The Pennsylvania State University

The Graduate School

Department of Chemistry

PART ONE: TOTAL SYNTHESES OF AGELADINE A;

PART TWO: STUDIES DIRECTED TOWARDS A TOTAL SYNTHESIS OF ACTINOPHYLLIC ACID

A Dissertation in

Chemistry

by

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Abstract

Part One

We have completed two unique total syntheses of the marine natural product ageladine A (**1**). Our first generation total synthesis of this angiogenesis-inhibitory marine metabolite features a 6π-1-azatriene electrocyclization of triene **63** to form the pyridine ring of intermediate **66**. A subsequent Suzuki-Miyaura coupling of *N*-Boc-pyrrole-2-boronic acid **67** with a chloroimidazopyridine **82** furnished tricycle **88**. Unfortunately, the dibromination of pyrrole **88** to give the natural product proved to be difficult to control, due to the high reactivity of this intermediate to various brominating conditions. After some experimentation, however, the optimal conditions found for the halogenation was to treat pyrrole **88** with Br_2 in an acetic acid/methanol solvent mixture at 0 ºC to give ageladine A in 17% yield.

The assessment of the biological activity of a variety of synthetic structural analogues of ageladine A prepared during this synthesis is described. However, as indicated from MMP inhibition testing results, none of our analogues was a more potent inhibitor than ageladine A itself.

We have recently completed a more efficient biogenetically-inspired, second generation total synthesis of ageladine A. Key transformations in this second synthesis included an effective 6π-2-azatriene electrocyclization of triene **128** to provide the desired imidazopyridine **129**, which contained the imidazopyridine core of the marine metabolite. The natural product was synthesized in seven steps from (*Z*)-vinyl iodide **115** and dibromopyrrole amide **125** and in 13% overall yield. In addition, both synthetic

routes to ageladine A allow for the facile synthesis of additional analogues for further biological testing.

Part Two

In work directed towards the total synthesis of the alkaloid actinophyllic acid (**158**), our proposed synthesis will incorporate several methods developed in the Weinreb lab including a vinyl chloride ring-closing metathesis (RCM) and an intramolecular vinyl nitroso cyclization.

Thus, cyclic vinyl chloride **376** was prepared in 90% yield via RCM of vinyl chloride olefin **375**, which was obtained in six steps from 3-formyl indole (**367**). Unfortunately, treatment of vinyl chloride **380** with sodium hypochlorite in acetic acid/acetone did not give the desired α-chloroketone **381**. Instead, a retro-Mannich fragmentation process occurred to give the corresponding 3-chloroindole product **383**. All other attempts to convert vinyl chloride **381** to α-chloroketone **383** using various reagents and reaction temperatures were unsuccessful.

A revised strategy focuses on RCM reactions to produce cyclic enol ethers in place of vinyl chlorides. Enol ethers, which are more electron rich than vinyl chlorides, can be regioselectively converted to α-chloroketones. Thus, we first investigated RCM reactions of olefinic silylenol ethers **393** and **394**, which were synthesized via an ene reaction of α-ethoxycarbamate **373**. Unfortunately, both TMS-enol ether **393** and TBS-enol ether **394** readily underwent desilylation during the RCM step. However, ethylenol ether diene **404** successfully underwent RCM to yield the desired cyclic enol ether **405**, which could be converted to the corresponding α-chloroketone **410** in high yield.

Furthermore, *N*-tosyl indole **405** could be metallated with a variety of organic bases and alkylated with methyl iodide to give the C-2 methylindole model substrate **412**.

Future studies will focus on completion of the synthesis of racemic actinophyllic acid (**158**). This work will include the alkylation of indole **405** with methyl iodoacetate to give ester **411**, a precursor for the key intramolecular Michael addition to a vinylnitroso intermediate. In addition, we will also investigate an enantioselective total synthesis of the alkaloid via an enantioselective addition of ketene **401** to imine **428** which would give the (R)-amine **429**.

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I want to thank family and friends who have supported me over these years. Your endless encouragement has truly been a blessing. Lastly, I am grateful to my wife, who has always supported me during the struggles and successes that have come with my research.

PART ONE: TOTAL SYNTHESES OF AGELADINE A

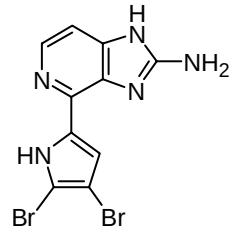
CHAPTER ONE

First Generation Total Synthesis of Ageladine A

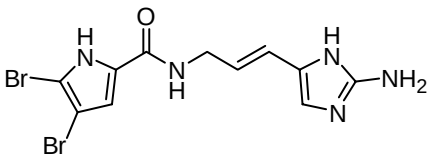
INTRODUCTION AND BACKGROUND

1.1 Isolation and Structural Identification of Ageladine A

Ageladine A (**1**) was isolated in 2003 by Fusetani, Nakao, and coworkers from the hydrophilic extract of the marine sponge *Agelas nakamurai* Hoshino, which was collected off the coast of Kuchinoerabu-jima Island in southern Japan (Figure 1).[1] Marine sponges of the genus *Agelas* have been reported to contain many bioactive polycyclic pyrrole-imidazole alkaloids, most of them derivatives of oroidin (**2**).[2] The structure of ageladine A was established primarily by 2D NMR studies of several methylated derivatives. Interestingly, the natural product is the first example of this family to contain a 2-aminoimidazolopyridine core.



ageladine A (**1**)



oroidin (**2**)

Figure 1. Natural Products Isolated from Marine Sponges of the Genus *Agelas*

1.2 Biological Activity of Ageladine A

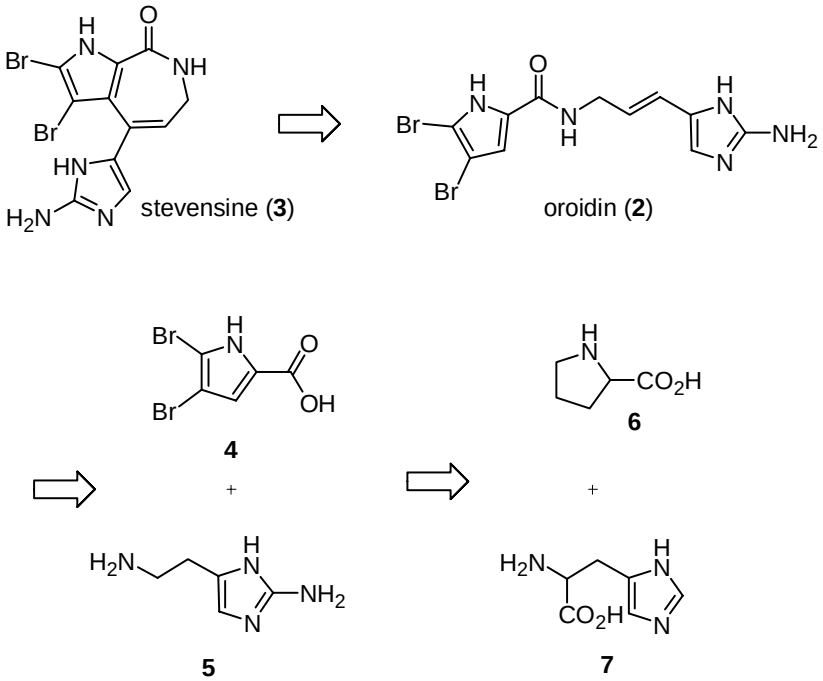
Ageladine A (**1**) displays inhibitory activity against matrix metalloproteinases (MMPs), particularly MMP-2 at micromolar levels. MMPs are a family of zinc-containing enzymes that regulate multiple steps of tumor angiogenesis.[3] These enzymes are involved in degradation of most components of the extracellular matrix (ECM) including collagens, elastins, and fibronectins, thereby allowing for tumor growth and expansion. The entire family of MMPs in humans now includes over two dozen related enzymes which are commonly grouped as either collagenases, gelatinases, stromelysins or membrane-type MMPs (MT-MMPs). One such gelatinase is MMP-2 which in addition to being involved in angiogenesis, is known to complex with other MMPs at the tumor migration front.[1,3] In addition, the ratio of activated to total MMP levels, particularly MMP-2, can be correlated with tumor aggressiveness.[3] As a result, MMP-2 inhibitors are presumed to be both antiangiogenic and antimetastatic, making MMP-2 inhibition an important area of cancer research.

The vast majority of MMP inhibitors act by chelation of the enzyme active-site zinc(II) ion and such compounds usually contain chelating groups like carboxylates, hydroxamates, or thiols. Interestingly, studies have revealed that ageladine A is not capable of zinc binding and that its MMP-2 inhibition is non-competitive by kinetic analysis.[1] Therefore, ageladine A is believed to have a novel and as yet unknown mode of MMP inhibition.

1.3 Proposed Biosynthesis of Ageladine A

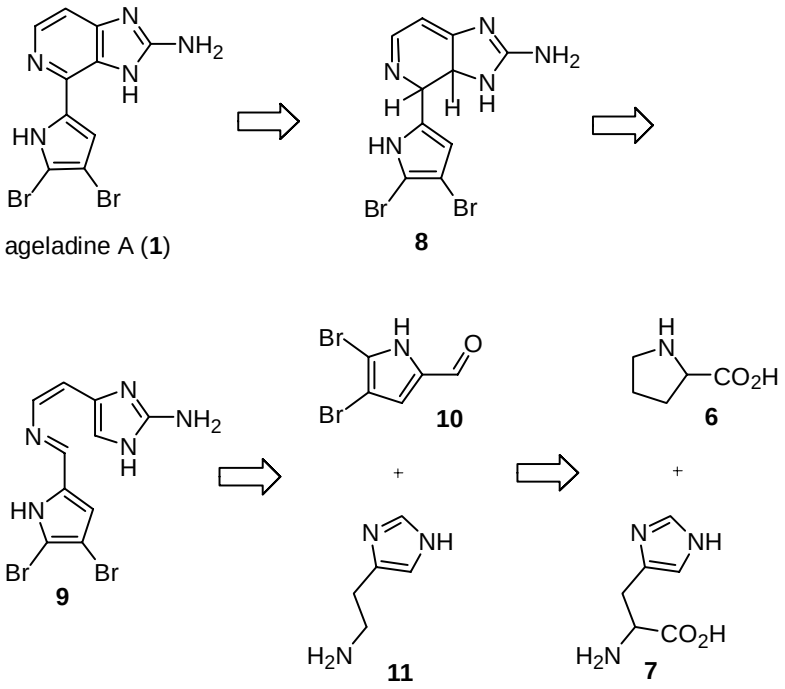
Marine sponges of the genus *Agelas* have been reported to contain numerous bioactive pyrrole-imidazole alkaloids, with most being derivatives of the oroidin class of natural products (Cf. **2**, Figure 1).[2] Kerr and coworkers have demonstrated through feeding studies of radio-labeled amino acids that the biogenetic precursors of one such metabolite, stevensine (**3**), are proline (**6**) and histidine (**7**) (Scheme 1).[4,5] 4,5-Dibromopyrrole carboxylic acid (**4**) and 2-aminoimidazole **5** would be derived from proline (**6**) and histidine (**7**), respectively. Condensation of carboxylic acid **4** and primary amine **5** would produce oroidin (**2**), which upon intramolecular cyclization and subsequent oxidation would yield stevensine (**3**).

Scheme 1



Based on these experimental results, Fusetani and coworkers proposed a biosynthesis for ageladine A (**1**) involving an intramolecular 6π-2-azatriene electrocyclization of *N*-vinyl imine **9**, followed by dehydrogenation of the resulting dihydropyridine **8** (Scheme 2). Formation of imine **9** could be envisioned from the precursors dibromopyrrole aldehyde **10** and histamine (**11**), which could be derived from proline (**6**) and histidine (**7**), respectively.[1]

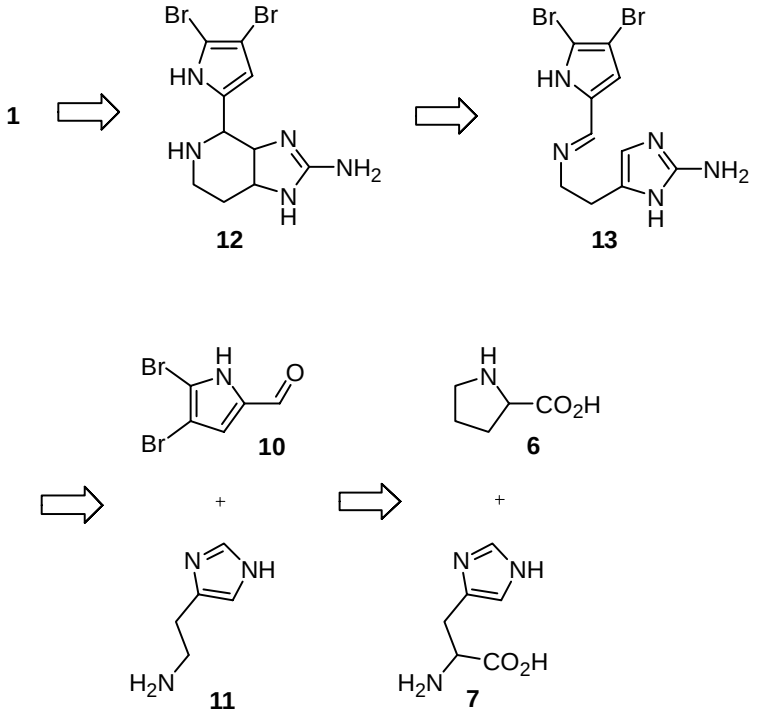
Scheme 2



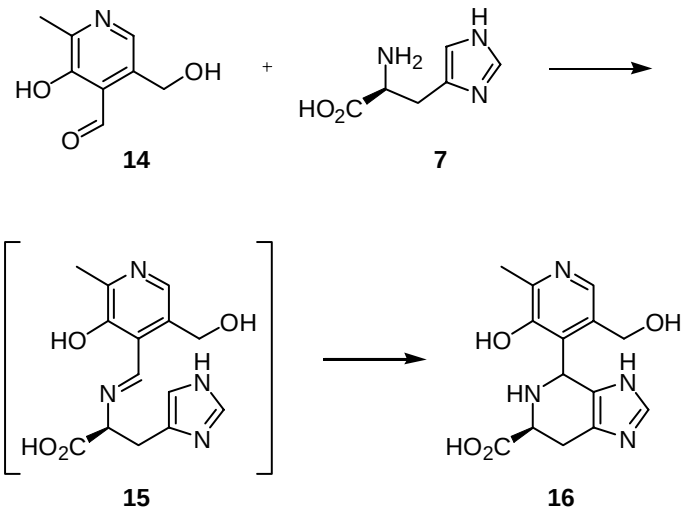
On the other hand, Karuso has proposed an alternative biogenetic pathway based on the same precursors proline (**6**) and histidine (**7**) (Scheme 3).[6] However, the formation of imine **13** is suggested from the condensation of 2-formylpyrrole **10** and histamine (**11**), which is in a lower oxidation state than the intermediate postulated by Fusetani (Cf. structure **9**). An intramolecular Pictet-Spengler-like cyclization between the imine and

imidazole subunits of **13** would give tetrahydroimidazopyridine **12**. Precedent for this cyclization can be found in the condensation of vitamin B_6 **14** with histidine (**7**) to form tetrahydroimidazopyridine **16** (Scheme 4).[7] Oxidation of imidazopiperidine **12** would provide ageladine A (**1**).

Scheme 3



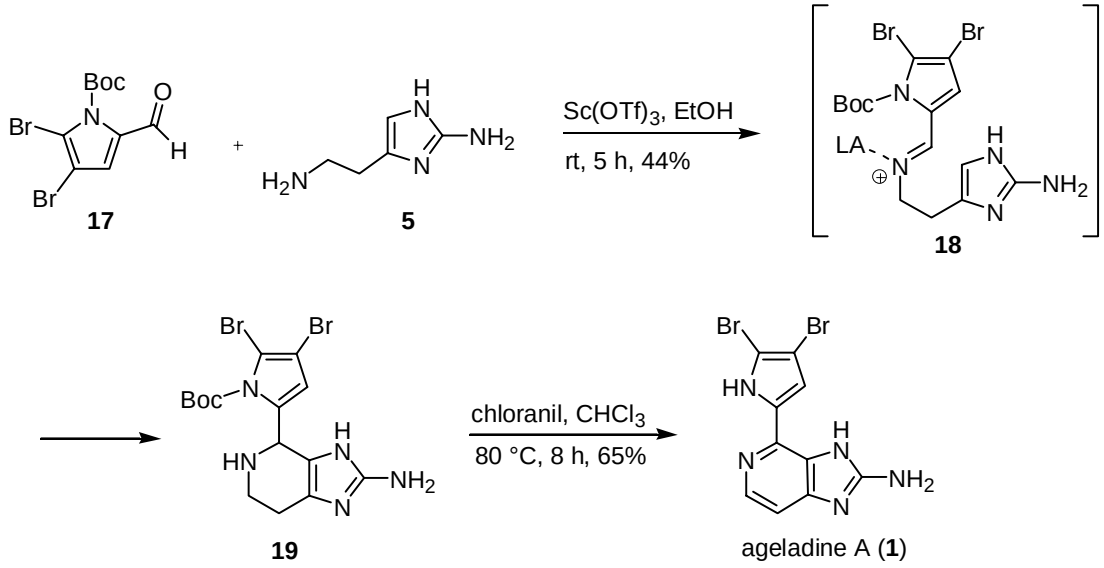
Scheme 4



1.4 Synthetic Approaches to Ageladine A

To date, three total syntheses of ageladine A have been reported. In 2006, we described the first synthesis of this marine metabolite using a 6π-1-azatriene electrocyclization and a Suzuki-Miyaura coupling involving a 2-chloropyridine derivative as key steps (*vide infra*).[8] Shortly afterwards an alternative route to ageladine A was completed by Shengule and Karuso based on their proposed biosynthesis involving a pivotal Pictet-Spengler reaction between 2-aminohistamine **5** and 4,5-dibromo-2-formylpyrrole **17**, which produced tricycle **19** in moderate yield (Scheme 5).[6] Deprotection of the pyrrole and oxidation of the piperidine subunit of **19** was accomplished using chloranil to ultimately give the natural product.

Scheme 5

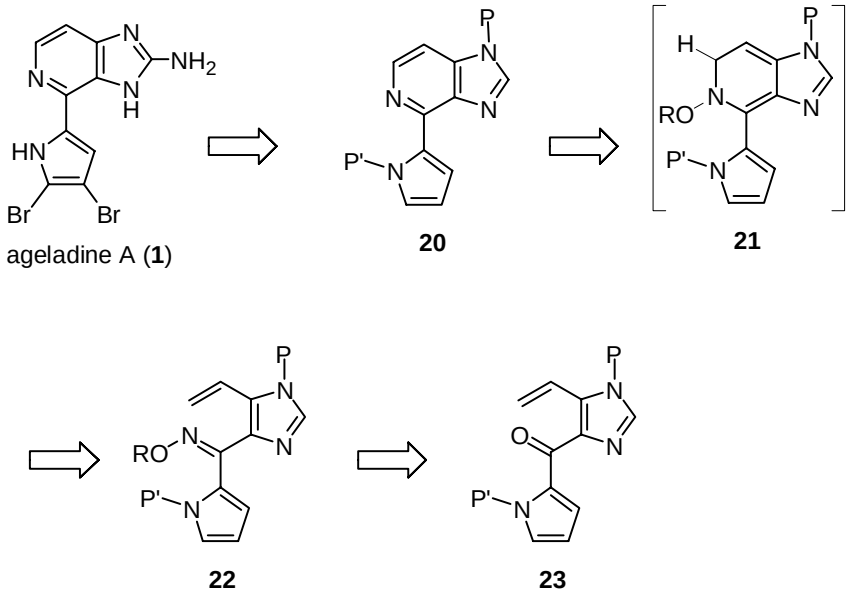


Recently, we described a second generation synthesis of **1** using a biomimetically inspired 6π-2-azatriene electrocyclization as the key step for construction of the imidazopyridine core.[9,10]

2.1 Retrosynthetic Analysis

Our initial retrosynthetic analysis for ageladine A involved a pivotal 6π-1-azaelectrocyclization of vinylimidazole oxime derivative **22** to give tricyclic intermediate **21** (Scheme 6).[11] Subsequent loss of ROH from tricycle **21** *in situ* would provide the key imidazopyridine **20**. Vinylimidazole oxime **22** would be derived from the corresponding ketone **23**.

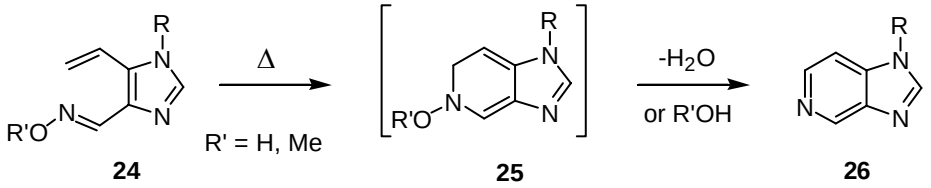
Scheme 6



3.1 6π-1-Azatriene Electrocyclizations

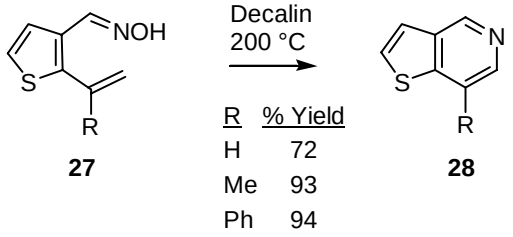
Given the biological importance of compounds containing fused pyridine ring systems, such as the imidazopyridine core of ageladine A, a large amount of work has been devoted to the development of methods to access such compounds. One such method is the 6π-cyclization of azatrienes to afford fused pyridines. For example, the electrocyclization of 1-azatriene **24** affords intermediate dihydropyridine **25**, which then eliminates water (or alcohol) to form fused imidazopyridine **26** (Scheme 7). These reactions are typically performed under photolytic conditions or thermally in dilute solution at high temperatures (typically 150 ˚C or greater).

Scheme 7

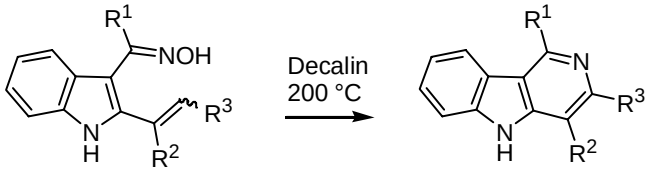


For example, initial work by Hibino and coworkers showed that fused pyridine ring systems could be formed from 1-aza-1,3,5-hexatrienes.[12] Thus, thiophene oximes like **27** undergo facile intramolecular 6π-1-azaelectrocyclizations when heated in decalin at high temperatures to produce thieno[3,2-*c*]pyridines **28** in good to excellent yield (Scheme 8). Similarly, 5*H*-pyrido[4,3-*b*]indoles **30** were synthesized from their indole oxime precursors **29**. Furthermore, these cyclizations tolerate substitution on the 1,3,5-triene system.

Scheme 8



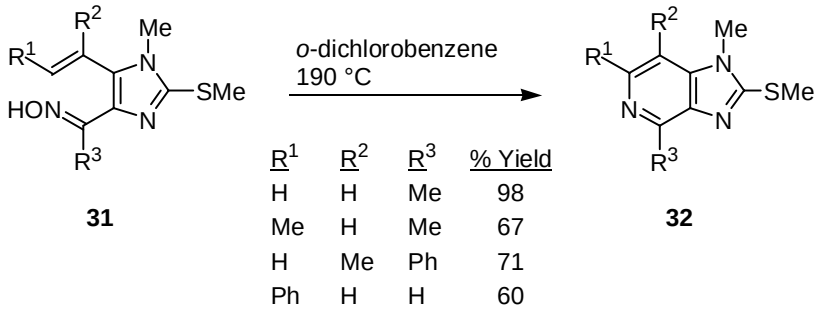
R	% Yield
H	72
Me	93
Ph	94



R^1	R^2	R^3	% Yield
H	Me	Ph	93
CO_2Me	H	Me	72
CO_2Me	Me	Ph	86

In addition, Hibino and coworkers have used 6π-azatriene electrocyclizations of related 1-azatrienes in the synthesis of various imidazopyridines.[13] Thus, heating dilute solutions of imidazole oximes **31** in *o*-dichlorobenzene at reflux provided the electrocyclic imidazopyridine products **32** (Scheme 9).

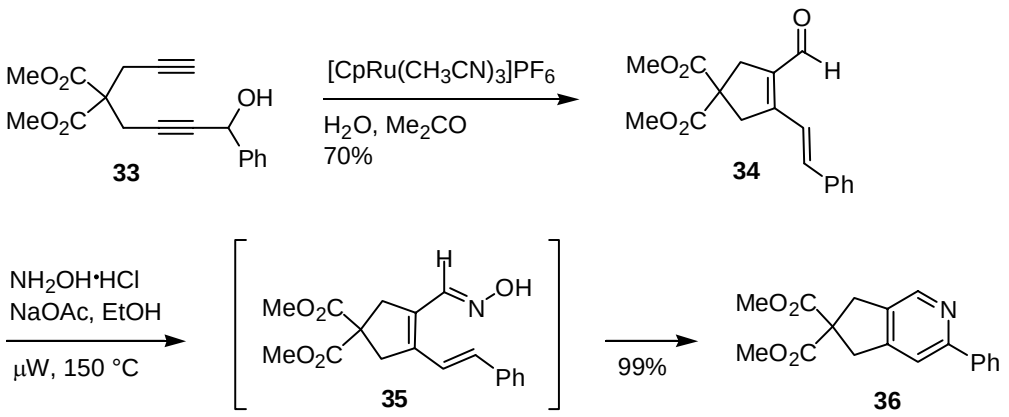
Scheme 9



R^1	R^2	R^3	% Yield
H	H	Me	98
Me	H	Me	67
H	Me	Ph	71
Ph	H	H	60

Recently, Trost and Gutierrez reported a novel route to pyridines utilizing a ruthenium-catalyzed cycloisomerization 6π-1-azaelectrocyclization sequence.[14] Thus, cycloisomerization of diynol **33** gave α,β,γ,δ-unsaturated aldehyde **34** in 70% yield using $[CpRu(CH_3CN)_3]PF_6$ as catalyst (Scheme 10). Subsequent treatment of aldehyde **34** with

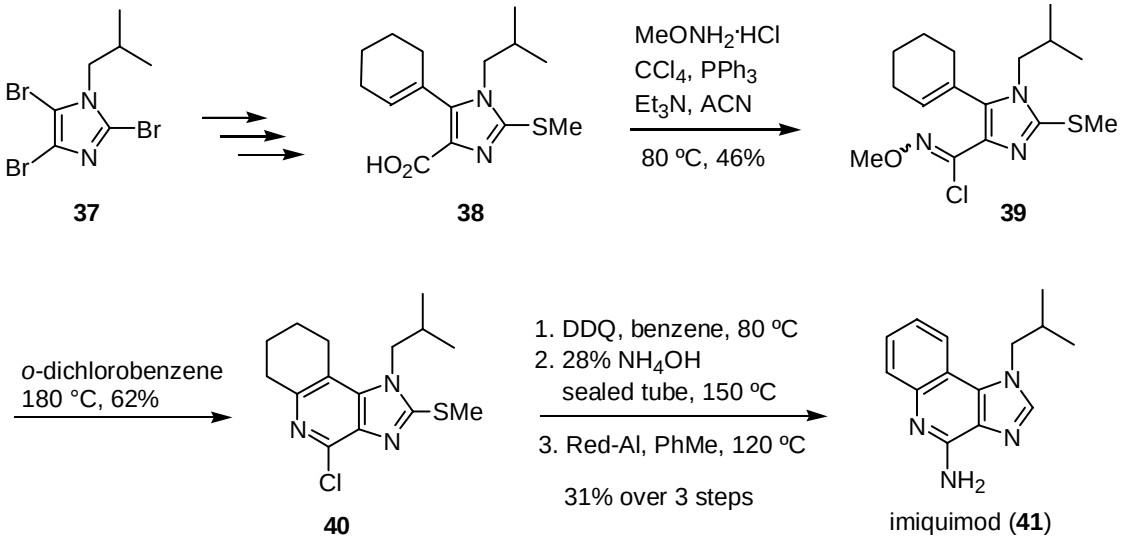
Scheme 10



hydroxylamine hydrochloride and sodium acetate in ethanol under microwave irradiation generated oxime intermediate **35**, which then cyclized thermally to provide pyridine **36** in nearly quantitative yield.

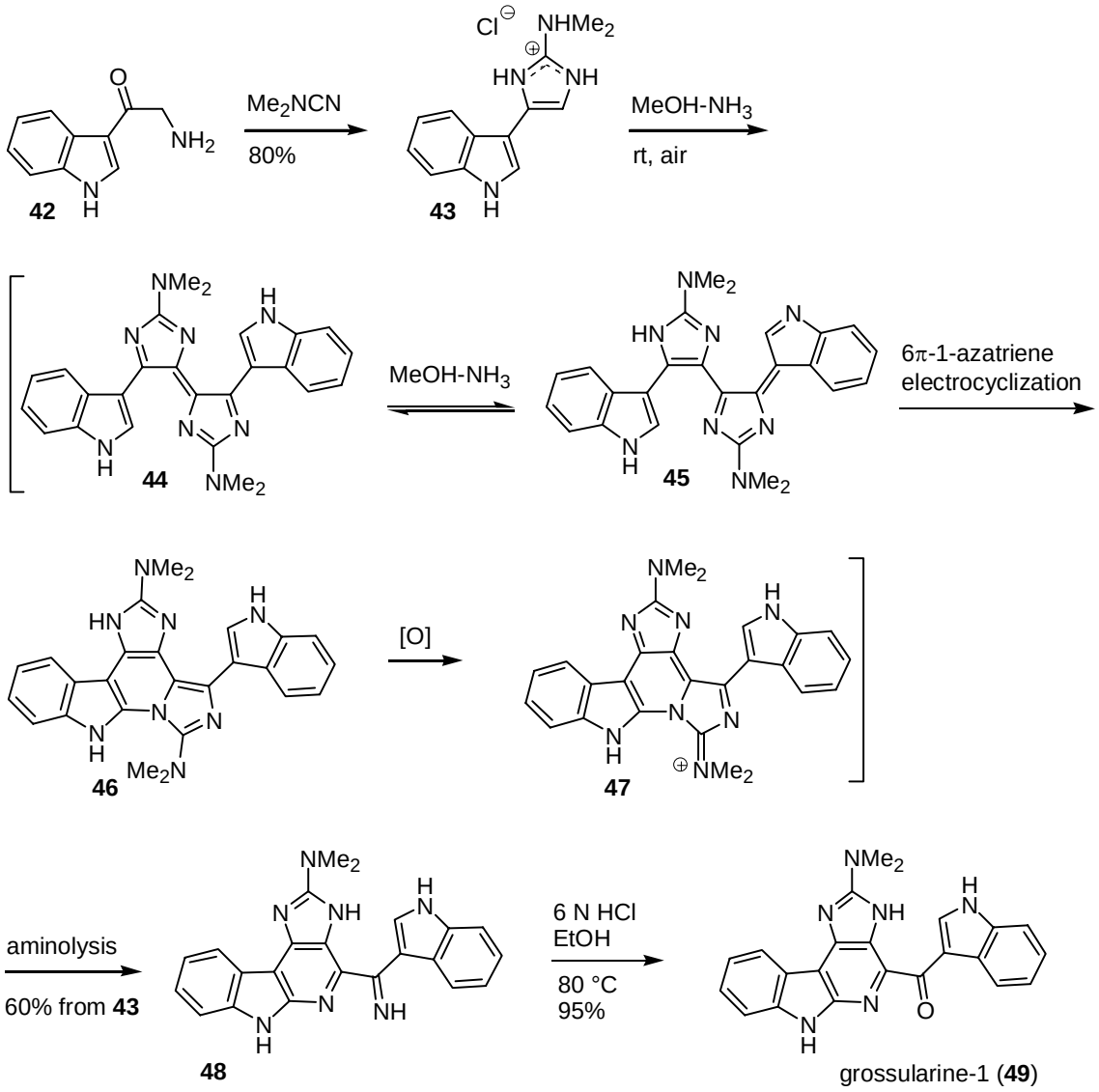
Although the basic electrocyclization reaction has been known for a number of years,[15] few natural product syntheses have utilized 6π-1-azaelectrocyclizations. In an application of their earlier work,[13a] Hibino et al. employed a 6π-1-azatriene electrocyclization in their total synthesis of the interferon-α (INF-α) inducer imiquimod (**41**).[13b] Functionalization of tribromoimidazole **37** gave carboxylic acid **38** in four steps in 25% overall yield (Scheme 11). Reaction of carboxylic acid **38** with *O*-methyl hydroxylamine, followed by addition of triphenylphosphine and carbon tetrachloride provided the α-chloromethoxime **39**. The 6π-1-azatriene electrocyclic reaction of **39** was carried out thermally in *o*-dichlorobenzene to afford tetrahydroimidazoquinoline **40** in good yield. Subsequent oxidation, amination, and desulfurization procedures gave imiquimod (**41**).

Scheme 11



Another notable application of 6π-1-azaelectrocyclizations is the recent biomimetically-patterened synthesis of grossularine-1 (**49**) by the Horne group.[16] The synthesis commenced with the cyclocondensation of oxotryptamine (**42**) and *N*,*N*'-dimethylcyanamide to give imidazole **43**, isolated as the stable HCl salt (Scheme 12). Exposure of **43** to methanolic ammonia provided α-carboline **48** in a one pot process. Mechanistically, it is proposed that initial oxidative dimerization of **43** forms dimer **44**,

Scheme 12



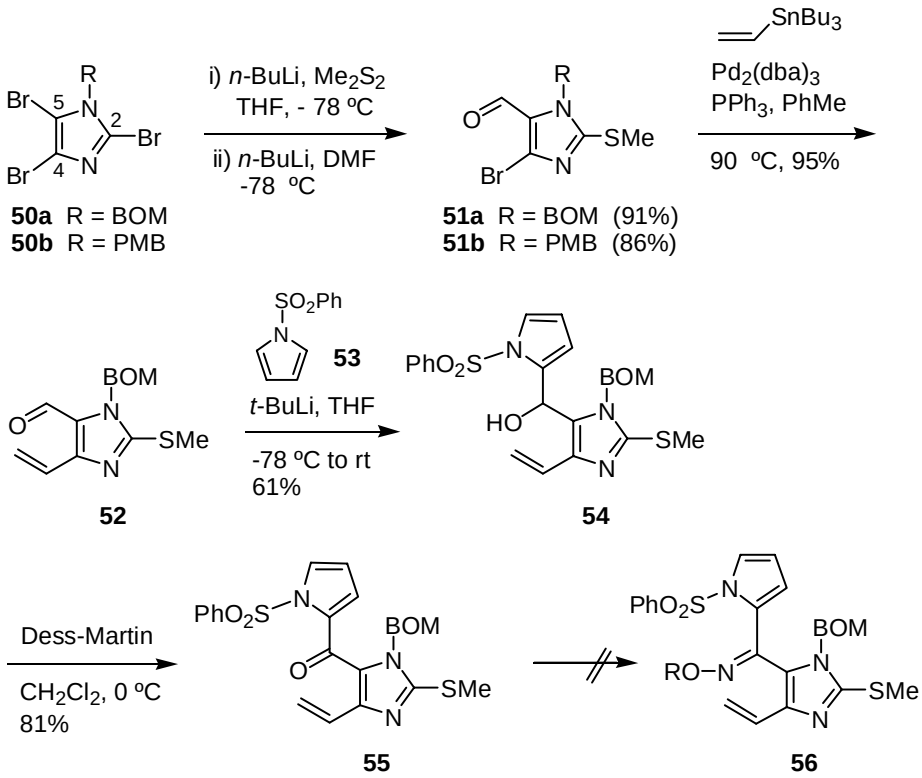
which undergoes an electrocyclization-aromatization sequence via tautomer **45** to give fused pyridine intermediate **46**. Air oxidation of the resulting intermediate **46** to **47**, followed by facile aminolysis would give α-carboline **48**. Finally, hydrolysis of imine **48** with 6 N HCl provided grossularine-1 (**49**).

RESULTS AND DISCUSSION

4.1 Initial Ageladine A Synthesis via a 6π-1-Azaelectrocyclization of a Vinyl Oxime

Our synthetic work initially focused on the formation of biaryl oxime **56**. Two different imidazole nitrogen protecting groups were investigated in these studies on ageladine A (**1**): benzyloxymethyl (BOM) and *p*-methoxybenzyl (PMB). Iddon and coworkers have shown that 2,4,5-tribromoimidazoles can be sequentially and predictably metallated, followed by trapping with various electrophiles.[17,18] Thus, using known BOM-protected tribromoimidazole (**50a**),[19] metallation using one equivalent of *n*-

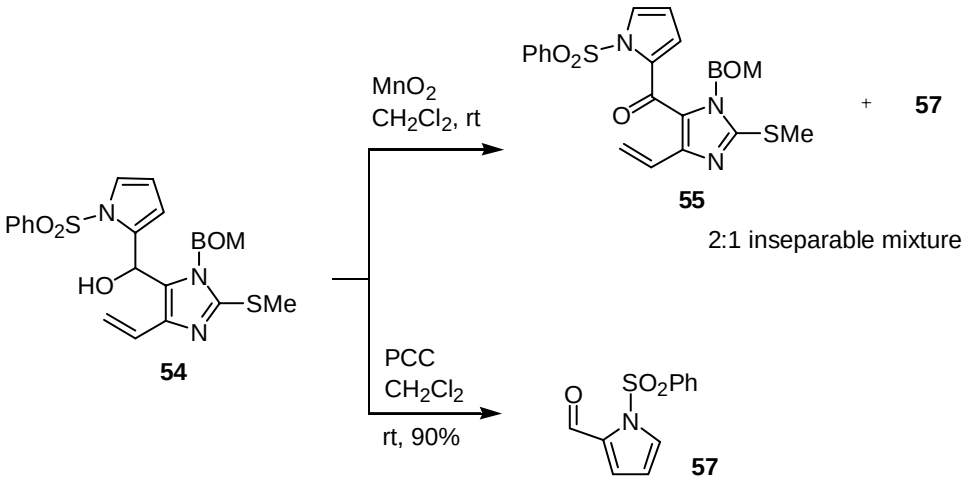
Scheme 13



butyllithium, followed by addition of dimethyl disulfide, selectively introduced a thiomethyl moiety at C-2 (Scheme 13). Without workup, the imidazole was then lithiated at C-5 using a second equivalent of *n*-butyllithium. Subsequent addition of DMF then afforded aldehyde **51a** in 91% overall yield. The corresponding PMB-protected imidazole aldehyde **52b** was generated in 86% yield using an identical series of reactions.

Stille coupling of bromoimidazole **51a** and vinyltributylstannane proceeded smoothly to give vinylimidazole **52**. The highly functionalized vinylimidazole aldehyde **52** reacted with 2-lithio-*N*-benzenesulfonylpyrrole[20] **53** to yield alcohol **54**, which was oxidized to the corresponding ketone **55** using Dess-Martin periodinane. Interestingly, oxidation of alcohol **54** with manganese dioxide produced an inseparable 2:1 mixture of ketone **55** along with pyrrole aldehyde **57**, while PCC oxidation afforded exclusively pyrrole aldehyde **57** as the only isolable product (Scheme 14).

Scheme 14



Unfortunately ketone **55** could not be converted to the desired oxime (**56**, R = H) or methoxime (**56**, R = Me). Moreover, formation of a hydrazone derivative using

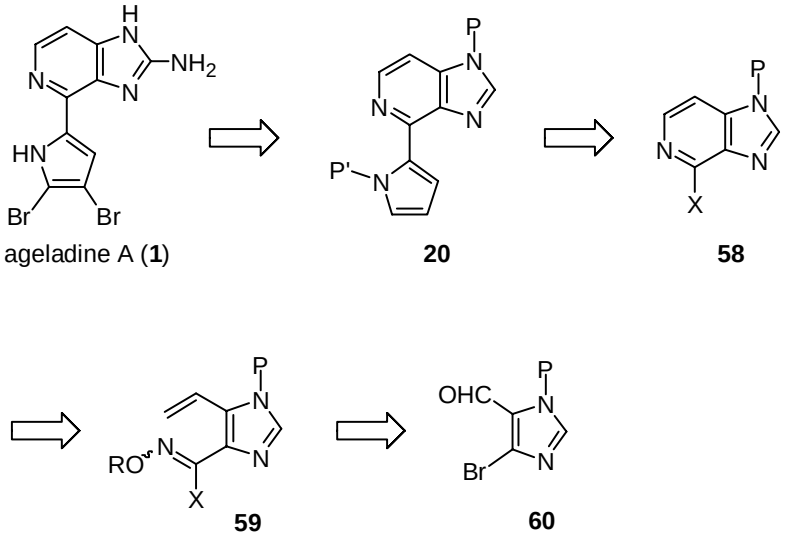
phenylhydrazine could not be effected. Oxime formation from the analogous *N*-Boc-protected or *N*-H pyrrole ketone substrates also failed. Only the starting ketone or the deprotected pyrrole was recovered in all of these reactions. Due to the inability to form the requisite oxime, an alternative synthetic route was therefore devised.

4.2 Revised Retrosynthetic Analysis of Ageladine A

4.2.1 *Revised Retrosynthesis: Electrocyclization without Pyrrole Unit Attached*

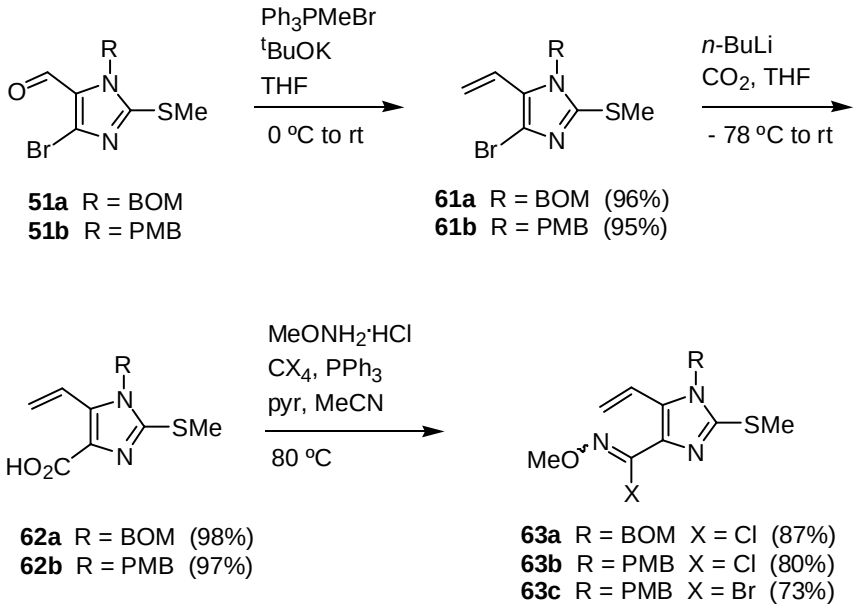
Our revised strategy was to form the pyridine ring prior to introducing the pyrrole moiety. The 6π-1-azaelectrocyclization precursor, halo *O*-alkyloxime **59** would be derived from manipulation of 4-bromoimidazole **60** (Scheme 15). Cyclization of oxime **59** would give halo imidazopyridine **58**, which has a handle for introducing the pyrrole functionality via cross coupling methodology.

Scheme 15



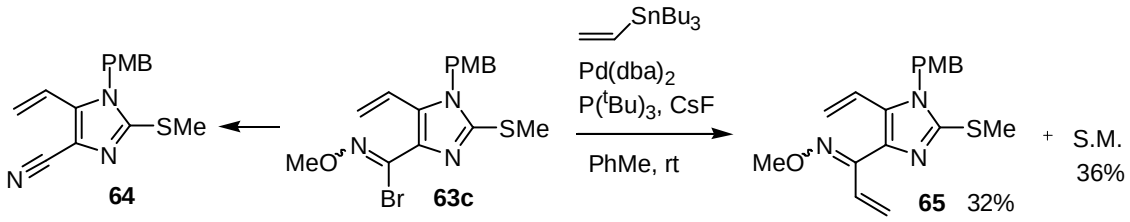
Synthetic routes were again performed with both the BOM- and PMB-protected imidazoles, which gave comparable product yields for most steps. Bromo vinylimidazoles **61a** and **61b** were produced in high yields from aldehydes **51a** and **51b** via a Wittig reaction (Scheme 16). Bromides **61a** and **61b** were then lithiated using *n*-butyllithium, followed by treatment with carbon dioxide, to afford carboxylic acids **62a** and **62b**, respectively. The yields of the acids were significantly higher when freshly crushed dry ice was added directly to a solution of the lithiated imidazole, rather than by bubbling CO_2 into the reaction mixture. Carboxylic acids **62a** and **62b** were then converted into the corresponding halomethoximes **63a** – **63c** in a single step using the methodology of Kikugawa and coworkers.[21] Chloro- or bromomethoximes **63** could be produced in good yield by using either carbon tetrachloride or tetrabromide, respectively.

Scheme 16



Based on the work of Kim et al., cross coupling of the halomethoximes **63b** and **63c** with a wide variety of stannanes, boronic acids and organozinc halides was explored.[22] However, the only coupled product that could be isolated was vinylimidazole **65**, obtained in low yield from Stille reaction of **63c** with vinyltributylstannane (Scheme 17). In all other cases, the only detectable product was nitrile imidazole **64**, derived from reductive elimination of the halomethoxime starting material.[23,24] Interestingly, Kim and coworkers did not report observing such a nitrile product during their studies.

Scheme 17

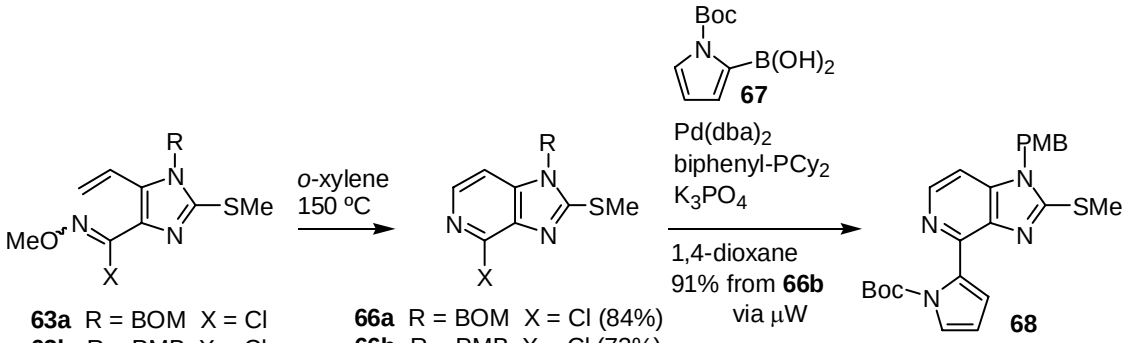


4.2.2 *6π-1-Azaelectrocyclizations of Halomethoximes and Subsequent Cross Coupling Reactions*

As a result of the failure of the halomethoxime cross coupling reactions, we turned to 6π-1-azaelectrocyclizations related to those of Hibino.[13] Thus, heating dilute solutions of halomethoximes **63b** and **63c** in *o*-xylene at 150 °C gave cyclized halo imidazopyridines **66b** (73%) and **66c** (46%), respectively (Scheme 18). When the cyclization of **63b** was performed in a microwave reactor, the product yield increased slightly to 81%. However, due to scale up problems associated with the microwave, this

procedure was not routinely used. Similarly, thermal cyclization of chloro methoxime **63a** in *o*-xylene at reflux afforded chloro imidazopyridine **66a** in 84% yield.

Scheme 18



63a R = BOM X = Cl
63b R = PMB X = Cl
63c R = PMB X = Br

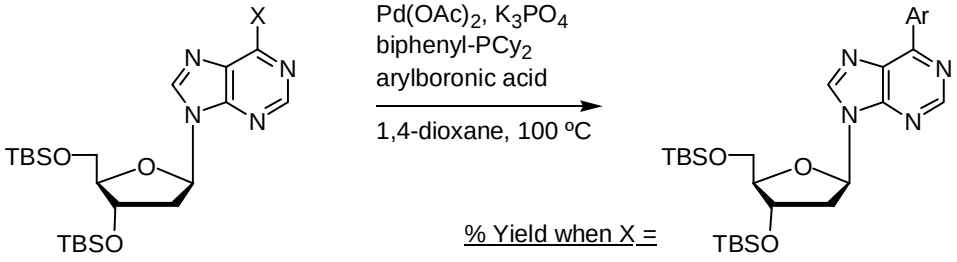
66a R = BOM X = Cl (84%)
66b R = PMB X = Cl (73%)
66c R = PMB X = Br (46%)

With the halopyridines **66a-c** in hand, cross couplings with the pyrrole moiety were then explored. Initial attempts at either Suzuki-Miyaura and Stille couplings using *N*-Boc-pyrrole-2-boronic acid (**67**)[25] or the analogous 2-tributylstannylpyrrole, respectively, afforded only the starting halopyridines. Negishi cross couplings of *N*-benzenesulfonyl-pyrrole-2-zinc chloride with the halopyridines were also unsuccessful.[26] After extensive experimentation, it was discovered that a Suzuki-Miyaura cross coupling using Buchwald's 2-biphenyldicyclohexylphosphine ligand afforded the desired product.[27] Thus, refluxing *N*-PMB-protected bromopyridine **66c** with pyrrole boronic acid **67** in 1,4-dioxane for 20 hours in the presence of 25% $Pd(dba)_2$, the Buchwald ligand, and potassium phosphate afforded tricycle **68** in 60% yield, along with 20% of recovered bromide (Scheme 6). Chloropyridine **66b** underwent cross coupling in higher yield (70%) along with 26% of recovered chloride. Interestingly, when the coupling of

66b with boronic acid **67** was performed in a microwave reactor,[28] the yield of **68** increased to 91% with only 5% recovered starting material.

It should be noted that the Lakshman group has found improved product yields for chloride over bromide substrates in purine derivatives **69** when performing Suzuki-Miyaura cross couplings (Scheme 19).[29] However, the reason for this trend is currently unclear.

Scheme 19



69 **70**

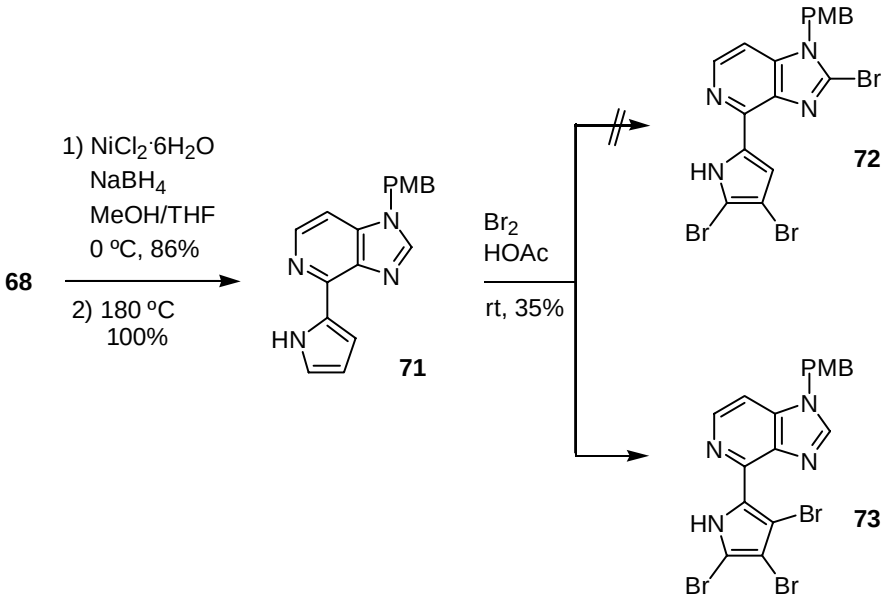
	% Yield when X =	
arylboronic acid	Cl	Br
phenyl	93	91
4-methoxyphenyl	83	69
3-nitrophenyl	84	59
4-acetylphenyl	84	49
4-thiophene	74	58

4.3 Installation of the C-2 Amino Functionality

To continue the synthesis, tricyclic sulfide **68** could be desulfurized using nickel boride[30] followed by thermolytic removal of the Boc protecting group to produce *N*-H pyrrole **71** (Scheme 20). We hoped it would then be possible to selectively tribrominate compound **71** to produce **72**. The bromine at the C-2 position of the imidazopyridine

could subsequently serve as a handle for the introduction of the amino group of ageladine A (**1**). Unfortunately, using Br_2 in acetic acid, *N*-H pyrrole **71** underwent tribromination at the three pyrrole carbons to give tricycle **73**, with no bromination observed at the imidazopyridine C-2 position. Bromination attempts using NBS gave an inseparable mixture of di- and tribrominated products. As a result of the high reactivity of the pyrrole towards bromination, an alternative route had to be devised for the selective dibromination of the pyrrole and introduction of the imidazole amino moiety.

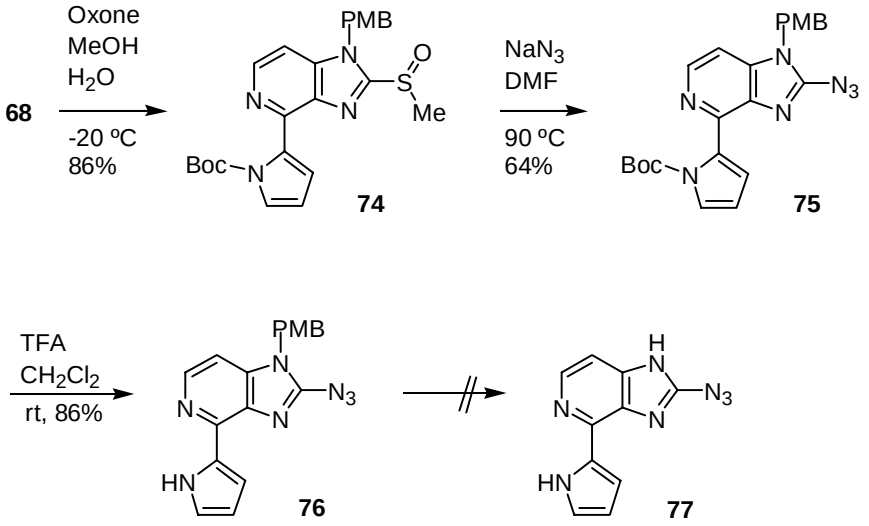
Scheme 20



Towards this end, we hoped to initially introduce the amine moiety at C-2 of imidazopyridine via displacement of an appropriate thio derivative. Therefore, methyl sulfide **68** was oxidized to the corresponding sulfoxide **74** using Oxone in high yield (Scheme 21).[31] Attempts to further oxidize the sulfoxide to the corresponding sulfone with Oxone or *m*-CPBA failed, resulting only in decomposition. Based on the work of

Jarosinski and Anderson, displacement of the sulfoxide moiety with sodium azide in DMF at 90 ºC afforded the desired azide **75** in 64% yield.[32] Removal of the Boc protecting group of **75** under acidic conditions then generated *N*-H pyrrole **76**. Unfortunately, removal of the PMB protecting group of imidazopyridine **76** either by treatment with acid or by catalytic hydrogenation failed. Similar attempts to remove the PMB group from precursors **68** and **74** also failed. In light of these difficulties, the PMB series was abandoned in favor of the BOM protected compounds.

Scheme 21

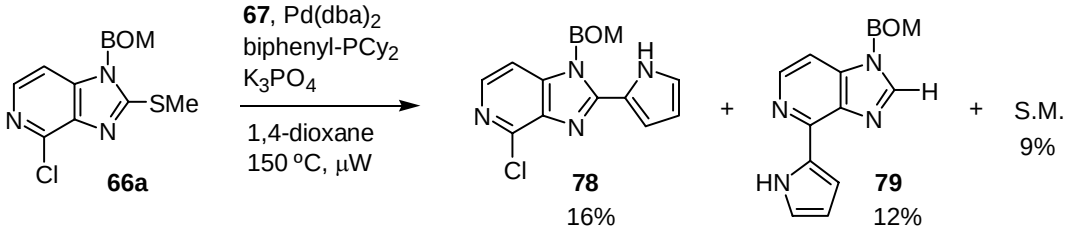


4.4 Amination and Cross Coupling Reactions of *N*-BOM-protected Chloro Imidazopyridine

Unfortunately, it was found that all attempts to cross couple the BOM-protected chloropyridine **66a** with boronic acid **67** under microwave irradiation at 150 ºC, as previously done with PMB-protected halopyridines **66b** and **66c**, resulted in a complex

mixture of products (Scheme 22). In addition to recovered starting material, 16% of the C-2 coupled product **78** and a desulfurized coupled product **79** (12%) were also isolated. Presumably these products arrive via BOM protecting group coordination with the palladium, placing the metal in close proximity to the C-S bond, thereby increasing the thiophilicity of the metal. In addition, the pyrrole Boc protecting group was also lost in both isolated products, probably due to the high temperature of the reaction. In light of these results, the synthetic strategy for ageladine A required further modification.

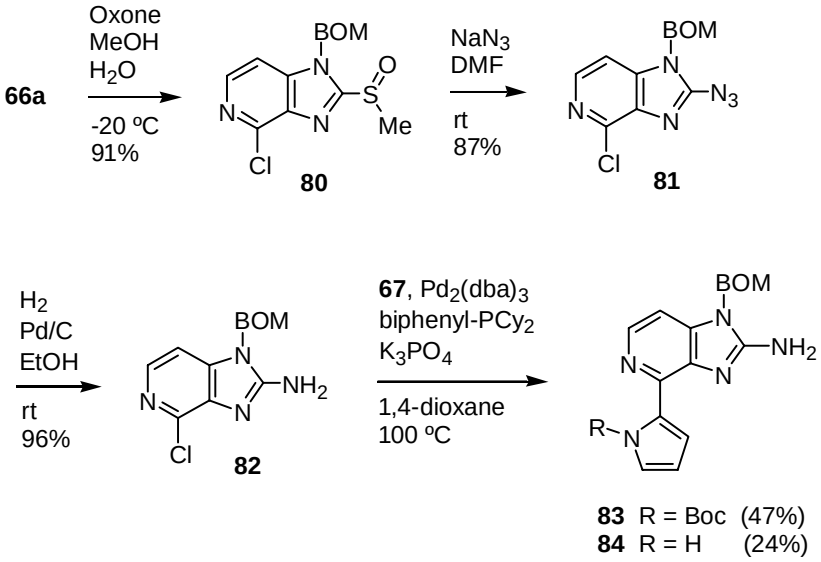
Scheme 22



To circumvent the above problems, we decided to install the imidazolo C-2-amino group prior to introducing the pyrrole fragment. Thus, Oxone oxidation of sulfide **66a** efficiently produced sulfoxide **80** (Scheme 23). Displacement of the sulfoxide moiety of **80** with sodium azide in DMF could be effected at room temperature in this case to afford azide **81**. A competing reaction at temperatures above 23 ºC was hydrolysis of the imidazole sulfoxide by adventitious moisture to produce the corresponding 2-imidazolone. Interestingly, the analogous imidazolone by-product had not been observed in the previous conversion of sulfoxide **74** to azide **75** (Cf. Scheme 21). Catalytic hydrogenation of azide **81** cleanly produced 2-aminoimidazolopyridine **82**. With the

amino group in place, Suzuki-Miyaura cross coupling using pyrrole boronic acid **67** then produced Boc-protected tricyclic pyrrole **83** and *N*-H compound **84** as a separable 2:1 mixture in good total yield. We were pleased to find that no arylation of the amino group of **82** with boronic acid **67** had occurred.[33]

Scheme 23

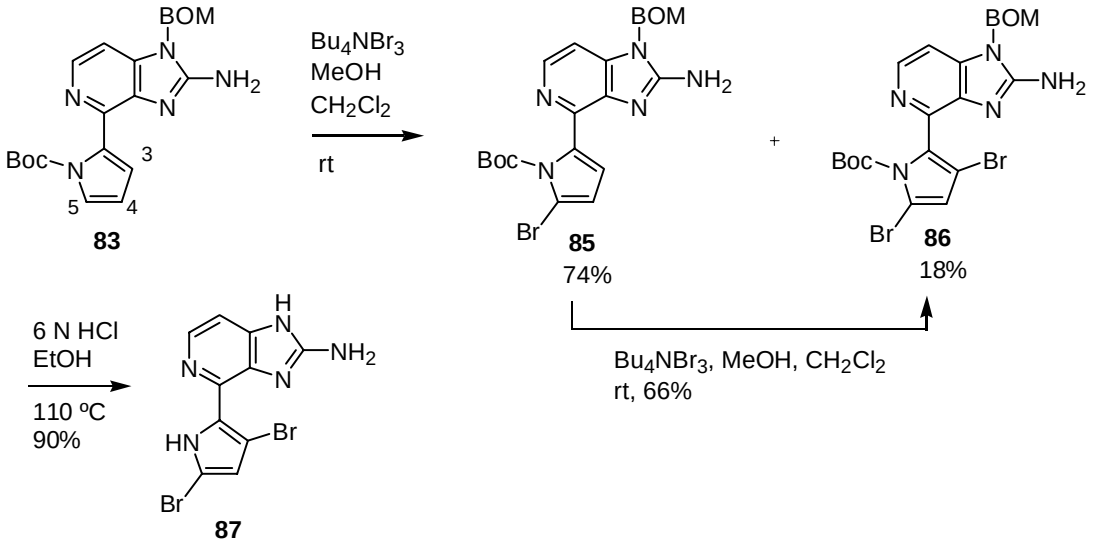


4.5 Pyrrole Bromination and Completion of the Synthesis

To continue the synthesis, Boc-protected tricyclic pyrrole **83** was brominated using tetrabutylammonium tribromide (Bu_4NBr_3), which to our surprise gave the 3,5-dibromopyrrole **86** in 18% yield along with monobromopyrrole **85** as the major product (74%) (Scheme 24).[34] The monobromopyrrole **85** could be brominated to generate additional dibromopyrrole **86**. Bromination of tricyclic pyrrole **83** using Br_2 in carbon tetrachloride also led to a mixture of starting material, along with the same mono-, and

dibrominated products but in poorer yields. The Boc protecting group of tricycle **86** was removed with refluxing 6 N HCl in ethanol to give the 3,5-dibromo regioisomer **87** of ageladine A. The positions of the bromines in bromopyrroles **85**, **86**, and **87** were established using ^{1}H NMR chemical shift data and proton-proton coupling constants.[35] At this point, we do not have a good rationale for the observed regioselectivity in the bromination step since there is little literature precedent for dibromination of pyrrole derivatives bearing a C-2 aryl substituent.[36]

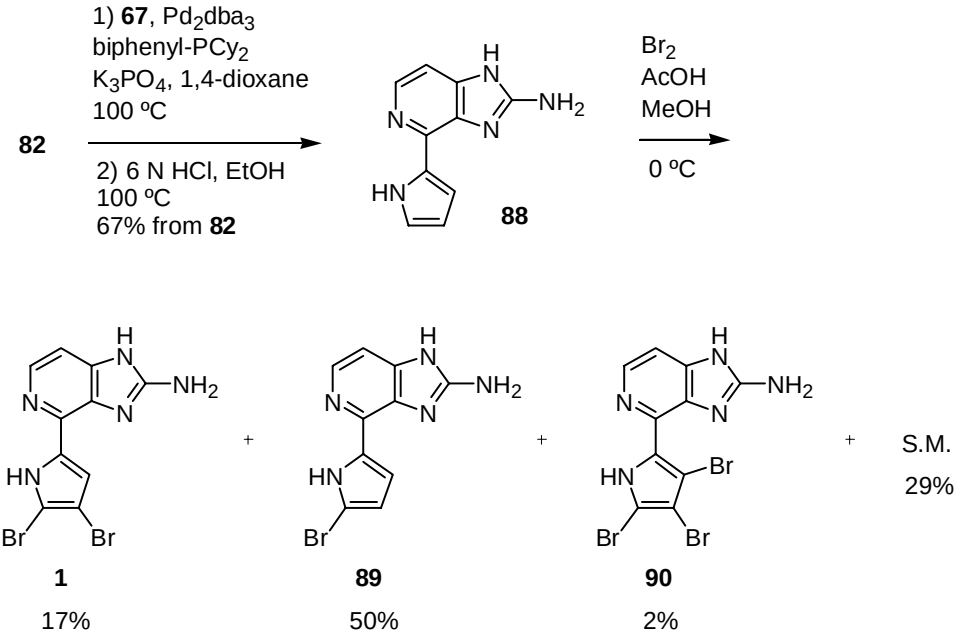
Scheme 24



Since the Boc protected pyrrole **83** led to the undesired dibromination product, we decided to investigate the bromination of the analogous unprotected system. Thus, the crude mixture of 2:1 Boc protected/*N*-H pyrrole tricycle products **83**/**84** was hydrolyzed to afford the fully deprotected tricycle **88** in 67% overall yield from chloropyridine **82** (Scheme 25). Bromination of the *N*-H pyrrole **88** with either Bu_4NBr_3 or NBS resulted in complex mixtures of dibromo and tribrominated pyrrole products. After some

experimentation, the optimal conditions found for halogenation were to treat pyrrole **88** with Br_2 in an acetic acid/methanol solvent mixture at 0 ºC. These conditions produced ageladine A (**1**) in 17% yield, along with recovered starting material (29%), monobromopyrrole **89** (50%) and tribromopyrrole **90** (2%). Purification of this mixture was accomplished via reverse-phase HPLC. Ageladine A (**1**) and the tribrominated product **90** were very difficult to separate since they have similar retention times. Bromination conditions, therefore, had to be optimized such that the maximum amount of ageladine A was produced, while minimizing the formation of undesired tribromopyrrole **90**. Both the recovered starting material and monobromopyrrole **89** could be resubjected to the same bromination conditions to produce additional ageladine A. Synthetic ageladine A had proton and carbon NMR spectra, as well as UV and fluorescence maxima, identical to those reported for the natural product.[1]

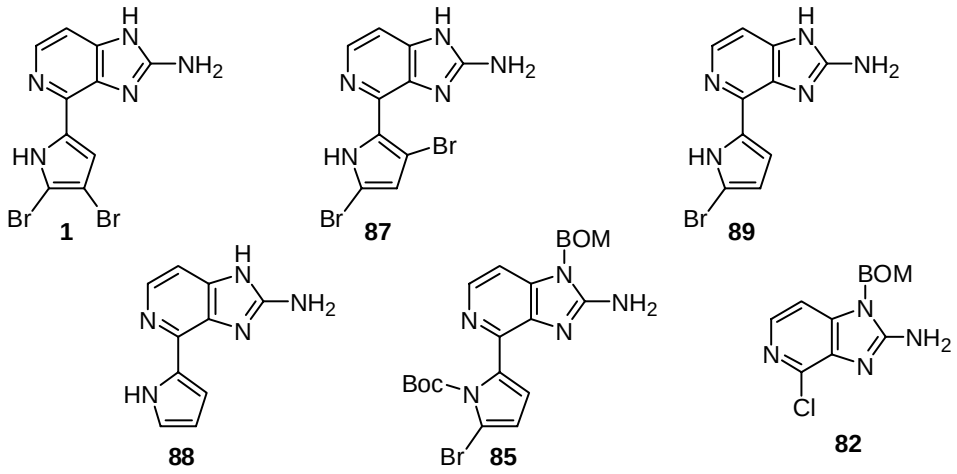
Scheme 25



4.6 Biological Activity of Synthetic Ageladine A and Analogues

Ageladine A (**1**) has been shown to be a potent inhibitor of matrix metalloproteinases (MMPs), particularly MMP-2.[1] In addition to significant inhibition of MMP-2 (5.60 μM), natural ageladine A has been found to display inhibitory activity against MMP-1, -8, -9, -12, and -13 with IC_{50} values of 3.36, 1.09, 2.21, 0.92, and 1.32 μM, respectively.

Our total synthesis of ageladine A not only supplied us with a sample of synthetic natural product, but also with several structural analogues that were screened by Nakao and Fusetani[8b] for MMP inhibition using procedures previously described.[1] The



	MMP-2 (μg/mL)	**MT1-MMP** (μg/mL)
ageladine A (**1**)	2	1.2
3,5-dibromo isomer **87**	10	5
debromoageladine A **89**	5.6	5
protected tricycle **85**	33% (@ 20 μg/mL)	20% (@ 20 μg/mL)
2-chloropyridine **82**	4% (@ 20 μg/mL)	0% (@ 20 μg/mL)

Figure 2. MMP Inhibition Testing Results of Synthetic Ageladine A and Analogues

compounds which were evaluated include synthetic ageladine A (**1**), 3,5-dibromo regioisomer **87**, monobromopyrrole **89**, its fully protected version **85**, tricyclic analogue **88**, and 2-chloropyridine **82** (Figure 1). The biological screening focused on MMP-2 and MT1-MMP.

The synthetic version of ageladine A displayed the same level of inhibition as the isolated natural product against MMP-2 and MT1-MMP. However, as indicated from the MMP inhibition testing results, none of our analogues was a more potent inhibitor than ageladine A (Figure 2). It appears that the quantity and location of the bromine atoms impacts MMP inhibition. Both brominated analogues **87** and **89** inhibited MMP-2 and MT1-MMP, but with about a 5-fold decrease relative to **1**. The complete removal of bromine from the molecule (i.e. **88**) appeared to substantially decrease MMP inhibition altogether. However, due to the strong fluorescence of **88** which interferes with the inhibition assay, the data is not entirely reliable. The data also indicated that the presence of the nitrogen protecting groups in **85** negatively impacts MMP inhibition, as does removal of the pyrrole ring (Cf. **82**).

4.7 Conclusion

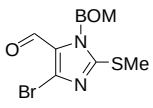
A twelve-step total synthesis of the tricyclic marine metabolite ageladine A (**1**) has been developed starting from 2,4,5-tribromoimidazole, utilizing a 6π-1-azaelectrocyclization and a Suzuki-Miyaura coupling of *N*-Boc-pyrrole-2-boronic acid **67** with a chloro imidazopyridine as key steps. The synthesis has led to the production of several structural analogues of **1** that were subjected to MMP inhibition testing. Although

none of the analogues prepared to date are as potent as the natural product, this route, along with our recently reported second generation synthesis of ageladine A,[6] allows for the facile synthesis of additional analogues for further biological testing.

EXPERIMENTAL SECTION

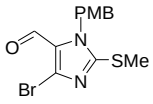
General Methods

All non-aqueous reactions were carried out under a positive atmosphere of nitrogen or argon in flame-dried glassware unless otherwise noted. Air and moisture sensitive liquid reagents were added via a dry syringe. Anhydrous THF, CH_2Cl_2, diethyl ether, and toluene were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Microwave irradiation reactions were performed on a CEM Discover microwave reactor. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300, CDPX-300, or DRX-400 MHz spectrometers. Chemical shifts of ^1H and ^{13}C NMR spectra were referenced to the solvent peaks: δ_H 3.30 and δ_C 49.0 for CD_3OD. Flash chromatography was performed using Sorbent Technologies silica gel 60 (230-400 mesh). Purification by preparative reverse phase HPLC employed an Agilent 1100 preparative pump/gradient extension instrument equipped with a Hamilton PRP-1 (polystyrene-divinylbenzene) reverse phase column (7 μm particle size, 21.5 mm x 25 cm). The following two solvent systems were used: solvent system A (99.9 % double deionized H_2O and 0.1 % TFA), and solvent system B (99.9 % acetonitrile and 0.1 % TFA). The HPLC gradient for the purification of ageladine A (20 mL/min flow rate) was as follows: 99 to 70 % A from 0 to 5 min and 70 to 60 % A from 5 to 25 min; retention time of **1** was 10.2 min.



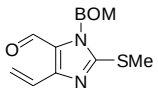
3-Benzyloxymethyl-5-bromo-2-methylsulfanylimidazole-4-carboxaldehyde (51a). To a solution of tribromoimidazole **50a** (6.00 g, 14.1 mmol) in THF (35 mL) was added *n*-BuLi in hexanes (2.4 M, 5.88 mL, 14.1 mmol)

at -78 ºC and the reaction mixture was stirred for 15 min. Dimethyl disulfide (1.33 g, 14.1 mmol) was then added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 15 h, and *n*-BuLi in hexanes (2.4 M, 5.88 mL, 14.1 mmol) was added dropwise. After the mixture was stirred for 15 min at -78 ºC, DMF (3.09 g, 3.29 mL, 42.4 mmol) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 6/1) afforded aldehyde **51a** (4.39 g, 91 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 4.52 (s, 2H), 5.68 (s, 2H), 7.21-7.23 (m, 5H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 155.3, 137.1, 132.1, 128.8, 128.6, 128.4, 128.1, 74.3, 71.8, 15.1; ESI (+): $[M+Na]^+$ calcd for $C_{13}H_{13}N_2O_2{}^{79}BrSNa$, 362.9779; found 362.9775.

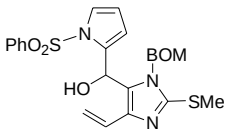


5-Bromo-3-(4-methoxybenzyl)-2-methylsulfanylimidazole-4-carbaldehyde (51b). To a solution of tribromoimidazole **50b** (7.75 g, 0.02 mol) in THF (70 mL) was added *n*-BuLi in hexanes (2.5 M, 7.30 mL, 0.02 mol) at -78 ºC and the reaction mixture was stirred for 15 min. Dimethyl disulfide (1.72 g, 1.64 mL, 0.02 mmol) was added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 15 min and then *n*-BuLi in hexanes (2.5 M, 7.30 mL, 0.02 mol) was added dropwise. After the mixture was stirred for 15 min at -78 ºC, DMF (4.00 g, 4.25 mL, 0.06 mol) was added dropwise. The reaction mixture was stirred at -78 ºC for 30 min and warmed to rt. The mixture was diluted with H_2O (100 mL), and was extracted with CH_2Cl_2 (3 x 30 mL). The extract was dried ($MgSO_4$) and concentrated. Purification of the residue by

recrystallization from ethanol afforded aldehyde **51b** (5.36 g, 86 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.70 (s, 3H), 5.33 (s, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz,), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 159.8, 153.7, 131.7, 129.7, 128.2, 127.7, 114.4, 55.6, 48.9, 15.2; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{14}N_2O_2S^{79}Br$, 340.9966; found 340.9962.

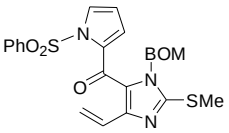


3-Benzyloxymethyl-2-methylsulfanyl-5-vinylimidazole-4-carboxaldehyde (52). To a solution of bromoimidazole **51a** (300 mg, 0.85 mmol) in toluene (5 mL) was added tributyl(vinyl)tin (352 mg, 1.11 mmol), $Pd_2(dba)_3$ (39 mg, 0.04 mmol) and triphenylphosphine (33 mg, 0.13 mmol). The reaction mixture was heated at 95 ºC for 17 h, diluted with H_2O (15 mL), and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 5/1) afforded vinylimidazole **52** (204 mg, 95 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H), 4.48 (s, 2H), 5.45 (dd, *J* = 10.8, 1.8 Hz, 1H), 5.66 (s, 2H), 6.20 (dd, *J* = 17.0, 1.8 Hz, 1H), 6.82 (dd, *J* = 17.0, 10.8 Hz, 1H), 7.17-7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 155.3, 152.3, 137.4, 128.8, 128.3, 128.1, 128.0, 125.2, 120.9, 74.3, 71.4, 15.0; ESI (+): $[M+Na]^+$ calcd for $C_{15}H_{16}N_2O_2SNa$, 311.0830; found 311.0804.



(1-Benzenesulfonylpyrrol-2-yl)-(3-benzyloxymethyl-2-methyl-sulfanyl-5-vinylimidazol-4-yl)methanol (54). To a solution of (1-phenylsulfonyl)pyrrole (**53**, 99 mg, 0.48 mmol) in THF (4.5 mL) was added dropwise *t*-BuLi in pentane (1.7 M, 0.40 mL, 0.60 mmol) at -78 ºC. The reaction mixture was stirred

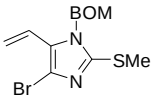
for 15 min, and aldehyde **52** (100 mg, 0.40 mmol) in THF (0.5 mL) was added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 1 h, quenched with H_2O (10 mL), and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 5/1) afforded alcohol **54** (111 mg, 61 %) as a dark solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.77 (d, *J* = 4.7 Hz, 1H), 4.23 (d, *J* = 2.6 Hz, 2H), 4.92 (dd, *J* = 10.9, 2.2 Hz, 1H), 5.05 (d, *J* = 2.8 Hz, 2H), 5.72 (dd, *J* = 17.2, 2.2 Hz, 1H), 6.05-6.10 (m, 1H), 6.13 (t, *J* = 3.4 Hz, 1H), 6.20 (d, *J* = 4.6 Hz, 1H), 6.35 (dd, *J* = 17.2, 10.9 Hz, 1H), 7.04-7.09 (m, 2H), 7.19-7.23 (m, 6H), 7.38-7.44 (m, 1H), 7.52-7.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 139.2, 139.0, 137.0, 135.4, 134.3, 129.7, 128.9, 128.8, 128.5, 128.4, 127.4, 127.0, 124.7, 115.8, 113.9, 112.1, 73.7, 70.8, 61.2, 16.5; ESI (+): $[M+H]^+$ calcd for $C_{25}H_{26}N_3O_4S_2$, 496.1365; found 496.1369.



(1-Benzenesulfonylpyrrol-2-yl)-(3-benzyloxymethyl-2-methyl-sulfanyl-5-vinylimidazol-4-yl)methanone (55). *Method A (Dess-Martin Oxidation).* To a solution of purified alcohol **54** (100 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin reagent (95 mg, 0.22 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min, then diluted with CH_2Cl_2 (15 mL) and H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 5/1) afforded ketone **55** (80 mg, 81 %) as a yellow oil along with 20 mg of impure ketone **55** contaminated with an unidentified compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 3H), 4.36 (s, 2H), 5.12 (dd, *J* = 10.5, 2.4 Hz, 1H), 5.50 (s, 2H), 6.03

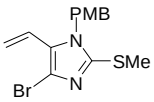
(dd, J = 17.0, 2.4 Hz, 1H), 6.05-6.10 (m, 1H), 6.17 (dd, J = 17.0, 10.5 Hz, 1H), 6.25 (t, J = 3.5 Hz, 1H), 6.60 (d, J = 3.6 Hz, 1H), 7.07-7.11 (m, 2H), 7.13-7.18 (m, 3H), 7.43 (m, 2H), 7.50-7.55 (m, 1H), 7.60-7.64 (m, 1H), 7.95-7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 152.7, 147.3, 139.3, 137.4, 134.6, 134.4, 129.7, 129.5, 128.8, 128.7, 128.3, 128.1, 127.7, 127.1, 124.9, 118.2, 111.8, 74.0, 71.1, 15.3; ESI (+): $[M+H]^+$ calcd for $C_{25}H_{24}N_3O_4S_2$, 494.1208; found 494.1231.

Method B (MnO_2 Oxidation). To a solution of alcohol **54** (100 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was added activated MnO_2 (Aldrich, 351 mg, 4.04 mmol) at rt. The reaction mixture was stirred at rt for 18 h, after which time additional activated MnO_2 (175 mg, 2.01 mmol) was added due to incomplete oxidation as determined by TLC. The reaction mixture was stirred at rt for another 23 h, then filtered through a small Celite pad which was washed with CH_2Cl_2 (200 mL). The total filtrate was concentrated and purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded ketone **55** along with pyrrole aldehyde **57** (74 mg, 2:1 mixture by ^{1}H NMR) as an inseparable mixture.

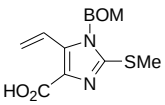


1-Benzyloxymethyl-4-bromo-2-methylsulfanyl-5-vinylimidazole (61a). To a solution of Ph_3PMeBr (6.54 g, 18.32 mmol) in THF (35 mL) was added *t*-BuOK (1.81 g, 16.12 mmol) in portions at 0 ºC. The reaction mixture was stirred at rt for 30 min and cooled to 0 ºC. A solution aldehyde **51a** (2.50 g, 7.33 mmol) in THF (5 mL) was added slowly after which the reaction mixture was warmed to rt and stirred for 3.5 h. The reaction mixture was diluted with saturated NH_4Cl (30 mL), and was

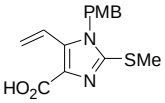
extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded vinylimidazole **61a** (2.39 g, 96 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 4.47 (s, 2H), 5.26-5.31 (m, 3H), 5.87 (d, *J* = 17.9 Hz, 1H), 6.45 (dd, *J* = 17.9, 12.1 Hz, 1H), 7.18-7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 135.4, 128.0, 127.5, 127.1, 126.7, 120.9, 116.1, 115.0, 72.3, 69.6, 15.0; ESI (+): $[M+H]^+$ calcd for $C_{14}H_{16}N_2OS^{79}Br$, 339.0167; found 339.0153.



4-Bromo-1-(4-methoxybenzyl)-2-methylsulfanyl-5-vinylimidazole (61b). To a solution of Ph_3PMeBr (2.62g, 7.33 mmol) in THF (15 mL) was added *t*-BuOK (0.72 g, 6.45 mmol) in portions at 0 ºC. The reaction mixture was stirred at rt for 30 min and cooled to 0 ºC. A solution of aldehyde **51b** (1.00 g, 2.93 mmol) in THF (5 mL) was added slowly, after which the reaction mixture was warmed to rt and stirred for 3.5 h. The reaction mixture was diluted with saturated NH_4Cl (60 mL), and was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded vinylimidazole **61b** (0.94 g, 95 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.69 (s, 3H), 5.02 (s, 2H), 5.18 (dd, *J* = 12.0, 0.9 Hz, 1H), 5.70 (dd, *J* = 17.8, 0.9 Hz, 1H), 6.27 (dd, *J* = 17.8, 11.9 Hz, 1H), 6.76-6.78 (m, 2H), 6.90-6.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 144.6, 128.8, 127.9, 127.8, 122.4, 117.1, 115.6, 114.7, 55.7, 48.3, 16.5; ESI (+): $[M+H]^+$ calcd for $C_{14}H_{16}N_2OS^{79}Br$, 339.0167; found 339.0156.

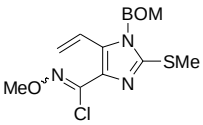


1-Benzyloxymethyl-2-methylsulfanyl-5-vinylimidazole-4-carboxylic Acid (62a). To a solution of bromoimidazole **61a** (3.50 g, 10.32 mmol) in THF (30 mL) was added *n*-BuLi in hexanes (2.4 M, 6.45 mL, 15.47 mmol) at -78 ºC and the reaction mixture was stirred for 1.25 h. Excess freshly crushed dry ice was then added at -78 ºC and the reaction mixture was slowly warmed to rt. The reaction mixture was quenched with H_2O (50 mL), and was extracted with Et_2O (2 x 25 mL). The aqueous layer was acidified to pH 3 with 1 M HCl and extracted with EtOAc (3 x 30 mL). The extract was dried ($MgSO_4$) and concentrated. Purification of the residue by recrystallization (hexanes/EtOAc) afforded acid **62a** (3.09 g, 98 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 4.55 (s, 2H), 5.31 (s, 2H), 5.55 (dd, *J* = 12.2, 1.0 Hz, 1H), 6.08 (dd, *J* = 18.1, 0.9 Hz, 1H), 7.02 (dd, *J* = 18.1, 12.2 Hz, 1H), 7.19-7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 146.9, 138.2, 136.7, 129.9, 129.0, 128.7, 128.2, 123.0, 122.7, 74.0, 71.5, 15.9; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_3S$, 305.0960; found 305.0947.

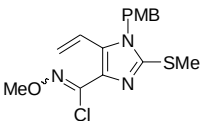


1-(4-Methoxybenzyl)-2-methylsulfanyl-5-vinylimidazole-4-carboxylic Acid (62b). To a solution of bromoimidazole **61b** (2.50 g, 7.37 mmol) in THF (50 mL) was added *n*-BuLi in hexanes (2.4 M, 4.61 mL, 11.05 mmol) at -78 ºC and the reaction mixture was stirred for 1.5 h. Excess freshly crushed dry ice was then added at -78 ºC and the reaction mixture was warmed to rt. The reaction mixture was diluted with H_2O (80 mL) and extracted with Et_2O (40 mL). The aqueous layer was acidified to pH 3 with 1 M HCl and extracted with EtOAc (3 x 40 mL). The extract was dried ($MgSO_4$) and concentrated. Purification of the residue by recrystallization

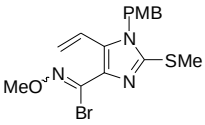
(hexanes/EtOAc) afforded acid **62b** (2.17 g, 97 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 3.69 (s, 3H), 5.08 (s, 2H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.70 (d, *J* = 18.1 Hz, 1H), 6.76-6.91 (m, 6H), 10.82 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 159.7, 146.7, 137.9, 129.9, 127.7, 127.3, 123.3, 121.9, 114.8, 55.7, 48.5, 15.8; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{17}N_2O_3S$, 305.0960; found 305.0965.



1-Benzyloxymethyl-2-methylsulfanyl-4-(*N*-methoxyimino-1-chloro-methyl)-5-vinylimidazole (63a). A solution of methoxylamine hydrochloride (82 mg, 0.99 mmol) and pyridine (78 mg, 0.08 mL, 0.99 mmol) in acetonitrile (15 mL) was stirred at rt for 10 min, and acid **62a** (250 mg, 0.82 mmol) and carbon tetrachloride (505 mg, 0.32 mL, 3.29 mmol) were added. The reaction mixture was stirred at rt for 10 min before the addition of triphenylphosphine (862 mg, 3.29 mmol). The mixture was refluxed at 80 ºC for 4 h and then concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 6/1) affording chloro-methoxime **63a** (251 mg, 87 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.97 (s, 3H), 4.51 (s, 2H), 5.28 (s, 2H), 5.36 (dd, *J* = 12.1, 1.0 Hz, 1H), 5.83 (dd, *J* = 18.0, 1.09 Hz, 1H), 6.77 (dd, *J* = 18.0, 12.1 Hz, 1H), 7.19-7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 137.0, 133.3, 133.1, 132.6, 128.9, 128.5, 128.1, 123.6, 119.9, 74.1, 71.2, 63.5, 16.5; ESI (+): $[M+H]^+$ calcd for $C_{16}H_{19}N_3O_2SCl$, 352.0887; found 352.0888.

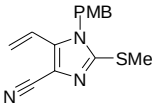


1-(4-Methoxybenzyl)-2-methylsulfanyl-4-(*N*-methoxyimino-1-chloromethyl)-5-vinylimidazole (63b). A solution of methoxylamine hydrochloride (0.13 g, 1.58 mmol) and pyridine (0.13 g, 0.13 mL, 1.58 mmol) in acetonitrile (25 mL) stirred at rt for 10 min, and acid **62b** (0.40 g, 1.31 mmol) and carbon tetrachloride (0.81 g, 0.51 mL, 5.26 mmol) were added. The reaction mixture was stirred at rt for 10 min before the addition of triphenylphosphine (1.38 g, 5.26 mmol). The reaction mixture was refluxed at 80 ºC for 4 h and then concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 6/1) affording chloro-methoxime **63b** (0.37 g, 80 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H), 3.69 (s, 3H), 3.98 (s, 3H), 5.07 (s, 2H), 5.24 (dd, *J* = 12.1, 0.9 Hz, 1H), 5.45 (dd, *J* = 18.0, 0.9 Hz, 1H), 6.64 (dd, *J* = 18.0, 12.0 Hz, 1H), 6.75-6.78 (m, 2H), 6.89-6.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 146.2, 133.5, 132.9, 132.1, 127.9, 127.8, 123.8, 119.3, 114.7, 63.5, 55.7, 48.5, 16.4; ESI (+): $[M+H]^+$ calcd for $C_{16}H_{19}N_3O_2SCl$, 352.0887; found 352.0882.

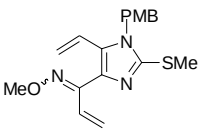


1-(4-Methoxybenzyl)-2-methylsulfanyl-4-(*N*-methoxyimino-1-bromomethyl)-5-vinylimidazole (63c). A solution of methoxylamine hydrochloride (0.40 g, 4.73 mmol) and pyridine (0.38 g, 0.0.38 mL, 4.73 mmol) in acetonitrile (20 mL) was stirred at rt for 10 min, and acid **62b** (1.20 g, 3.94 mmol) and carbon tetrabromide (5.23 g, 15.77 mmol) were added. The reaction mixture was stirred at rt for 10 min before the addition of triphenylphosphine (4.14 g, 15.77 mmol). The reaction mixture was refluxed at 80 ºC for 2 h and then concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 6/1) affording bromo-

methoxime **63c** (1.14 g, 73 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.72 (s, 3H), 4.02 (s, 3H), 5.08 (s, 2H), 5.25 (dd, *J* = 12.1, 0.8 Hz, 1H), 5.48 (dd, *J* = 18.0, 0.8 Hz, 1H), 6.61 (dd, *J* = 18.0, 12.0 Hz, 1H), 6.77-6.80 (m, 2H), 6.91-6.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 146.0, 134.0, 131.6, 127.9, 127.8, 125.3, 123.6, 113.2, 114.9, 63.4, 55.7, 48.5, 16.4; ESI (+): $[M+H]^+$ calcd for $C_{16}H_{19}N_3O_2S^{79}Br$, 396.0381; found 396.0374.

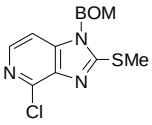


1-(4-Methoxybenzyl)-2-methylsulfanyl-5-vinylimidazole-4-carbonitrile (64). A solution of bromomethoxime **63c** (100 mg, 0.25 mmol), Boc-protected 2-tributylstannanylpyrrole (230 mg, 0.51 mmol), $Pd(PPh_3)_4$ (30 mg, 0.02 mmol), and CuI (10 mg, 0.05 mmol) in toluene (6 mL) was heated at 105 ºC for 17 h and concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 3/1) affording nitrile **64** (53 mg, 74 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.71 (s, 3H), 4.98 (s, 2H), 5.50 (d, *J* = 11.7 Hz, 1H), 6.00 (d, *J* = 17.7 Hz, 1H), 6.35 (dd, *J* = 17.7, 11.7 Hz, 1H), 6.78-6.82 (m, 2H), 6.92-6.95 (m, 2H); AP (+): $[M+H]^+$ calcd for $C_{15}H_{16}N_3OS$, 286.4; found 286.1.

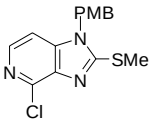


1-[1-(4-Methoxybenzyl)-2-methylsulfanyl-5-vinylimidazol-4-yl]-propenone *O*-methyloxime (65). A solution of bromomethoxime **63c** (25 mg, 0.06 mmol), tributyl(vinyl)tin (21 mg, 0.07 mmol), $Pd_2(dba)_3$ (10 mol %, 3 mg), P(*t*-Bu)$_3$ (20 mol %, 3 mg), and CsF (19 mg, 0.13 mmol) in toluene (2 mL) was stirred at rt for 39 h. The reaction mixture was diluted with Et_2O (5 mL), filtered through a silica gel plug, washed with Et_2O, and then concentrated. The residue was purified by column

chromatography (hexanes/EtOAc, 4/1) affording vinylimidazole **65** (7 mg, 32 %) as a clear oil, along with starting bromomethoxime **63c** (9 mg, 36 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.72 (s, 3H), 3.93 (s, 3H), 5.08-5.12 (m, 3H), 5.36 (dd, *J* = 17.9, 1.0 Hz, 1H), 5.53-5.55 (m, 1H), 5.58 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.44 (dd, *J* = 17.9, 11.9 Hz, 1H), 6.78-6.82 (m, 2H), 6.92-6.98 (m, 2H), 7.06 (dd, *J* = 17.5, 11.2 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{18}H_{22}N_3O_2S$, 344.5; found 344.1.



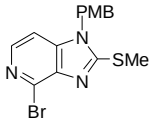
1-Benzyloxymethyl-4-chloro-2-methylsulfanylimidazopyridine (66a). A solution of methoxime **63a** (0.50 g, 1.42 mmol) in *o*-xylene (50 mL) was refluxed at 145 ºC for 17 h and concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 2/1) affording pyridine **66a** (0.38 g, 84 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (s, 3H), 4.43 (s, 2H), 5.43 (s, 2H), 7.12 (d, *J* = 5.5 Hz, 1H), 7.16-7.19 (m, 2H), 7.23-7.26 (m, 3H), 8.05 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 142.1, 140.6, 139.7, 137.2, 135.3, 128.1, 127.8, 127.3, 104.1, 72.5, 70.4, 14.3; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{15}N_3OSCl$, 320.0624; found 320.0616.



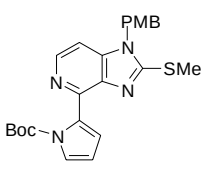
4-Chloro-1-(4-methoxybenzyl)-2-methylsulfanylimidazopyridine (66b). *Method A (Thermal Cyclization).* A solution of methoxime **63b** (0.30 g, 0.85 mmol) in *o*-xylene (50 mL) was refluxed in an oil bath at 145 ºC for 15 h and then concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 2/1) affording pyridine **66b** (0.20 g, 73 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, 3H), 3.69 (s, 3H), 5.10 (s, 2H), 6.75-6.78 (m, 2H), 6.97 (d, *J*

= 5.5 Hz, 1H), 7.01-7.05 (m, 2H), 7.96 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 154.6, 140.9, 138.9, 138.4, 135.9, 126.8, 124.4, 112.7, 102.7, 53.6, 46.1, 13.1; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{15}N_3OSCl$, 320.0624; found 320.0636.

Method B (Microwave Irradiation). To a 10 mL microwave reaction vial was added a solution of methoxime **63b** (40 mg, 0.11 mmol) in *o*-xylene (2.5 mL). The mixture was subjected to microwave irradiation at 165 ºC for 1 h, cooled to rt and concentrated. The residue was purified by preparative TLC (hexanes/EtOAc, 2/1) affording pyridine **66b** (29 mg, 81 %) as a yellow solid.



4-Bromo-1-(4-methoxybenzyl)-2-methylsulfanylimidazopyridine (66c). A solution of methoxime **63c** (0.40 g, 1.01 mmol) in *o*-xylene (50 mL) was refluxed at 145 ºC for 15 h and then concentrated. The residue was purified by column chromatography on Florisil (hexanes/EtOAc, 2/1) affording pyridine **66c** (0.17 g, 46 %) as a yellow solid, along with starting oxime **63c** (0.05 g, 13 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, 3H), 3.69 (s, 3H), 5.10 (s, 2H), 6.75-6.78 (m, 2H), 6.98 (d, *J* = 5.5 Hz, 1H), 7.01-7.04 (m, 2H), 7.95 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 155.2, 140.7, 140.1, 139.6, 138.5, 130.4, 127.5, 125.2, 113.4, 103.6, 54.3, 46.8, 13.8; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{15}N_3OS^{79}Br$, 364.0119; found 364.0115.



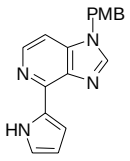
2-[1-(4-Methoxybenzyl)-2-methylsulfanylimidazopyridin-4-yl]-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (68) from Chloropyridine 66b. *Method A (Thermal Cyclization).* In an oven-dried Schlenk tube

was placed chloropyridine **66b** (100 mg, 0.37 mmol), boronic acid **67** (154 mg, 0.73 mmol), $Pd(dba)_2$ (21 mg, 0.04 mmol), (2-biphenyl)dicyclohexylphosphine (26 mg, 0.07 mmol), K_3PO_4 (310 mg, 1.46 mmol) and 1,4-dioxane (3 mL). The Schlenk tube was flushed with argon, sealed and heated at 100 ºC for 20 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by preparative TLC (hexanes/EtOAc, 1/1.5) affording the coupled pyridine **68** (115 mg, 70 %) as a yellow solid, along with starting chloropyridine **66b** (25 mg, 25 %).

Method B (Microwave Irradiation). To a 10 mL microwave reaction vial was added chloropyridine **66b** (75 mg, 0.23 mmol), boronic acid **67** (247 mg, 1.17 mmol), $Pd(dba)_2$ (13 mg, 0.02 mmol), (2-biphenyl)dicyclohexylphosphine (16 mg, 0.05 mmol), K_3PO_4 (349 mg, 1.64 mmol) and 1,4-dioxane (3 mL). The mixture was subjected to microwave irradiation at 150 ºC for 40 min. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by preparative TLC (hexanes/EtOAc, 1/1.5) affording the coupled pyridine **68** (96 mg, 91 %) as a yellow solid, along with starting chloropyridine **66b** (4 mg, 5 %).

Synthesis of 68 from Bromopyridine 66c. In an oven-dried Schlenk tube was placed bromopyridine **66c** (25 mg, 0.07 mmol), boronic acid **67** (29 mg, 0.14 mmol), $Pd(dba)_2$ (4 mg, 10 mol %), (2-biphenyl)dicyclohexylphosphine (5 mg, 20 mol %), K_3PO_4 (58 mg, 0.28 mmol) and 1,4-dioxane (2 mL). The tube was flushed with argon,

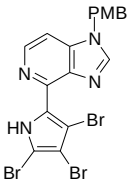
sealed and heated at 100 ºC for 20 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by preparative TLC (hexanes/EtOAc, 1/1.5) affording the coupled pyridine **68** (18 mg, 60 %) as a yellow solid, along with starting bromopyridine **66c** (5 mg, 20 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.69 (s, 3H), 3.70 (s, 3H), 5.11 (s, 2H), 6.26 (t, *J* = 3.3 Hz, 1H), 6.63 (q, *J* = 1.7 Hz, 1H), 6.75-6.79 (m, 2H), 6.98 (d, *J* = 5.5 Hz, 1H), 7.07-7.10 (m, 2H), 7.37 (q, *J* = 1.7 Hz, 1H), 8.22 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 154.9, 150.1, 143.7, 141.7, 141.2, 139.3, 131.5, 129.0, 127.4, 124.2, 116.9, 114.7, 111.2, 103.8, 83.3, 55.7, 47.8, 27.7, 15.1; ESI (+): $[M+H]^+$ calcd for $C_{24}H_{27}N_4O_3S$, 451.1804; found 451.1787.



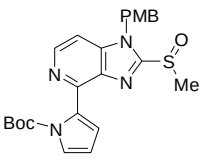
1-(4-Methoxybenzyl)-4-(1*H*-pyrrol-2-yl)imidazopyridine (71). To a solution of sulfide **68** (50 mg, 0.11 mmol) in MeOH/THF (10 mL, 1:1) at -25 ºC was added $NiCl_2 \cdot 6H_2O$ (185 mg, 0.78 mmol). The reaction mixture was stirred at -25 ºC for 10 min before the portion wise addition of $NaBH_4$ (88 mg, 2.33 mmol). The mixture was stirred for an additional 10 min at -25 ºC and then filtered through Celite, which was washed with the MeOH/THF solvent system (40 mL). The filtrate was concentrated and the residue was dissolved in CH_2Cl_2, and filtered again through Celite, which was washed with CH_2Cl_2. The filtrate was concentrated and the residue was purified by preparative TLC (hexanes/EtOAc, 1/1.5) affording the desulfurized imidazole (38 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 3.72 (s, 3H), 5.21 (s, 2H), 6.24 (t, *J* = 3.2 Hz, 1H), 6.61 (q, *J* = 1.7 Hz, 1H), 6.79-6.81 (m, 2H), 7.05-7.10 (m, 2H), 7.09 (d, *J* = 5.7 Hz, 1H), 7.36 (q, *J* = 1.7 Hz, 1H),

7.86 (s, 1H), 8.31 (d, J = 5.6 Hz, 1H) 10.92 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 149.7, 146.5, 144.1, 139.8, 139.0, 130.9, 129.4, 127.1, 124.3, 117.2, 114.9, 111.3, 105.0, 83.4, 55.8, 49.1, 27.8; ESI (+): $[M+H]^+$ calcd for $C_{23}H_{25}N_4O_3$, 405.1927; found 405.1929.

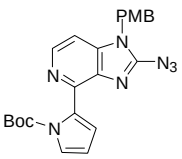
The desulfurized *N*-Boc-protected pyrrole (15 mg, 0.04 mmol) was heated neat at 180 ºC for 15 min and cooled to rt. The material turned from a white solid to a dark oil, and the reaction was complete upon the cessation of gas evolution. The residue was purified by preparative TLC (hexanes/EtOAc, 1/1.5) affording deprotected pyrrole **71** (11 mg, 100%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H) , 5.19 (s, 2H), 6.30-6.31 (m, 1H), 6.80-6.82 (m, 2H), 6.91 (d, J = 5.6 Hz, 1H), 6.95-6.96 (m, 1H), 7.05-7.07 (m, 2H), 7.25-7.26 (m, 1H), 7.84 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{18}H_{17}N_4O$, 305.1402; found 305.1398.



1-(4-Methoxybenzyl)-4-(3,4,5-tribromo-1*H*-pyrrol-2-yl)imidazopyridine (73). To a solution of pyrrole **71** (10 mg, 0.03 mmol) in acetic acid (1 mL) was added Br_2 (11 mg, 0.07 mmol) in acetic acid (0.5 mL). The reaction mixture was stirred at rt for 10 min and concentrated. The residue was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded tribromopyrrole **73** (5 mg, 35 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.20 (s, 2H), 6.81-6.84 (m, 2H), 6.99 (d, J = 5.6 Hz, 1H), 7.06-7.09 (m, 2H), 7.89 (s, 1H), 8.22 (d, J = 5.7 Hz, 1H); ESI (+) $[M+H]^+$ calcd for $C_{18}H_{14}N_4O^{79}Br_3$, 539.3; found 538.8.

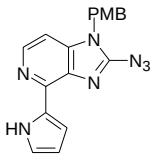


2-[2-Methanesulfinyl-1-(4-methoxybenzyl)imidazopyridin-4-yl]-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (74). To a solution of sulfide **68** (20 mg, 0.04 mmol) in MeOH (1 mL) at -20 ºC was added Oxone (Aldrich, 41 mg, 0.07 mmol) in H_2O (1 mL). The mixture was stirred at -20 ºC for 3 h, and the MeOH was removed *in vacuo*. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded sulfoxide **74** (18 mg, 86 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 9H), 3.10 (s, 3H), 3.71 (s, 3H), 5.23 (s, 2H), 6.28 (t, J = 3.3 Hz, 1H), 6.70 (q, J = 1.7 Hz, 1H), 6.78-6.80 (m, 2H), 7.15-7.19 (m, 3H), 7.39 (q, J = 1.7 Hz, 1H), 8.39 (d, J = 5.8 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{24}H_{27}N_4O_4S$, 467.6; found 467.2.

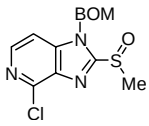


2-[2-Azido-1-(4-methoxybenzyl)imidazopyridin-4-yl]pyrrole-1-carboxylic Acid *tert*-Butyl Ester (75). To a solution of sulfoxide **74** (15 mg, 0.03 mmol) in DMF (2 mL) was added NaN_3 (11 mg, 0.16 mmol) at rt. The mixture was heated at 90 ºC for 18 h, cooled to rt, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded azide **75** (9 mg, 64 %) as a white solid, along with starting sulfoxide **74** (1 mg, 7 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H), 3.73 (s, 3H), 5.04 (s, 2H), 6.28 (t, J = 3.3 Hz, 1H), 6.72-6.73 (m, 1H), 6.78-6.84 (m, 2H), 7.01 (d, J = 5.2 Hz, 1H), 7.07-7.11 (m,

2H), 7.37-7.39 (m, 1H), 8.28 (d, J = 5.6 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{23}H_{24}N_7O_3$, 446.5; found 446.2.

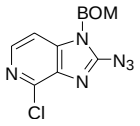


2-Azido-1-(4-methoxybenzyl)-4-(pyrrol-2-yl)imidazopyridine (76). To a solution of Boc-protected pyrrole **75** (10 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was slowly added trifluoroacetic acid (0.5 mL). The reaction mixture was stirred at rt for 2.5 h, then diluted with sat. Na_2CO_3 (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/2) afforded *N*-H pyrrole **76** (6 mg, 86 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3H), 5.01 (s, 2H), 6.31-6.32 (m, 1H), 6.77-6.80 (m, 2H), 6.82 (d, J = 5.6 Hz, 1H), 6.97-6.99 (m, 1H), 7.06-7.09 (m, 2H), 7.27-7.30 (m, 1H), 8.16 (d, J = 5.6 Hz, 1H), 10.65 (br s, 1H).

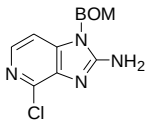


1-Benzyloxymethyl-4-chloro-2-methanesulfinylimidazopyridine (80). To a solution of sulfide **66a** (100 mg, 0.31 mmol) in MeOH (3 mL) at -20 ºC was added Oxone (Aldrich, 577 mg, 0.19 mmol) in H_2O (3 mL). The mixture was stirred at -20 ºC for 2.5 h, after which the MeOH was removed *in vacuo*. The mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded sulfoxide **80** (96 mg, 91 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 3H), 4.56 (s, 2H), 5.97 (s, 2H), 7.15-7.18 (m, 2H), 7.21-7.24 (m, 3H), 7.31 (d, J = 5.7 Hz, 1H), 8.21 (d, J = 5.6 Hz, 1H); ^{13}C NMR (75 MHz,

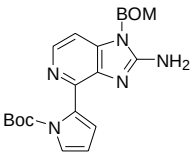
$CDCl_3$) δ 154.0, 143.1, 142.3, 141.5, 135.3, 135.1, 127.9, 127.7, 127.1, 105.3, 73.1, 70.8, 39.7; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{15}N_3O_2SCl$, 336.0574; found 336.0575.



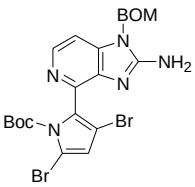
2-Azido-1-benzyloxymethyl-4-chloroimidazopyridine (81). To a solution of sulfoxide **80** (75 mg, 0.22 mmol) in DMF (5 mL) was added NaN_3 (73 mg, 1.12 mmol) at rt. The mixture was stirred at rt for 14 h, diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded azide **81** (61 mg, 87 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 2H), 5.34 (s, 3H), 7.12-7.16 (m, 3H), 7.20-7.24 (m, 3H), 8.05 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 143.3, 142.4, 142.0, 137.6, 137.4, 130.3, 130.2, 129.5, 107.0, 74.1, 73.1; ESI (+): $[M+H]^+$ calcd for $C_{14}H_{12}N_6OCl$, 315.0761; found 315.0765.



1-Benzyloxymethyl-4-chloroimidazopyridin-2-ylamine (82). A solution of azide **81** (50 mg, 0.16 mmol) in EtOH (3 mL) was reduced with 10 % Pd/C (16 mg) at rt under one atmosphere of H_2 for 3.5 h. The mixture was then filtered through a Celite pad, which was washed with MeOH. The filtrate was concentrated to afford amine **82** (44 mg, 96 %) as a white solid sufficiently pure for use in the next step. ^{1}H NMR (300 MHz, CD_3OD) δ 4.55 (s, 2H), 5.55 (s, 2H), 7.23-7.25 (m, 6H), 7.88 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.9, 141.5, 138.9, 137.1, 136.3, 136.0, 128.3, 127.9, 127.8, 104.4, 72.3, 71.0; ESI (+): $[M+H]^+$ calcd for $C_{14}H_{14}N_4OCl$, 289.0856; found 289.0866.



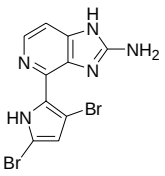
2-(2-Amino-1-benzyloxymethylimidazopyridin-4-yl)pyrrole-1-carboxylic Acid *tert*-Butyl Ester (83). In an oven-dried Schlenk tube was placed chloropyridine **82** (30 mg, 0.10 mmol), boronic acid **67** (88 mg, 0.42 mmol), $Pd_2(dba)_3$ (24 mg, 0.03 mmol), (2-biphenyl)dicyclohexylphosphine (36 mg, 0.10 mmol), K_3PO_4 (88 mg, 0.42 mmol) and 1,4-dioxane (3 mL). The Schlenk tube was flushed with argon, sealed and heated at 100 ºC for 13 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/2) afforded Boc-protected pyrrole **83** (20 mg, 47 %) as a white solid, along with *N*-H pyrrole **84** (8 mg, 24 %). *N*-H pyrrole Boc-protected tricycle **83**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 4.47 (s, 2H), 5.32 (s, 2H), 5.61 (br s, 2H), 6.23 (t, *J* = 3.2 Hz, 1H), 6.52 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.87 (d, *J* = 5.5 Hz, 1H), 7.19-7.24 (s, 2H), 7.31-7.36 (m, 4H), 8.21 (d, *J* = 5.4 Hz, 1H). *N*-H tricycle **84**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H), 4.99 (br s, 2H), 5.30 (s, 2H), 6.29 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 5.5 Hz, 1H), 6.93 (s, 1H), 7.19-7.21 (m, 3H), 7.29-7.31 (m, 3H), 8.11 (d, *J* = 5.4 Hz, 1H), 10.89 (br s, 1H); ESI (+): $[M+H]^+$ calcd for $C_{18}H_{17}N_5O$, 320.1511; found 320.1500.



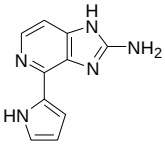
2-(2-Amino-1-benzyloxymethylimidazopyridin-4-yl)2,3-dibromo-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (86). *Method A (from pyrrole* **83***)*. To a solution of Boc-protected pyrrole **83** (8 mg, 0.02 mmol) in MeOH/CH_2Cl_2 (3 mL, 1:2) was added $CaCO_3$ (4 mg, 0.04 mmol) and tetrabutylammonium tribromide (15 mg, 0.04 mmol). The mixture was stirred at rt for 1 h and then concentrated. The residue was purified by preparative TLC (CH_2Cl_2/MeOH, 9/1) affording dibrominated pyrrole **86** (2 mg, 18 %) as a yellow solid, along with

monobrominated pyrrole **85** (7 mg, 74 %). Monobromopyrrole **85**: ^{1}H NMR (400 MHz, CD_3OD_1) δ 1.33 (s, 9H), 4.47 (s, 2H), 5.33 (br s, 4H), 6.29 (d, *J* = 3.7 Hz, 1H), 6.81 (d, *J* = 5.6 Hz, 1H), 6.87 (d, *J* = 3.7 Hz, 1H), 7.19-7.22 (m, 3H), 7.29-7.32 (m, 2H) 8.15 (d, *J* = 5.5 Hz, 1H). Dibromopyrrole **85**: ^{1}H NMR (400 MHz, CD_3OD_1) δ 1.06 (s, 9H), 4.51 (s, 2H), 5.39 (s, 2H), 5.81 (br s, 2H), 6.38 (s, 1H), 6.97 (d, *J* = 5.5 Hz, 1H), 7.21-7.24 (m, 2H), 7.29-7.32 (m, 3H), 8.28 (d, *J* = 5.5 Hz, 1H).

Method B (from monobromopyrrole **85***).* To a solution of monobromopyrrole **85** (7 mg, 0.02 mmol) in MeOH/CH_2Cl_2 (3 mL, 1:2) was added $CaCO_3$ (2 mg, 0.02 mmol) and tetrabutylammonium tribromide (6 mg, 0.02 mmol). The mixture was stirred at rt for 1 h and then concentrated. The residue was purified by preparative TLC (CH_2Cl_2/MeOH, 9/1) affording dibrominated pyrrole **86** (5 mg, 66 %).

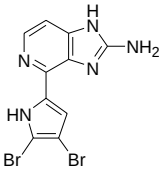


4-(3,5-Dibromo-1*H*-pyrrol-2-yl)imidazopyridin-2-ylamine (87). Protected imidazole **86** (4 mg, 0.01 mmol) was dissolved in EtOH (1.5 mL) and 6 N HCl (1 mL). The mixture was heated at 100 ºC for 14 h and then concentrated. Purification of the residue by reverse phase HPLC afforded deprotected imidazole **87** (2 mg, 90 %) as a white solid. ^{1}H NMR (300 MHz, CD_3OD_1) δ 6.42 (s, 1H), 7.43 (d, *J* = 6.5 Hz, 1H), 8.12 (d, *J* = 6.5 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{10}H_8N_5{}^{79}Br_2$, 356.2; found 355.9.



4-(1*H*-Pyrrol-2-yl)imidazopyridin-2-ylamine (88). In an oven-dried Schlenk tube was placed chloropyridine **82** (70 mg, 0.24 mmol), boronic acid **67** (205 mg, 0.97 mmol), $Pd_2(dba)_3$ (55 mg, 0.06 mmol), (2-

biphenyl)dicyclohexylphosphine (85 mg, 0.24 mmol), K_3PO_4 (206 mg, 0.97 mmol) and 1,4-dioxane (6 mL). The Schlenk tube was flushed with argon, sealed and heated at 100 ºC for 17 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the crude coupled product mixture **83** and **84** (2:1 mixture of **83**:**84**) was dissolved in EtOH (7 mL) and 6 N HCl (4 mL). The mixture was heated at 100 ºC for 12 h and then concentrated. The residue was redissolved in MeOH, neutralized with 1 % KOH and concentrated again. The residue was purified using a short silica plug (CH_2Cl_2/MeOH, 4/1) affording deprotected imidazole **88** (32 mg, 67 %) as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 6.41 (dd, *J* = 3.9, 2.6 Hz, 1H), 7.17 (dd, *J* = 3.9, 1.3 Hz, 1H), 7.23 (dd, *J* = 2.6, 1.3 Hz, 1H), 7.33 (d, *J* = 6.5 Hz, 1H), 7.94 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.3, 146.2, 136.5, 131.8, 131.5, 125.6, 123.5, 112.6, 112.0, 104.4; ESI (+): $[M+H]^+$ calcd for $C_{10}H_{10}N_5$, 200.0936; found 200.0923.



Ageladine A (1). To a solution of pyrrole **88** (20 mg, 0.1 mmol) in AcOH/MeOH (5 mL/1 mL) at 0 ºC was slowly added Br_2 in glacial AcOH (20 mM, 0.36 mL, 0.07 mmol). The mixture was stirred at 0 ºC for 20 min and then concentrated. Purification of the residue by reverse phase HPLC afforded ageladine A (**1**, 6 mg, 17 %) as a yellow solid, along with starting pyrrole **88** (6 mg, 29 %), monobromopyrrole **89** (14 mg, 50 %) and tribromopyrrole **90** (1 mg, 2 %). Ageladine A (**1**): ^{1}H NMR (300 MHz, CD_3OD) δ 7.17 (s, 1H), 7.41 (d, *J* = 6.4 Hz, 1H), 8.05 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.8, 147.1, 136.7, 133.0, 128.5, 125.7, 115.1, 107.7, 105.4, 102.3; ESI (+): $[M+H]^+$ calcd for $C_{10}H_8N_5{}^{79}Br_2$, 355.9146; found

355.9163. Monobromopyrrole **89**: ^{1}H NMR (400 MHz, CD_3OD) δ 6.34 (d, *J* = 6.0 Hz, 1H), 7.03 (d, *J* = 6.0 Hz, 1H), 7.30 (d, *J* = 6.5 Hz, 1H), 7.91 (d, *J* = 6.5 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{10}H_9N_5{}^{79}Br$, 278.2; found 278.0. Tribromopyrrole **90**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (s, 1H), 7.41 (d, *J* = 6.4 Hz, 1H), 8.05 (d, *J* = 6.4 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{10}H_7N_5{}^{79}Br_3$, 434.2; found 433.8.

CHAPTER TWO

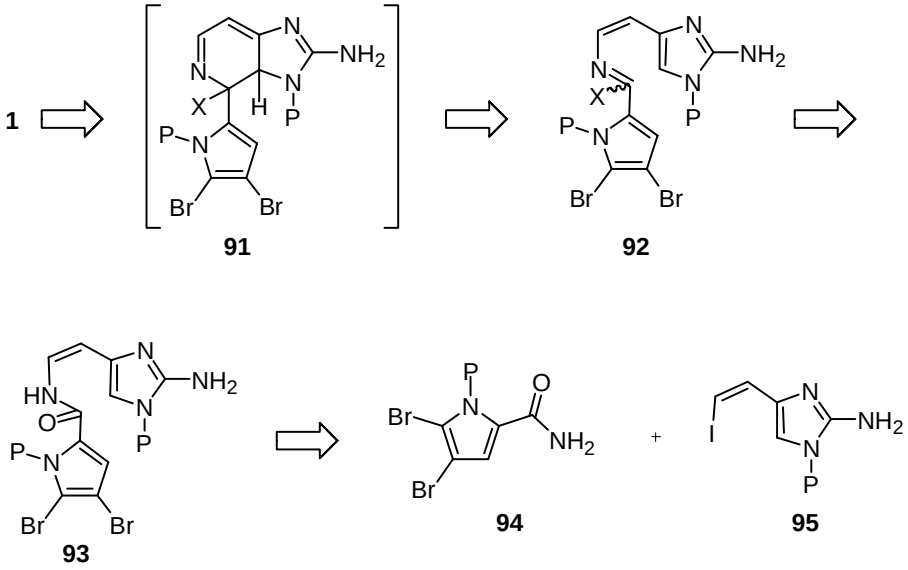
Biomimetically-Inspired, Second Generation Total Synthesis of Ageladine A

INTRODUCTION AND BACKGROUND

1.1 Retrosynthetic Analysis

Our biomimetic approach required the construction of a key 2-azatriene like **92** to be used for the 6π-2-azatriene electrocyclization (Scheme 26). This intermediate is similar to that proposed by Fusetani et al., except that **92** is in a higher oxidation state than imine **9** (Cf. Scheme 2). As a result, the cyclized product **91** could provide the fully aromatic imidazopyridine core of ageladine A simply via loss of H-X. Imidate derivative **92** should be available from the corresponding enamide **93**, which would be obtained from the coupling of dibromopyrrole amide **94** and (*Z*)-vinyl iodide **95**. We also planned to incorporate the pyrrole bromine atoms in to intermediate **93**, which would avoid the inefficient late stage pyrrole halogenation step that was used in our first generation total synthesis of ageladine A.[8]

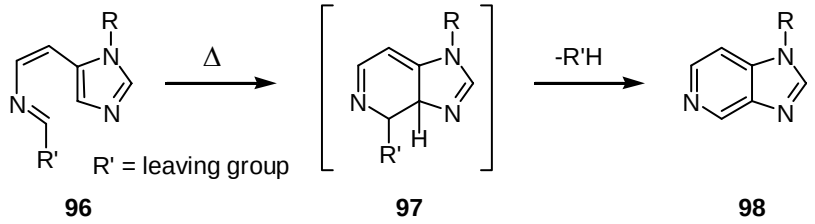
Scheme 26



2.1 6π-2-Azatriene Electrocyclizations

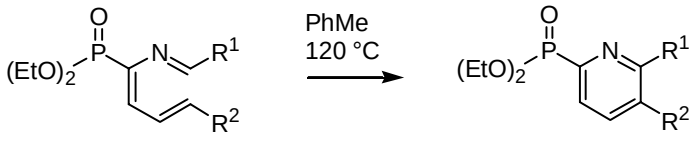
As previously mentioned, Fusetani proposed a key 6π-2-azatriene electrocyclization in the biogenesis of ageladine A. There have been a number of examples of 6π-2-azaelectrocyclizations reported in the literature. For instance, heating a solution of 2-azatriene **96** at high temperatures induces electrocyclization to generate intermediate dihydropyridine **97**, which then eliminates a leaving group (typically as water, alcohol, or an amine) to form a fused imidazopyridine **98** (Scheme 27).[11,37]

Scheme 27



Palacios and coworkers have shown that 2-azatrienes **99**, when refluxed in toluene for five days, undergo 6π-electrocyclization to give 2-phosphonylpyridines **100** (Scheme 28).[38] These compounds have generated some interest by medicinal chemists due to their biological properties and have shown promise as anti-inflammatory agents.

Scheme 28

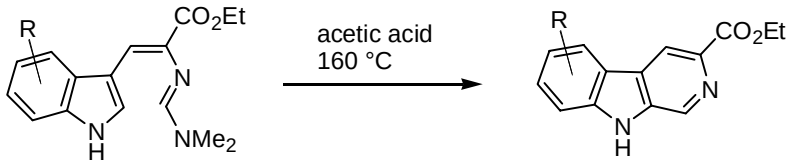


99 **100**

R^1	R^2	% Yield
p-MePh	Ph	50%
p-MePh	Me	60%
3-Py	Ph	50%

Similarly, Biere, Russe, and Seelen have synthesized substituted β-caboline derivatives **102** from the 2-azatriene precursors **101** via a 6π-electrocyclization (Scheme 29).[39] β-Cabolines are of interest due to their benzodiazepine receptor affinity.

Scheme 29

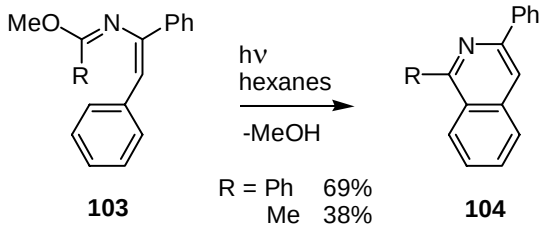


101 **102**

R	% Yield
H	66
5-Me	79
5-OBz	60
8-OMe	47
6-Cl	51

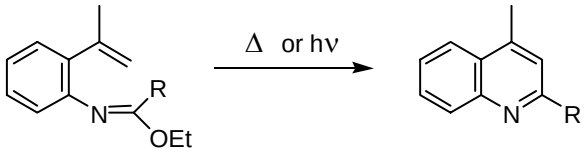
Other examples of 6π-2-azatriene electrocyclizations involve synthesis of isoquinolines, an important structural motif in many biologically-active molecules. Instead of performing these cyclizations thermally, Campos et al. reported the photocyclization of 1-methoxy-2-azadienes **103** in neutral medium to provide isoquinolines **104** in moderate to good yields (Scheme 30).[40]

Scheme 30



In addition, quinolines, another fundamental type of heterocyclic structure with biological and industrial applications, can also be synthesized via 6π-2-azaelectrocyclizations. Baine and Qiang have shown that subjection of imidates **105** to thermoylsis in dilute solutions of refluxing diphenyl ether, or to photolysis in cyclohexane at room temperature gave quinolines **106** in excellent yields (Scheme 31).[41]

Scheme 31



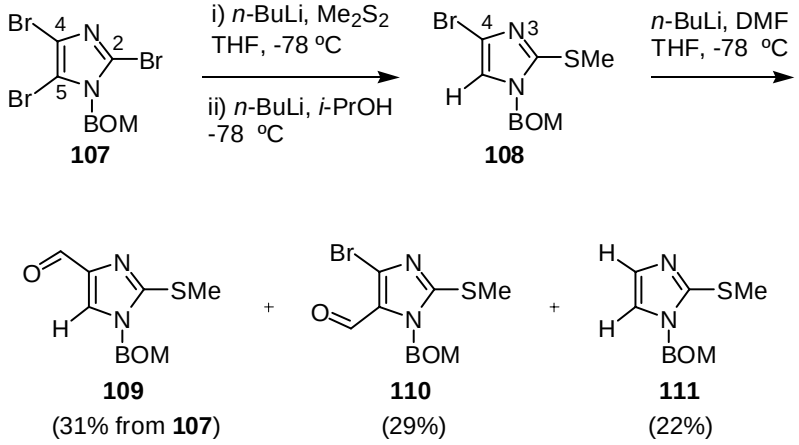
R	% Yield Thermal	Phot.
Et	91	91
Pr	82	92
Ph	92	92
2-furyl	84	71

RESULTS AND DISCUSSION

3.1 Model Study for 6π-2-Azatriene Electrocyclization

Our initial synthetic efforts focused on a model study of the pivotal 6π-2-azatriene electrocyclization where the dibromopyrrole fragment of the natural product was replaced by a phenyl group. The synthesis began with BOM-protected tribromoimidazole **107**, which was sequentially metallated as done previously (Cf. Scheme 13).[42] Thus, in a one-pot procedure, tribromoimidazole **107** was first metallated with *n*-butyllithium at C-2, and subsequent addition of dimethyl disulfide introduced a thiomethyl moiety. Without workup, addition of another equivalent *n*-butyllithium to the reaction mixture metallated C-5 and subsequent protonation of the lithiated species using isopropanol gave 4-bromoimidazole **108** (Scheme 32). Metallation of crude 4-bromoimidazole **108**, followed by addition of DMF gave the desired imidazole aldehyde **109** in 31% overall yield, along

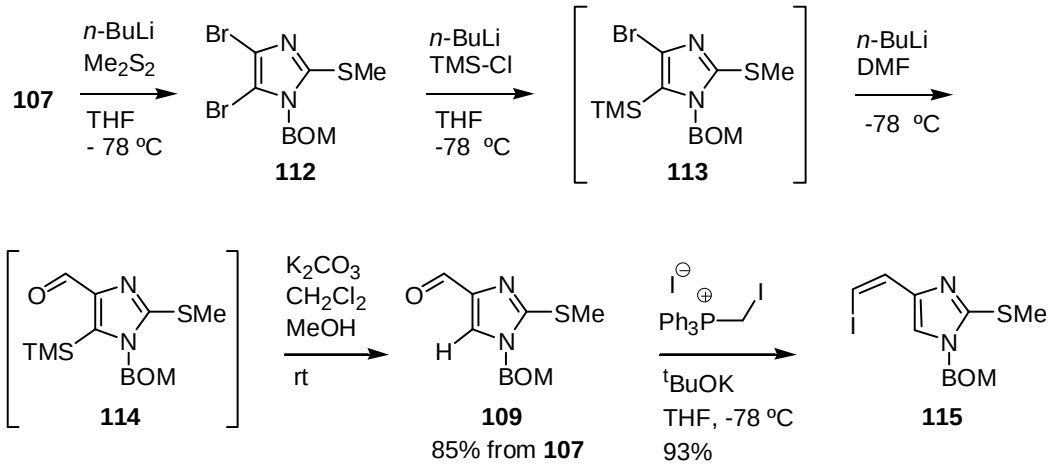
Scheme 32



with 4-bromo-5-formyl imidazole **110** and 4,5-unsubstituted imidazole **111** as significant byproducts. Due to the formation of these unwanted compounds in the formylation of **108**, an alternative, more efficient route to aldehyde **109** was devised.

The formation of significant amounts of the undesired aldehyde **110** can be rationalized by invoking the well documented adjacent lone pair effect (ALP effect),[43] where the carbanion resulting from halogen-metal exchange of imidazole **108** at C-4 is destabilized by the lone pair on N-3. However, we believed that placing a C-5 blocking group on the imidazole should obviate this problem. Thus, tribromoimidazole **107** was selectively metallated, followed by addition of dimethyl disulfide to afford sulfide **112** (Scheme 33). In a one-pot process based upon the methodology of Begtrup and coworkers,[44] dibromoimidazole **112** was then lithiated at C-5 and subsequent addition of trimethylsilyl chloride resulted in the 4-bromo-5-silylimidazole **113**. Without isolation, this compound was immediately metallated and formylated with DMF to yield the functionalized aldehyde **114**. Without purification, TMS-imidazole **114** was desilylated using potassium carbonate in methanol to afford the desired imidazole

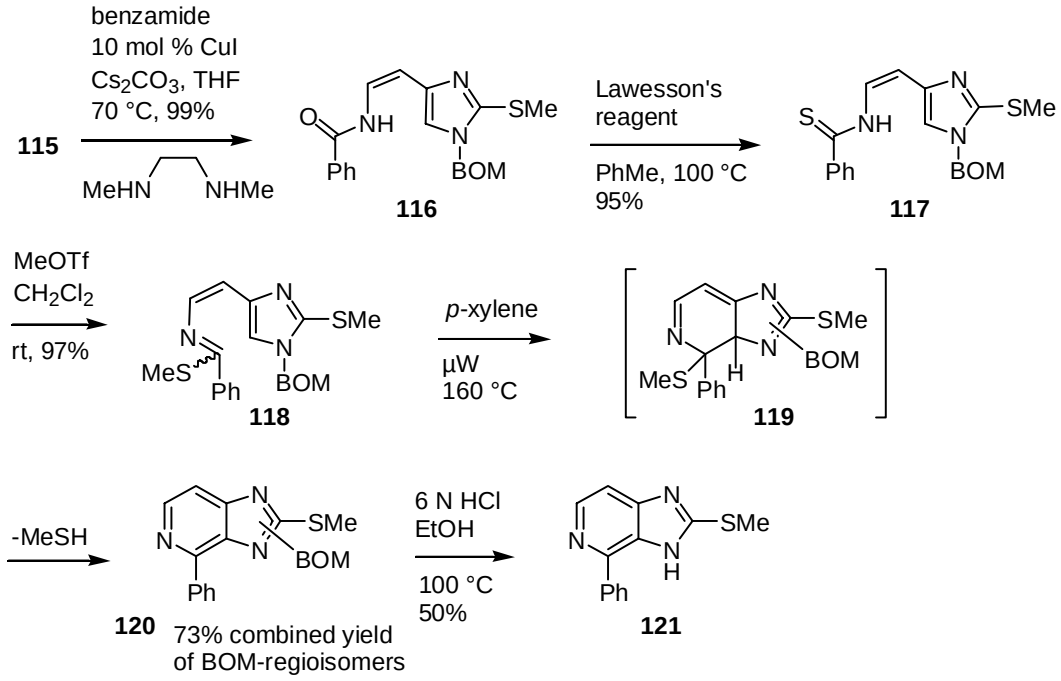
Scheme 33



aldehyde **109** in 85% overall yield from tribromoimidazole **107**. Utilizing the procedure of Stork and Zhao,[45] aldehyde **109** was then smoothly converted to the requisite (*Z*)-vinyl iodide **115** using (iodomethyl)triphenylphosphonium iodide[46] and potassium *t*-butoxide.

Continuing with the model study, an imidate substrate for the 6π-2-azatriene electrocyclization was fashioned.[11] Thus, the procedure of Buchwald and coworkers was used to couple (*Z*)-vinyl iodide **115** with benzamide to afford enamide **116** in high yield and with complete retention of the olefin geometry (Scheme 34).[47] Unfortunately, enamide **116** could not be directly converted to an imidate under a variety of conditions, including Meerwein's salt, triflic anhydride, trifluoroacetic anhydride, and several different silylating/base combinations. In all cases only starting enamide **116** was recovered. However, it was finally found that treatment of **116** with Lawesson's reagent gave the corresponding thioenamide **117** in 95% yield. Conversion of thioenamide **117** to the desired thioimidate **118** proceeded smoothly using methyl triflate.[48]

Scheme 34

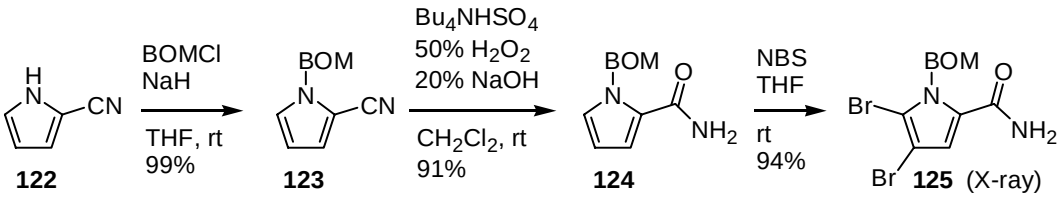


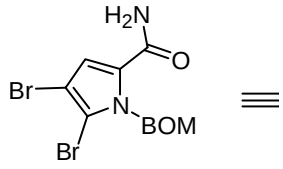
We were pleased to find that subjecting a dilute solution of thioimidate **118** in *p*-xylene to microwave irradiation at 160 °C gave the desired imidazopyridine **120** as a separable mixture of BOM-regioisomers in 73% combined yield. Furthermore, refluxing a solution of BOM-protected imidazopyridine regioisomers **120** in 6 N HCl in ethanol produced *N*-H imidazopyridine **121**. It might be noted that facile BOM migration has been noted in other imidazole systems.[49]

3.2 Applying the Synthetic Strategy to Ageladine A

With the successful model system tested, we addressed the synthesis of ageladine A by preparing the requisite dibromopyrrole amide substrate. Thus, commercially available 2-cyanopyrrole (**122**) was first BOM-protected to afford **123** in high yield (Scheme 35). Initial bromination attempts with unprotected nitrile **122** or BOM-protected nitrile **123** using a variety of brominating reagents led to complex mixtures of starting pyrrole, as well as mono-, di-, and tribrominated products in poor yields. Thus, basic hydrogen peroxide was utilized to convert the nitrile functionality of pyrrole **123** to the corresponding amide **124**.[50] Fortunately, bromination of pyrrole amide **124** with NBS gave the required 4,5-dibromopyrrole amide **125** in high yield. X-Ray crystallography was used to confirm that the pyrrole had the desired bromine regiochemistry required for the natural product (Figure 3).

Scheme 35





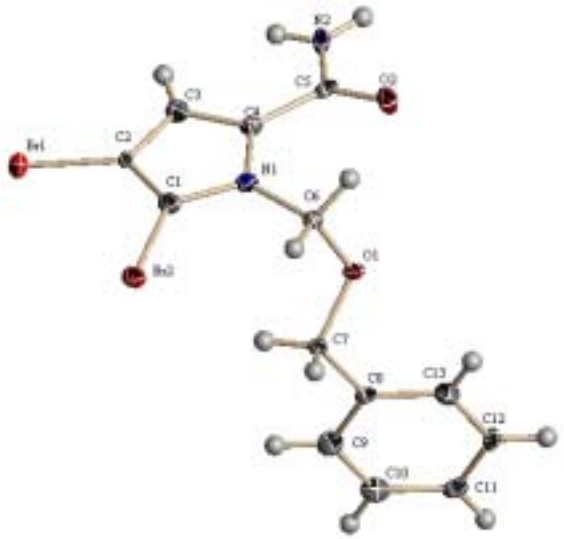
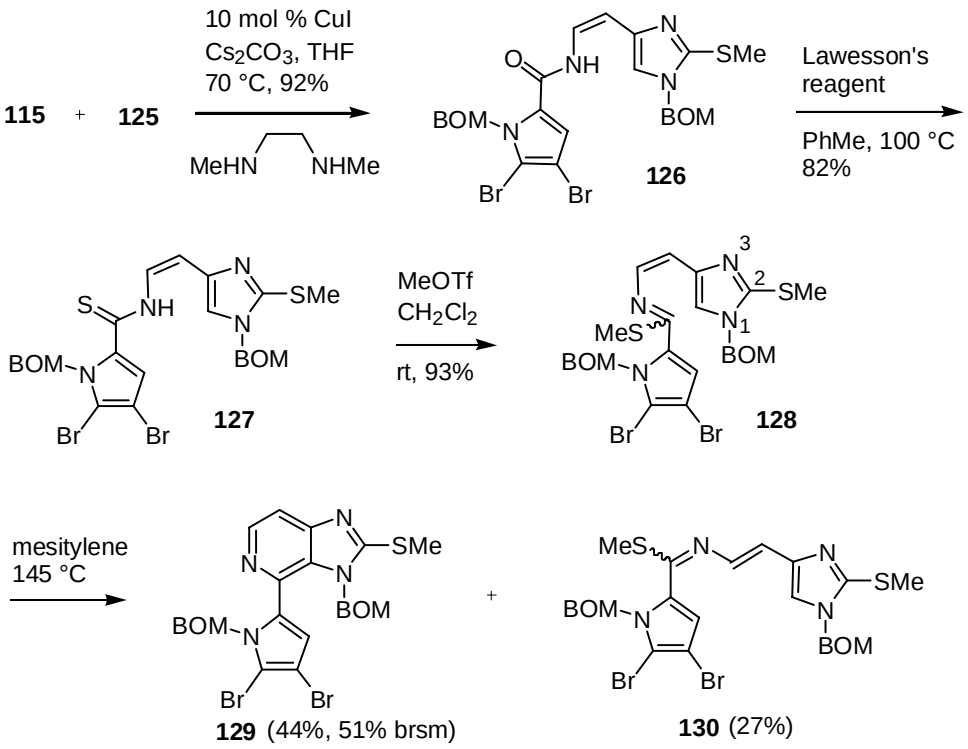


Figure 3. ORTEP Structure of 4,5-Dibromopyrrole Amide **125**

With both necessary substrates in hand, (*Z*)-vinyl iodide **115** and dibromopyrrole amide **125** were coupled using the Buchwald conditions to give (*Z*)-enamide **126** stereoselectively in 92% yield (Scheme 36). In addition, the copper-catalyzed coupling reaction was completely chemoselective, with the pyrrole bromine atoms being unaffected.[51] Following the protocol developed in the above model study, enamide **126** was first converted to the corresponding thioenamide **127** using Lawesson's reagent and treatment with methyl triflate then produced thioimidate **128** in good overall yield. However, attempts at the 6π-2-azatriene electrocyclization of thiomethyl imidate **128** in

p-xylene using microwave irradiation at 160 °C gave complex mixtures of starting (*Z*)-vinyl thioimidate **128**, isomerized (*E*)-vinyl imidate **130**, and both BOM-regioisomers of imidazopyridine **129**. On the other hand, when the cyclization was performed by heating a dilute solution of **128** in mesitylene at 145 °C, BOM-regioisomer **129** was produced in 44% isolated yield (51% based on recovered starting material). The major byproduct in this 6π-2-azaelectrocyclization was the isomerized (*E*)-vinyl imidate **130** (27%).

Scheme 36



A range of reaction temperatures and solvent systems were examined for the electrocyclization, as well as the addition of various Lewis acids and buffers. However, the partial (*E*)/(*Z*) isomerization of the thioenamide could not be suppressed. Unfortunately, (*E*)-isomer **130** did not undergo cyclization either thermally or via

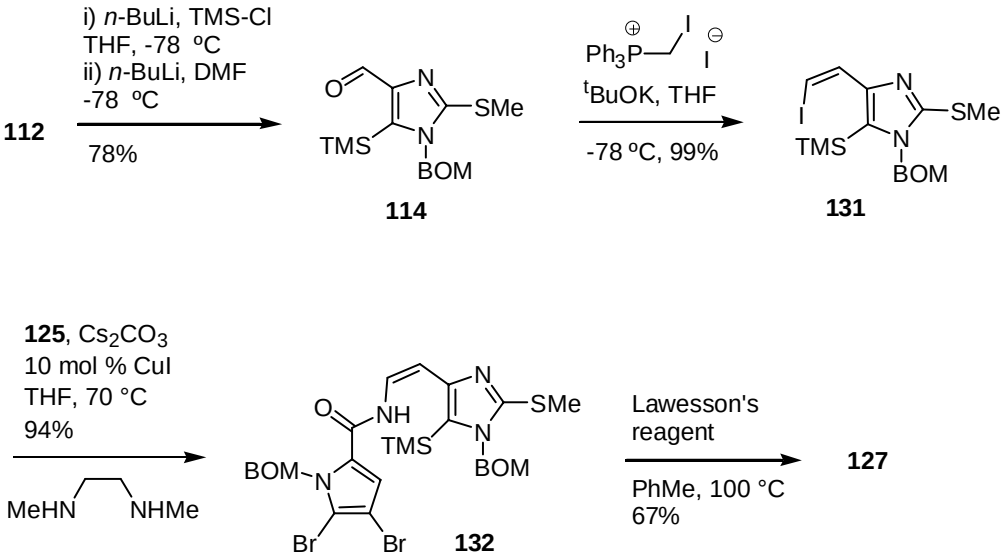
microwave irradiation to give the desired imidazopyridine **129**. It should also be noted that attempts to photochemically effect the cyclization of thioenamide **127** or thioimidate **128** to **129** failed to give any imidazopyridine products, with only starting material or isomerized (*E*)-vinyl imidate **130** being recovered, respectively.[52]

3.3 Attempts to Improve the Electrocyclization Results

3.3.1 *Incorporating TMS as a Leaving Group for the Electrocyclization*

At this point, we decided to examine an alternative system to possibly improve the yield of the 6π-2-azaelectrocyclization product **129**. We first examined the use of a better leaving group on C-5 of the imidazole, in particular a trimethylsilyl group, to aid in the cyclization. Using the same methodology as previously described (Cf. Scheme 33), aldehyde **114** was formed in 78% yield from dibromoimidazole **112**. After a Wittig olefination of aldehyde **114** and subsequent amide coupling of iodide **131** with pyrrole amide **125**, enamide **132** was produced in excellent yield with only the (*Z*)-product being observed (Scheme **37**). Treatment of enamide **132** with Lawesson's reagent did furnish the corresponding thioenamide. However concomitant loss of the TMS group gave the same thioenamide **127** as previously synthesized. As a result, we shifted our focus to probe the role of the imidazole *N*-protecting group on the electrocyclization.

Scheme 37

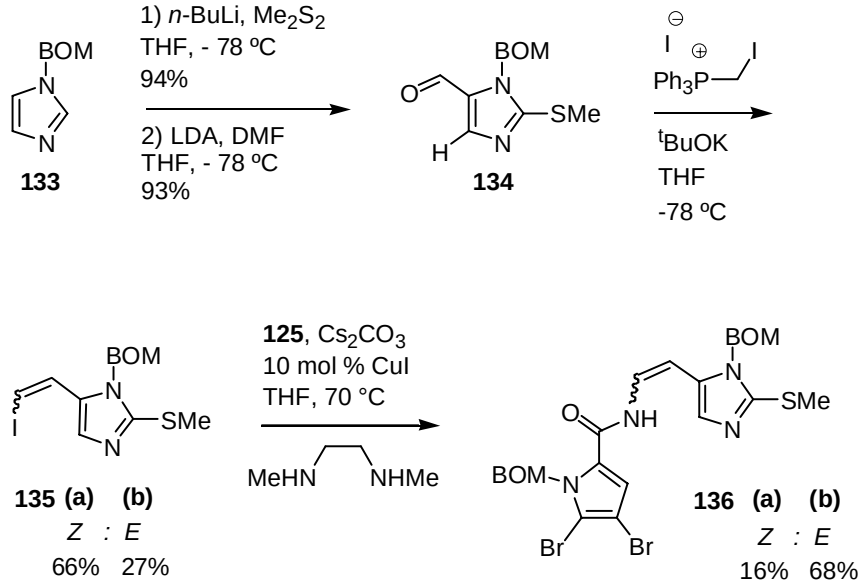


3.3.2 *Construction of a System with the Imidazole N-3 BOM-Regioisomer*

We chose to examine the imidazole N-3 BOM-regiosiomer of **128** where the protecting group is adjacent to the vinyl substituent, perhaps relieving steric strain during the 6π-2-azaelectrocyclization. Thus, BOM-protected imidazole **133**[53] was selectively metallated at C-2 using *n*-butyllithium and converted to the corresponding sulfide with dimethyl disulfide. The 2-methylthioimidazole was then selectively metallated at C-5 with lithium diisopropylamide and the resulting carbanion was formylated to afford aldehyde imidazole **134** in high yield (Scheme 38). Unfortunately, the Stork-Zhao Wittig reaction of aldehyde **134** was found to be non-stereoselective giving a separable mixture of (*Z*)- and (*E*)-vinyl iodides **135a** and **135b** in 66% and 27% yields, respectively.[54] Interestingly, the undesired (*E*)-vinyl iodide **135b** had not been observed in the other BOM-regioisomeric series (Cf. Scheme 33). Moreover, when (*Z*)-vinyl iodide **135a** and pyrrole amide **125** were subjected to the Buchwald copper-catalyzed coupling conditions,

the reaction produced (*E*)-enamide **136b** as the major product (68%) and the requisite (*Z*)-enamide **136a** in only 16% yield. Due to the poor overall yield of the (*Z*)-enamide **136a**, this route was abandoned.

Scheme 38



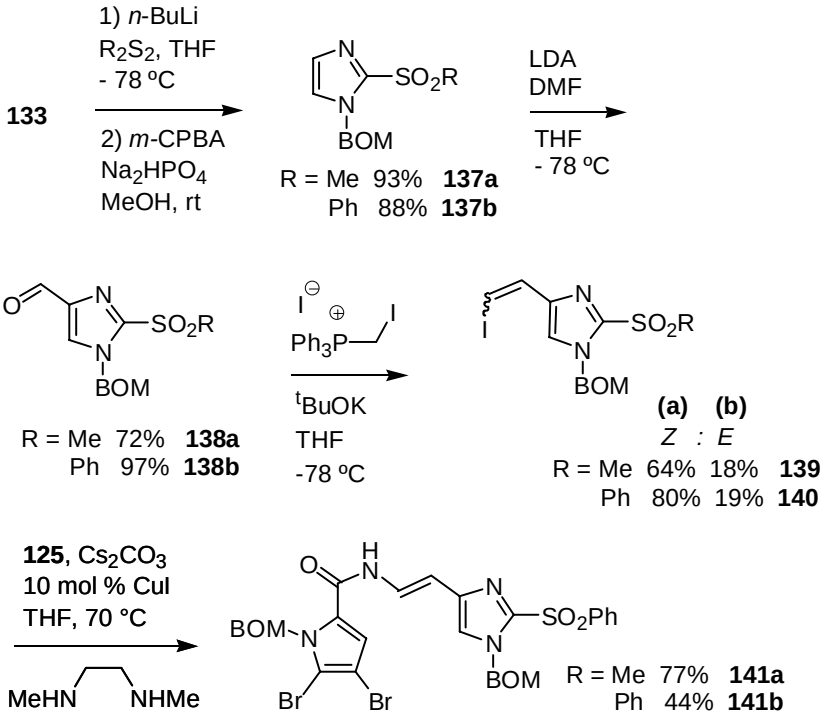
3.3.3 *Construction of a System with the Imidazole C-2 Thio Functionality in a Higher Oxidation State*

Our revised strategy was to keep the imidazole regiochemistry as it was in the original route, but to change the oxidation state of the sulfur functionality (Cf. Scheme 36). The sulfone functionality (as opposed to the sulfide) could be displaced to install the amino functionality of ageladine A before the electrocyclization step if necessary. Thus, metallation of BOM-protected imidazole **133** using *n*-butyllithium and subsequent addition of dimethyl or diphenyl disulfide gave the 2-methylthioimidazole and 2-

phenylthioimidazole, respectively. Both methyl and phenyl sulfides were explored for this route, and gave comparable yields for most steps. Oxidation of the sulfides using *m*-CPBA provided the corresponding sulfones **137a** and **137b** (Scheme 39).

Phillips and coworkers have reported that C-2 imidazole sulfones of type **137** can be selectively metallated at C-4 rather than C-5 using LDA instead of *n*-butyllithium.[55] Thus, lithiation of imidazole sulfones **137a** and **137b** using LDA, followed by addition of DMF, selectively formylated the imidazoles at C-4 to give aldehydes **138a** and **138b**, respectively. It should be noted that freshly prepared LDA was required or poor aldehyde yields usually resulted, with the starting imidazole being mainly recovered. In addition, imidazole aldehydes **138a** and **138b** have the same regiochemistry as aldehyde **109**, but could be synthesized without the aide of the C-5-TMS protecting group using the Phillips C-2-sulfone/LDA protocol (Cf. Scheme 33).

Scheme 39

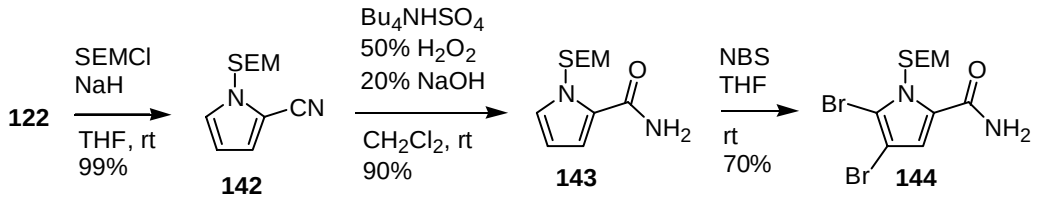


To continue the synthesis, aldehydes **138a** and **138b** were converted to vinyl iodides **139** and **140**, respectively. However, even though the desired (*Z*)-vinyl iodides were the major products in both series, the (*E*)-vinyl iodides were also produced in approximately 20% yield. Unfortunately, copper-catalyzed coupling of (*Z*)-vinyl iodides **139a** and **140a** with pyrrole amide **125** provided only the (*E*)-enamides **141a** and **141b**. These coupling results are puzzling given that this system is nearly identical to (*Z*)-enamide **127**, other than the imidazole C-2 sulfur oxidation state. In light of these coupling results, we decided to investigate the use of other pyrrole or imidazole *N*-protecting groups.

3.3.4 *Construction of a System with a SEM-Protecting Group on the Pyrrole*

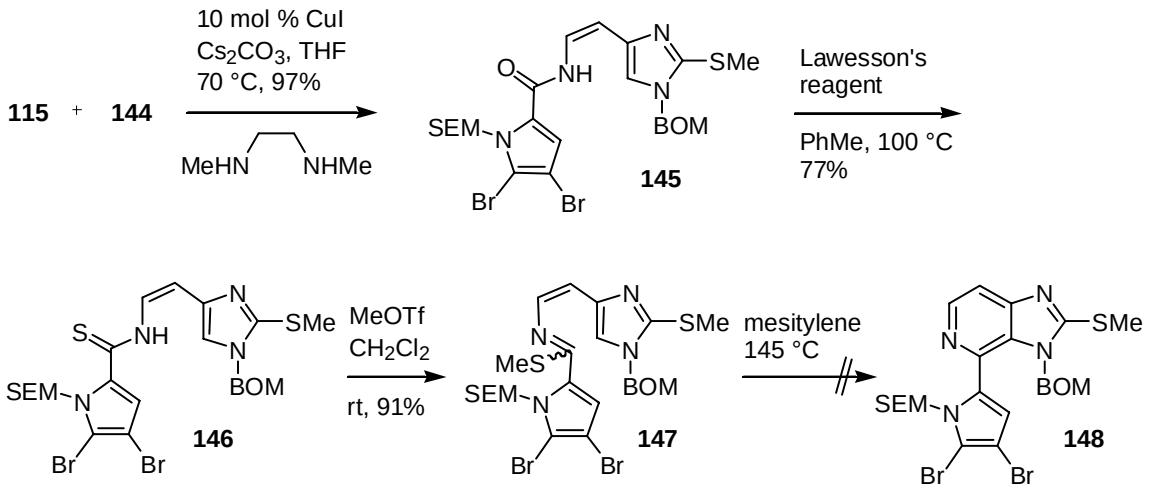
We were interested in seeing if the nature of the pyrrole protecting group played a role in controlling the (*Z*) to (*E*) isomeric ratios in the enamide step of the synthesis. Therefore, we first investigated a (trimethylsilyl)ethoxymethyl (SEM) protecting group in place of BOM. Using the methodology developed for preparing the corresponding *N*-BOM series (Cf. Scheme 35), the required *N*-SEM protected pyrrole amide **144** was synthesized in high yield by SEM protection of 2-cyanopyrrole (**122**) (Scheme 40). Conversion of the nitrile functionality of pyrrole **142** to the corresponding amide **143** was accomplished using basic hydrogen peroxide. Bromination of pyrrole amide **143** with NBS gave the required *N*-SEM-protected 4,5-dibromopyrrole amide **144** in good yield.

Scheme 40



With SEM-protected pyrrole **144** in hand, coupling with (*Z*)-vinyl iodide **115** using the Buchwald conditions provided (*Z*)-enamide **145** stereoselectively in 97% yield (Scheme 41). Following the standard protocol, enamide **145** was converted to the corresponding thioenamide **146** using Lawesson's reagent and treatment with methyl triflate then produced thioimidate **147** in good overall yield. Unfortunately, all attempts at effecting the 6π-2-azatriene electrocyclization of thiomethyl imidate **147** failed to give any of imidazopyridine **148**, with only decomposition being observed. The reason for this resistance of **147** to cyclize is currently unclear.

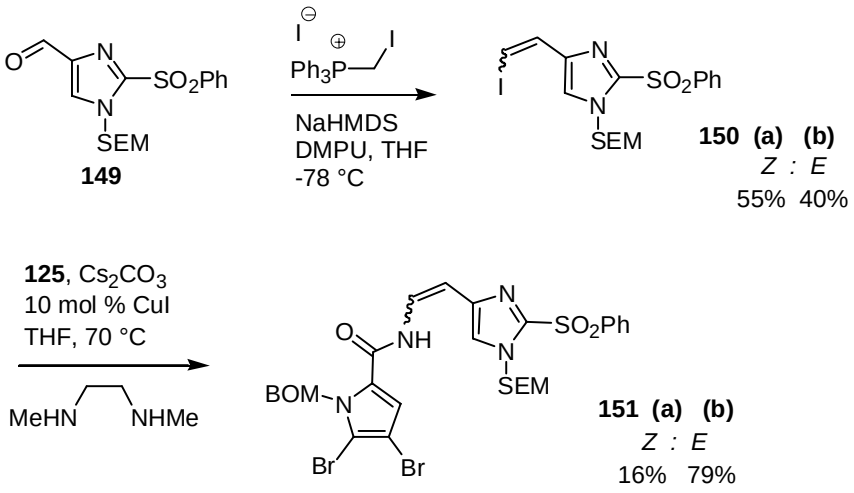
Scheme 41



3.3.5 *Construction of a System with a SEM-Protecting Group on the Imidazole*

Besides replacing the pyrrole protecting group, we also investigated the use of a SEM-protecting group in place of BOM on the imidazole fragment. We began with the known SEM-protected imidazole aldehyde **149**, which contained a phenylsulfone moiety at C-2 (Scheme 42).[55] Unfortunately, conversion of aldehyde **149** to the corresponding vinyl iodide gave a mixture of (*Z*)- and (*E*)-vinyl iodides **150a** and **150b**, respectively, with the (*Z*)-isomer being the major product (55%). Attempts to couple (*Z*)-vinyl iodide **150a** with pyrrole amide **125** led to (*E*)-enamide **151b** as the major component, affording the desired (*Z*)-enamide **151a** in only 16% yield. Since the *N*-SEM-protected imidazole series primarily gave the useless (*E*)-enamide **151b**, we returned to the original BOM-series, which furnished the required (*Z*)-enamide **126** (Cf. Scheme 36).

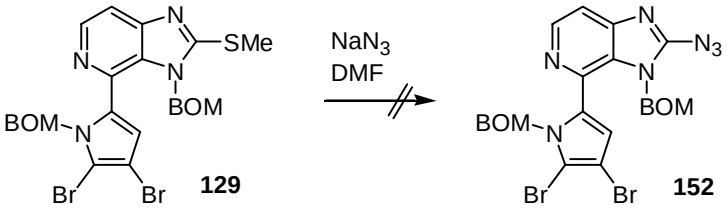
Scheme 42



3.4 Introducing the C-2 Amino Functionality and Completion of the Synthesis

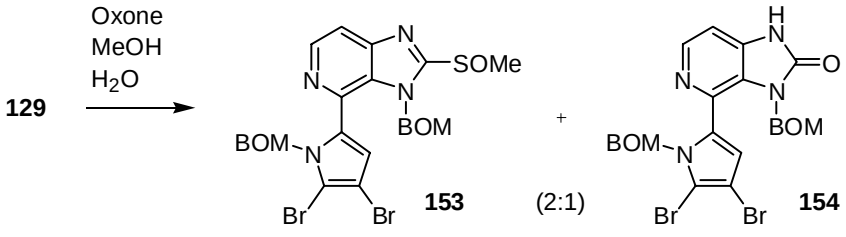
Continuing the synthesis from sulfide imidazopyridine **129**, it was necessary at this point to install the 2-amino moiety of ageladine A (**1**). Attempts to directly displace sulfide **129** with sodium azide failed, with only starting material being recovered (Scheme 43).

Scheme 43



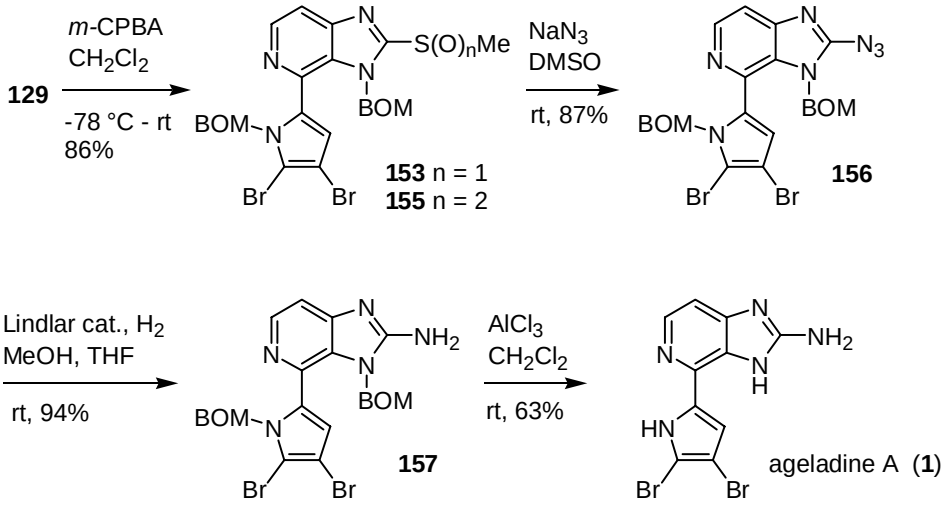
As a result, we explored oxidizing the sulfide to either the sulfoxide or sulfone to facilitate displacement by a nucleophile. Initial attempts to oxidize sulfide **129** using Oxone in a methanol/H_2O solvent system gave an inseparable 2:1 mixture of sulfoxide **153** and the corresponding 2-imidazolone derivative **154**, respectively (Scheme 44).

Scheme 44



The use of hydrogen peroxide with a variety of molybdenum and vanadium catalysts to oxidize sulfide **129** produced a complex mixture of products.[56] However, we were pleased to find that treatment of sulfide **129** with *m*-CPBA produced mainly sulfoxide **153** (76%) along with a small amount of the corresponding sulfone **155** (10%, Scheme 45). The reaction temperature in this step had to be carefully controlled in order to optimize the sulfoxide/sulfone yield. This sulfoxide/sulfone mixture was subsequently treated with sodium azide in DMSO at room temperature to provide 2-azidoimidazopyridine **156** in 87% yield. Inexplicably, when DMF was used as the solvent in this displacement as was done in our previous synthesis,[8] the reaction time was significantly longer and a substantial decrease in product yield was observed. The azide functionality was then hydrogenated to amine **157** in high yield using Lindlar catalyst. It should be noted that attempts at direct displacement of sulfone **155** with methanolic ammonia did not afford the desired amine **157**, but rather gave a complex mixture of products.[57]

Scheme 45



To complete the synthesis, both BOM protecting groups needed to be removed from tricycle **157**. Initial experimentation using refluxing 8 N HCl in ethanol led to complex mixtures that could not be separated. Attempts at using boron tribromide to partially cleave the BOM groups to the corresponding hydroxymethyl compounds, followed by treatment with aqueous potassium carbonate, failed to give the desired deprotected compound.[58] However, it was finally found that subjecting **157** to anhydrous aluminum chloride[59] in methylene chloride at room temperature provided ageladine A (**1**) in 63% yield. This material was identical to the alkaloid that we previously synthesized via our first-generation route.[8]

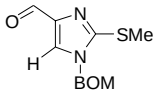
3.5 Conclusion

In conclusion, we have completed a concise, biogenetically-inspired total synthesis of ageladine A (**1**) requiring seven steps from (*Z*)-vinyl iodide **115** and dibromopyrrole amide **125**, with an overall yield of 13%. This second generation synthesis incorporates an effective 6π-2-azatriene electrocyclization to provide the imidazopyridine core of the marine metabolite. Furthermore, a variety of synthetic structural analogues of ageladine A for biological testing should be readily available via this approach.

EXPERIMENTAL SECTION

General Methods

All non-aqueous reactions were carried out under a positive atmosphere of nitrogen or argon in flame-dried glassware unless otherwise noted. Air and moisture sensitive liquid reagents were added via a dry syringe. Anhydrous THF, CH_2Cl_2, diethyl ether, and toluene were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Microwave irradiation reactions were performed on a CEM Discover microwave reactor. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300, CDPX-300, or DRX-400 MHz spectrometers. Chemical shifts of ^1H and ^{13}C NMR spectra were referenced to the solvent peaks: δ_H 3.30 and δ_C 49.0 for CD_3OD. Flash chromatography was performed using Sorbent Technologies silica gel 60 (230-400 mesh). Purification by preparative reverse phase HPLC employed an Agilent 1100 preparative pump/gradient extension instrument equipped with a Hamilton PRP-1 (polystyrene-divinylbenzene) reverse phase column (7 μm particle size, 21.5 mm x 25 cm). The following two solvent systems were used: solvent system A (99.9 % double deionized H_2O and 0.1 % TFA), and solvent system B (99.9 % acetonitrile and 0.1 % TFA). The HPLC gradient for the purification of ageladine A (20 mL/min flow rate) was as follows: 99 to 70 % A from 0 to 5 min and 70 to 60 % A from 5 to 25 min; retention time of **1** was 10.2 min.

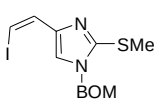


1-Benzyloxymethyl-2-methylsulfanylimidazole-4-carbaldehyde (109). To a solution of 2,4,5-tribromoimidazole (**107**, 7.15 g, 16.83 mmol) in THF (100 mL) was added *n*-BuLi in hexanes (2.5 M, 6.73 mL, 16.83 mmol) at -78 ºC and the reaction mixture was stirred for 10 min. Dimethyl disulfide (1.59 g, 16.83 mmol) was then added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 15 min and then warmed to rt. The mixture was diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated.

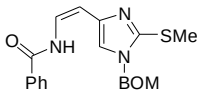
The crude mixture was dissolved in THF (100 mL) and *n*-BuLi in hexanes (2.5 M, 6.73 mL, 16.83 mmol) was added at -78 ºC. After the mixture was stirred for 10 min at -78 ºC, TMSCl (1.83 g, 16.83 mmol) was added slowly. The reaction mixture was stirred at -78 ºC for 20 min, before *n*-BuLi in hexanes (2.5 M, 6.73 mL, 16.83 mmol) was added at -78 ºC. After the mixture was stirred for 10 min at -78 ºC, DMF (3.69 g, 3.92 mL, 50.49 mmol) was added slowly. The reaction mixture was stirred at -78 ºC for 1 h and then warmed to rt. The mixture was diluted with H_2O (50 mL) and was extracted with CH_2Cl_2 (3 x 10 mL).

MeOH (20 mL) and K_2CO_3 (4.65 g, 33.66 mmol) were added to the combined organic extracts, and the reaction mixture was stirred at rt for 3 h. The mixture was diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded aldehyde **109** (3.79 g, 85 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 4.23 (s, 2H), 5.04 (s, 2H), 7.00-7.45 (m, 5H), 7.45 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 148.6,

142.7, 136.7, 129.4, 129.2, 129.1, 128.7, 75.9, 71.6, 16.2; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_2S$, 263.0854; found 263.0863.

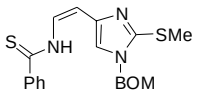


1-Benzyloxymethyl-4-(2-iodovinyl)-2-methylsulfanylimidazole (115). To a solution of $Ph_3PCH_2I_2$ (8.08 g, 15.25 mmol) in THF (50 mL) was added *t*-BuOK (1.71 g, 15.25 mmol). The reaction mixture was stirred at rt for 5 min and cooled to -78 ºC before a solution of aldehyde **109** (2.00 g, 7.62 mmol) in THF (10 mL) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (30 mL) and was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded vinylimidazole **115** (2.74 g, 93 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 4.37 (s, 2H), 5.18 (s, 2H), 6.26 (d, *J* = 8.7 Hz, 1H), 7.18-7.22 (m, 5H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 140.0, 136.7, 133.3, 129.0, 128.7, 128.5, 120.5, 76.7, 75.1, 70.8, 16.7; ESI (+): $[M+H]^+$ calcd for $C_{14}H_{16}N_2OSI$, 387.0028; found 387.0023.

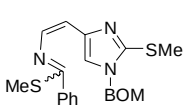


***N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)vinyl]-benzamide (116).** In an oven-dried Schlenk tube was placed (*Z*)-vinyliodide **115** (250 mg, 0.65 mmol), benzamide (94 mg, 0.78 mmol), CuI (12 mg, 0.07 mmol), Cs_2CO_3 (422 mg, 1.29 mmol), *N*,*N*′-dimethylethylenediamine (11 mg, 0.01 mmol) and THF (4 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 15 h. The reaction mixture was then cooled to rt and filtered through a Celite pad,

which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 2/1) affording the coupled (*Z*)-enamide **116** (243 mg, 99 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 4.39 (s, 2H), 5.18 (s, 2H), 5.49 (d, *J* = 8.9 Hz, 1H), 6.86 (s, 1H), 7.07-7.16 (m, 1H), 7.19-7.28 (m, 5H), 7.34-7.44 (m, 3H), 7.91-7.94 (m, 2H), 11.88 (d, *J* = 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 142.9, 139.5, 135.2, 133.2, 130.7, 127.6, 127.5, 127.2, 126.9, 126.4, 121.4, 117.2, 99.2, 73.5, 69.4, 14.8; ESI (+): $[M+H]^+$ calcd for $C_{21}H_{22}N_3O_2S$, 380.1433; found 380.1425.

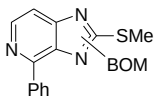


***N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]-thiobenzamide (117).** To a solution of enamide **116** (0.20 g, 0.53 mmol) in PhMe (20 mL) was added Lawesson's reagent (0.13 g, 0.32 mmol). The reaction mixture was heated at 100 ºC for 3.5 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded thioenamide **117** (0.20 g, 95 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 4.40 (s, 2H), 5.18 (s, 2H), 5.77 (d, *J* = 8.9 Hz, 1H), 6.95 (s, 1H), 7.17-7.42 (m, 8H), 7.61-7.68 (m, 1H), 7.92-7.95 (m, 2H), 13.19 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 144.0, 140.7, 138.7, 135.1, 130.2, 127.6, 127.3, 126.9, 126.4, 124.8, 118.4, 104.2, 73.5, 69.5, 14.6; ESI (+): $[M+H]^+$ calcd for $C_{21}H_{22}N_3OS_2$, 396.1204; found 396.1198.

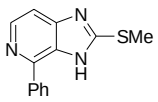


***N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]-thiobenzimidic Acid Methyl Ester (118).** To a solution of thioenamide **117** (150 mg, 0.38 mmol) in CH_2Cl_2 (15 mL) was added MeOTf (68 mg, 0.42 mmol).

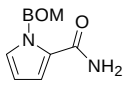
The reaction mixture was stirred at rt for 45 min and then concentrated. The crude reaction mixture was dissolved in CH_2Cl_2 (15 mL) and NaOH (1 N, 20 mL), then extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The reaction cleanly afforded thioimidate **118** (151 mg, 97 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (br s, 3H), 2.55 (s, 3H), 4.44 (s, 2H), 5.29 (s, 2H), 6.03 (br s, 1H), 6.64 (br s, 1H), 7.19-7.50 (m, 10 H) 7.75 (br s, 1H); ESI (+): $[M+H]^+$ calcd for $C_{22}H_{24}N_3OS_2$, 410.1361; found 410.1365.



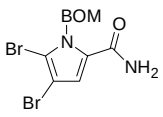
3-Benzyloxymethyl-2-methylsulfanyl-4-phenylimidazopyridine (120). A solution of thioimidate **118** (55 mg, 0.13 mmol) in *p*-xylene (2.5 mL) was subjected to microwave irradiation at 160 ºC for 1 h and then concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded imidazopyridine **120a** (19 mg, 40 %) and BOM-regioisomeric imidazopyridine **120b** (16 mg, 33 %) as clear oils. Imidazopyridine **120a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (s, 3H), 4.45 (s, 2H), 5.46 (s, 2H), 7.14 (d, J = 5.4 Hz, 1H), 7.18-7.28 (m, 5H), 7.36-7.38 (m, 1H), 7.43-7.47 (m, 2H), 8.39 (d, J = 5.4 Hz, 1H), 8.60 (d, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 147.3, 143.3, 141.7, 138.6, 137.5, 136.6, 129.7, 129.6, 129.0, 128.8, 128.7, 128.3, 104.3, 73.1, 71.3, 15.3. Imidazopyridine **120b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (s, 3H), 4.09 (s, 2H), 5.09 (s, 2H), 7.04-7.07 (m, 2H), 7.18-7.21 (m, 3H), 7.40-7.42 (m, 3H), 7.49 (d, J = 5.5 Hz, 1H), 7.53-7.55 (m, 2H), 8.40 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 150.3, 144.2, 142.3, 138.4, 136.9, 131.8, 129.6, 129.4, 129.0, 128.8, 128.4, 127.8, 112.6, 73.6, 71.0, 15.1; ESI (+): $[M+H]^+$ calcd for $C_{21}H_{20}N_3OS$, 362.1327; found 362.1310.



2-Methylsulfanyl-4-phenylimidazopyridine (121). A solution of BOM-protected imidazopyridine **120** (5 mg, 0.01 mmol) in EtOH (2 mL) and 6 N HCl (1.5 mL) was heated at 100 ºC for 1 h and then concentrated. Purification of the residue by preparative TLC (EtOAc) afforded *N*-H imidazopyridine **121** (1.5 mg, 50 %) as a clear oil. ^{1}H NMR (300 MHz, MeOD) δ 2.78 (s, 3H), 7.42 (d, J = 5.7 Hz, 1H), 7.46-7.55 (m, 3H), 8.18-8.21 (m, 2H), 8.23 (d, J = 5.7 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{13}H_{12}N_3S$, 242.0752; found 242.0738.

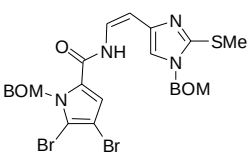


1-Benzyloxymethylpyrrole-2-carboxylic Acid Amide (124). To a solution of nitrile **123** (1.00 g, 4.71 mmol) and Bu_4NHSO_4 (1.60 g, 4.71 mmol) in CH_2Cl_2 (15 mL) was added 50 % H_2O_2 (3 mL), followed by 20 % aq NaOH (3 mL). The reaction mixture was stirred at rt for 3 h, diluted with H_2O (100 mL), and was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded amide **124** (0.99 g, 91 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (s, 2H), 5.64 (s, 2H), 6.07 (dd, J = 3.8, 2.8 Hz, 1H), 6.19 (br s, 2H), 6.66 (dd, J = 3.8, 1.7 Hz, 1H), 6.84 (dd, J = 2.8, 1.7 Hz, 1H), 7.17-7.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 139.1, 130.5, 129.9, 129.6, 127.6, 117.4, 110.6, 78.5, 72.1; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{15}N_2O_2$, 231.1134; found 231.1120.



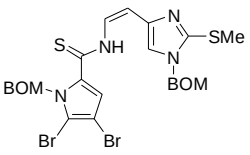
1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid Amide (125). To a solution of pyrrole amide **124** (1.00 g, 4.34 mmol) in THF (50 mL) was added NBS (1.62 g, 9.12 mmol). The reaction mixture was stirred at rt for 30

min and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded dibromopyrrole **125** (1.58 g, 94 %) as a white solid. X-ray crystal structure analysis[60] confirmed the assignment of dibromopyrrole **125** (recrystallized from CH_2Cl_2). mp 129-130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 (s, 2H), 5.82 (s, 2H), 6.71 (s, 1H), 7.19-7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 135.9, 127.4, 126.9, 126.6, 126.5, 116.2, 111.0, 99.3, 74.5, 69.7; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{13}N_2O_2{}^{79}Br_2$, 386.9344; found 386.9381.

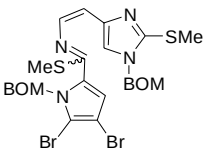


1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid [2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]amide (126). In an oven-dried Schlenk tube was placed imidazole vinyliodide **115** (0.50 g, 1.29 mmol), pyrrole amide **125** (0.55 g, 1.42 mmol), CuI (25 mg, 0.13 mmol), Cs_2CO_3 (0.84 g, 2.59 mmol), *N*,*N*´-dimethylethylenediamine (23 mg, 0.26 mmol) and THF (6 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 17 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 4/1) affording the coupled (*Z*)-enamide **126** (0.77 g, 92 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 4.35 (s, 2H), 4.51 (s, 2H), 5.13 (s, 2H), 5.43 (d, *J* = 8.9 Hz, 1H), 5.91 (s, 2H), 6.81 (s, 1H), 6.83 (s, 1H), 6.93 (dd, *J* = 10.2, 9.0 Hz, 1H), 7.11-7.23 (m, 10H), 11.63 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 144.5, 140.8, 137.9, 136.6, 129.1, 128.8, 128.7, 128.6, 128.4, 128.1, 128.0, 121.9, 118.8, 116.3, 112.5, 100.7, 100.6, 75.9, 75.0,

71.2, 70.9, 16.4; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_3S^{79}Br_2$, 645.0171; found 645.0167.

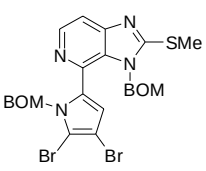


1-Benzyloxymethyl-4,5-dibromopyrrole-2-carbothioic Acid [2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]amide (127). To a solution of enamide **126** (0.60 g, 0.93 mmol) in PhMe (30 mL) was added Lawesson's reagent (0.56 g, 1.39 mmol). The reaction mixture was heated at 100 ºC for 2 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded thioenamide **127** (0.51 g, 82 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 4.37 (s, 2H), 4.41 (s, 2H), 5.13 (s, 2H), 5.71 (d, *J* = 8.8 Hz, 1H), 6.13 (s, 2H), 6.64 (s, 1H), 6.90 (s, 1H), 7.08-7.11 (m, 5H), 7.18-7.26 (m, 5H), 7.49 (t, *J* = 9.7 Hz, 1H), 13.00 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 145.8, 140.0, 137.6, 137.5, 136.6, 129.1, 128.8, 128.4, 128.2, 128.0, 124.8, 120.0, 114.5, 113.3, 105.7, 101.0, 75.5, 75.0, 71.2, 71.1, 16.0; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_2S_2{}^{79}Br_2$, 660.9942; found 660.9994.

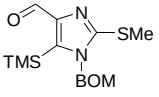


1-Benzyloxymethyl-*N*-[2-(1-benzyloxymethyl-2-methylsulfanyl-imidazol-4-yl)-vinyl]4,5-dibromopyrrole-2-carboximidothioic Acid Methyl Ester (128). To a solution of thioenamide **127** (100 mg, 0.15 mmol) in CH_2Cl_2 (15 mL) was added MeOTf (27 mg, 0.17 mmol). The reaction mixture was stirred at rt for 2 h and concentrated. The crude reaction mixture was dissolved in CH_2Cl_2 (5 mL) and NaOH (1 N, 10 mL), then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the

residue by column chromatography (hexanes/EtOAc, 3/1) afforded thioimidate **128** (95 mg, 93 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (br s, 3H), 2.56 (s, 3H), 4.30 (s, 2H), 4.39 (br s, 2H), 5.21-5.70 (m, 4H), 6.16 (br s, 1H), 6.49 (br s, 1H), 7.14-7.23 (m, 11H), 7.42 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 138.9, 137.2, 136.8, 133.0, 129.0, 128.8, 128.6, 128.3, 128.0, 123.1, 118.3, 101.3, 76.0, 75.0, 70.9, 70.7, 17.0; ESI (+): $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_2S_2{}^{79}Br_2$, 675.0099; found 675.0141.

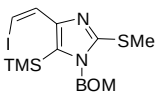


3-Benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)-2-methylsulfanyl-imidazopyridine (129). A solution of thioimidate **128** (75 mg, 0.11 mmol) in mesitylene (30 mL) was heated at 145 ºC for 16 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded pyridine **129** (31 mg, 44 %, 51 % brsm) as a clear oil, along with starting thioimidate **128** (9 mg, 12 %) and isomerized (*E*)-thioimidate **130** (20 mg, 27 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 3H), 4.30 (s, 2H), 4.42 (s, 2H), 5.14 (s, 2H), 5.41 (s, 2H), 6.65 (s, 1H), 6.92-6.96 (m, 2H), 7.19-7.21 (m, 3H), 7.27-7.37 (m, 5H), 7.61 (d, J = 5.4 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 150.5, 142.3, 137.2, 136.7, 133.9, 133.5, 130.5, 129.0, 128.7, 128.6, 128.2, 128.1, 127.7, 115.1, 113.6, 107.1, 100.4, 75.5, 73.3, 71.5, 70.6, 15.1; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_2S^{79}Br_2$, 627.0065; found 627.0047.



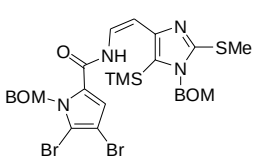
1-Benzyloxymethyl-2-methylsulfanyl-5-trimethylsilanylimidazole-4-carbaldehyde (114). To a solution of imidazole **112** (150 mg, 0.38 mmol) in THF (3 mL) at -78 ºC was slowly added *n*-BuLi in hexanes (2.3 M, 183 μL, 0.42

mmol). After the mixture was stirred for 10 min at -78 ºC, TMSCl (46 mg, 53 μL, 0.42 mmol) was added slowly. The reaction mixture was stirred at -78 ºC for 20 min, before *n*-BuLi in hexanes (2.3 M, 183 μL, 0.42 mmol) was added at -78 ºC. After the mixture was stirred for 10 min at -78 ºC, DMF (70 mg, 74 μL, 0.96 mmol) was added slowly. The reaction mixture was stirred at -78 ºC for 1 h and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded aldehyde **114** (96 mg, 75 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32 (s, 9H), 2.63 (s, 3H), 4.41 (s, 2H), 5.31 (s, 2H), 7.18-7.25 (m, 5H), 9.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 150.3, 149.8, 142.0, 136.2, 128.4, 128.0, 127.6, 74.3, 70.5, 15.8, 0.00.

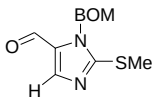


1-Benzyloxymethyl-4-(2-iodo-vinyl)2-methylsulfanyl-5-trimethylsilanylimidazole (131). To a solution of $Ph_3PCH_2I_2$ (198 mg, 0.37 mmol) in THF (7 mL) was added *t*-BuOK (37 mg, 0.33 mmol). The reaction mixture was stirred at rt for 5 min and cooled to -78 ºC before a solution of aldehyde **114** (50 mg, 0.15 mmol) in THF (1 mL) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded vinylimidazole **131** (67 mg, 99 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 9H), 2.69 (s, 3H), 4.39 (s, 2H), 5.26 (s, 2H), 6.43 (d, J = 8.6 Hz, 1H), 7.20-7.30 (m, 5H) 7.29 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 147.3, 147.1, 136.2, 131.6, 130.8, 127.8, 127.4, 127.2, 77.0, 73.7, 69.6, 15.6, 0.00.



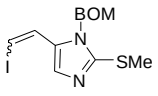
1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid [2-(1-Benzyloxymethyl-2-methylsulfanyl-5-trimethylsilanylimidazol-4-yl)vinyl]amide (132). In an oven-dried Schlenk tube was placed imidazole vinyliodide **131** (50 mg, 0.11 mmol), pyrrole amide **125** (47 mg, 0.12 mmol), CuI (2 mg, 0.01 mmol), Cs_2CO_3 (71 mg, 0.22 mmol), *N*,*N*′-dimethylethylenediamine (2 mg, 0.02 mmol) and THF (3 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 19 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 4/1) affording the coupled (*Z*)-enamide **132** (73 mg, 94 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 9H), 2.63 (s, 3H), 4.39 (s, 2H), 4.53 (s, 2H), 5.29 (s, 2H), 5.66 (d, *J* = 9.1 Hz, 1H), 5.94 (s, 2H), 6.84 (s, 1H), 6.97 (dd, *J* = 10.2, 9.2 Hz, 1H), 7.13-7.26 (m, 10H), 11.91 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 148.4, 146.6, 136.7, 135.9, 128.4, 127.7, 127.6, 127.5, 127.3, 127.0, 126.9, 126.8, 120.9, 115.1, 111.2, 100.7, 99.4, 74.7, 73.5, 70.0, 69.5.



3-Benzyloxymethyl-2-methylsulfanylimidazole-4-carbaldehyde (134). To a solution of imidazole **133** (1.40 g, 7.44 mmol) in THF (25 mL) was added *n*-BuLi in hexanes (2.4 M, 3.72 mL, 8.93 mmol) at -78 ºC and the reaction mixture was stirred for 15 min. Dimethyl disulfide (0.70 g, 7.44 mmol) was then added dropwise

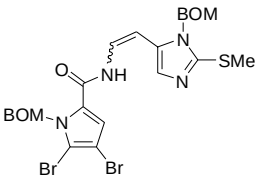
at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded the desired sulfide (1.74 g, 94 %) as a white solid.

To a solution of sulfide (0.10 g, 0.43 mmol) in THF (8 mL) was added LDA (1.9 M, 0.34 mL, 0.64 mmol) at -78 ºC and the reaction mixture was stirred for 15 min. DMF (0.17 mL, 2.13 mmol) was then added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded aldehyde **134** (0.10 g, 93 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 4.51 (s, 2H), 5.70 (s, 2H), 7.20-7.23 (m, 5H), 7.63 (s, 1H), 9.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 156.0, 144.6, 137.3, 133.4, 128.8, 128.3, 128.1, 74.3, 71.5, 15.0.

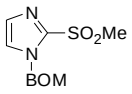


1-Benzyloxymethyl-5-(2-iodovinyl)2-methylsulfanylimidazole (135). To a solution of $Ph_3PCH_2I_2$ (202 mg, 0.38 mmol) in THF (6 mL) was added *tert*-BuOK (38 mg, 0.34 mmol). The reaction mixture was stirred at rt for 5 min and then cooled to -78 ºC before a solution of aldehyde **134** (40 mg, 0.15 mmol) in THF (1 mL) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification

of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded (*Z*)-vinylimidazole **135a** (39 mg, 66 %) as a yellow oil, along with (*E*)-vinylimidazole **135b** (16 mg, 27 %). (*Z*)-vinylimidazole **135a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H), 4.33 (s, 2H), 5.20 (s, 2H), 6.38 (d, *J* = 8.9 Hz, 1H), 7.11-7.20 (m, 6H), 7.94 (s, 1H). (*E*)-vinylimidazole **135b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H) 4.45 (s, 2H), 5.25 (s, 2H), 6.67 (d, *J* = 15.0 Hz, 1H), 7.09 (s, 1H), 7.19-7.32 (m, 6H).

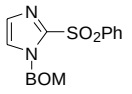


1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid [2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)vinyl]amide (136). In an oven-dried Schlenk tube was placed (*Z*)-vinyliodide **135a** (15 mg, 0.04 mmol), pyrrole amide **125** (15 mg, 0.04 mmol), CuI (7 mg, 0.004 mmol), Cs_2CO_3 (25 mg, 0.08 mmol), *N*,*N*′-dimethylethylenediamine (1 mg, 0.01 mmol) and THF (3 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 16 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 2/1) affording the coupled (*Z*)-enamide **136a** (2 mg, 16 %) as a white solid, along with (*E*)-enamide **136b** (17 mg, 68 %) and starting vinyliodide **135a** (2 mg, 13 %). (*Z*)-enamide **136a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 4.47 (s, 2H), 4.55 (s, 2H), 5.26 (s, 2H), 5.57 (d, *J* = 9.4 Hz, 1H), 5.87 (s, 2H), 6.61 (s, 1H), 7.03-7.09 (m, 2H), 7.17-7.29 (m, 10H), 8.00 (d, *J* = 11.0 Hz, 1H). (*E*)-enamide **136b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (s, 3H), 4.40 (s, 2H), 4.55 (s, 2H), 5.24 (s, 2H), 5.82 (s, 2H), 5.92 (d, *J* = 14.5 Hz, 1H), 6.76 (s, 1H), 7.08 (s, 1H), 7.17-7.27 (m, 10H), 7.37 (dd, *J* = 14.4, 10.6 Hz, 1H), 8.36 (d, *J* = 10.6 Hz, 1H).



1-Benzyloxymethyl-2-methanesulfonylimidazole (137a). To a solution of imidazole **133** (1.40 g, 7.44 mmol) in THF (25 mL) was added *n*-BuLi in hexanes (2.4 M, 3.72 mL, 8.93 mmol) at -78 ºC and the reaction mixture was stirred for 15 min. Dimethyl disulfide (0.70 g, 7.44 mmol) was then added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded the corresponding sulfide (1.74 g, 94 %) as a yellow solid.

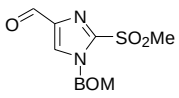
To a solution of sulfide (1.00 g, 4.27 mmol) in MeOH (25 mL) was added *m*CPBA (2.06 g, 8.96 mmol) followed by Na_2HPO_4 (3.03 g, 21.34 mmol). The reaction mixture was stirred at rt for 19 h, and then concentrated. The residue was diluted with H_2O (30 mL) and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded sulfone **137a** (1.12 g, 99 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (s, 3H), 4.47 (s, 2H), 5.63 (s, 2H), 7.09 (s, 1H), 7.12 (s, 1H), 7.18-7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 136.4, 129.6, 129.1, 128.8, 128.4, 124.7, 76.5, 71.7, 43.7.



2-Benzenesulfonyl-1-benzyloxymethylimidazole (137b). To a solution of imidazole **133** (0.20 g, 1.06 mmol) in THF (5 mL) was added *n*-BuLi in hexanes (2.4 M, 0.53 mL, 1.28 mmol) at -78 ºC and the reaction mixture was stirred for 15 min. Diphenyl disulfide (0.23 g, 1.06 mmol) was then added dropwise at -78 ºC. The

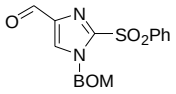
reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded the corresponding sulfide (0.28 g, 89 %) as a yellow solid.

To a solution of sulfide (0.12 g, 0.41 mmol) in MeOH (10 mL) was added *m*CPBA (0.15 g, 0.85 mmol) followed by Na_2HPO_4 (0.29 g, 2.02 mmol). The reaction mixture was stirred at rt for 17 h, and then concentrated. The residue was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded sulfone **137b** (0.13 g, 99 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (s, 2H), 5.69 (s, 2H), 7.07 (s, 1H), 7.09-7.11 (m, 3H), 7.20-7.24 (m, 3H), 7.34-7.38 (m, 2H), 7.46-7.50 (m, 1H), 7.94-7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 140.1, 136.4, 134.5, 130.4, 129.6, 129.0, 128.8, 128.7, 128.3, 124.9, 76.6, 71.4.

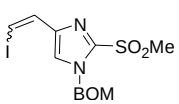


1-Benzyloxymethyl-2-methanesulfonylimidazole-4-carbaldehyde (138a). To a solution of imidazole **137a** (0.25 g, 0.94 mmol) in THF (10 mL) was added freshly prepared LDA (1.7 M, 1.00 mL, 1.69 mmol) at -78 ºC and the reaction mixture was stirred for 15 min. DMF (0.37 mL, 4.69 mmol) was then added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated.

Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded aldehyde **138a** (0.20 g, 72 %) as a yellow oil, along with starting imidazole **137a** (48 mg, 19 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 4.56 (s, 2H), 6.07 (s, 2H), 7.17-7.20 (m, 5H), 7.68 (s, 1H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 149.2, 141.0, 136.8, 133.2, 128.9, 128.6, 128.2, 75.4, 72.3, 43.5.

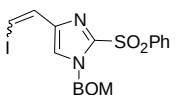


2-Benzenesulfonyl-1-benzyloxymethylimidazole-4-carbaldehyde (138b). To a solution of imidazole **137a** (40 mg, 0.12 mmol) in THF (5 mL) was added LDA (1.9 M, 0.08 mL, 0.15 mmol) at -78 ºC and the reaction mixture was stirred for 15 min. DMF (0.05 mL, 0.61 mmol) was then added dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded aldehyde **138b** (42 mg, 97 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2H), 6.20 (s, 2H), 7.05-7.07 (m, 2H), 7.17-7.20 (m, 3H), 7.37-7.41 (s, 2H), 7.53-7.57 (m, 1H), 7.66 (s, 1H), 7.99-8.01 (m, 2H), 9.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 150.0, 141.8, 138.9, 136.8, 135.1, 133.0, 129.7, 129.5, 128.8, 128.5, 128.1, 75.4, 72.1.



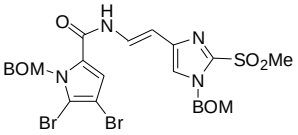
1-Benzyloxymethyl-4-(2-iodovinyl)2-methanesulfonylimidazole (139). To a solution of $Ph_3PCH_2I_2$ (72 mg, 0.14 mmol) in THF (3 mL) was added *tert*-BuOK (14 mg, 0.12 mmol). The reaction mixture was stirred at rt for 5 min and cooled to -78 ºC before a solution of aldehyde **138a** (20 mg, 0.07 mmol) in THF (1 mL)

was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded (*Z*)-vinylimidazole **139a** (18 mg, 64 %) as a yellow oil, along with (*E*)-vinylimidazole **139b** (5 mg, 18 %). (*Z*)-vinylimidazole **139a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 3H), 4.46 (s, 2H), 5.65 (s, 2H), 6.73 (d, *J* = 9.1 Hz, 1H), 7.11-7.19 (m, 5H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 136.7, 133.9, 129.5, 129.0, 128.7, 128.4, 125.8, 85.5, 74.2, 71.7, 43.4. (*E*)-vinylimidazole **139b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 (s, 3H), 4.58 (s, 2H), 5.69 (s, 2H), 6.95 (d, *J* = 15.1 Hz, 1H), 7.15-7.30 (m, 7H).

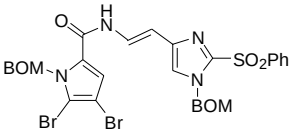


2-Benzenesulfonyl-1-benzyloxymethyl-4-(2-iodovinyl)imidazole (140). To a solution of $Ph_3PCH_2I_2$ (89 mg, 0.17 mmol) in THF (3 mL) was added *tert*-BuOK (17 mg, 0.15 mmol). The reaction mixture was stirred at rt for 5 min and cooled to -78 ºC before a solution of aldehyde **138b** (30 mg, 0.09 mmol) in THF (1 mL) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded (*Z*)-vinylimidazole **140a** (32 mg, 80 %) as a yellow oil, along with (*E*)-vinylimidazole **140b** (8 mg, 19 %). (*Z*)-vinylimidazole **140a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (s, 2H), 5.71 (s, 2H), 6.69 (d, *J* = 9.1 Hz, 1H), 7.07-7.11 (m, 2H), 7.15-7.22 (m, 4H), 7.36 (m, 2H),

7.47-7.51 (m, 1H), 7.88-7.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 139.8, 136.7, 134.7, 134.0, 130.4, 129.7, 129.0, 128.6, 128.3, 125.8, 85.4, 74.1, 71.4. (*E*)-vinylimidazole **140b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (s, 2H), 5.67 (s, 2H), 6.82 (d, *J* = 15.1 Hz, 1H), 7.15-7.22 (m, 6H), 7.37-7.51 (m, 3H), 7.87-7.90 (m, 3H).



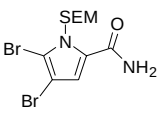
1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid [2-(1-Benzyloxymethyl-2-methanesulfonylimidazol-4-yl)-vinyl]amide (141a). In an oven-dried Schlenk tube was placed (*Z*)-vinyliodide **139a** (30 mg, 0.07 mmol), pyrrole amide **125** (34 mg, 0.09 mmol), CuI (2 mg, 0.001 mmol), Cs_2CO_3 (47 mg, 0.14 mmol), *N*,*N*′-dimethylethylenediamine (1 mg, 0.01 mmol) and THF (3 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 15 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 1/1) affording the coupled (*E*)-enamide **141a** (37 mg, 77 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (s, 3H), 4.51 (s, 2H), 4.55 (s, 2H), 5.64 (s, 2H), 5.82 (s, 2H), 5.94 (d, *J* = 14.5 Hz, 1H), 6.82 (s, 1H), 7.13 (s, 1H), 7.18-7.25 (m, 10H), 7.48 (dd, *J* = 14.4, 10.8 Hz, 1H), 8.38 (d, *J* = 10.8 Hz, 1H).



1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid [2-(2-Benzenesulfonyl-1-benzyloxymethylimidazol-4-yl)vinyl]-amide (141b). In an oven-dried Schlenk tube was placed (*Z*)-vinyliodide **140a** (30 mg, 0.06 mmol), pyrrole amide **125** (29 mg, 0.08 mmol), CuI (1 mg, 0.001 mmol), Cs_2CO_3 (41 mg, 0.13 mmol), *N*,*N*′-dimethylethylenediamine (1 mg, 0.01 mmol) and THF (3 mL).

The tube was flushed with nitrogen, sealed and heated at 70 ºC for 15 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 1/1) affording the coupled (*E*)-enamide **141b** (20 mg, 44 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (s, 2H), 4.52 (s, 2H), 5.69 (s, 2H), 5.78 (s, 2H), 5.96 (d, *J* = 14.5 Hz, 1H), 6.81 (s, 1H), 7.12-7.25 (m, 11H), 7.38-7.45 (m, 2H), 7.48-7.53 (m, 2H), 7.95-7.97 (m, 2H), 8.51-8.58 (m, 1H).

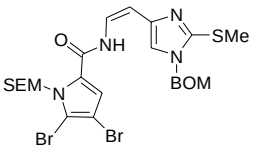
1-(2-Trimethylsilanyl-ethoxymethyl)pyrrole-2-carbonitrile (142). To a solution of 2-cyanopyrrole (**122**, 195 mg, 180 μL, 2.11 mmol) in THF (10 mL) at 0 ºC was added NaH (60 % in mineral oil, 102 mg, 2.54 mmol), followed by SEMCl (423 mg, 450 μL, 2.54 mmol). The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was then diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded SEM-protected pyrrole **142** (466 mg, 99 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.93 (t, *J* = 8.1 Hz, 2H), 3.54 (t, *J* = 8.1 Hz, 2H), 5.36 (s, 2H), 6.25 (dd, *J* = 3.8, 2.8 Hz, 1H), 6.85 (dd, *J* = 3.8, 1.5 Hz, 1H), 7.01 (dd, *J* = 2.8, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.3, 122.3, 114.8, 111.8, 105.6, 78.4, 68.0, 19.1, 0.00.



4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)pyrrole-2-carboxylic Acid Amide (144). To a solution of nitrile **142** (400 mg, 1.80 mmol) and Bu_4NHSO_4 (611 mg, 1.80 mmol) in CH_2Cl_2 (8 mL) was added 50 % H_2O_2 (2 mL),

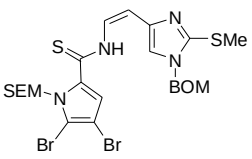
followed by 20 % aq NaOH (2 mL). The reaction mixture was stirred at rt for 2 h, diluted with H_2O (15 mL), and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded amide **143** (390 mg, 90 %) as a white solid.

To a solution of pyrrole amide **143** (350 mg, 1.46 mmol) in THF (15 mL) was added NBS (544 mg, 3.06 mmol). The reaction mixture was stirred at rt for 30 min and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded dibromopyrrole **144** (402 mg, 69 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.93 (t, J = 8.3 Hz, 2H), 3.65 (t, J = 8.3 Hz, 2H), 5.77 (s, 2H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 129.5, 118.9, 113.0, 101.6, 76.6, 67.7, 19.3, 0.00.

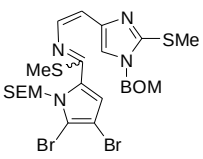


4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)pyrrole-2-carboxylic Acid [2-(1-Benzyloxymethyl-2-methylsulfanyl-imidazol-4-yl)vinyl]amide (145). In an oven-dried Schlenk tube was placed imidazole vinyliodide **115** (100 mg, 0.26 mmol), pyrrole amide **144** (113 mg, 0.29 mmol), CuI (5 mg, 0.03 mmol), Cs_2CO_3 (169 mg, 0.52 mmol), *N*,*N*′-dimethylethylenediamine (5 mg, 0.05 mmol) and THF (5 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 14 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 4/1) affording the coupled (*Z*)-enamide **145** (165 mg, 97 %) as a white solid. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.95 (t, *J* = 8.1 Hz, 2H), 2.78 (s, 3H), 3.66 (t, *J* = 8.1 Hz, 2H), 4.53 (s, 2H), 5.32 (s, 2H), 5.58 (d, *J* = 8.9 Hz, 1H), 5.96 (s, 2H), 6.98 (s, 1H), 7.04 (s, 1H), 7.08-7.11 (m, 1H), 7.33-7.40 (m, 5H), 11.83 (d, *J* = 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 145.5, 141.8, 137.7, 130.0, 129.7, 129.3, 123.0, 119.6, 117.2, 113.4, 101.4, 101.3, 76.4, 75.9, 71.9, 67.5, 19.2, 17.3, 0.00.

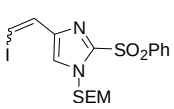


4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)pyrrole-2-carbothioic Acid [2-(1-Benzyloxymethyl-2-methylsulfanyl-imidazol-4-yl)-vinyl]amide (146). To a solution of enamide **145** (100 mg, 0.15 mmol) in PhMe (5 mL) was added Lawesson's reagent (62 mg, 0.15 mmol). The reaction mixture was heated at 100 ºC for 2 h and then concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded thioenamide **146** (79 g, 77 %) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.94 (t, *J* =8.1 Hz, 2H), 2.74 (s, 3H), 3.61 (t, *J* = 8.1 Hz, 2H), 4.59 (s, 2H), 5.36 (s, 2H), 5.92 (d, *J* = 8.8 Hz, 1H), 6.24 (s, 2H), 6.90 (s, 1H), 7.12 (s, 1H), 7.40-7.48 (m, 5H), 7.70 (t, *J* = 9.4 Hz, 1H), 13.32 (d, *J* = 9.8 Hz, 1H).

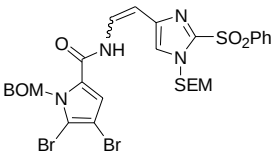


***N*-[2-(1-Benzyloxymethyl-2-methylsulfanylimidazol-4-yl)-vinyl]-4,5-dibromo-1-(2-trimethylsilanyl-ethoxymethyl)pyrrole-2-carboximidothioic Acid Methyl Ester (147).** To a solution of thioenamide **146** (75 mg, 0.11 mmol) in CH_2Cl_2 (6 mL) was added MeOTf (20 mg, 14 μL, 0.12 mmol). The reaction mixture was stirred at rt for 2 h and concentrated. The crude reaction mixture was dissolved in CH_2Cl_2 (5 mL) and NaOH (1 N, 10 mL), then

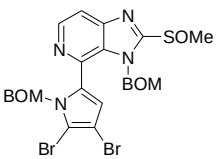
extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded thioimidate **147** (69 mg, 91 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.87 (t, *J*= 8.3 Hz, 2H), 2.58 (br s, 3H), 2.69 (s, 3H), 3.43 (t, *J* = 8.3 Hz, 2H), 4.57 (s, 2H), 5.23 (br s, 1H), 5.40 (s, 2H), 6.21 (br s, 1H), 6.56 (br s, 1H), 7.32-7.38 (m, 5H), 7.82 (br s, 1H).



2-Benzenesulfonyl-4-(2-iodovinyl)1-(2-trimethylsilanylethoxymethyl)-imidazole (150). To a solution of $Ph_3PCH_2I_2$ (122 mg, 0.23 mmol) in THF (2 mL) was added NaHMDS (1.8 M, 0.13 mL, 0.23 mmol). The reaction mixture was stirred at rt for 5 min and before adding DMPU (2 mL). The reaction mixture was cooled to -78 ºC, and then a solution of aldehyde **149** (70 mg, 0.19 mmol) in THF (1 mL) was added slowly. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to rt. The mixture was diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded (*Z*)-vinylimidazole **150a** (53 mg, 55 %) as a yellow oil, along with (*E*)-vinylimidazole **150b** (< 40 %) which could not be obtained cleanly. (*Z*)-vinylimidazole **150a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.85-0.91 (m, 2H), 3.57-3.62 (m, 2H), 5.79 (s, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.57-7.62 (m, 2H), 7.67-7.69 (m, 1H), 8.07-8.10 (m, 3H).

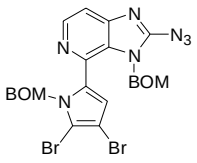


1-Benzyloxymethyl-4,5-dibromopyrrole-2-carboxylic Acid {2-[2-Benzenesulfonyl-1-(2-trimethylsilanylethoxymethyl)-imidazol-4-yl]vinyl}amide (151). In an oven-dried Schlenk tube was placed (*Z*)-vinyliodide **150a** (25 mg, 0.05 mmol), pyrrole amide **125** (20 mg, 0.05 mmol), CuI (1 mg, 0.005 mmol), Cs_2CO_3 (33 mg, 0.10 mmol), *N*,*N*′-dimethylethylenediamine (1 mg, 0.01 mmol) and THF (3 mL). The tube was flushed with nitrogen, sealed and heated at 70 ºC for 14 h. The reaction mixture was then cooled to rt and filtered through a Celite pad, which was washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (hexanes/EtOAc, 1/1) affording the coupled (*Z*)-enamide **151a** (6 mg, 16 %) as a white solid, along with (*E*)-enamide **151b** (30 mg, 79 %). (*Z*)-enamide **151a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.87-0.92 (m, 2H), 3.61-3.67 (m, 2H), 4.59 (s, 2H), 5.68 (d, *J* = 9.5 Hz, 1H), 5.75 (s, 2H), 5.91 (s, 2H), 6.68 (s, 1H), 7.20 (s, 1H), 7.24-7.34 (m, 6H), 7.56-7.61 (m, 2H), 7.66-7.68 (m, 1H), 8.08-8.15 (m, 3H). (*E*)-enamide **151b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.85-0.91 (m, 2H), 3.55-3.60 (m, 2H), 4.66 (s, 2H), 5.72 (s, 2H), 5.93 (s, 2H), 6.10 (d, *J* = 14.6 Hz, 1H), 6.91 (s, 1H), 7.25 (s, 1H), 7.30-7.35 (m, 5H), 7.52-7.60 (m, 3H), 7.63-7.66 (m, 1H), 8.05-8.08 (m, 2H), 8.49 (d, *J* = 10.8 Hz, 1H).



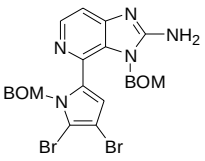
3-Benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)-2-methanesulfinyl-imidazopyridine (153). To a solution of sulfide **129** (40 mg, 0.06 mmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (29 mg, 0.13 mmol, dissolved in 1 mL of CH_2Cl_2) at -78 ºC. The reaction mixture was stirred at -78 ºC for 15 min, 0 ºC for 1 h, and then at rt for 20 min. The reaction mixture was

diluted with saturated Na_2SO_3 (15 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 1/1) afforded sulfoxide **153** (31 mg, 76 %) as a clear oil, along with the corresponding sulfone **155** (4 mg, 10 %). Sulfoxide **153**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 4.24 (s, 2H), 4.35 (s, 2H), 5.36-5.37 (m, 2H), 5.46-5.58 (m, 2H), 6.58 (s, 1H), 6.84-6.87 (m, 2H), 7.09-7.11 (m, 3H), 7.14-7.19 (m, 2H), 7.22-7.25 (m, 3H), 7.66 (d, *J* = 5.5 Hz, 1H), 8.47 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 148.7, 142.7, 137.0, 136.6, 136.3, 132.7, 129.8, 129.0, 128.7, 128.3, 128.2, 127.8, 127.7, 115.9, 115.6, 108.0, 100.6, 75.4, 73.4, 71.8, 70.8, 40.8; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_3S^{79}Br_2$, 643.0014; found 642.9984. Sulfone **155**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.25 (s, 2H), 4.38 (s, 2H), 5.32 (s, 2H), 5.57 (s, 2H), 6.60 (s, 1H), 6.85-6.87 (m, 2H), 7.09-7.11 (m, 3H), 7.17-7.26 (m, 5H), 7.68 (d, *J* = 5.3 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H).

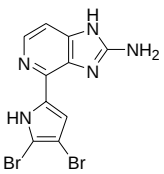


2-Azido-3-benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromo-pyrrol-2-yl)imidazo-pyridine (156). To a mixture of sulfoxide **153** (22 mg, 0.02 mmol) and sulfone **155** (3 mg, 3.0 μmol) in DMSO (0.5 mL) was added sodium azide (13 mg, 0.19 mmol). The reaction mixture was stirred at rt for 6 h, then directly purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **156** (21 mg, 87 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (s, 2H), 4.31 (s, 2H), 4.97 (s, 2H), 5.34 (s, 2H), 6.58 (s, 1H), 6.82-6.85 (m, 2H), 7.09-7.15 (m, 5H), 7.19-7.25 (m, 3H), 7.50 (d, *J* = 5.5 Hz, 1H), 8.41 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 149.1, 142.8, 137.2, 136.7, 134.7, 131.5, 129.9, 129.0, 128.7, 128.6,

128.2, 127.9, 127.7, 115.3, 113.6, 107.4, 100.3, 75.5, 72.3, 71.7, 70.5; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{22}N_7O_2{}^{79}Br_2$, 622.0202; found 622.0239.



3-Benzyloxymethyl-4-(1-benzyloxymethyl-4,5-dibromopyrrol-2-yl)-imidazopyridin-2-ylamine (157). A solution of azide **156** (17 mg, 0.03 mmol) in MeOH (1 mL) and THF (1 mL) was reduced with Lindlar catalyst (4 mg) at rt under one atmosphere of H_2 for 17 h. The mixture was then filtered through a Celite pad, which was washed with MeOH. The filtrate was concentrated to afford amine **157** (16 mg, 94 %) as a yellow solid sufficiently pure for use in the next step. ^{1}H NMR (300 MHz, CD_3OD) δ 4.21 (s, 2H), 4.30 (s, 2H), 5.00 (s, 2H), 5.14 (s, 2H), 6.55 (s, 1H), 6.85-6.88 (m, 2H), 7.13-7.15 (m, 3H), 7.17-7.21 (m, 2H), 7.23-7.28 (m, 4H), 8.16 (d, J = 5.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 159.1, 150.7, 141.9, 137.2, 131.6, 131.2, 130.7, 128.5, 128.3, 128.0, 127.8, 127.4, 114.4, 110.9, 106.1, 99.7, 75.0, 72.2, 70.5, 70.2; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{24}N_5O_2{}^{79}Br_2$, 596.0297; found 596.0313.



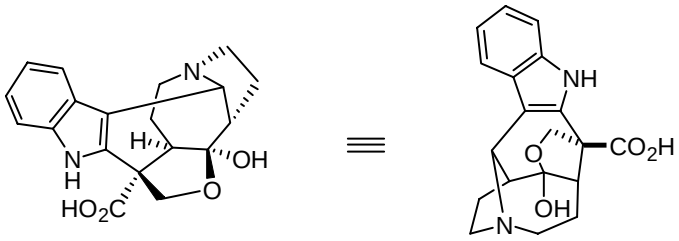
Ageladine A (1). To a solution of BOM-protected tricyclic compound **157** (15.1 mg, 25.2 μmol) in CH_2Cl_2 (6 mL) was added $AlCl_3$ (33.7 mg, 0.25 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt for 30 min. The mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The aqueous layer was concentrated and purification of the residue by reverse phase HPLC afforded ageladine A (**1**, 5.7 mg, 63 %) as a yellow solid, which was identical to previously prepared material.[3] ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (s, 1H), 7.42 (d, J = 6.4 Hz, 1H), 8.05 (d, J = 6.4 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{10}H_8N_5{}^{79}Br_2$, 355.9146; found 355.9146.

PART TWO: STUDIES DIRECTED TOWARDS A TOTAL SYNTHESIS OF ACTINOPHYLLIC ACID

INTRODUCTION AND BACKGROUND

1.1 Isolation and Structural Identification of Actinophyllic Acid

The structurally novel indole alkaloid actinophyllic acid (**158**) was isolated from the leaves of the Australian tree *Alstonia actinophylla* by Quinn, Carroll, and coworkers in 2005 (Figure 4).[61] Although more than 250 alkaloids have been isolated from genus *Alstonia*, actinophyllic acid is the only example with a skeletal structure which contains 1-azabicyclo[4.4.2]dodecane and 1-azabicyclo[4.2.1]nonane subunits. The structure of the alkaloid was established by a combination of NMR, IR, and mass spectrometric analysis. However, only the relative configuration of the natural product has been determined to date.



actinophyllic acid (**158**)

Figure 4. Structure of the Novel Indole Alkaloid Actinophyllic Acid

1.2 Biological Activity of Actinophyllic Acid

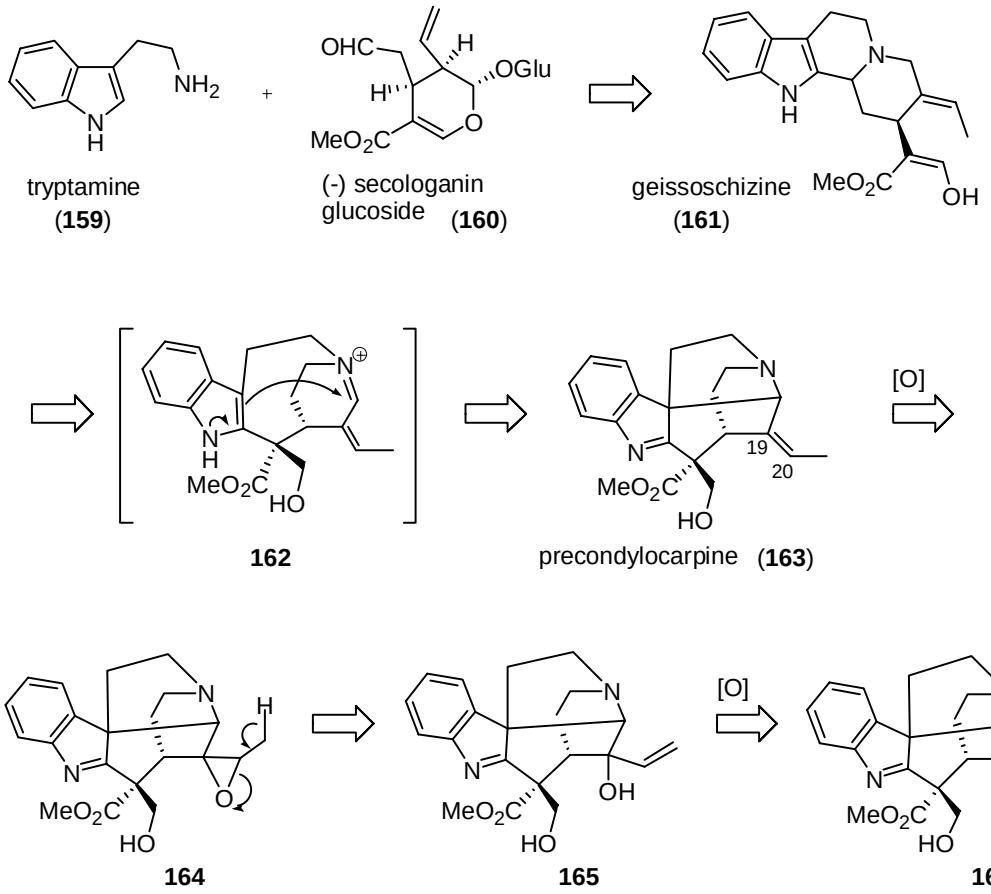
Actinophyllic acid has been shown to be a potent inhibitor of the enzyme carboxypeptidase U (CPU).[61] CPU is an endogenous inhibitor of fibrinolysis, a process used by the body to clear blood clots (fibrin) from circulation.[62] CPU (U refers to the

unstable nature of the enzyme) circulates in plasma as an inactive precursor, proCPU, until it is converted to its active form through the action of the serine proteases thrombin and plasmin during coagulation and fibrinolysis.[63] Once activated, CPU cleaves C-terminal lysine residues exposed on partially degraded fibrin, which are important for up-regulating fibrinolysis. By cleaving these lysine residues, CPU impedes fibrinolysis by destroying its inherent positive feedback mechanism.[64] However, given the ability of actinophyllic acid to inhibit CPU and thus facilitate fibrinolysis (IC_{50} of 0.84 μM), the alkaloid could be a potential treatment for cardiovascular disease.[61]

1.3 Proposed Biosynthesis of Actinophyllic Acid

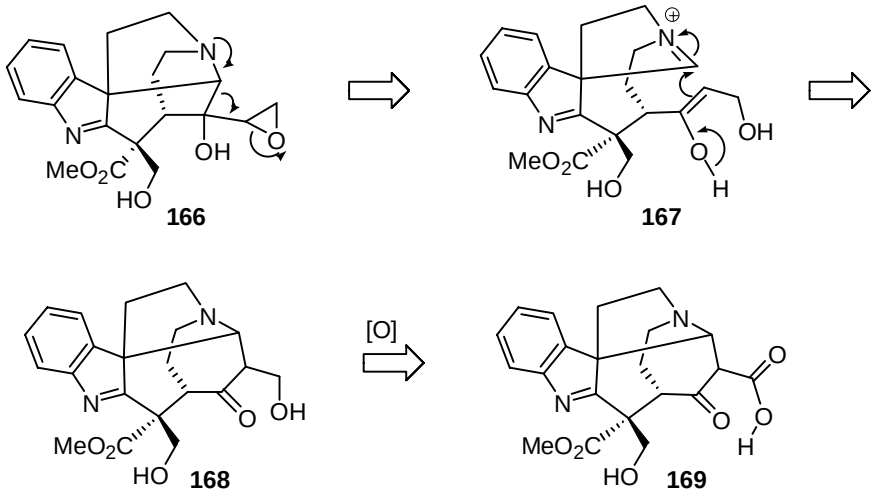
A schematic biogenetic pathway for actinophyllic acid proposed by Carroll et al. begins with the condensation of tryptamine (**159**) and (-)-secologanin glucoside (**160**) to provide the known alkaloid geissoschizine (**161**) (Scheme 46).[61] Rearrangement of geissoschizine (**161**) via stemmadenine iminium cation **162** would lead to precondylocarpine (**163**),[65] an alkaloid that has been isolated from *Vallesia dichromatoma* (Apocynaceae).[66] Oxidation of precondylocarpine (**163**) at the C-19 – C-20 double bond would give epoxide **164**. Subsequent epoxide rearrangement of **164** would produce allylic alcohol **165**, and further oxidation would then furnish epoxide **166**.

Scheme 46



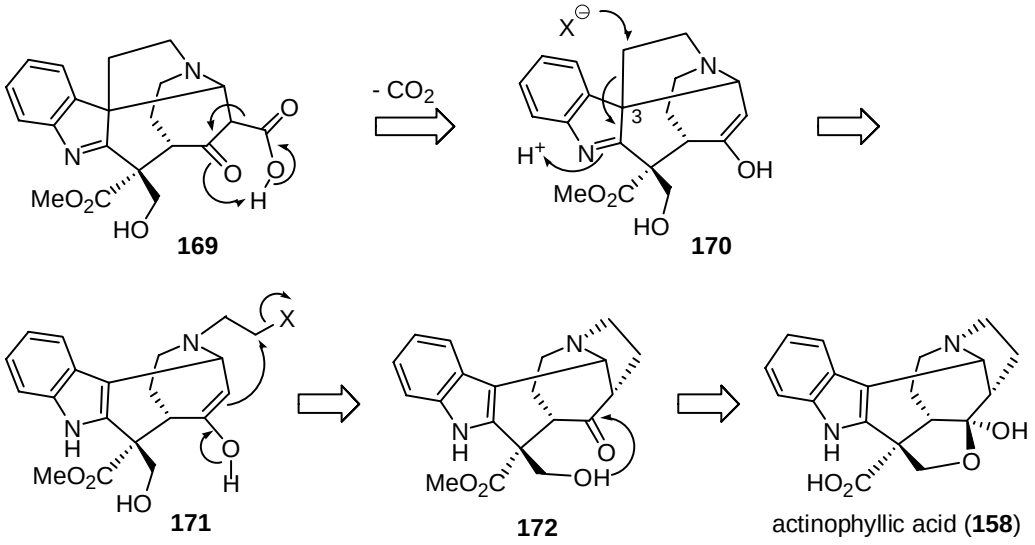
To continue the proposed biogenetic pathway, amine-induced epoxide opening of **166** would give iminium ion **167**, which upon intramolecular Mannich cyclization of the newly formed enol would provide keto alcohol **168** (Scheme 47). Oxidation of one of the primary alcohol groups of **168** would then provide β-ketoacid **169**.

Scheme 47



Decarboxylation of β-ketoacid **169** would produce enol **170** (Scheme 48). Re-aromatization of intermediate **170** to the indole would occur via cleavage at C-3 of the indoline to generate species **171**, which upon ring closure with the enol moiety would yield the alkaloid skeleton **172**. Hemiacetal formation via cyclization of the alcohol functionality onto the ketone in **172**, followed by hydrolysis of the methyl ester, would give actinophyllic acid.

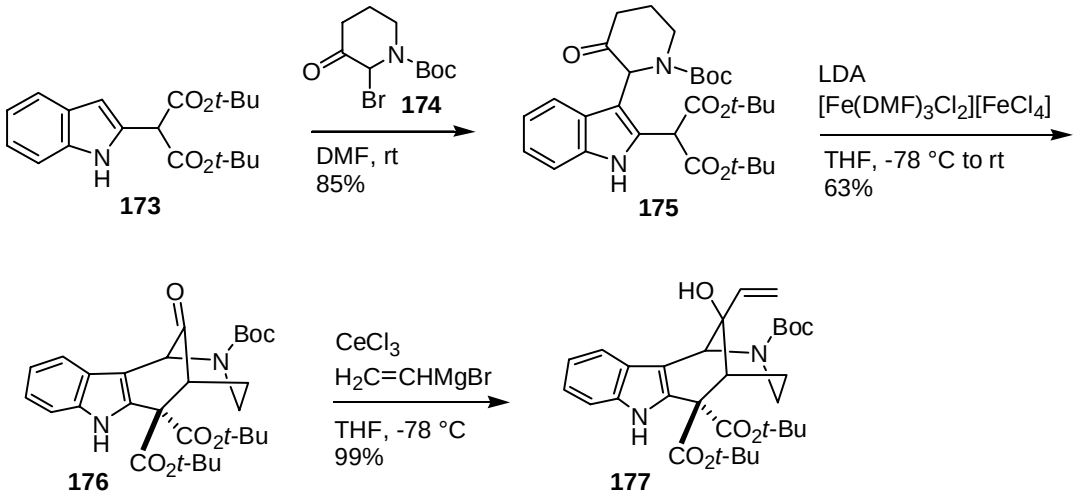
Scheme 48



1.4 Overman Synthetic Approach to Racemic Actinophyllic Acid

In 2008, Overman and coworkers reported the first and to date only total synthesis of actinophyllic acid in racemic form.[67] The synthesis commenced with the addition of indole-2-malonate **173** to bromopiperidone **174** to give tricyclic product **175** (Scheme 49). A key regioselective intramolecular oxidative coupling of the malonate functionality of **175** with a 3-piperidone enolate formed *in situ* furnished tetracyclic ketone **176** in good yield. Addition of vinylmagnesium bromide to ketone **176** in the presence of cerium trichloride at reduced temperature provided the single allylic alcohol product **177** in nearly quantitative yield.

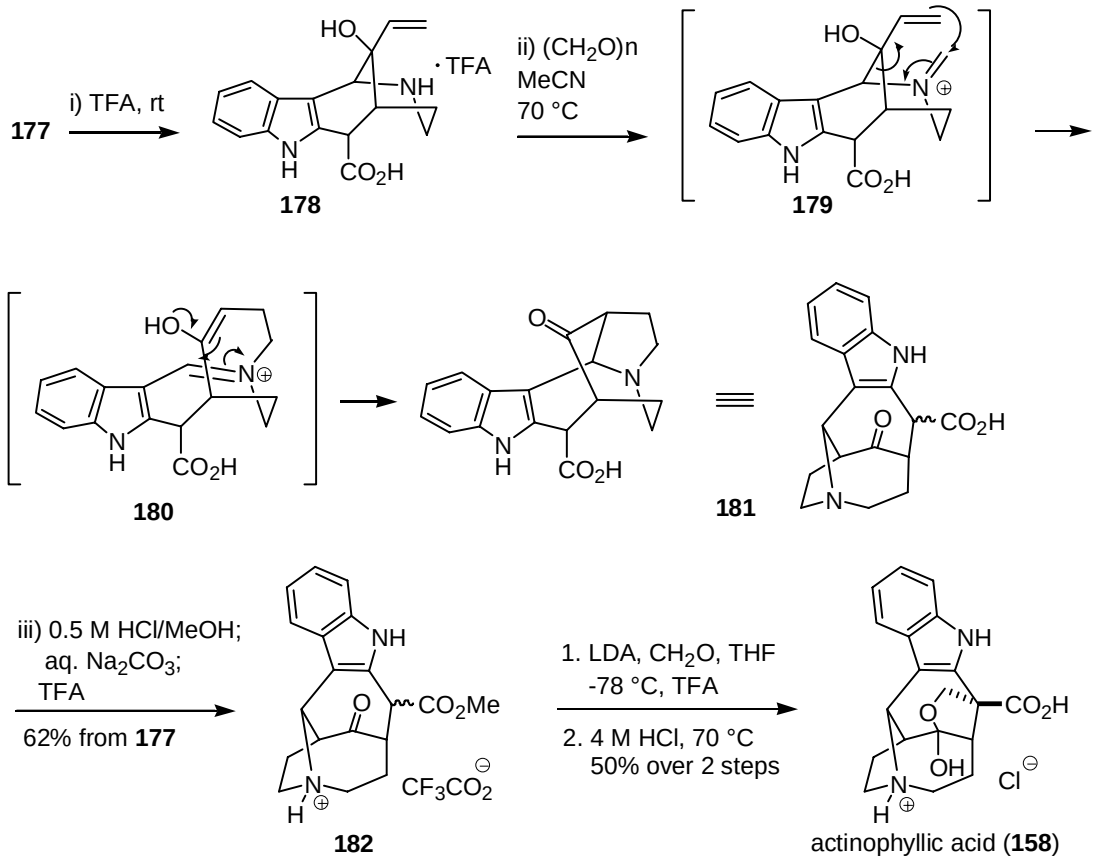
Scheme 49



To complete the synthesis, it was found that allylic alcohol **177** could be converted to pentacyclic ester **182** in a one-pot process involving a key aza-Cope-Mannich rearrangement. Thus, subjecting **177** to TFA removed the Boc-protecting group, cleaved the *t*-butyl esters to the corresponding carboxylic acids, and promoted

decarboxylation to give amine **178** (Scheme 50). After removal of TFA under reduced pressure, redissolving amine salt **178** in acetonitrile and exposure to paraformaldehyde induced the key aza-Cope-Mannich rearrangement via iminium ions **179** and **180** to the tertiary amine **181**. Subsequent esterification of **181** provided pentacyclic ester **182** as a 1:1 mixture of epimers. Installation of the tetrahydrofuran ring was accomplished by a stereoselective aldol reaction of the lithium enolate of ester **182** with anhydrous monomeric formaldehyde. Hydrolysis of the methyl ester to the carboxylic acid using 4 M HCl furnished the hydrochloride salt of racemic actinophyllic acid (**158**).

Scheme 50



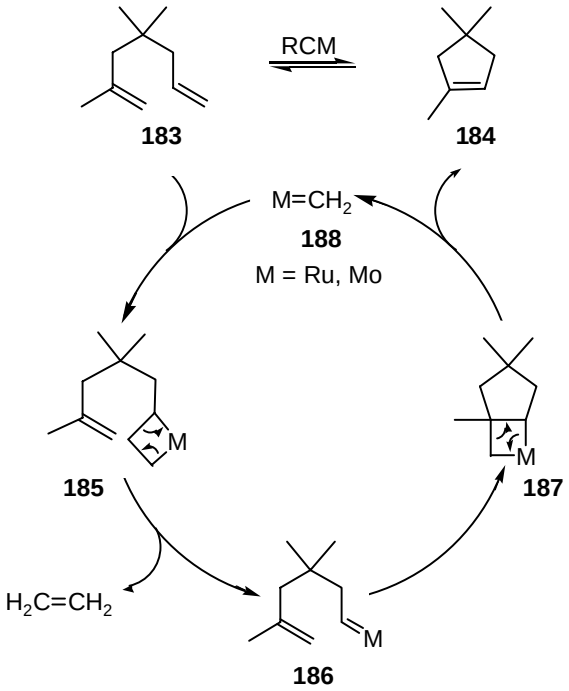
2.1 Background on Key Transformations

2.1.1 *Ring-Closing Metathesis Methodology*

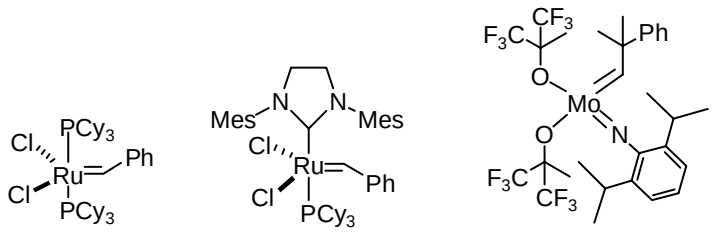
Olefin metathesis is the redistribution of carbon-carbon double bonds between two alkenes. Metathesis can occur between two olefins, referred to as diene metathesis, or between an alkene and alkyne, known as enyne metathesis. There are three main types of metathesis: ring-closing, ring-opening and cross metathesis (intermolecular). In addition, several ruthenium and molybdenum-based catalysts, which are stable and compatible with a variety of functional groups, have recently been developed for these reactions.[68] Ring-closing metathesis (RCM) has gained importance as a dependable and versatile tool for constructing carbo- and heterocyclic ring systems in organic synthesis.[69]

The generally accepted mechanism for RCM involves a sequence of alternating [2+2] cycloadditions and cycloreversions as shown in Scheme 51. The formation of the metallacyclobutane **185** has been shown to be the rate-determining step for the transformation of diene **183** to cyclic alkene **184**.[70] All steps in this sequence are reversible, but, the formation of volatile ethylene and derivatives drives the equilibrium towards the cyclic product **184**. The catalytic cycle then repeats with the regeneration of the active catalyst species **188**.

Scheme 51



There are now many commercially available RCM catalysts with notable differences in their structure and reactivity (Figure 5). Grubbs first generation ruthenium-based catalyst **189** has limited thermal stability and reactions are often slow with hindered olefins. This catalyst is effective with only a few trisubstituted olefins and with very few tetrasubstituted compounds. The second generation Grubbs catalyst **190**, which contains a *N*-heterocyclic carbene (NHC) ligand, leads to a more stable active species and is capable of producing tri- and tetrasubstituted cycloalkenes via RCM. Since NHC ligands are stronger Lewis bases than tricyclohexylphosphines, there is an increase in the electron density at the metal of **190**, leading to greater reactivity and stability of the catalyst and its intermediates.[71] Schrock's molybdenum alkylidene catalyst **191** is considered more reactive than Grubbs first generation catalyst **189**. However, it is also more sensitive to moisture and oxygen.

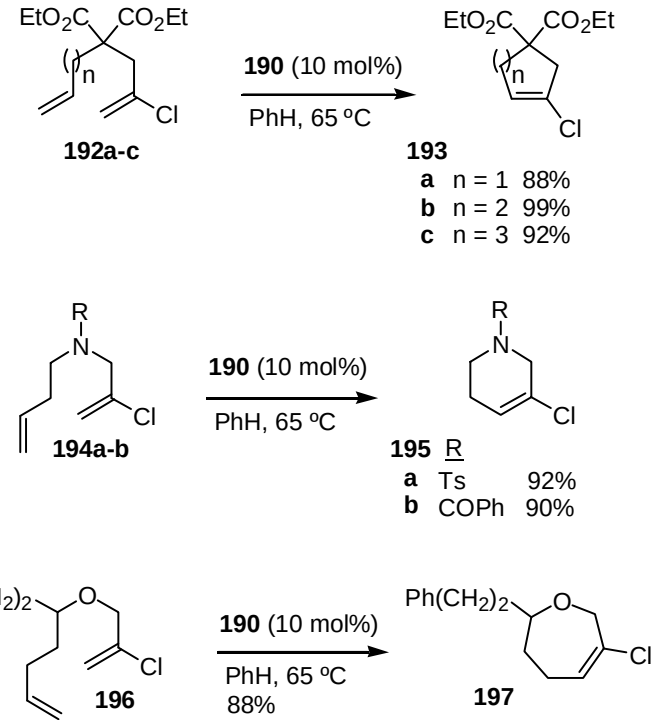


189 **190** **191**

Figure 5. Various Commercially Available Metathesis Catalysts

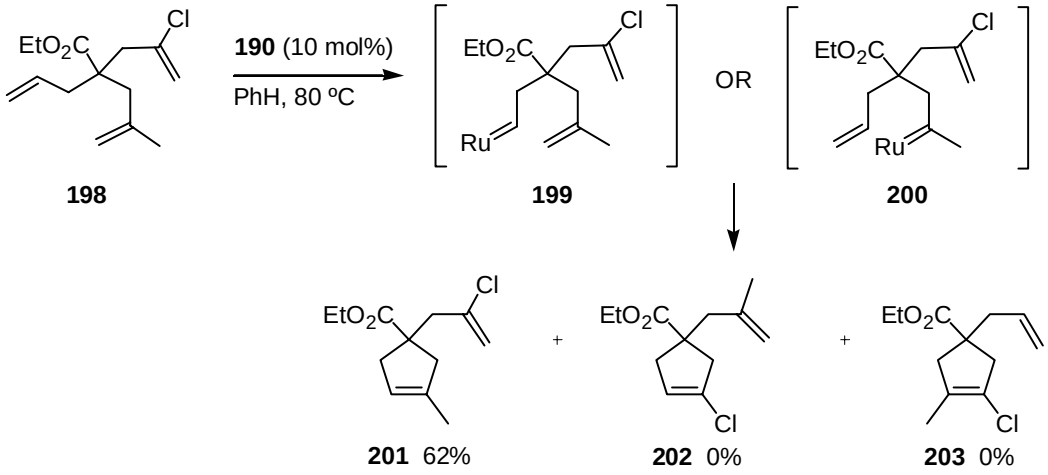
Heteroatom-substituted olefins have gained attention as synthetically-valuable RCM substrates.[72] Recent work in the Weinreb group has shown that olefinic vinyl chlorides readily undergo RCM in the presence of Grubbs second generation ruthenium catalyst **190** to produce five-, six-, and seven-membered carbo- and heterocyclic systems (Scheme 52).[73] For example, exposure of diene **192a** (n = 1) to the Grubbs catalyst **190** in benzene furnished the desired five-membered cyclic vinyl chloride **193a** in good yield. In addition, *N*-protected amino dienes **194a** and **194b** cyclized in excellent yield to give heterocyclic vinyl chlorides **195a** and **195b**, respectively. Seven-membered cyclic ether **197** was also produced in 88% yield via RCM from its acyclic diene precursor **196**. However, all efforts to form ring systems larger than seven were unsuccessful.[73]

Scheme 52



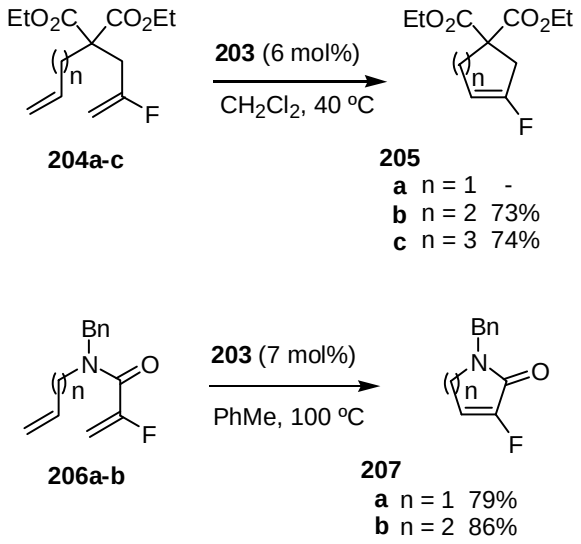
In an interesting internal competition experiment performed by Meketa to investigate the relative reactivity of alkenes versus vinyl chlorides, triene **198** was exposed to the standard RCM conditions with catalyst **190** (Scheme 53).[74] Even though three different RCM products could possibly be obtained from this reaction, (i.e. **201**-**203**), we only detected cyclopentene **201**. Thus, we concluded that the Grubbs catalyst **190** preferentially reacts with the mono- and 1,2-dialkyl-substituted olefins to give **199** and/or **200** rather than the vinyl chloride. It seems most likely that the catalyst first reacts with the less sterically-hindered monosubstituted olefin to give ruthenium intermediate **199**. However, initial formation of intermediate **200**, which is also capable of undergoing RCM to give the observed product, cannot be ruled out.

Scheme 53



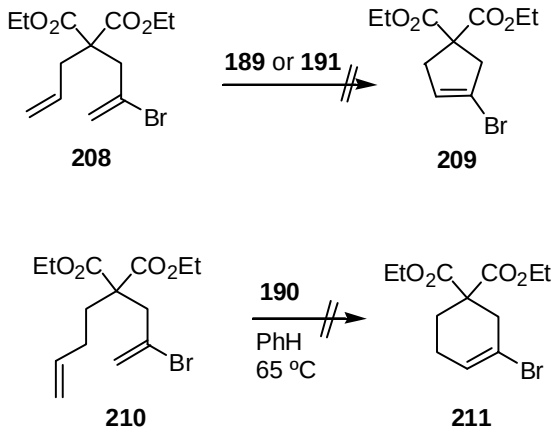
It was later demonstrated by other research groups that vinyl fluorides also undergo RCM reaction.[75] Thus, Brown and coworkers reported that subjecting fluoro-olefins **204b** and **204c** to standard RCM conditions gave six- and seven-membered cyclic vinyl fluorides **205b** and **205c** in good yields (Scheme 54).[75a] Interestingly, the corresponding five-membered ring system **205a** could not be synthesized by RCM. However, the Rutjes group later found that it is vital to add the catalyst portionwise over the course of the reaction to avoid catalyst decomposition.[76] Using this experimental technique, five- and six-membered vinyl fluoride lactams **207a** and **207b** were produced in good yields from acrylamides **206a** and **206b**, respectively.

Scheme 54



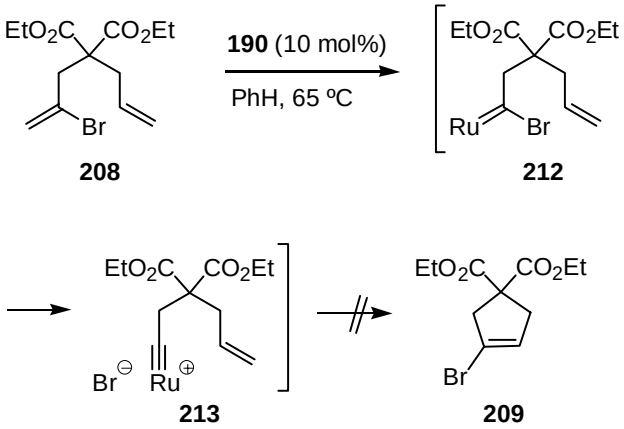
Both the Grubbs and Weinreb groups have described unsuccessful attempts to effect vinyl bromide RCM reactions. Treatment of vinyl bromide **218** with either Grubbs first generation catalyst **189** or Schrock's catalyst **191** gave only recovered starting material (Scheme 55).[77] Similarly, work in the Weinreb group has shown that exposure of vinyl bromide **210** to Grubbs second generation catalyst **190** failed to yield any of the desired cyclic product **211**.[73] It is believed that metatheses of vinyl halide substrates is kinetically controlled and steric factors override electronic factors. Based on *ab initio* calculations by Fomin et al., the activation energy of metathesis reactions is strongly dependant on the size of the olefin substituent.[78] As a result, vinyl bromides are considered too sterically-hindered to undergo metathesis.

Scheme 55



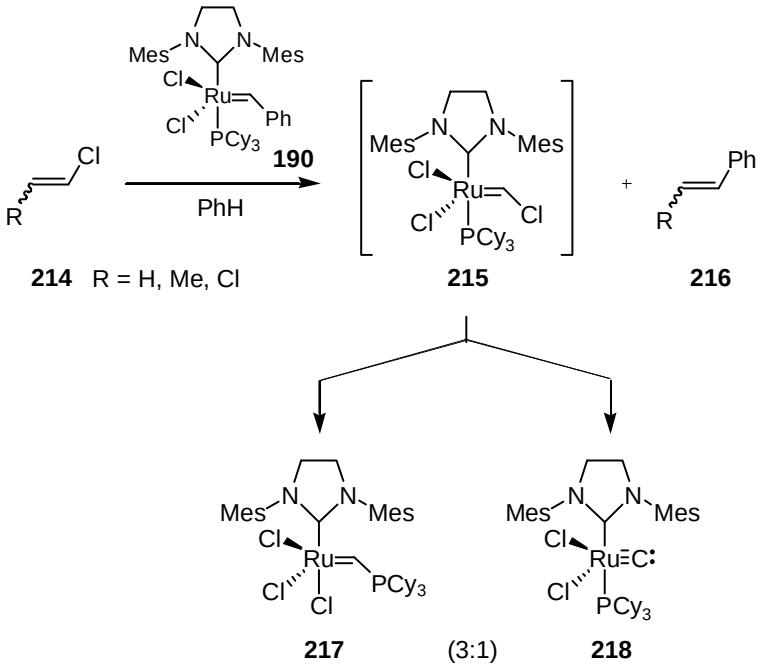
Another possible reason for the unsuitability of vinyl bromides as RCM substrates is the formation of an inactive ruthenium Fischer-type carbene complex **212** (Scheme 56). This carbene complex is only possible if the Grubbs catalyst reacts faster with the vinyl bromide moiety than the terminal olefin. Carbene **212** would rearrange to the stable ruthenium carbyne complex **213**, a type of intermediate which has been previously isolated.[79]

Scheme 56



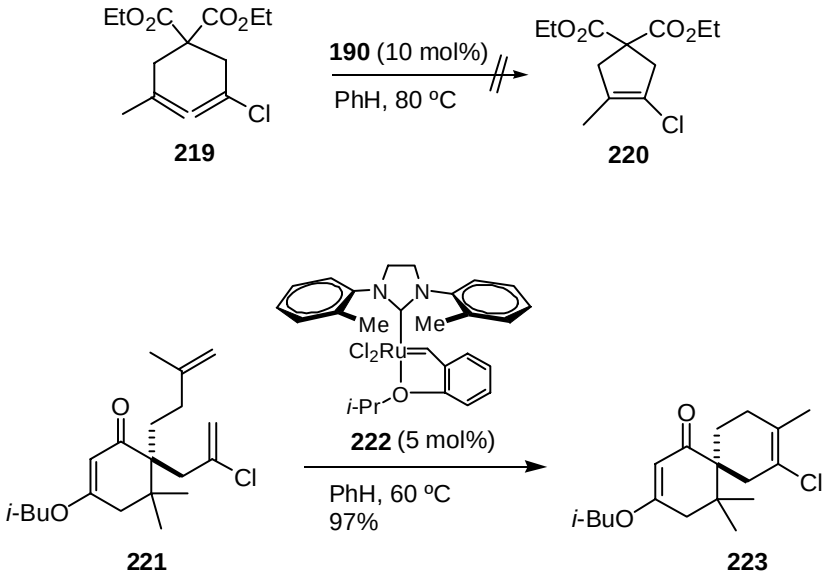
Recently, Johnson and coworkers reported that metathesis reactions of vinyl chlorides can also give rise to inactive ruthenium carbene complexes.[80] Therefore, exposure of vinyl chloride **214** to Grubbs second generation catalyst produced styrene derivative **216**, along with a 3:1 mixture of the phosphoniomethylidene complex **217** and terminal carbide complex **218** (Scheme 57). As in the vinyl bromide case, formation of these unreactive phosphoniomethylidene and carbide complexes is due to the rearrangement of the Fischer carbene **215**. Thus, the success of a vinyl halide RCM reaction appears to be dependant on the metal catalyst first reacting with the non-halogenated olefin.

Scheme 57



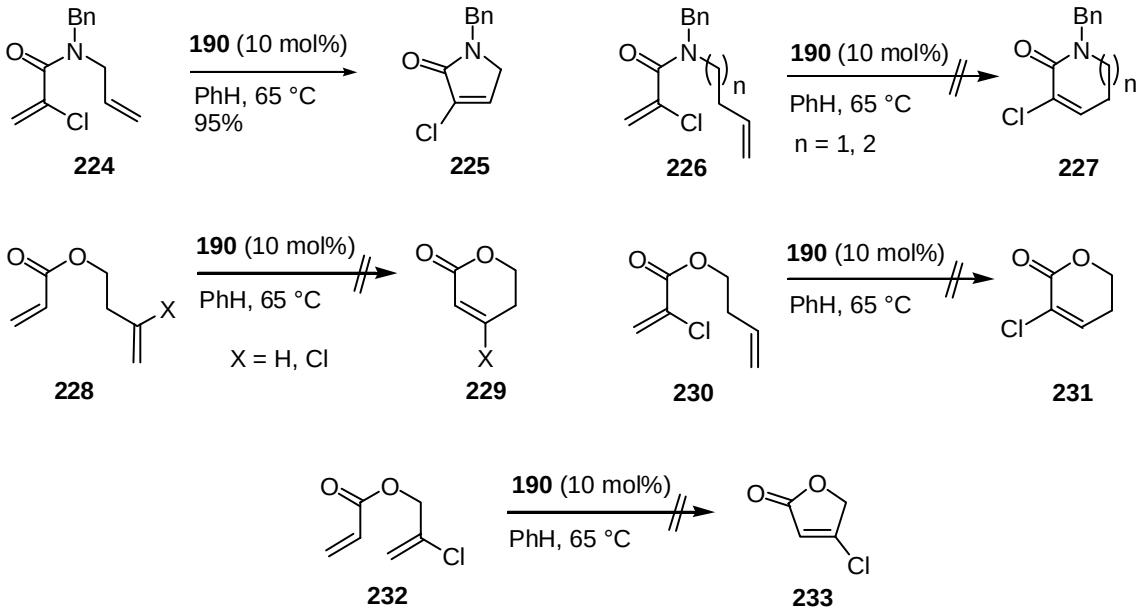
We have also investigated RCM reactions of vinyl chlorides containing olefinic partners such as 1,1-disubsituted olefins, acrylates and acrylamides. Unfortunately, numerous attempts to cyclize diene **219** using catalyst **190** did not produce the desired tetrasubstituted carbocyclic system **220**, but rather only starting material was recovered (Scheme 58). However, Grubbs and coworkers recently reported the first preparation of a tetrasubstituted chlorinated olefin via RCM.[81] In this case, exposure of vinyl chloride diene **221** to the newly developed catalyst **222**[82] provided tetrasubstituted cyclic product **223** in 87% yield. The greater reactivity of catalyst **222** towards highly substituted olefins, compared to previous Grubbs catalysts, was attributed to a more open steric environment around the ruthenium center, which allows the metal to accommodate larger organic fragments.

Scheme 58



Meketa and Weinreb have also examined RCM reactions of chloro-acrylate and acrylamide systems (Scheme 59). Interestingly, of the compounds tested, only the five-membered amide **224** could be cyclized in high yield to lactam **225** using Grubbs RCM catalyst **190**. Subjecting the six- and seven-membered systems **226** to a number of RCM reaction conditions resulted only in recovered starting acrylamide.

Scheme 59

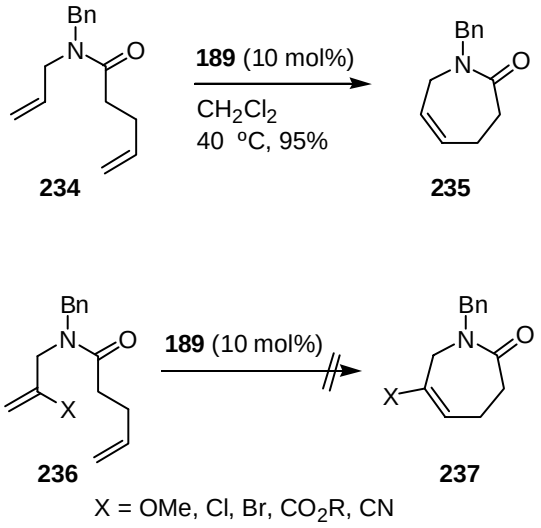


In exploring the formation of six-membered α,β-unsaturated lactones, we designed two acrylate systems that differed in the position of the chlorine atom. However, attempted RCM reactions of substrates **228** or **230** failed to yield the corresponding lactam products **229** or **231**, respectively. Interestingly, unlike lactam **225**, the five-membered butenolide **233** could not be synthesized from **232** using RCM.

Moreover, Guibe and coworkers reported similar RCM findings using amide substrates.[83] Thus, amide **234** smoothly underwent RCM with Grubbs first generation

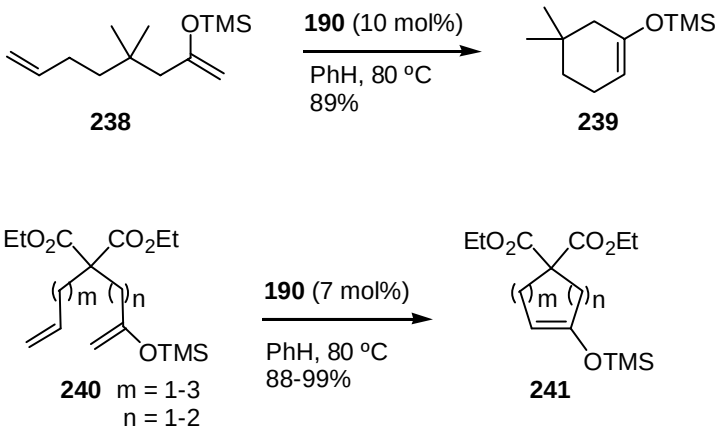
catalyst **189** to give seven-membered lactam **235** (Scheme 60). However, if one of the alkene moieties was substituted with a methyl ether, halide, ester, or cyano group as in diene **236**, then only the starting amide was recovered rather than products **237**. The reason for this lack of reactivity is presently unclear.

Scheme 60



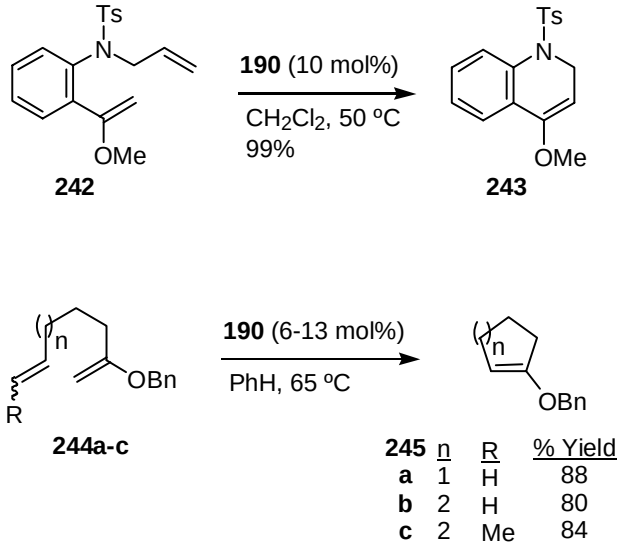
In addition to vinyl halides, ring-closing metathesis of other heteroatom-substituted olefins, including silyl- and alkylenol ethers, has recently been examined. For example, exposure of trimethylsilyl (TMS) enol ether diene **238** to Grubbs second generation catalyst **190** provided cyclic enol ether **239** in high yield (Scheme 61).[84] Likewise, Shibasaki et al. reported the formation of five- to eight-membered cyclic enol ethers **241** via RCM of the acyclic diene precursors **240**.[85]

Scheme 61



Alkylenol ethers, which are more stable than their silyl counterparts, can also undergo ring-closing metathesis. For example, Nakagawa and coworkers have shown that subjecting methylenol ether **242** to standard RCM conditions using catalyst **190** gave the bicyclic enol ether product **243** in nearly quantitative yield (Scheme 62).[86] Similarly, benzylenol ethers **244a-c** cyclized in good yield to afford five- and six-membered ring systems **245a-c**.

Scheme 62

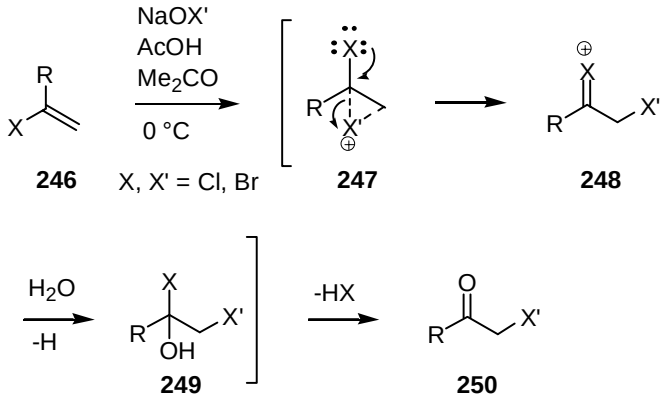


245	n	R	% Yield
a	1	H	88
b	2	H	80
c	2	Me	84

2.1.2 *Regioselective Conversion of Vinyl Chlorides to α-Chloroketones*

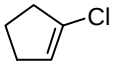
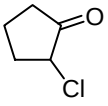
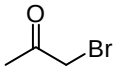
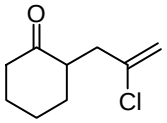
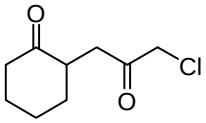
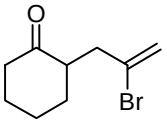
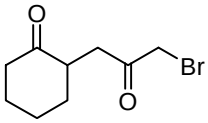
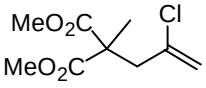
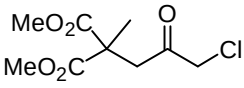
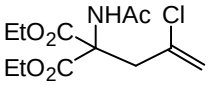
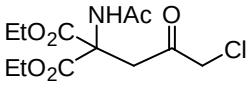
Vinyl chlorides have recently become increasingly useful intermediates in organic synthesis, and now can be used in Heck,[87] Suzuki,[88] and Negishi[89] cross couplings as well as the Sonogashira reaction.[90] Vinyl halides can also be converted to α-haloketones using NXS (X = Cl, Br, I) in aqueous acetonitrile with a catalytic amount of HX at room temperature.[91] Unfortunately, these reagents and conditions are incompatible with many functional groups and thus can detract from their synthetic usefulness. However, recent research by VanBrunt and Weinreb has shown that vinyl chlorides and bromides can be readily and regioselectively converted to the corresponding α-haloketones in high yields under mild reaction conditions.[92] Thus, treatment of vinyl halides **246** with aqueous sodium hypohalite in a 2:5 mixture of glacial acetic acid/acetone at 0 ºC for a short time affords α-haloketones **250** (Scheme 63). It is believed that this transformation occurs by reaction of the vinyl halide **246** with *in situ*-formed hypohalous acid, which generates a chloronium or bromonium cation **247** (X = Cl or Br, respectively). Nucleophilic attack by water on ion **248**, followed by loss of HX from **249** would give the α-haloketone **250**.

Scheme 63



As depicted in Table 1, this transformation is applicable to a variety of vinyl chlorides and bromides. For example, subjecting 1-chlorocyclopentene to these conditions with NaOCl gave 2-chlorocyclopentanone in good yield (Entry a, Table 1). Similarly, 2-bromopropene was converted to 1-bromopropan-2-one in 83% yield using sodium hypobromite (Entry b). Furthermore, the mild reaction conditions are compatible with a variety of functional groups including amides and esters.

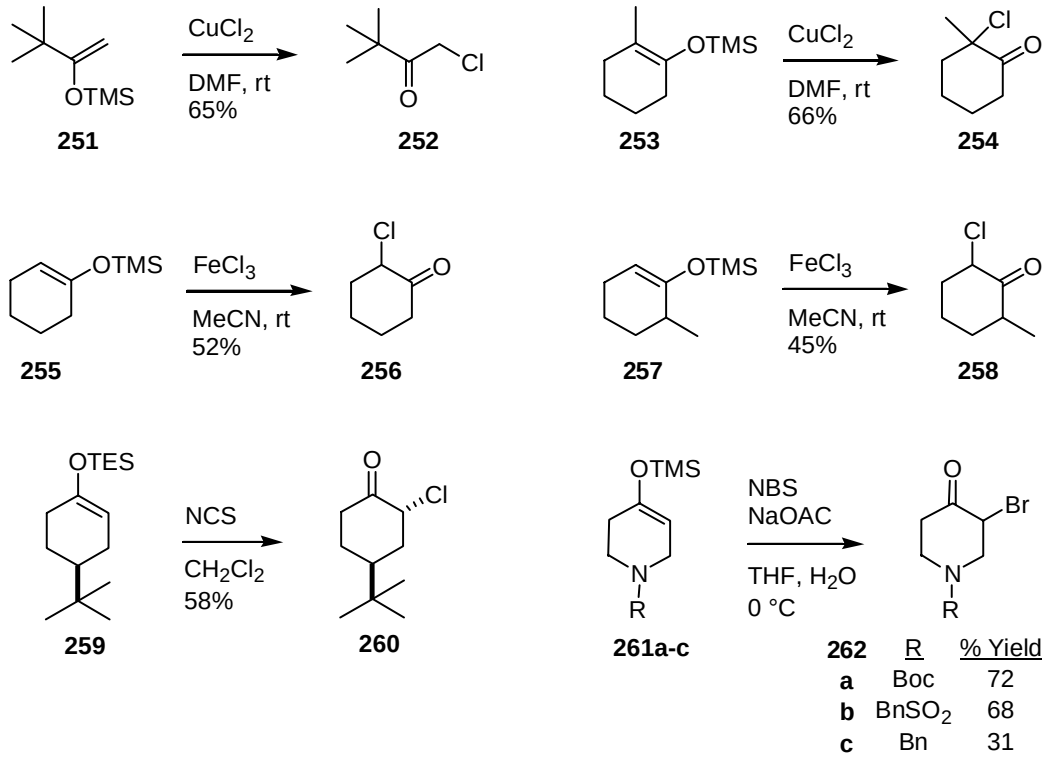
Table 1. Conversion of Vinyl Halides to α-Haloketones with Sodium Hypohalite in Acetone/Acetic Acid

Entry	Vinyl Halide	α-Haloketone	% Yield
a			72
b			83
c			66
d			95
e			82
f			99

2.1.3 *Regioselective Conversion of Enol Ethers to α-Chloroketones*

In addition to vinyl chlorides, there are many examples in the literature of the conversion of silyl- and alkylenol ethers to α-haloketones. Silylenol ethers are more electron rich than their vinyl chloride counterparts and thus are more reactive towards electrophilic chlorinating reagents. For example, the Saegusa group has reported a series of reactions of silylenol ethers, such as TMS-enol ethers **251** and **253**, with cupric chloride to give α-chloroketones **252** and **254**, respectively (Scheme 64).[93] Moreover, exposure of TMS-enol ethers **255** and **257** to ferric chloride in acetonitrile furnished the desired α-chloroketones **256** and **258** in moderate yields. *N*-Chlorosuccinimide is also an effective reagent for this transformation, where TES-enol ether **259** gave the desired

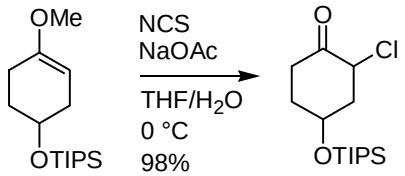
Scheme 64



product **260** in 58% yield.[94] Similarly, Meijere and coworkers reported the use of NBS to convert a variety of TMS-enol ethers **261a-c** to the corresponding α-bromoketones **262a-c** in good yields.[95]

Although fewer examples are reported in literature compared to silylenol ethers, more robust alkylenol ethers can also be converted to the corresponding α-chloroketones. For example, treatment of methylenol ether **263** with NCS in the presence of sodium acetate at low temperature gave α-chloroketone **264** in excellent yield (Scheme 65).[96] Furthermore, these mild conditions did not cleave the triisopropylsilyl (TIPS)-alcohol protecting group.

Scheme 65



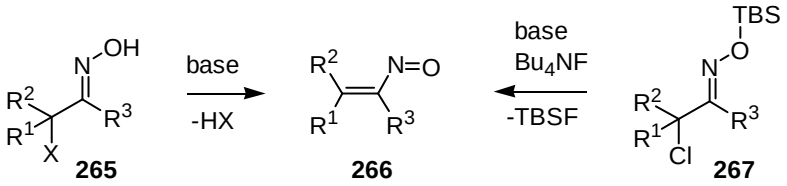
263 **264**

2.1.4 *Intramolecular Michael Cyclizations of Vinylnitroso Compounds*

Although vinylnitroso compounds have been known for many years, these highly reactive, unstable species have found relatively little application in organic synthesis.[97] One common way to generate a vinylnitroso intermediate **266** *in situ* is via a base-promoted 1,4-elimination of an α-heteroatom-substituted oxime **265** using an inorganic base such as calcium hydroxide or sodium carbonate (Scheme 66).[98] Halogens, particularly chlorine, are frequently employed as the leaving group in this transformation.

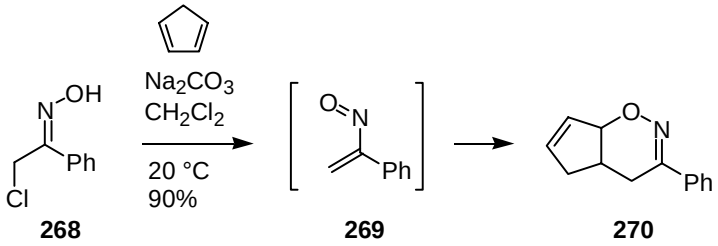
Moreover, a modification for preparing vinylnitroso compounds **266** from α-chlorosilyloximes **267** has been developed by Denmark and coworkers.[99] This methodology uses a fluoride source such as tetrabutylammonium fluoride to initiate the 1,4-elimination process from **267**.

Scheme 66



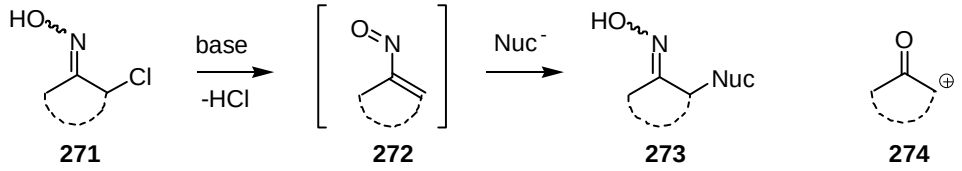
One use of these reactive vinylnitroso species is as a heterodiene in both inter- and intramolecular [4+2]-cycloadditions with olefins to produce 5,6-dihydro-1,2-oxazines.[97,100] For example, treatment of chlorooxime **268** with sodium carbonate generated vinylnitroso intermediate **269**, which underwent an intermolecular [4+2]-cycloaddition with cyclopentadiene to give adduct **270** (Scheme 67).[101]

Scheme 67



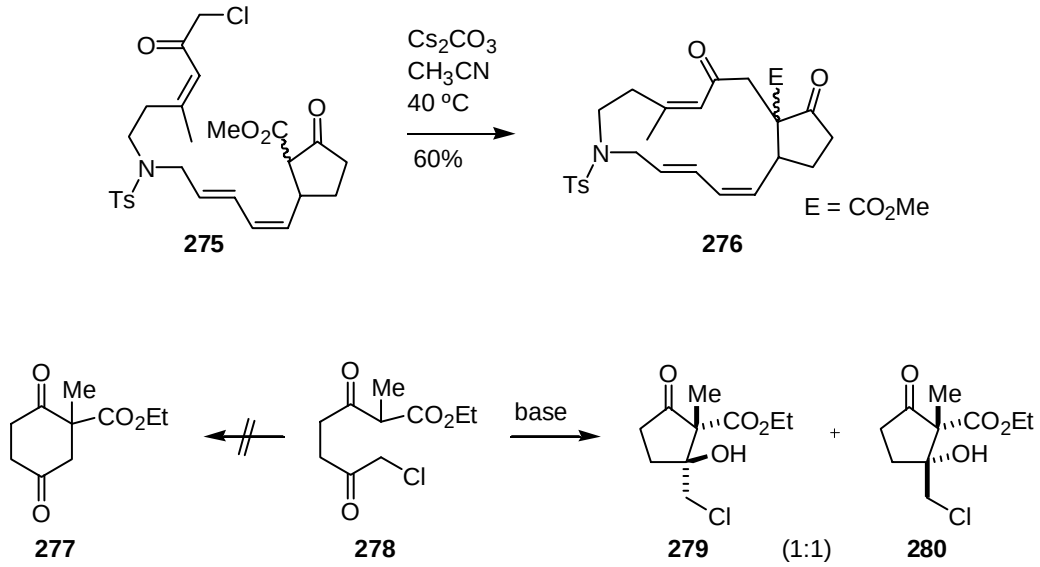
Another type of synthetic application of vinylnitroso compounds involves intermolecular Michael-type additions of hetero- and carbon nucleophiles to intermediates **272** to produce adducts **273** (Scheme 68).[102] The heteronucleophiles which have been used include alcohols, amines, and azides, and various thio compounds.[45] Carbon nucleophiles include malonates, β-ketoesters, Grignard reagents,[103] acetylides,[104] and simple ketone enolates.[105] Therefore, these vinylnitroso compounds can act as enolonium ion equivalents (i.e. **274**) and undergo enolate umpolung chemistry.

Scheme 68



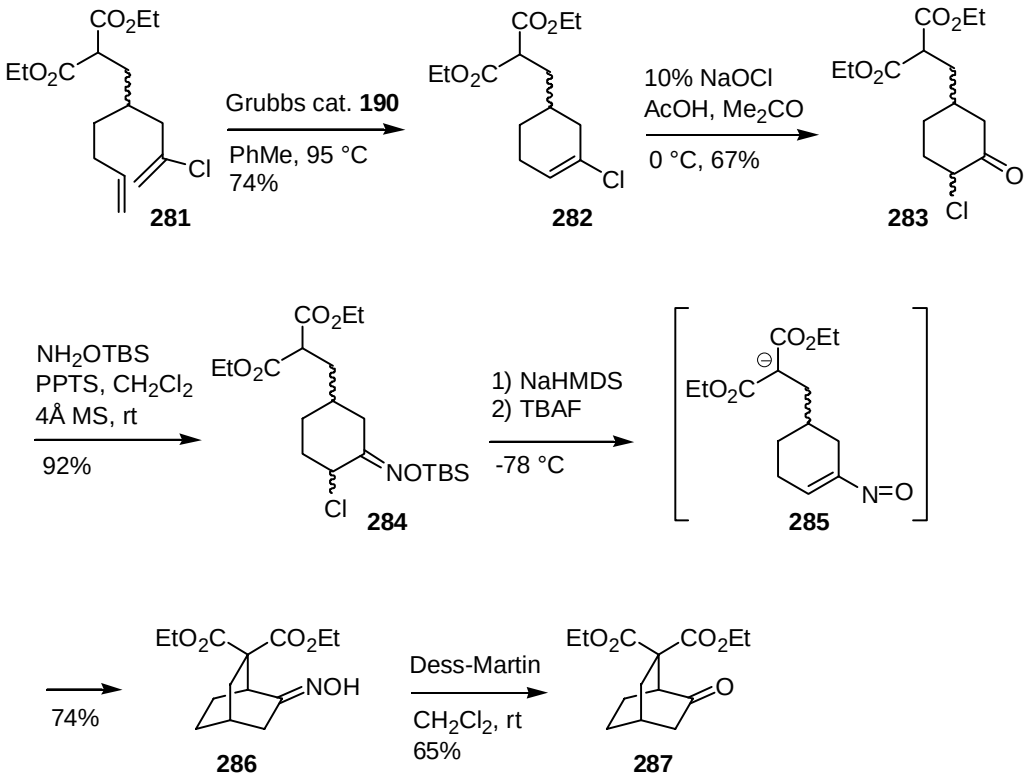
It should be noted that a few examples exist of both inter- and intramolecular direct displacements of α-chloroketones with carbon nucleophiles.[106] For example, Deslongchamps and coworkers reported that treatment of α-chloroketone **275** with cesium carbonate formed a β-ketoester anion that then displaced the primary chloride to give macrocyclic triene **276** in 60% yield (Scheme 69).[107] However, this displacement does not appear to be general, especially with secondary halides, and one can encounter problems associated with the reaction. For example, research in the Weinreb group noted that cyclizations of α-haloketone **278** under a variety of conditions gave a mixture of products **279** and **280**, and not the desired alkylation product **277**.

Scheme 69



To expand on the use of vinylnitroso compounds in organic synthesis, the Weinreb group has recently begun to investigate intramolecular Michael-type additions of carbon nucleophiles to vinylnitroso species to give a variety of highly functionalized bridged and fused ring systems.[108] Thus, vinyl chloride **282** (obtained via RCM of diene **281**) was converted to α-chloroketone **283** as a mixture of diastereomers in good yield using NaOCl in acetic acid/acetone (Scheme 70). Subsequent oximation of α-chloroketone **283** with TBS-hydroxylamine gave TBS-oxime **284** in high yield.

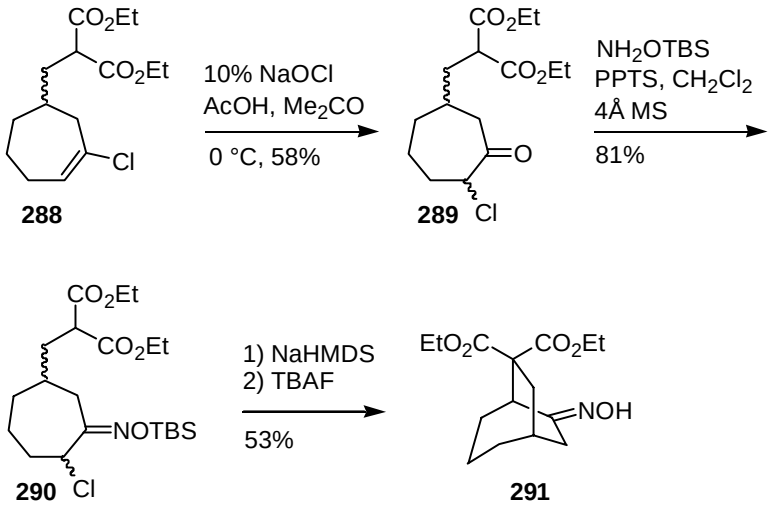
Scheme 70



Given the instability of vinylnitroso compounds, the tethered carbon nucleophile was first generated by deprotonating malonate *O*-silyloxime **284** with sodium hexamethyldisilazide at low temperature, followed by addition of tetrabutylammonium fluoride to give the desired bicyclic oxime diester **286** in 74% yield. It is believed that the cyclization occurs via an intramolecular addition of the malonate anion functionality to vinylnitroso intermediate **285**. The oxime product **286** can be converted to the corresponding ketone **287** using Dess-Martin periodinane.[109]

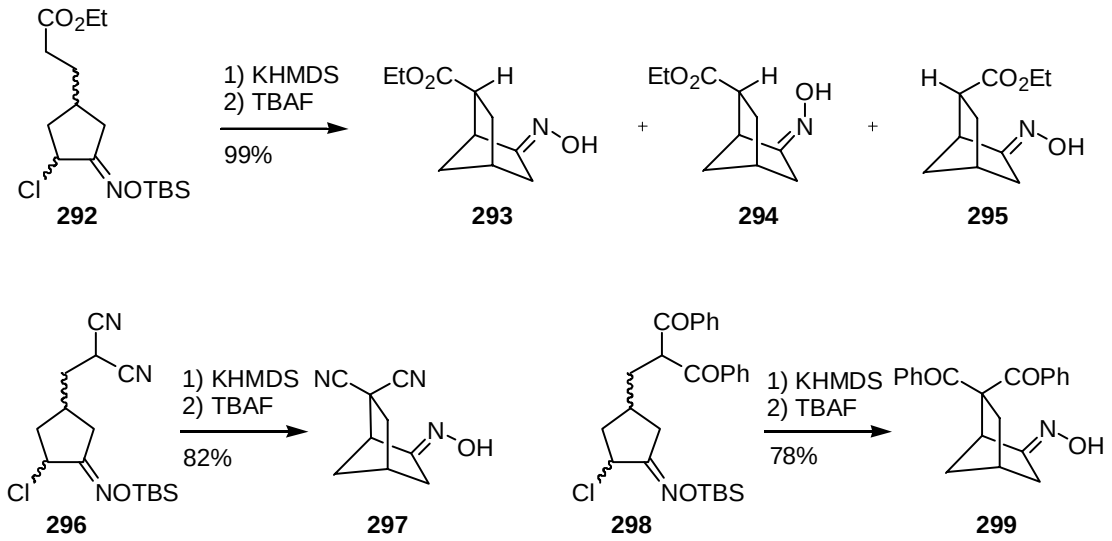
Moreover, larger fused ring systems could be produced using this methodology. For example, vinyl chloride **288** was converted to α-chloroketone **289** in moderate yield (Scheme 71). Oximation of ketone **289** gave the vinylnitroso precursor **290**, which was then cyclized to form bicyclo[3.2.2]-oxime ring system **291** in 53% yield.

Scheme 71



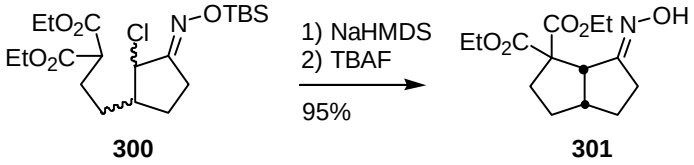
In addition, it was found that other soft carbon nucleophiles such as esters, β-ketoesters, malononitriles, and 1,3-diketones can be used in these intramolecular Michael-type additions to vinylnitroso compounds. For example, simple monoester **292** was selectively deprotonated, followed by cyclization using the standard conditions to yield a mixture of bicyclo[2.2.1]-oximes **293**, **294**, and **295** (ratio: ~10:7:8) in high total yield (Scheme 72). Moreover, malononitrile **296** underwent cyclization to afford the corresponding bicyclo[2.2.1]-oxime **297** as a single geometric isomer in 82% yield. Similarly, the cyclopentyl system **298** tethered with a 1,3-diketone cyclized in good yield to afford oxime **299**, which was also a single geometric isomer.

Scheme 72



In addition to forming bridged ring systems, this vinylnitroso methodology can also produce fused ring systems. For example, deprotonation of malonate **300**, followed by cyclization gave 5,5-fused ring system **301** in 95% yield (Scheme 73). Thus, the intramolecular Michael cyclization of vinylnitroso compounds provides a novel approach to a variety of highly functionalized fused and bridged ring systems.

Scheme 73

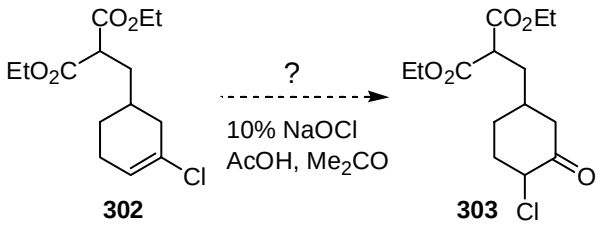


RESULTS AND DISCUSSION

3.1 Preliminary Studies on Halogenation of 1,3-Dicarbonyl Compounds with NaOCl/AcOH/Acetone

Prior to developing the intramolecular Michael-type additions of vinylnitroso compounds discussed in Section 2.1.4, Meketa, Mahajan, and Weinreb decided to examine the functional group selectivity of our sodium hypochlorite/AcOH reagent system. Specifically, we wanted to probe whether selectivity could be achieved in conversion of vinyl chlorides to α-chloroketones in the presence of a variety of 1,3-dicarbonyl compounds such as malonates, β-ketoesters, and 1,3-diketones, since this chemistry was to be used for preparation of the requisite Michael substrates (Cf. **302** to **303**, Scheme 74).

Scheme 74

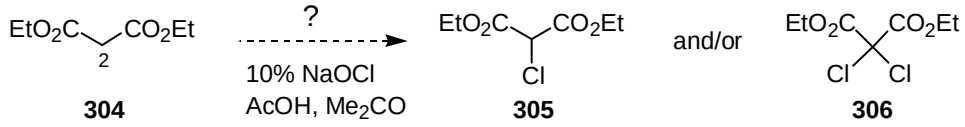


302 **303**

We first chose to examine whether simple 1,3-dicarbonyl compounds such as **304** are chlorinated with NaOCl/AcOH/acetone to give either mono- or dihalogenated products **305** and/or **306** (Scheme 75). Several research groups have reported that 1,3-dicarbonyl compounds readily undergo chlorination at C-2 (or the α-position) using a

variety of reagents such as sulfuryl chloride,[110] NaH/cupric chloride,[111] triethylamine/triflic chloride,[112] and NaH/NCS.[113] Moreover, a few scattered reports exist of chlorinations of simple malonate derivatives which are unsubstituted at the α-position using hypochlorite in the presence of bases such as Na_2CO_3 or KOH.[114] Brominations of β-dicarbonyl compounds have also been effected with NaH/Br_2,[115] NBS,[110,113] and NaH/cupric bromide.[111]

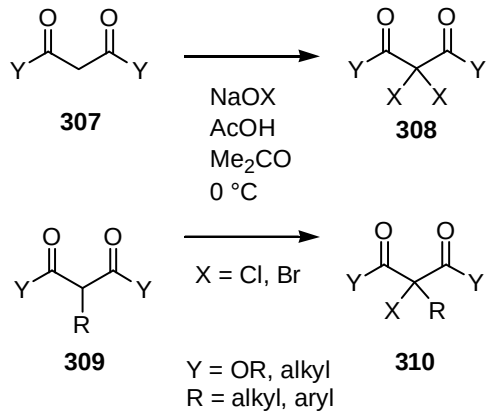
Scheme 75



304 **305** **306**

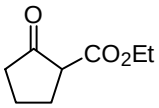
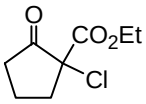
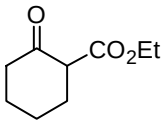
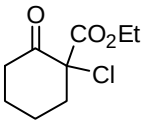
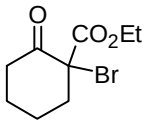
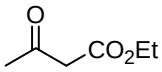
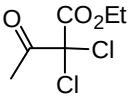
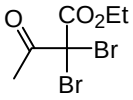
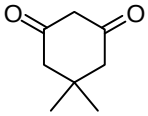
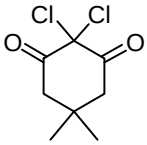
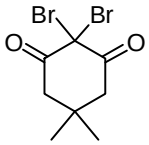
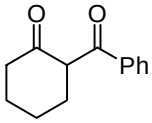
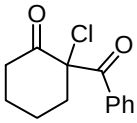
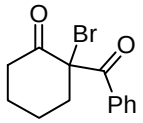
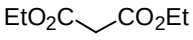
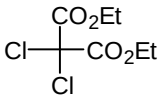
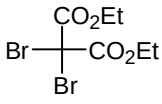
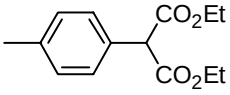
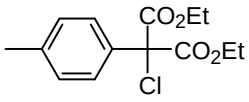
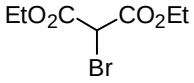
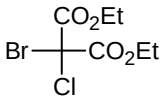
In order to first examine if sodium hypochlorite or hypobromite in glacial acetic acid/acetone would halogenate β-dicarbonyl compounds, we subjected various simple substrates to this reagent system. It was found, in general, that such substrates (i.e. malonates, β-ketoesters, β-diketones) are halogenated at the α-position, and the rate of the reaction is dependant on the structure.[116] Specifically, a β-dicarbonyl compound **307** that is unsubstituted at the α-position undergoes rapid dihalogenation to give products **308** upon treatment with 3.0 equivalents of sodium hypohalite solution in a 2:5 mixture of glacial acetic acid/acetone at 0 ˚C (Scheme 76). Similarly, exposure of α-monosubstituted system **309** to 1.5 equivalents of sodium hypohalite under the same reaction conditions provides monohalogenated product **310**.

Scheme 76



This mildly acidic, convenient halogenation method is applicable to a variety of β-dicarbonyl compounds and the yields of halogenated products were similar for both chlorinations and brominations (Table 2). For example, exposure of 3-oxobutyric acid ethyl ester to commercially available sodium hypochlorite furnished the dichlorinated product in nearly quantitative yield (Entry a, Table 2). Treating this β-ketoester with freshly prepared sodium hypobromite solution in the same solvent system[92] gave the dibrominated product in 96% yield. β-Diketones and malonates could also be halogenated in good to excellent yields (Entries c and d, respectively). Interestingly, diethyl 2-(*p*-tolyl)malonate is unchanged when exposed to the standard experimental conditions at 0 ºC, but can be chlorinated in good yield upon stirring at room temperature with the hypochlorite reagent (Entry g).

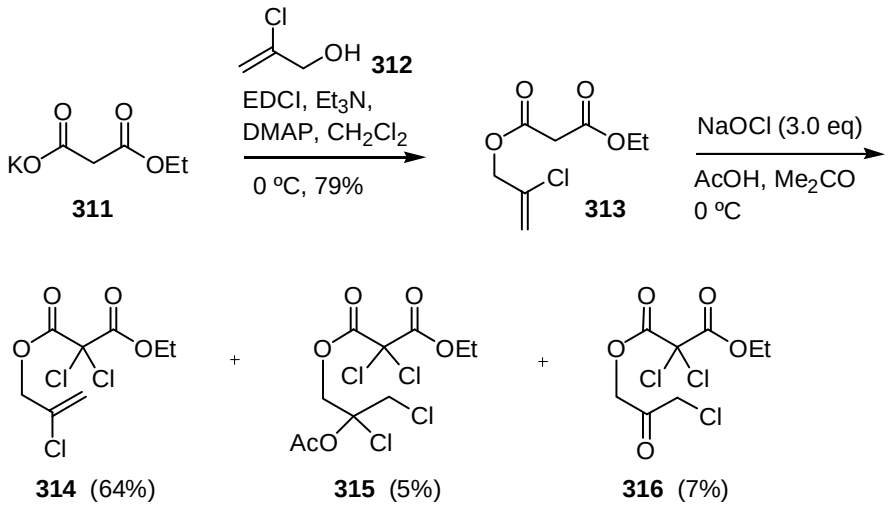
Table 2. Halogenation of Representative 1,3-Dicarbonyl Compounds

Entry	1,3-Dicarbonyl Substrate	Chlorinated Product	Brominated Product
a		 88%	—
b		 94%	 95%
c		 98%	 96%
d		 67%	 81%
e		 96%	 98%
f		 88%	 90%
g		 87%[a]	—
h		 99%	—

[a] After sodium hypochlorite addition at 0 ºC, the reaction was warmed to rt and stirred for 17 h.

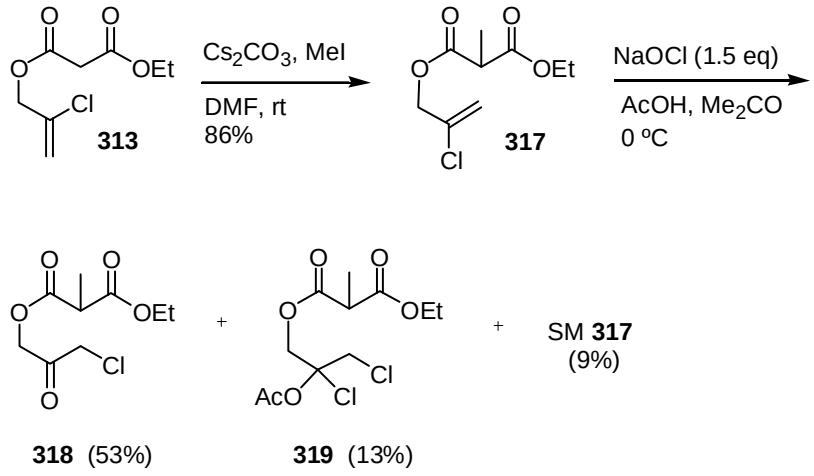
After exploring these initial halogenation experiments, we next investigated whether there is any selectivity of the NaOCl reagent in systems containing both vinyl chlorides and β-dicarbonyl compounds. Thus, O-alkylation of potassium ethyl malonate **311** with 2-chloropropene-3-ol (**312**) provided substrate **313**, which contains both vinyl chloride and malonate moieties, but is unsubstituted at C-2 (Scheme 77). Thus, in a competition experiment, treatment of vinyl chloride malonate **313** with three equivalents of sodium hypochlorite in acetic acid/acetone led to chemoselective α,α-dichlorination to give compound **314** as the major product, along with a small amount of α-chloroketone **316** that was also dichlorinated in the malonate. Surprisingly, chloroacetate **315**, a type of product not previously observed in our initial work with vinyl chlorides (Cf. Table 1), was also isolated from the reaction mixture, albeit in low yield (5%). We believe that chloroacetate **315** is formed via attack of acetic acid on the chloronium ion intermediate (Cf. **247**, Scheme 63).

Scheme 77



We next examined the chlorination of a vinyl chloride containing an α-substituted β-dicarbonyl function. To prepare a suitable substrate, alkylation of malonate **313** with methyl iodide furnished derivative **317** in 86% yield (Scheme 78). When the chlorination experiment was performed with 2-substituted malonate **317** using 1.5 equivalents of NaOCl in glacial acetic acid/acetone, the reaction was completely chemoselective for the vinyl chloride moiety. Thus, the conversion of vinyl chloride **317** to α-chloroketone **318** occurred in 53% yield, along with a small amount of the acetate addition product **319**. We were pleased to find that no malonate α-chlorination product was detected in this experiment, which was evocative of the slow chlorination previously observed with 2-*p*-tolylmalonic acid diethyl ester (Cf. Entry g, Table 1).

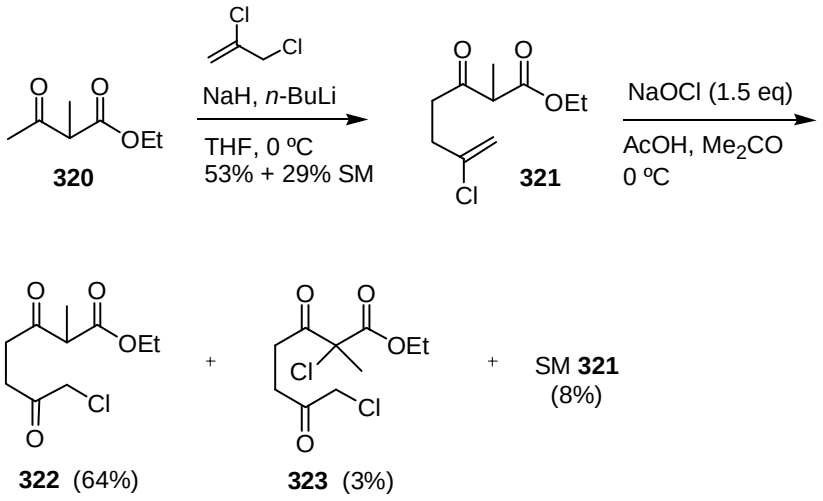
Scheme 78



In order to test the halogenation selectivity of other 1,3-dicarbonyl systems containing vinyl chlorides, we next examined β-ketoester vinyl chloride **321** (Scheme 79). Thus, alkylation of ketone **320** with 2,3-dichloropropene provided β-ketoester vinyl chloride **321**, which then was subjected to the standard chlorinating conditions to provide

α-chloroketone **322** as the major product in 64% yield. However, a small amount of chlorination at the β-ketoester moiety was observed, giving product **323** in only 3% yield. This chlorination of an α-substituted dicarbonyl compound might be rationalized by the greater enol content of β-ketoesters relative to malonates.

Scheme 79



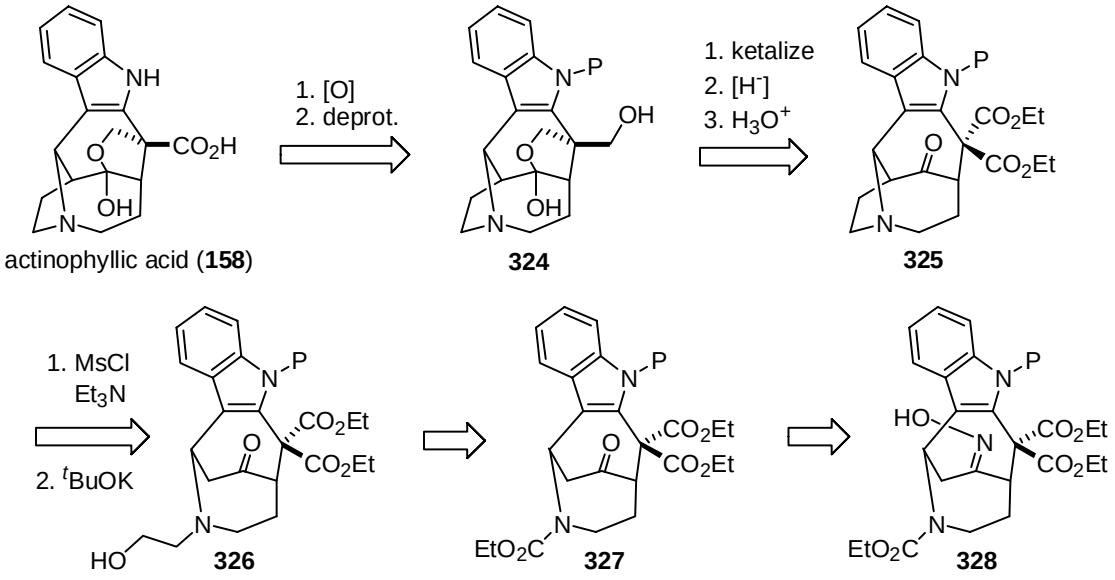
In summary, we have found that sodium hypochlorite and hypobromite in glacial acetic acid/acetone at 0 ºC are useful reagents for the halogenation of β-dicarbonyl compounds including malonates, β-ketoesters and 1,3-diketone substrates. In a series of competition experiments using NaOCl/AcOH/acetone, it was found that the reagent is highly selective for the conversion of a vinyl chloride moiety to the corresponding α-chloroketone over α-halogenation of α-substituted β-ketoesters and malonates. On the other hand, the selectivity of NaOCl is reversed with α-unsubstituted malonates, where substrate **313** gave predominately the α-dichlorinated malonate product **314**. Therefore, based on these model studies we believed that we could regioselectively synthesize the

required α-chloroketone substrates required for the intramolecular vinylnitroso methodology (Cf. Scheme 70).

4.1 Retrosynthetic Analysis for Actinophyllic Acid

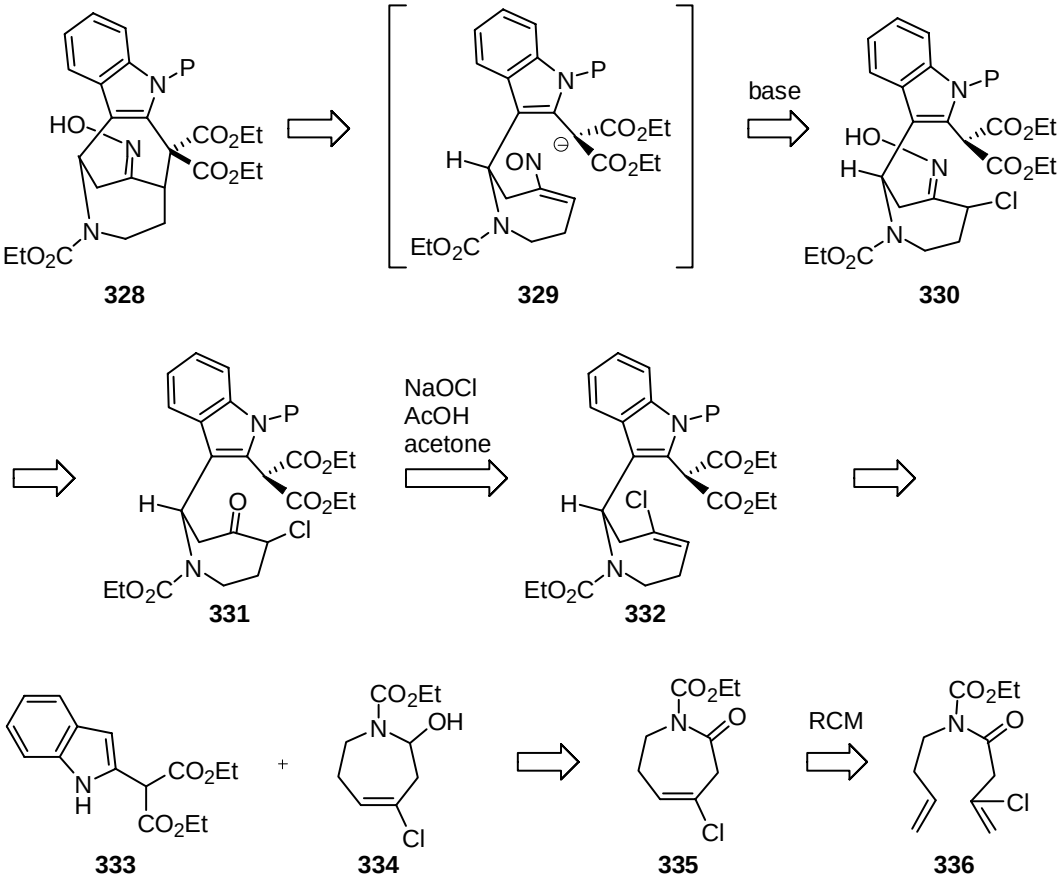
Our first generation synthetic strategy envisioned actinophyllic acid (**158**) being derived from the oxidation of primary alcohol **324** to the corresponding carboxylic acid, followed by indole deprotection (Scheme 80). To produce cyclic hemiketal **324**, ketone **325** would first be protected as a ketal, followed by reduction of the malonate to the diol and hydrolysis to give the desired cyclic system **324**. After conversion of alcohol **326** to the mesylate and subsequent treatment with potassium *t*-butoxide, the molecule would be subjected to an intramolecular enolate alkylation to install the two-carbon bridge and give ketone **325**. There is good literature precedent for similar transformations to introduce a two-carbon bridge in related β-aminoketone systems leading to other alkaloids.[117] Alcohol **326** would be derived from deprotection of carbamate **327**, followed by N-alkylation with 2-iodoethanol. Deoximation of **328** using Dess-Martin periodinane would provide ketone **327**.[109]

Scheme 80



Our proposed synthesis of actinophyllic acid incorporates several methods developed in the Weinreb group (*vide supra*). For example, an intramolecular conjugate addition of a malonate anion to vinylnitroso compound **329**, derived from α-chlorooxime **330**, would give advanced oxime **328** (Scheme 81).[108] Intermediate **329** should exist in the ring conformation shown, which has the indole moiety *quasi*-axial to minimize $A^{1,3}$-strain. In this conformation, the malonate anion is properly aligned stereoelectronically to react with the vinylnitroso functionality to yield the key intramolecular cyclization product **328**. The precursor to oxime **330**, α-chloroketone **331**, would be obtained from vinyl chloride **332** via a sodium hypochlorite oxidation.[92] Vinyl chloride **332** would be derived from the condensation of indole malonate **333** with the *N*-acyliminium ion derived from aminol **334**. Compound **334** would be generated from the partial reduction of lactam **335**. Ring-closing metathesis (RCM) of diene **336** would furnish cyclic vinyl chloride **335**.[73]

Scheme 81

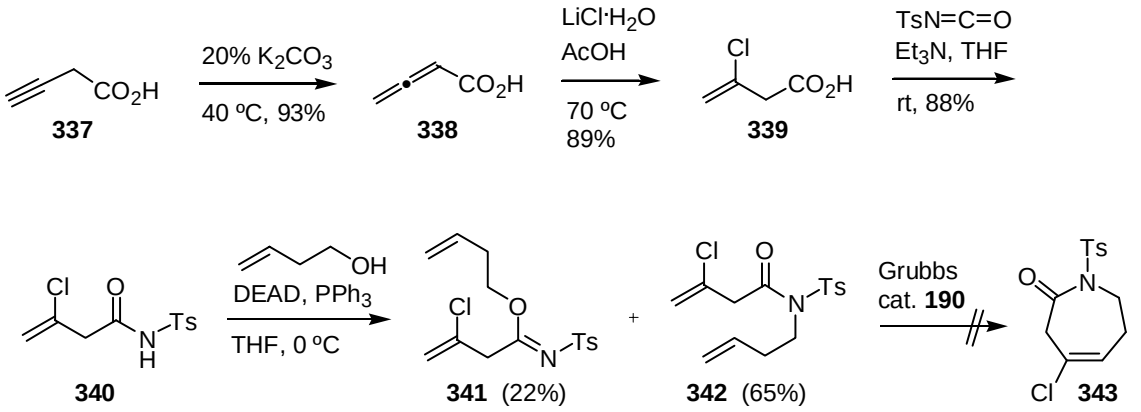


4.2 Lactam Approach to an Actinophyllic Acid Intermediate

Our synthetic approach to actinophyllic acid, as outlined in the strategy in Schemes 80 and 81, initially focused on the formation of lactam vinyl chloride **343**. Thus, treatment of 3-butynoic acid (**337**) with 20% aqueous potassium carbonate gave known allene **338**[118] in high yield, which was subsequently converted to known vinyl chloride **339**[119] using lithium chloride in acetic acid (Scheme 82). The carboxylic acid functionality of **339** reacted with tosylisocyanate in the presence of triethylamine to furnish *N*-tosylamide **340** in 88% yield.[120] Alkylation of compound **340** with 3-butenol

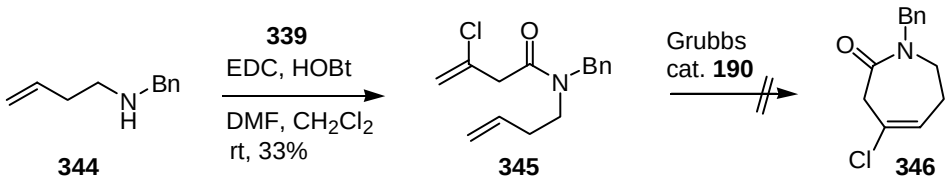
using Mitsunobu conditions, however, provided a 1:3 mixture of *O*- and *N*-alkylated products **341** and **342**, respectively.[121] Unfortunately, treatment of the desired amide **342** with either Grubbs first or second generation catalysts under various reaction conditions failed to give any of the RCM vinyl chloride product **343**.

Scheme 82



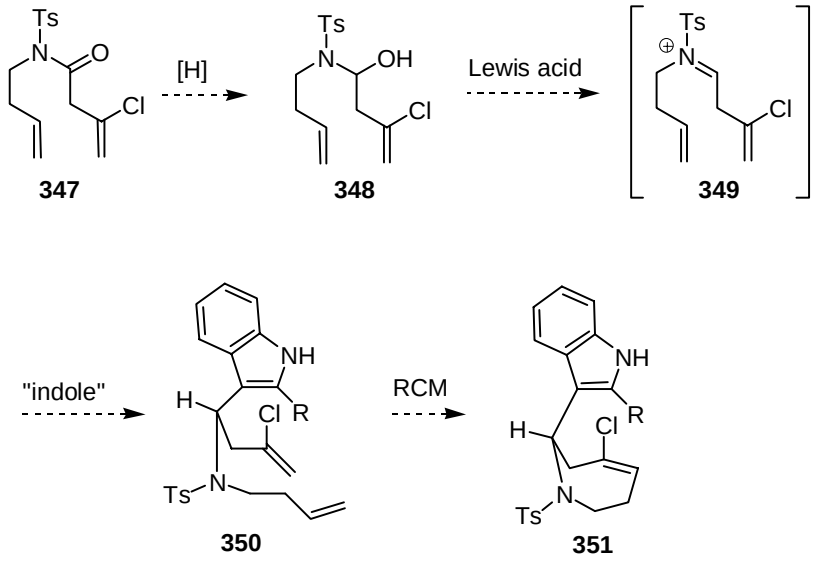
To determine if the nature of the amide *N*-protecting group in **342** influences the RCM results, we replaced the electron-withdrawing tosyl group with a simple benzyl protecting group. Thus, *N*-benzylamine **344** was coupled with carboxylic acid **339** using EDC and HOBt to give amide **345** (Scheme 83).[122] Unfortunately, as with the analogous *N*-tosyl compound **342**, RCM of **345** using a variety of conditions failed to provide the desired cyclic product **346**, with only recovered starting material being isolated. These results were not entirely surprising since previous RCM work to synthesize related lactams and lactones had met with failure (Cf. Scheme 59). Thus, an alternative route to access the requisite lactam **346** was devised.

Scheme 83



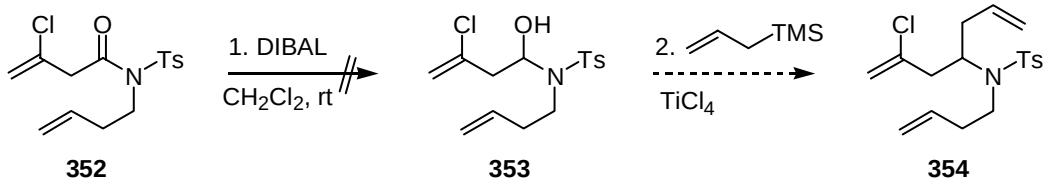
The strategy in the revised route was to partially reduce *N*-tosyl amide **347** to aminol **348**, which in the presence of a Lewis acid would generate *N*-sulfonyliminium ion **349** (Scheme 84). Subsequent condensation of iminium ion **349** with a 2-substituted indole would provide diene **350**. We hoped that the diene sulfonamide **350** would then readily undergo RCM to give the desired cyclic vinyl chloride **351**.

Scheme 84



Thus, to test this approach *N*-tosylamide **352** was treated with diisobutylaluminum hydride, followed by *in situ* addition of allyltrimethylsilane and a Lewis acid (Scheme 85).[123] Unfortunately, this reaction only produced an unidentifiable compound, along with recovered starting amide **352**. Attempting to perform the same reaction stepwise by first isolating aminol **353** and then subjecting it to allyltrimethylsilane also gave the same unidentified compound.[123c] In light of these difficulties, the synthetic strategy for actinophyllic acid required further modification.

Scheme 85

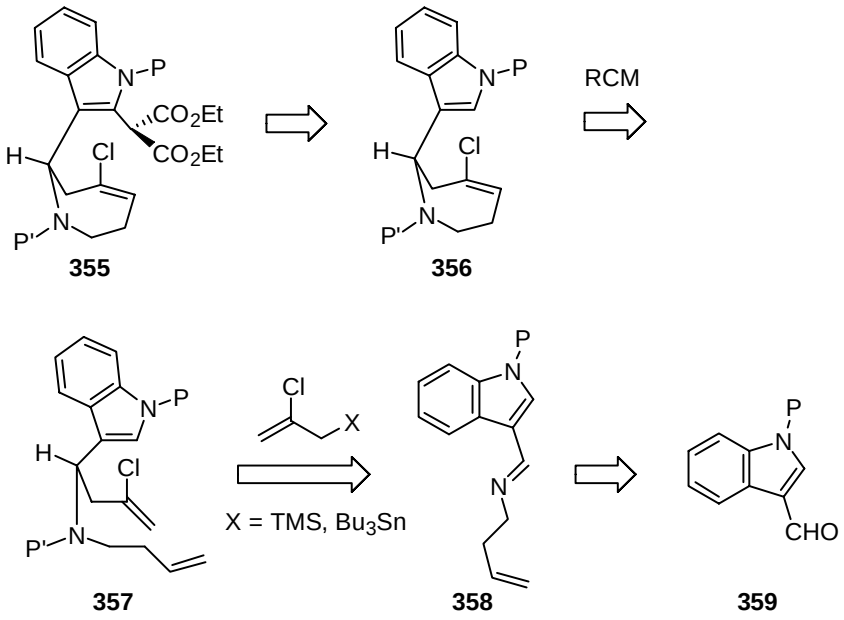


352 **353** **354**

4.3 Approach Involving an Imine Addition and Vinyl Chloride RCM

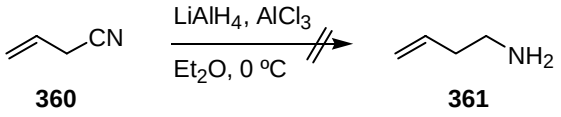
To circumvent the above problems, we decided to install the indole subunit into the system before the ring-closing metathesis step. Thus, RCM of diene **357** would give cyclic vinyl chloride **356**, and the malonate functionality would then be installed to give indole malonate **355** (Scheme 86). Diene **357** would be derived from Lewis acid-catalyzed nucleophilic addition of 2-chloroallyltrimethylsilane or the corresponding tributylstannane to imine **358**, followed by amine protection. Condensation of *N*-protected 3-formylindole **359** with 3-butenamine would produce imine **358**.

Scheme 86



Preparing known 3-butenamine (**361**) on large scale (>500 mg) via a literature procedure[124] from nitrile **360** proved to be difficult due to its volatility, which led to isolation problems (Scheme 87). As a result of this problem, a synthetic equivalent to amine **361** was required.

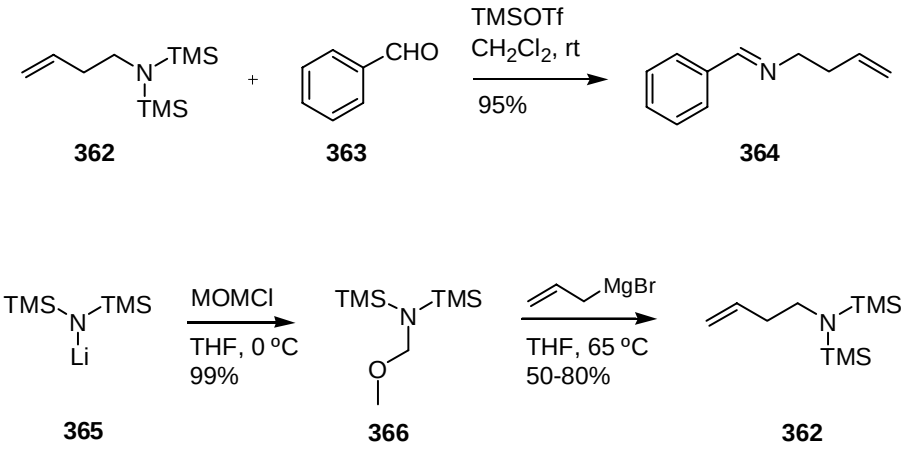
Scheme 87



Morimoto and Sekiya have reported that bis-TMS amine **362**, which can be used as a primary amine equivalent, undergoes condensation with benzaldehyde (**363**) catalyzed by TMS triflate to afford imine **364** in high yield (Scheme 88).[125] Thus, following literature procedures, treating methoxymethyl chloride (MOMCl) with lithium

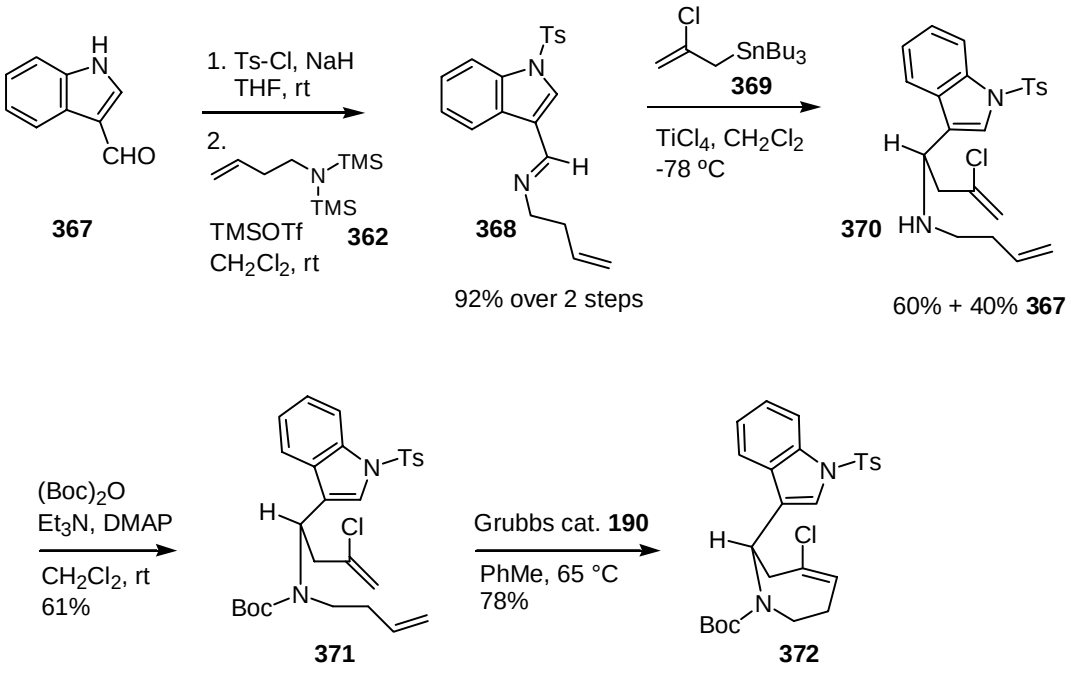
hexamethyldisilazide **365** cleanly provided MOM-protected bis-TMS amine **366** in nearly quantitative yield.[126] Exposure of amine **366** to allylmagnesium bromide in refluxing THF gave the known bis-TMS butenamine (**362**) in 50-80% yields, which was much less volatile than primary amine **361**. Interestingly, the yield of this Grignard addition step was quite variable, even when seemingly identical reactions were performed side-by-side.

Scheme 88



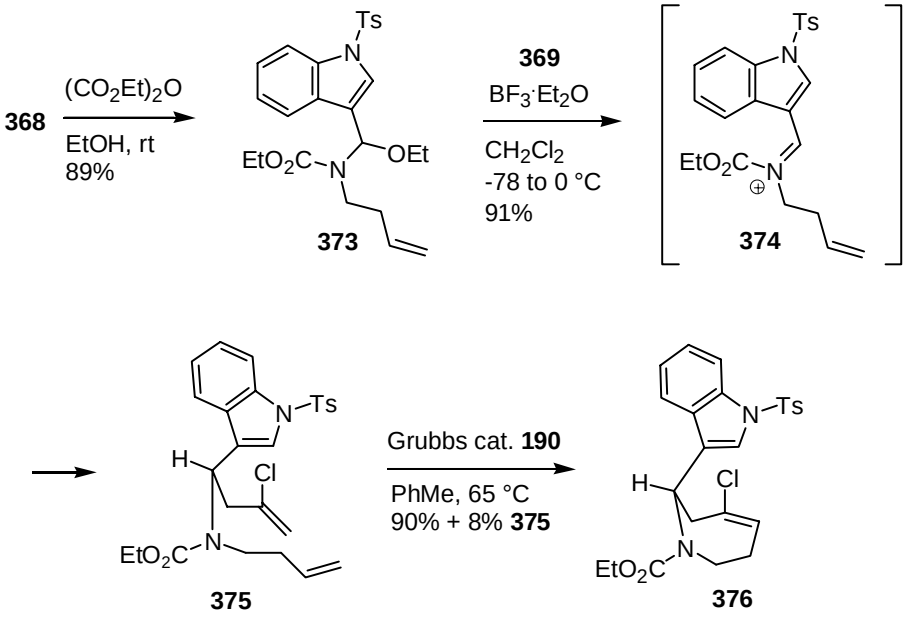
To continue with the synthesis, commercially available 3-formyl indole (**367**) was *N*-tosylated and then condensed with bis-TMS butenamine (**362**) in the presence of TMSOTf to provide imine **368** in 92% yield over two steps (Scheme 89).[125] Nucleophilic addition of vinyl chloride stannane **369**[127] to imine **368** gave 60% of the desired diene **370**, along with 40% of aldehyde **367** which is the result of imine hydrolysis.[128] Boc-protection of amine **370** furnished the RCM precursor **371** in good yield. We were pleased to find that subjecting diene **371** to Grubbs RCM catalyst **190** in toluene at 65 ºC provided cyclic vinyl chloride **372**.

Scheme 89



In an alternative sequence, imine **368** was reacted with diethyl pyrocarbonate in anhydrous ethanol to give α-ethoxycarbamate **373** in high yield (Scheme 90).[129] Treatment of **373** with a boron trifluoride etherate generated reactive iminium ion **374** *in situ*, followed by nucleophilic addition of vinyl chloride stannane **369** to afford diene **375**.[127] Subjecting diene **375** to Grubbs second generation catalyst in toluene provided cyclic vinyl chloride **376** in 90% yield, along with a small amount of recovered starting diene **375**. Since the overall yield of this second series was higher than the Boc-protected series (Cf. Scheme 89), we decided to optimize and proceed with this latter route.

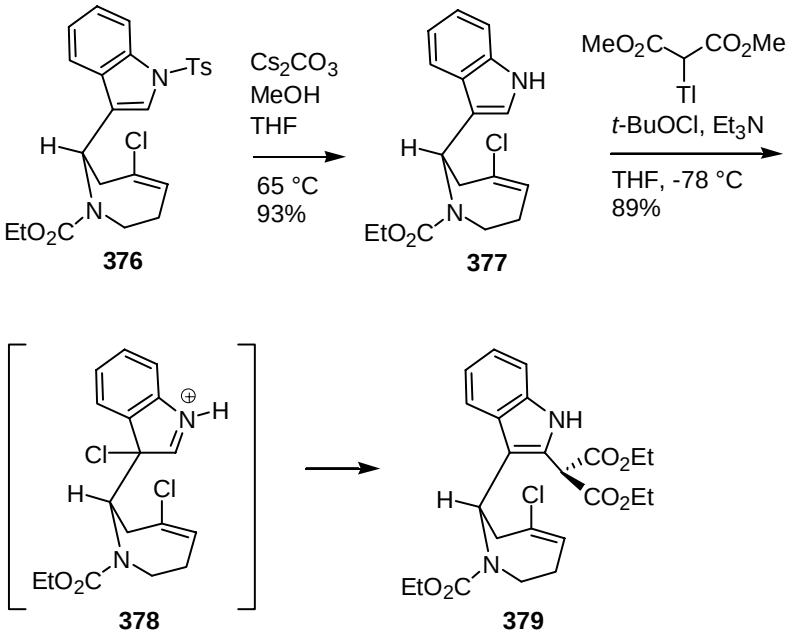
Scheme 90



4.4 Indole C-2 Functionalization and Vinyl Chloride Manipulation

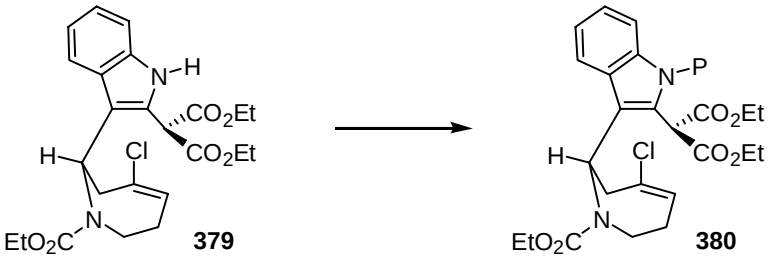
With the cyclic vinyl chloride **376** in hand, the next step was to introduce the malonate functionality at the C-2 position of the indole. Thus, deprotection of indole **376** with cesium carbonate in a refluxing methanol/THF mixture provided *N*-H indole **377** in excellent yield (Scheme 91).[130] Treatment of indole **377** with *t*-butyl hypochlorite at reduced temperature generated chloro indolonium intermediate **378** *in situ*. Subsequent addition of the thallium salt of dimethylmalonate[131] using methodology of Kuchne gave indole **379**, which contained the desired malonate functionality at C-2.[132]

Scheme 91



Protection of *N*-H indole **379** proved difficult. However, it was found that if **379** is treated with Boc anhydride, triethylamine, and 4'-dimethylaminopyridine (DMAP), *N*-Boc-protected indole **380a** is formed in 60% yield, along with some recovered starting

Scheme 92

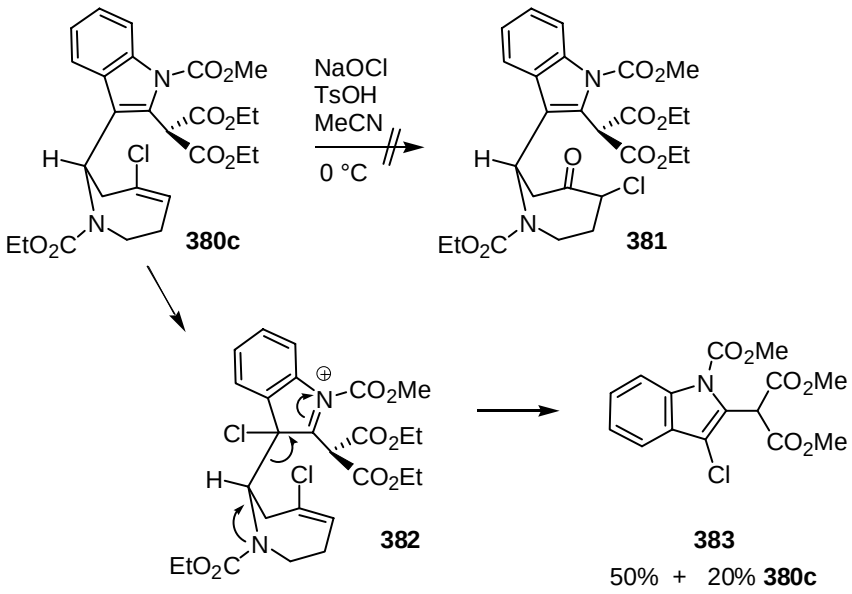


	Protecting Group	Conditions	Results
380a	Boc	$(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2	60% + 40% SM
380b	Ts	TsCl, Bu_4NBr, 30% NaOH, CH_2Cl_2	15% + decomp.
380c	CO_2Me	$ClCO_2Me$, Bu_4NBr, 30% NaOH, CH_2Cl_2	40% + decomp.

material (Scheme 92). Furthermore, *N*-H indole **379** could be tosyl-protected using phase transfer conditions to yield *N*-tosyl indole **380b**, albeit in low yield due to significant decomposition.[133] Using similar conditions, indole **379** could also be protected in moderate yield as the methyl carbamate **380c**.

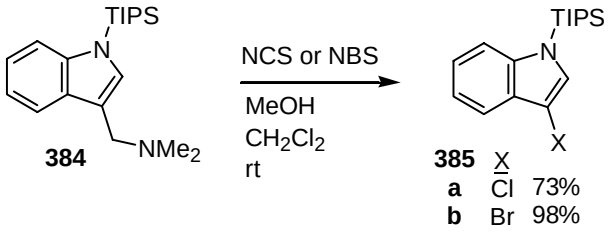
To continue the synthesis, we attempted to convert vinyl chloride **380** to the corresponding α-chloroketone **381** (Scheme 93). This chloroketone **380** is required for the key vinylnitroso cyclization in the synthesis of actinophyllic acid **158** (Cf. Scheme 81). Unfortunately, treatment of vinyl chloride **380c** with sodium hypochlorite and *p*-toluenesulfonic acid in acetonitrile at 0 ºC gave 3-chloroindole **383** in 50% yield, along with recovered starting vinyl chloride **380**. The use of other chlorinating agents and various reaction conditions was unsuccessful. Furthermore, the conversion of *N*-protected indole vinyl chlorides **380a** and **380b** to the corresponding α-chloroketones also failed, with only 3-chloroindole **383** being isolated in small quantities.

Scheme 93



We believe that 3-chloroindole **383** is a result of a retro-Mannich fragmentation of 3-chloroindolonium intermediate **382**. Precedent for this fragmentation process can be found in the work of the Snieckus group, where it was found that in the presence of NXS (X = Cl, Br, I), gramine derivatives rapidly undergo retro-Mannich fragmentation to afford 3-haloindoles in moderate to good yields.[134] For example, reaction of *N*-TIPS gramine (**384**) with either NCS or NBS gave 3-chloro- and 3-bromoindole, **385a** and **385b**, respectively (Scheme 94). As a result of the failed α-chloroketone formation, we decided to investigate functional groups other than a vinyl chloride that would be more easily converted to an α-chloroketone.

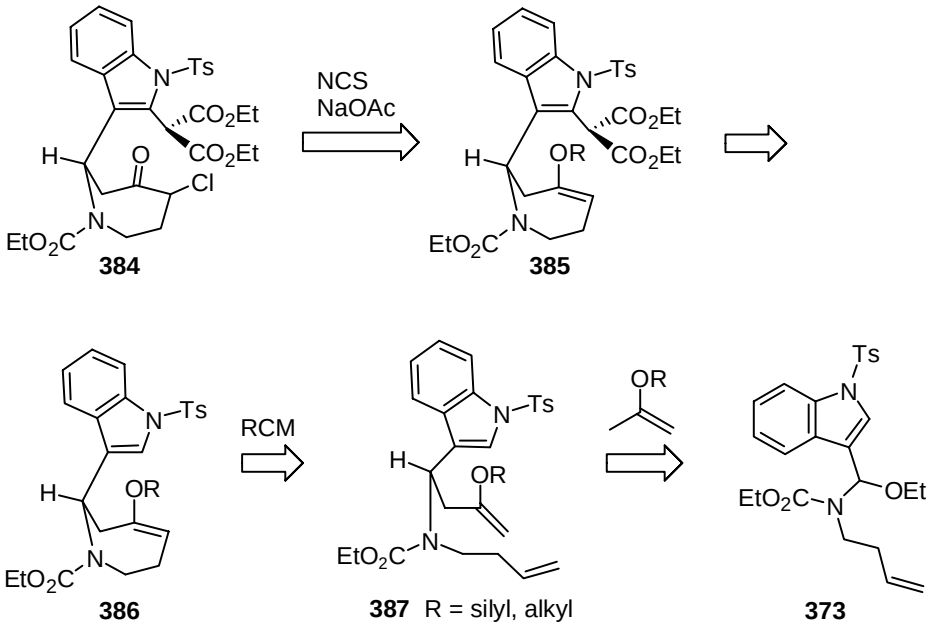
Scheme 94



4.5 Enol Ethers as Precursors to α-Chloroketones

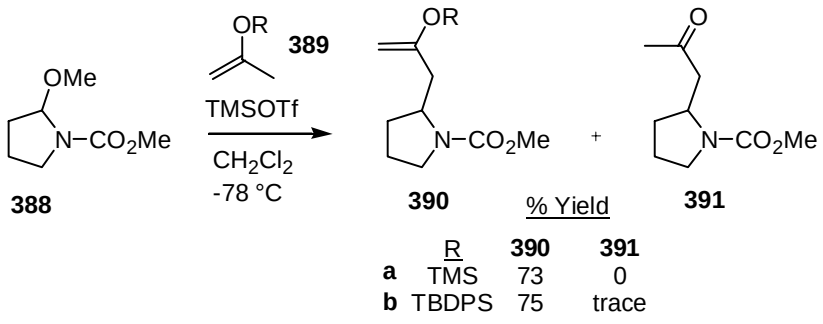
Our revised strategy was to synthesize cyclic enol ether **386** via ring-closing metathesis of diene **387** (Scheme 95). As previously discussed, both silyl- and alkylenol ether dienes undergo RCM and the electron rich cyclic enol ether products can be converted to the corresponding α-chloroketones (Cf. Schemes 61 and 64). Therefore, we envisioned that diene **387** would be derived from an ene-type reaction of an enol ether to α-ethoxycarbamate **373**. After installation of a C-2 malonate functionality on indole **386**, enol ether **385** would be converted to α-chloroketone **384**.

Scheme 95



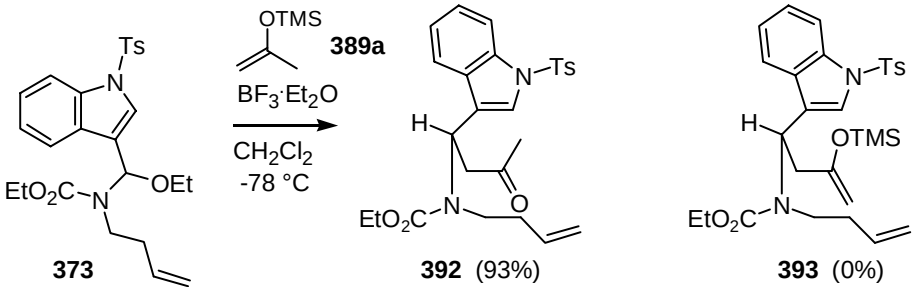
Mikami and Ohmura have recently reported that the ene-type reaction of TMS-enol ether **389a** (R = TMS) and α-methoxy pyrrolidine **388** in the presence of a Lewis acid (TMSOTf) gave the silylenol ether product **390a** in 73% yield (Scheme 96).[135] Similarly, when TBDPS-enol ether **389b** was used in the reaction, the enol ether product **390b** was obtained in slightly higher yield (75%). In addition, a trace amount of ketone **391b** due to desilylation of enol ether **390b** was also isolated from the reaction mixture.

Scheme 96



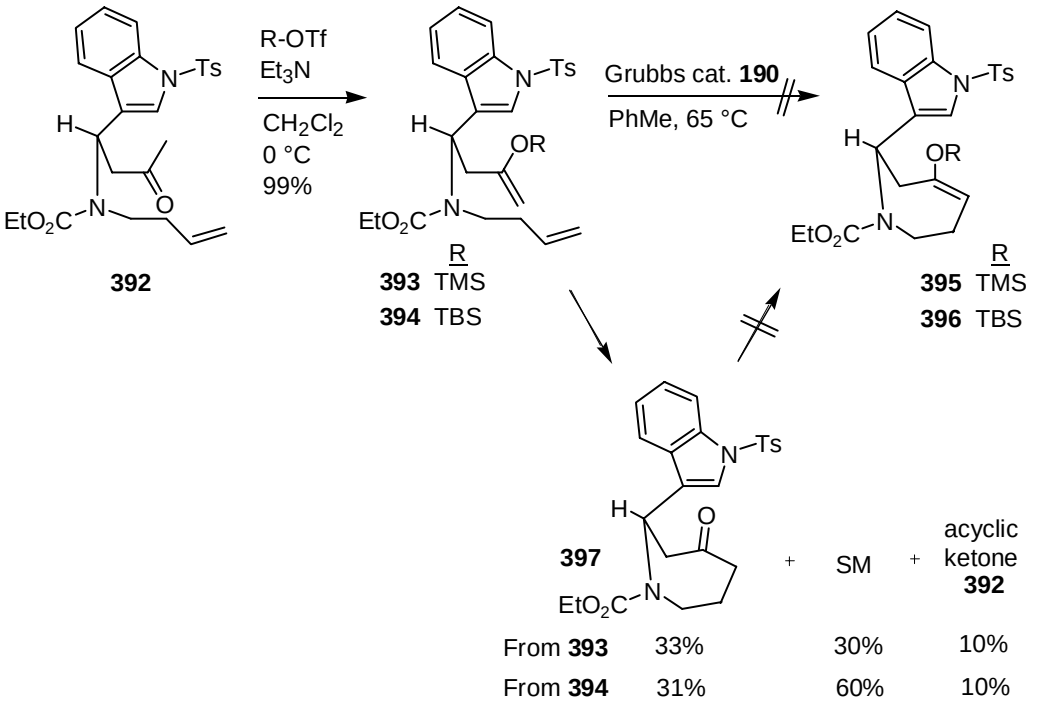
Thus, employing the Mikami ene reaction procedure, α-ethoxycarbamate **373** was condensed with TMS-enol ether **389a** in the presence of $BF_3 \cdot Et_2O$ to afford ketone **392** in excellent yield, but none of the desired TMS-enol ether product **393** was detected (Scheme 97).

Scheme 97

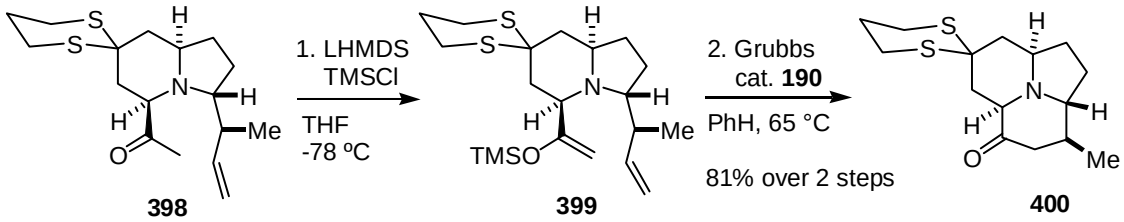


It was found, however, that treatment of ketone **392** with either TMSOTf or TBSOTf provided the corresponding TMS- or TBS-enol ether **393** or **394**, respectively (Scheme 98). Unfortunately, exposure of diene **393** to Grubbs RCM catalyst **190** gave the desilylated cyclic ketone **397** as the major product, along with recovered diene **393** and desilylated acyclic ketone **392**. Similar results were obtained from RCM attempts with TBS-enol ether diene **394**. In addition, various attempts at converting ketone **397** to cyclic enol ether **395** failed. It should be noted that Smith and Kim have reported that the RCM reaction of silylenol ether **399** using Grubbs second generation catalyst **190** provided the desilylated cyclic ketone **400** (Scheme 99). In light of these difficulties, we decided to examine a more stable alkylenol ether.

Scheme 98



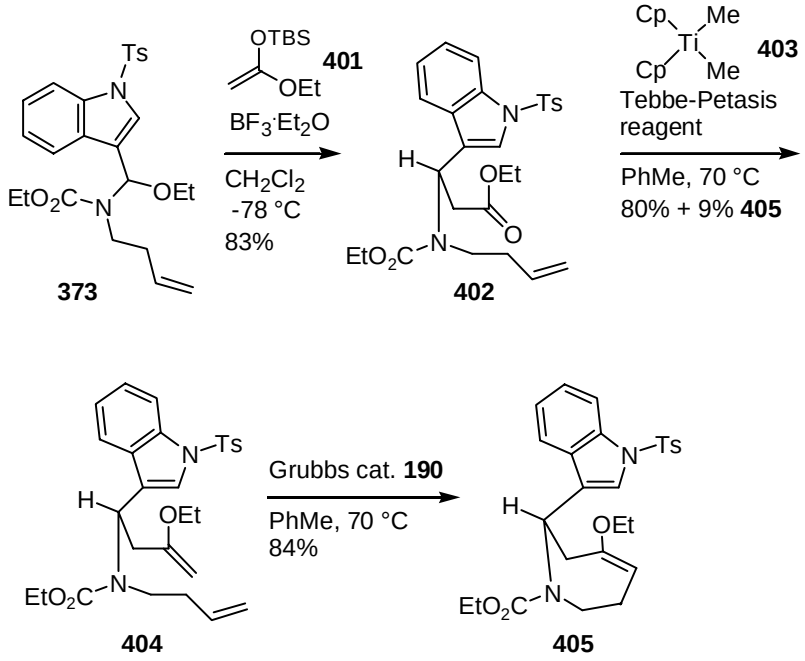
Scheme 99



Since, the ene-type reactions of electrophiles such as iminium ions or aldehydes with simple alkylenol ethers **389** (i.e. R = Me, Cf. Scheme 96) to form the corresponding condensation product **390** have not been reported, we therefore required another route to synthesize the alkylenol ether diene **404** (Scheme 100). Towards this end, α-ethoxycarbamate **373** was condensed with *O*-TBS ketene acetal **401** in the presence of boron trifluoride etherate to give carbamate ester **402** in good yield.[136] Conversion of

ester **402** to ethylenol ether **404** with Tebbe reagent[137] was successful on small scale reactions (<100 mg). However, decomposition problems occurred with this reaction on scale up. On the other hand, treatment of ester **402** with the less reactive Tebbe-Petasis reagent **403** produced ethylenol ether **404** in 80% yield, along with 9% of the desired metathesis product **405**.[138] We were pleased to find that subjecting diene **404** to Grubbs RCM ruthenium catalyst **190** gave the desired seven-membered cyclic ethylenol ether **405** in good yield.

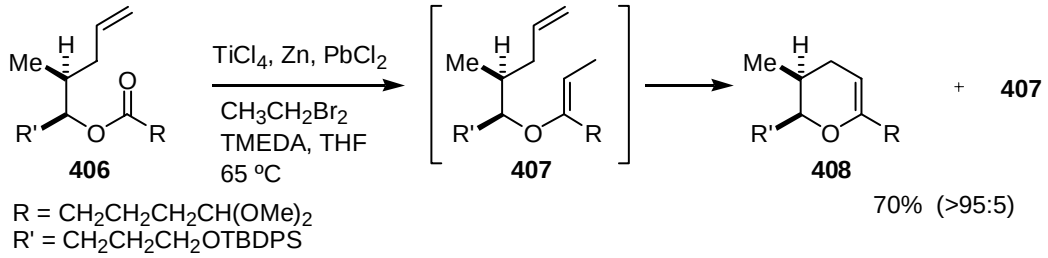
Scheme 100



The isolation of some of the metathesis product **405** from the Tebbe-Petasis methylenation of ester **402** was unexpected. However, prior work by Rainer and coworkers involved a similar RCM transformation of esters to cyclic enol ethers using a low valent titanium ethylidene reagent prepared *in situ*.[139,140] For example, treatment of

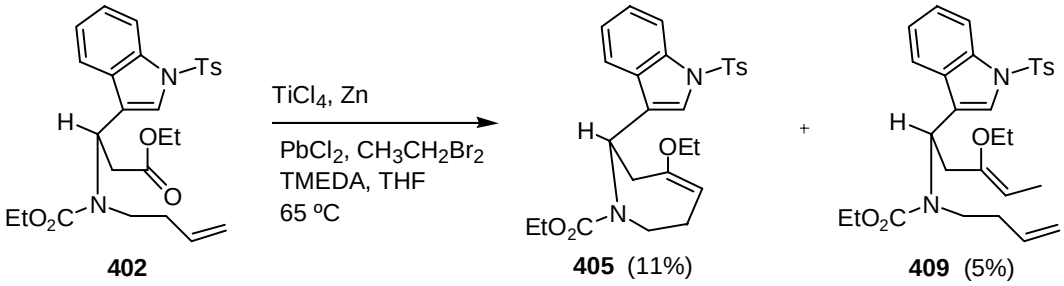
olefinic ester **406** under the reaction conditions outlined in Scheme 101 gave a >95:5 mixture of cyclic enol ether **408** and acyclic enol ether **407**, respectively, in 70% total yield. It is thought that acyclic enol ether **407** is first formed and then reacts further with the titanium ethylidene reagent to yield the metathesis product **408**. However, the exact nature of the active titanium species in the reaction is presently unknown.

Scheme 101



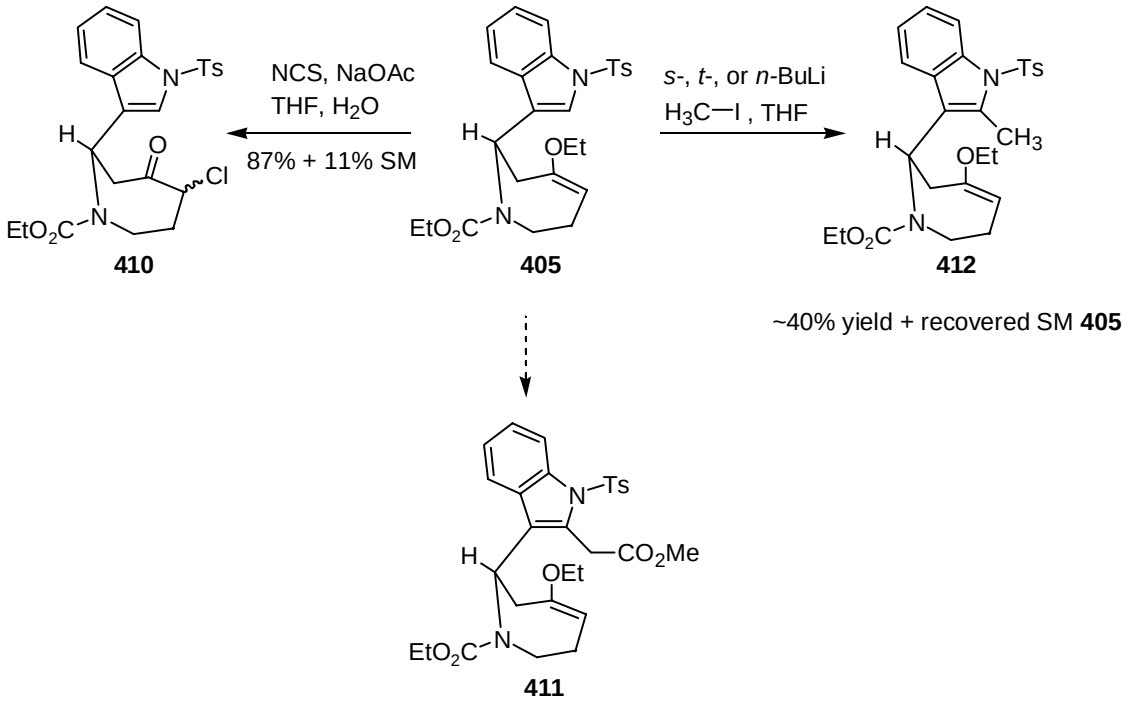
All of Rainier's acyclic ester substrates produced cyclic enol ethers, but attempts to produce cyclic systems with the oxygen atom exocyclic to the ring have not been reported to date. Unfortunately, when we subjected ester **402** to Rainer's conditions in an attempt to effect a one-pot methylenation/RCM, the desired exocyclic ethylenol ether **405** was obtained in only low yield, along with small amount of the acyclic enol ether diene **409** and decomposed starting material (Scheme 102).

Scheme 102



With cyclic enol ether **405** in hand, we next tested some of the steps we intended to use leading to an actinophyllic precursor like **331** (Cf. Scheme 81). Thus, we were pleased to see that exposure of enol ether **405** to NCS furnished α-chloroketone **410** as a diastereomeric mixture in 87% yield, along with a small amount of unreacted starting material (Scheme 103).

Scheme 103



In addition, we wanted to probe the possibilty of introducing functionality at the C-2 position of indole **405** to form an alkylated product such as **411**. This acetate ester functionality would be used as the nucleophile in the intramolecular vinylnitroso cyclization (Cf. **330** to **328**, Scheme 81). In a model experiment, it was found that indole **405** could be selectively metallated at C-2 using a variety of alkyllithium bases, followed by alkylation with methyl iodide to give 2-methylindole **412** in moderate yield along with

recovered starting indole **405**.[141] Attempts to form C-2 indole zinc[142] or cuprate[143] reagents before addition of an electrophile to the reaction mixture did not improve the yield of **412**. Since indole **405** can be successfully metallated and alkylated, the plan is to now use an appropriate electrophile such as methyl iodoacetate to form **411** (*vide infra*).

4.6 Conclusions and Future Work

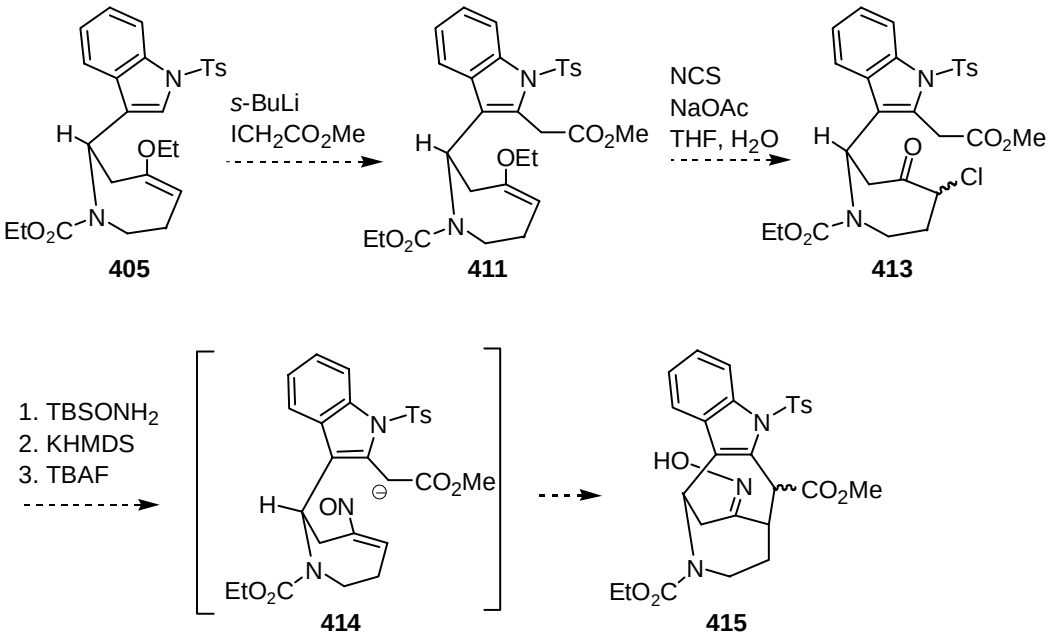
Synthetic efforts towards a total synthesis of actinophyllic acid (**158**) have been described. An initial route to the natural product which was investigated involves the conversion of cyclic vinyl chloride **380**, obtained via RCM of vinyl chloride olefin **375**, to α-chloroketone **381**. However, a retro-Mannich fragmentation process occurred during this reaction, giving the undesired 3-chloroindole **383**. To circumvent this problem, we have investigated the regioselective formation of the desired α-chloroketone via chlorination of silyl- and alkylenol ethers, which are more electron rich than their vinyl chloride counterparts and thus are more reactive towards electrophilic chlorinating reagents. Unfortunately, silylenol ethers **393** and **394** proved to be too labile and did not survive the ring-closing metathesis step.

On the other hand, exposure of ethylenol ether diene **404** to Grubbs second generation RCM catalyst **190** did furnish the desired cyclic product **405**. This enol ether product **405** could be converted to the corresponding α-chloroketone **410** in high yield. Furthermore, *N*-tosyl indole **405** could be metallated with a variety of organic bases and alkylated with methyl iodide to give the C-2 methylindole model substrate **412**. This tactic avoids the problems previously experienced with *N*-protection of a C-2 substituted

indole system (Cf. Scheme 92). The metallation chemistry should allow for installation of the proper nucleophilic handle, such as an ester, required for the intramolecular Michael addition to a vinylnitroso intermediate.

In light of the promising C-2 indole metallation chemistry (Cf. Scheme 103), future studies will focus on the alkylation of indole **405** with methyl iodoacetate to give ester **411** (Scheme 104). Ethylenol ether **411** will then be transformed to α-chloroketone **413**. Conversion of ketone **413** to the corresponding *O*-TBS-oxime, and subsequent treatment of with base and tetrabutylammonium fluoride should provide the key cyclization product **415** via vinylnitroso intermediate **414**.

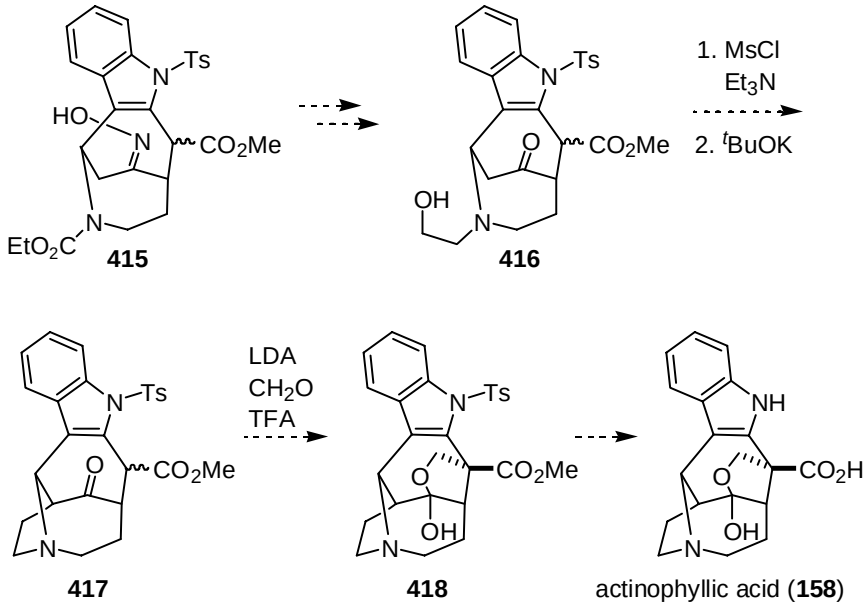
Scheme 104



To continue the synthesis, oxime **415** will then be converted to the corresponding ketone using Dess-Martin periodinane. Removal of the amine carbamate protecting

group, followed by *N*-alkylation with 2-iodoethanol should furnish alcohol **416** (Scheme 105). Formation of the mesylate of alcohol **416** and exposure to potassium *t*-butoxide would install the required two carbon bridge via an intramolecular enolate alkylation to produce ketone **417**. A stereoselective aldol reaction[144] of the enolate derived from ester **417** with monomeric formaldehyde would form lactol **418**, as was done by Overman in a closely related system (Cf. Scheme 50).[67] Finally, hydrolysis of ester **417** and indole deprotection would yield racemic actinophyllic acid (**158**).

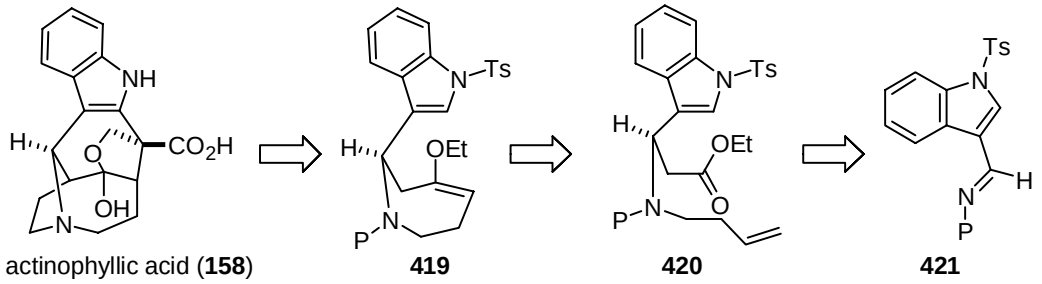
Scheme 105



Future work will also be directed towards an enantioselective synthesis of actinophyllic acid. Since the absolute stereochemistry of the alkaloid is unknown, we will arbitrarily prepare one of the enantiomers of ester **420** (i.e. R-configuration shown) via an enantioselective addition of a *O*-silylketene acetal of ethyl acetate to imine **421** (Scheme

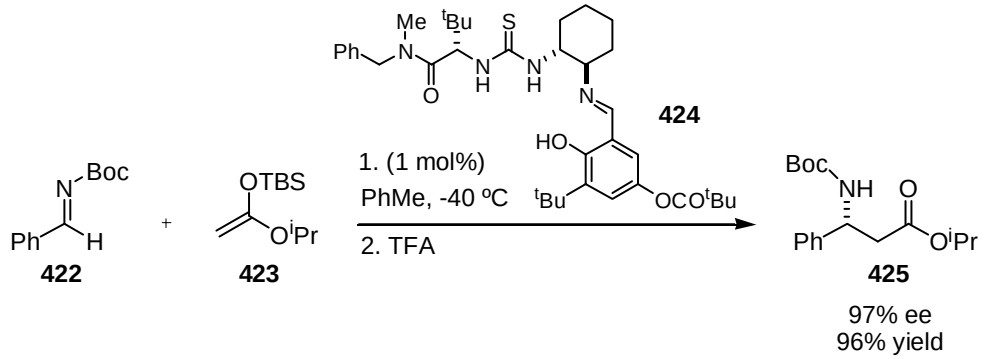
106). By setting this initial stereocenter, we would thereby control the configuration of the remaining four stereocenters leading to enantiopure actinophyllic acid (**158**).

Scheme 106



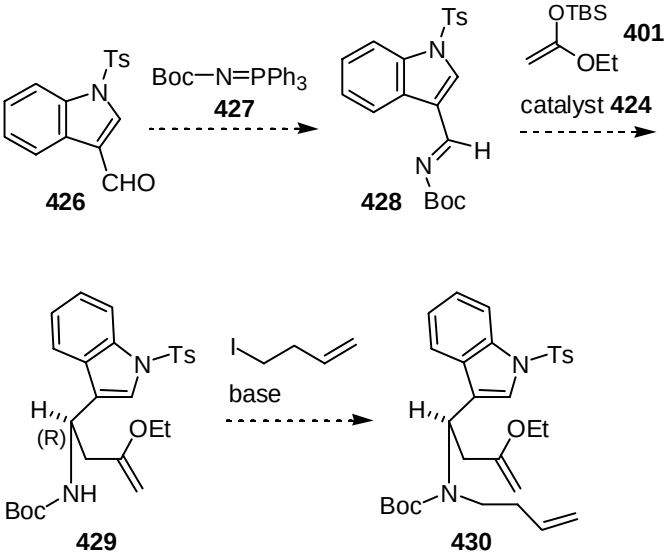
There is good literature precedent for the enantioselective addition of *O*-silylketene additions to *N*-acylimines.[145] For example, Jacobsen and coworkers have reported the enantioselective addition of ketene acetal **423** to *N*-Boc imine **422** using chiral catalyst **424** to afford β-aminoester **425** with the R-configuration in 97% ee and in high yield (Scheme 107).[146]

Scheme 107



For an enantioselective synthesis of actinophyllic acid, imine **428** will be prepared via condensation between aldehyde **426** and iminophosphorane **427** (Scheme 108).[147,148] An enantioselective addition of TBS ketene acetal **401** to imine **428** in the presence of Jacobsen's chiral catalyst **424** would afford *N*-Boc amine **429**. Subsequent deprotonation of *N*-Boc amine **429** with base, followed by alkylation with 4-iodobutene would then provide enantiopure diene **430**, which would be used for the synthesis of actinophyllic acid as previously done in the racemic series.[149]

Scheme 108

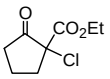


EXPERIMENTAL SECTION

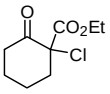
General Methods

All non-aqueous reactions were carried out under a positive atmosphere of nitrogen or argon in flame-dried glassware unless otherwise noted. Air and moisture sensitive liquid reagents were added via a dry syringe. Anhydrous THF, CH_2Cl_2, diethyl ether, and toluene were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300, CDPX-300, or DRX-400 MHz spectrometers. Chemical shifts of ^1H and ^{13}C NMR spectra were referenced to the solvent peaks: δ_H 3.30 and δ_C 49.0 for CD_3OD, δ_H 2.09 for toluene-d_8. Flash chromatography was performed using Sorbent Technologies silica gel 60 (230-400 mesh).

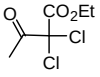
General Procedure for Monochlorination of a 1,3-Dicarbonyl Compound. To a solution of 1,3-dicarbonyl compound (1.20 mmol) in acetone (5 mL) and acetic acid (2 mL) cooled to 0 ºC was added dropwise sodium hypochlorite solution (0.83 mL, 1.80 mmol, 1.21 g/mL, 10-13% v/v). The solution was stirred for 1 h at 0 ºC, then poured into saturated Na_2CO_3 solution (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 10/1) to afford the monochlorinated product. Dichlorination was effected using the same procedure with 3.60 mmol of sodium hypochlorite.



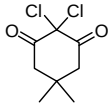
1-Chloro-2-oxocyclopentanecarboxylic Acid Ethyl Ester (Table 2, Entry a). Clear oil (88 %): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (t, J = 8.5 Hz, 3H), 2.05 (m, 2H), 2.34 (m, 2H), 2.47 (m, 1H), 2.68 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.6, 167.6, 70.1, 63.5, 38.8, 35.7, 19.5, 14.4; ESI (+): $[M+Na]^+$ calcd for $C_8H_{11}O_3ClNa$, 213.0294; found 213.0298.



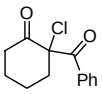
1-Chloro-2-oxocyclohexanecarboxylic Acid Ethyl Ester (Table 2, Entry b). Clear oil (94 %): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.69 (m, 1H), 1.83 (m, 3H), 2.06 (m, 1H), 2.38 (m, 1H), 2.75 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.9, 167.5, 73.9, 63.2, 40.0, 39.2, 27.0, 22.5, 14.2; ESI (+): $[M+Na]^+$ calcd for $C_9H_{13}O_3ClNa$, 227.0451; found 227.0444.



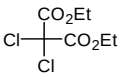
2,2-Dichloro-3-oxobutyric Acid Ethyl Ester (Table 2, Entry c). Clear oil (88 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 2.42 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 163.6, 82.2, 65.0, 23.8, 14.1; ESI (+): $[M+Na]^+$ calcd for $C_6H_8O_3Cl_2Na$, 220.9748; found 220.9750.



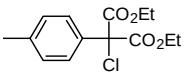
2,2-Dichloro-5,5-dimethylcyclohexane-1,3-dione (Table 2, Entry d). White solid (67 %): ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.97 (s, 6H), 2.89 (s, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 192.6, 85.5, 49.2, 30.8, 28.4; ESI (-): $[M-H]^+$ calcd for $C_8H_9O_2Cl_2$, 206.9980; found 206.9974.



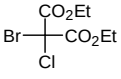
2-Benzoyl-2-chlorocyclohexanone (Table 2, Entry e). Clear oil (96 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 3H), 1.90 (s, 1H) 2.03 (m, 1H), 2.13 (m, 1H), 2.69 (m, 1H), 2.97 (m, 1H), 7.33 (m, 2H), 7.45 (m, 1H), 7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 191.2, 134.6, 134.0, 130.4, 128.9, 77.4, 41.7, 41.5, 28.7, 23.3; ESI (+): $[M+H]^+$ calcd for $C_{13}H_{14}O_2Cl$, 237.0682; found 237.0681.



2,2-Dichloromalonic Acid Diethyl Ester (Table 2, Entry f). Clear oil (98 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 6H), 4.30 (q, J = 7.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 77.7, 65.0, 14.1; ESI (+): $[M+Na]^+$ calcd for $C_7H_{10}O_4Cl_2Na$, 250.9854; found 250.9853.

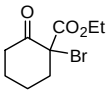


2-Chloro-2-(*p*-tolyl)malonic Acid Diethyl Ester (Table 2, Entry g). Clear oil (87 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 6H), 2.28 (s, 3H), 4.25 (q, J = 7.1 Hz, 4H), 7.10 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 139.5, 132.4, 129.3, 128.1, 72.6, 63.9, 21.5, 14.2; ESI (+): $[M+Na]^+$ calcd for $C_{14}H_{17}O_4ClNa$, 307.0713; found 307.0721.

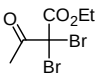


2-Bromo-2-chloromalonic Acid Dimethyl Ester (Table 2, Entry h). Clear oil (99 %): ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.695 (m, 1H), 1.83 (m, 3H), 2.06 (m, 1H), 2.387 (m, 1H), 2.75 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ ESI (+): $[M+H]^+$ calcd for $C_5H_7O_4ClBr$, 244.9216; found 244.9214.

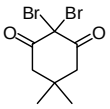
General Procedure for Monobromination of a 1,3-Dicarbonyl Compound. To a solution of sodium hydroxide (2.0 g, 50.0 mmol) in water (25 mL) at 0 ºC was slowly added bromine (0.85 mL, 16.6 mmol). The solution was stirred for 15 min and used immediately. To a solution of 1,3-dicarbonyl compound (1.20 mmol) in acetone (5 mL) and acetic acid (2 mL) cooled to 0 ºC was added dropwise sodium hypobromite solution (2.71 mL, 1.80 mmol, 0.66M). The solution was stirred for 1 h at 0 ºC, then poured into saturated Na_2CO_3 solution (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 10/1) to afford the monobrominated product. Dibromination was effected using the same procedure with 3.60 mmol of sodium hypobromite.



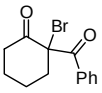
1-Bromo-2-oxocyclohexanecarboxylic Acid Ethyl Ester (Table 2, Entry b). Clear oil (95 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.69 (m, 1H), 1.85 (m, 3H), 2.16 (m, 1H), 2.38 (m, 1H), 2.84 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 167.9, 68.0, 63.3, 40.9, 39.2, 27.2, 23.5, 14.2; ESI (+): $[M+Na]^+$ calcd for $C_9H_{13}O_3BrNa$, 270.9946; found 270.9943.



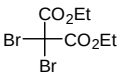
2,2-Dibromo-3-oxobutyric Acid Ethyl Ester (Table 2, Entry c). Clear oil (90 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 2.52 (s, 3H), 4.30 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 164.0, 65.1, 60.3, 23.9, 14.1; ESI (+): $[M+Na]^+$ calcd for $C_6H_8O_3Br_2Na$, 308.8738; found 308.8731.



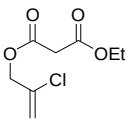
2,2-Dibromo-5,5-dimethylcyclohexane-1,3-dione (Table 2, Entry d). White solid (81 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 6H), 2.94 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 66.8, 48.6, 30.9, 28.1; ESI (+): $[M-H]^+$ calcd for $C_8H_9O_2Br_2$, 294.8969; found 294.8970.



2-Benzoyl-2-bromocyclohexanone (Table 2, Entry e). Clear oil (98 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (m, 3H), 1.92 (m, 1H) 2.17 (m, 2H), 2.75 (m, 1H), 3.10 (m, 1H), 7.33 (m, 2H), 7.47 (m, 1H), 7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 190.8, 134.9, 133.9, 130.5, 128.9, 72.5, 42.7, 41.6, 28.8, 24.1.

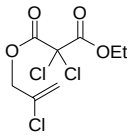


2,2-Dibromomalonic Acid Diethyl Ester (Table 2, Entry f). Clear oil (96 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6H), 4.29 (q, J = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 65.1, 51.1, 14.1; ESI (+): $[M+Na]^+$ calcd for $C_7H_{10}O_4Br_2Na$, 338.8844; found 338.8852.

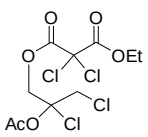


2-Oxosuccinic Acid 4-(2-chloro-allyl) Ester 1-Ethyl Ester (313). To a solution of potassium ethyl malonate **311** (2.02 g, 11.9 mmol) in CH_2Cl_2 (24 mL) was added EDCI (2.28 g, 11.9 mmol), TEA (1.09 g, 10.8 mmol), DMAP (0.13 g, 1.08 mmol) and 2-chloropropene-3-ol (**312**, 1.00 g, 10.8 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min, then warmed to rt and stirred for 22 h. The reaction mixture was washed with NH_4Cl (40 mL), saturated Na_2CO_3 (40 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/ether, 5/1) afforded ester **313** (1.76 g, 79 %)

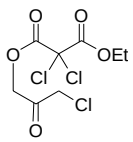
as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3H), 3.37 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.65 (s, 2H), 5.43 (d, *J* = 1.8 Hz, 1H), 5.44 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.0, 135.5, 115.6, 66.9, 62.0, 41.7, 14.4.



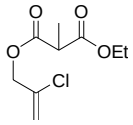
2,2-Dichloromalonic Acid 2-Chloroallyl Ester Ethyl Ester (314). To a solution of vinyl chloride malonate **313** (248 mg, 1.20 mmol) in acetone (5 mL) and acetic acid (2 mL) cooled to 0 ºC was added dropwise sodium hypochlorite solution (1.73 mL, 3.60 mmol, 1.21 g/mL, 10-13% v/v). The solution was stirred for 1 h at 0 ºC, then poured into saturated Na_2CO_3 solution (30 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 4/1) to afford the dichlorinated product **314** (211 mg, 64 %), along with trichloroacetate **315** (23 mg, 5 %) and α-chloroketone **316** (24 mg, 7 %). **314**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.78 (s, 2H), 5.42 (d, *J* = 2.0 Hz, 1H), 5.504 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 162.5, 134.2, 117.0, 69.4, 65.3, 65.1, 14.1.



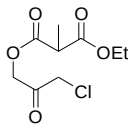
2,2-Dichloromalonic Acid 2-Acetoxy-2,3-Dichloropropyl Ester Ethyl Ester (315). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.08 (s, 3H), 3.90 (d, *J* = 12.1 Hz, 1H), 4.34 (m, 3H), 4.74 (d, *J* = 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 164.3, 163.6, 96.4, 79.2, 69.5, 67.0, 47.5, 23.5, 15.7; ESI (+): $[M+Na]^+$ calcd for $C_{10}H_{12}O_6Cl_4Na$, 392.9; found 392.9.



2,2-Dichloromalonic Acid 3-Chloro-2-oxo-propyl Ester Ethyl Ester (316). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 4.12 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 5.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 162.8, 162.7, 69.3, 65.5, 45.9, 30.1, 14.1.

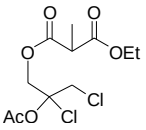


2-Methyl-3-oxosuccinic Acid 1-(2-chloroallyl) Ester 4-Ethyl Ester (317). To a solution of ester **313** (207 mg, 1.00 mmol) and Cs_2CO_3 (326 mg, 1.00 mmol) in DMF (1 mL) was added iodomethane (142 mg, 0.80 mmol) dropwise at rt. The reaction mixture was stirred at rt for 20 h, then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/ether, 8/1) afforded methylated ester **317** (152 mg, 86 %) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.38 (d, *J* = 7.3 Hz, 3H), 3.43 (q, *J* = 7.3 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.64 (d, *J* = 4.8 Hz, 2H), 5.34 (d, *J* = 1.8 Hz, 1H), 5.42 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.6, 135.6, 115.4, 66.8, 61.9, 46.4, 14.4, 13.9.

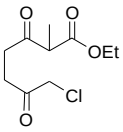


2-Methylmalonic Acid 3-Chloro-2-oxo-propyl Ester Ethyl Ester (318). To a solution of vinyl chloride malonate **317** (133 mg, 0.60 mmol) in acetone (2.5 mL) and acetic acid (1 mL) cooled to 0 ºC was added dropwise sodium hypochlorite solution (0.43 mL, 0.60 mmol, 1.21 g/mL, 10-13% v/v). The solution was stirred for 1 h at 0 ºC, then poured into saturated Na_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 4/1) to

afford α-chloroketone **318** (75 mg, 53 %), along with chloroacetate **319** (24 mg, 13 %) and recovered starting material **317** (12 mg, 9 %). **318**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.40 (d, *J* = 7.3 Hz, 3H), 3.51 (q, *J* = 7.3 Hz, 1H), 4.15 (m, 4H), 4.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 168.5, 168.4, 66.0, 60.8, 44.8, 44.7, 13.0, 12.6.

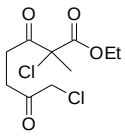


2-Methylmalonic Acid 2-Acetoxy-2,3-dichloropropyl Ester Ethyl Ester (319). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3H), 1.39 (d, *J* = 7.3 Hz, 3H), 2.08 (s, 3H), 3.44 (q, *J* = 7.3 Hz, 1H), 3.91 (d, *J* = 2.08 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.39 (d, *J* = 2.0 Hz, 1H), 4.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.1, 167.7, 95.5, 65.8, 62.1, 46.4, 46.0, 21.9, 14.5, 13.9; ESI (+): $[M+Na]^+$ calcd for $C_{11}H_{16}O_6Cl_2Na$, 337.2; found 337.0.



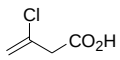
7-Chloro-2-methyl-3,6-dioxoheptanoic acid ethyl ester (322). To a solution of β-ketoester vinyl chloride **321** (131 mg, 0.60 mmol) in acetone (2.5 mL) and acetic acid (1 mL) cooled to 0 ºC was added dropwise sodium hypochlorite solution (0.43 mL, 0.60 mmol, 1.21 g/mL, 10-13% v/v). The solution was stirred for 1 h at 0 ºC, then poured into saturated Na_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ether, 4/1) to afford α-chloroketone **322** (90 mg, 64 %), along with chloroacetate **323** (5 mg, 3 %) and recovered starting material **321** (10 mg, 8 %). **322**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.42 (d, *J* = 7.2 Hz, 3H), 2.90 (m, 4H), 3.57 (q, *J* = 7.2 Hz, 1H), 4.17 (s,

2H), 4.23 (q, J = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 201.5, 170.5, 61.7, 52.9, 48.4, 35.4, 33.5, 14.3, 13.0.

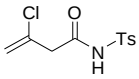


2,7-Dichloro-2-methyl-3,6-dioxoheptanoic acid ethyl ester (323). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 1.79 (s, 3H), 2.82 (m, 2H), 2.97 (m, 1H), 3.18 (m, 1H), 4.09 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H); ESI (+): $[M+Na]^+$ calcd for $C_{10}H_{14}O_4Cl_2Na$, 291.2; found 291.0.

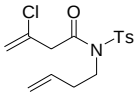
2,3-Butadienoic Acid (338). A solution of 3-butynoic acid (**337**, 1.00 g, 11.62 mmol) in 20 % aq. K_2CO_3 (40 mL) was heated at 40 ºC for 2.5 h. The mixture was then acidified with conc. HCl and was extracted with EtOAc (4 x 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated to cleanly afford allene **338** (934 mg, 93 %) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 4.91 (br s, 1H), 5.25 (d, J = 6.5 Hz, 2H), 5.59 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 217.7, 169.8, 88.7, 79.5.



3-Chlorobut-3-enoic Acid (339). To a solution of allene **338** (2.50 g, 29.04 mmol) in glacial acetic acid (15 mL) at rt was added $LiCl{\cdot}H_2O$ (1.60 g, 37.75 mmol). The reaction mixture was heated at 70 ºC for 24 h, diluted with H_2O (100 mL) and was extracted with CH_2Cl_2 (5 x 20 mL). The organic extracts were washed with H_2O (25 mL), dried ($MgSO_4$), and concentrated to give vinyl chloride **339** (3.17 g, 89 %) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (d, J = 0.8 Hz, 2H), 5.34 (dd, J = 12.1, 1.2 Hz, 2H), 11.47 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 133.9, 117.8, 44.8.

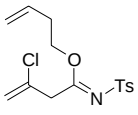


***N*-(3-Chlorobut-3-enoyl)-4-methylbenzenesulfonamide (340).** To a solution of acid **339** (150 mg, 1.22 mmol) and Et_3N (136 mg, 188 μL, 1.35 mmol) in THF (7 mL) at rt was slowly added *N*-tosyl isocyanate (266 mg, 206 μL, 1.35 mmol). The reaction mixture was stirred at rt for 1.5 h, and then *N,N*'-dimethylethylenediamine (100 μL) was added to destroy the excess isocyanate. The mixture was diluted with 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 9/1) afforded *N*-tosyl amide **340** (298 mg, 88 %) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 2.43 (s, 2H), 2.47 (s, 3H), 4.86 (s, 1H), 6.09 (s, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.7, 155.3, 146.7, 138.2, 131.0, 129.7, 120.6, 24.3, 22.0; ESI (+): $[M+H]^+$ calcd for $C_{11}H_{13}NO_3SCl$, 274.0305; found 274.0292.

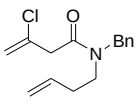


***N*-But-3-enyl-*N*-(3-chlorobut-3-enoyl)-4-methylbenzenesulfonamide (342).** To a solution of *N*-tosyl amide **340** (150 mg, 0.54 mmol) in THF (3 mL) at 0 ºC was added PPh_3 (200 mg, 0.76 mmol), 3-buten-1-ol (47 mg, 56 μL, 0.65 mmol), and DEAD (114 mg, 103 μL, 0.65 mmol). The reaction mixture was stirred at 0 ºC for 4 h and was concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded *N*-butenamine **342** (117 mg, 65 %) as a yellow oil, along with *O*-alkylated product **341** (40 mg, 22 %). **342**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.37-2.42 (m, 5H), 3.79-3.83 (m, 2H), 5.00-5.07 (m, 2H), 5.65-5.74 (m, 1H), 6.65 (d, *J* = 1.1 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100

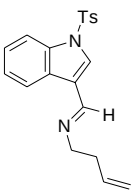
MHz, $CDCl_3$) δ 164.4, 151.3, 145.4, 137.1, 134.4, 130.2, 128.0, 120.9, 118.1, 46.2, 34.6, 24.4, 22.0; ESI (+): $[M+H]^+$ calcd for $C_{15}H_{19}NO_3SCl$, 328.0774; found 328.0776.



***N*-(1-But-3-enyloxy-3-chlorobut-3-enylidene)-4-methylbenzenesulfonamide (341).** ^1H NMR (400 MHz, $CDCl_3$) δ 2.25-2.40 (m, 8H), 4.14-4.17 (m, 2H), 5.00-5.05 (m, 2H), 5.63-5.70 (m, 1H), 6.99 (d, *J* = 1.2 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H).



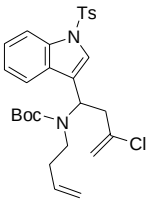
3-Chlorobut-3-enoic Acid Benzylbut-3-enylamide (345). To a solution of benzylbut-3-enylamine (**344**, 65 mg, 0.40 mmol) in a DMF/CH_2Cl_2 solvent mixture (1/3 mL) at rt was added acid **339** (50 mg, 0.40 mmol), EDC-HCl (108 mg, 0.56 mmol), and HOBt (11 mg, 0.08 mmol). The reaction mixture was stirred at rt for 20 h and was then washed with H_2O (20 mL) and sat. $NaHCO_3$ (2 x 20 mL). The organic extract was dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded amide **345** (35 mg, 33 %) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.17-2.89 (m, 2H), 2.34 (dd, *J* = 18.8, 10.5 Hz, 3H), 3.23 (t, *J* = 7.4 Hz, 1H), 3.37 (t, *J* = 7.4 Hz, 1H), 4.51 (d, *J* = 26.6 Hz, 2H), 4.94-5.02 (m, 2H), 5.59-5.75 (m, 1H), 6.25 (dd, *J* = 26.6, 0.6 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 1H), 7.16-7.32 (m, 4H); ESI (+): $[M+H]^+$ calcd for $C_{15}H_{18}NOCl$, 264.1155; found 264.1146.



3-Butenyl-[1-(toluene-4-sulfonyl)indol-3-ylmethylene]amine (368). To a solution of 3-formylindole (**367**, 5.08 g, 35.00 mmol) in THF (200 mL) was added NaH (60 % in mineral oil, 1.40 g, 35.00 mmol) in several portions at 0

ºC. The reaction mixture was warmed to rt and stirred for 20 min before tosyl chloride (6.67 g, 35.00 mmol) in THF (20 mL) was added slowly. The reaction mixture was heated at 65 ºC for 1 h, then cooled to rt, diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded *N*-tosyl-3-formylindole (10.36 g, 99 %) as a white solid.

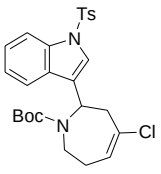
To a solution of *N*-tosyl-3-formylindole (5.21 g, 17.40 mmol) in CH_2Cl_2 (60 mL) was added bis-TMS amine **362** (3.75 g, 17.40 mmol) and TMSOTf (0.39 g, 0.32 mL, 1.74 mmol). The reaction mixture was stirred at rt for 22 h, diluted with 1 *N* NaOH (150 mL), and was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford imine **368** (6.01 g, 93 %) as a yellow oil, along with starting aldehyde **367** (257 mg , 5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.38 (q, *J* = 6.9 Hz, 2H), 3.59 (t, *J* = 7.0 Hz, 2H), 4.94-5.06 (m, 2H), 5.78-5.84 (m, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.17-7.29 (m, 2H), 7.69-7.73 (m, 3H), 7.88 (d, *J* = 8.2 Hz, 1H), 8.24 (d, *J* = 7.7 Hz, 2H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 144.3, 135.4, 134.5, 133.9, 129.0, 128.3, 127.1, 125.9, 124.5, 123.1, 122.0, 119.5, 115.0, 112.2, 60.8, 34.5, 20.5; ESI (+): $[M+H]^+$ calcd for $C_{20}H_{21}N_2O_2S$, 353.1324; found 353.1319.



3-Butenyl-{3-chloro-1-[1-(toluene-4-sulfonyl)indol-3-yl]but-3-enyl}-carbamic Acid *tert*-Butyl Ester (371). To a solution of imine **368** (30 mg, 0.09 mmol) in CH_2Cl_2 (0.5 mL) at -78 ºC was added $TiCl_4$ (19 mg, 11 µL, 0.10 mmol). The reaction mixture was warmed to rt, stirred for 5 min, and was cooled back to -78 ºC before stannane **369** (62 mg, 0.17 mmol) was slowly added. The reaction

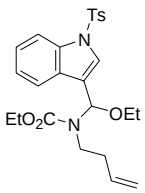
mixture was stirred at -78 ºC for 2 h, warmed to rt, and was diluted with H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded vinyl chloride diene **370** (22 mg, 60 %) as a yellow oil, mixed with aldehyde **367** (11 mg, 40%) due to hydrolysis of the starting imine.

To a solution of *N*-H amine **370** (15 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) at rt was added Et_3N (7 mg, 10 μL, 0.07 mmol), DMAP (1 mg, 0.01 mmol), and Boc anhydride (38 mg, 40 μL, 0.18 mmol). The reaction mixture was stirred at rt for 18 h, diluted with H_2O (10 mL), and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 3/1) afforded *N*-Boc-protected amine **371** (11 mg, 61 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.84-2.09 (m, 2H), 2.67 (s, 3H), 2.90-3.10 (m, 4H), 4.58-4.81 (m, 2H), 5.25-5.41 (m, 3H), 5.56-5.75 (m, 1H), 7.14-7.21 (m, 4H), 7.23-7.36 (m, 1H), 7.46-7.57 (m, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.1 Hz, 3H); ESI (+): $[M+H]^+$ calcd for $C_{28}H_{34}N_2O_4ClS$, 551.1747; found 551.1721.

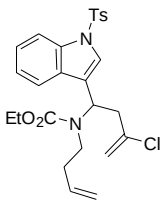


4-Chloro-2-[1-(toluene-4-sulfonyl)indol-3-yl]2,3,6,7-tetrahydroazepine-1-carboxylic Acid *tert*-Butyl Ester (372). A solution of vinyl chloride diene **371** (10 mg, 0.02 mmol) and Grubbs 2nd generation catalyst **190** (2 mg, 2 μmol) in PhMe (3 mL) was heated at 65 ºC under Ar for 15 h and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 3/1) afforded cyclic vinyl chloride **372** (7 mg, 78 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.48 (s, 6H), 2.27 (s, 3H), 2.86-3.22 (m, 3H), 3.55-4.61 (m, 1H), 3.83-4.06 (m, 1H),

5.40-5.70 (m, 1H), 5.87-5.99 (m, 1H), 7.14-7.17 (m, 3H), 7.21-7.29 (m, 2H), 7.41-7.48 (m, 1H), 7.58 (dd, *J* = 16.9, 1.1 Hz, 1H), 7.66-7.72 (m, 2H), 7.91 (d, *J* = 8.3 Hz, 1H) ; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{30}N_2O_4ClS$, 523.1434; found 523.1411.

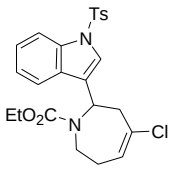


3-Butenyl-{ethoxy-[1-(toluene-4-sulfonyl)indol-3-yl]methyl}carbamic Acid Ethyl Ester (373). A solution of imine **368** (5.00 g, 14.20 mmol) and diethyl pyrocarbonate (2.76 g, 17.04 mmol) in EtOH (180 mL) was stirred at rt for 6.5 h and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded *α*-ethoxycarbamate **373** (5.81 g, 89 %) as a yellow solid. ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 1.08 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.0 Hz, 3H), 1.80 (s, 3H), 1.83-1.89 (m, 1H), 2.07-2.15 (m, 1H), 2.95-3.05 (m, 1H), 3.12-3.20 (m, 1H), 3.44-3.50 (m, 1H), 3.55-3.66 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.63-4.68 (m, 1H), 4.69-4.70 (m, 1H), 5.30-5.44 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.74 (s, 1H), 6.95-7.13 (m, 3H), 7.56-7.59 (m, 3H), 7.79 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 ºC) δ 144.3, 136.9, 136.4, 136.0, 129.7, 129.3, 126.9, 125.4, 125.0, 123.6, 122.1, 120.5, 115.5, 114.4, 82.0, 63.4, 61.4, 41.6, 34.2, 20.8, 14.9, 14.5; ESI (+): $[M+Na]^+$ calcd for $C_{25}H_{30}N_2O_5SNa$, 493.1773; found 493.1776.



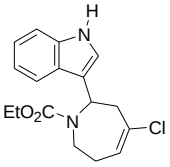
3-Butenyl-{3-chloro-1-[1-(toluene-4-sulfonyl)indol-3-yl]-3-butenyl}-carbamic Acid Ethyl Ester (375). To a solution of *α*-ethoxycarbamate **373** (1.50 g, 3.27 mmol) in CH_2Cl_2 (80 mL) at -78 ºC was added chlorostannane **369** (1.32 g, 3.60 mmol) and $BF_3{\cdot}OEt_2$ (0.93 g, 0.82 mL, 6.55 mmol). The reaction mixture was stirred at -78 ºC for 3 h, diluted with sat. $NaHCO_3$ (100 mL), and was

extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded vinyl chloride diene **375** (1.49 g, 91 %) as a yellow solid. ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 1.07 (t, *J* = 7.1 Hz, 3H), 1.72-1.78 (m, 1H), 1.81 (s, 3H), 2.01-2.09 (m, 1H), 2.71-2.76 (m, 1H), 2.85-2.95 (m, 2H), 3.07-3.12 (m, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.63-4.72 (m, 2H), 5.04 (d, *J* = 14.1 Hz, 2H), 5.27-5.39 (m, 1H), 5.76-5.81 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.96-7.08 (m, 2H), 7.10-7.13 (m, 1H), 7.53 (s, 1H), 7.57-7.61 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 ºC) δ 156.2, 144.5, 139.6, 136.8, 136.2, 135.7, 130.7, 129.8, 126.9, 125.3, 124.9, 123.8, 122.3, 120.5, 115.8, 114.7, 114.3, 61.3, 51.1, 44.4, 41.9, 34.0, 20.8, 14.6; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{30}N_2O_4SCl$, 501.1615; found 501.1624.

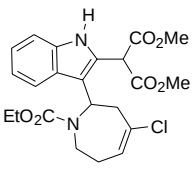


4-Chloro-2-[1-(toluene-4-sulfonyl)indol-3-yl]-2,3,6,7-tetrahydro-azepine-1-carboxylic Acid Ethyl Ester (376). A solution of vinyl chloride diene **375** (100 mg, 0.20 mmol) and Grubbs 2nd generation catalyst (17 mg, 0.02 mmol) in PhMe (25 mL) was heated under Ar at 85 ºC for 39 h and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 4/1) afforded cyclic vinyl chloride **376** (85 mg, 90 %) as a white solid, along with recovered diene **375** (8 mg, 10 %). ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.61-1.72 (m, 1H), 1.81 (s, 3H), 2.08-2.23 (m, 1H), 2.66-2.75 (m, 1H), 2.79-2.93 (m, 2H), 3.53-3.58 (m, 1H), 3.98-4.08 (m, 2H), 5.60-5.68 (m, 2H), 6.66 (d, *J* = 8.1 Hz, 2H), 7.00 (ddd, *J* = 7.9, 7.9, 0.8 Hz, 1H), 7.12 (ddd, *J* = 7.3, 7.3, 1.0 Hz, 1H), 7.52 (d, *J* = 4.6 Hz, 1H), 7.60-7.64 (m, 3H), 8.10 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz,

toluene-d_8, 90 ºC) δ 155.7, 144.5, 136.7, 136.5, 130.9, 130.2, 129.7, 127.6, 126.9, 125.1, 125.0, 123.7, 122.4, 120.4, 114.4, 61.4, 50.4, 41.8, 40.1, 29.1, 20.9, 14.6; ESI (+): $[M+H]^+$ calcd for $C_{24}H_{26}N_2O_4SCl$, 473.1302; found 473.1304.

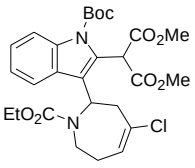


4-Chloro-2-(indol-3-yl)-2,3,6,7-tetrahydroazepine-1-carboxylic Acid Ethyl Ester (377). A solution of *N*-tosyl protected indole **376** (130 mg, 0.28 mmol) and cesium carbonate (270 mg, 0.82 mmol) in a MeOH/THF mixture (5/10 mL) was heated at 65 ºC for 15 h and concentrated. The residue was dissolved in H_2O (20 mL) and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded *N*-H indole **377** (81 mg, 93 %) as a white solid. ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 1.07 (t, *J* = 9.4 Hz, 3H), 1.63-1.73 (m, 1H), 2.19-2.24 (m, 1H), 2.84-2.92 (m, 1H), 2.93-2.99 (m, 1H), 3.05-3.12 (m, 1H), 3.63-3.68 (m, 1H), 4.06-4.17 (m, 2H), 5.67-5.71 (m, 1H), 5.85 (t, *J* = 6.9 Hz, 1H), 6.88 (dd, *J* = 3.3, 1.4 Hz, 1H), 6.99-7.10 (m, 3H), 7.56 (br s, 1H), 7.64 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 ºC) δ 156.0, 137.3, 131.7, 127.4, 127.1, 122.9, 122.5, 120.2, 119.7, 115.4, 111.4, 61.4, 50.8, 42.8, 40.1, 29.2, 14.7; ESI (+): $[M+H]^+$ calcd for $C_{17}H_{20}N_2O_2Cl$, 319.1213; found 319.1218.



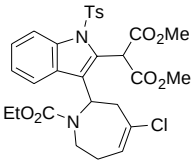
2-[3-(4-Chloro-1-ethoxycarbonyl-2,3,6,7-tetrahydroazepin-2-yl)-indol-2-yl]malonic Acid Dimethyl Ester (379). To a solution of indole **377** (50 mg, 0.16 mmol) in THF (6 mL) at -78 ºC was added Et_3N (20 mg, 26 μL, 0.19 mmol) and *tert*-butyl hypochlorite (20 mg, 22 μL, 0.19 mmol). The

reaction mixture was stirred at -78 ºC for 30 min before thallium malonate salt (80 mg, 0.23 mmol) was added in one portion. The reaction mixture was warmed to rt and stirred for 16 h. After filtering through a Celite pad, the mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded 2-malonylindole **379** (62 mg, 89 %) as a white solid. ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 0.84 (t, *J* = 7.1 Hz, 3H), 1.83-1.93 (m, 1H), 2.30-2.36 (m, 1H), 2.59 (dd, *J* = 17.0, 4.6 Hz, 1H), 3.38 (s, 3H), 3.43 (s, 3H), 3.63-3.68 (m, 2H), 3.82-3.94 (m, 3H), 5.61-5.68 (m, 3H), 6.96-7.05 (m, 3H), 7.50-7.55 (m, 1H), 9.10 (br s, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 ºC) δ 168.3, 167.6, 156.1, 136.8, 129.9, 126.4, 126.0, 122.5, 120.2, 119.7, 116.2, 112.0, 61.1, 54.2, 52.5, 52.3, 49.3, 40.9, 40.6, 30.8, 14.3; ESI (+): $[M+H]^+$ calcd for $C_{22}H_{26}N_2O_6Cl$, 449.1479; found 449.1494.

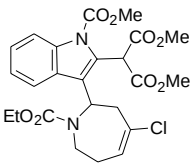


2-[1-*tert*-Butoxycarbonyl-3-(4-chloro-1-ethoxycarbonyl-2,3,6,7-tetrahydroazepin-2-yl)indol-2-yl]malonic Acid Dimethyl Ester (380a). To a solution of *N*-H indole **379** (4 mg, 0.01 mmol) in THF (2 mL) at rt was added Et_3N (2 mg, 3 μL, 0.01 mmol), DMAP (1 mg, 1 μmol), and Boc anhydride (3 mg, 3 μL, 0.01 mmol). The reaction mixture was stirred at rt for 40 h, diluted with H_2O (10 mL), and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 3/1) afforded *N*-Boc protected indole **380a** (3 mg, 60 %) as a yellow oil, along with recovered starting material **379** (1 mg, 25 %). ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 0.77 (t, *J* = 7.1 Hz, 3H), 1.47 (s, 9H), 1.78-1.86 (m, 1H),

2.28-2.35 (m, 1H), 2.62 (dd, J = 17.4, 4.4 Hz, 1H), 3.47-3.49 (m, 1H), 3.52 (s, 6H), 3.76-3.90 (m, 3H), 3.98-4.03 (m, 1H), 5.48-5.58 (m, 2H), 5.89-5.65 (m, 1H), 7.10-7.20 (m, 2H), 7.47-7.51 (m, 1H), 8.11-8.14 (m, 1H); ESI (+): $[M+H]^+$ calcd for $C_{27}H_{34}N_2O_8Cl$, 549.2004; found 549.2020.

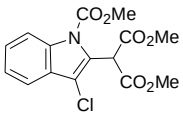


2-[3-(4-Chloro-1-ethoxycarbonyl-2,3,6,7-tetrahydroazepin-2-yl)-1-(toluene-4-sulfonyl)indol-2-yl]malonic Acid Dimethyl Ester (380b). To a solution of *N*-H indole **379** (10 mg, 0.02 mmol), tetrabutylammonium bromide (1 mg, 2 μmol), 30 % NaOH (1 mL), and CH_2Cl_2 (3 mL) was added tosyl chloride (5 mg, 3 μmol). The reaction mixture was warmed to rt and stirred for 17 h. The mixture was then diluted with H_2O (10 mL), and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 2/1) afforded *N*-tosyl indole **380b** (2 mg, 15 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76-0.90 (m, 3H), 2.24-2.39 (m, 2H), 2.82-2.94 (m, 1H), 3.49-3.59 (m, 3H), 3.62 (s, 3H), 3.82 (s, 3H), 3.83-4.20 (m, 5H), 5.23-5.33 (m, 1H), 5.68-5.84 (m, 2H), 7.24-7.36 (m, 3H), 7.56 (d, J = 8.1 Hz, 1H), 7.74-7.85 (m, 1H), 7.95 (d, J = 8.3 Hz, 2H), 8.10-8.22 (m, 1H); ESI (+): $[M+Na]^+$ calcd for $C_{29}H_{31}N_2O_8SClNa$, 625.1387; found 625.1375.

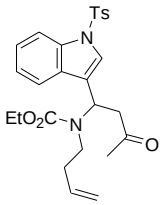


2-[3-(4-Chloro-1-ethoxycarbonyl-2,3,6,7-tetrahydroazepin-2-yl)-1-methoxycarbonylindol-2-yl]malonic Acid Dimethyl Ester (380c). To a solution of *N*-H indole **379** (5 mg, 0.01 mmol), tetrabutylammonium bromide (1 mg, 1 μmol), 30 % NaOH (1 mL), and CH_2Cl_2 (1 mL) was added methyl

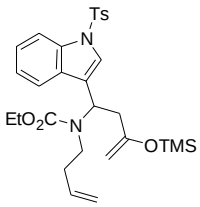
chloroformate (2 mg, 2 μL, 1 μmol). The reaction mixture was stirred at rt for 18 h, diluted with H_2O (10 mL), and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 2/1) afforded *N*-protected indole **380c** (2 mg, 40 %) as a yellow oil, along with recovered starting material **379** (1 mg, 20 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76-0.81 (m, 3H), 2.24-2.36 (m, 2H), 2.42-2.61 (m, 2H), 3.68 (s, 3H), 3.72 (s, 3H), 3.83-4.06 (m, 6H), 5.34-5.46 (m, 1H), 5.76-5.83 (s, 1H), 7.19-7.21 (m, 1H), 7.26-7.30 (m, 1H), 7.48 (d, J = 7.9 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{24}H_{28}N_2O_8Cl$, 507.1534; found 507.1535.



2-(3-Chloro-1-methoxycarbonylindol-2-yl)malonic Acid Dimethyl Ester (383). To a solution of indole **380c** (6 mg, 0.01 mmol) in MeCN (2 mL) at 0 ºC was added *p*-toluenesulfonic acid (7 mg, 0.04 mmol) and 10 % NaOCl (10 mg, 8 μL, 0.01 mmol). The reaction mixture was stirred at 0 ºC for 1 h, diluted with sat. $NaHCO_3$ (10 mL), and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 1/1) afforded 3-chloroindole **383** (2 mg, 50 %) as a yellow oil, along with recovered starting material **380c** (1 mg, 20 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 6H), 3.91 (s, 3H), 5.36 (s, 1H), 7.27-7.30 (m, 1H), 7.33-7.35 (m, 1H), 7.54 (d, J = 7.7 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{15}H_{15}NO_6Cl$, 340.0588; found 340.0583.

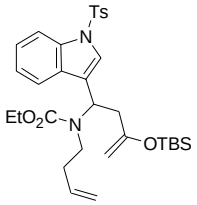


3-Butenyl-{3-oxo-1-[1-(toluene-4-sulfonyl)indol-3-yl]-butyl}carbamic Acid Ethyl Ester (392). To a solution of α-ethoxycarbamate **373** (300 mg, 0.65 mmol) in CH_2Cl_2 (15 mL) at -78 ºC was added silylenol ether (102 mg, 132 µL, 0.79 mmol) and $BF_3{\cdot}OEt_2$ (184 mg, 165 µL, 1.31 mmol). The reaction mixture was stirred at -78 ºC for 1.5 h, diluted with H_2O (30 mL), and was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded ketone **392** (286 mg, 93 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17-1.31 (m, 3H), 1.57-72 (m, 1H), 1.85-1.98 (m, 1H), 2.09 (s, 3H), 2.24 (s, 3H), 2.80-2.92 (m, 2H), 3.02 (t, J = 7.6 Hz, 2H), 4.14 (br s, 2H), 4.65 (d, J = 12.9 Hz, 1H), 4.73 (d, J = 10.2 Hz, 1H), 5.31-5.38 (m, 1H), 5.77-5.99 (m, 1H), 7.11-7.19 (m, 3H), 7.23-7.27 (m, 1H), 7.33-7.53 (m, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 155.5, 144.1, 134.2, 134.1, 133.8, 128.9, 128.7, 125.7, 124.3, 123.2, 122.6, 120.8, 119.2, 115.1, 112.7, 60.6, 47.1, 45.3, 42.0, 32.8, 28.7, 20.5, 13.6; ; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{31}N_2O_5S$, 483.1954; found 483.1957.

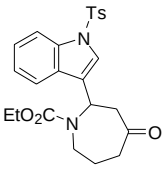


3-Butenyl-{1-[1-(toluene-4-sulfonyl)indol-3-yl]-3-trimethylsilanyl-oxybut-3-enyl}carbamic Acid Ethyl Ester (393). To a solution of ketone **392** (50 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was added Et_3N (50 µL) and TMSOTf (28 mg, 23 µL, 0.13 mmol). The reaction mixture was stirred at 0 ºC for 1.5 h, diluted with sat. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The organic layer was washed with H_2O (3 x 10 mL), dried ($MgSO_4$) and was concentrated. The reaction afforded TMS enol ether **393** (58 mg, 99 %) which was sufficiently pure for

further use. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 1.07-1.13 (m, 3H), 1.32-1.35 (m, 1H), 1.86-2.00 (m, 1H), 2.18 (s, 3H), 2.51-2.61 (m, 2H), 2.71-3.01 (m, 2H), 3.91-4.18 (m, 4H), 4.55-4.73 (m, 2H), 5.22-5.32 (m, 1H), 5.58-5.77 (m, 1H), 7.04-7.10 (m, 3H), 7.13-7.19 (m, 1H), 7.29-7.51 (m, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.83-7.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 145.1, 135.5, 135.3, 135.2, 130.0, 126.9, 125.2, 124.3, 123.6, 120.8, 116.0, 113.7, 91.6, 61.5, 49.2, 42.5, 38.9, 36.8, 33.9, 24.8, 23.5, 21.7, 14.8, 8.1, 0.0; ESI (+): $[M+H]^+$ calcd for $C_{29}H_{39}N_2O_5SSi$, 555.2349; found 555.2350.

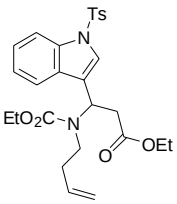


3-Butenyl-{3-(*tert*-butyldimethylsilanyloxy)-1-[1-(toluene-4-sulfonyl) indol-3-yl]but-3-enyl}carbamic Acid Ethyl Ester (394). To a solution of ketone **392** (50 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was added Et_3N (50 μL) and TBSOTf (34 mg, 29 μL, 0.13 mmol). The reaction mixture was stirred at 0 ºC for 1.5 h, diluted with sat. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The organic layer was washed with H_2O (3 x 10 mL), dried ($MgSO_4$) and was concentrated to afford TBS enol ether **394** (62 mg, 99 %) which was sufficiently pure for further use. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.11 (s, 3H), 0.85 (s, 9H), 1.21-1.28 (m, 3H), 1.62-1.71 (m, 1H), 1.88-2.12 (m, 1H), 2.29 (s, 3H), 2.63-2.74 (m, 2H), 2.91-3.10 (m, 2H), 4.07-4.29 (m, 4H), 4.68-4.84 (m, 2H), 5.34-5.45 (m, 1H), 5.72-6.04 (m, 1H), 7.15-7.20 (m, 3H), 7.23-7.32 (m, 1H), 7.41-7.61 (m, 2H), 7.69-7.73 (m, 2H), 7.95 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 143.9, 134.3, 134.2, 134.1, 128.8, 125.7, 124.0, 123.3, 122.4, 119.6, 114.9, 112.5, 90.7, 60.3, 47.9, 45.4, 41.6, 38.0, 33.0, 24.7, 24.6, 20.5, 16.9, 13.7, 8.4, 0.0, -4.6; ESI (+): $[M+H]^+$ calcd for $C_{32}H_{45}N_2O_5SSi$, 597.2818; found 597.2831.



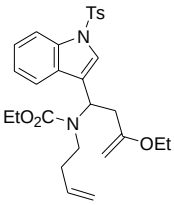
4-Oxo-2-[1-(toluene-4-sulfonyl)indol-3-yl]azepane-1-carboxylic Acid Ethyl Ester (397). *Method A (from TMS enol ether **393**)*. A solution of TMS enol ether diene **393** (30 mg, 0.05 mmol) and Grubbs 2nd generation catalyst (5 mg, 5 μmol) in PhMe (8 mL) was heated under Ar at 65 ºC for 2 h and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 3/1) afforded cyclic ketone **397** (8 mg, 33 %) as a yellow oil, along with recovered starting diene **393** (10 mg, 30 %) and acyclic ketone **392** (3 mg, 10 %).

*Method B (from TBS enol ether **394**)*. A solution of TBS enol ether diene **394** (25 mg, 0.04 mmol) and Grubbs 2nd generation catalyst **190** (4 mg, 4 μmol) in CH_2Cl_2 (8 mL) was heated under Ar at 45 ºC for 5 h and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 3/1) afforded cyclic ketone **397** (6 mg, 31 %) as a yellow oil, along with recovered starting diene **394** (15 mg, 60 %) and acyclic ketone **392** (2 mg, 10 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64-0.88 (m, 3H), 1.31-1.59 (m, 2H), 2.18 (s, 3H), 2.64-2.99 (m, 2H), 3.95-4.04 (m, 2H), 5.76-5.93 (m, 2H), 7.04-7.11 (m, 3H), 7.13-7.17 (m, 1H), 7.29-7.51 (m, 2H), 7.55-7.62 (m, 2H), 7.79 (d, J = 8.2 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{24}H_{27}N_2O_5S$, 455.5; found 455.1.



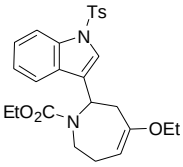
3-(But-3-enyl-ethoxycarbonyl-amino)-3-[1-(toluene-4-sulfonyl)indol-3-yl]propionic Acid Ethyl Ester (402). To a solution of α-ethoxycarbamate **373** (3.00 g, 6.37 mmol) in CH_2Cl_2 (100 mL) at -78 ºC was added enol ether **401** (5.16 g, 25.50 mmol) and $BF_3{\cdot}OEt_2$ (3.62 g, 3.20 mL, 25.50 mmol). The reaction mixture was stirred at -78 ºC for 5 h, diluted with sat. $NaHCO_3$ (100

mL) and was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded ethyl ester **402** (2.70 g, 83 %) as a yellow oil. ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.80-1.83 (m, 1H), 1.87 (s, 3H), 2.04-2.11 (m, 1H), 2.81-2.87 (m, 2H), 2.94-2.99 (m, 1H), 3.05-3.08 (m, 1H), 3.94 (q, *J* = 7.6 Hz, 2H), 4.10 (q, *J* = 2.8 Hz, 2H), 4.64-4.71 (m, 2H), 5.29-5.42 (m, 1H), 6.00 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.98-7.15 (m, 3H), 7.56-7.64 (m, 4H), 8.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 ºC) δ 170.1, 156.3, 144.8, 136.8, 136.4, 136.0, 130.7, 130.0, 127.1, 125.5, 125.0, 123.4, 122.8, 120.8, 116.0, 114.4, 61.6, 60.6, 50.2, 44.2, 38.2, 34.3, 21.1, 14.8, 14.2; ESI (+): $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_6S$, 513.2059; found 513.2048.

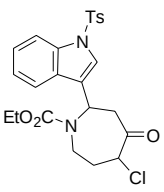


3-Butenyl-{3-ethoxy-1-[1-(toluene-4-sulfonyl)indol-3-yl]-but-3-enyl}-carbamic Acid Ethyl Ester (404). A solution of ethyl ester **402** (2.50 g, 4.88 mmol) and Tebbe-Petasis reagent **403** (8 % in PhMe, 5.08 g, 24.38 mmol) in PhMe (200 mL) was heated in the dark at 70 ºC for 15 h. The reaction mixture was cooled to rt and diluted with sat. K_2CO_3 (200 mL). The mixture was filtered through a Celite pad and was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography on basic alumina (hexanes/EtOAc, 3/1) afforded enol ether **404** (1.99 g, 80 %) as a yellow solid, along with recovered starting material **402** (120 mg, 5 %) and cyclic enol ether **405** (203 mg, 9 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99-1.15 (m, 6H), 1.28-1.36 (m, 1H), 1.77-1.90 (m, 1H), 2.11 (s, 3H), 2.47-2.53 (m, 2H), 2.55-2.71 (m,

1H), 2.76-2.99 (m, 1H), 3.44 (q, *J* = 7.0 Hz, 2H), 3.72-3.76 (m, 2H), 3.89-4.05 (m, 2H), 4.43-4.59 (m, 2H), 5.08-5.22 (m, 1H), 5.50-5.74 (m, 1H), 6.96-7.02 (m, 3H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.25-7.39 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{28}H_{35}N_2O_5S$, 511.2267; found 511.2286.

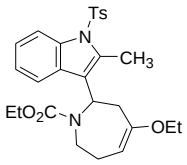


4-Ethoxy-2-[1-(toluene-4-sulfonyl)indol-3-yl]-2,3,6,7-tetrahydro-azepine-1-carboxylic Acid Ethyl Ester (405). A solution of enol ether diene **404** (1.75 g, 3.43 mmol) and Grubbs 2nd generation catalyst **190** (0.29 g, 0.34 mmol) in PhMe (200 mL) was heated under Ar at 70 ºC for 20 h and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 3/1) afforded cyclic enol ether **405** (1.39 g, 84 %) as a white solid. ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 1.05 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.78 (s, 3H), 1.80-1.88 (m, 1H), 2.24-2.35 (m, 1H), 2.59-2.70 (m, 2H), 2.87 (dd, *J* = 15.7, 4.1 Hz, 1H), 3.45-3.61 (m, 2H), 3.76-3.81 (m, 1H), 4.05-4.14 (m, 2H), 4.53 (dd, *J* = 7.4, 4.6 Hz, 1H), 5.78 (s, 1H), 6.62 (d, *J* = 8.0 Hz, 2H), 6.96-6.99 (m, 1H), 7.06-7.11 (m, 1H), 7.52-7.64 (m, 3H), 7.71-7.75 (m, 1H), 8.08 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, toluene-d_8, 90 ºC) δ 156.1, 155.9, 144.4, 136.8, 136.4, 130.7, 129.7, 126.9, 125.5, 124.9, 123.6, 122.4, 120.7, 114.2, 96.5, 62.7, 61.3, 49.2, 41.6, 38.4, 30.0, 26.6, 20.9, 14.7, 14.6; ESI (+): $[M+H]^+$ calcd for $C_{26}H_{31}N_2O_5S$, 483.1954; found 483.1945.



5-Chloro-4-oxo-2-[1-(toluene-4-sulfonyl)indol-3-yl]azepane-1-carboxylic Acid Ethyl Ester (410). To a solution of *N*-chlorosuccinimide (15 mg, 0.11 mmol) and NaOAc (1 mg, 0.01 mmol) in a THF/H_2O solvent

mixture (3/3 mL) at 0 ºC was slowly added enol ether **405** (45 mg, 0.09 mmol) in THF (6 mL). The reaction mixture was stirred at 0 ºC for 7 h, and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (hexanes/EtOAc, 2/1) afforded α-chloroketone **410** (39 mg, 87 %) as a yellow oil, along with starting enol ether **405** (5 mg, 11 %). ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 0.84-0.92 (m, 3H), 1.52-1.60 (m, 1H), 1.77-1.84 (m, 4H), 2.52-2.69 (m, 1H), 2.90-3.14 (m, 1H), 3.51 (dd, *J* = 12.8, 10.1 Hz, 1H), 3.58-3.65 (m, 1H), 3.86-3.95 (m, 2H), 4.03-4.11 (m, 1H), 5.52-5.60 (m, 1H), 6.62-6.68 (m, 2H), 6.98-7.03 (m, 1H), 7.08-7.14 (m, 1H), 7.44-7.51 (m, 2H), 7.57-7.63 (m, 2H), 8.09 (dd, *J* = 8.3, 0.8 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{24}H_{26}N_2O_5SCl$, 489.1251; found 489.1270.



4-Ethoxy-2-[2-methyl-1-(toluene-4-sulfonyl)indol-3-yl]-2,3,6,7-tetra-hydroazepine-1-carboxylic Acid Ethyl Ester (412). To a solution of *N*-tosyl indole **405** (10 mg, 0.02 mmol) in THF (2 mL) at -78 ºC was slowly added *s*-BuLi (1.4 M in hexanes, 30 μL, 0.04 mmol) and the reaction mixture changed from a yellow to a reddish color during the addition. The reaction mixture was stirred at -78 ºC for 2 h before methyl iodide (29 mg, 13 μL, 0.21 mmol) was added dropwise. The mixture was warmed to rt overnight, diluted with H_2O (10 mL) and was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by preparative TLC (hexanes/EtOAc, 2/1) afforded 2-methyl indole **412** (4 mg, 40 %) as a yellow oil, along with recovered starting material **405** (6 mg, 60 %). ^{1}H NMR (300 MHz, toluene-d_8, 90 ºC) δ 0.71 (t. *J* = 7.1 Hz,

3H), 1.07 (t, J = 7.0 Hz, 3H), 1.78 (s, 3H), 2.04-2.06 (m, 1H), 2.16-2.18 (m, 1H), 2.44-2.53 (m, 1H), 2.60 (s, 3H), 3.16-3.27 (m, 1H), 3.38-3.45 (m, 2H), 3.53-3.63 (m, 1H), 3.78 (q, J = 8.3 Hz, 2H), 4.10-4.18 (m, 1H), 4.32-4.38 (m, 1H), 5.41 (dd, J = 13.0, 4.0 Hz, 1H), 6.58 (d, J = 8.1 Hz, 2H), 7.00-7.03 (m, 1H), 7.09-7.12 (m, 1H) 7.40-7.46 (m, 3H), 8.39 (d, J = 7.6 Hz, 1H); ESI (+): $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_5S$, 497.2110; found 497.2097.

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