by Zn reduction afforded the O^{12}-acetyl-O^4, O^9-dimethylstealthin A **332** in good yield.

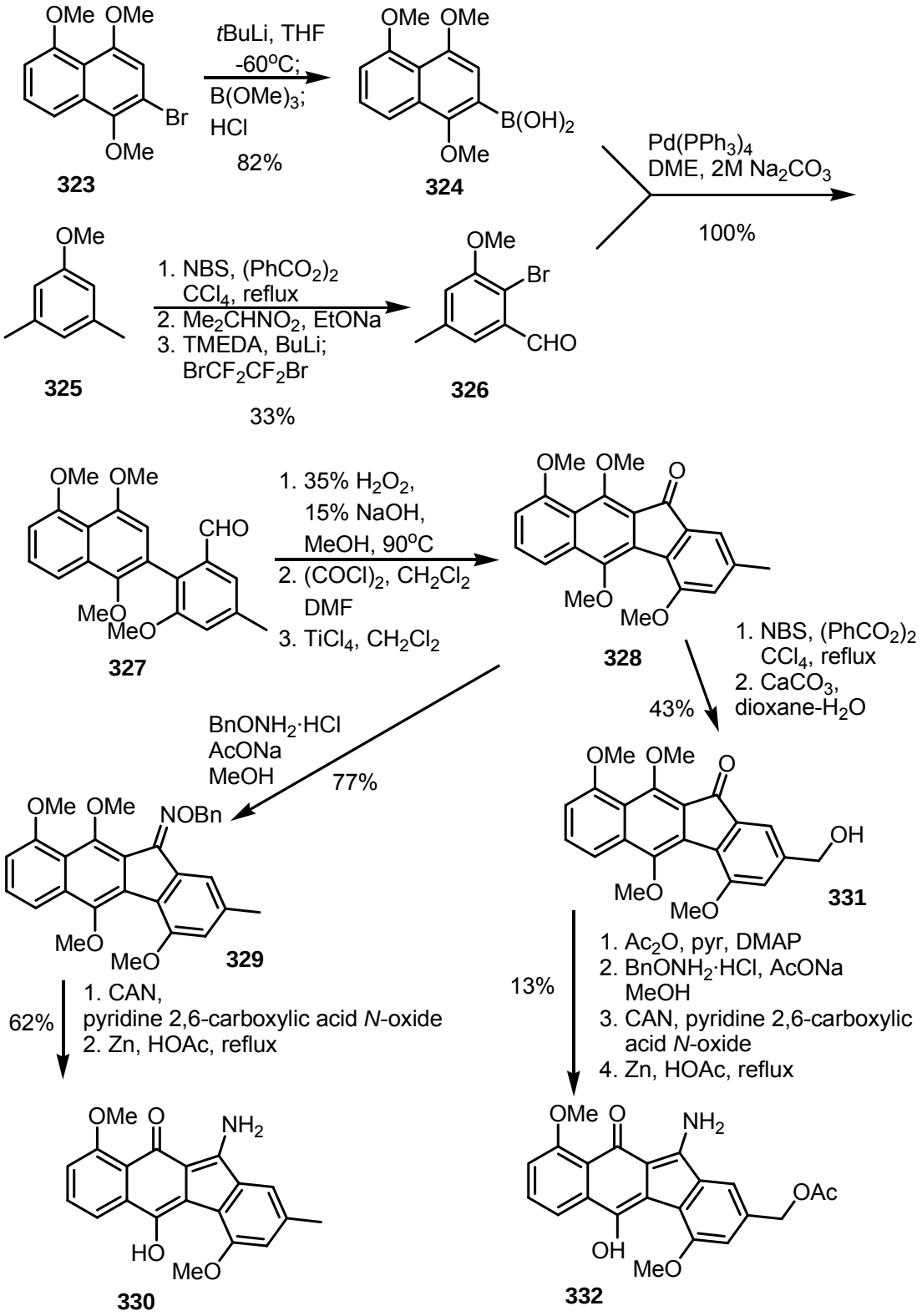


Figure **3-10**: Kamikawa's synthesis of *O*[4], *O*[9]-dimethylstealthin A and C.[154,155]

3.4.4 Synthesis of the Benzi[*b*]fluroenone core

It was shown by Hauser and Gould that the benzo[*b*]fluorene ketone core **(321)** can be converted to many of the kinamycins including: the stealthins, prekinamycin and kinobscurinone. Thought of as a key intermediate in the biosynthesis of the kinamycins, many others have reported efforts towards the synthesis of this key interemediate **321**.

Snieckus and coworkers reported the synthesis of this benzofluorenone intermediate **321** using similar bond disconnections as those employed by Gould.[156,157] The two key bond transformations for the formation of the C-ring start with the palladium catalyzed coupling of bromide **333** with the phenyl boronic acid **334** (Figure **3-11**). The silylation of the D-ring, followed by a carbamoyl transfer yields compound **337** after methylation of the formed phenol (not shown). Metallation and then cyclization of the C-ring afforded **338**, which was deprotected to generate the benzo[*b*]fluorone core **(321)** in 7 steps.

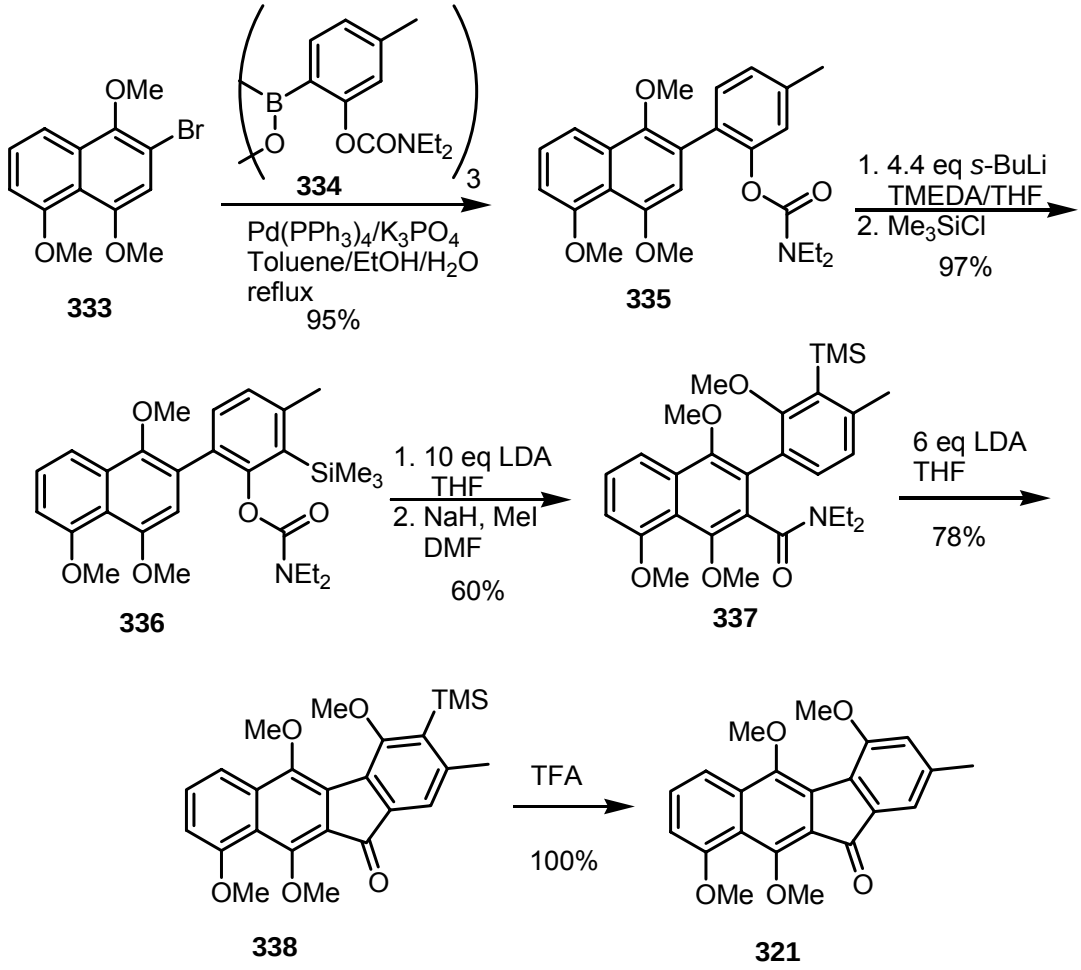


Figure **3-11**: Snieckus' synthesis of the benzo[*b*]fluorenone core.[156,157]

Another attempt towards the synthesis of a fluorenone core derivative **341**, was reported by Mal and Hazra in 1996, using annulation chemistry, which was an extension of the work done by Hauser.[158,159] Their approach employed the strategy used by Hauser[151] for annulation of cyclohexenones, to indenones **339**. By reacting the lithium anion of the phthalide sulfone **340** with indenone **339**, the hydroquinone compound **341** was generated in good yield (Figure **3-12**).

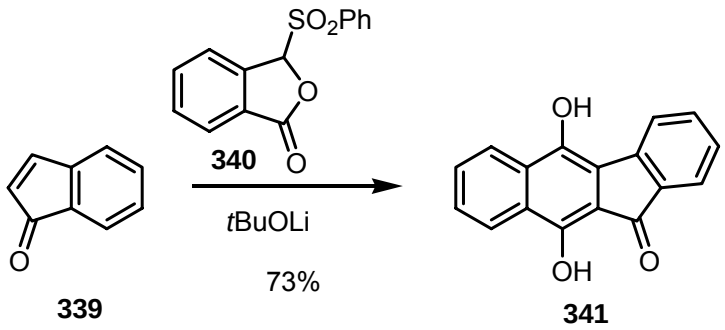


Figure **3-12**: Annulation chemistry explored by Mal.[158,159]

Another approach to the benzo[*b*]fluorene structure focused on the closure of the C-ring (through the phenyl-phenyl bond) via reductive cyclization (Figure **3-13**).[160] Beginning with methylation of naphthol **342**, followed by lithiation and condensation reactions, the AB-D rings of the benzofluorene were synthesized. Hydrolysis of the acetate to generate the aniline (not shown), which was then deaminated with isoamyl nitrite in acetic acid, followed by reductive cyclization with the hydroquinone moiety, yielded the tetracycle **345** in good yield. Demethylation with boron tribromide, followed by formation of the hydrazone, then reduction, generated the diazofluorene compound **346**.

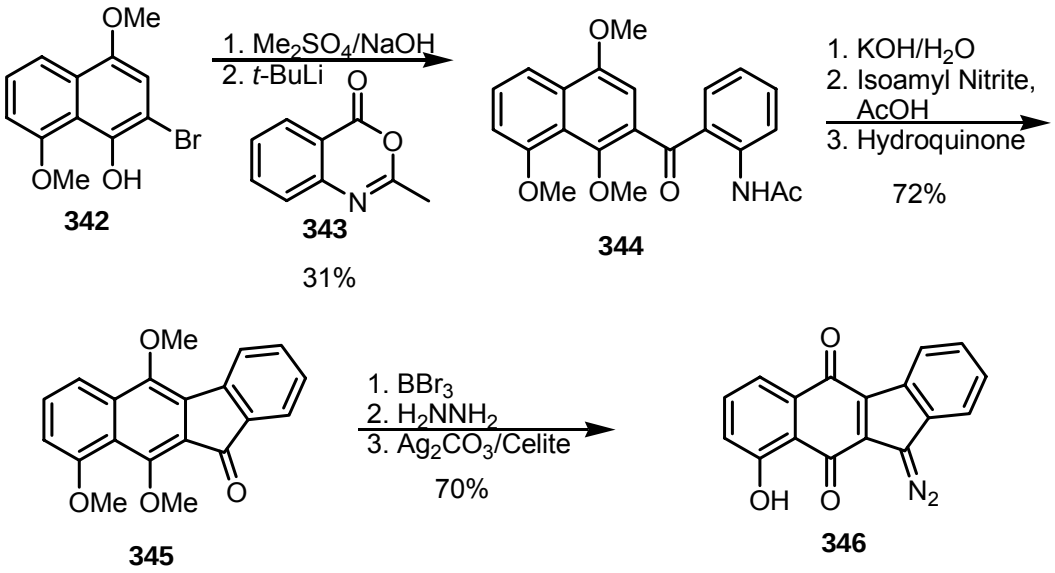


Figure **3-13**: Jebaratnam's study of the synthesis of the diazofluorene core structure.[160]

Two other completely different approaches involve the formation of the benzo[*b*]fluorone core via radical cyclization. The first was reported by Echaverren in 1997, who used the arylalkyne-allene compound **349** to generate the tetracycle **351** (Figure **3-14**).[161] This reaction was shown to proceed through a diradical **350** followed by the formation of a six-membered ring by collapse of the benzyl radical with the vinyl radical to form **351** in modest yields. Another radical cyclization to afford the fluorene structure was reported by Domínguez and Saá, who utilized radicals generated from conjugated polyenyne systems **352** (Figure **3-15**).[162] Upon heating the polyenyne system, thermal intramolecular cyclization gives the biradical **353**, which undergoes radical cyclization to yield biradical **354**. Further hydrogen abstraction generates the benzo[*b*]fluorene **355**.

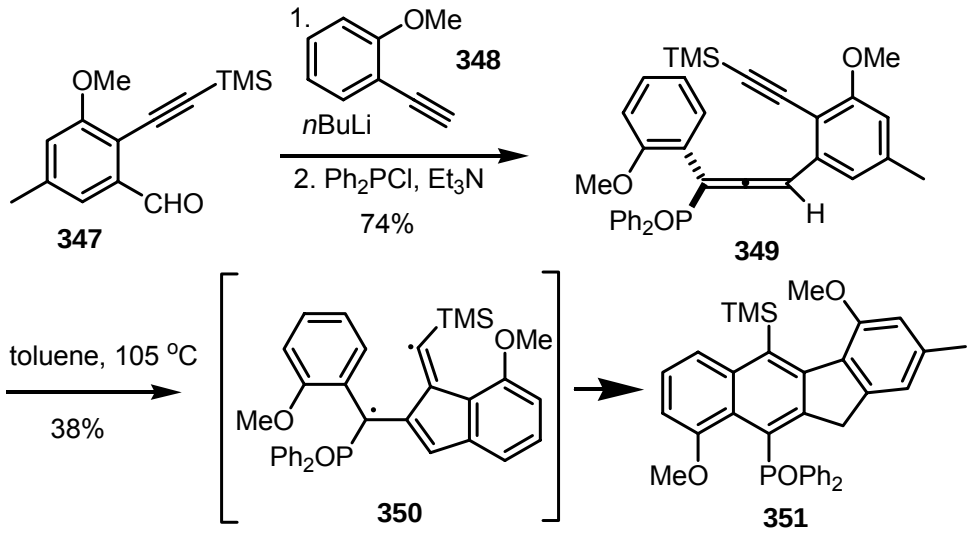


Figure **3-14**: Arylalkyne-allene radical cyclization to generate fluorene structure.[161]

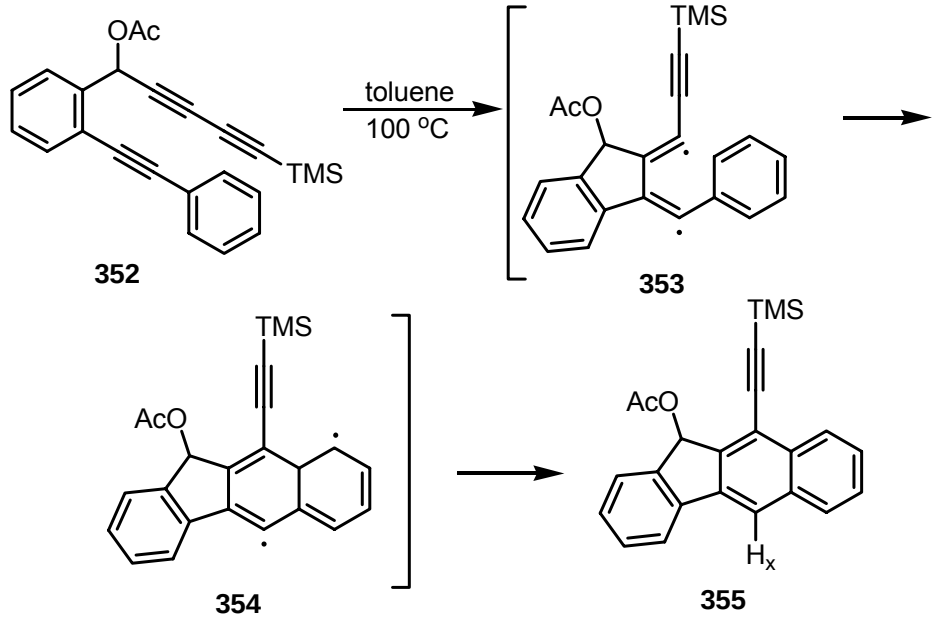


Figure **3-15**: Polyenyne cyclization for the synthesis of the fluorene structure of the kinamycins.[162]

In 2000, Jones and Qubaja demonstrated the utility of palladium mediated closures in the synthesis of the benzo[*b*]fluorone core **(321)** (Figure **3-16**).[163,164] This synthesis commences with the formation of the iodoaldehyde **357** from dimethylanisole **(356)**. 1,2-Addition of the lithium salt of the arylbromide **359**, to the aldehyde **357**, followed by oxidation of the resultant alcohol afforded ketone **360**. Intramolecular palladium mediated coupling of the ketone **360** using microwave irradiation, generated the benzo[*b*]fluorene ketone core **(321)** in moderate yield.

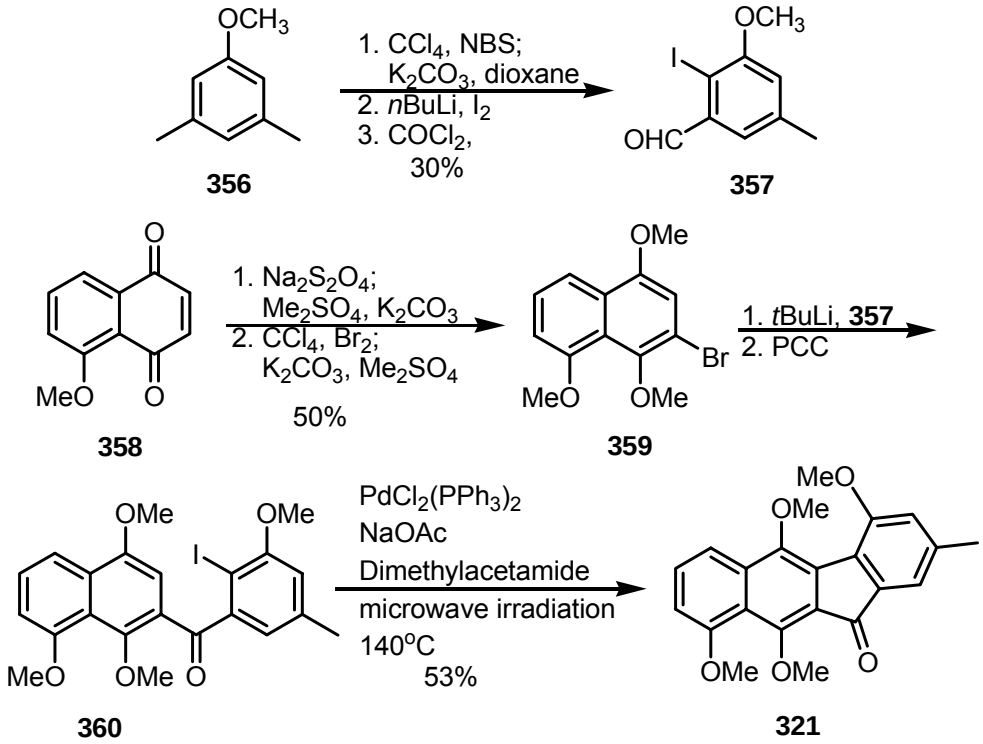


Figure **3-16**: Palladium mediated cyclization to generate the benzofluorenone core of the kinamycins[163,164]

3.4.5 D-Ring Synthesis of Kinamycin A-F

More recently the focus of the synthesis of the kinamycins has shifted towards the synthesis of kinamycin A-F, which contain a highly oxygenated, non-aromatic D-ring. A model system structure of this oxygenated D-ring was reported in 2000 by Ishikawa and coworkers, using the BCD rings as a model (Figure **3-17**).[165,166] This synthesis commences with the benzyl indenone **361**, which is reacted with Danishefsky's diene **362** via a Diels-Alder reaction to produce the tricycle **363**, a species containing the BCD rings of the kinamycins. The desilylation of **363**, under acidic conditions, followed by oxygenation, yielded alcohol **364**. The enone of **364** was converted to the corresponding silyl dienol ether (not shown), which was hydroxylated with osmium tetraoxide (OsO_4), followed by treatment with diisobutylaluminum hydride (DIBAl-H) to give tetra-ol **365**. The protection of three of the hydroxyl groups allowed for a second dihydroxylation using OsO_4 to afford the highly oxygenated compound **366**. Acetonide protection of the newly formed diol, followed by deprotection of one of the hydroxyl groups and then oxidation afforded ketone **367**. The tertiary hydroxyl group was then converted to the xanthate (not shown), and pyrolysis under vacuum afforded the enone **368**. The enone **368** was treated with hydrazine, followed by dehydrogenation to afford the diazo compound **369**, which contains the fully oxygenated BCD ring system of the kinamycins.

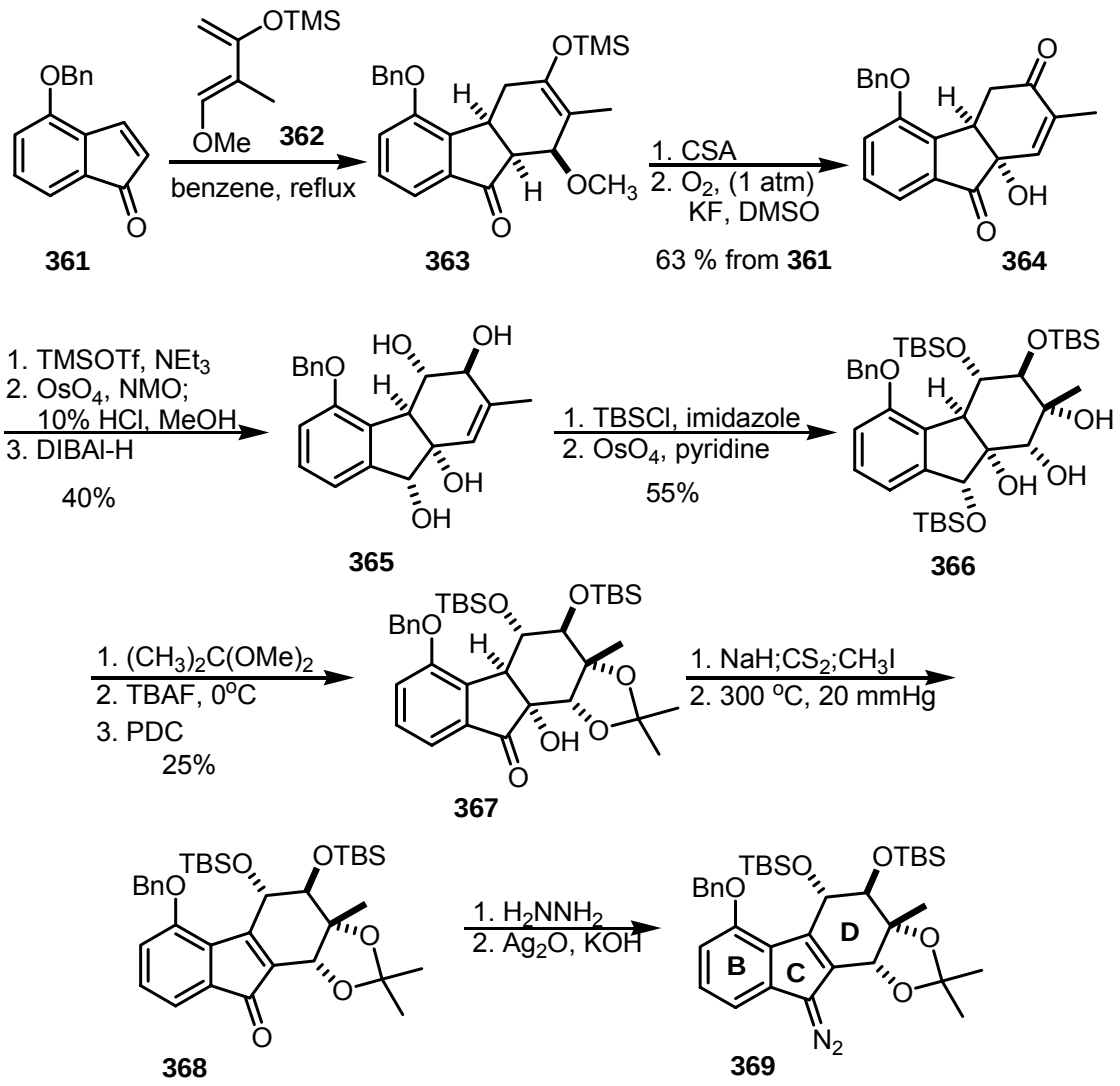


Figure **3-17**: Model system for the synthesis of the highly oxygenated D-ring of the kinamycin A-F.[165,166]

Further progress towards the kinamycins A-F was reported by Ishikawa and coworkers in 2002.[167] The target of this synthesis was the formation of the benzofluorenone compound **376** which contains an identical D-ring to **369** (Figure **3-18**). The synthesis commenced with the acetylation of 5-hydroxynaphthol **(370)**, followed by an oxidative bromination, deacetylation, and methylation to afford quinone **371**. The quinone **371** was then reduced with tin (II) chloride and methylated. Metallation and carbonylation of the methylated

hydroquinone (not shown) generated aldehyde **372**, which was subsequently reacted with malonic acid and sonicated to afford the acid **373**. Acid **373** was then hydrogenated followed by cyclization to afford the cyclopentanone compound **374**. Oxidation to the cyclpentenone (not shown) generated the dienophile ready to react with Danishefsky's diene **362**. Camphorsulfonic acid deprotected the silyl enol ether to generate the enone **375**. Further air oxidation of **375** resulted in the formation of γ-hydroxyenone **376**, which has an identical D-ring to that of **369** (Figure **3-17**).

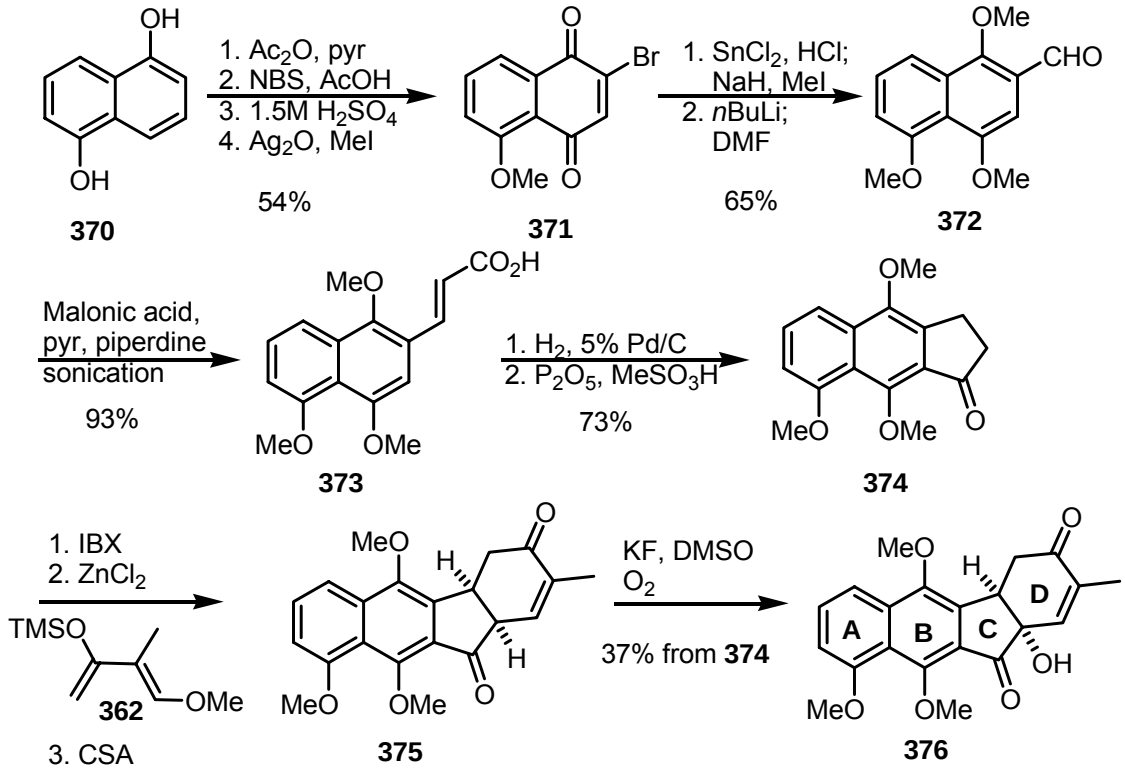


Figure **3-18**: Synthesis of the ABC rings of the kinamycins.[167]

3.4.6 Synthesis of Diazobenzo[*b*]fluorene

The final kinamycin-like compound that has been synthesized is the diazobenzo[*b*]fluorene structure **381**, which is similar to isoprekinamycin **(292)**. This synthesis was reported in 2002, by Dmitrienko.[143] This synthesis uses a modified Suzuki coupling to generate the aryl system **379** (Figure **3-19**). Bromination using N-bromosuccinimide (NBS), followed by Friedel-Crafts cyclization afforded the fluorenone structure **380**. A palladium catalyzed amination was then performed, followed by hydrogenolysis, diazotization, and demethylation to afford the isoprekinamycin like compound **381**.

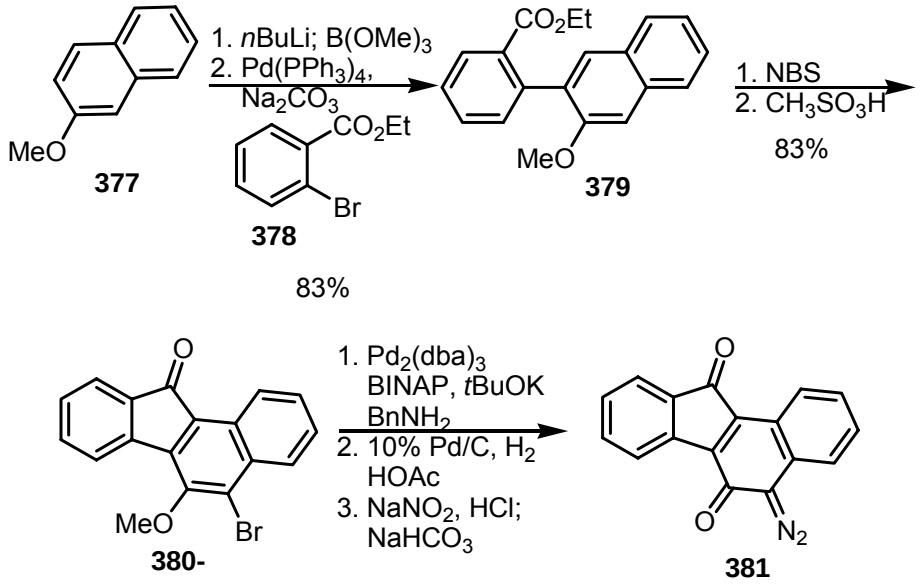


Figure **3-19**: Synthesis of the isoprekinamycin skeleton.[143]

3.5 Retrosynthesis of Kinamycin F

The following synthesis plan for kinamycin F **(281)** follows some of the same key bond disconnections as those shown previously. Retrosynthetically, kinamycin F **(281)** can be formed from fully protected tetracycle **382** via deprotection, formation of the diazo moiety, and oxidation to the quinone (Figure **3-20**). The C-ring formation can be envisioned to proceed via a Nazarov cyclization from the dienone **383**. The dienone **383** can be generated from a coupling of the bromo-jugulone derivative **384** with the fully oxygenated D-ring **386**, which comes from commercially available bromo-*cis*-bromocyclohexadiene-5,6-diol **(279)**.

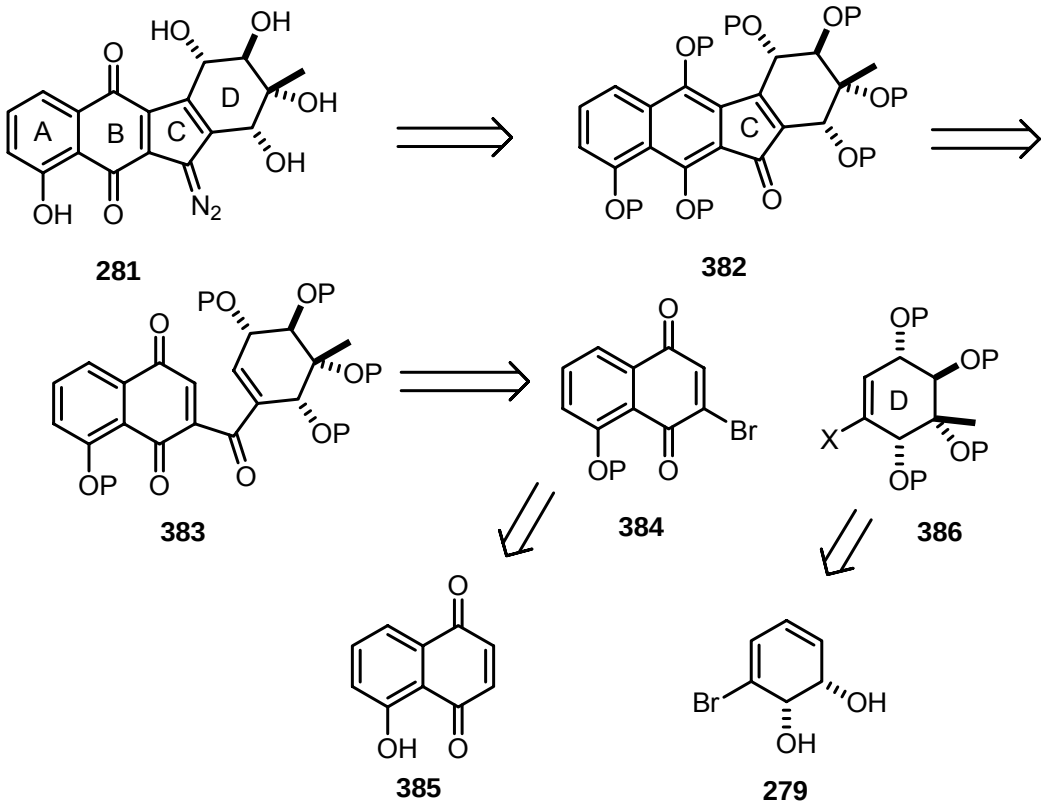
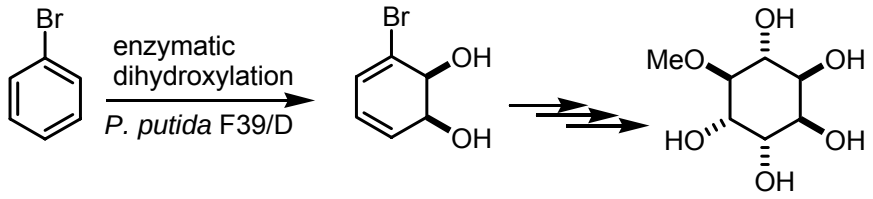


Figure **3-20**: Retrosynthetic analysis of kinamycin F.

3.6 Synthesis of the D-Ring

The synthesis of the D-ring of kinamycin F was based upon the observations reported by Hudlicky and coworkers for the enzymatic dihydroxylation of aromatic compounds in the context of syntheses of carbohydrate type poly-hydroxylated natural products (Figure **3-21**).[168-170] It was reported that *P. pudita* contains an enzyme that can catalyze an enantiospecific dihydroxylation of a variety of different aromatic compounds to give the *cis*-cyclohexadiene-diols **(279)**, which was shown to be further elaborated to give (+)-pinitol **(388)**. Taking advantage of the selectivity available for the enzymatic dihydroxylation, the synthesis started with the bromo *cis*-diol **279**, which could undergo further asymmetric transformation, to afford the D-ring of kinamycin F.



387 **279** **388 - (+)-Pinitol**

Figure **3-21**: Hudlicky's synthesis of (+)-pinitol based on enzymatic dihydroxylation of aromatic comounds.[168-170]

The synthesis of kinamycin F starts with commercially available (1*S*-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol **(279)** (Figure **3-22**). Acetonide protection of the *cis*-diol followed by epoxidation with *m*-chloroperoxybenzoic acid afforded epoxide **390** regio- and diastereoselectively. Using 10 % potassium hydroxide (aqueous) opens the epoxide ring to generate the dihydroxyl compound **391**. The acetonide protecting group was then removed under acidic conditions to afford the tetrahydroxyl compound **392**, containing the appropriate stereochemistry of the hydroxyl groups. Three of the four hydroxyls groups were protected using *t*-butyldimethylsilyl chloride with imidazole to generate hydroxyl product **393** following a procedure by Banwell *et al*.[171] Dess-Martin oxidation of

this final hydroxyl group afforded the ketone **394**, which was subsequently attacked with methyl lithium to generate product **395** exclusively. Trimethylsilyl triflate was then used to protect the final alcohol to afford the fully protected cyclohexene compound **396**, which contains the appropriate stereochemistry for the D-ring of kinamycin F.

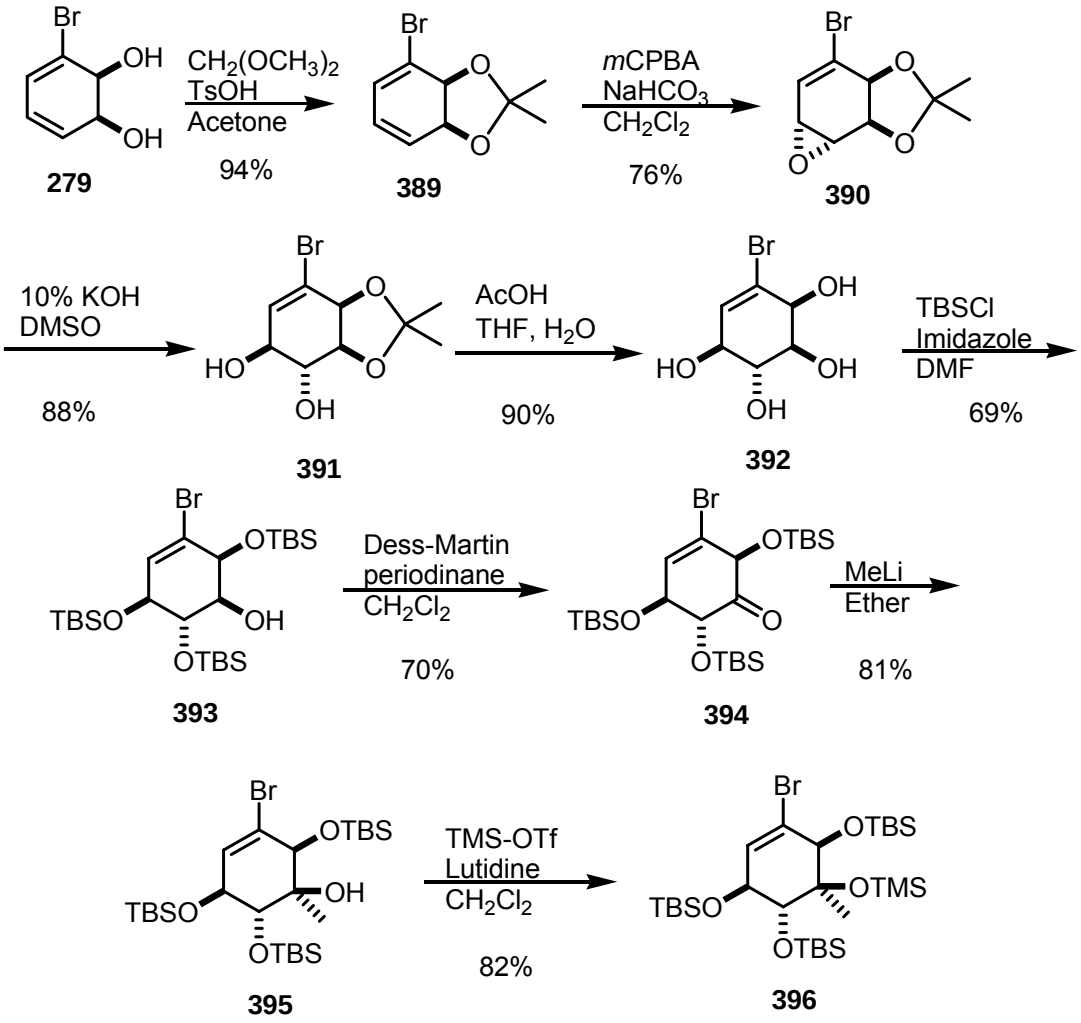


Figure **3-22**: Synthesis of the highly oxygenated D-ring of kinamycin F.

3.7 Model System Coupling of D-Ring to AB-Ring

The AB ring portion of kinamycin F was synthesized from juglone **(385)** as a coupling partner with the oxygenated D-ring for the key Nazarov cyclization. Juglone **(385)** was brominated, followed by benzylation of the hydroxyl moiety to afford **398** (Figure **3-23**).[172] The quinone was reduced with disodium dithionite to generate the unisolated hydroquinone **399**. Benzyloxymethyl chloride (BOM-Cl) was used to protect the hydroquinone. However, using diisopropylethylamine as a base in this ether forming reaction only protected one hydroxyl group to form **400**. A second BOM group was then installed using sodium hydride and BOM-Cl to generate the fully protected hydroquinone **401**. Metallalation of this bromo naphthalene compound **401** was attempted using both *n*-butyllithium and *t*-butyllithium in both THF and ether solvents. However, the lithiation procedure showed no evidence of the desired alcohol **403** from reaction with the cyclohexene-1-carboxylaldehyde **(402)**. The starting bromide **401** was the only product obtained after work up, which signified that the lithium anion was not being formed by metal-halogen exchange.

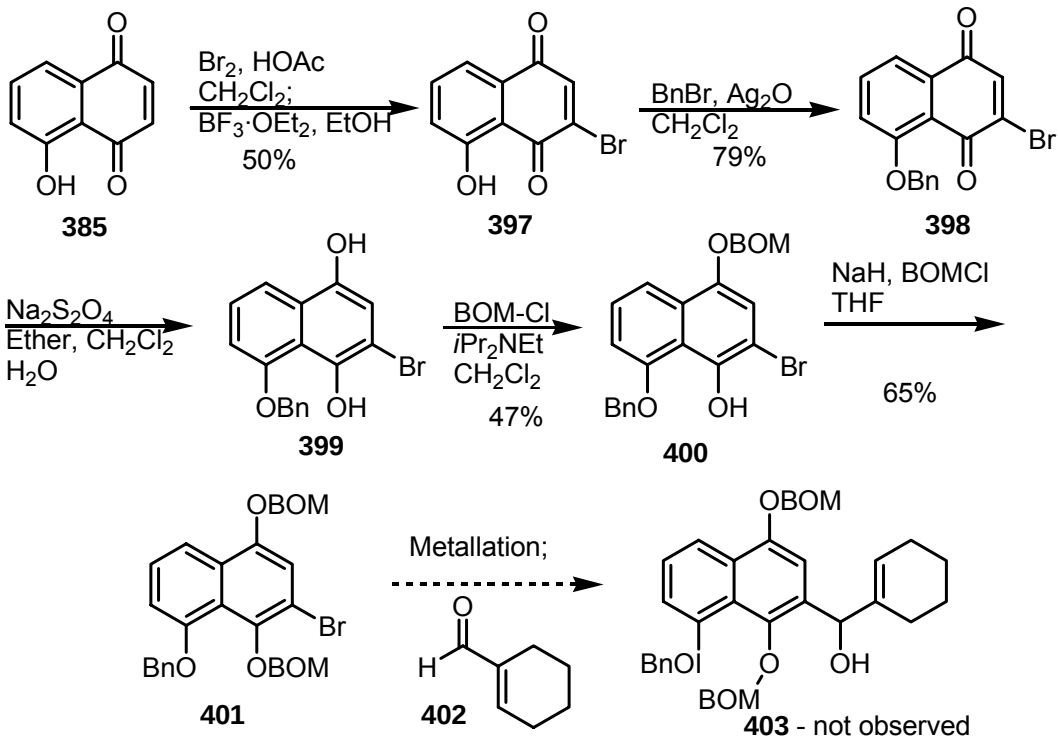


Figure **3-23**: Metallation chemistry to couple bromohydroquinone with the aldehyde as a model system for AB coupling to the D-ring of kinamycin F.

The inability to metalate the BOM protected hydroquinone led to the examination of a palladium catalyzed coupling to generate the desired tricycle **405** (Figure **3-24**). Initial attempts at coupling the BOM protected hydroquinone **401** with 1-trimethylstannyl-1-cyclohexene **(404)**, which was synthesized via a Bamford-Stevens reaction of cyclohexanone (not shown), using allylpalladium chloride dimer in the presence of carbon monoxide, afforded no coupled product **405** and only returned hydroquinone starting material **401**. However, stepping back to the bromoquinone compound **397**, palladium mediated carbonylation occurred at atmospheric pressure to afford 47% of the desired dienone **406**. By increasing the pressure of the reaction to 35 psi, the yield was increased to 70%.

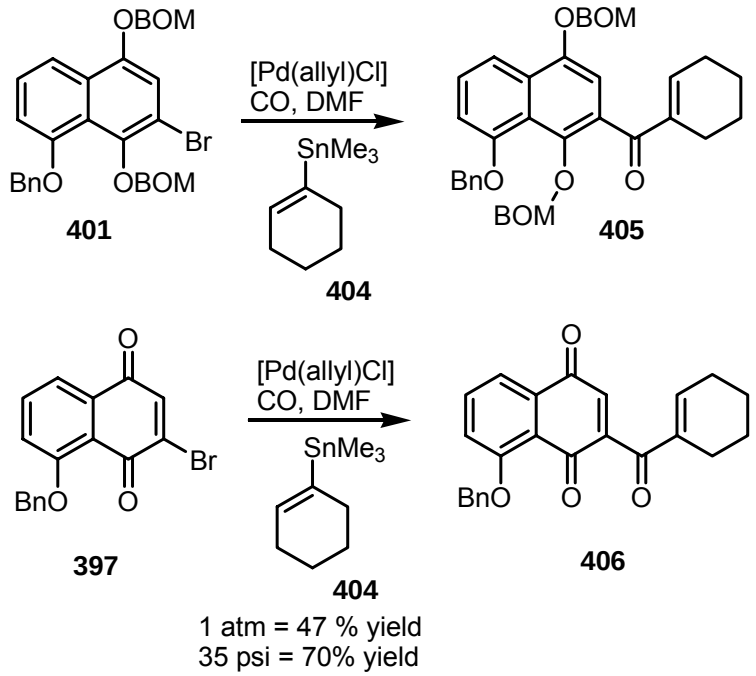


Figure **3-24**: Palladium catalyzed carbonylation for the coupling of the D-ring.

3.8 Nazarov Cyclization of Model System for C-Ring Closure

The formation of the coupled dienone **406**, allowed for model system attempts towards a Nazarov cyclization to generate the C-ring of the benzo[*b*]fluorone system **407** (Figure **3-25**). Initial attempts at cyclization utilized photochemistry to facilitate cyclization. Unfortunately, irradiation with 350 nm light in a variety of solvents yielded either no reaction or decomposition of the dienone (Table **3-2**).

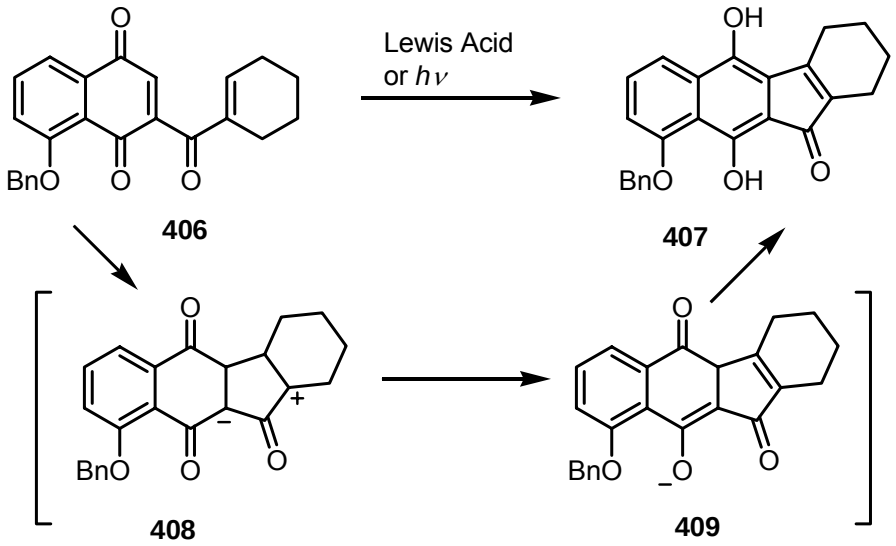


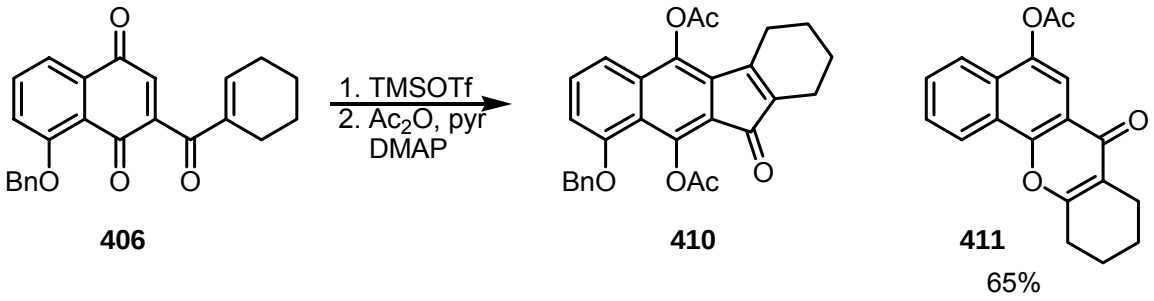
Figure **3-25**: Attempted Nazarov cyclization of the synthesized dienone model system.

Table **3-2**: Photochemical mediated Nazarov cyclization at 350 nm.

Solvent	**Time**	**Results**
CD_3CN	10 hours	No reaction
C_6D_6	10 hours	Decomposition
$(CD_3)_2CDOD$	24 hours	No reaction, dienone insoluble
$(CF_3)_2CDOD$	7 hours	Decomposition
1% D_2SO_4 in CD_3OD	24 hours	No reaction, dienone insoluble
10% D_2SO_4 in CD_3OD	24 hours	No reaction, dienone insoluble
10% D_2SO_4 in CD_3CN	0 hours	Immediate decomposition

The Lewis acid trimethylsilyl triflate (TMS-OTf) was also examined as a mediator of the dienone **406** cyclization (Figure **3-26**). Upon reaction with TMS-OTf at room temperature, complete disappearance of starting material was observed (within five minutes). Unfortunately, chromatographic isolation of the products was unsuccessful. A second attempt at this reaction employing the same cyclization conditions with TMS-OTf, followed by immediate protection of the resulting hydroquinone with acetic anhydride was thought to generate the diacetate compound **410**. Unfortunately, **410** was not formed. Rather, the pyran

411 was formed in 65% yield. This species apparently resulted from the cyclization the ketone of the quinone.



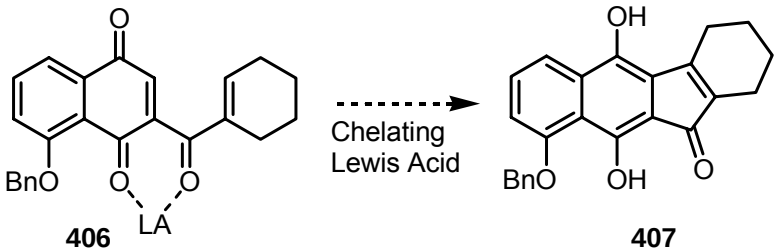
406 **410** **411**

65%

Figure **3-26**: Lewis acid catalyzed Nazarov cyclization.

3.9 Future Directions Towards the Completion of Kinamycin F

For the completion of the synthesis of kinamycin F, initial efforts are being focused on the Nazarov cyclization of the model system. The data obtained using the Lewis acid TMS-OTf, have shown that cyclization is feasible, but that different Lewis acids need to be screened. Immediate attempts will focus on Lewis acids that can coordinate the diketone to give the proper orientation of **406** to obtain the desired product **407** (Figure **3-27**).



406 **407**

Figure **3-27**: Chelation control from the Lewis acid to generate C-ring.

3.10 Conclusions

The kinamycins are a class of highly potent antimicrobial compounds. Their mechanism of action, presumably via DNA cleavage, is still being explored and the total syntheses of these compounds will help to better elucidate their biological activity. The progress made towards the synthesis of kinamycin F has been reported herein. The D-ring of has been stereoselectively synthesized from (1*S*-*cis*)-3-bromo-cyclohexadiene-1,2-diol. Model system work is currently underway for the cyclization of the C-ring, and once cyclization conditions can be determined, investigations with the appropriately functionalized D-ring will begin.

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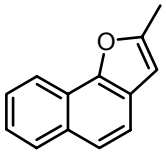
Chapter 4

EXPERIMENTALS

4.1 General Experimental

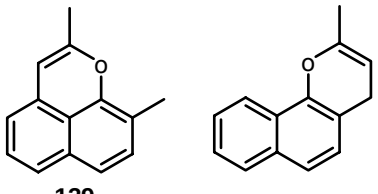
All reactions involving air and moisture sensitive reagents and solvents were performed in flame-dried glassware under an argon atmosphere. Prior to use tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl, and 1,2-dimethoxyethane (DME) and toluene from sodium fluorenone ketyl under argon. Dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from calcium hydride (CaH_2) under argon before use. Methanol (CH_3OH) was distilled from magnesium turnings under argon prior to use. All organic reagents were used as purchased unless otherwise noted. Crude reaction products were purified via flash chromatography on 32 – 63 μm silica gel (SiO_2) using the indicated solvent systems. The purification solvents used (hexanes, ether, ethyl acetate, and methylene chloride) were distilled from CaH_2. For the compounds related to the synthesis of kinamycin F, the solvents THF, ether, CH_2Cl_2, and hexanes were passed through alumina columns and dispensed under nitrogen from a Glass Contour Solvent Purification System. APCI MS, ESI MS and HRMS were obtained from the Mass Spectroscopy Facility at The Pennsylvania State University. Midwest Microlab (Indianapolis, IN) performed combustion analyses.

4.2 Naphthol Derivatives



135

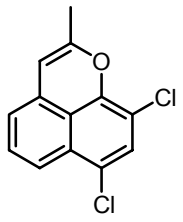
2-Methyl-naphtho[1,2-*b*]furan (135). 1-Naphthol **(132)** (137 mg, 0.950 mmol) was dissolved in DME (15.0 mL) under argon and the solution cooled to 0 ^{o}C. A solution of *n*-butyllithium (1.9M) in hexanes (550 μL, 1.0 mmol) was added dropwise and stirred 15 minutes. The solution was warmed to room temperature then reflux. Propynyliodonium salt **133** (561 mg, 1.43 mmol) in DME (4.0 mL) was added dropwise to the refluxing solution via syringe pump over 5 minutes and allowed to react at reflux for 30 minutes. The solution was cooled to room temperature, then poured into ice cold aqueous 1M H_3PO_4 (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give an orange oil. This crude oil was purified via SiO_2 chromatography using hexanes to yield 66 mg (38%) of **135** as a colorless oil. IR (CH_2Cl_2) 1621 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6)) δ 8.42 (dd, *J* = 8.2 Hz, 0.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.38 (m, 1H), 7.27 (m, 1H) 6.17 (t, *J* = 0.9 Hz, 1H,), 2.12 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (300MHz, C_6D_6) δ 151.3, 150.4, 131.5, 128.8, 126.6, 124.8, 124.7, 123.5, 121.9, 120.0, 119.6, 104.0, 13.8; MS APCI^{+} *m/z* (relative intensity) 182 (M^{+}, 100) HRMS Calcd. for $C_{13}H_{11}O$:183.0810; Found: 183.0814.



139 **138**

2,9-Dimethyl-benzo[*de*]chromene (139) and 2-Methyl-4*H*-benzo[*h*]chromene (138). 2-Methyl-1-naphthol **(136)** (160 mg, 1.01 mmol) was

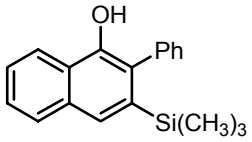
dissolved in CH_3CN (7.0 mL) and cooled to 0 ^oC. A solution of *n*-butyllithium (1.9 M) in hexanes (590 μL, 1.1 mmol) was added dropwise and stirred 15 minutes. The solution was then warmed to room temperature, and then to reflux. Propynyliodonium salt **133** (590 mg, 1.51 mmol) in CH_3CN (3.0 mL) was added slowly to the refluxing solution then allowed to react for 45 minutes. The solution was then cooled to room temperature and poured into ice cold 1M H_3PO_4 (20 mL), followed by extraction with ether (2 x 25mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield an orange oil. This oil was purified via SiO_2 chromatography using hexanes to yield 72 mg (36 %) of a 1.5 : 1 mixture of the two products **139 : 138**. The isomers were separated via reverse phase HPLC using 45 % CH_3CN / 10 % MeOH / 45 % H_2O. **139**: IR (CH_2Cl_2) 1534 cm^{-1} ; ^1H NMR (300 MHz, C_6D_6) δ 7.23 (d, *J* = 8.4 Hz, 1H), 7.09 (m, 3H), 6.48 (d, *J* = 6.9 Hz, 1H), 5.37 (d, *J* = 0.9 Hz, 1H), 2.15 (s, 3H), 1.62 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (300 MHz, C_6D_6) δ 152.8, 148.2, 133.9, 130.4, 130.3, 127.0, 123.3, 123.2, 119.2, 114.6, 113.9, 96.0, 19.3, 15.2; MS APCI$^+$ *m/z* (relative intensity) 197.1 (MH^+, 100) HRMS Calcd for $C_{14}H_{13}O$: 197.0966, Found: 197.0975. **138**: IR (CH_2Cl_2) 1249 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.40 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.35 (m, 3H), 6.87 (d, *J* = 8.4Hz, 1H), 4.46 (m, 1H), 3.23 (m, 2H), 1.78(m, 3H); ^{13}C NMR (300MHz, C_6D_6) δ 150.6, 147.0, 133.8, 127.9, 127.2, 126.0, 125.9, 124.8, 123.7, 121.7, 115.9, 104.1, 24.9, 19.2; MS APCI$^+$ *m/z* (relative intensity) 197.1 (MH^+, 100) HRMS Calcd for $C_{14}H_{13}O$: 197.0966, Found: 197.0976



142

7,9-Dichloro-2-methyl-benzo[*de*]chromene (142). 2,4-Dichloro-1-napthol **(140)** (204 mg, 0.960 mmol) was dissolved in DME (15.0 mL) and cooled

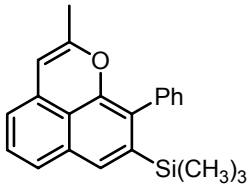
to 0 °C. A solution of *n*-butyllithium (1.6 M) in hexanes (650 μL, 1.1 mmol) was added dropwise. The reactions flask was warmed to room temperature and then brought to reflux. Propynyliodonium salt **133** (1.15 g, 2.93 mmol) dissolved in DME (4 mL) was added slowly to the refluxing solution and stirred for 45 min. The reaction mixture was then cooled to room temperature and poured into 1M H_3PO_4 (15 mL) and extracted with ether (2 x 25mL). The combined organic layers were washed with water (20 mL), dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated in vacuo to yield a brown oil. This oil was purified by SiO_2 chromatography using hexanes to give 112 mg (47 %) of **142** as a white solid. m.p. 162-163 °C; IR (CH_2Cl_2) 1672 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.6 Hz, 1H), 7.42 (s, 1H), 7.36 (dd, *J* = 8.6 Hz, 7.1Hz, 1H), 6.78 (d, *J* = 7.1 Hz, 1H), 5.88 (d, 0.8Hz, 1H), 2.14 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 153.2, 147.6, 130.3, 130.1, 129.0, 128.1, 123.8, 122.5, 120.1, 116.4, 111.3, 104.1, 76.7; MS APCI$^+$ *m/z* (relative intensity) 251 (MH^+, 100); Anal. Calcd for $C_{13}H_8Cl_2O$: C, 62.18; H, 3.12; Cl, 28.24; Found: C, 62.10; H, 3.29; Cl, 28.40.



145

2-Phenyl-2-trimethylsilyl-1-naphthol (145)[173]**.** To a solution of niobium (III) chloride (1.31 g, 4.51 mmol, 1.5 eq) in THF (65 mL), was added 1-phenyl-2-trimethylsilylacetylene **(144)** (880 μL, 4.5 mmol, 1.5 eq) under argon. The solution was heated to reflux for 18 hours, then the dark solution was cooled to 0 °C. A solution of terephthaldehyde **(143)** (402 mg, 3.00 mmol) in THF (5.0 mL) was then added dropwise, then allowed to react for 1.5 hours at 0 °C. The solution was warmed to room temperature and poured into a 10% aq KOH solution (70mL) and shaken until the aqueous layer was colorless. The aqueous layer was then extracted with ether (3 x 50 mL), and the resultant ethereal layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. A

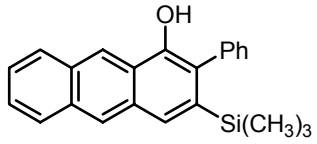
crude yellow oil was obtained, which was purified via SiO_2 chromatography using 5 % ethyl acetate in hexanes to yield 418 mg (48 %) of **145** as a white solid. m.p. 102-104 ^oC; IR (CH_2Cl_2) 3535 cm^{-1} (OH); ^1H NMR (300 MHz, C_6D_6) δ 8.56 (m, 1H), 7.82 (s, 1H), 7.75 (m, 1H), 7.39 (m, 2H), 7.13 (m, 5H), 5.10 (s, 1H), 0.08 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 147.5, 137.7, 137.0, 133.5, 131.4, 129.1, 128.6, 127.6, 127.0, 126.3, 126.0, 124.2, 122.2, 0.4; MS CI^+ *m/z* (relative intensity) 293 (MH^+, 100%); Anal. Calcd. for $C_{19}H_{20}OSi$: C, 78.03; H, 6.89; Found: C, 77.85; H, 6.88.



147

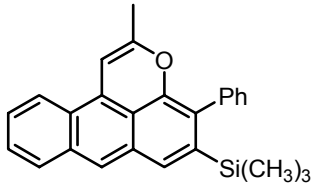
Trimethyl-(2-methyl-9-phenyl-benzo[*de*]chromen-8-yl)silane (147). 2-Phenyl-3-trimethylsilyl-1-naphthol **(145)** (204 mg, 0.70 mmol) was dissolved in DME (10.0 mL) under argon and the solution was cooled to 0 ^oC. A solution of n-butyllithium (1.8M) in hexanes (430 μL, 0.77 mmol) was added dropwise and stirred for 10 minutes. The resulting reddish solution was warmed to room temperature, then heated to reflux. Propynyliodonium salt **133** (841 mg, 2.15 mmol) in DME (4.0 mL) was added slowly to the refluxing solution. The dark red solution was refluxed for 45 minutes, then cooled to room temperature. The reaction solution was poured into ice cold 1M H3PO_4 (15 mL) and extracted with ether (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield a black oil. This oil was purified via SiO_2 chromatography using 10 % CH_2Cl_2 in hexanes to yield 82 mg (36 %) of **147** as a tan solid. m.p. 145-146 ^oC; IR (CH_2Cl_2) 1669 cm^{-1}; ^1H NMR (300 MHz, d8-THF) δ 7.57 (s, 1H), 7.51 (m, 6H), 7.18 (dd, *J* = 7.0 Hz, 8.4 Hz, 1H), 6.64 (dd, *J* = 7.0 Hz, 0.8 Hz, 1H), 5.81 (d, *J* = 1.0 Hz, 1H), 1.85 (d, *J* = 1.0 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR (300 MHz, d8-THF) δ 154.2, 150.1, 140.3, 139.9, 134.6, 131.8, 131.4, 128.6 (2C), 128.4, 127.9, 127.1, 123.7, 123.6, 115.7, 104.1, 19.2, 0.8; MS CI^+ *m/z* (relative intensity) 331

(MH^+, 100); Anal. Calcd. for $C_{22}H_{22}OSi$: C, 79.95; H, 6.71. Found: C, 79.77; H, 6.87.



149

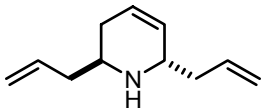
2-Phenyl-3-trimethylsilyl-1-anthrol (149).[173] To a solution of niobium (III) chloride (1.47 g, 5.08 mmol, 1.5 eq) in THF (70 mL) was added 1-phenyl-2-trimethylsilylacetylene **(144)** (1.0 mL, 5.1 mmol, 1.5 eq) under argon. The solution was heated to reflux for 18 hours, then dark solution was cooled to 0 ^oC. A solution of 2,3-naphthalenedicarboxaldehyde **(148)** (622 mg, 3.37 mmol) in THF (10.0 mL) was then added dropwise to the cooled solution. After 1.5 hours at 0 ^oC, the solution was warmed to room temperature and poured into a 10 % aq potassium hydroxide (KOH) solution (80mL) and shaken until the aqueous layer was colorless. The aqueous layer was extracted with ether (3 x 40 mL), and the organic layer was washed with brine 40 mL, dried over $MgSO_4$, filtered, and concentrated. The crude yellow oil was purified via SiO_2 using 5 % ethyl acetate in hexanes to give 664 mg (56 %) of **149** as a white solid. m.p. 117-120^oC; IR (CH_2Cl_2) 3532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.83 (s, 1H), 8.45 (s, 1H), 8.09 (m, 2H), 8.02 (s, 1H), 7.86 (m, 7H), 5.35 (s, 1H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 147.2, 137.7, 137.1, 132.0, 131.9, 131.7, 131.5, 129.2, 128.7, 128.6, 128.2, 127.8, 126.1, 125.6, 125.3, 123.6, 123.5, 121.2, 0.4; MS ESI^- *m/z* (relative intensity) 341 (MH^+, 100%).



151

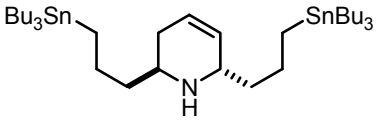
Trimethyl-(2-methyl-4-phenyl-naphtho[1,2,3-*de*]chromen-5-ypl)-silane (151). 2-Phenyl-3-trimethylsilyl-1-anthrol **(149)** (142 mg, 0.411 mmol) was dissolved in DME (6.0 mL) under argon and cooled to 0 ^{o}C. A solution of *n*-butyllithium (1.8 M) in hexanes (260 μL, 0.46 mmol) was added dropwise and stirred 15 minutes. The solution was warmed to room temperature and then to refluxed. Propynyliodonium salt **133** (499 mg, 1.27 mmol) in DME (2.3 mL) was added slowly to the refluxing solution and the resulting black solution was refluxed for 45 minutes. The reaction was cooled to room temperature, then poured into ice cold 1M H3PO_4 (25 mL) and extracted with ether (2 x 25 mL). The organic layer dried over $MgSO_4$ and concentrated in vacuo to yield a dark oil. The crude oil was purified via SiO_2 chromatography using 5 % ethyl acetate in hexanes to yield 45 mg (28 %) of **151** as a yellow solid. m.p. 148-150^{o}C; IR (CH_2Cl_2) 1669.2 cm^{-1}; ^{1}H NMR (300 MHz, d8-THF) δ 8.38 (s, 1H) 7.95 (t, *J* = 9.0 Hz, 2H), 7.84 (s, 1H), 7.60 (m, 4H), 7.32 (s, 1H), 7.20 (m, 3H), 1.94 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 148.5, 138.6, 137.0, 134.1, 133.8, 133.3, 130.6, 130.5, 129.4, 129.0 (2C), 128.4, 128.0, 127.6, 127.1, 126.6, 126.2, 82.5, 78.8, 56.9, 4.5, 0.3; MS APCI^{+} *m/z* (relative intensity) 381 (MH^{+}, 100); Anal. Calcd. for $C_{26}H_{24}OSi$: C, 82.06; H , 6.36; Found: C, 82.07; H, 6.43.

4.3 Halichlorine



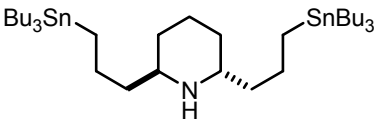
223

***trans*-2,6-Diallyl-1,2,5,6-tetrahydropyridine (223).**[174] Boron trifluoride diethyl etherate (24.91 g, 0.1760 mol) was added to a cooled (0 ^{o}C) suspension of magnesium (50.81 g, 2.090 mol) in ether (360 mL) under argon. Distilled allyl bromide (61 mL, 85 g, 0.71 mol) was added dropwise to flask (at a rate to maintain gentle refluxing). Upon complete addition, the reaction mixture was stirred at 0^{o}C for 1.5 hours, then slowly warmed to room temperature and stirred an additional 2 hours or until refluxing stops. The solution was cannulated off excess magnesium and the ether was distilled off. Triallylborane **228** was then purified via distillation at 55-57 ^{o}C at 15 mmHg to afford 7.59 g (32 %) as an air sensitive colorless oil. Freshly distilled pyridine (9.2 mL, 9.1 g, 0.11 mol) was added via syringe pump over 20 minutes to cooled (-78 ^{o}C) triallylborane under argon. The mixture was warmed to 0 ^{o}C. When all the solid had melted, anhydrous isopropanol (17.3 mL, 0.226 mol) was added slowly. The solution was then heated to reflux. After 12 hours, the orange solution was cooled to room temperature and poured into a 15% solution of sodium hydroxide (30 mL) and extracted with ether (3 x 30mL). The organic layer was dried over potassium carbonate, filtered and concentrated. The product was purified via distillation to afford **223** as a colorless oil (5.72 g, 62 %) which distill at 37-38 ^{o}C at 0.08 mmHg. Analytical data matches that previously reported.[174]



229

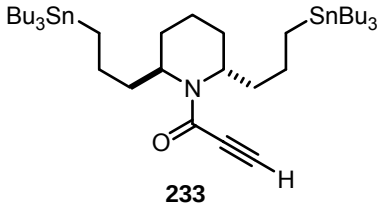
***trans*-2,6-Bis-(3-tributylstannanyl-propyl)-1,2,3,6-tetrahydro-pyridine (229).** *trans*-2,6-Diallyl-1,2,5,6-tetrahydropyridine **(223)** (2.72 g, 16.7 mmol) was combined with freshly distilled tributyltin hydride (Bu_3SnH) (9.9 mL, 37 mmol) and AIBN (112 mg, 0.682 mmol) in a sealed tube. The sealed tube was evacuated and heated to 100 ^oC. Additional portions of AIBN (60 mg) and Bu_3SnH (6.0 mL) were added after 24, 48, 72, and 96 hours. The crude reaction mixture was purified via silica gel chromatography using 0.5 % NEt_3 /2 % ethyl acetate in hexanes - 0.5 % NEt_3 /5 % ethyl acetate in hexanes to afford 11.06 g (89 %) of bisstannane **229** as a colorless oil: IR (neat) 3406 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 2H), 3.32 (m, 1H), 2.87 (m, 1H), 2.02 (m, 2H), 1.79 (m, 1H), 1.67 - 1.37 (m, 20H), 1.35 - 1.23 (m, 12H), 0.91 - 0.87 (t, *J* = 7.5 Hz, 18H), 0.84 - 0.65 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 125.0, 52.4, 47.6, 41.3 ($J^{13}_{C\text{-}Sn}$ = 23.5 Hz), 40.6 ($J^{13}_{C\text{-}Sn}$ = 23.4 Hz), 32.4, 29.7, 27.8 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 26.4 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 25.3 Hz), 24.3 ($J^{13}_{C\text{-}Sn}$ = 9.4 Hz), 23.8 ($J^{13}_{C\text{-}Sn}$ = 9.4 Hz), 14.1, 9.4, 9.3, 9.2 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 157.2 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 150.0 Hz); MS APCI$^+$ *m/z* (relative intensity) 746.1 (M + H, 100) Anal. calcd. for $C_{35}H_{73}NSn_2$: C, 56.40; H, 9.87; N, 1.88; Found: 56.52; H, 9.79; N, 1.78.



231

***trans*-2,6-Bis-[3-(tributylstannyl)-propyl]-piperidine (231).** The bisstannane **229** (8.01 g, 10.7 mmol) was dissolved in absolute ethanol (120 mL) and PtO_2 (1.22 g, 5.37 mmol) was added. The reaction mixture was purged of air and stirred at room temperature under a balloon of H_2 for 14 h (frequently recharged H_2 balloon). The mixture was filtered through Celite with ether and the filtrate was concentrated in vacuo. The resulting crude solution was purified via

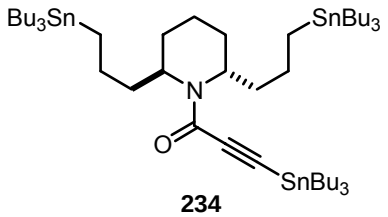
silica gel chromatography using 1 % NEt_3 /5 % ethyl acetate in hexanes to afford 7.45 g of **231** as a colorless oil (92 %). IR (neat) 3448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (m, 2H), 1.66 (m, 3H), 1.56 - 1.21 (m, 20H), 1.20 - 1.08 (m, 16H), 0.90 - 0.85 (t, *J* = 7.2 Hz, 18H), 0.83 - 0.69 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.4, 39.2, 31.1, 29.3 ($J^{13}_{C\text{-}Sn}$ = 9.9 Hz), 27.4 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 26.6 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 25.5 Hz), 23.7 ($J^{13}_{C\text{-}Sn}$ = 9.6 Hz), 19.8, 13.7, 9.0 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 154.0 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 147.2 Hz), 8.7 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 156.9 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 150.0 Hz); MS APCI$^+$ *m/z* (relative intensity) 748.5 (M + H, 100); Anal. calcd. for $C_{35}H_{75}NSn_2$: C, 56.25; H, 10.11; N, 1.87; Found: 56.44; H, 10.23; N, 1.67.



233

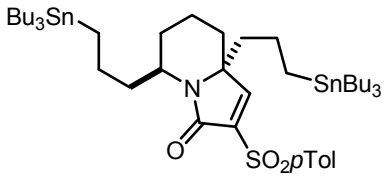
1-{*trans*-2,6-Bis-[3-(tributylstannanyl)-propyl]-piperin-1-yl}-propynone (233). 1-Chloro-*N*,*N*,2-trimethylpropenylamine (2.13 g, 15.9 mmol) was slowly added to a solution of 3-(trimethylsilyl)propynoic acid **(230)** (2.09 g, 14.7 mmol) in 75 mL of CH_2Cl_2 at 0 °C. The reaction solution was slowly warmed to room temperature and stirred for 6 h to generate the propynoyl acid chloride **232**. This acid chloride solution was then slowly added to a cooled (-45 °C) solution of amine **231** (7.09 g, 9.47 mmol) and distilled (*i*-Pr)$_2$NEt (2.5 mL, 14 mmol) in CH_2Cl_2 (95 mL). This yellowish solution was stirred for 12 h at –45 °C. After 12 h, tetrabutylammonium fluoride (1.0 M in THF, 16.2 mL, 16.2 mmol) was added to the solution at –45 °C and stirring was continued for 30 min, followed by warming to room temperature. The reaction mixture was poured into 100 mL of water and the organic layer was separated. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residual brown oil was purified via SiO_2 chromatography using 10 % ether in hexanes to yield 7.17 g (95 %) of alkynyl amide **233** as a colorless oil. IR (neat) 2101 cm^{-1}, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (m, 1H), 3.89 (m, 1H), 2.97 (s, 1H), 1.90-1.59 (m, 9H), 1.58-1.37

(m, 17H), 1.33-1.22 (m, 12H), 0.90-0.68 (m, 34H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 77.2, 77.1, 54.7, 51.3, 39.8 ($J^{13}_{C\text{-}Sn}$ = 23.5 Hz), 38.0 ($J^{13}_{C\text{-}Sn}$ = 25.5 Hz), 29.2 ($J^{13}_{C\text{-}Sn}$ = 9.9 Hz), 27.3 ($J^{13}_{C\text{-}Sn}$ = 25.8 Hz), 27.3 ($J^{13}_{C\text{-}Sn}$ = 25.8 Hz), 24.6 ($J^{13}_{C\text{-}Sn}$ = 9.1 Hz), 24.5 ($J^{13}_{C\text{-}Sn}$ = 9.2 Hz), 23.7, 23.2, 14.4, 13.7, 8.8, 8.7 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 158.0 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 151.0 Hz), 8.7 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 157.2 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 150.2 Hz), 8.6; MS APCI$^+$ *m/z* (relative intensity) 800.4 (M + H, 100), 742.3 (M - C_4H_9, 100); Anal. calcd. for $C_{38}H_{75}NSn_2$: C, 57.09; H, 9.46; N, 1.75; Found: C, 57.29; H, 9.51; N, 1.58.



234

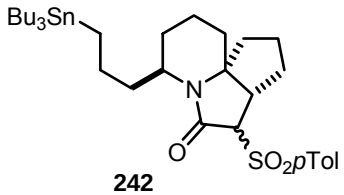
1-{*trans*-2,6-Bis-[3-(tributylstannyl)-propyl]-piperin-1-yl}-3-tributylstannyl-propynone (234). To a stirring suspension of alkyne **233** (7.10 g, 8.88 mmol) and magnesium sulfate (4.32 g, 35.9 mmol) in ether (90 mL) was added bis(tributyltin)oxide (4.5 mL, 8.8 mmol). The suspension was stirred at room temperature for 48 h. The reaction mixture filtered through Celite with ether and concentrated in vacuo. The resulting colorless oil was filtered through a SiO_2 plug using 10 % ethyl acetate in hexanes to afford 9.46 g (98 %) of alkynyl stannane **234**. IR ($CHCl_3$) 2244 cm^{-1}, 1595 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (m, 1H), 3.92 (m, 1H), 1.83 - 1.74 (m, 3H), 1.70 - 1.64 (m, 5H), 1.62 - 1.36 (m, 23H), 1.34 - 1.22 (m, 19H), 1.16 – 1.02 (m, 6H), 0.98 - 0.85 (m, 31H), 0.82 - 0.67 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 102.5, 96.2, 54.7, 51.0, 39.8, 38.3, 29.3 ($J^{13}_{C\text{-}Sn}$ = 9.8 Hz, two carbons), 28.9 ($J^{13}_{C\text{-}Sn}$ = 11.6 Hz), 27.4, 27.3, 27.1, 24.6 ($J^{13}_{C\text{-}Sn}$ = 9.5 Hz, two carbons), 23.4, 23.2, 14.4, 13.7 (two carbons), 13.6, 11.2, 8.9, 8.88, 8.77 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 157.6 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 150.6Hz), 8.73 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 156.8 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 149.9Hz); MS APCI$^+$ *m/z* (relative intensity) 1088.5 (M + H, 50), 1030.4 (M-C_4H_9, 50), 748.4 (M - $C_{12}H_{27}Sn$, 100); HRMS calcd. for $C_{50}H_{102}NOSn_3$: 1088.5041; Found: 1088.5019.



238

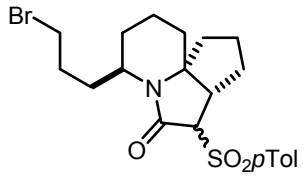
2-(Toluene-4-sulfonyl)-5,8a-bis-[3-(tributylstannyl)-propyl]-6,7,8,8a-tetrahydro-5H-indolizin-3-propynone (238). To a cooled (-45 ^{o}C) suspension of cyanophenyl iodonium triflate (1.79 g, 4.72 mmol) in 15 mL of CH_2Cl_2 was added a solution of alkynyl stannane **234** (4.25 g, 3.91 mmol) in 25 mL of CH_2Cl_2. The reaction mixture stirred at –45 ^{o}C for approximately 2 h until a yellow homogeneous solution formed and then stirred for an additional 30 min. The solvent was removed in vacuo at –30 ^{o}C to give a yellow oil. This oil was then redissolved in DME (prechilled to -30 ^{o}C) (30 mL) and slowly added via cannula into a refluxing suspension of anhydrous sodium *p*-toluenesulfinate (842 mg, 4.73 mmol) in DME (50 mL). Upon complete addition, the solution was refluxed for an additional 20 min. The reaction solution was cooled to room temperature and poured into 80 mL of distilled water and extracted with ether (2 x 100mL). The organic layer was dried over $MgSO_4$ and concentrated to give an orange oil, which was purified via SiO_2 column chromatography using 10 % ether in hexanes to yield 2.52 g (65 %) of **238** as a light yellow oil. IR (neat) 1698 cm^{-1}, 1327 cm^{-1}, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.78 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.02 (m, 1H), 2.60 (app dq, *J* = 14.4 Hz, 7.2 Hz, 1H), 2.41 (s, 1H), 1.90-1.38 (m, 24H), 1.31-1.22 (m, 12H), 1.18-1.08 (m, 3H), 0.89-0.84 (m, 18H), 0.81-0.74 (m, 12H), 0.72-0.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 157.6, 144.6, 140.1, 136.3, 129.6, 128.7, 65.9, 55.4, 36.3, 35.9, 34.0, 31.7, 29.2 ($J^{13}_{C\text{-}Sn}$ = 9.9 Hz), 29.1 ($J^{13}_{C\text{-}Sn}$ = 10.0 Hz), 27.3 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 26.3 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 25.2 Hz), 27.3 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 26.4 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 25.3 Hz), 25.1 ($J^{13}_{C\text{-}Sn}$ = 9.0 Hz), 21.6, 20.5, 20.4, 13.7 (two carbons), 8.9, 8.8 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 158.8 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 151.7 Hz), 8.6 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 157.3 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 150.2 Hz), 8.6 ; MS APCI^{+}

m/z (relative intensity) 954.4 (M + H, 100); Anal. calcd. for $C_{45}H_{81}NO_3SSn_2$: C, 56.68; H, 8.56; N, 1.47; S, 3.36; Found: C, 56.80; H, 8.41; N, 1.47; S, 3.33.



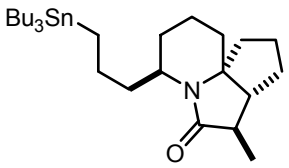
242

4-(Toluene-4-sulfonyl)-6-(3-tributylstannyl-propyl)-octahydro-5a-aza-cyclopenta[c]inden-5-one (242). A suspension of **238** (3.87 g, 4.06 mmol) and $MgBr_2$ (896 mg, 4.87 mmol) in dry toluene (40 mL) was refluxed for 14 h. Upon cooling to room temperature, 20 mL of water was added and the reaction was stirred for 1 h. This mixture was poured into 40 mL of water and extracted with ether (2 x 40 mL). The organic layer was separated, dried via $MgSO_4$, filtered and concentrated to a yellow oil. The crude oil was purified via SiO_2 column using 15 % ether in hexanes to give 1.86 g (69 %) of **242** as a pale yellow oil. IR (neat) 1695 cm^{-1}, 1317 cm^{-1}, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.4 Hz, 1.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 3.68 (d, *J* = 4.0 Hz, 1H), 3.11 (m, 1H), 2.82 (ddd, *J* = 8.6 Hz, 5.8 Hz, 4.0 Hz, 1H), 2.56 (app dq, *J* = 13.8 Hz, 6.9 Hz, 1H), 2.42 (s, 3H), 2.16 (m, 1H), 1.78-1.19 (m, 26H), 0.88 (t, *J* = 7.2 Hz, 9H), 0.79-0.66 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 144.6, 135.4, 129.4, 129.4, 73.8, 71.3, 56.7, 43.3, 36.4, 36.0, 35.6, 31.1, 29.2 ($J^{13}_{C\text{-}Sn}$ = 9.9 Hz), 27.3 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 26.4 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 25.3 Hz), 25.0, 24.7, 24.6 ($J^{13}_{C\text{-}Sn}$ = 8.9 Hz), 22.4, 21.6, 13.7, 8.6 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 157.2 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 150.1 Hz), 8.4 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 153.9 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 146.9 Hz); MS $APCI^+$ *m/z* (relative intensity) 666.4 (M + H, 100); Anal. calcd. for $C_{33}H_{55}NO_3SSn$: C, 59.64; H, 8.34; N, 2.11; S, 4.82; Found: C, 59.76; H, 8.22; N, 2.20; S, 4.95.



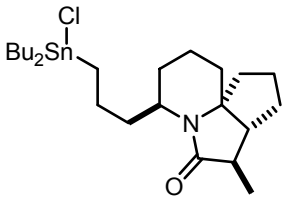
245

4-(Toluene-4-sulfonyl)-6-(3-bromo-propyl)-octahydro-5a-aza-cyclopenta[*c*]inden-5-one (245). Bromine (140 μL, 2.73 mmol, 9 eq) was added dropwise to a solution of tributyltin compound **242** (204 mg, 0.307 mmol) in CH_2Cl_2 (7 mL). The solution was stirred at room temperature for 1 hour. The reaction solution was then poured into H_2O (10mL) and CH_2Cl_2 (10 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The resulting orange oil was redissolved in ether (10 mL) and stirred with saturated aqueous potassium fluoride (10 mL). After 1.5 hours, the white precipitate that formed was filtered through celite with ether (30 mL). The filtrate was separated, and the organic layer was dried over $MgSO_4$, filtered and concentrated to give 175 mg of an orange oil. The resulting oil was purified via SiO_2 chromatography using 20 % EtOAc / 2 % HOAc in hexanes then 2 % AcOH in EtOAc to afford 35 mg (25 %) of bromo compound **245** and 119 mg (66 %) of dihydroxyl compound **246**. Data for **245**: m.p. 99 – 100 ^{o}C; IR ($CHCl_3$) 1687 cm^{-1}, 1420 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 3.68 (d, *J* = 3.5 Hz, 1H), 3.45-3.32 (m, 2H), 3.12 (m, 1H), 2.82 (m, 1H), 2.54 (m, 1H), 2.44 (s, 3H), 2.16-1.90 (m, 2H), 1.88-1.58 (m, 11 H), 1.55-1.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 145.3, 135.7, 130.0, 129.8, 74.3, 71.9, 57.3, 43.9, 36.7, 36.1, 34.4, 34.2, 32.0, 31.4, 31.0, 25.4, 22.8, 22.1; MS $APCI^{+}$ *m/z* (relative intensity) 454 (M + H, 100 %); HRMS calcd. for $C_{21}H_{29}BrNO_3S$: 454.1052; Found: 454.1023.



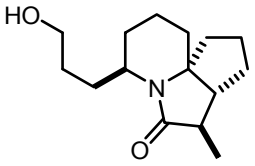
251

4-Methyl-6-(3-tributylstannyl-propyl)-octahydro-5a-aza-cyclopenta[c]inden-5-one (251). To a solution of naphthalene (212 mg, 1.65 mmol) in THF (2.1 mL) was added lithium beads (40 mg, 5.8 mmol). The reaction mixture was then sonicated for 30 min. An additional 4.5 mL of THF was added and sonication was continued for an additional hour. The dark green reaction mixture was cooled to –78 ^{o}C and a solution of sulfone **242** (356 mg, 0.536 mmol) in 6.7 mL THF was added dropwise over 30 minutes. The dark green mixture was stirred for 1 h and then warmed to –60 ^{o}C. Methyl iodide (freshly filtered through basic Al_2O_3) (510 μL, 8.0 mmol) was added quickly and the reaction mixture turned from dark green to yellow. This solution was stirred for 1 h and then diluted at –60 ^{o}C with 2.5 mL of methanol and warmed to room temperature. The reaction mixture was poured into 30 mL of water and extracted with ether (2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to a yellow oil, which was purified via SiO_2 column using 8 % ether in hexanes to afford 154 mg (55 %) of **251** as a colorless oil. IR (neat) 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (m, 1H), 2.63 (m, 1H), 2.11 (m, 1H), 1.93 (m, 1H), 1.84-1.71 (m, 3H), 1.70-1.34 (m, 18H), 1.33-1.23 (m, 6H), 1.22 (d, J = 7.4 Hz, 3H), 0.87 (t, J = 7.3 Hz, 9H), 0.83-0.71 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 71.5, 55.6, 51.3, 44.5, 38.8, 36.6 ($J^{13}_{C\text{-}Sn}$ = 28.0 Hz), 35.4, 33.2, 31.3, 29.2 ($J^{13}_{C\text{-}Sn}$ = 9.8 Hz), 27.4 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 26.3 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 25.2 Hz), 25.3, 24.8 ($J^{13}_{C\text{-}Sn}$ = 9.1 Hz), 22.5, 18.6, 13.7, 8.7 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 156.7 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 149.7 Hz), 8.6 ($J^{13}_{C\text{-}}{}^{119}_{Sn}$ = 155.2 Hz, $J^{13}_{C\text{-}}{}^{117}_{Sn}$ = 148.7 Hz); MS APCI^{+} *m/z* (relative intensity) 526.3 (M + H, 100); HRMS calcd. for $C_{27}H_{52}NOSn$ (M + H): 526.3065; Found: 526.3046.



257

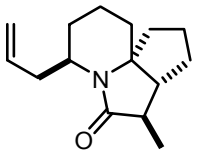
4-Methyl-6-(3-chlorodibutylstannyl-propyl)-octahydro-5a-aza-cyclopenta[c]inden-5-one (257). To a stirring suspension of **251** (52 mg, 0.10 mmol) and iodosylbenzene (25 mg, 0.11 mmol) in 2.0 mL of CH_2Cl_2 at 0 ^oC was added dropwise BF_3•OEt_2 (14 μL, 0.11 mmol). A bright yellow solution formed which was stirred at 0 ^oC for 45 min. Saturated aqueous NH_4Cl (3.0 mL) was then added and the solution was vigorously stirred at 0 ^oC for 1 h. The reaction mixture was warmed to room temperature and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 49 mg of crude chlorostannane **257** as a yellow oil which was used without further purification. ^1H NMR (360 MHz, $CDCl_3$) δ 3.09 (m, 1H), 2.22 (m, 1H), 2.05 (m, 1H), 1.98-1.50 (m, 16H), 1.48-1.21 (m, 14H), 1.20 (d, *J* = 7.4Hz, 3H), 0.94-0.88 (m, 6H); MS $APCI^+$ *m/z* (relative intensity) 504.2 (M + H, 30), 468.3 (M - Cl, 100).



258

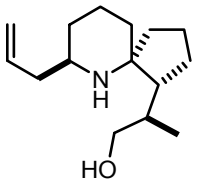
4-Methyl-6-(3-hydroxypropyl)-octahydro-5a-aza-cyclopenta[c]inden-5-one (258). To a solution of the crude chlorostannane **257** from above (49 mg, 0,10 mmol) and $KHCO_3$ (29 mg, 0.29 mmol) in 1.1 mL of THF and 1.1 mL of MeOH was added 30 % H_2O_2 (520 μL, 4.5 mmol), and the reaction solution was stirred for 18 h at room temperature. The reaction solution was poured into 5 % aqueous Na_2SO_4 (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to afford 25 mg of a crude colorless oil. The alcohol **258** was used

without further purification. IR (neat) 3417 cm^{-1}, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (m, 2H), 3.12 (m, 1H), 2.62 (m, 1H), 2.51 (br s, 1H), 2.11 (m, 1H), 1.92 (m, 1H), 1.86-1.73 (m, 3H), 1.72-1.50 (m, 9H), 1.49-1.35 (m, 3H), 1.21 (d, *J* = 7.3 Hz, 3H); MS $APCI^+$ *m/z* (relative intensity) 252.1 (M + H, 100).



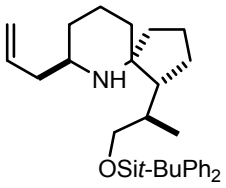
217

6-Allyl-4-methyl-octahydro-5a-aza-cyclopenta[c]inden-5-one (217). To a solution of the crude alcohol **258** (25 mg, 0.10 mmol) and 2-nitrophenylselenocyanate (117 mg, 0.515 mmol) in 2.0 mL of THF was slowly added tributylphosphine (130 μL, 0.52 mmol). The dark brown solution was stirred at room temperature. After 10 hours, 30 % aqueous H_2O_2 (125 μL, 1.10 mmol) was added. After 16 h the reaction solution was poured into water (10 mL) and extracted with ether (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 157 mg of an orange oil. The crude orange oil was purified via SiO_2 using CH_2Cl_2 and then 1 % MeOH in CH_2Cl_2 to give 17 mg (72 %) of **217** as a light yellow oil. IR (neat) 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.3 Hz, 10.0 Hz, 7.5 Hz, 6.1 Hz, 1H), 5.11 (dd, *J* = 17.1 Hz, 1.4 Hz, 1H), 5.03 (dd, *J* = 10.1 Hz, 0.9 Hz, 1H), 3.33 (app dt, *J* = 14.1, 6.3 Hz, 1H), 3.19 (m, 1H), 2.64 (app dt, *J* = 14.5 Hz, 7.5 Hz, 1H), 2.15 (m, 1H), 1.92 (m, 1H), 1.85–1.51 (m, 7H), 1.49-1.26 (m, 5H), 1.24 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 137.0, 116.2, 71.5, 55.8, 51.5, 44.5, 38.7, 36.7, 35.3, 32.9, 30.9, 25.2, 22.1, 18.5; MS $APCI^+$ *m/z* (relative intensity) 234.2 (M + H, 100); HRMS calcd. for $C_{15}H_{24}NO$ (M + H): 234.1852; Found: 234.1858.



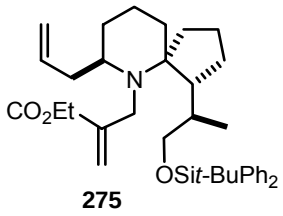
265

2-(7-Allyl-6-aza-spiro[4.5]dec-1-yl)-propan-1-ol (265). To a cooled (0 ^{o}C) solution of **217** (11 mg, 0.05 mmol) in 0.9 mL of 1,2-dichloroethane was added methyl triflate (16 μL, 0.14 mmol). The reaction solution was heated to 60 ^{o}C for 1 h. Upon cooling to room temperature, the reaction solution was concentrated in vacuo. The residue was redissolved in THF (0.9 mL), distilled H_2O (90 μL) was added, and the solution was stirred for 18 h at room temperature. The reaction solution was then dried over $MgSO_4$, filtered, and concentrated to furnish 18 mg of a crude light yellow solid. The crude solid was dissolved in 0.7 mL of THF and added drop wise to a cooled (0 ^{o}C) suspension of lithium aluminum hydride (15 mg, 0.40 mmol) in THF (0.7 mL). The reaction mixture was slowly warmed to room temperature. After 5 h at room temperature the reaction suspension was treated with 0.3 mL of a saturated aqueous solution of NH_4Cl and filtered through Celite with ethyl acetate (30 mL). The filtrate was washed with brine (10 mL) and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The crude oil was purified via SiO_2 using 3 % (9:1 MeOH : 29% NH_4OH) in CH_2Cl_2 to give 8 mg (68 %) of **265** as a colorless oil. IR (neat) 3304 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dddd, *J* = 17.2 Hz, 9.9 Hz, 7.2 Hz, 6.2 Hz, 1H), 5.17 (d, *J* = 17.2Hz, 1 H), 5.14 (d, *J* = 10.2 Hz, 1H), 3.79 (dd, *J* = 11.3 Hz, 2.1 Hz, 1H), 3.47 (app t, *J* = 10.7 Hz, 1H), 2.93 (m, 1H), 2.65 (m, 1H), 2.31 (m, 1H), 2.17 (m, 1H), 2.02 – 1.89 (m, 5H), 1.87 – 1.14 (m, 10H), 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 118.1, 68.6, 58.3, 54.4, 49.0, 37.2, 35.2, 32.3, 29.3, 28.9, 27.0, 23.7, 21.7, 13.4; MS $APCI^{+}$ *m/z* (relative intensity) 238.2 (M + H, 100); HRMS calcd. for $C_{15}H_{28}NO$ (M + H): 238.2165; Found 238.2143.



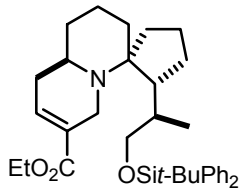
273

7-Allyl-1-[2-(tert-butyl-diphenyl-silanyloxy)-1-methyl-ethyl]-6-aza-spiro [4.5]decane (273). To a solution of **265** (9 mg, 0.04 mmol) in CH_2Cl_2 (0.8 mL) was added 4-(dimethylamino)pyridine (1 mg, 0.008 mmol), distilled triethylamine (9 μL, 0.07 mmol) and *t*-butylchlorodiphenylsilane (11 μL, 0.042 mmol) and the reaction solution was stirred at room temperature for 2 h. The reaction mixture was diluted with 10 mL of ether and washed with 10 mL saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude oil was purified via SiO_2 using 2 % (9:1 MeOH : 29 % NH_4OH) in CH_2Cl_2 to give 14 mg (75 %) of **273** as a colorless oil. Analytical data matches that previously reported.[175]



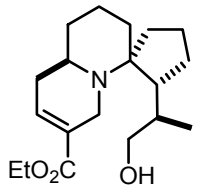
275

Ethyl 2-{[7-allyl-1-(2-(*tert*-butyldiphenylsilyloxy)-1-methylethyl)-6-azaspiro[4.5]dec-6-yl]methyl}acrylate (275). To a suspension of **273** (6 mg, 0.01 mmol) and K_2CO_3 (8 mg, 0.06 mmol) in CH_3CN was added 2-(bromomethyl)acrylic acid ethyl ester **(274)** (11 mg, 0.058 mmol). The mixture was heated to 60 ^oC for 14 h. The reaction mixture was poured into water (10 mL) and extracted with 20 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude oil was purified via SiO_2 using 5 % ether in hexanes to give 5 mg (71 %) of **275** as a colorless oil. Analytical data matches that previously reported.[175]



277

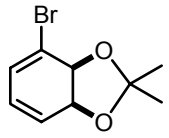
Ethyl 1',2',3',6',9',9'a-Hexahydro-2-[2-{*tert*-butyl(diphenyl)silyloxy}-1-methylethyl]spirocyclopentane-1,4'-[4H]quinolizine-7'-carboxylate (277). To a solution of the silyl ether **275** (5 mg, 0.009 mmol) in CH_2Cl_2 (0.8 mL) was added ruthenium complex **276** (1 mg, 0.001 mmol) and the solution was heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product was purified by SiO_2 using 5 % ether in hexanes to give 4 mg (80 %) of **277** as a colorless oil. Analytical data matches that previously reported.[175]



278

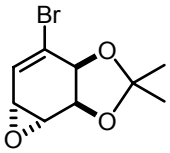
Ethyl 1', 2', 3', 6', 9', 9'a-Hexahydro-2-(2-hydroxy-1-methylethyl) spirocyclopentane-1,4'-[4H]quinolizine-7'-carboxylate (278) A solution of **277** (4 mg, 0.007 mmol) and HF·Pyridine (2 mg, 0.1 mmol) in CH_3CN was stirred at room temperature for 2 h. The solution was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude oil was purified with 2 % (9:1 MeOH : 29 % NH_4OH) in CH_2Cl_2 to give 2 mg (75 %) of **278** as a colorless oil. Analytical data matches that previously reported.[175]

4.4 Kinamycin



389

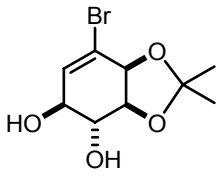
(3a*S*, 7a*S*)-4-Bromo-3a, 7a-dihydro-2, 2-dimethyl-1, 3-benzodioxole (389). A catalytic amount of *p*-toluenesulfonic acid (50 mg, 0.26 mmol, 0.01 eq) was added to a solution of (1S-*cis*)-3-bromo-3,5-cyclohexadiene-1,2-diol **(279)** (4.85 g, 25.4 mmol), and dimethoxypropane (4.7 mL, 38.2 mmol, 1.5 eq) in acetone (50 mL) was added catalytic. The reaction was stirred at room temperature under nitrogen. After 3 hours, 15 % aqueous NaOH (5 mL) and brine (15 mL) were added followed by ether (50 mL), and the solution was stirred for 15 minutes. The reaction mixture was poured into brine (50 mL) and extracted with ether (2 x 40 mL). The organic layer was dried over MgSO4, filtered and concentrated to give 5.53 g (94 %) of **389** as a light yellow oil. This was used immediately without further purification.



390

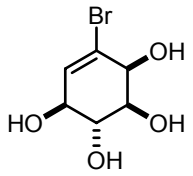
(3a*S*, 4*R*, 5*R*, 7a*S*)-7-Bromo-3a, 4, 5, 7a-tetrahydro-2, 2-dimethyl-4, 5-epoxy-1, 3-benzodioxole (390). *m*-Chloroperbenzoic acid (6.25 g, 36.2 mmol, 1.5 eq) was added in 5 portions over 1 hour to a suspension of acetamide **389** (5.53 g, 23.9 mmol) in of CH_2Cl_2 (50 mL) with sodium bicarbonate (6.04 g, 71.9 mmol, 3 eq). After 4 hours the reaction was filtered to remove the white solid and the solid rinsed with ether (150 mL). The filtrate was then washed with saturated aqueous $NaHSO_3$ (50 mL), then saturated aqueous $NaHCO_3$ (3 x 50 mL) (until pH of water layer is no longer acidic), then washed with brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting

white solid was purified via SiO_2 chromatography using 10 % ether in hexanes to give 4.48 g (76 %) of epoxide **390** as a white solid. m.p. 80-81 ^oC; IR (neat) 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 4.4 Hz, 1.2 Hz, 1H), 4.88 (app dq, *J* = 6.8 Hz, 1.8 Hz, 1.1 Hz, 1H), 4.42 (dd, *J* = 6.8 Hz, 1.0 Hz, 1H), 3.59 (dd, *J* = 3.7 Hz, 1.9 Hz, 1H), 3.34 (ddd, *J* = 4.6 Hz, 3.6 Hz, 1.0 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6, 126.3, 111.1, 73.8, 72.4, 49.2, 48.0, 27.3, 25.8; MS APCI$^+$ *m/z* (relative intensity) 246 (M + H, 100 %); Anal. Calcd. for $C_9H_8O_3Br$: C, 43.75; H, 4.49; Br, 32.34; Found: C, 43.93; H, 4.53; Br, 32.40.



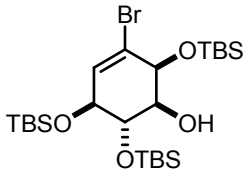
391

(3a*S* ,4*R* ,5*S* ,7a*S*)–7-Bromo-3a, 4, 5, 7a-tetrahydro-2, 2-dimethyl-1, 3-benzodioxole-4, 5-diol (391). A solution of epoxide **390** (2.21 g, 8.94 mmol) in DMSO (23 mL) was cooled to 0^oC. A 10 % aqueous solution of KOH (23 mL) was then added. The solution was warmed to room temperature after 15 minutes, then heated to reflux. After 3 hours, the solution was cooled to room temperature and extracted with ethyl acetate (4 x 30 mL). The organic layer was washed with brine (2 x 30 mL) and then dried over $MgSO_4$, filtered and concentrated to give 2.10 g (88 %) of **391** as a white solid. Analytical data matches that previously reported.[176]



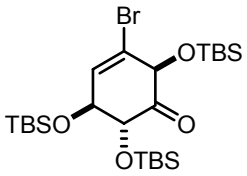
392

(1*S*, 2*R*, 3*S*, 4*S*)-5-Bromo-5-cyclohexene-1, 2, 3, 4-tetrol (392). A solution of **391** (898 mg, 3.39 mmol) in AcOH : H_2O : THF (2 : 1 : 1) was heated to 60^{o}C for 18 hours. The reaction was cooled to room temperature and then concentrated to give **392** as a white solid (687 mg, 90 %). Analytical data matches that previously reported.[176]



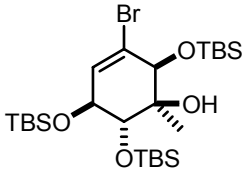
393

(1*S*, 2*S*, 5*S*, 6*R*)-3-Bromo-2, 5, 6-*tris*-(*tert*-butyldimethylsiloxy)-3-cyclohexen-1-ol (393). *t*-Butyldimethylsilyl chloride (4.59 g, 30.5 mmol, 4 eq) was added to a solution of tetrol **392** (1.71 g, 7.60 mmol), and imidazole (4.15 g, 61.0 mmol, 8 eq) in anhydrous DMF (7.6 mL) under nitrogen. The solution was heated to 50^{o}C. After 24 hours, the reaction solution was cooled to room temperature. The solution was diluted with water (50 mL) and extracted with ether (2 x 30 mL). The organic layer was then washed with brine (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated to a brown oil. This material was purified via SiO_2 chromatography using 15% toluene in petroleum ether to afford **393** (2.69 g, 60%) as a colorless oil. Analytical data matches that previously reported.[176]



394

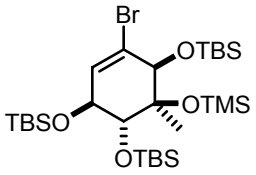
(2*S*, 5*S*, 6*R*)-3-Bromo-2, 5, 6- *tris*-(*tert*-butyl-dimethylsiloxy)-cyclohex-3-enone (394). Dess-martin periodinane[177,178] (3.61 g, 8.51 mmol, 2 eq) was added to a solution of alcohol **393** (2.41 g, 4.24 mmol) in CH_2Cl_2 (21 mL) under nitrogen. The reaction was stirred at room temperature under nitrogen. After 3 hours, a 20 % solution of sodium hydrosulfite ($Na_2S_2O_4$) in saturated aqueous $NaHCO_3$ (20 mL) was slowly added to the milky reaction suspension (bubbles vigorously upon addition) and stirred until the solid dissolved. The solution was then extracted with ether (2 x 40 mL), dried over $MgSO_4$, filtered and concentrated to a yellow solid. The crude reaction mixture was purified via SiO_2 using 10 % toluene in pet ether to give 1.69 g (70 %) of ketone **394** as a colorless oil. IR (neat) 1747 cm^{-1}, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (d, *J* = 2.62 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.41 (s, 1H), 4.17 (dd, J = 6.8 Hz, 2.5 Hz, 1H), 0.93 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.21 (s, 3H), 0.11 (m, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 135.5, 123.5, 77.9, 76.9, 74.3, 25.9, 25.9, 25.7, 18.3, 18.2, 18.1, -4.3, -4.5, -4.6, -4.8, -4.9 (2C's); MS $APCI^+$ *m/z* (relative intensity) 565 (M + H, 80 %); Anal. calcd. for $C_{24}H_{49}BrO_4Si_3$: C, 50.95; H, 8.73; Br, 14.12; Found: C, 50.76; H, 8.50; Br, 14.08.



395

(1*S*, 2*S*, 5*S*, 6*R*)-3-Bromo-2, 5, 6-*tris*-(*tert*-butyldimethylsiloxy)-1-methyl-cyclohex-3-ol (395). A solution (1.5 M in ether) of methyl lithium (2.3 mL, 3.5 mmol, 2 eq) was slowly added to a cooled (-30 ^oC) solution of the ketone **394** (961 mg, 1.70 mmol) in ether (35 mL) under nitrogen. After 30 minutes, no

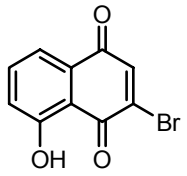
starting material remained by TLC. A saturated aqueous solution of NH_4Cl (40 mL) was added to the solution, and the reaction mixture was extracted with ether (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified via SiO_2 using 15 % toluene in petroleum ether to afford alcohol **395** (801g, 81 %) as a white solid. IR (neat) 3564 cm^{-1}, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (d, *J* = 3.2 Hz, 1H), 4.02 (s, 1H), 3.93 (dd, *J* = 6.5 Hz, 3.2 Hz, 1H), 3.73 (d, *J* = 6.4 Hz, 1H), 2.64 (s, 1H, OH), 1.13 (s, 3H), 0.95 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.26 (s, 3H), 0.18 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.6, 124.2, 79.8, 76.0, 74.4, 74.2, 26.1 (2C's), 26.0, 19.1, 18.5, 18.3, 18.2, -3.4, -3.5, -3.8, -4.1, -4.1, -4.4; MS ESI^- *m/z* (relative intensity) 579.1 (M-H, 100%); HRMS calcd. for $C_{25}H_{53}BrO_4Si_3Na$: 603.2333; Found: 603.2328.



396

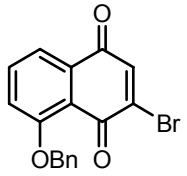
(3*S*, 4*R*, 5*S*, 6*S*)-1-Bromo-3, 4, 6-*tris*-(*tert*-butyldimethylsiloxy)-5-methyl-5-trimethylsiloxy-cyclohexene (396). Trimethylsilyl triflate (TMS-OTf) (650 μL, 3.6 mmol, 2.6 eq) was added to a cooled (0°C) solution of alcohol **395** (800 mg, 1.38 mmol) and distilled 2,6-lutidine (740 μL, 6.4 mmol, 4.6 eq) in CH_2Cl_2 (14.0 mL). The solution was slowly warmed to room temperature and stirred overnight. The solution was poured into a saturated aqueous solution of NH_4Cl (30 mL) and was extracted with ether (2 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified via SiO_2 using hexanes to give 733 mg (82 %) of **396** as a white solid. m.p. 79 – 81 °C; IR (neat) 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 5.97 (m, 1H), 4.16 (s, 1H), 3.88 (m, 2H), 1.22 (s, 3H), 0.94 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H), 0.15 (m, 9H), 0.09 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.7, 125.5, 78.3 (2C's), 77.2, 75.6, 29.7, 26.2 (2C's), 26.1, 18.6, 18.2,

18.1, 3.0, -3.2 (2C's), -3.7 (2C's), -3.8 (2C's); MS APCI$^+$ *m/z* (relative intensity) 670 (M + NH_4Cl, 100%); HRMS calcd. for $C_{28}H_{62}BrO_4Si_4$: 653.2909; Found: 653.2903.



397

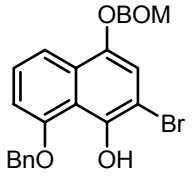
2-Bromo-8-hydroxy-1, 4-naphthoquinone (397). A solution of 5-hydroxy-1, 4-naphthoquinone (juglone) **(385)** (5.00 g, 28.7 mmol) in CH_2Cl_2 (50 mL) with HOAc (0.5 mL) was cooled to 0 ^oC under nitrogen. A solution of bromine (1.6 mL, 31.1 mmol, 1.1 eq) in CH_2Cl_2 (25 mL) was added slowly. This dark orange solution was stirred at 0 ^oC. After 1.5 hours, the dark solution was concentrated to give an orange solid. This resulting orange solid was resuspended in EtOH (80 mL) and $BF_3{\cdot}OEt_2$ (12 mL) was slowly added. This suspension was heated to reflux. After 15 minute, the dark brown suspension was cooled to room temperature, and diluted with CH_2Cl_2 (100 mL). The reaction was then filtered through a pad of celite with CH_2Cl_2 (100 mL) to remove the black solid. The filtrate was then washed with brine (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting brown solid was purified via SiO_2 chromatography using a solution of 4 : 1 toluene / hexanes to afford bromo-juglone **397** as an orange solid (3.66 g, 50 %). Analytical data matches that previously reported.[179]



398

8-Benzyloxy-2-bromo-1, 4-naphthoquinone (398). Silver oxide (13.2 g, 57.1 mmol, 4 eq) was added to a solution of bromo-juglone **397** (3.61 g, 14.3

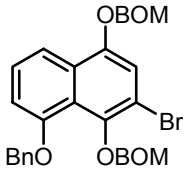
mmol) and benzyl bromide (3.4 mL, 28.4 mmol, 2 eq) in CH_2Cl_2 (36 mL) under nitrogen. The resulting suspension was stirred at room temperature. After 3 hours, the suspension was filtered through celite with CH_2Cl_2 (50 mL) and concentrated to give an orange solid. This orange solid was purified via SiO_2 chromatography using 20 % ether in hexanes to afford 3.87 g (79%) of **398** as an orange solid. Analytical data matches that previously reported.[179]



400

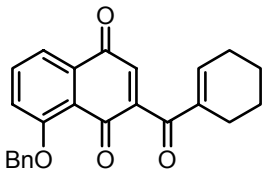
8-Benzyloxy-4-benzyloxymethoxy-2-bromo-1-naphthol (400). A solution of disodium dithionite (2.34 g, 13.4 mmol) in 22 mL of water was added to a vigorously stirring solution of bromo-quinone **398** in a 3 : 1 mixture of ether and CH_2Cl_2 (28.5 mL : 9.5 mL). The suspension was vigorously stirred for 10 minutes. The organic layer was then separated, dried over $MgSO_4$, filtered and concentrated to afford 652 mg (100%) of crude hydroquinone **399**. Hydroquinone was then redissolved in CH_2Cl_2 (19 mL) and cooled to 0^oC under nitrogen. Tetrabutylammonium iodide (1.52 g, 4.12 mmol, 2.2 eq) was added along with di-*i*-propylethylamine (1.4 mL, 8.04 mmol, 4.3 eq) and the resulting brown solution was stirred for 10 minutes, followed by addition of benzyloxymethyl chloride (530 μL, 3.81 mmol, 2 eq). The resulting solution was slowly warmed to room temperature. After 36 hours, the reddish solution was poured into brine (20 mL). The organic layer was separated and the water layer was washed with CH_2Cl_2 (2 x 15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting red oil was purified via SiO_2 chromatography using 10 % ether in hexanes to afford 405 mg (47%) of **400** as a light yellow solid. m.p. 138-139 ^oC; IR (neat) 3366 cm^{-1}, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.50 – 7.31 (m, 12H), 7.00

(d, *J* = 7.7 Hz, 1H), 5.40 (s, 2H), 5.25 (s, 2H), 4,79 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 145.6, 145.4, 137.0, 134.6, 129.1, 129.0, 128.5, 128.3, 128.0, 127.9, 127.8, 125.8, 116.2, 115.6, 114.8, 106.9, 103.0, 93.3, 71.9, 70.2; MS ESI$^+$ *m/z* (relative intensity) 465 (M+H, 100%); HRMS Calcd. for $C_{25}H_{22}BrO_4$: 465.0701; Found: 465.0698.



401

8-Benzyloxy-1, 4-bis(benzyloxymethoxy)-2-bromo-naphthalene (401). A solution of naphthol **400** (294 mg, 0.632 mmol) in THF (10 mL) was cannulated into a suspension of sodium hydride (26 mg, 1.1 mmol, 1.7 eq) in THF (2.5 mL) at 0 ^{o}C under nitrogen. The suspension was stirred at 0 ^{o}C for 20 minutes, followed by the addition of the benzyloxymethyl chloride (115 μL, 0.827 mmol, 1.3 eq). The reaction mixture was slowly warmed to room temperature. After 1 hour at room temperature, the saturated aqueous NH_4Cl (20 mL) was added. The organic layer was extracted with ether (2 x 25 mL), dried over $MgSO_4$, filtered and concentrated to afford 350 mg of crude solid. This brown solid was purified via SiO_2 chromatography using 10 % ether in hexanes to afford **401** (241 mg, 65 %) as an orange solid. m.p. 114-116 ^{o}C; IR 1578 cm^{-1}, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.5 Hz, 0.9 Hz, 1H), 7.55 (m, 2H), 7.43 – 7.29 (m, 15H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.45 (s, 2H), 5.18 (s, 2H), 5.12 (s, 2H), 4.87 (s, 2H), 4.79 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 154.2, 149.4, 144.6, 138.0, 136.9, 136.5, 128.7, 128.6, 128.5, 128.3, 128.1, 128.1, 128.0, 127.9, 127.8, 127.5, 126.1, 121.3, 115.6, 114.6, 113.1, 110.0, 99.3, 92.9, 72.0, 71.8, 70.3; MS ESI$^+$ *m/z* (relative intensity) 609 (M + Na, 50%); HRMS Calcd. for $C_{33}H_{29}BrO_5Na$: 607.1096; Found: 607.1091.



406

8-Benzyloxy-2-(cyclohex-1-enecarbonyl)-[1,4]naphthoquinone (406). Allylpalladium chloride dimer (64 mg, 0.18 mmol, 0.05 eq) was added to a solution of cyclohex-1-enyl-trimethylstannane **(404)** and quinone **397** in DMF. The reaction flask was evacuated and charged with carbon monoxide gas to 35 psi. After shaking flask for 18 hours, the excess gas was release and the resulting suspension was filtered through celite. The filtrate was poured into H_2O (50 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was washed with water (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated. The resulting orange solid was purified via SiO_2 chromatography using 20 % ether in hexanes to 40 % ether in hexanes to obtain 903 mg (70 %) of **406** as a light orange solid. m.p. 171-172 ^oC; IR (neat) 1667 cm^{-1}, 1631 cm^{-1}, 1584 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 1H), 7.68 (dd, *J* = 8.2 Hz, 7.8 Hz, 1H), 7.54 (m, 2H), 7.41 – 7.28 (m, 4H), 6.82 (m, 1H), 6.72 (s, 1H), 5.28 (s, 2H), 2.38 (m, 2H), 2.27 (m, 2H), 1.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 184.6, 182.2, 158.8, 149.5, 148.2, 139.5, 135.7, 135.2, 133.9, 132.2, 128.7, 128.0, 126.7, 119.9, 119.7, 119.3, 70.9, 26.5, 22.3, 21.5, 21.4; MS $APCI^+$ *m/z* (relative intensity) 373 (M + H, 100%); Anal. calcd. for $C_{24}H_{20}O_6$: C, 77.40; H, 5.41; Found: C, 77.34; H, 5.50.

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Publications and Presentations

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