APPROACHES TOWARD THE TOTAL SYNTHESIS OF OROIDIN ALKALOIDS:

NAGELAMIDE A, C AND AGELIFERIN

By

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APPROACHES TOWARD THE TOTAL SYNTHESIS OF OROIDIN ALKALOIDS: NAGELAMIDE A, C AND AGELIFERIN

ABSTRACT

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The University of Texas at Arlington, 2018

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Nagelamides and ageliferin are oroidin-derived alkaloids which have gained the attention of the scientific community, because of their significant biological activity as well as the unprecedented structural diversity. Our work is directed toward the development of synthetic methods for the construction of oroidin dimers. Accordingly, this dissertation is composed of two sections; the chapter one provides an overview of the oroidin alkaloids with a particular focus on the nagelamide family and the third chapter describes synthetic studies towards ageliferin.

The first part of chapter two focuses on the Palladium-catalyzed Stille cross-coupling reaction for the construction of the main dimeric scaffolds of the nagelamide molecules. First, we describe new methodology to synthesize the iodoimidazole fragment for use in the Stille cross-coupling reaction and subsequent progress in optimizing the yield of Stille reaction. Additional advancement of the synthesis has been achieved via azide installation in allylic and alkyl side chains of the basic framework of nagelamides A and C. A convenient method of dimethylaminosulfonyl group

deprotection was reported on these advanced intermediates prior to the installation of pyrrole carboxamide moieties.

The second part of chapter two details a novel approach for acylation was developed in azide-containing imidazole systems using thio acid chemistry providing amides in one step. The reaction conditions were optimized in diverse monomeric imidazole containing-azide systems, and excellent yields of acetamide and benzamide formation were obtained. Interestingly, a newly synthesized pyrrole thio acid offers promising results for the installation of the pyrrole carboxamide moiety in oroidin-derived systems. This chemistry can be employed in the final transformation of nagelamide A and C to install the pyrrole carboxamide moieties, however; the final reaction conditions still require optimization.

The third chapter describes a potential intermediate en route to ageliferin which was constructed through an intramolecular Diels-Alder reaction using 4-vinylimidazole tethered to a urazole as the starting material. The Diels-Alder precursor was synthesized through palladium-catalyzed Tsuji-Trost cross-coupling reaction between *t*-butyl carbonate protected vinylimidazole and *N*-phenylurazole in excellent yield.

We have explored three different protecting groups (DMAS, Bn, and SEM) on the imidazole nitrogen which can affect both the Diels-Alder reactivity and the electronic nature of the tetrahydrobenzimidazole ring system. For example, this can influence the oxidative rearrangement and introduction of the C2-amino moiety at the later in the synthesis. Further studies are in progress to complete the total synthesis of ageliferin using these advanced intermediates.

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LIST OF ABBREVIATIONS

Boc	tert-Butoxycarbonyl
Bn	Benzyl
DCC	Dicyclohexylcarbodiimide
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMAS	N,N-Dimethylaminosulfonyl
DMF	N,N-Dimethylformamide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionization
FT	Fourier Transform
HRMS	High resolution mass spectroscopy
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
im	Imidazole
LC_{50}	Median lethal dose
LDA	Lithium diisopropylamide
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
MIC	Minimum inhibitory concentration
n-BuLi	n-Butyl lithium
NMR	Nuclear magnetic resonance
TBAF	Tetra-n-butylammonium fluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

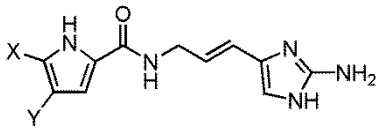
DPPA	Diphenylphosphoryl azide
Lut	Lutidine
Ms	Mesyl

CHAPTER 1
INTRODUCTION

1:1 Pyrrole-imidazole alkaloids (PIAs)

Marine sponges are the most abundant and diverse of marine organisms and are a rich source of secondary metabolites.[1] During the last 20 years, one group of the secondary metabolites, the pyrrole-imidazole alkaloids (PIAs) has gained the attention of scientific community because of their broad range of biological activities and their unprecedented skeletal diversity. The ecological role of the PIAs is thought to provide a defensive mechanism against predatory reef-fishes in the marine environment.[1]

There are nearly 200 members of the PIA family reported in the literature and a number of biosynthesis conjectures have been suggested in the past few decades.[2] According to these hypotheses, oroidin is considered as the biogenetic precursor for these diverse alkaloids.



1: X = Y = Br, Oroidin
2: X = H, Y = Br, Hymenidin
3: X = Y = H, Clathrodin

Figure 1.1 Oroidin and derivatives

PIAs are classified into five different groups according to the number of oroidin units present and the primary organization of these in the structure.[1] These subfamilies are acyclic monomers, cyclic monomers, acyclic dimers, cyclic dimers and cyclic tetramers. Oroidin is the most abundant member of the acyclic monomeric class and consists of a linear structure which is composed of a bromopyrrole carboxamide and a 2-aminoimidazole moiety linked through a *E*-propenyl chain. This derivative was isolated first from *Agelas oroides* in 1971. The first successful total synthesis

of (**1**) was reported by Ando *et al.* from a 2-aminoimidazole-4-carbaldehyde intermediate.[3] The cyclic monomeric family consists of the agelastatins,[4] dibromophakellstatin,[5] axinohydantoins[6] and hymenialdisine (**11**)[7] and their synthetic approaches also have been reported.

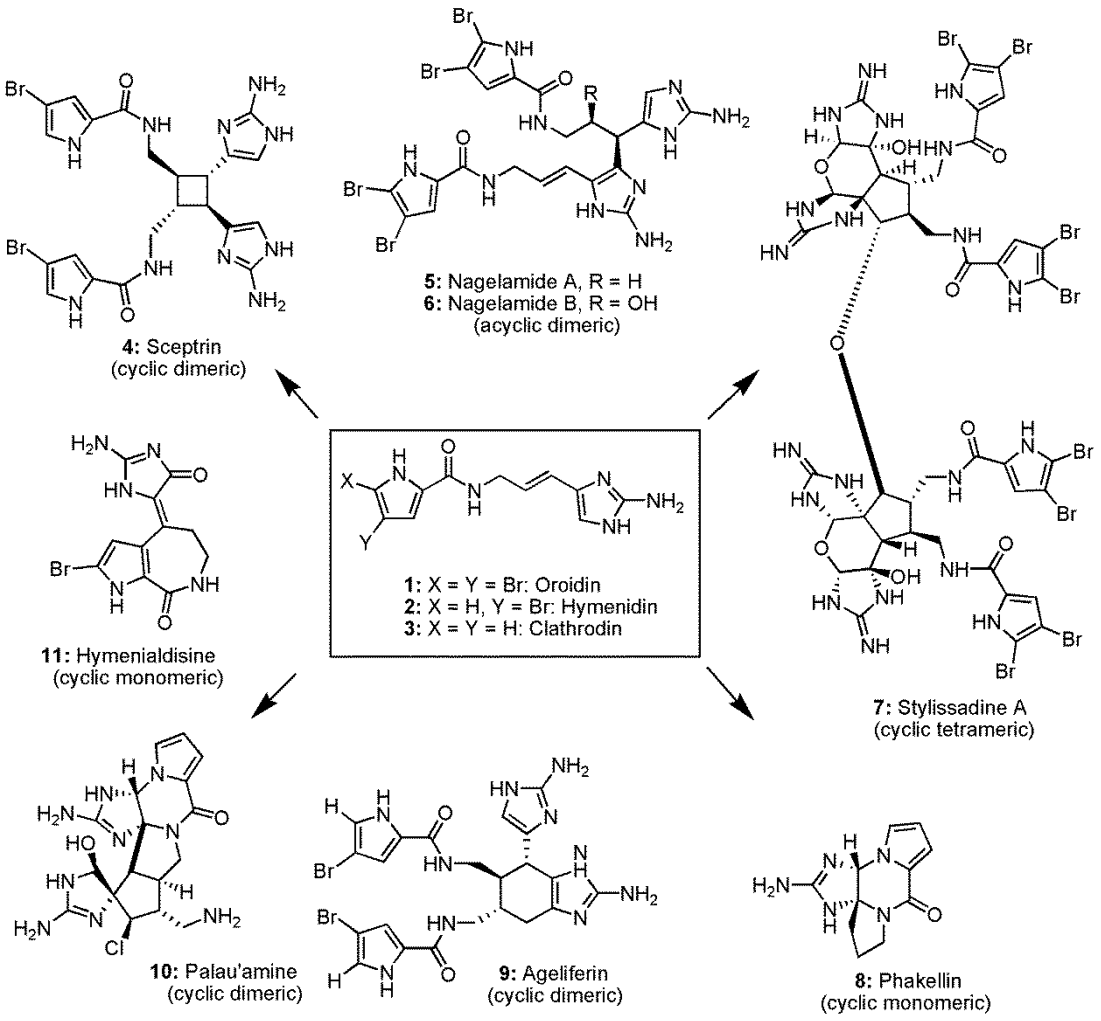


Figure 1.2 Some members of oroidin family

Most of the nagelamides e.g. **5-6**[8-15] are classified as acyclic dimeric PIAs, and their biological activities were also studied during the isolation.[11] Ageliferin (**9**),[16-19] palau'amine (**10**),[20] axinellamines,[21] and massadines[22] are examples of cyclic dimers and stylissadine A (**7**),[23] the cyclic tetramer is the largest, and the most complicated member of PIAs isolated to date.

1:2 Nagelamides

Nagelamides are PIAs, isolated from Pacific and Caribbean marine sponges of the *Agelas* species. The first isolation was reported in 2004 by Kobayashi and co-workers, and they were able to identify eight members of this family, nagelamides A-H (**5-6**), (**12-17**) (Figure 1.3).[11] Later, other members of this family of alkaloids were identified, and now the collection consists of more than 30 family members.[10]

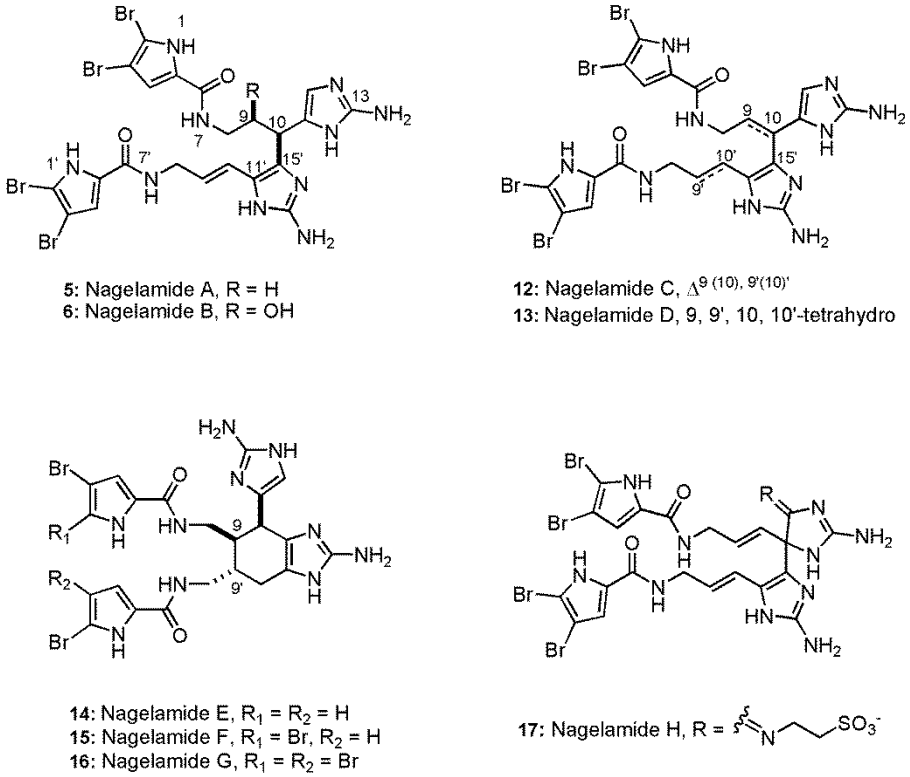


Figure 1.3 Initial group of nagelamides described in 2004

Nagelamides A-H (**5-6**) and (**12-17**) showed antimicrobial activity against Gram-positive bacteria including *Micrococcus luteus* and *Bacillus subtilis* and the Gram-negative bacterium *Escherichia coli*.[11] Moreover, nagelamides A (**5**), G (**16**) and H (**17**) showed inhibitory activity against protein phosphatase type 2A ((IC$_{50}$, 48, 13 and 46 µg/mL respectively).[11]All eight of these are oroidin dimers and most of them have a connection between C10 and C15' to link both oroidin units

together.[10] Nagelamides A (**5**), C (**12**) and D (**13**) have similar structures except for the oxidation state of two three-carbon chains those connecting imidazole and pyrrolecarboxamide moieties differs from each other. Nagelamide B (**6**) differs from A (**5**) through the presence of the hydroxy group at C9 on the upper fragment of the nagelamide B (**6**) molecule. Nagelamide E-G (**14-16**) are tetrahydrobenzimidazoles, and also they are diastereomers at the C10 stereocenter of ageliferin (**9**).

Nagelamide I (**18**),[24] reported in 2014, contains a unique connection between the two oroidin units at C15 and C15' bond, that is absent in other members of this family. In nagelamide J (**19**),[25] one of the oroidin units is bonded to a cyclopentene moiety next to the aminoimidazole, and this alkaloid exhibited antimicrobial activity against *Cryptococcus neoformans* and *Staphylococcus aureus* (MIC; 16.7 μg/mL and 8.35 μg/mL). Nagelamide K (**20**) has a connection between C9 and C9'of two orodin units and a taurine unit (2-aminoethane sulfonic acid) in the structure. Nagelamide L (**21**)[9] is an isomer of nagelamide B and differs from other members since one of the pyrrole group is connected by an ester linkage and not through an amide bond. Both nagelamide K (**20**) and L (**21**) showed antimicrobial activity against *M. luteus* with MIC values of 16.7 μg/mL.

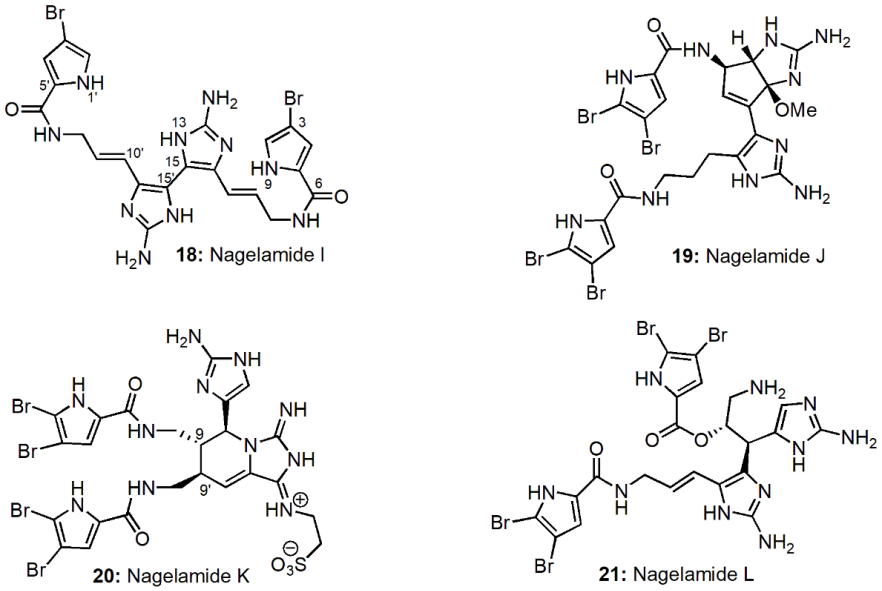


Figure 1.4 Nagelamides I to L

Nagelamides M (**22**) and N (**23**)[13] are monomeric examples of this family and contain taurine units as part of their framework, showed antibacterial activity against *Aspergillus niger* (MICs of 33.3 mg/mL). However, in contrast, nagelamide M contains an octahydropyrrolo[2,3-*d*]imidazole unit compared to the 4-imidazolone unit present in the scaffold of nagelamide N.

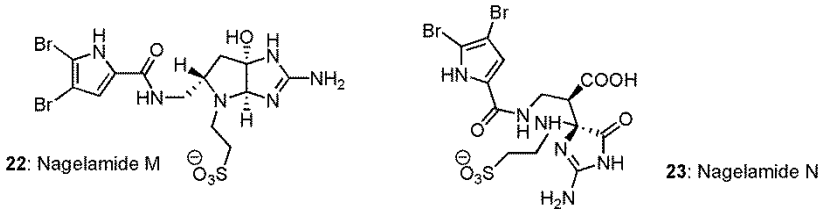


Figure 1.5 Nagelamide M and N

The isolation of nagelamide O (**24**) and P (**25**) was reported in 2009; nagelamide O is an analogue of axinellamine A, containing oroidin/hymenidin building blocks rather than two oroidins. Both of these nagelamides showed antibacterial activity against *B. subtilis*, *M. luteus*, and *S. aureus* (MIC; 33.3 µg/mL). At the same time, Kobayashi and co-workers have reported the isolation of nagelamide Q (**26**), R (**27**) and T (**28**)[8] and they contain a pyrrolidine system and an oxazoline ring

in their structures. Interestingly they exhibited a very high inhibitory activity against *T. mentagrophytes* (MIC = 6.0 μg/mL).

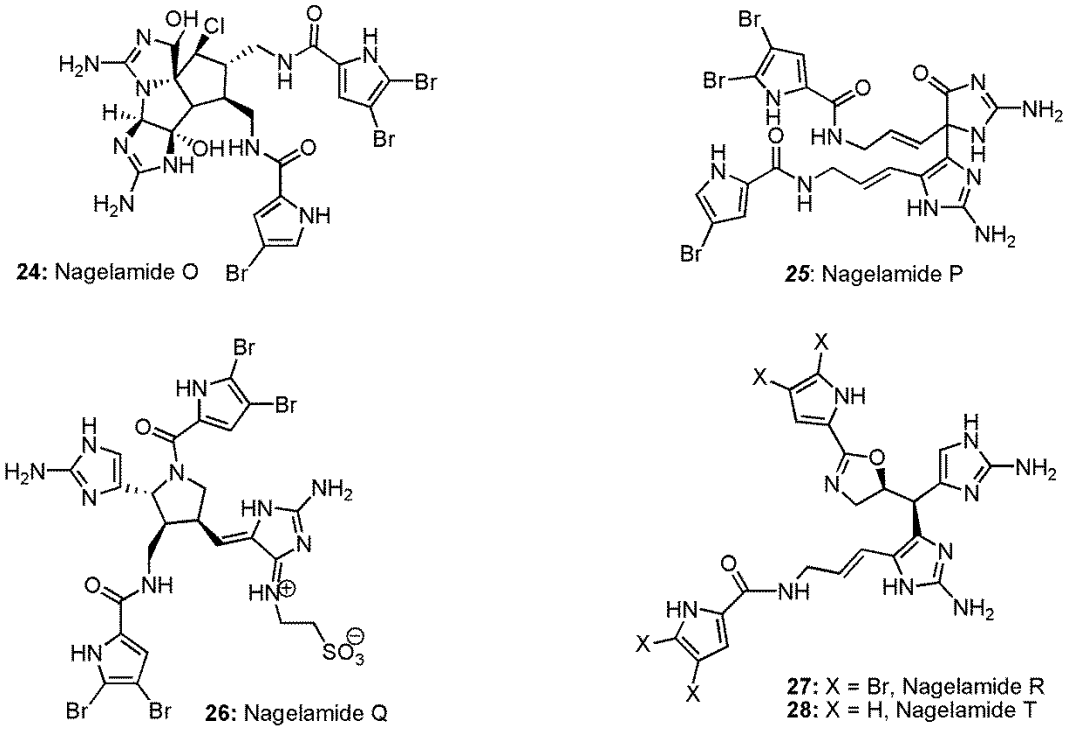


Figure 1.6 Nagelamide O to T

The isolation of nagelamide U-W (**30-32**)[14] from an Okinawan marine sponge, *Agelas sp* was reported in 2013. Nagelamides U (**30**) and W (**32**) have the antibacterial activity against *C. albicans* (MIC; 4μg/mL). Nagelamide X (**33**), Y (**34**), and Z (**35**)[15] were reported very recently, and they are dimeric forms of oroidin alkaloids. Nagelamide X (**33**) and Y (**34**) are the spiro-fused members of the nagelamide family and exist as the racemic molecules. Nagelamide Z (**35**) has a comparable assembly like nagelamide C, except the presence of connectivity between C8 and C15' contrasting to the linkage of C10 and C15'. Moreover, it displays a significant inhibitory activity against *C. albic*ans (IC_{50}; 0.25 μg/mL).

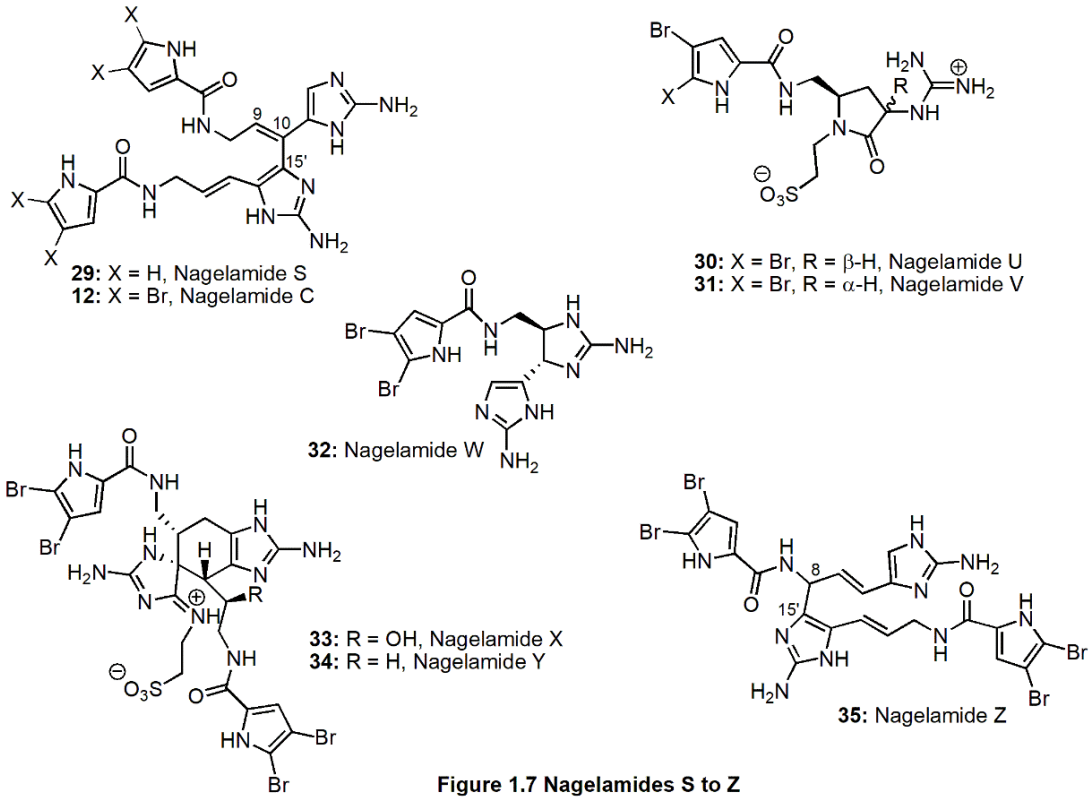
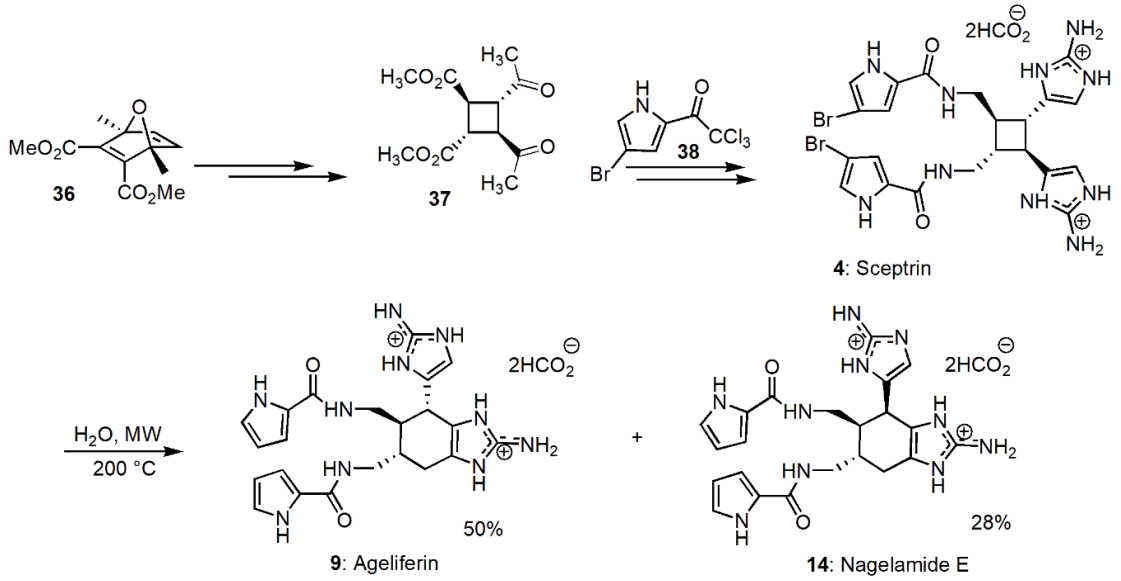


Figure 1.7 Nagelamides S to Z

1:3 Baran's approach to nagelamide E

Baran and co-workers reported the first successful total synthesis of a member of the nagelamide family in 2004 although this was not their initial goal.[18] They were able to isolate nagelamide E (**14**) as a by-product during the total synthesis of ageliferin (**9**), it is the C10 *epi*-configuration of ageliferin. Their synthesis began with a Diels-Alder reaction between 2,5-dimethylfuran and dimethyl acetylene dicarboxylate to furnish the key framework **36**, followed by a couple of steps to provide the sceptrin (**4**) as the primary product. Microwave irradiation of the sceptrin (**38**) gave ageliferin (**9**) and nagelamide E (**14**) in 2:1 ratio through a unique cyclobutane rearrangement. According to computational studies, the rearrangement of **38** occurs through radical scission of the cyclobutane followed by olefin recombination and re-aromatization to obtain the most stable

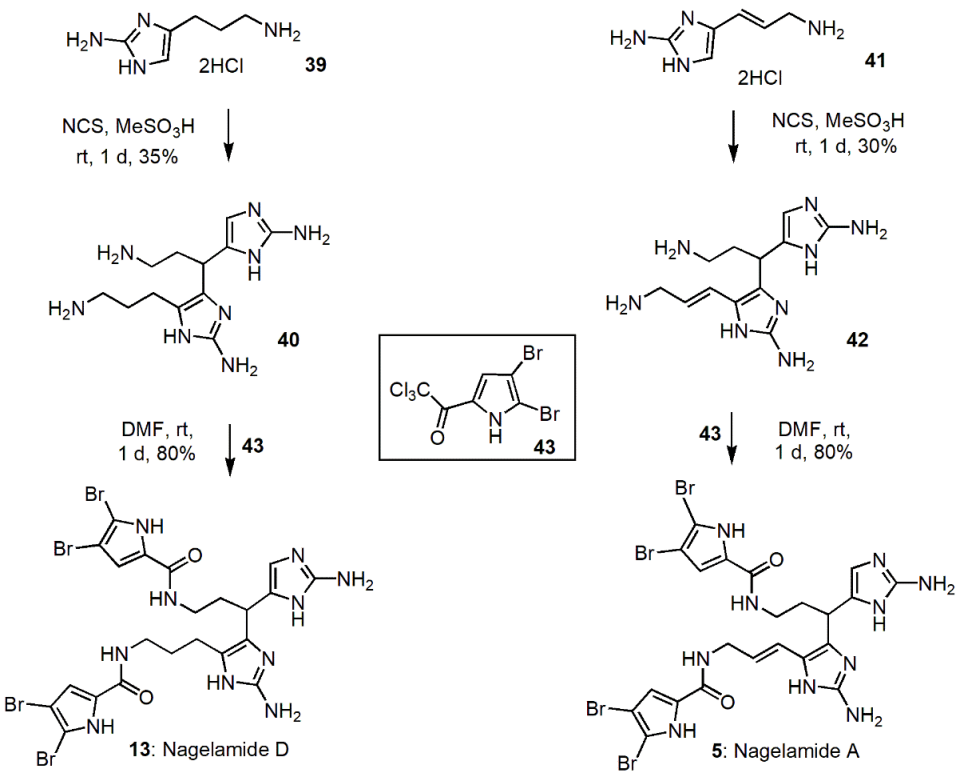
product. Nagelamide E (**14**) can be formed via inversion of the radical center before recombination or alternatively epimerization of ageliferin (**9**) under the given reaction conditions.[18]



Scheme 1.1 Total synthesis of nagelamide E and ageliferin

1:4 Horne's approach to nagelamide A and D

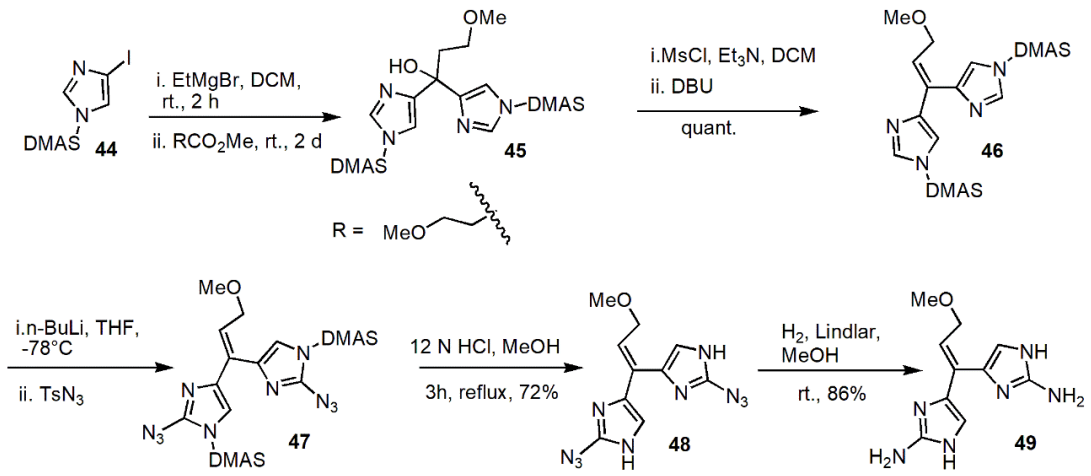
Horne and co-workers described the first total syntheses of nagelamide A (**5**) and D (**13**) in 2006. Tonsiengsom from Horne's group reported in her dissertation that this was accomplished by oxidative homodimerization of diamine **39** to produce tetraamine **40** using NCS and subsequent acylation of tetraamines (**42** and **40**) with dibromopyrrole **43** to give nagelamides A (**5**) and D (**13**).



Scheme 1.2 Horne's approaches toward nagelamides A and D

1:5 Lindel's Approach to C10/C15' Dimers

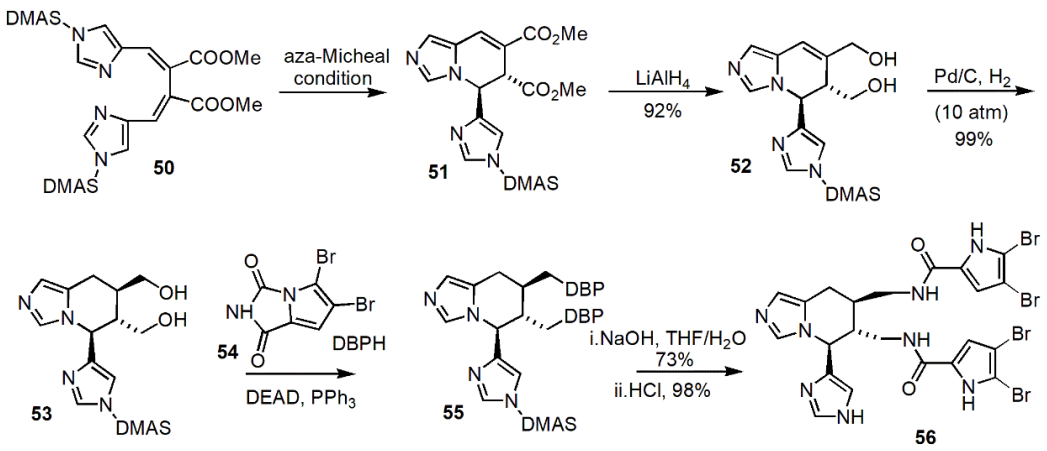
Lindel and coworkers reported an exciting pathway to synthesize the composite-scaffold for two members of the nagelamide family, nagelamide C, and S in 2010.[12] They were able to construct a bisimidazole containing tertiary alcohol **45** from a Grignard addition between 4-iodoimidazole **44** and the methyl ester. The unsaturated ether **46** resulted from mesylation followed by elimination and subsequent azidation of **46** resulted in formation of **47**. Importantly, they were able to remove the DMAS protecting groups initially via acid hydrolysis[26-28] and then the resulting product **48** was used for chemoselective hydrogenation of the azides, and amine **49** was obtained. Even though this approach does not complete the total synthesis, but the concepts of installation of amine and the protecting group removal supported the similar sequence reported by our group during the the total synthesis of nagelamide D.[26]



Scheme 1.3 Lindel's approach towards nagelamide C

1:6 Jiang's Approach to Nagelamide K

Jiang and co-workers[29] were able to synthesize a de-taurine and de-diamino analog of the nagelamide K (**56**) in 2012. A Ni-catalyzed coupling reaction was utilized to synthesize the dimeric imidazole acrylate **50**. Then the resulting product was subjected to an intramolecular aza-Micheal reaction to produce the cyclized product **51** in which one of the DMAS groups also cleaved off during that step. The resulting product **52** was subjected to catalytic hydrogenation, and then the pyrrole units were introduced to the diol **53** by double Mitsunobu reaction in the presence of dibromopyrrolehydantoin (**54**).[26] Then **55** was treated with NaOH to hydrolyze and liberate the pyrrole group. Finally, the remaining DMAS group was removed by acid hydrolysis to obtain **56**. This approach is chemoselective, and potentially this strategy can be applied to synthesize nagelamide Q (**26**) as well as ageliferin (**9**).



Scheme 1.4 Jiang's approach towards nagelamide K

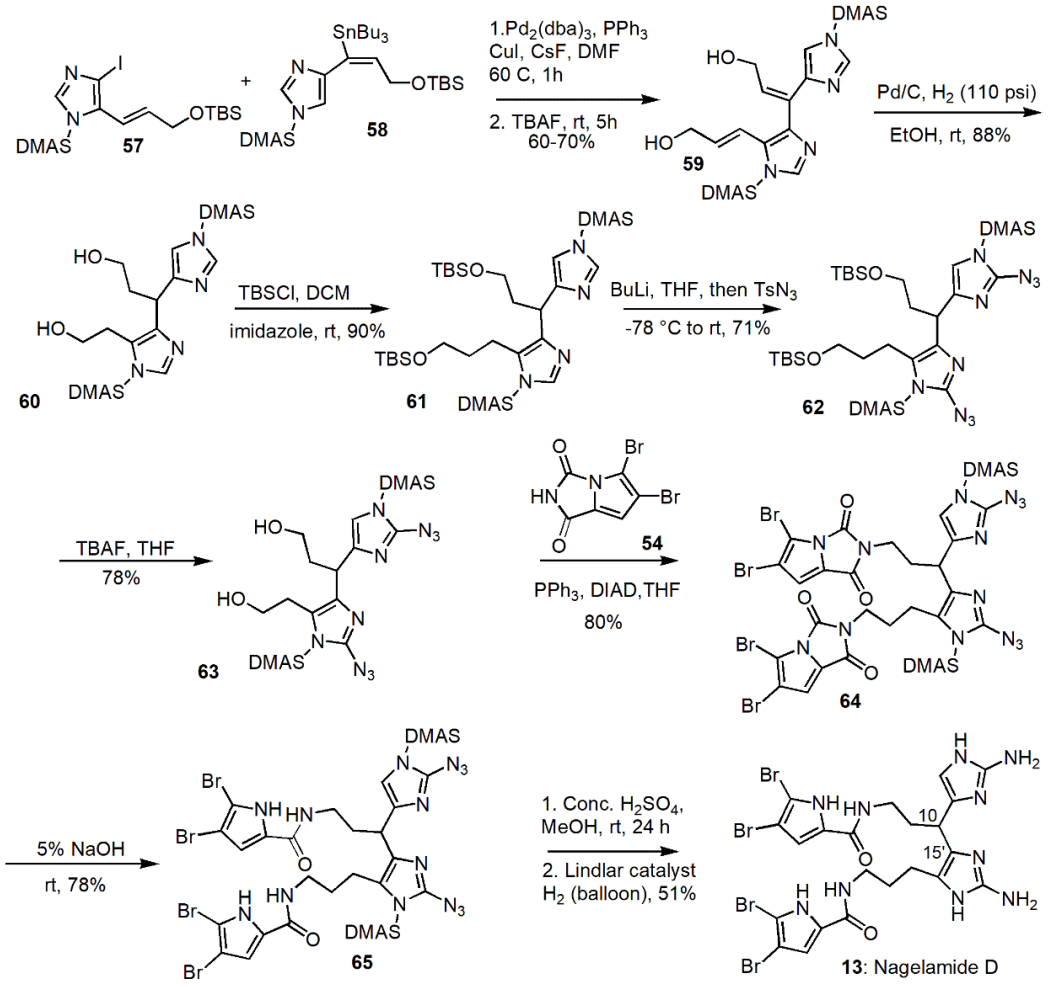
1:7 Lovely's Approach to Nagelamide D

In 2010, our group reported the first successful total synthesis of nagelamide D (**13**) using a divergent strategy, which is based on the synthesis of a common intermediate to be utilized en route to other members the nagelamide family.[26] A Stille cross-coupling reaction was the vital step to build-up the key scaffold **59**, followed by catalytic hydrogenation of the free diol resulted in the complete reduction of the two double bonds and **60** was obtained. Silylation of the diol **61** was performed to allow the introduction of azide at C2 through a lithiation reaction and electrophilic capture of with tosyl azide **62**. After removing the silyl protecting groups, the resulting diol **63** was reacted with dibromohydantoin (**54**)[30-31] under Mitsunobu conditions to install the pyrrole rings. Basic hydrolysis of the urea **64** leaves the pyrrolecarboxamide, and then the DMAS groups were removed by acid hydrolysis. Finally, hydrogenation with Lindlar catalyst reduced the C2 azides to the corresponding amines to complete the total synthesis of nagelamide D (**13**).

However, several notable discrepancies were found in the ^{1}H and ^{13}C spectra during comparison of the spectroscopic data of the natural product and the synthetic nagelamide D (**13**). Attempts to obtain a authentic sample or the copies of original spectra from the Kobayashi group were not

successful. However, during this time, we became aware that Horne's group also reported the total synthesis of nagelamide D (**13**) and interestingly their spectroscopic data were consistent with the data which we had obtained. After extensive analysis of related molecules, we were unable to adequately determine the underlying basis for this disagreement and were forced to conclude that either the data were misreported or the structure was misassigned.

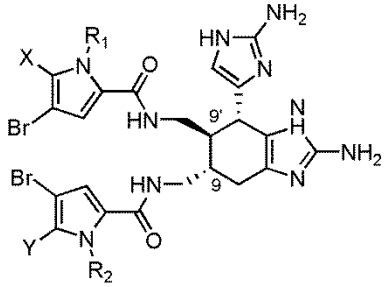
In this document, we discuss current approaches toward the total synthesis of nagelamide A (**5**), C (**12**), and S following a similar strategy as nagelamide D to build up the main scaffold, and later studies toward the completion.



Scheme 1.5 Lovely's approach towards nagelamide D

1:8 Ageliferin

Ageliferin (**9**), bromoageliferin (**9a**) and dibromoageliferin (**9b**) were isolated and reported in 1990 by Kobayashi and co-workers from an Okinawan marine sponge, *Agelas* species.[11, 17] In 1991, Rinehart and co-workers isolated the same natural products from a Caribbean marine sponge of the *Agelas* species.[32] In 1996, Williams and Faulkner[33] reported related N-methyl derivatives of ageliferin (**66a-b, 67a-c**) from a calcareous sponge *Astroscera willeyana* from Pohnpei.



9: X = Y = H, Ageliferin
9a: X = Br, Y = H, Bromoageliferin
9b: X = Y = Br, Dibromoageliferin
66a: X = Y = R_2 = H, R_1 = Me, *N*(1')-Methylageliferin
66b: X = Y = H, R_1 = R_2 = Me, *N*(1)-*N*(1')-Dimethylageliferin
67a: X = R_2 = H, Y = Br, R_1 = Me, *N*(1')-Methyl-2-bromoageliferin
67b: X = Br, Y = H, R_1 = Me, R_2 = H, *N*(1')-Methyl-2'-bromoageliferin
67c: X = Y = Br, R_1 = Me, R_2 = H, *N*(1')-methyl-2,2'-dibromoageliferin

Figure 1.8 Ageliferin and deravatives

According to the authors,[11, 17] ageliferin (**9**) showed antiviral activity and exerted an influence on barnacle settling; later it was determined to possess antimicrobial activity and used as a significant chemical tool to study the molecular mechanisms of actin-myosin contractile systems.[11, 17]

Table 1.1 Biological activities of ageliferin and the derivatives

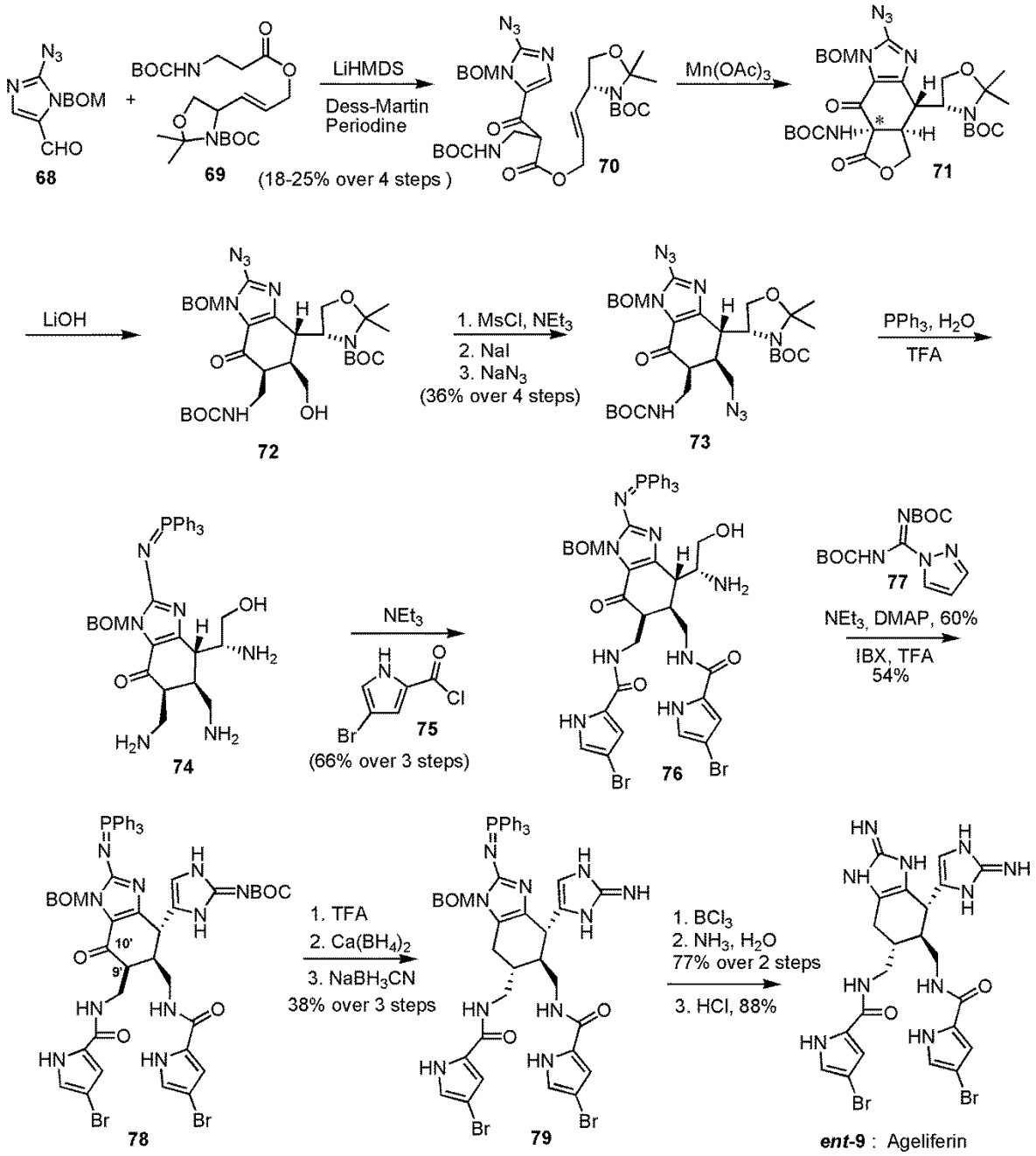
Compound	antibacterial activity (MIC, µg/mL)			protein phosphatase 2A (IC_{50}, µM)
	M. luteus	*B. subtilis*	*E. coli*	
9	4.17	8.33	8.33	>50
9a	2.08	2.08	16.7	>50
9b	2.08	4.16	16.7	>50

The first successful total synthesis was reported in 2004 by Baran[18] and co-workers via microwave irradiation of sceptrin (**38**) at 195 ˚C resulted in ageliferin (**9**) through a radical fragmentation (see Scheme 1.1) of the embedded vinylcyclobutane **38**, which was identical to the natural product (**9**). A different approach was recorded in 2012 by Chen and *et al.*[19] through a Mn^{III}-mediated oxidative heterobicyclization of a β-ketoester. Also, Ohta[34] and co-workers reported the synthesis of a

dimethylated congener of ageliferin and an alternative approach was reported by Harran and *et al.*[16] via an acyl *N*-amidinyliminium ion-rearrangement.

1:9 Chen's Approach to ageliferin

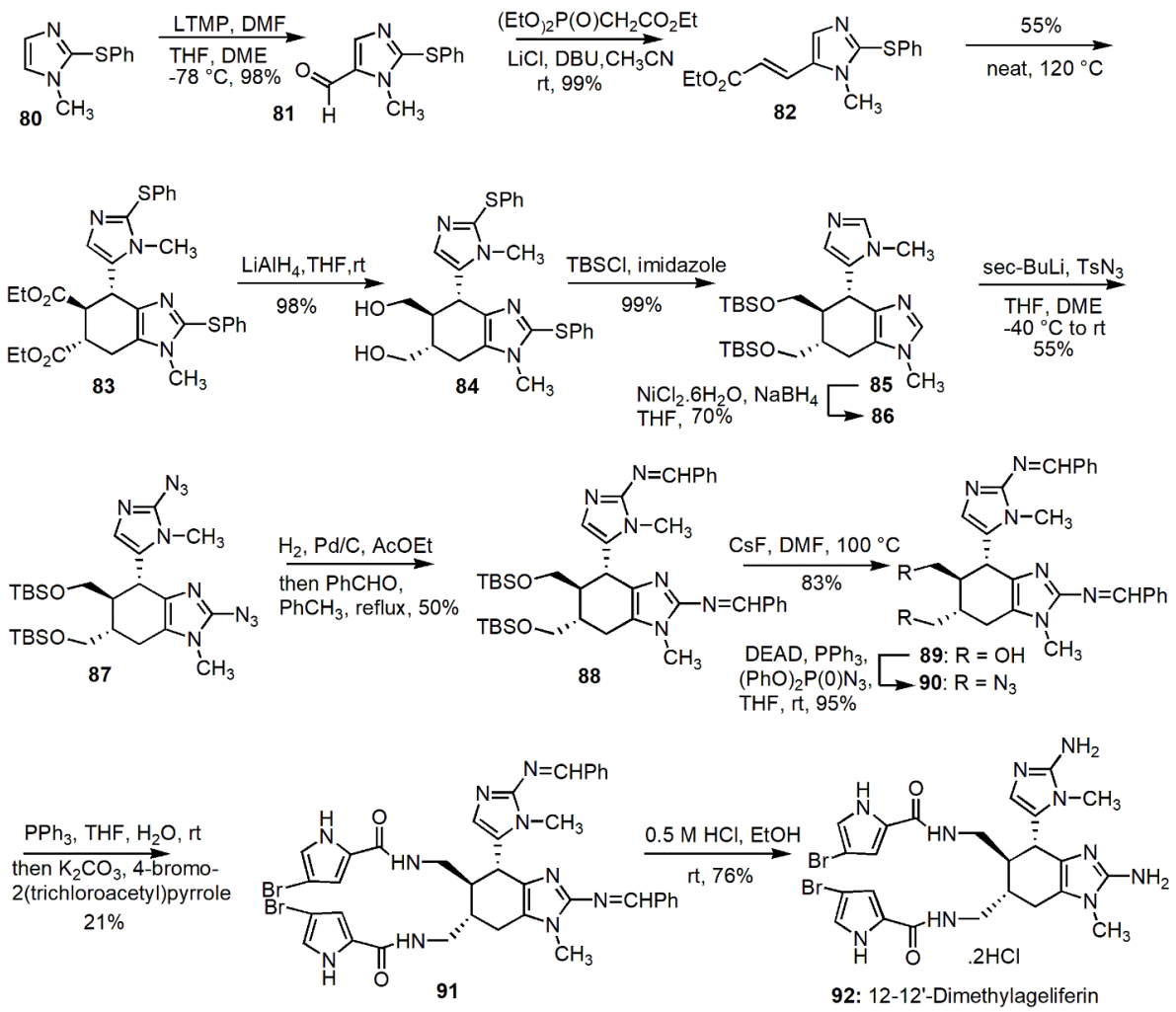
Chen and co-workers[19] reported the total synthesis of *ent*-ageliferin (**9**) using a Mn-mediated asymmetric radical cyclization (Scheme 1.6). This route permitted the build-up the central scaffold, the β-ketoester **70** from **68** and **69** via an aldol condensation followed by Dess-Martin oxidation. Then the Mn-oxidation of **70** followed by decarboxylation of **71** giving **72**. The second amine group installed by mesylation, iodination and subsequent reaction with NaN_3. Triphenyl imidophosphorane at C2-imidazole showed unexpected stability towards the hydrolysis conditions and resulted in only triamine **74** upon treatment of **73** with PPh_3 and H_2O. Next the pyrrole groups **75** were installed, and **76** was isolated in good yield. The introduction of the second aminoimidazole group was accomplished by reacting with guanidine moiety **77**, and subsequent oxidative cyclization gave a **78**. At this stage, they have found that the acidic conditions C9' epimerization and provide the correct C9' configuration. The consecutive reduction of carbonyl group at the central ring provided **79** and the BOM protecting group was removed in two sequential steps. First, the benzyl group was cleaved by BCl_3 and the resulting *N*-hydroxymethyl group was removed by basic hydrolysis. Finally, the triphenylphosphine imine group was hydrolyzed under acidic conditions giving the enantiomer of ageliferin (**9**).



Scheme 1.6 Chen's approach towards ageliferin

1:10 Ohta's Approach to ageliferin

An intermolecular Diels-Alder reaction was used as the key step to construct the framework of ageliferin (**9**).[35] Formyl imidazole **81** was prepared from **80** via 5-lithioimidazole and treated that



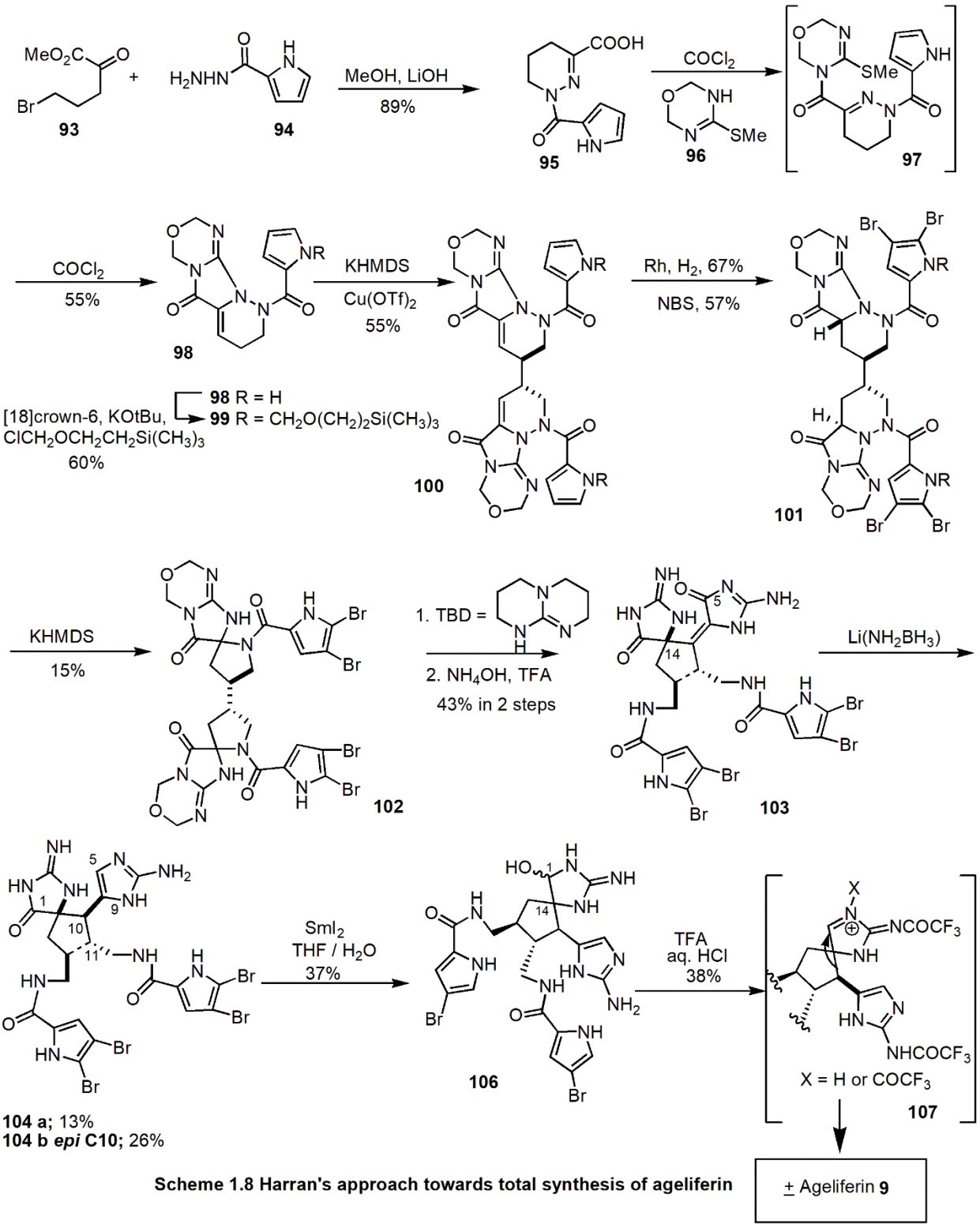
Scheme 1.7 : Ohta's approach towards ageliferin

with DMF. 5-Vinylimidazole **82** was obtained under Horner-Wadsworth-Emmons reaction conditions and an intermolecular Diels-Alder cyclization of **82** resulted in the formation of the cyclic framework **83** which contains the 4,5,6,7-tetrahydrobenzimidazole moiety. Interestingly, the reported stereochemistry of **83** cycloadduct was consistent with that of ageliferin (**9**), and X-ray crystallographic analysis confirmed the acquired results. Reduction of diester **83** to diol **84** followed by the silyl protection resulted in the formation of compound **85**. Desulfurization with $NiCl_2$ and $NaBH_4$ resulted in **86** which underwent C2-azidation by bis lithiation, followed by the treatment with trisyl azide. The resulting azides **87** were reduced to the corresponding amine and

protected as imines with benzaldehyde. Then desilylation, followed by azidation delivered compound **90** and the installed alkyl azides were selectively reduced to diamine via Staudinger reaction with PPh_3 and water. The amines were acylated with (tricholoroacetyl)bromopyrrole and subsequential acidic hydrolysis of imines gave 12, 12'-dimethylageliferin dihydrochloride **92** as shown above which is a non-natural occurring analog of the orodin dimer.

1:11 Harran's Approach to ageliferin

Harran and co-workers[16] were able to build up the compound **95** via condensation of methyl-5-bromo-2-oxopentanoate **93** and pyrrole-2-carboxylic acid hydrazide **94**. The acid from **95** was used to N-acylate the methylisothiourea **96**, resulting in the formation of **97**. The insitu ring closure occurred via removal of methylmercaptan affording glycocyamidine **98**. The pyrrole nitrogen in **98** derivatized with 2-(trimethylsilyl)ethoxymethyl chloride to increase the solubility and oxidative homodimerization of the enolate ɤ-position in **99** resulted in product **100**. Then the bromination of **100** by the treatment with NBS afforded **101**. A base mediated cascade reaction resulted in compound **102** and 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD) at room temperature initiated the isomerization to a common monoalkylidine containing spirocycle and base hydrolysis with NH_4OH resulted in unmasked bisguanidine **103**. Myers' lithium amidotrihydroborate (LAB) deoxygenate C5 and stirring with TFA resulted in dehydration and the aminoimidazole **103** was obtained. HPLC methods were used to isolate the anti-diastereomer **104a** in C10 and C11. Then the intermediate **104a** explored with SmI_2 to debrominate selectively at C6 and C6,' and the C1 carbonyl reduces to a hemiaminal resulting in the formation of **106**. Finally, **106** reacted with the TFAA and TFA to induce the ring expansion to a tetrahydrobenzimidazole and from that agelferin (**9**) was isolated via an acidic workup.

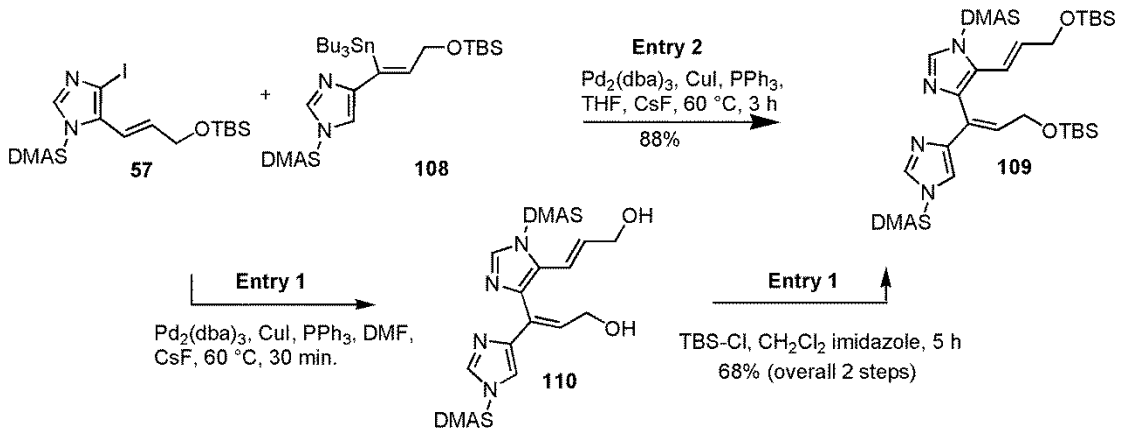


Scheme 1.8 Harran's approach towards total synthesis of ageliferin

CHAPTER 2:
RESULTS AND DISCUSSION

2.1 Approaches toward the total synthesis of nagelamide A, C, and S

Our studies were targeted toward the total synthesis of nagelamide A, C, and S using a divergent strategy, which means accessing the alkaloids in the family through a common late stage intermediate. The main scaffolds of these oroidin-dimers were constructed through the Stille cross-coupling reaction between iodo fragment **57** and the vinylstannane fragments **108** and **58** for nagelamide C and nagelamide A respectively.



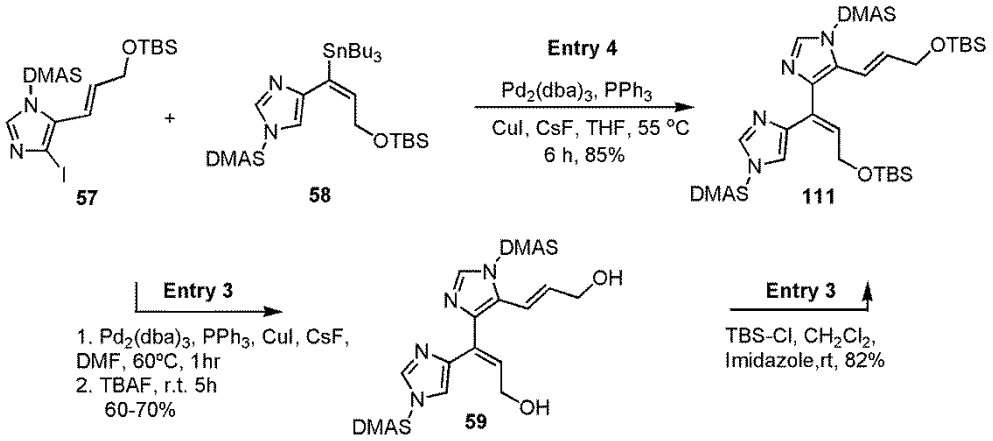
Scheme 2.1

In the first-generation approach to nagelamide C (entry 1- Table 2.1, Scheme 2.1),[26, 31] the core framework **109** was synthesized through a Stille cross-coupling between **57** and **108** in DMF. The cross-coupling between **57** and **58** provided the scaffold of nagelamide A **111** as shown in Scheme 2.2. In both the cases, the Stille reaction was accelerated by the addition of a stoichiometric amount of CsF.[36] However, the utilized reaction conditions (entries 1 and 3, Table 2.1) led to partial desilylation, and the reported yields while serviceable, were not in the satisfactory range. Moreover, an additional re-silylation step was required to obtain product **109** and **111** from **110**

and **59** respectively. Interestingly, the modified second-generation approaches (entries 2 and 4, Table 2.1) avoided the loss of silyl ether groups during the Stille reaction and resulted in much high on yields (88% and 85%) compared to the previous approaches.

Table 2.1: Stille reactions in first and second-generation approaches

Entry	Reaction condition	% Yield
1	1. $Pd_2(dba)_3$, CuI, PPh_3, DMF, CsF, 60 °C, 30min 2. TBS-Cl, CH_2Cl_2, imidazole, 5 h	68 (2 steps)
2	$Pd_2(dba)_3$, CuI, PPh_3, THF, CsF, 60 °C, 3 h	88
3	1. $Pd_2(dba)_3$, CuI, PPh_3, DMF, CsF, 60 °C, 30min 2. TBS-Cl, CH_2Cl_2, imidazole, 5 h	66 (2 steps)
4	$Pd_2(dba)_3$, CuI, PPh_3, THF, CsF, 60 °C, 3 h	85

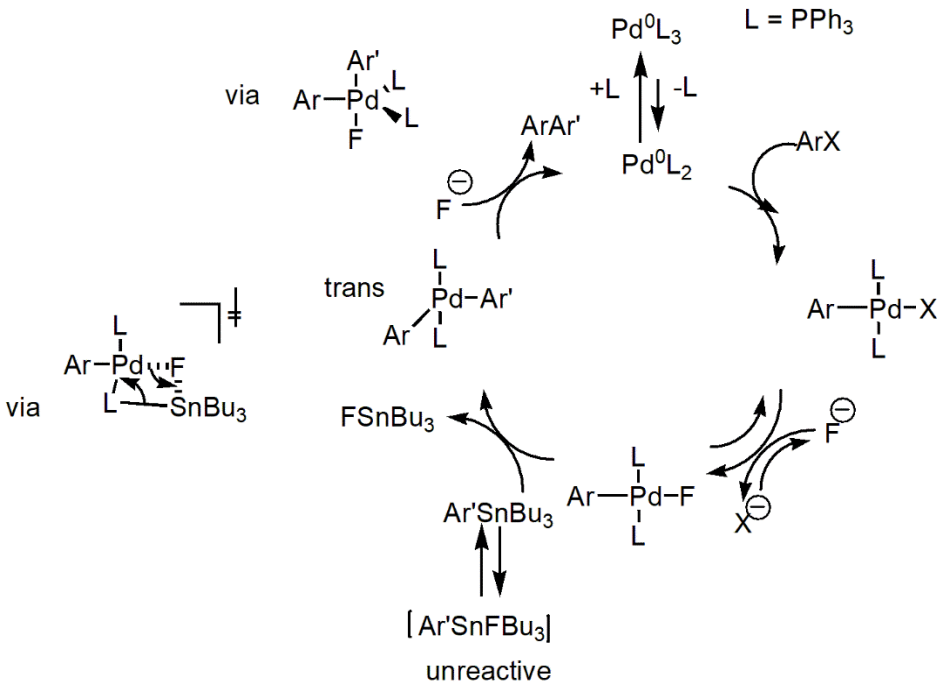


Scheme 2.2

2.2 Stille cross-coupling reaction

$$ArX + Ar'SnBu_3 \xrightarrow[F^-]{\text{Pd catalyst}} ArAr' + XSnBu_3$$

The Stille reaction (shown above) is the cross-coupling between an aryl halide (ArX) and an arylstannane (Ar'$SnBu_3$) in the presence of CsF; this is the key step in the constructing the main scaffold of the nagelamide molecule. However, the original Stille reaction was carried out in the presence of TBAF, as the fluoride source which resulted in low yields as well as inconsistency of the reactive outcome. These reasons forced us to consider replacing TBAF ultimately using CsF during studies toward nagelamide D.[31]



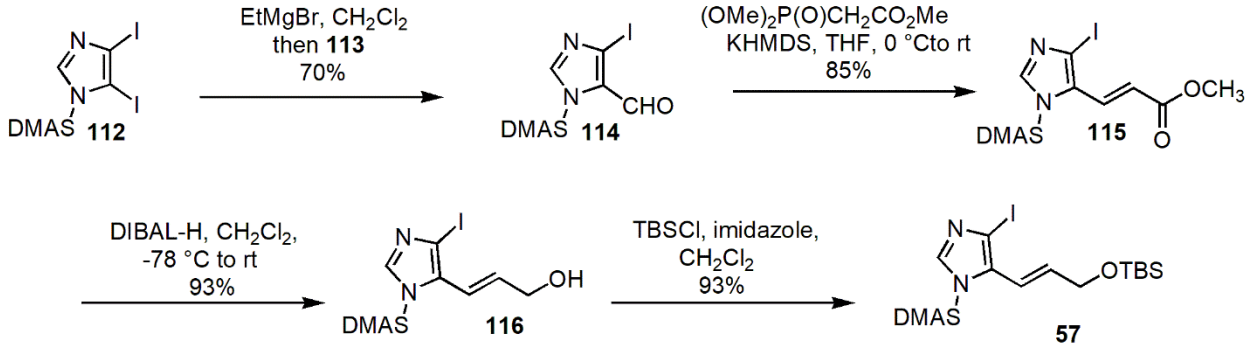
Scheme 2.3

Fluoride ion plays a triple role in accelerating the catalytic cycle of the Stille reaction[36-37] (Scheme 2.3). They can be listed as; the formation of trans-$ArPdFL_2$ species prior to transmetalation, the formation of unreactive aryl-fluorostannanes, and the catalysis of reductive elimination in the

trans-ArPdAr'L_2 complex.[37] Kinetic studies suggested that transmetalation is the rate-determining step in the catalytic cycle. Moreover, these studies[37] found that fluoride ions have two opposing effects on transmetalation. If the [F^-] is too high, it decelerates the rate of the reaction, and if the [F^-] is low (than that of [vinylSnBu_3]), it also slows down the rate. In the latter case, F^- ions are neutralized by excess vinyl stannane to form an unreactive fluorostannate species, [vinylSnFBu_3]$^-$ which is the reason for retradation of the rate of the reaction. According to these observations, the rate of the reaction is maximum, when [F^-/ vinylSnFBu_3]$^-$ is less than one.[36-37] These kinetic explanations can be understood in the present situation based on the solubility of fluoride ions in THF is presumably lower than DMF and it facilitates efficient transmetalation which led to a higher yield. The presence of a substantial amount of precipitated fluoride salt in the reaction mixture after performing a Stille reaction is an evidence of this low solubility in THF than in DMF. Additionally, this lower solubility presumably preserving the loss of silyl ether groups during the Stille coupling en route to products **109** and **111**.

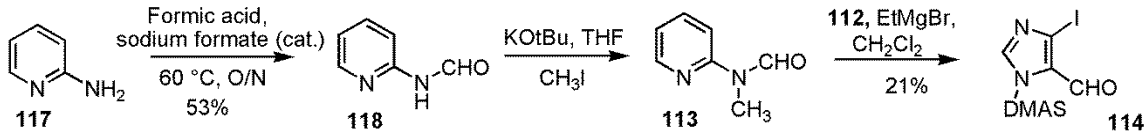
2.3 Second-generation synthesis of the iodo fragment **57**

The iodo fragment **57** was synthesized by using the chemistry outlined in below scheme 2.4 during the first-generation approach. Accordingly, 4,5-diiodoimidazole **112** was metalated by Grignard exchange (EtMgBr) followed by formylation with *N*-methyl-*N*-(2-pyridyl)formamide **113** at C5, providing the aldehyde **114**.[38-39] Then **114** was treated under Horner-Wadsworth-Emmons reaction conditions through which acrylate derivative **115** was isolated.[26, 31] Treatment with DIBAL reduced **115** to the primary alcohol **116**[26, 31] and protection by TBSCl afforded the silyl ether fragment **57**.[26, 31] However while this route was reasonable, the high reagent cost associated with *N*-methyl-*N*-(2-pyridyl)formamide **113** did not encourage us to pursue this route in the scale-up reactions.



Scheme 2.4

At this point, several attempts (Table 2.2) were made to synthesize the aldehyde **114** at the initial stage of our studies. First, we attempted synthesizing the commercially available reagent **113** in the laboratory (Scheme 2.5).[40]



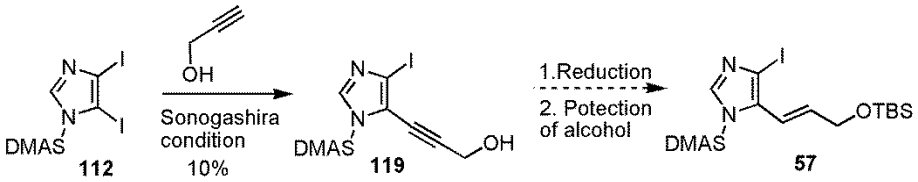
Scheme 2.5

2-Aminopyridine **117** was treated with formic acid in the presence of sodium formate (cat.) and resulted *N*-2-pyridinylformamide **118** was then methylated by CH_3I. The desired product **113** was isolated and purified by vacuum distillation. However, the purified product **113** (Scheme 2.5) did not reach the expected purity as the commercial material and did not provide a considerable yield in synthesizing **114** to continue our studies.

Table 2.2 Approaches to synthesize fragment 57

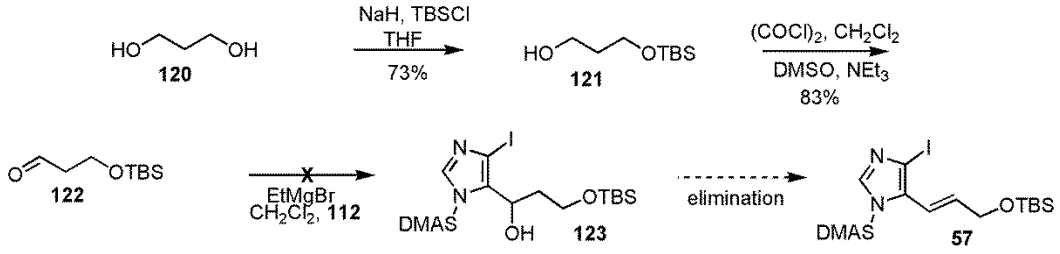
Entry	Method	Results
1	Sonagashira reaction with propargylic alcohol	Low yield
2	Grignard reaction with propanal **122**	No product
3	Grignard reaction with $(CHO)_n$	58%

We then moved forward and explored other approaches to prepare the iodo fragment **114**, and some of these attempts are listed in the Table 2.2. As shown in the entry 1, diiodoimidazole **114** was first treated with propargylic alcohol under Sonagashira cross-coupling conditions and later, it was planned to reduce to the resulting allylic alcohol **119**. Unfortunately, the yield obtained from the cross-coupling reaction was low and thus we did not continue with this route further (Scheme 2.6).



Scheme 2.6

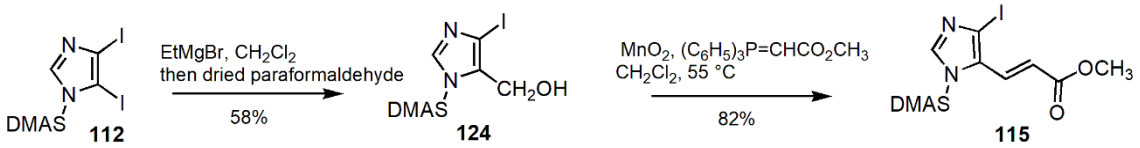
In a different approach (Scheme 2.7), commercially available propanediol **120** was selectively protected as a silyl ether, and the remaining alcohol **121** was oxidized to an aldehyde **122** under Swern oxidation conditions. The obtained **122** was used in a Grignard reaction with diiodoimidazole **112**. However, the formation of desired product **123** was not identified, but instead 4-iodoimidazole **44** was found as the major product formed via the deiodination followed by protonation at C5 of imidazole ring.



Scheme 2.7

At this point, we considered the use of paraformaldehyde in the Grignard reaction, since it is well-known for decades and also importantly, the use of it is very cost-effective. The alcohol **124** was

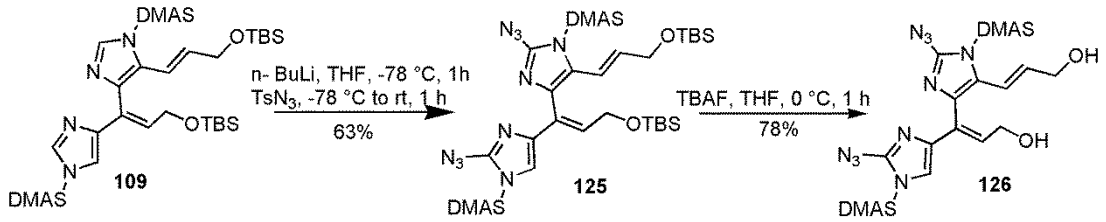
obtained via metalation of diiodoimidazole **112** with a Grignard reagent (EtMgBr) and treatment with vacuum-dried paraformaldehyde. Then, the alcohol **124** converted to the ester **115** (Scheme 2.8) by treatment with MnO_2 and the Wittig reagent, $Ph_3P{=}CHCO_2Me$, following the procedure reported by Blackburn and co-workers.[41] This one-pot method has other advantages as, it avoids isolation of the product at the aldehyde stage and importantly, saving one step over the total synthesis. In other applications, this one-pot process is useful to avoid isolating the unstable, problematic to handle or even poisonous aldehydes.[41] The worth of this one-pot reaction is apparent as it preserves, the same step count as the synthesis of iodo fragment, in the first-generation approach.



Scheme 2.8

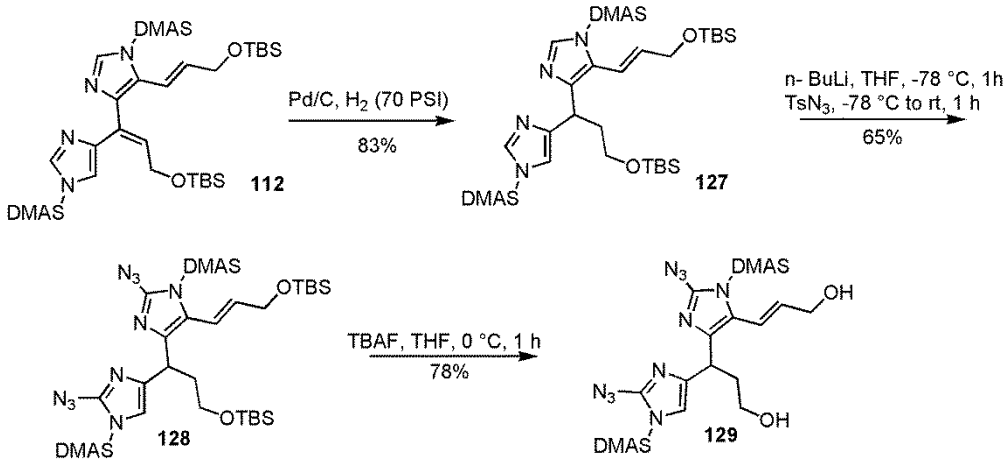
2.4 Progress towards nagelamide A and C

After constructing the bis imidazolyl scaffolds **109** and **112**, the next challenge was to install the amino groups at C2 of the imidazole rings. This challenge was overcome by C2 lithiation followed by an electrophilic attack by tosyl azide, and **125** isolated in 63%. Subsequently, we planned to reduce these azide groups to the corresponding primary amines using an appropriate reducing agent. The silyl ether groups in **125** were removed by TBAF at 0 °C giving diol **126** in good yield (Scheme 2.9). The reactions conditions, above the 0 °C lead to an undesired product without giving **126**.



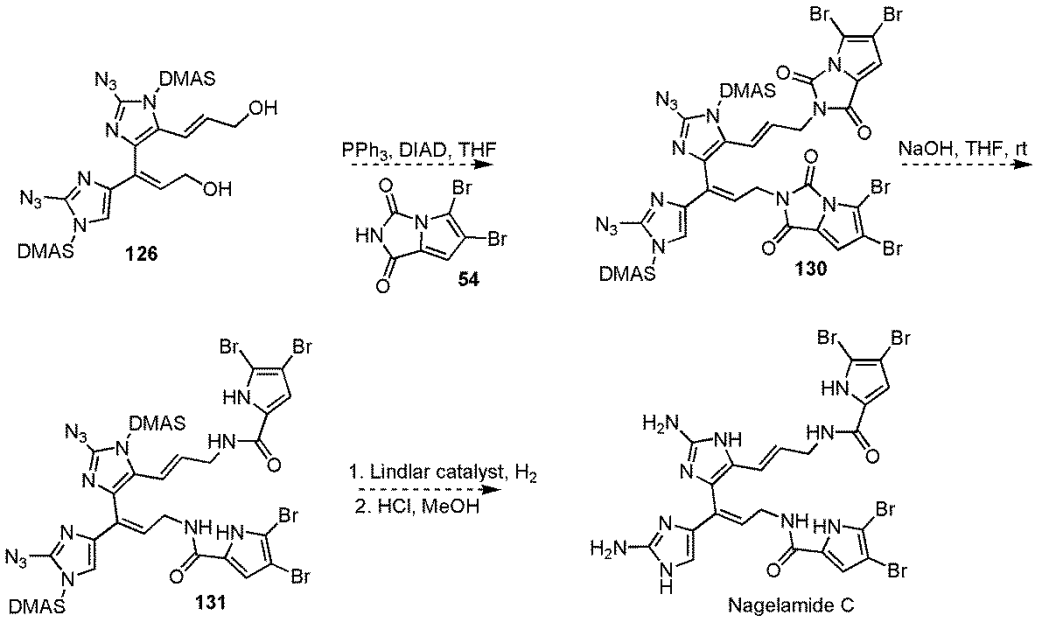
Scheme 2.9

The nagelamide A **111** scaffold was subjected to catalytic hydrogenation which partially reduced the diolefin system. These conditions were found accidentally by Dr. Manoj Bhandari in our group during his studies toward the total synthesis of nagelamide D.[31] Then **127** was subjected to the same series of steps as discribed in Scheme 2.9; the azidation followed by desilylation provided **129** (Scheme 2.10).



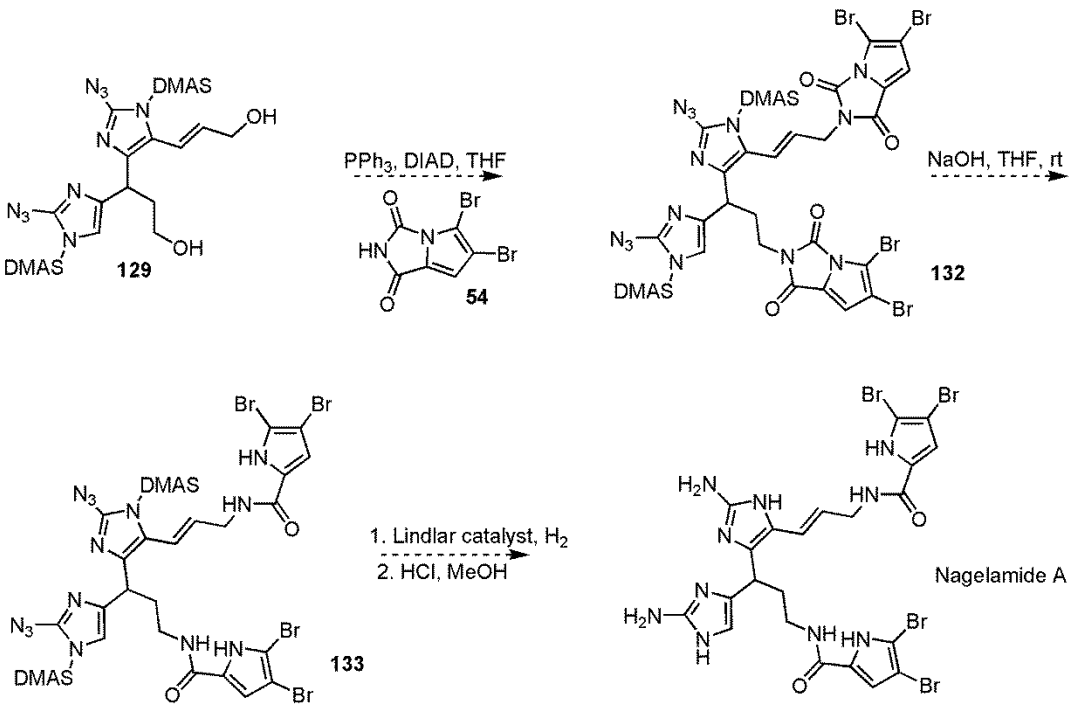
Scheme 2.10

2.5 Failure in the first-generation approach



Scheme 2.11

The introduction of pyrrole carboxamide groups was the significant challenge in the completion of these natural products. Typically, these have been introduced in a classical fashion via acylation of amine with a pyrrole trichloroketone; such an approach requires the preparation of a primary amine. In 2009, our group reported the successful application of Mitsunobu reaction in the installation of pyrrolecarboxamide moieties during the total synthesis of nagelamide D. A similar route was explored to install the dibromohydantoin moieties during the exploratory studies in the first-generation synthesis of nagelamide C and A, but an unanticipated allylic transposition was observed and the desired products (**130** and **132**) were not obtained as shown in Scheme 2.11 and 2.12.



Scheme 2.12

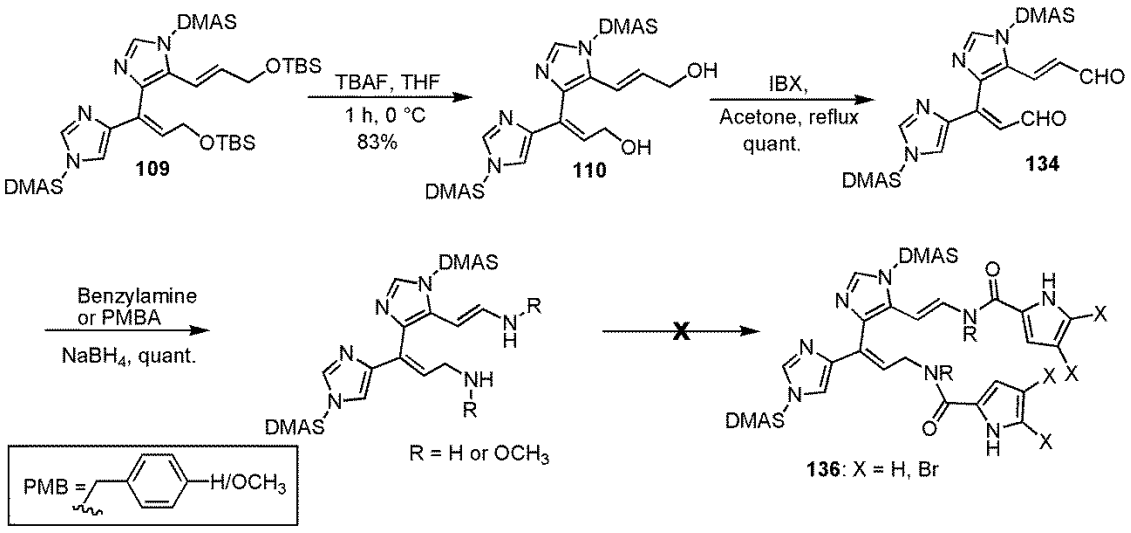
At this point, we have to develop alternatives to install of pyrrole carboxamide groups below we discuss the evolution of a second-generation approach in detail.

2.6 Allylic amine/amide installation-second generation approach to nagelamide C

2.6.1 Via Reductive Amination

In a first iteration, we examined the concept of reductive amination chemistry to install the nitrogen atoms at the terminal position of the allylic moieties, prior studies from our lab had demonstrated the feasibility of such an approach. Desilylation of silyl ether **109** followed by oxidation of the resulting diol **110** provided the dialdehyde **134**. The dialdehyde was treated with benzylamine to obtain the bisimine intermediate and to the same reaction mixture, $NaBH_4$ was added to reduce imine to the corresponding primary amine **135a**. After successful installation of the nitrogen atoms, next, we focused on approaching to another derivative of benzylamine which can be

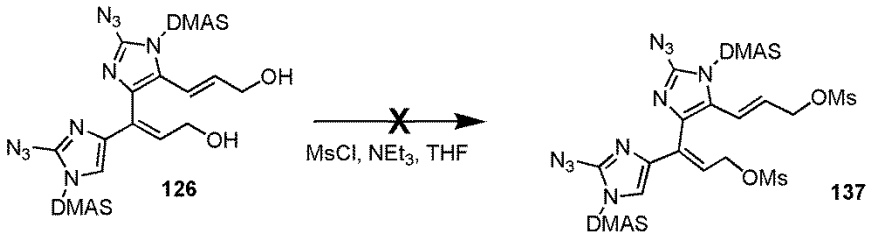
removed at the final stage under milder non-reductive conditions avoiding potential chemoselectivity issues. Methoxybenzylamine (PMBA) was selected as the best candidate for imine formation, since PMB group can be removed under mild oxidative conditions. The primary amine **135b** was synthesized successfully, however, attempts to install the pyrrole groups were not successful at this stage. Accordingly, work on this approach was discontinued to focus on alternative ways of installing the nitrogen onto of nagelamide C scaffold.



Scheme 2.13

2.6.2 Mesylation followed by amination

Next we investigated briefly converting the allylic diol to the corresponding dimesylate product and introducing the nitrogen atoms via replacing with an amine or surrogate. Unfortunately, under the conditions employed, without giving the dimesylated product **137**, an undesired cyclic ether compund was isolated.



Scheme 2.14

2.6.3 Azidation followed by reduction

Azidation of an alcohol followed by reduction to the corresponding amine is a very common technique in organic synthesis.[42] This method is advantageous since, azides are synthesized under mild conditions.[43] Interestingly, azides can undergo electrophilic as well as nucleophilic reactions depending on the chemical environment.

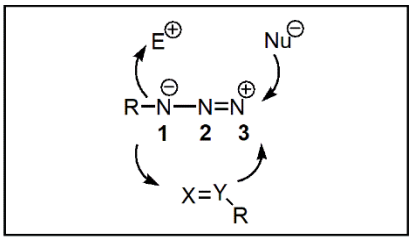
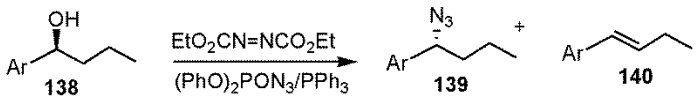


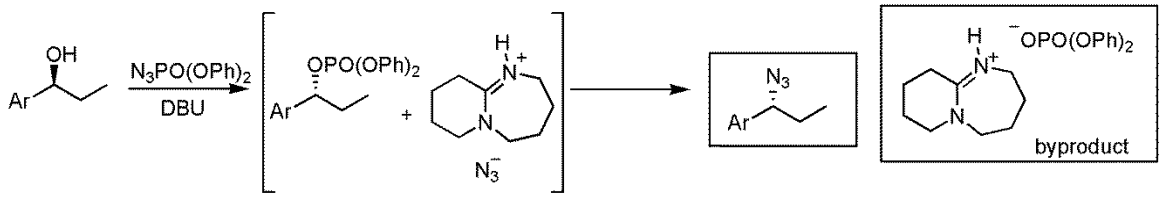
Figure 2.1 Azides reactivity with nucleophiles and electrophiles

There are different methods for allylic azidations reported to date; employing a Mitsunobu reaction is among the most common method. However, Mitsunobu-azidation processes have some drawbacks such as; a series of purification steps required to remove the by-products, resulting in yields that are not always high and in some cases undesired olefin formation is observed (Scheme 2.15).[44] This olefin formation was taken as evidence of a highly reactive intermediate.



Scheme 2.15

Fortunately, Thompson and co-workers[44] found that use of DPPA (diphenylphosphoryl azide) and a base, DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) help to avoid the unstable intermediate so that the overall reaction is under complete stereocontrol condition. As a consequence of that, only traces of the undesired olefin product was formed. Importantly, a simple workup procedure is required for the purification in comparison to the original Mitsunobu reaction. These reasons encouraged us to evaluate this chemistry in azide installation for our projects.[44]

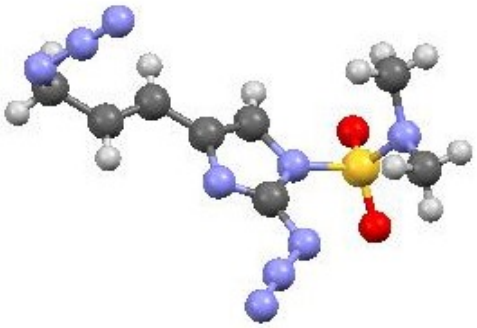


Scheme 2.16

Thompson and co-workers[44] proposed that the reaction occurred in two distinct steps as depicted in Scheme 2.16. First, the formation of a phosphate intermediate followed by azide displacement and the product can be isolated from an aqueous work-up.

Allylic alcohol **141** was used as the test compound during optimizing the conditions for azidation to resulted in **142**. The same developed conditions were able to use to introduce second azide group in the allylic position in **146**. We haven't observed any allylic transposition takes place under this reaction conditions and only gave our desired product. So, with these encouraging results, we were able to install diazides in nagelamide A **148** and C **147** systems.

Most importantly, all the following allylic azides can be prepared without using a secondary azide source except in the alkyl azide of nagelamide A (Scheme 2.17). So, we have used TBAA as the secondary azide source to convert alkyl phosphonate ester to the corresponding alkyl azide to resulted in **148**.



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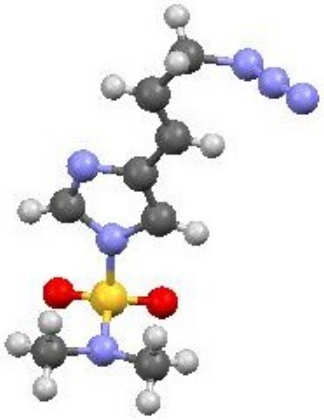
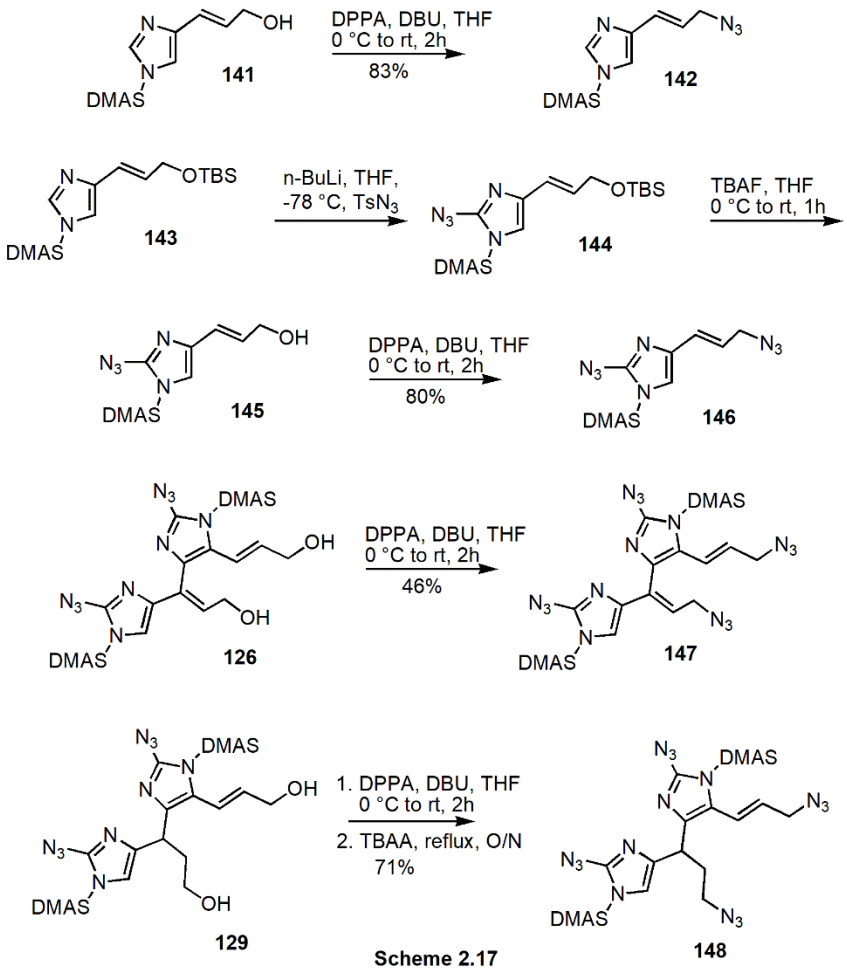


Figure 2.2 X-ray crystal structure of 146



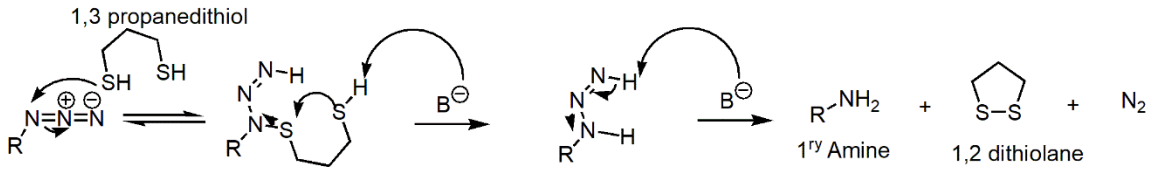
Scheme 2.17

Catalytic hydrogenation[45-46] and reduction with $LiAlH_4$[47] are the most frequent methods of reducing the azides. Other methods include, reaction with H_2S/pyridine/water,[48] transfer

hydrogenation,[49] Ph_3P/H_2O (Staudinger reaction),[50] H_2/Lindlar catalyst,[46] $Cr(II)/H^+$,[51] $Na_2S/Et_3N/MeOH$,[52] $SnCl_2/MeOH$,[53] $NaBH_4/THF/MeOH$.[54] In the recent literature it also has been reported that use of $InCl_2H/MeCN$,[55] $BF_3.OEt_2/NaI$,[56] affords amines from azides. Some of these methods involve the use of expensive reagents, sometimes the absence of chemoselectivity and the relatively harsh-conditions during the transformation.

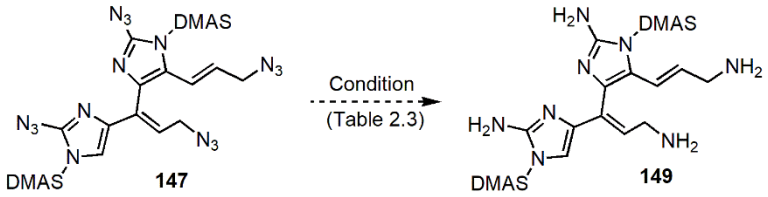
In our studies, first we thought to investigate the Staudinger condition[57] to reduce azides to amines (Scheme 2.19). Azides react with triarylphosphines to form aza-ylides in excellent yields and an aqueous medium hydrolyzes the ylide to the corresponding amine. However, in our case, Staudinger conditions led to formation of a complex reaction mixture formation, and we were not able to isolate the desired product **149**.

Next, we explored use of 1,3-propanenedithiol in the reduction of allylic azide system. This method was reported by Cartwright and coworkers in 1976[58], and they have proposed the following mechanism to obtain the primary amine from an azide (Scheme 2.18). Nucleophilic attack of sulfur on the interior N in the azide initiates the reduction. Next, intramolecular cyclization results in eliminating 1,2-dithiolane as the byproduct. A sequential proton capture by base resulted in the dinitrogen elimination from the triazine intermediate, and finally, a primary amine was formed as shown below (Scheme 2.18).



Scheme 2.18

In our studies, we observed the formation of **149** from LC-MS analysis, however, it was just a trace amount with compared to other detected products in the mass spectrum.

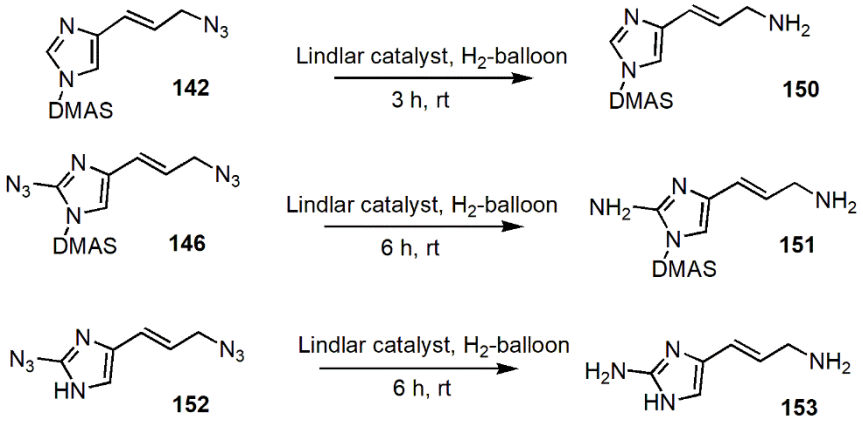


Scheme 2.19

Table 2.3 Attempts on tetraazide reduction

Entry	Method	Results
1	PPh_3, H_2O (Staudinger condition)	Complex reaction mixture observed
2	Propanedithiol	HRMS showed the desired peak for tetraamine
3	Lindlar catalyst, H_2	Only C2 azides are reduced

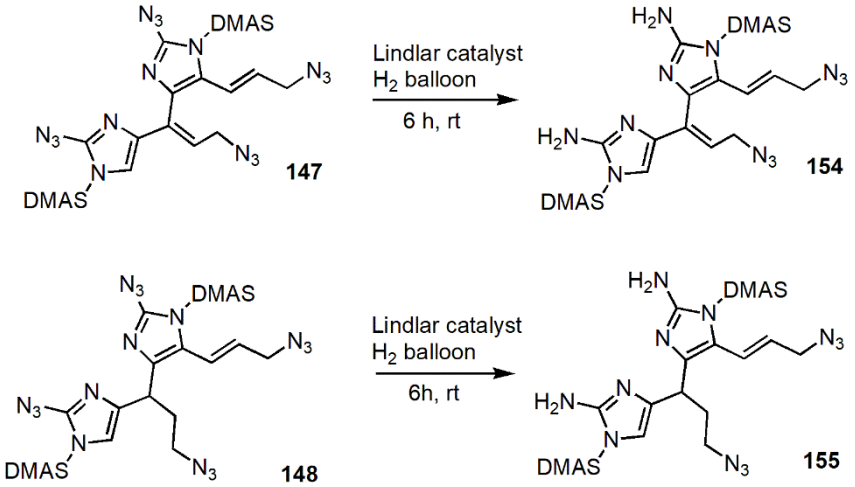
At this point, we focused on the catalytic hydrogenation to reduce azides since this method has been employed in many azides en route to oroidin systems, both in our lab and others in the process of installing the C2 amino groups.[31] But, our concern was to ‘‘protect’’ the allylic systems in nagelamide A and C and only reduce the azide groups.



Scheme 2.20

So, we chose Lindlar catalyst for our studies as it can selectively reduce the allylic azides without affecting to the double bond.[46] Our studies on monomeric model systems were successful, and we were able to isolate **150**, **151** and **153** (the formation of **152** is described below in Scheme 2.22)

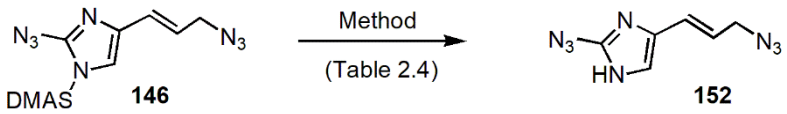
quantitatively. So, next we targeted the dimeric systems en route to nagelamide C **147** and nagelamide A **148** with the Lindlar catalyst and hydrogen. Surprisingly, only the C2 azides were reduced in both systems. Increasing the reaction time or the catalyst loading did not lead to reduction of the tetraazides to the corresponding tetraamines. However, while adding potentially an additional step, the chemoselectivity observed in these experiments may prove advantageous.



147 **154** **148** **155**

Scheme 2.21

Previous studies[12, 31] have shown that removal of DMAS group in systems containing a C2 amines is not possible at this stage and thus deprotection of the DMAS groups before the reduction of tetraazide was required. Several methods were explored to remove the DMAS group as shown below in Table 2.4. Primarily, our studies focused on a monomeric model system and later the studies were extended to the targeting tetraazides.



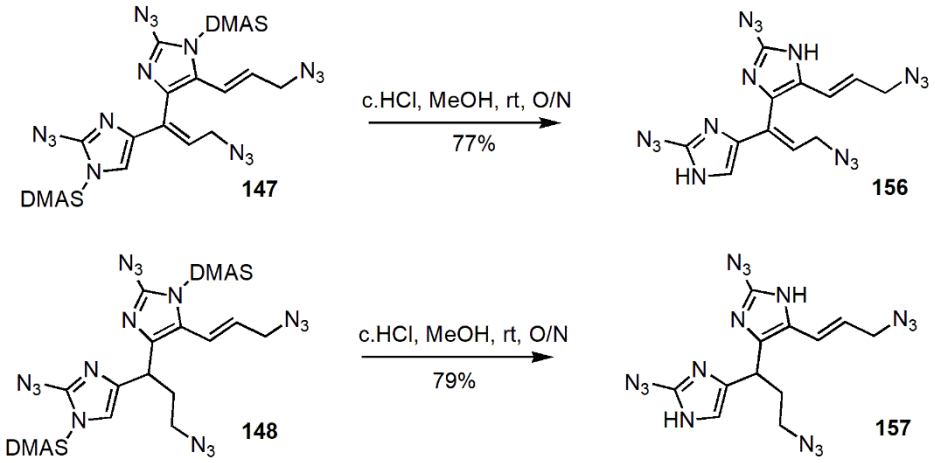
146 **152**

Scheme 2.22

Table 2.4 Attempts at removing the DMAS groups

Entry	Method	Results
1	Base hydrolysis (KOH, reflux)	Decomposition was observed
2	Aqueous hydrolysis	Starting material was isolated
3	Acid hydrolysis (HCl, reflux)	Decomposition was observed
4	Acid hydrolysis (HCl, rt)	96% of **152** was isolated

The identified acidic conditions were used for the tetraazide systems (**147** and **148**) and both the DMAS groups were removed successfully in the nagelamide C and A systems affording **156** and **157** respectively (Scheme 2.23).



Scheme 2.23

At this stage, completion of the syntheses required reduction of the azides and incorporation of the pyrrole carboxamides. Ideally, this would be accomplished either via the tetra amine and acylation or if feasible by chemoselective reaction or the allylic azides to the pyrrole carboxamides followed by reduction of the C2-azides. In the course of examining our options, we become aware of the reaction between thioacids and azides which leads directly to the formation of amides. As noted above, the chemoselective reduction of the C2-azides leaving the alkyl azides intact offered an opportunity to exploit the reactivity difference. Therefore, at this time, we focused on the

development thioacid/azide chemistry since the tetraamine seems to decompose under the given conditions.

2.7 Thioacid-mediated conversion of azides to amides

Synthesis of different amides, which are found widely in natural products, pharmaceuticals, and protein chemistry can be a challenging task, especially in the final step of the sequence.[43]

However, a one-pot process to convert azides to desired amides can be achieved by simply reacting the target azide with the corresponding thioacid. This transformation was initially reported by Just,[59] and in detail by Rosen in 1988.[43] Initially, he proposed that the amide formation occurred via reduction to an amine, followed by fast acetylation of the intermediate (Figure 2.4).

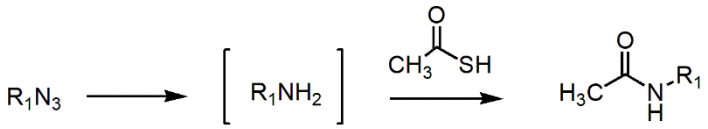
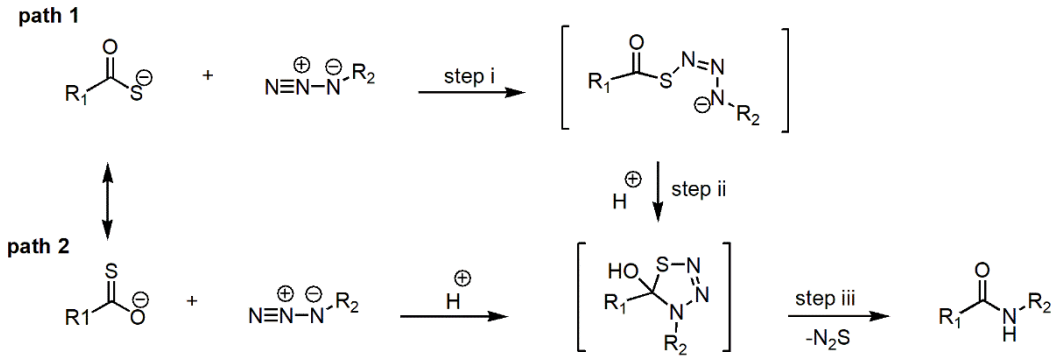


Figure 2.4 Initially proposed mechanism

But in 2003, Williams and co-workers[60] investigated the mechanistic studies of the acylation and found that azides give the corresponding amides without reduction to the amines in the presence of thioacids. Moreover, the reaction occurs independent of polar or non-polar solvents and the addition of the base, 2,6-lutidine to the reaction mixture expressively accelerates the rate of the reaction.

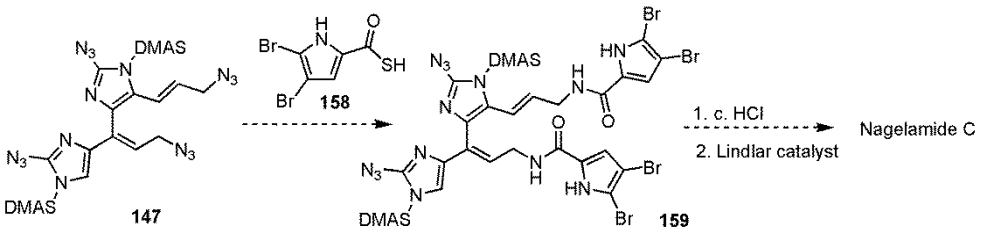
According to these observations, a new mechanism (Scheme 2.24) was proposed by Willams and co-workers for the amide formation. According to their hypothesis electron-deficient and electron rich systems undergo reaction through a common intermediate, a thiatriazoline, during the formation of amides. However, their arrival at this intermediate is not identical, electron poor

systems have one extra step involving intermolecular coupling of sulfur of the acid and the terminal nitrogen of the azide, and the resulting product proceeds to the five-membered intermediate, thiatriazoline, and finally, it decomposes to an amide, molecular nitrogen, and sulfur. Electron rich systems behave differently with thioacids, by forming the five-membered intermediate in a single step via a [3+2] cycloaddition.

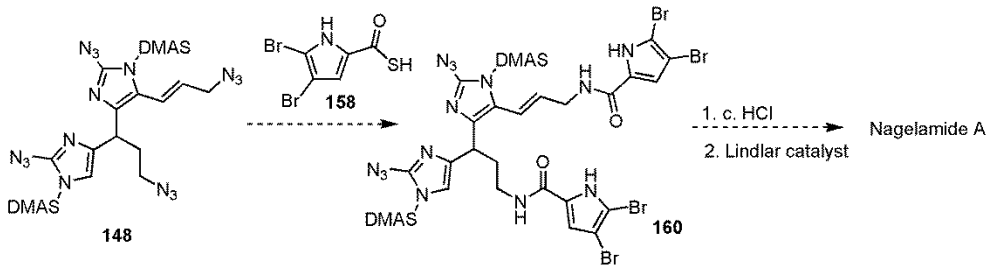


Scheme 2.24

This section will concentrate on the development of a novel approach for thioacid-mediated amidation in the imidazolic systems, which can be extended to install the pyrrole groups in the oroidin alkaloids. Moreover, the application of this method in nagelamide A, C, and S can be used install the pyrrole groups at the final stage (Scheme 2.25-2.26).



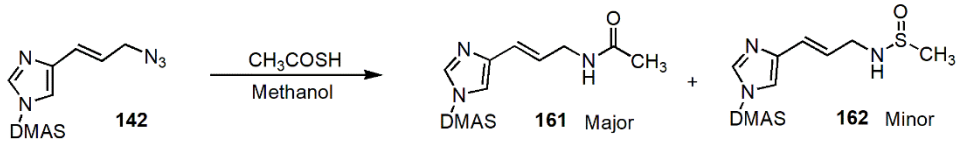
Scheme 2.25



Scheme 2.26

2.7.1 Reaction conditions optimization with thioacetic and thiobenzoic acid

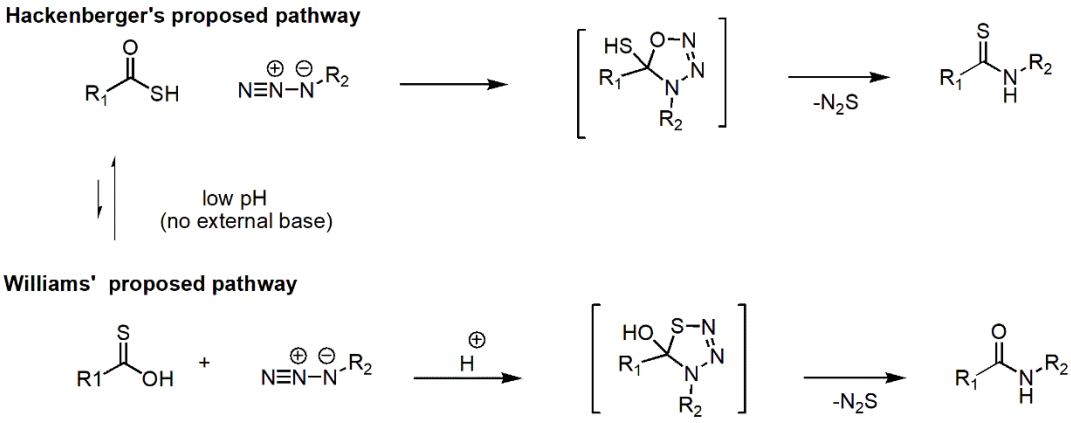
The urocanic acid-derived substrate **142** was chosen as the test compound for preliminary experiments as it was readily available and could be easily elaborated to possess many of the structural features that might be present in advanced intermediates in our planned total synthesis endeavors.



Scheme 3.27

The allylic azide **142** was reacted (Scheme 2.27) with neat thio acetic acid according to Rosen's report,[43] which delivered the expected acetamide **161** in a good yield along with a small amount of the corresponding thioamide **162** formation (entry 1; Table 2.5). In 2014, Hackenberger[61] reported that, thioacid-mediated reactions could proceed through a relatively different mechanism at lower pH conditions. According to Williams'[62] DFT calculations, the formation of a five-membered ring of thiatriazolidine occurred via a concerted reaction starting with C=S of a thioacid with R-N_3. Sulfur atom has a larger covalent radius compared to the oxygen, and the low-efficient overlap of C_{2P}-S_{3P} lead to make the C=S bond more reactive than C=O in the cycloaddition step. However, at lower pH conditions, thioacid prefers to stay as C=O in a larger extent, and only a trace quantity of C=S tautomer is present according to the data shown by Liu and Gordy[63]

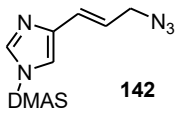
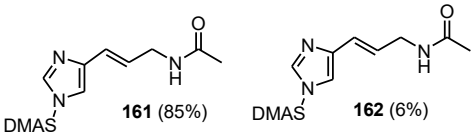
respectively. So, Hackenberger[61] proposed that C=O can forms oxatriazolidine which leads to the formation of thioamide **162** as shown in the below (Scheme 2.28). This type of thioamide formation was previously proposed by Rademann and co-workers[64] for a system composed of thioacid and azide with a Lewis acid. So, C=O is reactive enough to undergo the cycloaddition and results the thioamide since, only traces of C=S present in the acidic conditions.

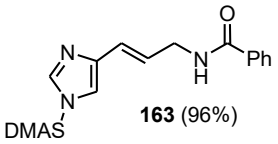
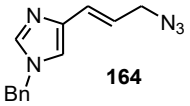
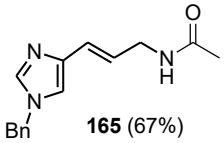


Scheme 2.28

Similarly, the reaction with thiobenzoic acid provided the corresponding benzamide **163** in good yield and the structure was confirmed by the X-ray crystallography (entry 5, Table 2.5). The benzyl-protected substrate **164** provided the expected amide **165** in moderately good yield, but the process is slower (entry 6, Table 2.5). The electron-rich benzyl group making sufficient azide systems than in the electron withdrawing DMAS group and that may lead to a slower rate in the formation of **165**.

Table 2.5 Products from reactions of imidazole-containing monoazides with thioacids.

Entry	Substrate	Conditions	Products
1	 **142**	Neat MeCOSH (4 equiv), 1 h	 **161** (85%) **162** (6%)

2	**142**	Neat, MeCOSH (4 equiv), lut., 1 h	**163** (81%) -
3	**142**	MeCOSH, lut., 3 h	**163** (68%)
5	**142**	PhCOSH (4 equiv), lut., O/N	 **163** (96%)
6	 **164**	MeCOSH (4 equiv), lut., 20 h	 **165** (67%)

Reactions were conducted with 2 equiv of thioacid, 2 equiv of lutidine in MeOH (0.26 M) at room temperature unless indicated otherwise; where increased equivalents of thioacid were used the corresponding amount of lutidine was used.

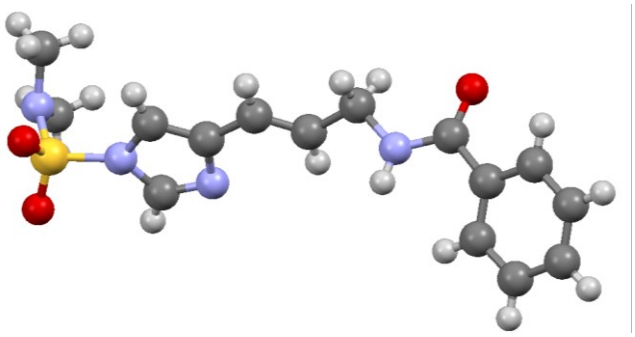
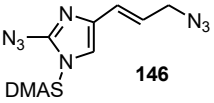
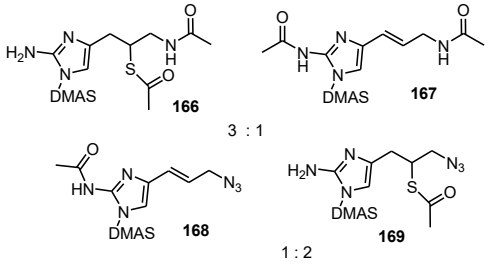
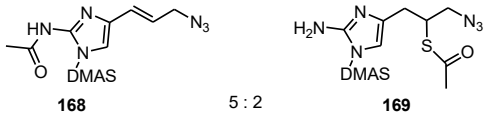
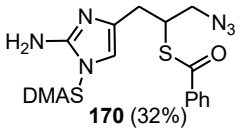


Figure 2.5 X-ray crystal structure of 163

With the above encouraging results, we determined that the thioacid chemistry can be applied on the allylic imidazole systems, warranting a further investigation. At this point, we moved forward to approach the natural products, and **146** was selected as a model system to optimize the reaction conditions. The reaction of the diazide **146** with thioacetic acid under the neat conditions afforded

a total of four different products that were isolated as two-component mixtures (Table 2.6). One of the mixtures contained the diamide **167** along with a second product **166** in which acylation of the allylic azide occurred with concomitant reduction of the 2-azido group to the amine and hydrosulfenylation; this latter material was the major product in the mixture. The second two-component mixture contained the C2-acetamide **168** and again a product **169** which had undergone reduction and hydrosulfenylation. Under solution conditions, a mixture of the same C2-monoacetamide **168** and addition product **169** was isolated favoring the C2-amide (entry 2, Table 2.6).

Table 2.6 Products from reactions of imidazole-containing bisazides with thioacids

Entry	Substrate	Conditions	Products
1	 **146**	Neat MeCOSH (4 equiv), 2.5 h	 **166** 3 : 1 **167** **168** 1 : 2 **169**
2	**146**	MeCOSH (2 equiv), lut. (2 equiv), 4.5 h	 **168** 5 : 2 **169**
3	**146**	PhCOSH, lut., 4 h	 **170** (32%)

When the same diazide **146** was reacted with thiobenzoic acid rather than the benzamide the product from hydrosulfenylation in addition to the reduction of 2-azido moiety **170** was obtained (entry 3, Table 2.6). The constitution of this product was firmly established through X-ray crystallography (Figure 2.6).

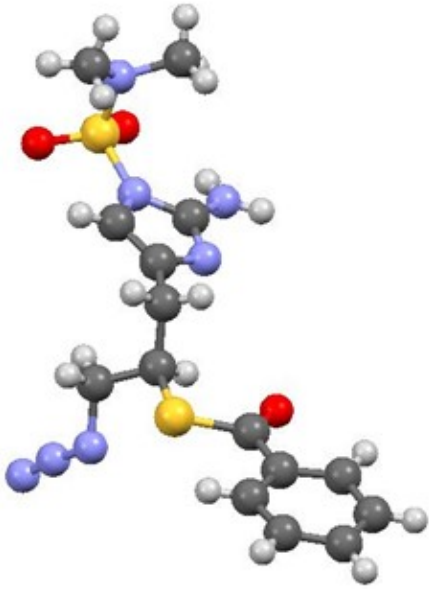


Figure 2.6 X-ray crystal structure of 170

ExperimentS were performed to address the origin of these addition/reduction products, in the presence of BHT (2 equiv) as a radical scavenger to assures whether the hydrosulfenylation products were derived from a radical pathway.

Table 2.7.1 Products from the mechanistic studies

Compound	Test 1	Test 2 (control)	Test 3
146	Yes	Yes	Yes
BHT	Yes	No	No
TEMPO	No	No	Yes

Product	**170**	**170**	**146** + piperidinyl ester (**170a**)

Reactions were conducted with 2 equiv of PhCOSH, 2 equiv of lutidine in MeOH (0.26 M) at room temperature.

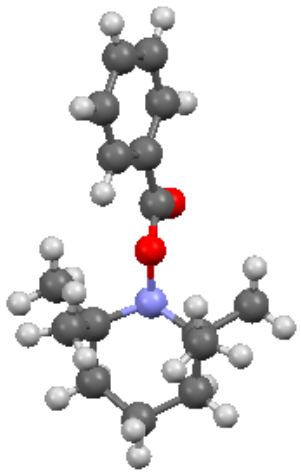
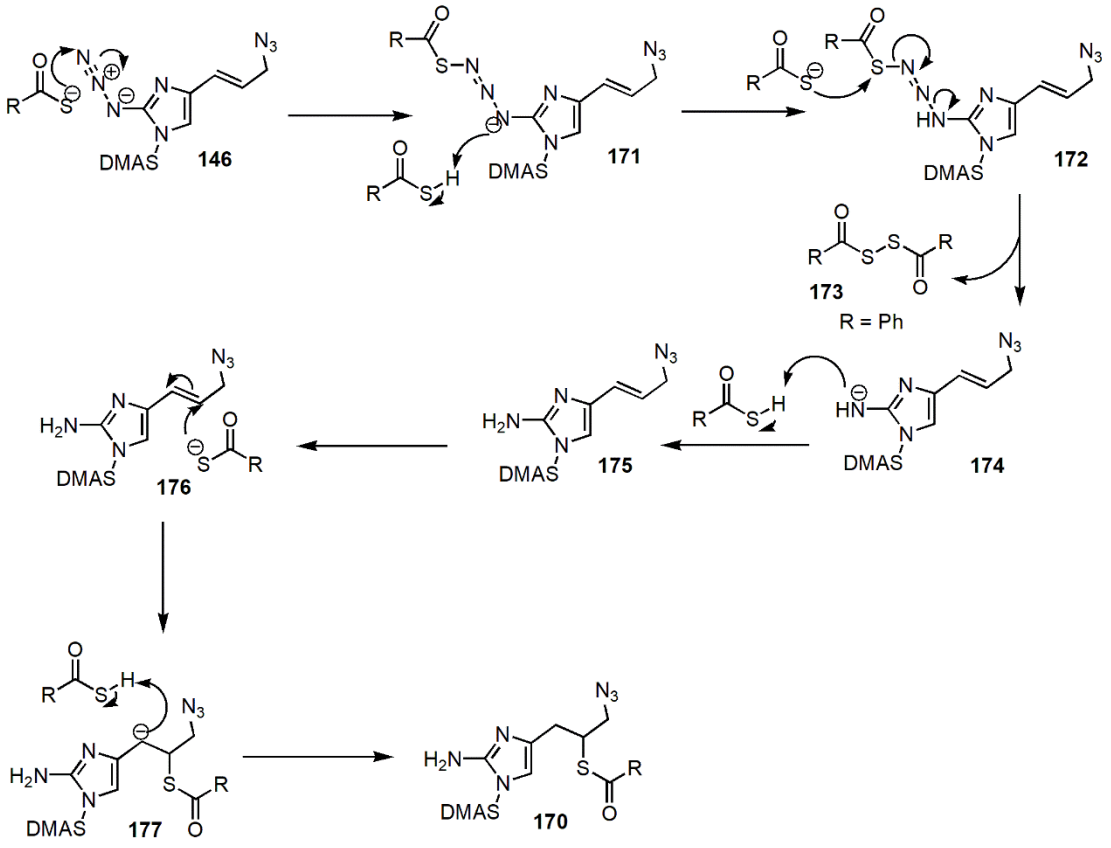


Figure 2.7 X-ray crystal structure of 170a

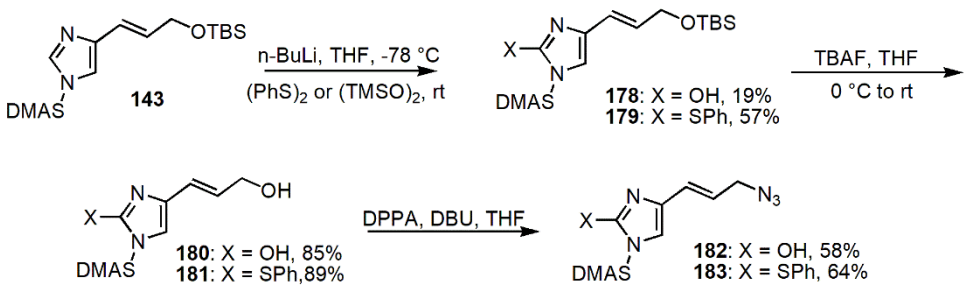
BHT is a free radical scavenger and TEMPO is a stable free radical and both of the tests 1 and 3 gave the product **170**. These results were somewhat ambiguous in that there appeared to be an induction period, but the formation of the reduction/addition product **170** was observed in comparable yield, suggesting that formation of **170** is not via a radical pathway.[65] Interestingly, we were able to isolate the piperidinyl ester from TEMPO experiment and the obtained X-ray structure is shown above (Figure 2.7). Also we did isolate and fully characterized **173** (R = Ph, Scheme 2.26) which indicated that the thioacid served as the reductant.[66] A control reaction in which only the azide was absent from the reaction mixture demonstrated that **173** was not formed in the absence of the C2-azide. Presumably, reduction of the azide begins by nucleophilic attack

of the thioacid on the terminal nitrogen to afford **146** after protonation (Scheme 2.29).[60, 62, 67] Cleavage of the N-S bond through the attack of the thioacid sulfur produces the diacyl disulfide **173** and expels nitrogen, and upon protonation of **174** the reduction is completed[68] and in this way, we proposed that hydrosulfenylation proceeds via nucleophilic addition and subsequent protonation. Another control reaction was carried out with **175** as the starting material and observed the formation of the addition product (**170**; R = CH_3) with CH_3COSH and this is also providing some support to the proposed mechanism below.



Scheme 2.29

Based on these observations, we considered the use of other C2 amino surrogates instead of C2 azides, since there are chemoselectivity issues thus not leading to the desired allylic acylation. So, we found that 2-thiophenyl and 2-oxo can be used as the surrogates (Scheme 2.30).

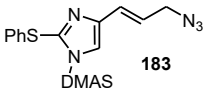
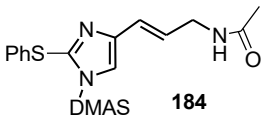


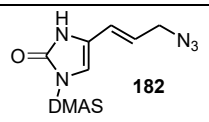
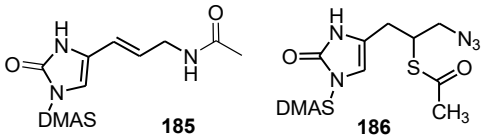
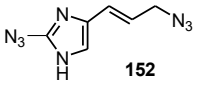
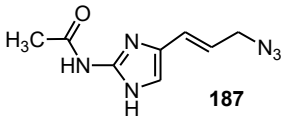
Scheme 2.30

Introduction of substituents at C2 can be accomplished readily by deprotonation of the known allylic silyl ether **143**[69] with *n*-BuLi and then exposure to a suitable electrophile. In the case of thioether **179**, it can be accessed in good yield by treatment of the deprotonated imidazole with purified phenyl disulfide. The reaction of the deprotonated imidazole with $(TMSO)_2$ provided the 2-oxo derivative **178** in low but usable yield. Desilylation of each of these derivatives was accomplished with TBAF and introduction of the allylic azide was performed as before with DPPA and DBU providing the corresponding allylic azides **183** and **182** (Scheme 2.30) and we observed that azidation occurred without allylic transposition.

When the 2-thiophenyl substituted derivative **183** was subjected to reaction with thioacetic acid under standard conditions the expected amide **184** was obtained in 58% yield (entry 2, Table 2.7).

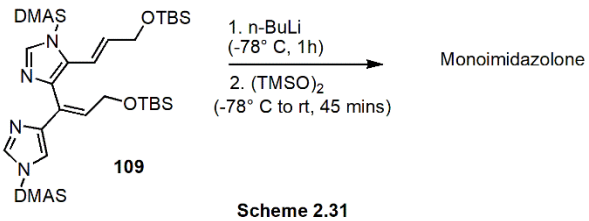
Table 2.7.2 Yields for preparation of C2-functionalized allylic amides.

Entry	Substrate	Conditions	Products
1	 **183**	MeCOSH (4 equiv), lut. (4 equiv), O/N 58%	 **184**
2			

	 **182**	MeCOSH (4 equiv), lut. (4 equiv), O/N 40%	 **185** 1 : 3 **186**
3	 **152**	MeCOSH (4 equiv), lut. (4 equiv), 3 mins 63%	 **187**

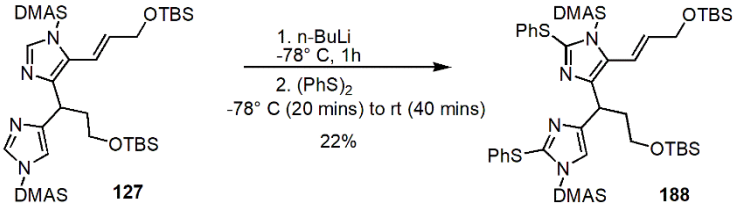
On the other hand, when the 2-oxo derivative **182** was reacted with thioacetic acid, the anticipated amide **185** was isolated in admixture with the addition product **186**, with the addition product being the major component (entry 1, Table 2.7). Encouragingly, the diazide substrate **152** lacking the imidazole protecting group underwent reaction very selectively and rapidly (2–3 min) delivering **187**, with no evidence of hydrosulfenylation (entry 3, Table 2.7). Interestingly, this reaction also proceeds equally-rapidly in the absence of lutidine suggesting that the imidazole is acting as a base. Solution conditions (MeOH) were also effective for the preparation of the amide resulting in similar efficiencies (entries 3–6, Table 2.5). Also, importantly we noticed that heating of the reaction mixture to reflux did not lead to increase yield of **161**. When this reaction conducted in the absence of lutidine, the yield of amide was dropped (entry 2, Table 2.5).

At this point, we thought that the basic process was sufficiently robust to move forward and use these modified conditions on the dimeric systems. Initially, we selected the scaffold of nagelamide C for our studies. But unfortunately, we were unable isolate the desired diimidazolone product, and, instead a monoimidazolone product was isolated (Scheme 2.31).



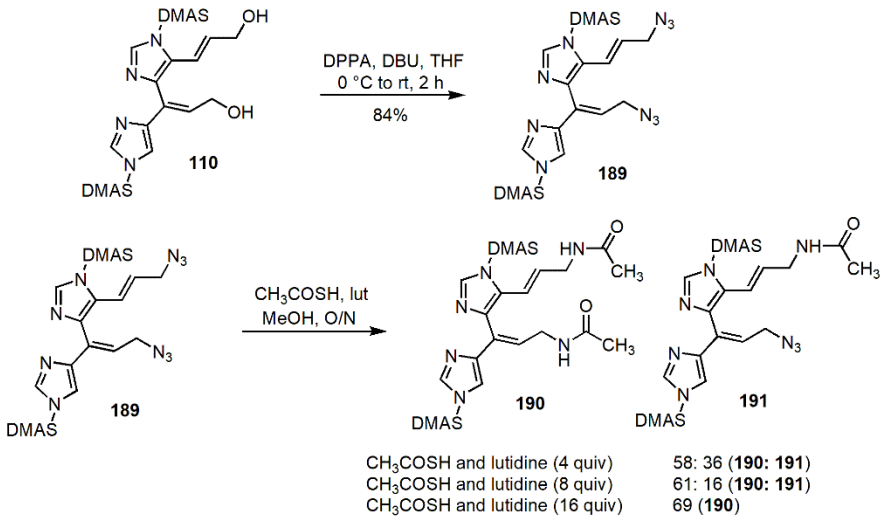
Scheme 2.31

Potentially, the monoimidazolone resulted because the TMS-peroxide may not react completely with the substrate after the lithiation to give the bis-imidazolone and instead of that just ended up with a mono-imidazolone, as we did not observe a promising result in the monomeric (**182**) system also. So, we decided to move forward by functionalizing the scaffold of nagelamide A with phenyl thioether since it has shown comparatively good results than TMS-peroxide (Scheme 2.32).



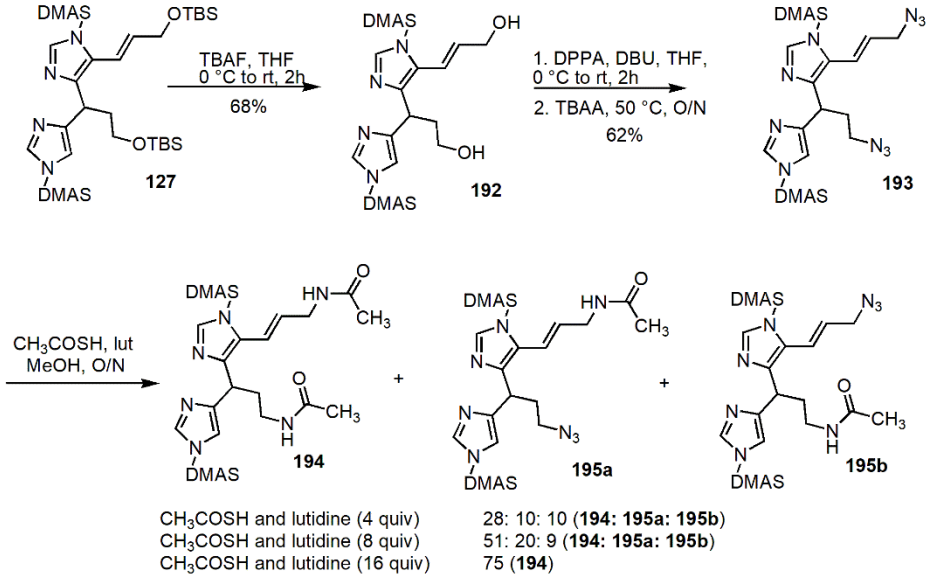
Scheme 2.32

However, the yield for this conversion did not give us the confidence to move forward and thus did not continue further studies on this route. Next, our studies focus on dimeric diazides related to nagelamide A and C to optimize their reactivities toward thioacids. Both the systems underwent acylation with thioacetic acid (16 equiv.) to give the bis acetamides **190** and **194** in good yields (Scheme 2.33-2.34). Using lower equivalents of the thioacids resulted in the formation mono acetamides in modest yields in addition to the bis amides.



Scheme 2.33

Interestingly, in the case of the nagelamide C model, the less substituted allylic azide was more reactive leading to the formation of only one mono azide **191**, the structure of which was easily assignable based on the ^{1}H NMR data.



Scheme 2.34

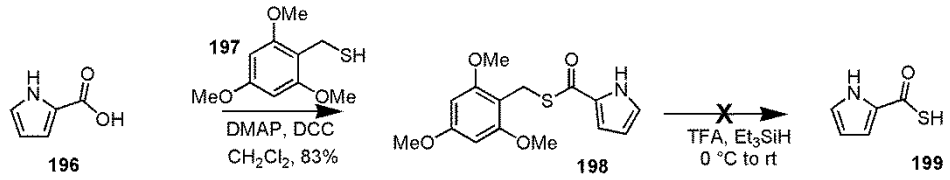
2.7.2 Attempts toward the synthesis of pyrrole thioacid

In order to complete the total synthesis nagelamide A, C and S we must employ 2-pyrrolethiocarboic acid, this is not commercially available, and we have to synthesize it in the laboratory. Several attempts have been investigated (Table 2.8) to convert 2-pyrrolecarboxylic acid to 2-pyrrolethiocarboic acid. Initial attempts to accomplish this via the acid chloride and NaSH were unsuccessful although eventually we were able to achieve their synthesis via this route (See Scheme 2.37). However, prior to this we have prepared and evaluated thioesters as masked thioacids.

2.8 Table Attempts on pyrrole carboxylic acid formation

Entry	Method	Results
1	Hydrolysis of thioester **198**	Thioester was synthesized. Hydrolysis did not work.
2	Deprotection of thioester **157**, **158**	Deprotection did not work.
3	Treating with NaSH	Prepared with 25-30% yield

Williams and co-workers[70] reported in 2006 that trimethoxybenzyl (TMOB) thio esters could be used as the thioacid precursors. The absence of aqueous workup, not finding any significant byproducts or using excess reagents added considerable value to this method.

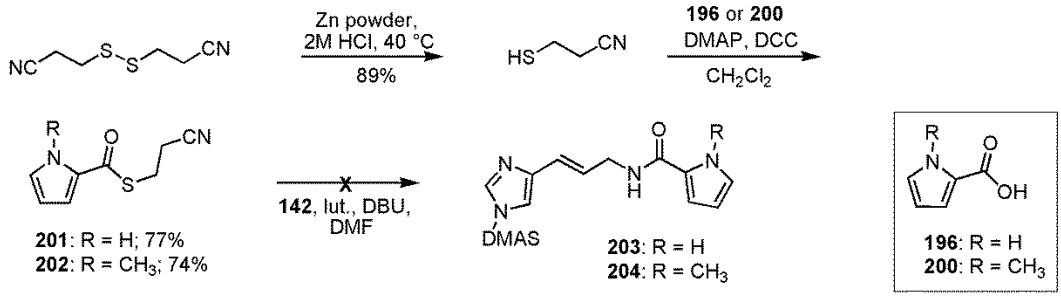


Scheme 2.35

We have successfully synthesized the thioester **198** in excellent yield, using pyrrole carboxylic acid **196** and TMBO-thiol **197** via a DCC-mediated coupling reaction. The treatment of TFA/Et_3SiH is used to facilitate the cleavage the TMOB group and release the crude thioacid to

the reaction medium. Our plan was to employ the stepwise addition of target azide to the above mixture after reductive release of the thioacid, and thus converting to the corresponding amide in the presence of lutidine.[71] Several attempts were made to convert **198** from **199**, using the above method with some modifications, but we were not able to see the formation of thioacid.

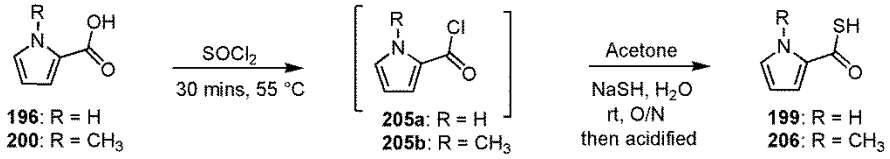
Rademann and coworkers have reported that the 2-cyanoethyl group could be used as a protecting group in the formation of thioacids.[64] 3-Mercaptopropionitrile was prepared from the reduction of disulfide, and that was coupled with pyrrole acid **196** or **200** to give 2-cyanoethyl thioester **201** and **202** in good yields. Unfortunately, upon the base treatment, we were not able to observe either the desired acid thioacid **196** deprotection nor the product **203** formation (Scheme 2.36).



Scheme 2.36

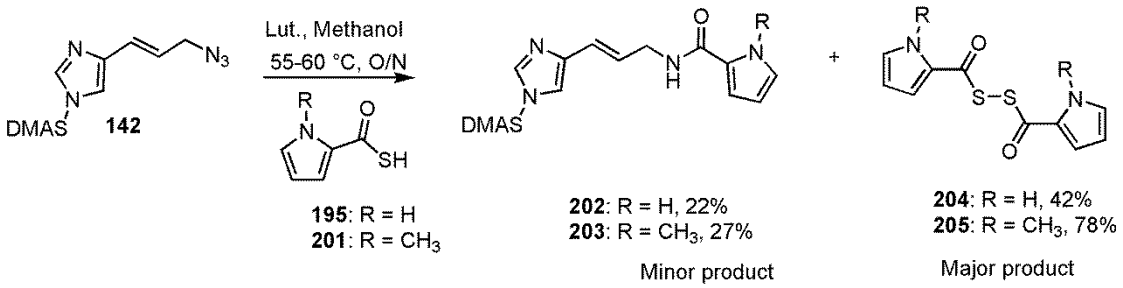
Our main concern was the acidity of the N-H of the pyrrole carboxylic acid, and we suspected that it might deprotonate during the process of pyrrole thioacid synthesis. So we examined a methyl protected pyrrole carboxylic acid to avoid this unnecessary deprotonation. After many unsuccessful approaches, finally, we were able to synthesize the *N*-methylpyrrole thioacid **206** as follows (Scheme 3.37). The pyrrole acid **200** converted to the corresponding acid chloride **205b** using thionyl chloride, and upon the treatment with NaSH, followed by the acidic workup provided the product **206**. The same procedure was able to use to access the pyrrole thioacid **199** also, with only a slight pH adjustment during the work-up process. The isolated yield was good enough to continue the studies, but still, we need to optimize the yield of the synthesis of pyrrole thioacid

199 if this method is to be practical. The discovered conditions are very important during the industrial synthesis of pyrrole thioacid since it is cost effective and easily prepared in gram scale.



Scheme 2.37

Next, we used our model system to optimize the amidation condition with these newly synthesized thioacids (Scheme 2.38).



Scheme 2.37

We noticed that the above reaction is not taking place at room temperature, requires heating at 50-60 °C overnight. The problem associated with this step is a comparatively low yield of **207** and **208** due to a significant oxidative homo-coupling and formation of the pyrroledisulfides **209** and **210**. We were able to get X-ray crystallographic data for both of these coupled products as shown in figures 2.7 and 2.8.

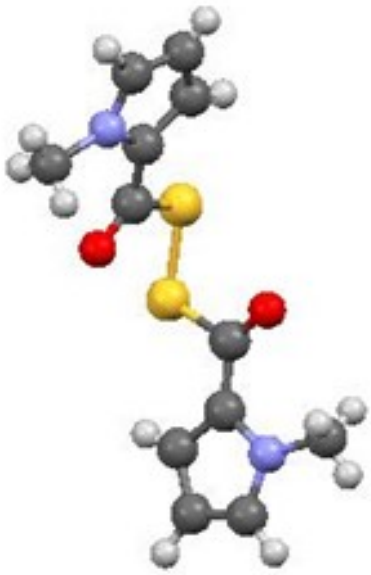


Figure 2.8 X-ray crystal structure of 205

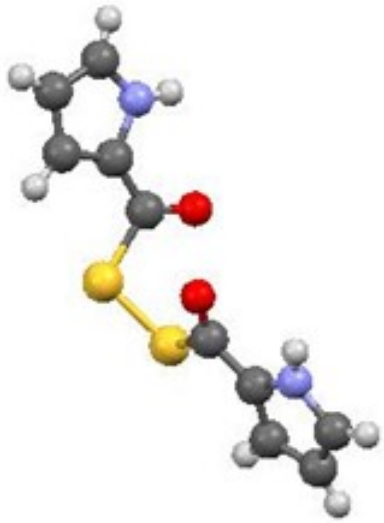


Figure 2.9 X-ray crystal structure of 204

Conclusions

Successful progress toward nagelamide A and C was achieved. Modified conditions were developed to increase the yield of key Stille cross-coupling reaction. A successful approach was reported for azide installation in alkyl and allylic systems. A new thioacid-mediated amidation method was introduced to the oroidin-derived systems and excellent results were obtained in acetamide and benzamide formation. A new method for pyrrole thio acid formation was reported and promising results were observed in the pyrrolecarboxamide installation in oroidin systems. Initial screening studies on pyrrolecarboxamide installation in the final products, nagelamide A and C were not successful due to unexpected pyrroledisulfide formation and current studies are under going to improve the pyrrole thio acid based-amidation to complete the natural products.

CHAPTER 3

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF AGELIFERIN

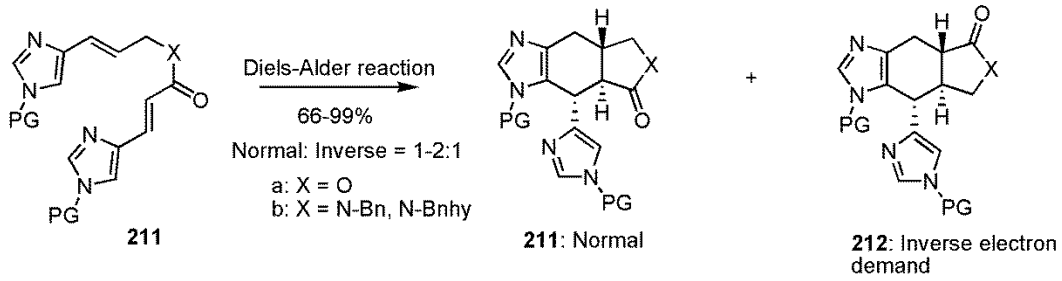
3.1 First-generation approach:

The construction of 6-membered rings with a high degree of control of regioselectivity and stereoselectivity are continuing challenges in natural products synthesis. Remarkably, Diels-Alder reactions allow synthesis of molecules with the required structural complexity in a single step reaction.[72] Ohta and co-workers[35] have shown that an intermolecular Diels-Alder cyclization could be used to construct the tetrahyrdobenzimidazole (THB) moiety of the ageliferin molecule using 5-vinylimidazoles as the precursors. In this study, it was observed that easily removable protecting groups resulted in low yields in the Diels-Alder reaction; however, excellent yields were obtained from the more robust methyl protected substrates. The resulting Diels-Alder product was subsequently employed in an to approach the non-natural 14,14'-dimethylageliferin.[35]

3.1.1 Via formation of ester or amide-linked system

Our laboratory is exploring an intramolecular Diels-Alder reaction to construct the key THB framework of ageliferin using 4-vinylimidazoles as the starting material. In the first-generation approach, ester and amide-linked systems were constructed through the intramolecular Diels-Alder reaction, and those were thought to be the key scaffolds of the natural product (Scheme 3.1).[69, 73] However, this approach revealed several problems, such as an inadequate reactivity of esters, diene-dienophile selectivities of the amides were observed resulting in the formation of the undesirable inverse electron demanding product **212** from electron-poor diene systems in addition

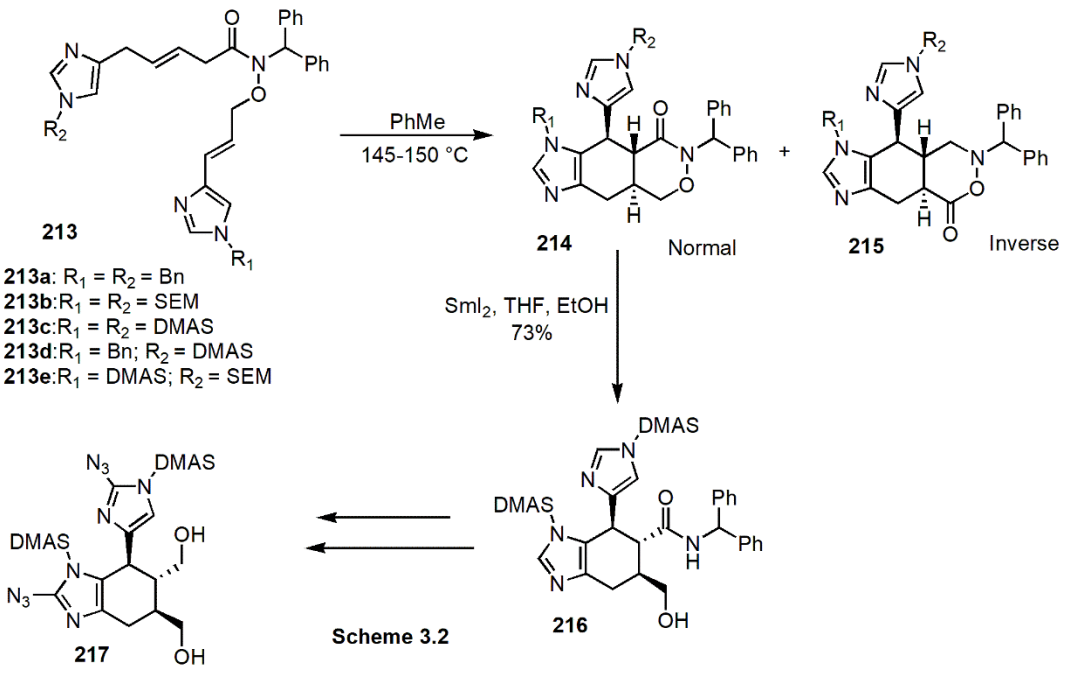
to issues with post cycloaddition elaboration. As a consequence of these problems, our group became interested in alternative strategies to access the scaffold of the natural product.



Scheme 3.1

3.1.2 Via hydroxamate linkage

A modified approach was required to increase the efficiencies, the selectivities of the [4+2] cycloaddition and more importantly, the ease of cleaving the linker of the cycloadduct at a later stage, to provide the access to install the pyrrole derivatives. Initial studies investigated the hydroxamate linkage (Scheme 3.2), since the N-O bond is more convenient to break while progressing towards the natural product. Following this strategy, we observed that the Diels-Alder reaction provided the all-trans, normal product **214** as the predominant adduct, and the inverse-electron demand product **215** was a minor byproduct. Next, the N-O bond was successfully cleaved by reduction with SmI_2, and hydroxyamide moiety was obtained in moderate yield. This intermediate has been successfully elaborated to the diol **217**, first requiring the incorporation of the pyrrole carboxamides. Using classical procedures and those developed by our lab have not been effective due to competitive intramolecular processes. Therefore, we began to explore the pre-installation of the nitrogen atoms derived to become amides.

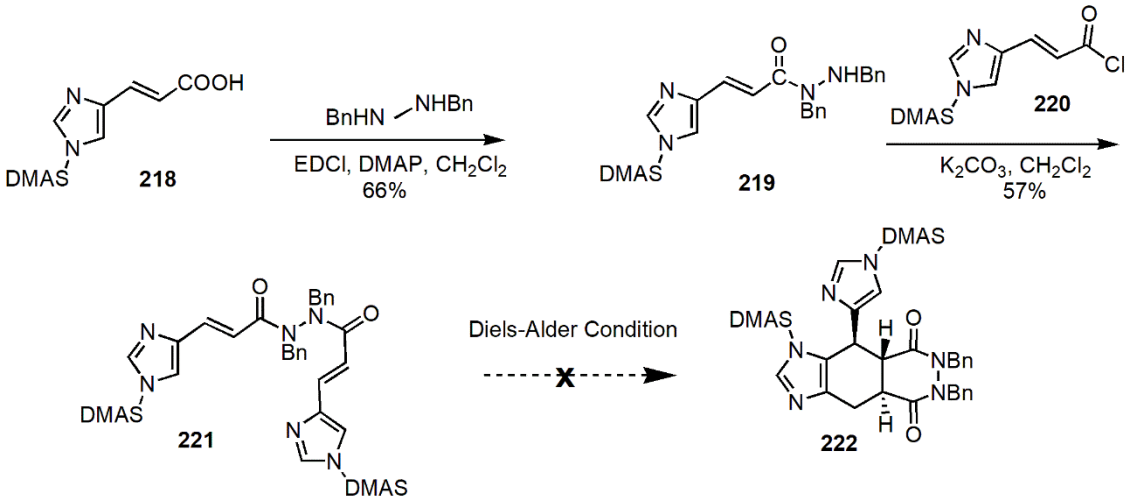


Scheme 3.2

3.1.3 Via N-N bonded system

Based on the lessons learned with the hydroxamate linkage (Scheme 3.2), our laboratory has explored the application of hydrazine moiety. Cleavage of the N-N bond results in the direct formation of primary amines, which can then act as an entry to install the pyrrole groups as in the natural product.

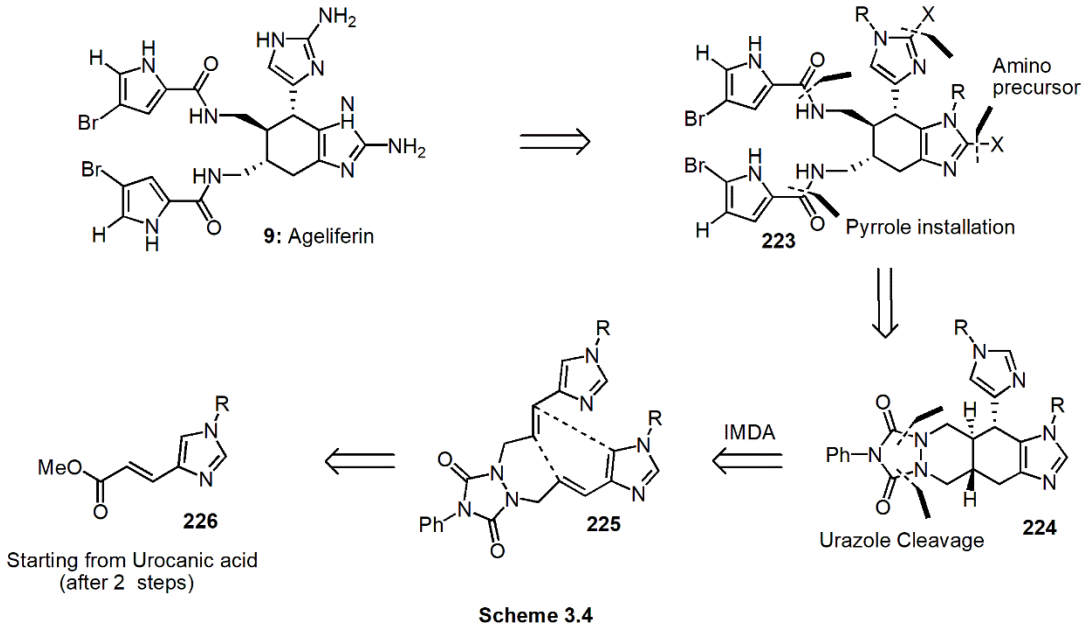
Initial studies began with N,N'-dibenzylhydrazine derivative **221** prepared by monoacylation of acid derivative **218** and followed by the reaction with acid chloride **220** provided the symmetric hydrazine **221** in moderate yield. Next, a Diels-Alder reaction was performed at 135 °C, but the precursor **221** did not undergo the cycloaddition, decomposition was observed.



Schme 3.3

3.2 Current Approach to Ageliferin

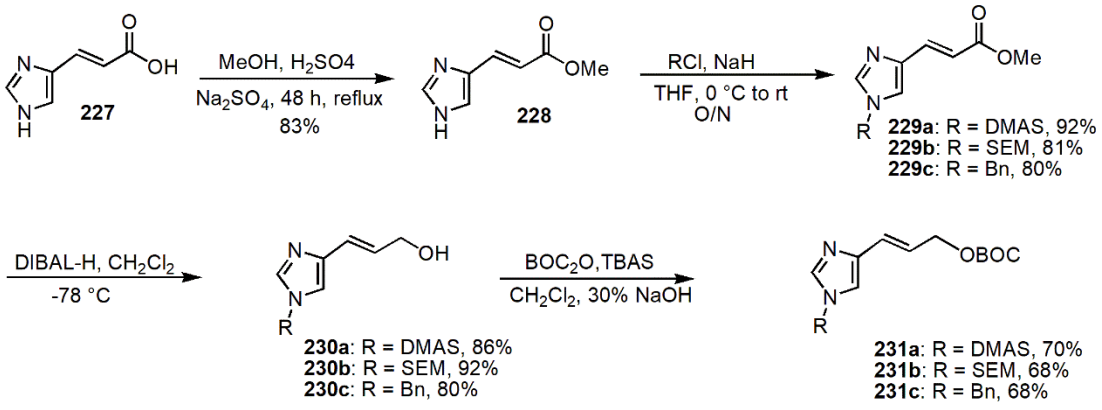
At this point, with concern about the thermal fragility of **221**, our studies were focused on identifying a thermally more robust system. The urazole moiety to carry out our intramolecular Diels-Alder reactions (IMDA).



Scheme 3.4

Urazoles, after oxidation produce PTAD (4-phenyl-1,2,4-triazoline-3,6-diones) derivatives that are classical dienophiles in the DA reactions, however their use in the present context is unprecedented. According to the synthetic Scheme 3.4, the scaffold was constructed through a [4+2] cycloaddition of precursor **225** and the C2 amino groups and the pyrrole groups can be installed in **224**, after the IMDA reaction. Diene **225** was obtained by two molecules of urocanic methyl ester **226** as given below (Scheme 3.4).

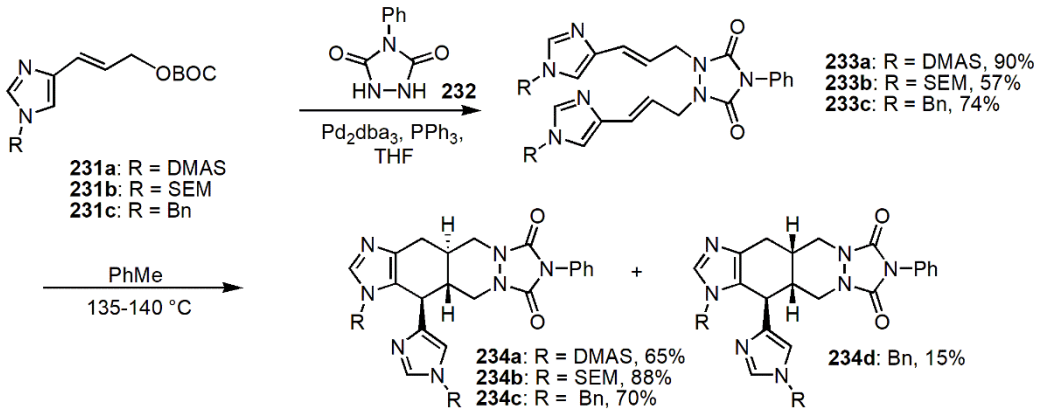
In Scheme 3.5, the allylic alcohol **230** was prepared according to literature procedure reported by our group.[69] Commercially available, urocanic acid **227** was converted to methyl ester **228** using the Fischer esterification. Then, we selected three different protecting groups to install on imidazole nitrogen which shows the distinct electronic properties, these potentially influence the subsequent introduction of the C2-substituent of the natural product. According to these requirements, we evaluated the strong electron withdrawing DMAS group, weakly electron withdrawing SEM group, and weakly electron donating Bn groups (Dr. Doundulakis in our lab performed the latter).



Scheme 3.5

DIBAL-mediated reduction of esters **229a-c** to the corresponding primary alcohols **230a-c** and then converted to *t*-butyl carbonate derivatives **231a-c**. Interestingly, we have found that *N*-

phenylurazole **232** would be the best candidate to synthesize the Diels-Alder precursors **233a-c** in decent yields. The cycloaddition reaction was carried out at 140-130 °C in an inert condition in a sealed tube. All Diels-Alder precursors **233a-c** gave the cyclic trans-isomer **234a-c**, but interestingly, the Bn-protected precursor **233c** resulted in cis isomer **234d** as well, which was isolated from the column chromatography.



Scheme 3.6

Conclusions

The key scaffold of the ageliferin was constructed in excellent yield through an intermolecular Diels-Alder reaction with the required stereochemistry as in the natural product. The intermediates **234a-c** were constructed using three different protecting groups with the diverse electronic environment in the imidazolic rings. The opening urazole ring, followed by the pyrrole groups installation will provide access to complete the total synthesis of the natural product.

CHAPTER 4
EXPERIMENTAL

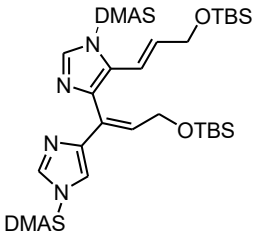
General Considerations

All reagents were purchased from commercial suppliers and were used as received unless otherwise noted. All reactions involving air- or water-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen.

THF was distilled from sodium/benzophenone under a nitrogen atmosphere. A Pure-Solv 400 solvent purification system from Innovative Technology Inc. was used to obtain dry THF, CH_2Cl_2, CH_3CN and benzene. Flash column chromatography was performed using silica gel (230-400 mesh) from SiliCycle Inc.

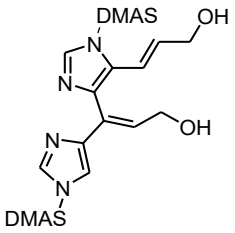
^1H and ^{13}C NMR (δ in ppm) spectra were recorded in $CDCl_3$ (unless otherwise noted) at 500 and 125 MHz, respectively; using a JEOL Eclipse+ 500 spectrometer in $CDCl_3$ unless otherwise noted. Residual $CHCl_3$ was used as reference for ^1H NMR spectra (δ = 7.26 ppm) and the central carbon absorption of $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectra. Infrared spectra were recorded as neat films using a Bruker Alpha spectrometer (ATR spectroscopy). Melting points are uncorrected and recorded on Mel-Temp Laboratory Devices Inc, USA apparatus. High-resolution mass spectra (HR-MS) were obtained by Mr. M. Kukula through the mass spectrometry service at the Shimadzu center for advanced analytical chemistry, the University of Texas at Arlington, Arlington.

4-((*Z*)-1-Dimethylsulfamoyl-4-(3-(*t*-butyldimethylsilyloxy)-2-propenyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-((*E*)-3-(tbutyldimethylsilyloxy)-2-propenyl) imidazole (109): N_2 was



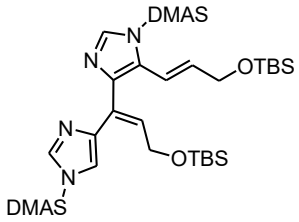
bubbled through solution of imidazolyl iodide[26] **57** (1.25 g, 2.65 mmol) and stannane **108**[26] (2.52 g, 3.97 mmol) in dry THF (40.0 mL) for 15 minutes. PPh_3 (138 mg, 0.530 mmol), CuI (101 mg, 0.530 mmol) and $Pd_2(dba)_3$ (121 mg, 0.130 mmol) were added and bubbling of N_2 was continued for additional 2 minutes. Next, CsF (1.81 g, 11.9 mmol) was added under the inert condition and stirred for 3 minutes at the rt. After that, the mixture was heated at 55 °C for another 4 h under the same conditions. The reaction solution was concentrated and the resulting crude material was dissolved in EtOAc which was stirred for few minutes, followed by filtration through bed of Celite and again concentrated under vacuum. The crude product was purified by flash chromatography (Hexanes/EtOAc, 60:40 → Hexanes/EtOAc, 10:90) to give **109**[31] (1.54 g, 85%) as a yellowish semi-solid. ^{1}H NMR: δ = 7.94 (s, 1H), 7.82 (d, *J* = 1.3 Hz, 1H), 6.81-6.74 (m, 3H), 6.11 (dt, *J* = 16.0, 3.7 Hz, 1H), 4.19 (d, *J* = 6.4 Hz, 2H), 4.12 (dd, *J* = 3.7, 2.3 Hz, 2H), 2.87 (s, 6H), 2.79 (s, 6H), 0.86 (s, 9H), 0.83 (s, 9H), 0.00 (s, 6H), -0.01 (s, 6H); ^{13}C NMR: δ = 142.3, 137.8, 136.7, 136.0, 135.9, 132.5, 127.2, 125.4, 114.7, 113.8, 62.7, 61.1, 38.3, 38.2, 25.9, 25.8, 18.4, 18.3, -5.1, -5.4; IR (neat, cm^{-1}): 3129, 2953, 2856, 1471, 1389, 1252, 1175, 1071, 962, 833, 723; HR-ESIMS *(m/z)*: Calcd. for $C_{28}H_{53}N_6O_6S_2Si_2$ $[M+H]^+$ 689.3001, found 689.2988; Calcd.for $C_{28}H_{52}N_6O_6S_2Si_2Na$ $[M+Na]^+$ 711.2820, found 711.2813.

4-((*Z*)-1-Dimethylsulfamoyl-4-(3-hydroxypropenyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-((*E*))-3-hydroxypropenyl)imidazole (110): Bis silyl ether **109** (1.82 g, 2.64 mmol) was converted to diol **110** (1.01 g, 83%, yellow solid) following the general procedure (A). The resulting residue



was immediately purified by the column chromatography (EtOAc/MeOH, 98:2). m.p. 124-127 °C; ^{1}H NMR: δ = 7.88 (s, 2H), 7.03 (s, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.27 (t, *J* = 6.9 Hz, 1H), 6.00 (dt, *J* = 16.1, 5.6 Hz, 1H), 4.31 (d, *J* = 6.9 Hz, 2H), 4.02 (d, *J* = 5.0 Hz, 2H), 2.83 (s, 6H), 2.84 (s, 6 H); ^{13}C NMR: δ = 140.4, 140.0, 137.6, 137.5, 136.2, 134.8, 128.1, 126.1, 117.2, 115.4, 62.5, 58.5, 38.34, 38.26; IR (neat, cm^{-1}): 3352, 3128, 2928, 2862, 1475, 1386, 1268, 1171, 1079, 959, 850, 722, 581, 511; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{24}N_6O_6S_2Na$ $[M+Na]^+$ 483.1091, found 483.1095.

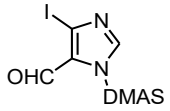
4-((*E*)-1-Dimethylsulfamoyl-4-(3-(*t*-butyldimethylsilyloxy)-2-propenyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-((*E*)-3-(*t*-butyldimethylsilyloxy)-2-propenyl)imidazole (111): N_2 was



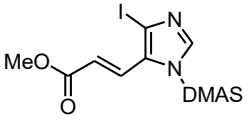
bubbled through a solution of imidazolyl iodide **57**[26] (700 mg, 2.65 mmol) and stannane **58**[26] (1.41 g, 3.97 mmol) in dry THF (28.0 mL) for 15 minutes. PPh_3 (77.0 mg, 0.530 mmol), CuI (56.0 mg, 0.530 mmol) and $Pd_2(dba)_3$ (68.0 mg, 0.130 mmol) were added and bubbling of N_2 was continued for additional 2 min. CsF (560 mg, 11.9 mmol) was added and continued the bubbling of N_2 for another 3 minutes. The reaction mixture was heated at 55 °C for 6 h under the same conditions. The reaction solution was concentrated and resulting crude material was dissolved in EtOAc and stirred for few minutes, followed by filtration through a bed of Celite and again concentrated under vacuum. The crude compound was purified by flash chromatography (Hexanes/EtOAc, 60:40 → Hexanes/EtOAc,

10:90) to give **111**[31] (870 mg, 85%) as a yellow color semi-solid; ^{1}H NMR: δ = 7.89 (s, 1H), 7.82 (d, *J* = 1.1 Hz 1H), 7.03 (d, *J* = 1.1 Hz 1H), 6.68 (dt, *J* = 15.7, 2.3 Hz, 1H), 6.13 (t, *J* = 6.0 Hz, 1H), 6.02 (dt, *J* = 15.7, 3.8 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 2H), 4.05 (dd, *J* = 3.8, 2.3 Hz, 2H), 2.86 (s, 6H), 2.81 (s, 6H), 0.88 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.00 (6H); ^{13}C NMR: δ = 140.9, 140.3, 137.4, 136.7, 136.5, 135.9, 126.3, 124.8, 116.9, 114.3, 62.8, 61.3, 38.3, 38.2, 26.0, 25.9, 18.4, 18.3, 4.9, -5.4; IR (neat, cm^{-1}): 3124, 2928, 2856, 471, 1384, 1252, 1176, 1074, 955, 834, 775, 725; HR-ESIMS *(m/z)*: Calcd. for $C_{28}H_{52}N_6O_6S_2Si_2Na$ $[M+Na]^+$ 711.2820, found 711.2837.

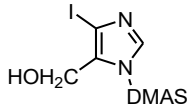
1-Dimethylsulfamoyl-4-iodoimidazole-5-carboxaldehyde (114): MnO_2 (1.97 g, 22.6 mmol) was added to a solution of alcohol **124** (0.50 g, 1.51 mmol) in CH_2Cl_2 (31 ml) and heated at reflux overnight. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated to give **114** (0.48 g, 96%) as a light-yellow solid; m.p. 108-110 ˚C (Lit. m.p.[74] 109-109.5 °C). All the characterization data exactly matched with the reported values.[74]



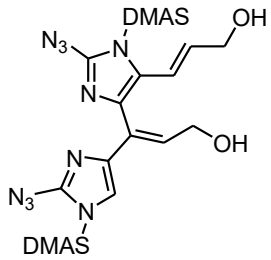
(*E*)-Methyl-3-(4-iodo-1-dimethylsulfamoylimidazol-5-yl)-2-propenoate (115): MnO_2 (5.91 g, 67.9 mmol) was added to a solution of alcohol **124** (1.50 g, 4.53 mmol) in CH_2Cl_2 (72 mL) followed by addition of methyl (triphenylphosphoranylidene)acetate (1.80 g, 5.38 mmol) and the mixture was heated at reflux overnight. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by column chromatography (Hexanes/EtOAc, 50:50) to afford **115** (1.43 g, 82%, yellow solid); m.p. 129-133 °C (Lit. m.p.[26] 128-131 °C). All the characterization data exactly matched with the reported values.[26]



1-Dimethylsulfamoyl-4-iodoimidazole-5-methanol (**124**): A solution of 3.0 M EtMgBr in ether (10.1 mL, 30.4 mmol) was added dropwise to a solution of ice-cooled diiodoimidazole **112**[75] (10.0 g, 23.4 mmol) in dry CH_2Cl_2 (100 ml), under N_2. The resulting mixture was stirred at rt for 30 minutes followed by the portionwise addition of vacuum dried paraformaldehyde (3.52 g, 117 mmol). The resulting solution was stirred at 55 ˚C until the reaction went to completion (3-4 h) and quenched by the addition of NH_4Cl (50 mL) solution at 0 ˚C. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic solutions were washed with brine solution (25 mL), dried (Na_2SO_4) and concentrated to give the crude product which was purified by column chromatography (Hexanes/EtOAc, 50:50) to give **124** (4.62 g, 58%) as a white solid; m.p. 142-144 ˚C; ^{1}H NMR: δ = 7.89 (s, 1H), 4.74 (d, *J* = 5.2 Hz, 2H), 2.96 (s, 6H), 2.31 (brs,1H); ^{13}C NMR: δ = 140.0, 132.6, 90.5, 54.9, 38.3; IR (neat, cm^{-1}): 3236, 3117, 1705, 1541, 1457, 1420, 1390, 1160, 1020, 725, 576; HRMS *(m/z)*: calcd. for $C_6H_{10}N_3O_3SINa$ $[M+Na]^+$ 353.9380, found 353.9358.

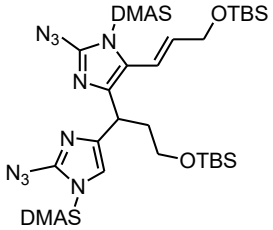


2-Azido-4-(2-azido-1-dimethylsulfamoyl-4-(3-hydroxypropenyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-(3-hydroxypropenyl)imidazole (**126**): TBAF (1 M in THF, 1.20 mL, 1.17 mmol) was added dropwise to an ice-cooled solution of **125**[31] (150 mg, 0.195 mmol) in dry THF (3.0 mL). Then the solution was stirred at 0 ˚C for 1 h, followed by addition of 5% citric acid (1.00 mL) to the reaction mixture. The aqueous solution was extracted with EtOAc (3×3 mL) and the organic solutions were combined, dried with anhydrous Na_2SO_4 and concentrated. The resulting residue was purified immediately by column



chromatography (EtOAc/MeOH, 98:2) to give diol **126** (82 mg, 78%) as a brown semi-solid; ^{1}H NMR: δ = 6.77 (s, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.65 (dd, *J* = 16.1, 1.1 Hz, 1H), 5.98 (dt, *J* = 16.0, 5.7 Hz, 1H), 4.11 (d, *J* = 7.3 Hz, 2H), 4.08 (dd, *J* = 5.4, 1.4 Hz, 2H) , 3.05 (s, 6H), 2.97 (s, 6H); ^{13}C NMR: δ = 141.0, 140.5, 137.3, 134.9, 132.2, 130.5, 128.3, 127.3, 117.9, 117.0, 63.1, 59.9, 38.6, 38.5; IR (neat, cm^{-1}): 3579, 3356, 3150, 2925, 2855, 2149, 1511, 1460, 1391, 1372, 1175, 970, 775, 591, 515; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{22}N_{12}O_6S_2Na$ $[M+Na]^+$ 565.1119, found 565.1132.

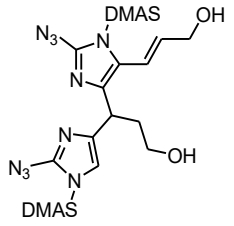
2-Azido-4-(2-azido-1-dimethylsulfamoyl-4-(3-*t*-butyldimethylsilyloxypropyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-((*E*)-3-*t*-butyldimethylsilyloxypropenyl)imidazole (**128**): Silyl ether



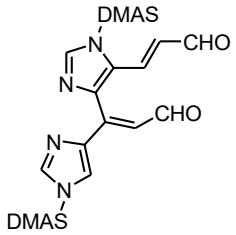
intermediate **127**[31] (460 mg, 0.666 mmol) was dissolved in anhydrous THF (30.0 mL) and the reaction mixture was cooled to -78 ºC and n-BuLi (2.5 M, 0.930 mL, 2.33 mmol) was added dropwise to the reaction mixture and stirred for 1 h. Then tosyl azide (485 mg, 2.46 mmol) was added dropwise to the reaction mixture which was then allowed to come to rt and stirred for an additional 30 minutes. The mixture was quenched by addition of aqueous NH_4Cl (10 mL) at rt and the organic layer was separated. The aqueous layer was extracted with EtOAc (2×10 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. The crude product was purified on silica gel (Hexanes/EtOAc, 80:20) to give diazide **128** (330 mg, 65%) as a thick yellow oil; ^{1}H NMR: 6.84 (d, *J* = 1.0 Hz, 1H), 6.62 (dt, *J* = 15.8, 2.0 Hz, 1H), 6.19 (dt, *J* = 15.8, 4.4 Hz, 1H), 4.30 (td, *J* = 4.2, 2.0 Hz, 2H), 4.07 (t, *J* = 7.5 Hz, 1H), 3.63-3.50 (m, 1H), 3.45 (dt, *J* = 10.2, 6.8 Hz, 1H), 2.95 (s, 6H), 2.93(s, 6H), 2.26-2.10 (m, 2H), 0.91 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H), -0.01 (s, 6H); ^{13}C NMR δ = 142.3, 140.5, 139.1, 137.2, 135.1, 127.9, 116.6, 115.7, 63.2, 60.7, 38.5,

38.4, 36.3, 33.4, 26.4, 25.95, 18.3, -5.3. IR (neat, cm^{-1}): 3355, 2926, 2874, 2142, 1508, 1512, 1170, 1073, 967, 724, 582, 516; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{24}N_{12}O_6S_2Na$ $[M+Na]^+$ 567.1275, found 567.1276; IR (neat, cm^{-1}): 2953, 2929, 2856, 2141, 1509, 1471, 1461, 1392, 1376, 1251, 1171, 1075, 969, 945, 832, 773, 721, 580, 514; HR-ESIMS *(m/z)*: Calcd. for $C_{28}H_{53}N_{12}O_6S_2Si_2$ $[M+H]^+$ 772.3113, found 772.3110.

2-Azido-4-(2-azido-1-dimethylsulfamoyl-4-(3-hydroxypropyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-(3-hydroxypropenyl)imidazole (129): TBAF (1 M in THF, 0.84 mL, 0.84 mmol) was added dropwise to an ice-cool solution of diazide **128** (0.31 g, 0.40 mmol) in dry THF (21 mL). Then the solution was stirred at rt for 2 h, followed by addition of 5% citric acid (10 mL) to the reaction mixture. The aqueous solution was extracted with EtOAc (2×5 mL) and the organic solutions were combined, dried with anhydrous Na_2SO_4 and concentrated. The resulting residue was immediately purified by the column chromatography (EtOAc/MeOH, 9:1) to give diol **129** (90 mg, 41%) as a brown semi-solid; ^{1}H NMR: δ = 6.88 (d, *J* = 1.0 Hz, 1H), 6.56 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.08 (dt, *J* = 15.9, 5.5 Hz, 1H), 4.26 (d, *J* = 5.4 Hz, 2H), 4.19 (t, *J* = 6.7 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.49 (ddd, *J* = 11.6, 7.0, 5.0 Hz, 1H), 2.97 (s, 6H), 2.96 (s, 6H), 2.19 – 2.14 (m, 2H); ^{13}C NMR: δ = 141.1, 140.5, 139.1, 137.2, 135.0, 127.2, 118.2, 116.0, 62.8, 59.8, 38.5, 38.5, 36.7, 33.5; IR (neat, cm^{-1}): 3355, 2926, 2874, 2142, 1508, 1512, 1170, 1073, 967, 724, 582, 516; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{24}N_{12}O_6S_2Na$ $[M+Na]^+$ 567.1275, found 567.1276.



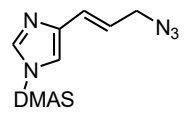
4-(1-Dimethylsulfamoyl-4-(3-propenal)imidazol-4-yl)-1dimethylsulfamoyl-5-(3-propenal)imidazole (134): IBX (0.800 g, 2.86 mmol) was added to a solution of diol **110** (0.600 g, 1.30 mmol) in acetone (15.7 mL) and heated at reflux for 1.5 h. After the disappearance of starting material (TLC), the reaction mixture was cooled to rt, filtered and concentrated. The resulting solid was dissolved in EtOAc and re-filtered, concentrated under vacuum to give brownish semi-solid **134** (quant.) as the product. The crude material was clean enough to continue the next step. ^{1}H NMR: δ = 9.58 (d, *J* = 7.9 Hz, 1H), 9.53 (d, *J* = 7.3 Hz, 1H), 8.22 (s, 1H), 7.92 (d, *J* = 1.3 Hz, 1H), 7.73 (d, *J* = 16.3 Hz, 1H), 7.20 (d, *J* = 1.3 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.39 (dd, *J* = 16.3, 7.3 Hz, 1H), 2.98 (s, 6H), 2.86 (s, 6H); ^{13}C NMR: δ = 192.2, 191.2, 143.0, 141.0, 139.7, 139.4, 137.9, 135.2, 132.1, 128.3, 126.4, 119.5, 38.5, 38.3; IR (neat, cm^{-1}): 3118, 2926, 2854, 1724, 1664, 1605, 1458, 1389, 1263, 1172, 1108, 1079, 961, 851, 722, 575, 510; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{20}N_6O_6S_2$ $[M+H]^+$ 457.0959, found 457.0971.



General procedure A for azidation of allylic alcohols:

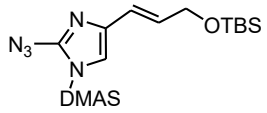
Allylic alcohol **141** (1.51 g, 6.54 mmol) was dissolved in anhydrous THF (195 mL) and the reaction mixture was cooled to 0 ˚C in an ice bath. To the above solution, diphenylphosphoryl azide (1.62 mL, 7.54 mmol) followed by DBU (1.14 mL, 7.54 mmol) were added dropwise. After the completion of addition, the ice-bath was removed and the reaction mixture was warmed to rt and stirred for another 2 h. The solution was quenched with NH_4Cl (25 mL) at rt and the aqueous solution was extracted with EtOAc (2×30 mL). The organic extracts were combined, dried (Na_2SO_4), concentrated and purified.

4-[(1*E*)-3-azidoprop-1-enyl]-1-dimethylsulfamoylimidazole (142): Allyl alcohol[69] (1.51 g, 6.54 mmol) was converted to azide **141** (1.38 g, 83%, white solid) following the general procedure A,



as shown above. The resulting residue was purified by the column chromatography (EtOAc/hexanes, 50:50). m.p. 70-72 ˚C; ^{1}H NMR: δ = 7.83 (d, *J* = 1.3 Hz, 1H), 7.15 (d, *J* = 1.3 Hz, 1H), 6.49-6.46 (m, 2H), 3.93-3.90 (m, 2H), 2.85 (s, 6H); ^{13}C NMR: δ = 140.5, 137.1, 124.4, 124.1, 115.0, 52.7, 38.3; IR (neat, cm^{-1}): 3124, 2925, 2089, 1486, 1387, 1169, 1090, 953, 853, 722, 590, 512; HR-ESIMS *(m/z)*: Calcd. for $C_8H_{13}N_6O_2S$ $[M+H]^+$ 257.0815, found 257.0809.

2-Azido-4-(1-dimethylsulfamoyl-(3-(*t*-butyldimethylsilyloxy)-propenyl)imidazole (144):

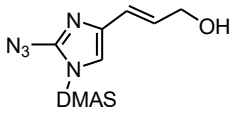


Silyl ether **143**[69] (2.40 g, 6.95 mmol) was dissolved in distilled THF (86.0 mL) and the reaction mixture was cooled to -78 ºC and n-BuLi (2.5 M, 4.73 mL, 11.8 mmol) was added dropwise to the reaction mixture and stirred at the same temperature for 40 mins and then tosyl azide (2.74 g, 13.9 mmol) was added. The cooling-bath was removed and the reaction mixture was warmed to rt and stirred for an additional 30 minutes, followed by addition of aqueous NH_4Cl (5 mL) to dilute the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×3 mL) and organic extracts were combined, dried (anhydrous Na_2SO_4) and concentrated. The crude material was purified by chromatography (Hexanes/EtOAc, 75:25) giving **144** (1.92 g, 71%) as a thick dark brown oil); ^{1}H NMR; δ = 6.97 (s, 1H), 6.46 (dt, *J* = 15.0, 4.8 Hz, 1H), 6.36 (dt, *J* = 15.5, 1.7 Hz, 1H), 4.33 (dd, *J* = 4.3, 1.9 Hz, 2H), 2.96 (s, 6H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR: δ = 140.5, 137.2, 131.0, 118.8, 115.7, 63.2, 38.5, 26.1, 18.5, -5.2; IR (neat, cm^{-1}): 3158, 2952, 2929, 2855, 2158, 1521, 1373, 1250, 1174, 1117, 1073, 957, 833, 774, 718, 587, 516; HR-ESIMS *(m/z)*: Calcd. for $C_{14}H_{27}N_6O_3SSi$ $[M+H]^+$ 387.1556, found 387.1558.

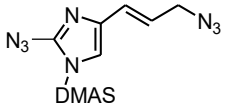
General procedure B for desilylation of allylic silyl ether:

TBAF (1 M in THF, 7.31 mL, 7.31 mmol) was added dropwise to an ice-cooled solution of silyl ether **144** (1.88 g, 4.87 mmol) in dry THF (51.0 mL). Then the solution was stirred at 0 ˚C for 1 h, followed by addition of 5% aqueous citric acid (10 mL) to the reaction mixture. The aqueous solution was extracted with EtOAc (2×25 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. The resulting residue was immediately purified by the column chromatography.

2-Azido-4-(1-dimethylsulfamoyl-(3-hydroxypropenyl)imidazole (145): Silyl ether **144** (1.88 g, 4.87 mmol) was converted to allylic alcohol (0.84 g, 62%, yellow solid) following the general procedure B. The resulting residue was purified by the column chromatography (EtOAc/hexanes, 70:30). m.p. 73-76 ˚C; ^{1}H NMR: δ = 6.99 (s, 1H), 6.53 (dt, *J* = 15.5, 5.2 Hz, 1H), 6.37 (dt, *J* = 15.5, 1.5 Hz, 1H), 4.31 (d, *J* = 4.5 Hz, 2H), 2.96 (s, 6H); ^{13}C NMR; δ = 140.7, 136.8, 124.4, 124.1, 114.9, 52.7, 38.5; IR (neat, cm^{-1}): 3242, 3153, 2923, 2856, 2155, 1521, 1457, 1387, 1269, 1237, 1174, 1123, 1072, 853, 722, 514. Note: The accurate mass was not observed by HR-ESIMS analysis.

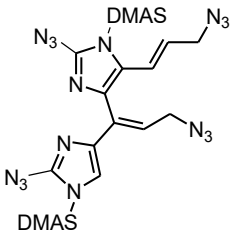


2-Azido-4-(1-dimethylsulfamoyl-5-(3-azidopropenyl)imidazole (146): Allyl alcohol **144** (0.80 g, 2.9 mmol) was converted to bisazide (0.70 g, 80%, white solid) following the general procedure A, using DBU (0.53 mL, 3.5 mmol) and DPPA (0.76 mL, 3.5 mmol) in anhydrous THF (90 mL). The resulting residue was purified by the column chromatography (EtOAc/hexanes, 20:80). m.p. 78-81 ˚C; ^{1}H NMR: δ = 7.03 (s, 1H), 6.46 – 6.34 (m, 2H), 3.92 (d, *J* = 5.6 Hz, 2H), 2.98 (s, 6H); ^{13}C NMR: δ = 140.9,



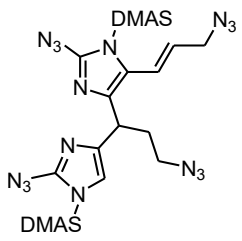
136.1, 124.1, 123.9, 116.8, 52.6, 38.6; IR (neat, cm^{-1}): 3154, 2926, 2855, 2154, 2090, 1521, 1463, 1417, 1246, 1228, 1181, 1067, 962, 883, 847, 723, 580, 517; HR-ESIMS *(m/z)*: Calcd. for $C_8H_{12}N_9O_2S$ $[M+H]^+$ 298.0829, found 298.0823.

2-Azido-4-(2-azido-1-dimethylsulfamoyl-4-(3-azidopropenyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-(3-azidopropenyl)imidazole (147): Allylic diol **126** (58 mg, 0.11 mmol) was dissolved in anhydrous THF (3.3 mL) and the reaction mixture was cooled to 0 ˚C in an ice-bath. To the above solution, diphenylphosphoryl azide (DPPA) (0.060 mL, 0.30 mmol) followed by DBU (0.040 mL, 0.30 mmol) were added dropwise. After the completion of addition, the ice-bath was removed and the reaction mixture was warmed to rt and stirred for another 2 h. The solution was diluted with NH_4Cl (2.5 mL) at rt and the aqueous solution was extracted with EtOAc (2×3 mL). The organic extracts were combined, dried (Na_2SO_4), concentrated and purified on silica gel (hexanes/EtOAc, 60:40) to give tetraazide **147** (29 mg, 46%) as a brownish oil; ^{1}H NMR: δ = 6.75 (dt, J = 16.0, 1.2 Hz, 1H), 6.70 (s, 1H), 6.67 (t, J = 7.5 Hz, 1H), 5.87 (dt, J = 16.1, 6.3 Hz, 1H), 3.85 (d, J = 7.5 Hz, 2H), 3.79 (dd, J = 6.3, 1.2 Hz, 2H), 3.05 (s, 6H), 2.97 (s, 6H); ^{13}C NMR: δ = 141.7, 140.9, 136.8, 132.1, 129.1, 128.5, 127.7, 125.4, 120.8, 117.2, 52.7, 49.5, 38.6, 38.4; IR (neat, cm^{-1}): 2925, 2855, 2143, 2097, 1512, 1488, 1391, 1173, 1073, 958, 723, 578, 514; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{20}ClN_{18}O_4S_2$ $[M+Cl]^-$ 627.1050, found 627.1075.



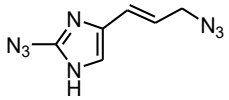
6

2-Azido-4-(2-azido-1-dimethylsulfamoyl-4-(3-azidopropyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-(3-azidopropenyl)imidazole (148): Diol **129** (90.0 mg, 0.165 mmol) was



dissolved in anhydrous THF (5.30 mL) and the reaction mixture was cooled to 0 ˚C in an ice-bath. To the above solution, diphenylphosphoryl azide (90.0 µL, 0.383 mmol) followed by DBU (60.0 µL, 0.383 mmol) were added dropwise. After the completion of addition, the ice-bath was removed and the reaction mixture was warmed to rt and stirred for another 2 h. Tetrabutylammonium azide (96.0 mg, 0.330 mmol) was added to the reaction mixture and then heated at 50 °C overnight. The solution was quenched with NH_4Cl (2.5 mL) at rt and the aqueous layer was extracted with EtOAc (2×3 mL). The organic extracts were combined, dried (Na_2SO_4), concentrated and purified on silica gel (Hexanes/EtOAc, 60:40) to give tetraazide **148** (70 mg, 71%) as a brownish oil; ^{1}H NMR: δ = 6.86 (d, *J* = 1.1 Hz, 1H), 6.69 (dt, *J* =1.5, 15.8 Hz, 1H), 6.14 (dt, *J* = 6.5, 15.8 Hz, 1H), 3.99 (ddd, *J* = 9.4, 5.6, 1.1 Hz, 1H), 3.95 (dd, *J* = 6.5, 1.5 Hz, 2H), 3.29 (ddd, *J* = 12.5, 6.7, 5.7 Hz, 1H), 3.16 (ddd, *J* = 12.4, 7.9, 6.4 Hz, 1H), 2.97 (s, 6H), 2.97 (s, 6H), 2.30-2.22 (m, 2H); ^{13}C NMR: δ = ^{13}C NMR (126 MHz, CHLOROFORM-*D*) δ 141.3, 141.1, 139.6, 137.31, 128.6, 127.1, 121.9, 115.8, 52.8, 49.5, 38.7, 38.5, 34.6, 32.4; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{25}N_6O_6S_2$ $[M+H]^+$ 595.1591, found 595.1586.

2-Azido-4-(3-azidopropenyl)imidazole (152): Diazide **148** (0.20 g, 0.67 mmol) was dissolved in

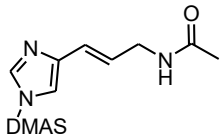


methanol (17 mL) and few drops of c. HCl were added dropwise to the reaction mixture at the room temperature. Then it was stirred at the room temperature O/N and quenched with saturated $NaHCO_3$ solution until pH 8 was reached. Next the aqueous layer was extracted with EtOAc (3×5 mL) and the organic extracts were combined, dried

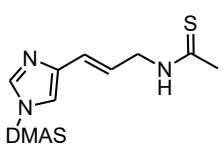
(Na_2SO_4), concentrated and purified on silica gel (Hexanes/EtOAc, 75:25) to give free imidazole (123 mg, 96%) as a brown oil; ^{1}H NMR: 6.82 (s, 1H), 6.44 (d, J = 15.7, Hz, 1H), 6.10 (dt, J = 15.7, 6.5 Hz, 1H), 3.8 (d, J = 6.6 Hz, 2H); ^{13}C NMR: δ = 141.9, 130.0, 124.5, 121.1, 120.7 52.9; IR (neat, cm^{-1}): 3122, 3016, 2921, 2840, 2129, 2096, 1523, 1499, 1389, 1222, 1142, 961, 824, 559; HR-ESIMS *(m/z)*: Calcd. for $C_6H_6N_8$ [M-H]$^-$ 189.0643, found 189.0643.

4-[(1*E*)-3-*N*-prop-1-enyl-ethanamide]-1-dimethylsulfamoylimidazole (161) and 4-[(1*E*)-3-*N*-prop-1-enyl-ethanethioamide]-1-dimethylsulfamoylimidazole (162): The allylic azide **142** (100 mg, 0.39 mmol) was converted to an acetamide **161** and thioamide **162** following the dropwise addition of CH_3COSH (0.11 mL, 1.6 mmol) stirred at rt for 1 h. After the consumption of the starting material, the reaction mixture was concentrated and the crude material was purified on silica gel (EtOAc/methanol, 97:3).

Acetamide (161): (90 mg, 85%, white solid); m.p. 124-126 ˚C; ^{1}H NMR: δ = 7.77 (d, J = 1.4 Hz, 1H), 7.07 (d, J = 1.3 Hz, 1H), 6.40 – 6.32 (m, 2H), 6.27 – 6.20 (brt, J = 13 Hz, 1H), 3.95 (t, J = 5.5 Hz, 2H), 2.80 (s, 6H), 1.96 (s, 3H); ^{13}C NMR: δ = 170.2, 140.9, 136.9, 127.6, 121.9, 114.1, 41.3, 38.2, 23.2; IR (neat, cm^{-1}): 3329, 3135, 2924, 1643, 1534, 1375, 1160, 1087, 1050, 961 735, 599, 514; HR-ESIMS *(m/z)*: Calcd. for $C_{10}H_{16}N_4O_3SNa$ [M+Na]$^+$ 295.0835, found 295.0829.



Thioamide (162): (6.8 mg, 6%, yellow solid); m.p. 123-125 ˚C; ^{1}H NMR: δ = 7.84 (d, J = 1.4 Hz, 1H), 7.37 (brs, 1H), 7.14 (d, J = 1.3 Hz, 1H), 6.52 – 6.45 (m, 2H), 4.44 (t, J = 5.1 Hz, 2H), 2.87 (s, 6H), 2.58 (d, J = 0.6 Hz, 3H); ^{13}C NMR: δ = 201.1, 140.8, 137.4, 125.1, 124.6, 115.0, 48.4, 38.6, 34.6; IR (neat, cm^{-1}): 3187, 3157, 3108,



2922, 1558, 1478, 1420, 1389, 1177, 1074, 960, 719, 549; HR-ESIMS *(m/z)*: Calcd. for $C_{10}H_{16}N_4O_2S_2Na$ $[M+Na]^+$ 311.0607, found 311.0613.

General procedure C for synthesis acetamide 161:

The allylic azide **142** (50 mg, 0.19 mmol) was dissolved in methanol (0.15 mL). To above solution, 2,6-lutidine (45 µL, 0.39 mmol) followed by CH_3COSH (28 µL, 0.39 mmol) were added dropwise and stirred at rt for 3 h. After the consumption of the starting material, the reaction mixture was concentrated and the crude material was purified on silica gel (EtOAc/methanol, 97:3).

Effect of temperature, solvent and base:

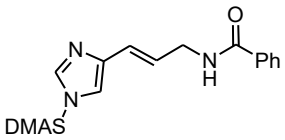
The above general procedure C was used to determine the product formation at 0 °C, rt and 55 °C as follows (Entries 3-5, Table 4.1). The effect of solvent (entry 1) and the base (entry 2) were also measured as in the following table.

Table 4.1 Conditions optimization for acetamide formation

Entry	Condition	% Yield
1	Neat, CH_3COSH (4 equiv.), 1 h	85 (**135**), 6 (**136**)
2	Neat, CH_3COSH (4 equiv.), lut., 1 h	81 (**135**)
3	CH_3COSH, lut., 3 h[a]	68 (**135**)
4	CH_3COSH, lut., 55 °C, 3 h[a]	63 (**135**)
5	CH_3COSH, lut., 0 °C, 4.5 h[b]	55 (**135**)
6	CH_3COSH, 3 h	38 (**135**), 10 (**136**)

[a] Reactions were conducted with 2 equiv. of thioacid, 2 equiv. of lutidine in MeOH (0.26 M) at room temperature unless indicated otherwise; where increased equivalents of thioacid were used the corresponding amount of lutidine was used. [b] This reaction was conducted at 0.94 M.

4-[(1*E*)-3-*N*-prop-1-enyl-benzamide]-1-dimethylsulfamoylimidazole (**163**): The allylic azide

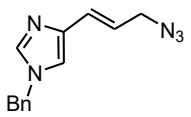


142 (20 mg, 0.078 mmol) was converted to benzamide **163** (25 mg, 96%, white solid) following the general procedure C, using 2,6-lutidine (36 µL, 0.31 mmol) followed by PhCOSH (36 µL, 0.31 mmol) in methanol (0.30 mL) and stirred overnight at the rt (Table 4.2). After completion (TLC) of the reaction, the mixture was concentrated in-vacuo and the crude material was purified on silica gel (EtOAc/hexane, 90:10); m.p.156-159 ˚C; ^{1}H NMR: δ = 7.82 (s, 1 H), 7.83-7.77 (m, 2 H), 7.53-7.39 (m, 3H), 7.11 (brs, 1H), 6.55 (dt, *J* = 15.4, 5.8 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 2H), 6.39 (brt, *J* = 6.5 Hz, 1H), 4.22 (t, *J* = 5.5 Hz, 2H), 2.84 (s, 6H); ^{13}C NMR: δ = 167.4, 141.0, 136.9, 134.4, 131.7, 128.7, 127.3, 127.0, 122.4, 114.3, 41.8, 38.3; IR (neat, cm^{-1}): 3328, 3125, 2923, 1630, 1526, 1479, 1382, 1165, 1079, 954, 727, 600; HR-ESIMS *(m/z)*: Calcd. for $C_{15}H_{19}N_4O_3S$ $[M+H]^+$ 335.1172, found 335.1176.

Table 4.2 Conditions optimization for the benzamide formation

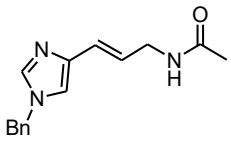
Entry	Condition	% Yield
1	PhCOSH (2 equiv), lut. (2 equiv), O/N	46
2	PhCOSH (4 equiv.), lut. (2 equiv), O/N	96

4-[(1*E*)-3-azidoprop-1-enyl]-1-benzylimidazole (140): Allyl alcohol[69] (0.25 g, 1.2 mmol) was converted to azide **140** (0.17 g, 61%, brown oil) following the general procedure A, using DBU



(0.21 mL, 1.4 mmol) and DPPA (0.30 mL, 1.4 mmol) in anhydrous THF (36 mL) and stirred for 43 h. All the characterization data exactly matched with the reported values.[76]

4-[(1*E*)-3-*N*-prop-1-enyl-ethanamide]-1-benzylimidazole (165): The allylic azide **164** (31 mg,

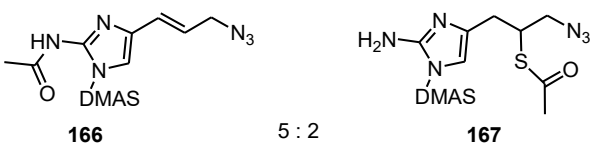


0.13 mmol) was converted to acetamide **165** (22 mg, 67%, yellow solid) following the general procedure C using 2, 6-lutidine (59 µL, 0.52 mmol) followed by CH_3COSH (37 µL, 0.52 mmol) in methanol (0.50 mL) and stirred overnight at the rt (Table 4.3). Then the reaction mixture was concentrated and the crude material was purified on silica gel (EtOAc/Methanol, 70:30). m.p. 102-104 °C; ^{1}H NMR: δ = 7.51 (d, *J* = 1.4 Hz, 1 H), 7.39-7.31 (m, 3H), 7.14 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H 2H) 6.80 (s, 1H), 6.38 dt, *J* = 15.7, 1.4 Hz, 1H), 6.27 (dt, *J* = 15.6, 6.3 Hz, 1H, 5.74 (brs, 1H), 5.05 (s, 2H), 3.96 (t, 2H), 1.97 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 170.0, 140.0, 137.6, 135.8, 129.1, 128.5, 127.4, 124.2, 124.0 117.0, 51.1, 41.6, 23.3; IR (neat, cm^{-1}): 3268, 3065, 2925, 1650, 1545, 1497, 1371, 1203, 966, 712; HR-ESIMS *(m/z)*: Calcd. for $C_{15}H_{17}N_3ONa$ $[M+Na]^+$ 278.1264, found 278.1260.

Table 4.3 Conditions optimization for benzyl protected system

Entry	Condition	% Yield
1	CH_3COSH (2 equiv), lut. (2 equiv), O/N	51
2	CH_3COSH (4 equiv.), lut. (4 equiv), O/N	67

4-[(1*E*)-3-azidopropenyl-2-ethanamide]-1-dimethylsulfamoylimidazole (166) and 2-Amino-4-(1-dimethylsulfamoyl-(3-azidopropoyl-2-thioethanoate)) imidazole (167)

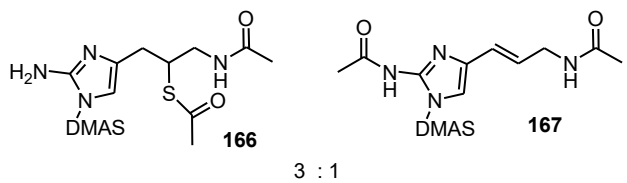


The allylic diazide **148** (0.10 g, 0.34 mmol) was converted to **166** and **167** following the general procedure C, using 2,6-lutidine (75 µL, 0.68 mmol) and CH_3COSH (48 µL, 0.68 mmol) in methanol (1.3 mL) for 2.5 h. The crude material was purified on silica gel (EtOAc/hexane, 20:80 → 60:40) as a 5:2 mixture. ^{1}H NMR: δ = 8.37 (s, 5H), 6.95 (s, 5H), 6.55 (s, 2H) 6.42– 6.56 (m, 10H), 5.37 (brs, 4H), 3.92 (d, *J* = 5.2 Hz, 10H), 3.50 (dd, *J* = 12.6, 7.5 Hz, 4H), 2.91 (s, 42H), 2.74 (dd, *J* = 15.2, 6.9 Hz, 4H), 2.34 (s, 15H), 2.31 (s, 6H); ^{13}C NMR δ = 193.8, 148.2, 134.8, 124.7, 123.8, 113.2, 110.5, 54.1, 52.6, 43.3, 38.7, 38.5, 30.9, 30.2, 24.1; IR (neat, cm^{-1}): 3455, 3369, 3147, 2928, 2098, 1690, 1625, 1547, 1418, 1381, 1248, 1174, 1159, 1074, 1054, 911, 722, 579, 516; HR-ESIMS *(m/z)*: Calcd. for $C_{10}H_{16}N_7O_3S$ $[M+H]^+$ 314.1030, found 314.1035 and Calcd. for $C_{10}H_{18}N_7O_3S_2$ $[M+H]^+$ 348.0907, found 348.0897.

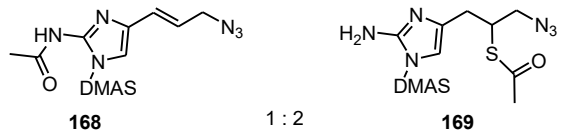
Neat thioacid conditions:

2-Amino-4-(1-dimethylsulfamoyl-(2-thioethanoate-3-*N*-propenylethanamide))imidazole (166) and 4-[2-*N*-ethanamide(1*E*)-3-*N*-propenylethanamide]-1-dimethylsulfamoylimidazole (167), 4-[(1*E*)-3-azidopropenyl-2-ethanamide]-1-dimethylsulfamoylimidazole (168) and 2-Amino-4-(1-dimethylsulfamoyl-(3-azidopropoyl-2-thioethanoate)) imidazole (169):

The allylic diazide **148** (0.100 g, 0.340 mmol) was converted **166**, **167** and **168**, **169** following

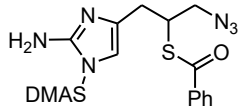


the general procedure C, using 2,6-lutidine (156 µL, 1.36 mmol) and CH_3COSH (96.0 µL, 1.36 mmol) for 2.5 h. The crude material was purified on silica gel (EtOAc/hexanes, 95:5 → EtOAc/methanol 95:5). The first two component mixture (46.7 mg, 39%, yellow semi-solid) contained a 3:1 mixture of **166** and **167**. ^{1}H NMR: δ = 8.52 (brs, 1H), 6.89 (s, 1H), 6.86 (brs, 1H), 6.59 (brt, *J* = 5.2 Hz, 3H, 6.55 (s, 3H), 6.36-6.28 (m, 1H), 6.24 (d, *J* = 15.4 Hz, 1H), 6.15 (brs, 1H), 5.39 (brs, 6H), 3.94 (t, *J* = 5.7 Hz, 1H), 3.80-3.76 (m, 3H), 3.46 (dd, *J* = 12.1, 5.8 Hz, 3H), 3.37 (dd, *J* = 13.8, 6.3 Hz, 3H), 2.84 (s, 24H), 2.65 (t, *J* = 5.2 Hz, 6H), 2.28 (s, 12H), 1.97 (s, 3H), 1.93 (s, 9H); ^{13}C NMR: δ = 195.8, 170.6, 170.3, 148.4, 134.7, 127.7, 121.7, 112.9, 110.4, 43.5, 42.7, 41.3, 38.7, 38.4, 30.9, 30.7, 23.3. IR (neat, cm^{-1}): 3293, 2924, 2105, 1686, 1631, 1549, 1538, 1418, 1375, 1283, 1173, 1051, 961, 723, 595. Calcd. for $C_{12}H_{22}N_5O_4S_2$ $[M+H]^+$ 364.1108, found 364.1114 and Calcd. for $C_{12}H_{20}N_5O_4S$ $[M+H]^+$ 330.1231, found 330.1238.



The second two component mixtures (42.1 mg, 37%, yellow semi-solid) contained **168** and **169** as a ratio of 1:2.

2-Amino-4-(1-dimethylsulfamoyl-(3-azidopropoyl-2-thiobenzoate))imidazole (170): Diazide



148 (50 mg, 0.17 mmol) was dissolved in methanol (0.64 mL) under the N_2 atmosphere. Then 2,6-lutidine (38 µL, 0.34 mmol) was added followed by addition of the thioacid (40 µL, 0.34 mmol) at rt and then stirred for 4 h. After completion (TLC) of the reaction, the mixture was concentrated in-vacuo. The crude

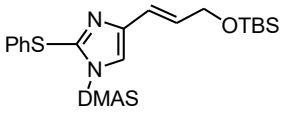
reaction mixture was purified on silica gel (Hexane/EtOAc, 80:20 → 40:60) to give thioester **170** (22 mg, 32%) as a yellow solid; m.p 74-80 ˚C; ^{1}H NMR: δ = 7.98 – 7.92 (m, 2H), 7.62 – 7.54 (m, 1H), 7.49 – 7.42 (m, 2H), 6.62 (d, *J* = 0.9 Hz, 1H), 5.60 (brs, 2H), 4.17 (tt, *J* = 7.0, 5.2 Hz, 1H), 3.68 (dd, *J* = 12.6, 4.9 Hz, 1H), 3.61 (dd, *J* = 12.6, 5.6 Hz, 2H), 2.90 (dd, *J* = 6.5, 1.6 Hz, 1H), 2.87 (s, 6H), 2.85 – 2.80 (m, 1H); ^{13}C NMR: δ =190.7, 148.4, 136.7, 134.3, 133.8, 128.8, 127.4, 110.4, 54.3, 43.3, 38.7, 30.5; IR (neat, cm^{-1}): 3450, 3134, 2925, 2098, 1637, 1377, 1205, 1171, 1051, 961, 905, 687,597; HR-ESIMS *(m/z)*: Calcd. for $C_{15}H_{20}N_7O_3S_2$ $[M+H]^+$410.1064, found 410.1068.

2-Oxo-4-(1-dimethylsulfamoyl-(3-(*t*-butyldimethylsilyloxy)-propenyl)imidazole (178):

Silyl ether **143**[69] (0.500 g, 1.45 mmol) was dissolved in distilled THF (18.0 mL) and the reaction mixture was cooled to -78 ºC and n-BuLi (2.5 M, 1.00 mL, 2.47 mmol) was added dropwise. Then the reaction mixture was stirred at the same temperature for 1 hour and bis(trimethylsilyl)peroxide (0.600 mL, 2.61 mmol) was added dropwise. The cooling-bath was removed after 15 minutes and the reaction mixture was warmed to rt and stirred for 1 hour, followed by addition of aqueous NH_4Cl (5 mL) to dilute the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×5 mL). The organic extracts were combined, dried (anhydrous Na_2SO_4) and concentrated. The crude material was purified by chromatography (Hexanes/EtOAc, 85:15) giving C2-imidazolone **178** (100 mg, 19%) as a white solid; m.p. 72-74 ˚C; ^{1}H NMR: δ = 10.52 (brs, 1H), 6.53 (d, *J* = 1.8 Hz, 1H), 6.17 (dt, *J* = 15.9, 1.9 Hz, 1H), 6.00 (dt, *J* = 15.9, 4.3 Hz, 1H), 4.29 – 4.24 (dd, 4.3, 1.9 Hz, 2H), 3.02 (s, 6H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR: δ = 152.5, 129.8, 122.5, 114.9, 108.9, 62.9, 38.6, 26.0, 18.5, -5.3; IR (neat, cm^{-1}): 2969, 2930, 2857, 1738, 1459,

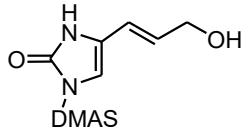
1365, 1228, 1205, 1160, 1050, 968, 834, 776, 719, 568, 517; HR-ESIMS *(m/z)*: Calcd. for $C_{14}H_{28}N_3O_4SiS$ $[M+H]^+$ 362.1564, found 362.1562.

2-Phenylthio-4-(1-dimethylsulfamoyl-(3-(*t*-butyldimethylsilyloxy)-propenyl)imidazole

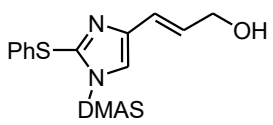


(**179**): Allylic silyl ether **143**[69] (0.500 g, 1.45 mmol) was dissolved in distilled THF (18.0 mL) and the reaction mixture was cooled to -78 ºC and n-BuLi (2.5 M, 1.00 mL, 2.47 mmol) was added dropwise. Then the reaction mixture was stirred at the same temperature for 1 hour and recrystallized-phenyldisulfide (0.570 g, 2.61 mmol) was added portionwise. The cooling-bath was removed after 15 minutes and the reaction mixture was warmed to rt and stirred for 6 h, followed by addition of aqueous NH_4Cl (5 mL) to dilute the reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×10 mL). The organic extracts were combined, dried (anhydrous Na_2SO_4) and concentrated. The crude material was purified by chromatography (Hexanes/EtOAc, 75:25) giving **179** (0.374 g, 57%) as a thick brown oil. ^{1}H NMR; δ = 7.46 – 7.42 (m, 2H), 7.35 – 7.27 (m, 4H), 6.44 (dt, *J* = 15.6, 4.0 Hz, 1H), 6.38 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.29 (dd, *J* = 4.0, 1.2 Hz, 2H), 2.94 (s, 6H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR; δ = 141.0, 140.4, 132.2, 131.5, 131.4, 129.5, 128.3, 119.2, 119.1, 63.5, 38.9, 26.3, 18.8, -4.9; IR (neat, cm^{-1}): 2951, 2927, 2854, 1580, 1471, 1455, 1418, 1389, 1252, 1176, 1102, 1051, 967, 836, 778, 726, 604; HR-ESIMS *(m/z)*: Calcd. for $C_{20}H_{32}N_3O_3SiS_2$ $[M+H]^+$ 454.1649, found 454.1653.

2-Oxo-4-(1-dimethylsulfamoyl-(3-hydroxypropenyl)imidazole (180): Silyl ether **178** (41.0 mg, 0.114 mmol) was converted to alcohol **180** (24.0 mg, 85%, yellow semi-solid) following the general procedure B, using TBAF (1 M in THF, 10.2 mL, 10.2 mmol) in dry THF (1.20 mL) for 2 h. The resulting

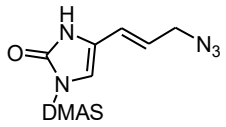


residue was purified by the column chromatography (EtOAc/methanol, 99:1). ^{1}H NMR: δ = 10.24-10.19 (brs, 1H), 6.53 (d, *J* = 1.9 Hz, 1H), 6.15 (d, *J* = 15.9 Hz, 1H), 6.06 (dt, *J* = 16.1, 5.3 Hz, 1H), 4.25 (dd, *J* = 5.3, 1.3 Hz, 2H), 3.02 (s, 6H); ^{13}C NMR; δ = 152.0, 129.2, 121.9, 116.4, 109.3, 63.1, 38.8; IR (neat, cm^{-1}): 3296, 2937, 1737, 1454, 1365, 1205, 1159, 1067, 961, 717; HR-ESIMS *(m/z)*: Calcd. for $C_8H_{12}N_3O_4S$ $[M-H]^-$ 246.0554, found 246.0554.



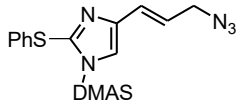
2-Phenylthio-4-(1-dimethylsulfamoyl-(3-hydroxypropenyl)imidazole (181): Allylic silyl ether **127** (374 mg, 0.825 mmol) was converted to alcohol **181** (249 mg, 89%, brown oil) following the general procedure B, using TBAF (1 M in THF, 1.25 mL, 1.25 mmol) in dry THF (8.70 mL) for 3 h. The resulted residue was purified by the column chromatography (EtOAc/hexanes, 80:20). ^{1}H NMR: δ = 7.48 – 7.42 (m, 2H), 7.35 – 7.27 (m, 3H), 6.44 (dt, *J* = 15.6, 5.2 Hz, 1H), 6.34 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.19 (dd, *J* = 5.2, 1.5 Hz, 2H), 2.93 (s, 6H), 2.50 (brs, 1H); ^{13}C NMR; δ = 141.4, 139.9, 131.7, 131.7, 131.0, 129.5, 128.5, 120.5, 119.3, 63.1, 38.8; IR (neat, cm^{-1}): 3318, 3142, 2914, 2848, 1476, 1439, 1388, 1275, 1109, 1109, 1051, 970, 728, 602; HR-ESIMS *(m/z)*: Calcd. for $C_{14}H_{17}N_3O_3S_2Na$ $[M+Na]^+$ 362.0604, found 362.0598.

2-Oxo-4-(1-dimethylsulfamoyl-(3-azidopropenyl)imidazole (182): The allylic alcohol **180** (23 mg, 0.093 mmol) was converted to **182** (16 mg, 64%, yellow semi-solid) following the general procedure A, using DBU (17 µL, 0.11 mmol), DPPA (24 µL, 0.11 mmol in dry THF (2.8 mL). The resulting residue was purified by the column chromatography (EtOAc/hexanes, 50:50). ^{1}H NMR: δ = 11.03 (s, 1H), 6.62 (d, *J* = 2.2 Hz, 1H), 6.19 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.96 (dt, *J* = 15.9, 6.2 Hz, 1H), 3.90 (dd, *J* = 6.4, 1.5



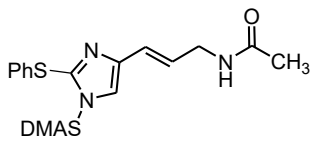
Hz, 2H), 3.05 (s, 6H); ^{13}C NMR: δ = 152.4, 122.9, 121.4, 119.7, 110.2, 52.4, 38.4; IR (neat, cm^{-1}): 3153, 2095, 1698, 1549, 1458, 1365, 1162, 970, 717, 587; HR-ESIMS *(m/z)*: Calcd. for $C_8H_{12}N_6O_3SNa$ $[M+Na]^+$ 295.0584, found 295.0585.

2-Phenylthio-4-(1-dimethylsulfamoyl-(3-azidopropenyl)imidazole (183): The allylic alcohol **181** (220 mg, 0.649 mmol) was converted to azide **183** (190 mg, 80%, brownish oil) following the general procedure A, using DBU (121 µL, 1.56 mmol), DPPA (171 µL, 1.56 mmol in dry THF (20.0 mL). The resulting residue was purified by the column chromatography (EtOAc/hexanes, 80:20 → EtOAc/Methanol).



^{1}H NMR: δ = 7.49 (m, 1H), 7.38 – 7.34 (m, 3H), 7.32 (s, 1H), 7.27 – 7.19 (m, 1H), 6.44 – 6.32 (m, 2H), 3.88 (d, *J* = 5.3 Hz, 2H), 2.98 (s, 6H); ^{13}C NMR: δ = 132.1, 130.2, 129.6, 128.7, 125.8, 124.5, 124.2, 120.4, 120.0, 52.9, 38.9; IR (neat, cm^{-1}): 3143, 3059, 2918, 2849, 2096, 1389, 1279, 1177, 1108, 1050, 986, 727, 603; HR-ESIMS *(m/z)*: Calcd. for $C_{14}H_{17}N_6O_2S_2$ $[M+H]^+$ 365.0843, found 365.0843.

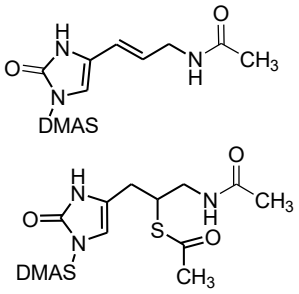
2-Phenylthio-4-[(1*E*)-3-*N*-prop-1-enyl-ethanamide]-1-dimethylsulfamoylimidazole (184):



Azide **183** (180 mg, 0.490 mmol) was converted to acetamide **184** (108 mg, 58%, yellow semi-solid) following the general procedure C using 2,6-lutidine (230 µl, 1.96 mmol) and thioacid (140 µl, 1.96 mmol) in methanol (1.90 mL) and stirred for 20 h. The crude reaction mixture was purified on silica gel (methanol/EtOAc, 20:80). ^{1}H NMR: δ = 7.48-7.42 (m, 2H), 7.38-7.28 (m, 3H), 6.28-6.22 (m, 2H), 6.07-6.02 (brm, 1H), 3.90 (m, 2H), 2.94 (s, 6H), 1.95 (s, 3H); ^{13}C NMR: δ = 170.2, 141.4, 139.5, 131.6, 131.4, 129.3, 128.4, 127.4, 121.7, 119.0, 41.2, 38.6, 23.2; IR (neat, cm^{-1}): 3290,

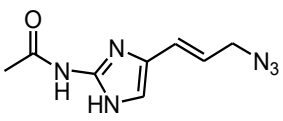
3074, 2930, 1649, 1539, 1438, 1386, 1276, 1242, 1173, 1104, 1049, 963, 723, 596; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{20}N_4O_3S_2Na$ $[M+Na]^+$ 403.0869, found 403.0871.

2-Oxo-4-[(1*E*)-3-*N*-prop-1-enyl-ethanamide]-1-dimethylsulfamoylimidazole (185) and 2-Oxo-4-(1-dimethylsulfamoyl-(3-azidopropoyl-2-ethanethiooate)) imidazole (186): Azide **182** (10 mg, 0.036 mmol) was converted to **185** and **186** following the general procedure C using



lutidine (17 µL, 0.14 mmol) and CH_3COSH (10 µL, 0.14 mmol) in methanol (0.14 mL) and stirred for O/N. The crude reaction mixture was purified on silica gel (Hexane/EtOAc, 80:20 → 40:60) to give **185** and **186** as a 1:3 mixture. ^{1}H NMR: δ = 9.99 (s, 1H), 9.90 (s, 3H), 6.51 (s, 1H), 6.39 (s, 3H), 6.22 (brt, 4H), 6.04 (d, *J* = 16.1 Hz, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 3.68-3.65 (m, 3H), 3.57-3.51 (m, 6H), 3.39-3.34 (m, 3H) 3.00 (s, 9H), 2.60-2.58 (m, 6H), 2.34 (s, 9H), 2.06 (s, 9H), 2.01 (s, 3H); IR (neat, cm^{-1}): 3293, 3155, 2928, 2104, 1704, 1653, 1547, 1371, 1280, 1242, 1164, 1104, 911, 723, 579; HR-ESIMS *(m/z)*: Calcd. for $C_{12}H_{20}N_4O_5S_2Na$ $[M+Na]^+$ 387.0767, found 387.0774 and $C_{10}H_{16}N_4O_4S$ $[M-H]^-$ 287.0819, found 287.0820.

4-(3-azidopropenyl)-2-ethanamideimidazole (187): Diazide **152** (15 mg, 0.079 mmol) was converted to acetamide **187** (10 mg, 63%, white solid) following the general procedure C, using 2, 6-lutidine (18 µL, 0.16 mmol)

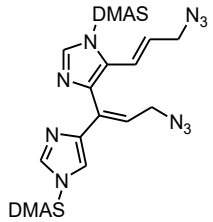


followed by thioacid (11 µL, 0.16 mmol) in methanol (0.30 mL) and stirred for 2-3 minutes. m.p. 70-72 ˚C; ^{1}H NMR (DMSO-d_6): δ = 11.67 (brs, 1 H), 11.19 (brs, 1H), 6.86 (s, 1H), 6.51 (d, *J* = 15.5 Hz, 1H), 6.10 (dt, *J* = 15.5 Hz, 6.9 Hz, 1H), 3.97-3.92 (m, 2H), 2.05

(s, 3H); ^{13}C NMR (DMSO): δ = 169.1, 157.4, 141.9, 132.9, 126.5, 119.0, 52.8, 23.3; IR (neat, cm^{-1}): 3316, 2922, 2773, 2084, 1737, 1628, 1538, 1450, 1364, 1270, 1163, 972, 702; HR-ESIMS *(m/z)*: Calcd. for $C_8H_{11}N_6O$ $[M+H]^+$ 207.0989, found 207.0987.

In the absence of Lutidine; This reaction was conducted at the same reaction conditions without adding an external base, lutidine and the same product, **187** (63%) was observed after 2-3 minutes.

4-(1-Dimethylsulfamoyl-4-(3-azidopropenyl)imidazol-4-yl)-1dimethylsulfamoyl-5-(3-azidopropenyl)imidazole (189): The diol **110** (100 mg, 0.217 mmol) was converted to diazide



189 (70.0 mg, 84%, brownish oil) following the above general procedure A using DPPA (75.0 µL, 0.492 mmol) and DBU (110 µL, 0.492 mmol) in THF (6.70 mL) and stirred for 2 h. The resulting residue was purified by column chromatography (EtOAc/hexane, 95:5). ^{1}H NMR: δ = 8.02 (s, 1H), 7.86 (d, *J* = 1.4 Hz, 1H), 6.87 – 6.76 (m, 3H), 6.02 (dt, *J* = 16.0, 6.0 Hz, 1H), 3.86 (d, *J* = 7.3 Hz, 2H), 3.82 (dd, 4.3, 1.7 Hz, 2H), 2.92 (s, 6H), 2.83 (s, 6H); ^{13}C NMR: δ = 141.3, 138.6, 137.1, 136.4, 129.9, 129.7, 126.4, 125.6, 118.8, 115.6, 52.6, 49.5, 38.4, 38.3; IR (neat, cm^{-1}): 3128, 2925, 2856, 2094, 1460, 1418, 1458, 1388, 1269, 1174, 1082, 964, 842, 727, 515; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{22}N_{12}O_4S_2$ $[M+H]^+$ 511.1401, found 511.1399.

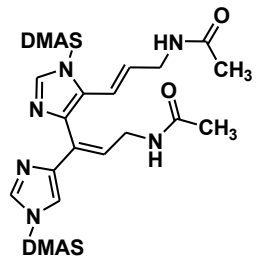
4-(*Z*)-1-Dimethylsulfamoyl-4-(-[(3-azidopropenyl)imidazole-4-yl)]-1-dimethylsulfamoyl-5-(1*E*)-3-*N*-propenylethanamide)imidazole (191) and 4-(1-Dimethylsulfamoyl-4-(-[(1*E*)-3-*N*-propenylethanamide]-1-dimethylsulfamoyl-5-(1*E*)-3-*N*-propenylethanamide)imidazole (190): The allylic diazide **189** (24 mg, 0.047 mmol) was dissolved in methanol (0.18 mL), to this

solution, 2,6-lutidine (22 μL, 0.188 mmol) followed by CH_3COSH (13 μL, 0.188 mmol) was added and stirred overnight at room temperature concentrated. The crude material was purified on silica gel (EtOAc/hexane, 80:20) and obtained the acetamides as follow (Table 4.4).

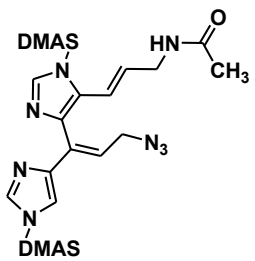
Table 4.4 Conditions for nagelamide C model system

Entry	Condition	% Yield **190**	% Yield **191**
1	CH_3COSH, (4 equiv.), lut (4 equiv.), O/N	58	36
2	CH_3COSH, (8 equiv.), lut (8 equiv.), O/N	61	16
3	CH_3COSH, (16 equiv.), lut (16 equiv.), O/N	69	-

Diacetamide 190: (14 mg, 58%, yellow semi-solid); δ = 7.97 (s, 1 H), 7.85 (d, *J* = 1.3 Hz, 1H),



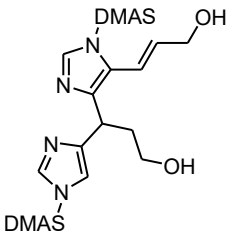
6.88 (d, *J* = 1.1 Hz, 1H), 6.64 (dt, *J* = 1.7, 16.1 Hz, 1H), 6.57 (t, *J* = 3.4 Hz, 1H), 6.49 (brt, *J* = 5.5 Hz, 1H), 6.29 (brt, *J* = 5.8 Hz, 1H), 5.99 (dt, *J* = 5.1 Hz, 16.6 Hz, 1H), 3.87 (m, 4H), 2.91 (s, 6H), 2.86 (s, 6H); 1.99 (s, 3H), 1.97 (s, 3H); ^{13}C NMR: δ = 170.6, 170.4, 142.1, 138.2, 136.8, 136.1, 133.3, 128.8, 127.3, 126.9, 116.7, 114.9, 41.6, 38.6, 38.4, 38.3, 23.3, 23.1; IR (neat, cm^{-1}): 3273, 3117, 2926, 1737, 1650, 1461, 1386, 1173, 1079, 961, 723, 584; HR-ESIMS *(m/z)*: Calcd. for $C_{20}H_{30}N_8O_6S_2Na$ $[M+Na]^+$ 565.1622, found 565.1614.



Monoacetamide 191: (9.0 mg, 36%, yellow semi-solid); ^1H NMR: δ = 8.01 (s, 1H), 7.89 (s, 1H), 6.86 (s, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 5.93 (dt, *J* = 16.1, 5.5 Hz, 1H), 5.65 (brt, *J* = 5.5 Hz, 1H), 3.97 – 3.79 (m, 4H), 2.91 (s, 6H), 2.87 (s, 6H), 1.99 (s, 3H); ^{13}C NMR: δ

= 170.0, 141.6, 138.4, 136.9, 135.6, 133.8, 130.0, 127.0, 125.4, 116.3, 115.7, 49.6, 41.4, 38.4, 38.3, 23.2; IR (neat, cm^{-1}): 3273, 3117, 2926, 1737, 1650, 1461, 1386, 1173, 1079, 961, 723, 584; HR-ESIMS *(m/z)*: Calcd. for $C_{18}H_{26}N_{10}O_5S_2Na$ $[M+Na]^+$ 549.1421, found 549.1416.

4-(1-Dimethylsulfamoyl-4-(3-propanol)imidazol-4-yl)-1dimethylsulfamoyl-5-(3-propenol)imidazole (192): The bissilyl ether **127** (321 mg, 0.465 mmol) was converted to diol

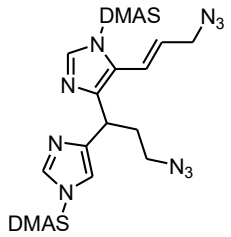


192 (144 mg, 68%, off-white solid) following the above general procedure A (4 h), using 1.0 M TBAF (1.85 mL, 1.85 mmol) in dry THF (2.10 mL). The resulting residue was purified by column chromatography (EtOAc/MeOH, 98:2). ^1H NMR: δ = 7.88 (s, 1H), 7.82 (d, *J* = 1.4 Hz, 1H), 7.08 (d, *J* = 1.4 Hz, 1H), 6.67 (dt, *J* = 16.1, 1.7 Hz, 1H), 6.22 (dt, *J* = 16.1, 5.2 Hz, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 4.25 (td, *J* = 5.0, 1.7 Hz, 2H), 3.60 (dt, *J* = 10.7, 5.2 Hz, 1H), 3.48 – 3.40 (m, 1H), 2.83 (s, 6H), 2.82 (s, 6H), 2.23 (dd, *J* = 7.4, 5.0 Hz, 2H); ^{13}C NMR: δ = 146.1, 141.7, 138.1, 137.2, 136.3, 126.3, 116.9, 115.0, 63.0, 59.9, 53.8, 38.6, 38.1, 33.9; IR (neat, cm^{-1}): 3354, 3090, 2925, 1473, 1418, 1274, 1172, 1090, 959, 803, 715, 595, 512; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{26}N_6O_6S_2Na$ $[M+Na]^+$ 485.1247, found 485.1247.

Diol **192** (99.0 mg, 0.214 mmol) was dissolved in anhydrous THF (6.70 mL) and the reaction mixture was cooled to 0 ˚C in an ice bath. To the above solution, DPPA (106 µL, 0.492 mmol) followed by DBU (74.0 µL, 0.492 mmol) were added dropwise. After the completion of addition, the ice-bath was removed and the reaction mixture was warmed to rt and stirred for another 2 h. Then tetrabutylammonium azide (120 mg, 428 mmol) was added to the reaction mixture and heated at 50 °C overnight. The solution was quenched with NH_4Cl (2.5 mL) at rt and the aqueous layer was extracted with EtOAc (2×3 mL). The organic extracts were combined, dried (Na_2SO_4),

concentrated and purified by column chromatography (EtOAc/hexanes, 95:5 → EtOAc/meOH, 90:10).

4-(1-Dimethylsulfamoyl-4-(3-azidopropyl)imidazol-4-yl)-1dimethylsulfamoyl-5-(3-azidopropenyl)imidazole (193): Diol **192** (99.0 mg, 0.214 mmol) was dissolved in anhydrous THF (6.70 mL) and the reaction mixture was cooled to 0 ˚C in an ice bath. To the above solution, DPPA (106 μL, 0.492 mmol) followed by DBU (74.0 μL, 0.492 mmol) were added dropwise. After the completion of addition, the ice-bath was removed and the reaction mixture was warmed to rt and stirred for another 2 h. Then tetrabutylammonium azide (120 mg, 428 mmol) was added to the reaction mixture and heated at 50 °C overnight. The solution was quenched with NH_4Cl (2.5 mL) at rt and the aqueous layer was extracted with EtOAc (2×3 mL). The organic extracts were combined, dried (Na_2SO_4), concentrated and purified by column chromatography (EtOAc/hexanes, 95:5 → EtOAc/meOH, 90:10). ^{1}H NMR: δ = 7.91 (s, 1H), 7.81 (d, *J* = 1.4 Hz, 1H), 7.05 (d, *J* = 1.4 Hz, 1H), 6.80 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.22 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.21 (dd, *J* = 8.8, 6.3 Hz, 1H), 4.00 (dd, *J* = 6.2, 1.6 Hz, 2H), 3.36 – 3.26 (m, 1H), 3.14 (ddd, *J* = 12.4, 7.8, 6.1 Hz, 1H), 2.85 (s, 6H), 2.84 (s, 6H), 2.35 (m, 2H); ^{13}C NMR: δ = 145.4, 141.6, 138.4, 136.3, 129.9, 125.5, 120.5, 114.3, 52.8, 49.5, 38.3, 38.3, 34.6, 33.5; IR (neat, cm^{-1}): 3125, 2923, 2096, 1418, 1388, 1269, 1173, 1155, 1084, 963, 727, 597, 516; HR-ESIMS *(m/z)*: Calcd. for $C_{16}H_{25}N_{12}O_4S_2$ $[M+H]^+$ 513.1558, found 513.1562.



4-(1-Dimethylsulfamoyl-4-(3-*N*-propenylethanamide)imidazol-4-yl)-1-dimethylsulfamoyl-5-((1-*E*)-3-*N*-propenylethanamide)imidazole (194), 4-(1-Dimethylsulfamoyl-4-(3-

azidopropyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-((1-*E*)-3-*N*-propenylethanamide) imidazole (195a) and 4-(1-Dimethylsulfamoyl-4-(3-*N*-azidopropyl)imidazol-4-yl)-1-dimethylsulfamoyl-5-((1*E*)-3-*N*-propenylethanamide) imidazole (195b): The allylic diazide (36 mg, 0.070 mmol) was dissolved in methanol (0.28 mL). To above solution, 2,6-lutidine (34 µL, 0.28 mmol) followed by CH_3COSH (22 µL, 0.28 mmol) was added and stirred overnight at room temperature concentrated. The crude material was purified on silica gel (EtOAc/hexane, 90:10 → EtOAc/methanol 80:20) to give acetamides as follow (Table 4.5).

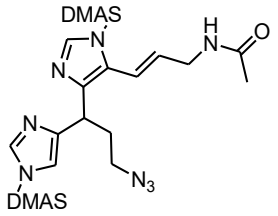
Table 4.5 Conditions optimization for nagelamide A system

Entry	Condition	% Yield **194**	% Yield **195a**	% Yield **195b**
1	CH_3COSH, (4 equiv.), lut (4 equiv.), O/N	28	10	10
2	CH_3COSH, (8 equiv.), lut (8 equiv.), O/N	51	20	9
3	CH_3COSH, (16 equiv.), lut (16 equiv.), O/N	75	-	-

Diacetamide 194: (10.8 mg, 28%, yellowish semi-solid). ^{1}H NMR: δ = 7.87 (s, 1H), 7.80 (d, *J* = 1.4 Hz, 1H), 7.09 (s, 1H), 6.59 (dt, *J* = 16.1, 1.8 Hz, 1H), 6.42 (brt, *J* = 5.9 Hz ,1H), 6.23 (brt, *J* = 5.8 Hz, 1H), 6.04 (dt, *J* = 16.1, 5.4 Hz, 1H), 4.17 – 4.07 (m, 1H), 4.01 (m, 2H), 3.22 – 3.12 (m, 2H), 2.85 (s, 6H), 2.83 (s, 6H), 2.26 – 2.20 (m, 2H), 2.04 (s, 3H), 1.94 (s, 3H); ^{13}C NMR: δ = 170.9, 170.8, 146.0, 142.0, 138.2, 136.5, 133.7, 126.2, 118.0, 114.9, 41.9, 38.6, 38.0, 35.2, 34.8, 23.7, 23.5, 14.6; IR (neat, cm^{-1}): 3272, 2927, 1646, 1551, 1385, 1275,

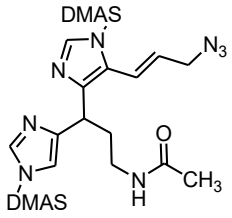
1172, 1084, 960, 723, 586; HR-ESIMS *(m/z)*: Calcd. for $C_{20}H_{32}N_8O_6S_2Na$ $[M+Na]^+$ 567.1275, found 567.1276.

Allylic monoacetamide 195a: (4 mg, 10%, yellowish semi-solid). ^1H NMR: δ = 7.89 (s, 1H), 7.81



(d, *J* = 1.4 Hz, 1H), 7.07 (s, 1H), 6.63 (dt, *J* = 16.1, 1.8 Hz, 1H), 6.11 (dt, *J* = 16.1, 5.4 Hz, 1H), 5.94 (brt, *J* = 5.5 Hz, 2H), 4.22 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.15 – 4.05 (m, 1H), 4.06 – 3.96 (m, 1H), 3.34-3.28 (m, 1H), 3.18 – 3.08 (m, 1H), 2.85 (s, 6H), 2.82 (s, 6H), 2.37 – 2.28 (m, 2H), 2.03 (s, 3H); ^{13}C NMR: δ = 170.6, 145.7, 141.1, 138.4, 136.6, 133.8, 126.3, 117.7, 114.7, 49.8, 41.7, 38.7, 38.6, 34.7, 34.1, 23.6; IR (neat, cm^{-1}): 3284, 2930, 2102, 1651, 1553, 1470, 1386, 1155, 1182, 960, 723, 588, 513; HR-ESIMS *(m/z)*: Calcd. for $C_{18}H_{29}N_{10}O_5S_2$ $[M+H]^+$ 529.1758, found 529.1768.

Alkyl monoacetamide 195b: (3.9 mg, 10%, yellowish semi-solid). ^1H NMR ($CDCl_3$): δ = δ 7.92



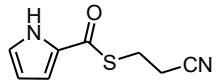
(s, 1H), 7.81 (d, *J* = 1.3 Hz, 1H), 7.07 (s, 1H), 6.78 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.13 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.92 (brt, *J* = 7.8 Hz, 1H), 4.12 (m, 1H), 3.99 (dd, *J* = 6.3, 1.5 Hz, 2H), 3.28-3.25 (m, 1H), 3.12 – 3.04 (m, 1H), 2.90 (s, 6H), 2.85 (s, 6H), 2.31 – 2.23 (m, 2H), 1.93 (s, 3H); ^{13}C NMR: δ = 170.2, 145.4, 142.1, 138.2, 136.2, 129.7, 125.3, 120.7, 114.5, 52.7, 38.3, 37.6, 35.0, 34.1, 29.8, 23.3; IR (neat, cm^{-1}): 3271, 2926, 2096, 1654, 1551, 1471, 1386, 1270, 1155, 1083, 955, 722, 587, 512; HR-ESIMS *(m/z)*: Calcd. for $C_{18}H_{28}N_{10}O_5S_2Na$ $[M+Na]^+$ 551.1578 found 551.1589.

***S*-[(2,4,6-trimethoxyphenyl)methyl]-1H-pyrrole-2-carboxamide (198)**: Thiol **197** (21.4 mg, 0.100 mmol) and DMAP (0.600 mg, 5.00 μg) were added to a stirred solution of pyrrole carboxylic acid **196** (11.0 mg, 0.100 mmol) in anhydrous (CH_2Cl_2 100 μL). Then the solution was cooled to 0 °C and DCC (21.6 mg, 0.106 mmol) was added. The reaction mixture was stirred for 5 minutes at 0 °C and further 10 h at the rt. The precipitated dicyclohexylurea was filtered-off, the filtrate concentrated and re-dissolved in a small volume of CH_2Cl_2 and if necessary, dicyclohexylurea was removed again by filtration. Finally, the filtrate was concentrated to give the crude product which was purified by column chromatography (SiO_2; 18 cm) using CH_2Cl_2 as the eluent to give ester (25 mg, 83%) as a white solid. ^{1}H NMR: δ 9.41 (s, 1H), 7.00 – 6.92 (m, 2H), 6.22 (dd, J = 3.8, 2.5 Hz, 1H), 6.12 (s, 2H), 4.38 (s, 2H), 3.83 – 3.81 (s, 9H); ^{13}C NMR: δ = 182.8, 160.7, 159.1, 130.3, 122.9, 114.4, 110.4, 104.8, 90.5, 55.7, 55.7, 21.1; HR-ESIMS *(m/z)*: Calcd. for $C_{15}H_{17}NO_4SNa$ $[M+Na]^+$ 330.0771, found 330.0776.

Pyrrole-2-carbothioic acid (199): Thionyl chloride (555 mg, 5.00 mmol) was added dropwise to pyrrole carboxylic acid **196** in a round bottom flask under the inert condition and heat the mixture was heated at 55 °C for 30 minutes. The excess thionyl chloride (5.00 mL, 75.0 mmol) was removed in vacuo and dried under vacuum. The residue was dissolved in acetone (25 mL) and stirred under N_2 for 5 minutes. NaHS (330 mg, 7.50 mmol) was dissolved in water (4 mL) and added dropwise to the above pyrrole mixture. The solution was stirred overnight at rt and evaporated the acetone. The solution was acidified with 2M HCl and the extracts were isolated between pH 2-6 using ethyl acetate. All the layers were combined and concentrated and the resulting crude product was purified by quick flash

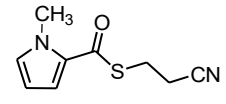
chromatography (hexane/EtOAc, 95:5 → hexane/EtOAc, 80:20) to give **160** (170 mg, 27%) as a yellowish solid. ^{1}H NMR: δ = 9.39 (brs, 1H), 7.10 – 6.85 (m, 2H), 6.30 (m, 1H), 4.43 (brs, 1H); ^{13}C NMR: δ = 179.7, 130.1, 125.1, 117.4, 111.3; IR (neat, cm^{-1}): 3285, 3105, 2959, 2554, 1614, 1536, 1426, 1379, 1292, 1132, 1092, 1041, 1002, 979, 882, 816, 581. Note: The desired mass was not observed by HR-ESIMS.

2-cyanoethylpyrrole-2-thiocarboxylate (201): To a flame dried round bottom flask filled and evacuated with nitrogen was added the pyrrole acid **196** (122 mg, 1.09 mmol) and dissolved in dry

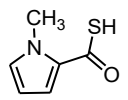


CH_2Cl_2 (3.30 mL). Then DMAP (14.0 mg, 0.115 mmol) and 3-mercaptopropanenitrile (100 mg, 1.05 mmol) were added and the mixture cooled to 0 °C followed by addition of DCC (237 mg, 1.15 mmol) in one portion and cooling bath was removed allowed to come in the rt. This solution was stirred for 15 h and the solvent was removed in vacuo. The resulted crude mixture was dissolved in CH_2Cl_2 and filtered (×2) through a pad of celliete. The filtrate dried (Na_2SO_4) and concentrated to give the crude product which was purified by column chromatography (SiO_2; 18 cm) using CH_2Cl_2 as the eluent to give ester (150 mg, 77%) as a white solid. ^{1}H NMR: δ = ^{1}H NMR; δ = 9.79 (s, 1H), 7.12 – 7.01 (m, 2H), 6.28-6.26 (m, 1H), 3.25 (t, *J* = 7.0 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR: δ = 179.8, 129.1, 124.7, 118.0, 116.1, 110.8, 23.7, 18.8; IR (neat, cm^{-1}): 3361, 2943, 2245, 1626, 1540, 1391, 1340, 1298, 1287, 1210, 1127, 1094, 1032, 898, 846, 822, 751 696, 668, 641; HR-ESIMS *(m/z)*: Calcd. for $C_8H_9N_2OS$ $[M+H]^+$ 181.0430, found 181.0431.

***N*-Methylpyrrole-2-carbothioic acid (206)**: *N*-methylpyrrole-2-carboxylic acid **200** (136 mg, 1.09 mmol) was converted to the corresponding ester (156 mg, 74%, colorless oil) following the above general procedure (**201**) using mercaptopropanenitrile (100 mg, 1.05 mmol), DMAP (14.0 mg, 0.115 mmol) and DCC (237 mg, 1.15 mmol) in 3.30 mL of CH_2Cl_2. ^{1}H NMR: δ = 7.05 (dd, *J* = 4.2, 1.7 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.10 (dd, *J* = 4.2, 2.5 Hz, 1H), 3.86 (s, 3H), 3.17 (t, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR: δ = 179.7, 131.3, 128.6, 119.1, 118.3, 109.0, 37.2, 24.2, 19.2; IR (neat, cm^{-1}): 3110, 2930, 2852, 2249, 1638, 1520, 1465, 1397, 1371, 1315, 1234, 1202, 1090, 1058, 1028, 899, 851, 741, 689, 604, 587; HR-ESIMS *(m/z)*: Calcd. for $C_9H_{11}N_2OS$ $[M+H]^+$ 195.0587, found 195.0589.



***N*-Methylpyrrole-2-carbothioic acid (206)**: Thionyl chloride (500 mg, 4.00 mmol) was added dropwise to pyrrole carboxylic acid **200** in a round bottom flask under the inert condition and heated the mixture at 55 °C for 30 minutes. The excess thionyl chloride (4.40 mL, 60.0 mmol) was removed in vacuo and dried the sample under the vacuum. Then it was dissolved in acetone (20 mL) and stirred under N_2 for 5 minutes. NaHS (330 mg, 6.00 mmol) was dissolved in water (4 mL) and added dropwise to the above pyrrole mixture. The solution was stirred overnight at rt and evaporated the acetone, acidified with 2M HCl and the extracts were isolated between pH 2-6 with ethylacetate. All the layers were combined and concentrated, the resulting crude product was purified by a quick flash chromatography (hexane/EtOAc, 95:5 → hexane/EtOAc, 80:20) to give **159** (146 mg, 25%) as a yellowish solid. ^{1}H NMR: δ = 7.01 (dd, *J* = 4.2, 1.7 Hz, 1H), 6.85 – 6.79 (m, 1H), 6.13 (dd, *J* = 4.2, 2.5 Hz, 1H), 4.16 (brs, 1H), 3.86 (s, 3H); ^{13}C NMR: δ = 179.8, 131.4, 128.7, 119.2, 109.1, 37.4; IR (neat, cm^{-1}); 3319, 2950, 2498, 1636, 1519, 1480, 1462, 1438, 1393, 1369, 1315, 1236, 1199, 1090, 1057,



956, 894, 819, 731, 686, 605, 582, 460; HR-ESIMS *(m/z)*: Calcd. for C_6H_6NOS $[M-H]^-$ 140.0176, found 140.0181.

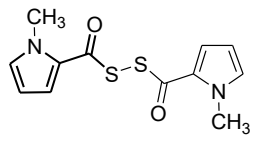
4-[(1*E*)-3-*N*-propenyl-1H-pyrrole-2-carboxamide]-1-dimethylsulfamoylimidazole (207):

Azide **142** (25 mg, 0.098 mmol) was converted to **207** (7.0 mg, 22%, yellow solid) following the general procedure E using pyrrole thioacid **199** (25 mg, 0.20 mmol) and 2,6-lutidine (23 µL, 0.20 mmol) in methanol (0.40 mL) and heated at 55 °C for overnight. The crude reaction mixture was purified on silica gel (EtOAc/hexanes, 25:75 → EtOAc/hexanes 90:10) to give **207** as the product. m.p. 152-154. ^{1}H NMR: δ = 9.57 (s, 1H), 7.84 (s, 1H), 7.10 (s, 1H), 6.96 – 6.91 (m, 1H), 6.60 – 6.56 (m, 1H), 6.51 (dt, *J* = 15.7, 5.6 Hz, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.25 – 6.21 (m, 1H), 6.12 – 6.04 (brt, *J* = 5.2 Hz, 1H), 4.19 (t, *J* = 5.6 Hz, 2H), 2.85 (s, 6H); ^{13}C NMR: δ = 161.1, 140.9, 137.0, 127.4, 125.8, 122.0, 121.7, 114.3, 110.0, 109.1, 41.0, 38.3; IR (neat, cm^{-1}): 3383, 3312, 3140, 3109, 1618, 1572, 1558, 1522, 1476, 1454, 1382, 1335, 1306, 1263, 1192, 1163, 1080, 1007, 961, 935, 757, 730, 600, 509; HR-ESIMS *(m/z)*: Calcd. for $C_{13}H_{18}N_5O_3S$ $[M+H]^+$ 324.1125, found 324.1125.

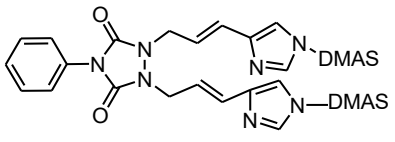
4-[(1*E*)-3-*N*-propenyl-*N*-methylpyrrole-2-carboxamide]-1-dimethylsulfamoylimidazole (208): Azide **142** (25 mg, 0.098 mmol) was converted to **208** (8.9 mg, 27%, yellow solid) following the general procedure E using 2,6-lutidine (23 µl, 0.20 mmol) and thio acid **206** (33 mg, 0.23 mmol) in methanol (0.40 mL) and heated at 55 °C for 24 h. The crude mixture was purified on silica gel (EtOAc/hexanes, 25:75 → EtOAc/hexanes 90:10) to isolate desired product **208** and **209 (**24 mg, 73%, white shiny solid) as the major product . ^{1}H NMR: δ = 7.83 (s, 1H), 7.10 (s, 1H), 6.75 – 6.70

(m, 1H), 6.55 (dd, *J* = 3.9, 1.6 Hz, 1H), 6.54 – 6.48 (m, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.08 (dd, *J* = 3.9, 2.6 Hz, 1H), 5.95 (brs, 1H), 4.15 (t, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 2.85 (s, 6H). ^{13}C NMR: δ = 161.6, 140.9, 136.8, 129.7, 127.9, 127.7, 121.7, 114.0, 111.4, 107.1, 40.7, 38.1, 36.8; IR (neat, cm^{-1}); 3386, 3312, 3139, 3108, 2920, 1618, 1572, 1558, 1521, 1476, 1454, 1382, 1334, 1305, 1263, 1192, 1163, 1080, 1007, 961, 757, 729, 660, 600, 509; HR-ESIMS *(m/z)*: Calcd. for $C_{14}H_{20}N_5O_3S$ $[M+H]^+$, 338.1281 found 338.1275.

Dipyrrolyl disulfide (**209**): ^{1}H NMR δ = 7.34 (dd, *J* = 4.3, 1.6 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.19 (dd, *J* = 4.3, 2.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR δ = 175.9, 131.9, 127.1, 120.4, 109.4, 37.2; IR (neat, cm^{-1}); 3107, 2922, 1675, 1638, 1465, 1362, 1314, 1236, 1196, 1091, 1055, 1024, 893, 817, 739, 610, 548; HR-ESIMS *(m/z)*: Calcd. for $C_{12}H_{13}N_2O_2S_2$ $[M+H]^+$, 281.0413 found 281.0400.

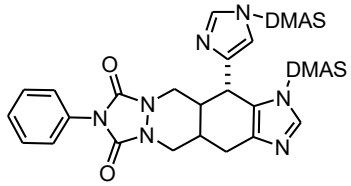


4-phenyl-1,2-bis[(2E)-3-(1-(N,N-dimethylsulfamoyl-1H-imidazol-4-yl) prop-2-en-1-yl]-1,2,4-triazolidine-3,5-dione (233a): BOC derivative **231a** (4.46 g, 13.5 mmol), urazole **232** (1.20 g, 6.75 mmol) and PPh_3 (177 mg, 0.680 mmol) were dissolved in DCM (91 mL) and deoxygenated for 10 minutes by sparging with nitrogen. Then Pd_2dba_3 (169 mg, 0.185 mmol) was added to the mixture and stirred overnight. The reaction mixture was concentrated and the resulting residue was dissolved in DCM and filtered of using a pad of Celite. The filtrate was concentrated and purified by flash chromatography (silica, DCM to DCM/EtOH; 97:3)) to give **233a** (3.13 g, 90%) as an off-white solid; m.p.165-168 °C; ^{1}H NMR: δ = 7.84 (d, *J* = 1.3 Hz, 2H), 7.56 – 7.51 (m, 2H), 7.47 – 7.44 (m, 2H), 7.38 – 7.33 (m, 1H), 7.15 (d, *J* = 1.3 Hz, 2H), 6.55 (d, *J* = 16.0 Hz,



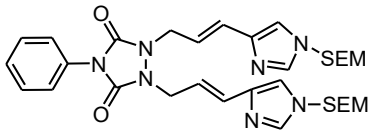
2H), 6.50 – 6.43 (dt, 15.5, 4.0 Hz, 2H), 4.43 (dd, J = 6.4, 1.0 Hz, 4H), 2.88 (s, 12H). ^{13}C NMR: δ = 153.5, 140.1, 137.1, 131.5, 129.2, 128.2, 125.4, 125.3, 123.5, 115.2, 47.5, 38.3; IR (neat, cm^{-1}): 3140, 2928, 1758, 1689, 1452, 1387, 1257, 1166, 1076, 960, 763, 596, 510; HR-ESIMS (*m/z*): Calcd. for $C_{24}H_{29}N_9O_6S_2$ $[M+H]^+$ 604.1755, found 604.1744.

(4aS,11aR,12S)-1-benzyl-12-(1-*N*,*N*-dimethylsulfamoyl-1H-imidazol-4-yl)-8-phenyl-4a,5,8,11,11a,12-hexahydroimidazo[4,5-g][1,2,4]triazolo[1,2-b]phthalazine-7,9(1H,4H)-dione (234c): Urazole **233c** (1.00g, 1.65 mmol) and toluene (125 mL) were degassed by bubbling



nitrogen through it for 10-15 minutes and then the tube was sealed and mixture was left at 140 °C for 48 hours. After that the reaction mixture was allowed to cool for few hours until the solid appeared. The product was isolated from suction filtration and finally the crude material was washed with ether and isolated (0.65 g, 65%) as an off-white color solid; m.p. 216-218 °C; ^{1}H NMR ($CDCl_3$): δ =7.84 (d, J = 1.4 Hz, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.51 – 7.43 (m, 5H), 7.36 (ddt, J = 6.3, 5.5, 2.7 Hz, 1H), 7.15 (d, J = 1.4 Hz, 1H), 4.31 (dd, J = 12.1, 4.5 Hz, 1H), 4.22 (dd, J = 12.0, 4.4 Hz, 1H), 3.95 – 3.91 (m, 1H), 3.07 – 3.00 (m, 2H), 2.89 (s, 6H), 2.81 (s, 6H), 2.66 – 2.59 (m, 1H), 2.22 (ddd, J = 11.3, 9.5, 4.5 Hz, 1H), 2.12 (dt, J = 11.4, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 152.5, 152.2, 142.9, 139.2, 137.6, 136.9, 131.5, 129.6, 128.6, 125.9, 125.7, 116.6, 48.4, 47.1, 44.0, 38.5, 38.3, 36.9, 36.2, 28.3; IR (neat, cm^{-1}): 3117, 2925, 1764, 1707, 1455, 1427, 1173, 1078, 962, 722, 593, 511; HR-ESIMS (*m/z*): Calcd. for $C_{24}H_{30}N_9O_6S_2$ $[M+H]^+$ 604.1755, found 604.1746.

4-phenyl-1,2-bis[(2E)-3-(1-(trimethylsilylethoxymethyl-1H-imidazol-4-yl) prop-2-en-1-yl]-1,2,4-triazolidine-3,5-dione (233b): The carbonate derivative **231b** (96 mg, 0.271 mmol), urazole



232 (24 mg, 0.135 mmol) and PPh_3 (7.1mg, 0.0271 mmol) were dissolved in DCM (0.64 mL) and deoxygenated for 10 minutes by sparging with nitrogen. Then $Pd_2(dba)_3$ (12 mg, 0.013 mmol) was added to the mixture and stirred overnight. The reaction mixture was concentrated and the resulting residue was dissolved in DCM and filtered through a pad of Celite. The filtrate was concentrated and purified by flash chromatography (silica, DCM to DCM/EtOH; 97:3)) to give **233b** (50 mg, 57%) as a yellow semi solid. ^{1}H NMR: δ = 7.51-7.48 (m, 4 H), 7.41-7.37 (m, 2H), 7.31-7.27 (m, 1H), 6.95 (d, *J* =1.3 Hz, 2H), 6.55 (d, *J* = 15.5 Hz, 2H), 6.32 (dt, *J* =15.8, 6.3 Hz, 2 H), 5.17 (s, 4H), 4.38 (d, 6.3 Hz, 4H), 3.43 (t, *J* =16.7 Hz, 4H), 0.86 (t, *J* =16.1 Hz, 4H), -0.04 (s, 18 H); ^{13}C NMR: δ = 153.2, 139.8, 137.8, 131.7, 129.0, 127.9, 126.9, 125.5, 120.4, 117.3, 76.1, 66.5, 47.4, 17.7, -1.3; IR (neat, cm^{-1}): 2952, 1761, 1693, 1539, 1421, 1247, 1084, 832; HR-ESIMS (*m/z*): Calcd. for $C_{32}H_{48}N_7O_4Si_2$ $[M+H]^+$ 650.3301, found 650.3299.